(continued)

Extragranular	
Magnesium stearate	2.43 ± 0.5
Total layer weight	323

[0160] In one embodiment a tablet is provided wherein less than about 30 weight percent of the first layer is the compound of Formula I or a pharmaceutically acceptable salt thereof. In one embodiment a tablet is provided wherein less than about 25 weight percent of the first layer is the compound of Formula I or a pharmaceutically acceptable salt thereof. In one embodiment a tablet is provided wherein less than about 22 weight percent of the first layer is the compound of Formula I or a pharmaceutically acceptable salt thereof. In one embodiment a tablet is provided wherein about 15 to about 27 weight percent, or about 17 to about 25 weight percent, or about 19 to about 23 weight percent of the first layer is the compound of Formula I or a pharmaceutically acceptable salt thereof. In one embodiment a tablet is provided wherein about 21 weight percent of the first layer is the compound of Formula I or a pharmaceutically acceptable salt thereof.

[0161] In one embodiment a tablet is provided wherein the first layer comprises 78 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 320 mg.

[0162] In one embodiment a tablet is provided wherein the first layer comprises 78 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 330 mg.

[0163] In one embodiment a tablet is provided wherein the first layer comprises 78 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 340 mg.

[0164] In one embodiment a tablet is provided wherein the first layer comprises 78 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 350 mg.

[0165] In one embodiment a tablet is provided wherein the first layer comprises 78 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 360 mg.

[0166] In one embodiment a tablet is provided wherein the first layer comprises 78 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 370 mg.

[0167] In one embodiment a tablet is provided wherein the first layer comprises 78 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 380 mg.

[0168] In one embodiment a tablet is provided wherein the first layer comprises 78 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 390 mg.

[0169] In one embodiment a tablet is provided wherein the first layer comprises 78 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 320 mg and is less than about 390 mg.

[0170] In one embodiment a tablet is provided wherein the first layer comprises 78 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 330 mg and is less than about 380 mg.

[0171] In one embodiment a tablet is provided wherein the first layer comprises 78 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 350 mg and is less than about 360 mg.

[0172] In one embodiment, the first layer of the multilayer tablet has a total weight of 353 ± 75 mg, or 353 ± 25 mg, or 353 ± 10 mg, or 353 mg.

[0173] In one embodiment, the first layer of the multilayer tablet comprises:

Ingredient	Mass (mg)
The compound of Formula I or a salt thereof	40-85
Microcrystalline cellulose	200-400
Croscarmellose sodium	1-40
Magnesium stearate	1-10

[0174] In one embodiment, the first layer of the multilayer tablet comprises:

Ingredient	Mass (mg)
The compound of Formula II	30-90
Microcrystalline cellulose	200-400

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(continued)

Ingredient	Mass (mg)
Croscarmellose sodium	1-40
Magnesium stearate	2-8

[0175] In one embodiment, the first layer of the multilayer tablet comprises:

Ingredient	Mass (mg)
The compound of Formula II	80 ± 6
Microcrystalline cellulose	250 ± 20
Croscarmellose sodium	20 ± 5
Magnesium stearate	5 ± 1.5

[0176] In one embodiment, the first layer of the multilayer tablet consists of:

Ingredient	Mass (mg)
The compound of Formula II	78 ± 5.6
Microcrystalline cellulose	250 ± 10
Croscarmellose sodium	20 ± 2.5
Magnesium stearate	5 ± 0.75

[0177] In one embodiment, the first layer of the multilayer tablet consists of:

Ingredient	Mass (mg)
the compound of Formula II	78 ± 2.8
Microcrystalline cellulose	247 ± 5
Croscarmellose sodium	21 ± 1.75
Magnesium stearate	5 ± 0.5

[0178] In one embodiment, the first layer of the multilayer tablet consists of:

Ingredient	Mass (mg)
the compound of Formula II	78.7
Microcrystalline cellulose	247.8
Croscarmellose sodium	21.2
Magnesium stearate	5.3

[0179] In one embodiment, the first layer of the multilayer tablet consists of:

Ingredient	Mass (mg)
Intergranular	
the compound of Formula II	78.7
Microcrystalline cellulose	212.5

(continued)

Ingredient	Mass (mg)
Intergranular	
Croscarmellose sodium	21.2
Magnesium stearate	2.65
Extragranular	
Microcrystalline cellulose	35.3
Magnesium stearate	2.65
Total layer weight	*353*

[0180] In one embodiment, the second layer of the multilayer tablet does not comprise lactose. In one embodiment, the second layer of the multilayer tablet does not comprise starch. In one embodiment, the second layer of the multilayer tablet comprises neither lactose nor starch.

[0181] In one embodiment, the second layer of the multilayer tablet comprises one or more excipients, for example, one or more diluents, disintegrants, binders, or lubricants.

[0182] In one embodiment, the second layer of the multilayer tablet comprises microcrystalline cellulose and croscarmellose sodium.

[0183] In one embodiment, the second layer of the multilayer tablet comprises microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

[0184] In one embodiment, the second layer of the multilayer tablet comprises 20-40 mg of croscarmellose sodium. In one embodiment, the second layer of the multilayer tablet comprises 105-125 mg of microcrystalline cellulose. In one embodiment, the second layer of the multilayer tablet comprises 1-8 mg of magnesium stearate.

[0185] In one embodiment, the second layer of the multilayer tablet does not comprise lactose. In one embodiment, the second layer of the multilayer tablet does not comprise starch. In one embodiment, the second layer of the multilayer tablet comprises neither lactose nor starch.

[0186] In one embodiment, the second layer of the multilayer tablet has a total weight of less than 600 mg, or less than 500 mg, or less than 400 mg, or less than 380 mg. In one embodiment, the second layer of the multilayer tablet has a total weight of 377 mg ± 50 mg or 377 mg ± 25 mg, or 377 mg ± 5 mg, or 377 mg.

[0187] In one embodiment, over 50 % by weight of the second layer of the multilayer tablet is emtricitabine or a salt thereof and tenofovir alafenamide or a salt thereof. In one embodiment, over 55 % by weight of the second layer of the multilayer tablet is emtricitabine or a salt thereof and tenofovir alafenamide or a salt thereof. In one embodiment, over 60 % by weight of the second layer of the multilayer tablet is emtricitabine or a salt thereof and tenofovir alafenamide or a salt thereof. In one embodiment, about 55 % to about 65% by weight of the second layer of the multilayer tablet is emtricitabine or a salt thereof and tenofovir alafenamide or a salt thereof. In one embodiment, over 60 % by weight of the second layer of the multilayer tablet is emtricitabine and tenofovir alafenamide hemifumarate. In one embodiment, about 55 % to about 65% by weight of the second layer of the multilayer tablet is emtricitabine and tenofovir alafenamide hemifumarate.

[0188] In one embodiment, the second layer of the multilayer tablet contains less than 250 mg of excipients, for example less than 200 mg, or less than 150 mg.

[0189] In one embodiment, at least 50% by weight of the second layer of the multilayer tablet is emtricitabine. In one embodiment, at least 53% by weight of the second layer of the multilayer tablet is emtricitabine. In one embodiment, about 45% to about 55% by weight of the second layer of the multilayer tablet is emtricitabine. In one embodiment, about 50% to about 60% by weight of the second layer of the multilayer tablet is emtricitabine. In one embodiment, about 51% to about 53% by weight of the second layer of the multilayer tablet is emtricitabine.

[0190] In one embodiment, at least 4% by weight of the second layer of the multilayer tablet is tenofovir alafenamide hemifumarate. In one embodiment, at least 6% by weight of the second layer of the multilayer tablet is tenofovir alafenamide hemifumarate. In one embodiment, at least 7% by weight of the second layer of the multilayer tablet is tenofovir alafenamide hemifumarate. In one embodiment, about 5% to about 10% by weight of the second layer of the multilayer tablet is tenofovir alafenamide hemifumarate. In one embodiment, about 6% to about 9% by weight of the second layer of the multilayer tablet is tenofovir alafenamide hemifumarate. In one embodiment, about 7% to about 8% by weight of the second layer of the multilayer tablet is tenofovir alafenamide hemifumarate. In one embodiment, about 7% by weight of the second layer of the multilayer tablet is tenofovir alafenamide hemifumarate.

[0191] In one embodiment, less than 20% by weight of the second layer of the multilayer tablet is croscarmellose

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sodium. In one embodiment, less than 10% by weight of the second layer of the multilayer tablet is croscarmellose sodium. In one embodiment, about 5% to about 10% by weight of the second layer of the multilayer tablet is croscarmellose sodium. In certain embodiments, the use of about 5 to 7% (e.g. about 6%) croscarmellose sodium by weight of the second layer may provide enhanced dissolution of the compound of Formula I or a pharmaceutically acceptable salt thereof, relative to other disintegrants e.g. polyvinylpyrrolidone (crospovidone). In certain embodiments, the use of about 5 to 10% croscarmellose sodium by weight of the second layer may provide enhanced dissolution of the compound of Formula I or a pharmaceutically acceptable salt thereof, relative to other disintegrants e.g. polyvinylpyrrolidone (crospovidone).

[0192] In one embodiment, less than 50% by weight of the second layer of the multilayer tablet is microcrystalline cellulose. In one embodiment, less than 40% by weight of the second layer of the multilayer tablet is microcrystalline cellulose. In one embodiment, less than 31% by weight of the second layer of the multilayer tablet is microcrystalline cellulose.

[0193] In one embodiment, less than 5% by weight of the second layer of the multilayer tablet is magnesium stearate. In one embodiment, less than 3% by weight of the second layer of the multilayer tablet is magnesium stearate. In one embodiment, less than 2% by weight of the second layer of the multilayer tablet is magnesium stearate. In one embodiment, about 0.5% to about 1.5% by weight of the second layer of the multilayer tablet is magnesium stearate. In certain embodiments, the use of about 1% to about 2% (e.g. about 1.5%) magnesium stearate by weight of the second layer may provide enhanced dissolution of the compound of Formula I or a pharmaceutically acceptable salt thereof, relative to other lubricants e.g. sodium stearyl fumarate.

[0194] In one embodiment, the total weight of the second layer is less than 150% of the total weight of the first layer. In one embodiment, the total weight of the second layer is less than 125% of the total weight of the first layer. In one embodiment, the total weight of the second layer is less than 116% of the total weight of the first layer. In one embodiment, the total weight of the second layer is less than 106% of the total weight of the first layer.

[0195] In one embodiment, the second layer of the multilayer tablet comprises:

Ingredient	Mass (mg)
Emtricitabine or a salt thereof	150-250
Tenofovir alafenamide or a salt thereof	20-35
Microcrystalline cellulose	90-130
Croscarmellose sodium	20-35
Magnesium stearate	1-7

[0196] In one embodiment, the second layer of the multilayer tablet comprises:

Ingredient	Mass (mg)
Emtricitabine	170-230
Tenofovir alafenamide hemifumarate	22-32
Microcrystalline cellulose	100-120
Croscarmellose sodium	20-35
Magnesium stearate	1-7

[0197] In one embodiment, the second layer of the multilayer tablet consists of:

Ingredient	Mass (mg)
Emtricitabine	200 ±20
Tenofovir alafenamide hemifumarate	28 ±3
Microcrystalline cellulose	113 ±9
Croscarmellose sodium	30 ±3
Magnesium stearate	5.6 ±1.1

[0198] In one embodiment, the second layer of the multilayer tablet consists of:

Ingredient	Mass (mg)
Emtricitabine	200 ±10
Tenofovir alafenamide hemifumarate	28 ±1.4
Microcrystalline cellulose	113 ±4
Croscarmellose sodium	30 ±1.4
Magnesium stearate	5.6 ±0.5

[0199] In one embodiment, the second layer of the multilayer tablet consists of:

Ingredient	Mass (mg)
Emtricitabine	200
Tenofovir alafenamide hemifumarate	28.1
Microcrystalline cellulose	113.2
Croscarmellose sodium	30.2
Magnesium stearate	5.7

[0200] In one embodiment, the second layer of the multilayer tablet consists of:

Ingredient	Mass (mg)
Intergranular	
Emtricitabine	200.00
Tenofovir alafenamide hemifumarate	28.1
Microcrystalline cellulose	113.2
Croscarmellose sodium	30.2
Magnesium stearate	2.85
Extragranular	
Magnesium stearate	2.85
Total layer weight	377

[0201] In one embodiment, the second layer of the multilayer tablet includes:

Ingredient	Mass (mg)
Emtricitabine	200 ±20
Tenofovir alafenamide	25 ±3
Microcrystalline cellulose	115 ±9
Croscarmellose sodium	30 ±3
Magnesium stearate	3.8 ±1.1

[0202] In one embodiment, the second layer of the multilayer tablet includes:

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Ingredient	Mass (mg)
Emtricitabine	200 ±20
Tenofovir alafenamide hemifumarate	28 ±3
Microcrystalline cellulose	115 ±9
Croscarmellose sodium	30 ±3
Magnesium stearate	3.8 ±1.1

[0203] In one embodiment, the second layer of the multilayer tablet includes:

Ingredient	Mass (mg)
Emtricitabine	200 ±10
Tenofovir alafenamide hemifumarate	28 ±1.4
Microcrystalline cellulose	115 ±4
Croscarmellose sodium	30 ±1.4
Magnesium stearate	3.8 ±0.5

[0204] In one embodiment, the second layer of the multilayer tablet includes:

Ingredient	Mass (mg)
Emtricitabine	200
Tenofovir alafenamide hemifumarate	28.1
Microcrystalline cellulose	115
Croscarmellose sodium	30.2
Magnesium stearate	3.8

[0205] In one embodiment, the second layer of the multilayer tablet includes:

Ingredient	Mass (mg)
Intergranular	
Emtricitabine	200
Tenofovir alafenamide hemifumarate	28
Microcrystalline cellulose	115
Croscarmellose sodium	30.2
Magnesium stearate	1.9
Extragranular	
Magnesium stearate	1.9
Total layer weight	377

[0206] In one embodiment, the second layer of the multilayer tablet includes:

Ingredient	Mass (mg)
Emtricitabine	200
Tenofovir alafenamide hemifumarate	28
Microcrystalline cellulose	113.2
Croscarmellose sodium	30.2
Magnesium stearate	5.7

[0207] In one embodiment, the second layer of the multilayer tablet includes:

Ingredient	Mass (mg)
Emtricitabine	200
Tenofovir alafenamide hemifumarate	28
Microcrystalline cellulose	115
Croscarmellose sodium	30.2
Magnesium stearate	3.8

[0208] In one embodiment, the second layer of the multilayer tablet includes:

Ingredient	Mass (mg)
Intergranular	
Emtricitabine	200
Tenofovir alafenamide hemifumarate	28
Microcrystalline cellulose	113.2
Croscarmellose sodium	30.2
Magnesium stearate	2.85
Extragranular	
Magnesium stearate	2.85
Total layer weight	377

[0209] In one embodiment of the multilayer tablet formulations disclosed herein, the first layer is in contact with the second layer.

[0210] In one embodiment, the first layer is produced first, followed be the second layer. That is, in one embodiment, the first layer is prepared and pressed into a first layer, followed by the second layer being prepared and being pressed with the first layer into a multilayer tablet. In one embodiment, the second layer is produced first, followed be the first layer. That is, in one embodiment, the second layer is prepared and pressed into a second layer, followed by the first layer being prepared and being pressed with the second layer into a multilayer tablet.

[0211] As used herein, when describing the multilayer tablets disclosed herein, the terms "first layer" and "second layer" are not intended to indicate the method by which the tablets are produced, in particular the order in which the layers are obtained.

[0212] In certain embodiments, the multilayer tablet further comprises additional layers. In certain embodiments, the additional layer or layers are located between the first and second layers. In certain embodiments, the additional layer or layers are located on either side of the first and/or second layer, such that they are an outside layer of the table and/or are disposed between the first and/or second layer and a coating layer. In some embodiments, the additional layer or layers encapsulate the first and second layers.

[0213] In one embodiment, the multilayer tablet further comprises a third layer that is between and that separates the first layer and the second layer. In one embodiment, the third layer of the multilayer tablet comprises lactose monohydrate,

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or microcrystalline cellulose, or a mixture thereof.

[0214] In one embodiment, the multilayer tablet further comprises a film coating. In one embodiment, the multilayer tablet further comprises about 14 mg to about 28 mg of a film coating. In one embodiment, the multilayer tablet further comprises about 19 mg to about 23 mg of a film coating. In one embodiment, the multilayer tablet further comprises about 21 mg of a film coating.In one embodiment the film coating comprises polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, and black iron oxide. In one embodiment the film coating consists of 21 ± 7 mg of Opadry II Brown 85F165072. In one embodiment the film coating consists of 21 ± 7 mg of Opadry II Yellow 85F92259.

[0215] In one embodiment, the multilayer tablet further includes a film coating. In one embodiment, the multilayer tablet further comprises about 1.9% to about 3.9% w/w of a film coating. In one embodiment, the multilayer tablet further comprises about 2.5% to about 3.5% w/w of a film coating. In one embodiment, the multilayer tablet further comprises about 3% of a film coating. In one embodiment the film coating includes polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, iron oxide red, and black iron oxide. In one embodiment the film coating includes 36%-40% polyvinyl alcohol, 18%-22% polyethylene glycol, 13%-16% talc, 20%-24% titanium dioxide, 2%-3% iron oxide red, and 0.5%-0.7% black iron oxide.

[0216] In one embodiment a tablet is provided comprising about 6.4-6.5% w/w of the compound of Formula II, about 25-32% w/w mg emtricitabine, about 3.5-4.5% w/w mg tenofovir alafenamide hemifumarate, about 46-57% w/w mg microcrystalline cellulose, about 5.9-8.5% w/w mg croscarmellose sodium, and about 1.0-2.0% w/w mg magnesium stearate.

[0217] In one embodiment a tablet is provided comprising 52 ± 6 mg of the compound of Formula II, 200 ± 20 mg emtricitabine, 28 ± 3 mg tenofovir alafenamide hemifumarate, 360 ± 30 mg Microcrystalline cellulose, 50 ± 8 mg Croscarmellose sodium, and 10.5 ± 3 mg magnesium stearate and wherein the total weight of the tablet is at least about 685 mg.

[0218] In one embodiment a tablet is provided comprising 52 ± 6 mg of the compound of Formula II, 200 ± 10 mg emtricitabine, 28 ± 1.5 mg tenofovir alafenamide hemifumarate, 360 ± 15 mg Microcrystalline cellulose, 50 ± 4 mg Croscarmellose sodium, and 10.5 ± 1.5 mg magnesium stearate and wherein the total weight of the tablet is at least about 685 mg and is less than about 715 mg.

[0219] In one embodiment a tablet is provided comprising 52 ± 6 mg of the compound of Formula II, 200 ± 20 mg emtricitabine, 28 ± 3 mg Tenofovir alafenamide hemifumarate, 360 ± 30 mg Microcrystalline cellulose, 50 ± 8 mg Croscarmellose sodium, and 8.6 ± 3 mg magnesium stearate and wherein the total weight of the tablet is at least about 685 mg.

[0220] In one embodiment a tablet is provided comprising 52 ± 6 mg of the compound of Formula II, 200 ± 10 mg emtricitabine, 28 ± 1.5 mg Tenofovir alafenamide hemifumarate, 360 ± 15 mg Microcrystalline cellulose, 50 ± 4 mg Croscarmellose sodium, and 8.6 ± 1.5 mg magnesium stearate and wherein the total weight of the tablet is at least about 685 mg and is less than about 715 mg.

[0221] In one embodiment, the tablet has a total weight of 700 ± 75 mg, or 700 ± 25 mg, or 700 ± 10 mg, or 700 mg. In one embodiment, the tablet is uncoated and has a total weight of about 700 ± 75 mg, or about 700 ± 25 mg, or about 700 ± 10 mg, or about 700 mg. In one embodiment, the tablet has a total weight of about 720 ± 75 mg, or about 720 ± 25 mg, or about 720 ± 10 mg, or about 720 mg, or about 721 mg, or about 722 mg, or about 723 mg, or about 724 mg, or about 725 mg, or about 726 mg, or about 727 mg, or about 728 mg, or about 729 mg, or about 730 mg.

[0222] In one embodiment a tablet is provided comprising 80 ± 8 mg of the compound of Formula II, 200 ± 20 mg emtricitabine, 28 ± 3 mg Tenofovir alafenamide hemifumarate, 360 ± 30 mg Microcrystalline cellulose, 50 ± 8 mg Croscarmellose sodium, and 11 ± 3 mg magnesium stearate and wherein the total weight of the tablet is at least about 715 mg.

[0223] In one embodiment a tablet is provided comprising 78 ± 2.3 mg of the compound of Formula II, 200 ± 10 mg emtricitabine, 28 ± 1.5 mg Tenofovir alafenamide hemifumarate, 361 ± 15 mg Microcrystalline cellulose, 51 ± 4 mg Croscarmellose sodium, and 11 ± 1.5 mg magnesium stearate and wherein the total weight of the tablet is at least about 715 mg and is less than about 745 mg.

[0224] In one embodiment, the tablet has a total weight of 730 ± 75 mg, or 730 ± 25 mg, or 730 ± 10 mg, or 730 mg. In one embodiment, the tablet has a total weight of about 750 ± 75 mg, or about 750 ± 25 mg, or about 750 ± 10 mg, or about 750 mg, or about 751 mg, or about 752 mg, or about 753 mg, or about 754 mg, or about 755 mg.

[0225] In one embodiment, a tablet is provided comprising:

Ingredient	Mass (mg)
The compound of Formula II	52 ± 6
Emtricitabine	200 ± 20
Tenofovir alafenamide hemifumarate	28 ± 3

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Ingredient	Mass (mg)
Microcrystalline cellulose	360 ± 30
Croscarmellose sodium	50 ± 8
Magnesium stearate	10.5 ± 3

[0226] In one embodiment, a tablet is provided comprising:

Ingredient	Mass (mg)
The compound of Formula II	52.5 ± 3
Emtricitabine	200 ± 10
Tenofovir alafenamide hemifumarate	28.1 ± 1.5
Microcrystalline cellulose	360 ± 15
Croscarmellose sodium	50 ± 4
Magnesium stearate	10.5 ± 1.5

[0227] In one embodiment, a tablet is provided including:

Ingredient	Mass (mg)
The compound of Formula I, or a pharmaceutically acceptable salt thereof	50 ± 5
Emtricitabine	200 ± 20
Tenofovir alafenamide, or a pharmaceutically acceptable salt thereof	25 ± 3
Microcrystalline cellulose	360 ± 30
Croscarmellose sodium	50 ± 8
Magnesium stearate	8.6 ± 3

[0228] In one embodiment, a tablet is provided including:

Ingredient	Mass (mg)
The compound of Formula I, or a pharmaceutically acceptable salt thereof	50 ± 2.5
Emtricitabine	200 ± 10
Tenofovir alafenamide, or a pharmaceutically acceptable salt thereof	25 ± 1.5
Microcrystalline cellulose	360 ± 15
Croscarmellose sodium	50 ± 4
Magnesium stearate	8.6 ± 1.5

[0229] In one embodiment, a tablet is provided including:

Ingredient	Mass (mg)
The compound of Formula I, or a pharmaceutically acceptable salt thereof	52 ± 6
Emtricitabine	200 ± 20
Tenofovir alafenamide hemifumarate	28 ± 3

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Ingredient	Mass (mg)
Microcrystalline cellulose	360 ± 30
Croscarmellose sodium	50 ± 8
Magnesium stearate	8.6 ± 3

[0230] In one embodiment, a tablet is provided including:

Ingredient	Mass (mg)
The compound of Formula II	52 ± 6
Emtricitabine	200 ± 20
Tenofovir alafenamide hemifumarate	28 ± 3
Microcrystalline cellulose	360 ± 30
Croscarmellose sodium	50 ± 8
Magnesium stearate	8.6 ± 3

[0231] In one embodiment, a tablet is provided including:

Ingredient	Mass (mg)
The compound of Formula II	52.5 ± 3
Emtricitabine	200 ± 10
Tenofovir alafenamide hemifumarate	28.1 ± 1.5
Microcrystalline cellulose	360 ± 15
Croscarmellose sodium	50 ± 4
Magnesium stearate	8.6 ± 1.5

[0232] In one embodiment, a tablet is provided comprising a first layer consisting of:

Ingredient	Mass (mg)
The compound of Formula II	50 ± 6
Microcrystalline cellulose	250 ± 20
Croscarmellose sodium	20 ± 5
Magnesium stearate	5 ± 1.5

and a second layer consisting of:

Ingredient	Mass (mg)
Emtricitabine	200 ± 20
Tenofovir alafenamide hemifumarate	28 ± 3
Microcrystalline cellulose	113 ± 9
Croscarmellose sodium	30 ± 3
Magnesium stearate	5.6 ± 1.1

[0233] In one embodiment, a tablet is provided comprising a first layer including:

Ingredient	Mass (mg)
The compound of Formula I, or a pharmaceutically acceptable salt thereof	50 ± 6
Microcrystalline cellulose	250 ± 20
Croscarmellose sodium	20 ± 5
Magnesium stearate	5 ± 1.5

and a second layer including:

Ingredient	Mass (mg)
Emtricitabine	200 ± 20
Tenofovir alafenamide, or a pharmaceutically acceptable salt thereof	25 ± 3
Microcrystalline cellulose	113 ± 9
Croscarmellose sodium	30 ± 3
Magnesium stearate	4 ± 1.1

[0234] In one embodiment, a tablet is provided comprising a first layer including:

Ingredient	Mass (mg)
The compound of Formula I, or a pharmaceutically acceptable salt thereof	50 ± 6
Microcrystalline cellulose	250 ± 20
Croscarmellose sodium	20 ± 5
Magnesium stearate	5 ± 1.5

and a second layer including:

Ingredient	Mass (mg)
Emtricitabine	200 ± 20
Tenofovir alafenamide hemifumarate	28 ± 3
Microcrystalline cellulose	113 ± 9
Croscarmellose sodium	30 ± 3
Magnesium stearate	4 ± 1.1

[0235] In one embodiment, a tablet is provided comprising a first layer including:

Ingredient	Mass (mg)
The compound of Formula II	50 ± 6
Microcrystalline cellulose	250 ± 20
Croscarmellose sodium	20 ± 5
Magnesium stearate	5 ± 1.5

and a second layer including:

Ingredient	Mass (mg)
Emtricitabine	200 ± 20
Tenofovir alafenamide hemifumarate	28 ± 3
Microcrystalline cellulose	113 ± 9
Croscarmellose sodium	30 ± 3
Magnesium stearate	4 ± 1.1

[0236] In one embodiment, a tablet is provided comprising a first layer consisting of:

Ingredient	Mass (mg)
The compound of Formula II	52 ± 2.6
Microcrystalline cellulose	246 ± 5
Croscarmellose sodium	19 ± 1.75
Magnesium stearate	5 ± 0.5

and a second layer consisting of:

Ingredient	Mass (mg)
Emtricitabine	200 ± 10
Tenofovir alafenamide hemifumarate	28 ± 1.4
Microcrystalline cellulose	113 ± 4
Croscarmellose sodium	30 ± 1.4
Magnesium stearate	5.6 ± 0.5

[0237] In one embodiment, a tablet is provided comprising a first layer including:

Ingredient	Mass (mg)
The compound of Formula I, or a pharmaceutically acceptable salt therof	50 ± 3
Microcrystalline cellulose	246 ± 5
Croscarmellose sodium	19 ± 1.75
Magnesium stearate	5 ± 0.5

and a second layer including:

Ingredient	Mass (mg)
Emtricitabine	200 ± 10
Tenofovir alafenamide, or a pharmaceutically acceptable salt thereof	25 ± 3
Microcrystalline cellulose	113 ± 4
Croscarmellose sodium	30 ± 1.4
Magnesium stearate	4 ± 0.5

[0238] In one embodiment, a tablet is provided comprising a first layer including:

Ingredient	Mass (mg)
The compound of Formula II	52 ± 2.8
Microcrystalline cellulose	246 ± 5
Croscarmellose sodium	19 ± 1.75
Magnesium stearate	5 ± 0.5

and a second layer including:

Ingredient	Mass (mg)
Emtricitabine	200 ± 10
Tenofovir alafenamide hemifumarate	28 ± 1.4
Microcrystalline cellulose	113 ± 4
Croscarmellose sodium	30 ± 1.4
Magnesium stearate	4 ± 0.5

[0239] In one embodiment, a tablet is provided comprising:

Ingredient	Mass (mg)
The compound of Formula II	80 ± 6
Emtricitabine	200 ± 20
Tenofovir alafenamide hemifumarate	28 ± 3
Microcrystalline cellulose	360 ± 30
Croscarmellose sodium	50 ± 8
Magnesium stearate	11 ± 3

[0240] In one embodiment, a tablet is provided comprising:

Ingredient	Mass (mg)
The compound of Formula II	78.6 ± 2.3
Emtricitabine	200 ± 10
Tenofovir alafenamide hemifumarate	28.1 ± 1.5
Microcrystalline cellulose	361 ± 15
Croscarmellose sodium	51 ± 4
Magnesium stearate	11 ± 1.5

[0241] In one embodiment, a tablet is provided comprising a first layer consisting of:

Ingredient	Mass (mg)
The compound of Formula II	80 ± 6
Microcrystalline cellulose	250 ± 20
Croscarmellose sodium	20 ± 5
Magnesium stearate	5 ± 1.5

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and a second layer consisting of:

Ingredient	Mass (mg)
Emtricitabine	200 ± 20
Tenofovir alafenamide hemifumarate	28 ± 3
Microcrystalline cellulose	113 ± 9
Croscarmellose sodium	30 ± 3
Magnesium stearate	5.6 ± 1.1

[0242] In one embodiment, a tablet is provided comprising a first layer consisting of:

Ingredient	Mass (mg)
The compound of Formula II	78 ± 2.8
Microcrystalline cellulose	247 ± 5
Croscarmellose sodium	21 ± 1.75
Magnesium stearate	5 ± 0.5

and a second layer consisting of:

Ingredient	Mass (mg)
Emtricitabine	200 ± 10
Tenofovir alafenamide hemifumarate	28 ± 1.4
Microcrystalline cellulose	113 ± 4
Croscarmellose sodium	30 ± 1.4
Magnesium stearate	5.6 ± 0.5

[0243] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in tablet)
The compound of Formula I, or a pharmaceutically acceptable salt thereof	5-10
Microcrystalline cellulose	25-44
Croscarmellose sodium	2-4
Magnesium stearate	0.5-0.9

and a second layer including:

	% w/w (in tablet)
Emtricitabine	21-36
Tenofovir alafenamide, or a pharmaceutically acceptable salt thereof	3-5
Microcrystalline cellulose	12-20
Croscarmellose sodium	3-6
Magnesium stearate	0.3-0.7

and optionally a film coating.

[0244] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in tablet)
The compound of Formula II	5-10
Microcrystalline cellulose	25-44
Croscarmellose sodium	2-4
Magnesium stearate	0.5-0.9

and a second layer including:

	% w/w (in tablet)
Emtricitabine	21-36
Tenofovir alafenamide hemifumarate	3-5
Microcrystalline cellulose	12-20
Croscarmellose sodium	3-6
Magnesium stearate	0.3-0.7

and optionally a film coating.

[0245] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in tablet)
The compound of Formula I, or a pharmaceutically acceptable salt thereof	6-9
Microcrystalline cellulose	30-40
Croscarmellose sodium	2.4-3.2
Magnesium stearate	0.6-0.8

and a second layer including:

	% w/w (in tablet)
Emtricitabine	24-33
Tenofovir alafenamide, or a pharmaceutically acceptable salt thereof	3.4-4.6
Microcrystalline cellulose	14-19
Croscarmellose sodium	3.6-4.9
Magnesium stearate	0.6-0.8

and optionally a film coating.

[0246] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in tablet)
The compound of Formula II	6-9
Microcrystalline cellulose	30-40
Croscarmellose sodium	2.4-3.2
Magnesium stearate	0.6-0.8

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and a second layer including:

	% w/w (in tablet)
Emtricitabine	24-33
Tenofovir alafenamide hemifumarate	3.4-4.6
Microcrystalline cellulose	14-19
Croscarmellose sodium	3.6-4.9
Magnesium stearate	0.6-0.8

and optionally a film coating.

[0247] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in tablet)
The compound of Formula II	7-8
Microcrystalline cellulose	32-37
Croscarmellose sodium	2.7-2.9
Magnesium stearate	0.6-0.8

and a second layer including:

	% w/w (in tablet)
Emtricitabine	26-30
Tenofovir alafenamide hemifumarate	3.7-4.6
Microcrystalline cellulose	15-17
Croscarmellose sodium	4.0-4.5
Magnesium stearate	0.5-0.6

and optionally a film coating.

[0248] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in tablet)
The compound of Formula II	7-8
Microcrystalline cellulose	33-36
Croscarmellose sodium	2.7-2.8
Magnesium stearate	0.7-0.8

and a second layer including:

	% w/w (in tablet)
Emtricitabine	27-29
Tenofovir alafenamide hemifumarate	3.8-4.2
Microcrystalline cellulose	16-17
Croscarmellose sodium	4.1-4.4
Magnesium stearate	0.5-0.8

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and optionally a film coating.

[0249] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in tablet)
The compound of Formula II	7.5
Microcrystalline cellulose	35.2
Croscarmellose sodium	2.8
Magnesium stearate	0.7

and a second layer including:

	% w/w (in tablet)
Emtricitabine	28.6
Tenofovir alafenamide hemifumarate	4.0
Microcrystalline cellulose	16.4
Croscarmellose sodium	4.3
Magnesium stearate	0.5

and optionally a film coating.

[0250] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in tablet)
The compound of Formula II	7.5
Microcrystalline cellulose	35.2
Croscarmellose sodium	2.8
Magnesium stearate	0.7

and a second layer including:

	% w/w (in tablet)
Emtricitabine	28.6
Tenofovir alafenamide hemifumarate	4.0
Microcrystalline cellulose	16.2
Croscarmellose sodium	4.3
Magnesium stearate	0.8

and optionally a film coating.

[0251] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in layer)
Intergranular	
The compound of Formula I, or a pharmaceutically acceptable salt thereof	11-19
Microcrystalline cellulose	51-86
Croscarmellose sodium	4-7

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(continued)

	% w/w (in layer)
Intergranular	
Magnesium stearate	0.5-0.9
Extragranular	
Microcrystalline cellulose	7-12
Magnesium stearate	0.5-0.9

and a second layer including:

	% w/w (in layer)
Intergranular	
Emtricitabine	39-67
Tenofovir alafenamide, or a pharmaceutically acceptable salt thereof	5-10
Microcrystalline cellulose	22-38
Croscarmellose sodium	6-10
Magnesium stearate	0.3-0.7
Intergranular	
Magnesium stearate	0.3-0.7

and optionally a film coating.

[0252] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in layer)
Intergranular	
The compound of Formula II	11-19
Microcrystalline cellulose	51-86
Croscarmellose sodium	4-7
Magnesium stearate	0.5-0.9
Extragranular	
Microcrystalline cellulose	7-12
Magnesium stearate	0.5-0.9

and a second layer including:

	% w/w (in layer)
Intergranular	
Emtricitabine	39-67
Tenofovir alafenamide hemifumarate	5-10
Microcrystalline cellulose	22-38
Croscarmellose sodium	6-10
Magnesium stearate	0.3-0.7

(continued)

Intergranular	
Magnesium stearate	0.3-0.7

and optionally a film coating.

[0253] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in layer)
Intergranular	
The compound of Formula I, or a pharmaceutically acceptable salt thereof	13-17
Microcrystalline cellulose	58-79
Croscarmellose sodium	4.6-6.3
Magnesium stearate	0.6-0.8
Extragranular	
Microcrystalline cellulose	5-11
Magnesium stearate	0.6-0.8

and a second layer including:

	% w/w (in layer)
Intergranular	
Emtricitabine	45-61
Tenofovir alafenamide, or a pharmaceutically acceptable salt thereof	6-9
Microcrystalline cellulose	25-35
Croscarmellose sodium	6.5-9.2
Magnesium stearate	0.4-0.5
Intergranular	
Magnesium stearate	0.4-0.5

and optionally a film coating.

[0254] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in layer)
Intergranular	
The compound of Formula I	13-17
Microcrystalline cellulose	58-79
Croscarmellose sodium	4.6-6.3
Magnesium stearate	0.6-0.8
Extragranular	
Microcrystalline cellulose	5-11
Magnesium stearate	0.6-0.8

and a second layer including:

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	% w/w (in layer)
Intergranular	
Emtricitabine	45-61
Tenofovir alafenamide hemifumarate	5-9
Microcrystalline cellulose	25-35
Croscarmellose sodium	6.5-9.2
Magnesium stearate	0.4-0.5
Intergranular	
Magnesium stearate	0.4-0.5

and optionally a film coating.

[0255] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in layer)
Intergranular	
The compound of Formula I, or a pharmaceutically acceptable salt thereof	14-16
Microcrystalline cellulose	66-73
Croscarmellose sodium	5.2-5.8
Magnesium stearate	0.65-0.75
Extragranular	
Microcrystalline cellulose	8-10
Magnesium stearate	0.65-0.75

and a second layer including:

	% w/w (in layer)
Intergranular	
Emtricitabine	50-56
Tenofovir alafenamide, or a pharmaceutically acceptable salt thereof	7-8
Microcrystalline cellulose	28-32
Croscarmellose sodium	7.5-8.5
Magnesium stearate	0.45-0.55
Intergranular	
Magnesium stearate	0.45-0.55

and optionally a film coating.

[0256] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in layer)
Intergranular	
The compound of Formula II	14-16
Microcrystalline cellulose	66-73

(continued)

	% w/w (in layer)
Intergranular	
Croscarmellose sodium	5.2-5.8
Magnesium stearate	0.65-0.75
Extragranular	
Microcrystalline cellulose	8-10
Magnesium stearste	0.65-0.75

and a second layer including:

	% w/w (in layer)
Intergranular	
Emtricitabine	50-56
Tenofovir alafenamide hemifumarate	7-8
Microcrystalline cellulose	28-32
Croscarmellose sodium	7.5-8.5
Magnesium stearate	0.45-0.55
Intergranular	
Magnesium stearate	0.45-0.55

and optionally a film coating.

[0257] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in layer)
Intergranular	
The compound of Formula II	15
Microcrystalline cellulose	69
Croscarmellose sodium	5.5
Magnesium stearate	0.7
Extragranular	
Microcrystalline cellulose	9
Magnesium stearate	0.7

and a second layer including:

	% w/w (in layer)
Intergranular	
Emtricitabine	53
Tenofovir alafenamide hemifumarate	7.5
Microcrystalline cellulose	30
Croscarmellose sodium	8

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	% w/w (in layer)
Intergranular	
Magnesium stearate	0.5
Intergranular	
Magnesium stearate	0.5

and optionally a film coating.

[0258] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in layer)
Intergranular	
The compound of Formula II	15
Microcrystalline cellulose	69
Croscarmellose sodium	5.5
Magnesium stearate	0.7
Extragranular	
Microcrystalline cellulose	9
Magnesium stearate	0.7

and a second layer including:

	% w/w (in layer)
Intergranular	
Emtricitabine	53
Tenofovir alafenamide hemifumarate	7.5
Microcrystalline cellulose	30
Croscarmellose sodium	8
Magnesium stearate	0.7
Intergranular	
Magnesium stearate	0.7

and optionally a film coating.

[0259] In one embodiment, a tablet is provided comprising a first layer including:

	Mass (mg)	% w/w (in layer)
Intragranular		
The compound of Formula II	52.5	16.24
Microcrystalline cellulose	149.9-246.3	46.41-76.26
Croscarmellose sodium	19.4	6.00
Magnesium stearate	1.98-2.45	0.6-1.0

(continued)

Extragranular		
Microcrystalline cellulose	0-97.0	0-30
Magnesium stearate	1.98-2.45	0.6-1.0

and a second layer including:

	Mass (mg)	% w/w (in layer)
Intergranular		
Emtricitabine	200.00	53.05
Tenofovir alafenamide hemifumarate	28.1	7.45
Microcrystalline cellulose	113.2	30
Croscarmellose sodium	30.2	8.00
Magnesium stearate	1.93-2.85	0.50-0.75
Extragranular		
Magnesium stearate	1.93-2.85	0.50-0.75

and optionally a film coating.

[0260] In one embodiment, a tablet is provided comprising a first layer consisting of:

	Mass (mg)	% w/w (in layer)
Intergranular		
The compound of Formula II	52.5	16.24
Microcrystalline cellulose	149.9-246.3	46.41-76.26
Croscarmellose sodium	19.4	8.00
Magnesium stearate	1.96-2.45	0.6-1.0
Extragranular		
Microcrystalline cellulose	0-97.0	0-30
Magnesium stearate	1.98-2.45	0.6-1.0

and a second layer consisting of:

	Mass (mg)	% w/w (in layer)
Intergranular		
Emtricitabine	200.00	53.05
Tenofovir alafenamide hemifumarate	28.1	7.45
Microcrystalline cellulose	113.2	30
Croscarmellose sodium	30.2	8.00
Magnesium stearate	1.93-2.85	0.50-0.75
Extragranular		
Magnesium stearate	1.93-2.85	0.50-0.75

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and optionally a film coating.

[0261] In one embodiment, a tablet is provided comprising a first layer consisting of:

	Mass (mg)	% w/w (in layer)
Intergranular		
The compound of Formula II	78.7	22.3
Microcrystalline cellulose	212.5	60.2
Croscarmellose sodium	21.2	6.00
Magnesium stearate	2.65	0.75
Extragranular		
Microcrystalline cellulose	35.30	10.0
Magnesium stearate	2.65	0.75

and a second layer consisting of:

	Mass (mg)	% w/w (in layer)
Intergranular		
Emtricitabine	200.00	53.05
Tenofovir alafenamide hemifumarate	28.0	7.4
Microcrystalline cellulose	113.2	30
Croscarmellose sodium	30.2	8.00
Magnesium stearate	2.83	0.75
Extragranular		
Magnesium stearate	2.83	0.75

and optionally a film coating.

[0262] In one embodiment, a tablet is provided comprising a first layer consisting of:

	Mass (mg)	% w/w (in layer)
Intergranular		
The compound of Formula II	52.5	16.25
Microcrystalline cellulose	0-246.3	0-76.25
Croscarmellose sodium	19.4	8.00
Magnesium stearate	1.98-2.45	0.6-1.0
Extragranular		
Microcrystalline cellulose	0-97.0	0-30
Magnesium stearate	2.45	0.6-1.0

and a second layer consisting of:

	Mass (mg)	% w/w (in layer)
Intergranular		
Emtricitabine	200.00	53.05

(continued)

	Mass (mg)	% w/w (in layer)
Intergranular		
Tenofovir alafenamide hemifumarate	28.1	7.45
Microcrystalline cellulose	113.2	30
Croscarmellose sodium	30.2	8.00
Magnesium stearate	2.85	0.75
Extragranular		
Magnesium stearate	2.85	0.75

and a film coating consisting of 21 mg of Opadry II Brown 85F165072 (a combination of polyvinyl alcohol, polyethylene glycol (PEG), talc, titanium dioxide, iron oxide red, and iron oxide black).

[0263] In one embodiment, a tablet is provided comprising a first layer including:

	Mass (mg)	% w/w (in layer)
Intergranular		
The compound of Formula II	52.5	13-21
Microcrystalline cellulose	0-246	0-59
Croscarmellose sodium	19	5-25
Magnesium stearate	2.0-2.5	0.5-3.2
Extragranular		
Microcrystalline cellulose	0-97	0-30
Magnesium stearate	2.0-2.5	0.5-3.2

and a second layer including:

	Mass (mg)	% w/w (in layer)
Intergranular		
Emtricitabine	200	35
Tenofovir alafenamide hemifumarate	28	4.9
Microcrystalline cellulose	113	20
Croscarmellose sodium	30	5.2
Magnesium stearate	2.9	0.5
Extragranular		
Magnesium stearate	2.9	0.5

and a film coating consisting of 21 mg of Opadry II Brown 85F165072 (a combination of polyvinyl alcohol, polyethylene glycol (PEG), talc, titanium dioxide, iron oxide red, and iron oxide black).

[0264] In one embodiment, a tablet is provided comprising a first layer including:

	Mass (mg)	% w/w (in tablet)
The compound of Formula II	47-53	8.75-8.25
Microcrystalline cellulose	222-271	32-59

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(continued)

	Mass (mg)	% w/w (in tablet)
Croscarmellose sodium	17-21	2.5-3.1
Magnesium stearate	4.4-5.4	0.6-0.8

and a second layer including:

	Mass (mg)	% w/w (in tablet)
Emtricitabine	180-220	26-31
Tenofovir alafenamide hemifumarate	25-31	3.6-4.4
Microcrystalline cellulose	104-127	15-18
Croscarmellose sodium	27-33	2.6-4.7
Magnesium stearate	3.4-6.0	0.4-1.0

and optionally a film coating (e.g., Opadry II Brown 85F165072 (a combination of polyvinyl alcohol, polyethylene glycol (PEG), talc, titanium dioxide, iron oxide red, and iron oxide black).

[0265] In one embodiment, a tablet is provided comprising a first layer including:

	Mass (mg)	% w/w (in tablet)
The compound of Formula II	52.5	7.5
Microcrystalline cellulose	246	35
Croscarmellose sodium	19	2.8
Magnesium stearate	5	0.7

and a second layer including:

	Mass (mg)	% w/w (in tablet)
Emtricitabine	200	29
Tenofovir alafenamide hemifumarate	28	4
Microcrystalline cellulose	115	16
Croscarmellose sodium	30	4.3
Magnesium stearate	4	0.5

and optionally a film coating (e.g., Opadry II Brown 85F165072 (a combination of polyvinyl alcohol, polyethylene glycol (PEG), talc, titanium dioxide, iron oxide red, and iron oxide black).

[0266] In one embodiment, a tablet is provided comprising a first layer consisting of:

	Mass (mg)	% w/w (in layer)
Intergranular		
The compound of Formula II	78.6	22.3
Microcrystalline cellulose	212.5	60.2
Croscarmellose sodium	21.2	6.00
Magnesium stearate	2.65	0.75

(continued)

Extragranular		
Microcrystalline cellulose	35.3	10.0
Magnesium stearate	2.65	0.75

and a second layer consisting of:

	Mass (mg)	% w/w (in layer)
Intergranular		
Emtricitabine	200.00	53.05
Tenofovir alafenamide hemifumarate	28.1	7.45
Microcrystalline cellulose	113.1	30
Croscarmellose sodium	30.2	8.00
Magnesium stearate	2.85	0.75 (0.5-0.75)
Extragranular		
Magnesium stearate	2.83	0.75 (0.5-7.5)

and a film coating consisting of 21.9 mg of Opadry II Yellow 85F92259 (a combination of polyvinyl alcohol, polyethylene glycol (PEG), talc, titanium dioxide and iron yellow).

[0267] In one embodiment, a composition is provided including about 75 mg of a compound of Formula I, or a pharmaceutically acceptable salt thereof (e.g., a compound of Formula II), about 25 mg tenofovir alafenamide, or a pharmaceutically acceptable salt thereof, and about 200 mg emtricitabine, or a pharmaceutically acceptable salt thereof, wherein the mean AUC_{last} of each component following a single dose administered to a human is from about 81700 h-ng/mL to about 140000 h-ng/mL of the compound of Formula I, from about 7500 h-ng/mL to about 15000 h-ng/mL of emtricitabine, and from about 165 h-ng/mL to about 400 h-ng/mL of tenofovir alafenamide. In certain embodiments, the composition is administered to the human in a fasted state. In certain embodiments, the composition is a tablet. In certain embodiments, the tablet is a bilayer tablet. In certain embodiments, the tablet is a bilayer tablet, with the Compound of Formula I in one layer and emtricitabine and tenofovir alafenamide in the other layer.

[0268] In one embodiment, a composition is provided including a compound of 50 mg Formula I, or a pharmaceutically acceptable salt thereof (e.g., a compound of Formula II), 25 mg tenofovir alafenamide, or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine, or a pharmaceutically acceptable salt thereof, wherein the mean AUC_{last} of each component following a single dose is from about 87,000 h-ng/mL to about 131,000 h-ng/mL of the compound of Formula I, from about 8500 h-ng/mL to about 12,800 h-ng/mL of emtricitabine, and from about 186 h-ng/mL to about 227 h-ng/mL of tenofovir alafenamide. In certain embodiments, the composition is administered to the human in a fasted state. In certain embodiments, the composition is a tablet. In certain embodiments, the tablet is a bilayer tablet. In certain embodiments, the tablet is a bilayer tablet, with the Compound of Formula I in one layer and emtricitabine and tenofovir alafenamide in the other layer. In certain embodiments, the subject is fasted. In other embodiments, the subject is fed.

[0269] In one embodiment, a composition is provided including a compound of Formula I, or a pharmaceutically acceptable salt thereof (e.g., a compound of Formula II), tenofovir alafenamide, or a pharmaceutically acceptable salt thereof, and emtricitabine, or a pharmaceutically acceptable salt thereof, wherein the mean AUC_{inf} of each component following a single dose administered to a human is from about 84450 h-ng/mL to about 141000 h-ng/mL of the compound of Formula I, from about 8100 h-ng/mL to about 136000 h-ng/mL of emtricitabine, and from about 200 h-ng/mL to about 500 h-ng/mL of tenofovir alafenamide. In certain embodiments, the composition is administered to the human in a fasted state. In certain embodiments, the composition is a tablet. In certain embodiments, the tablet is a bilayer tablet. In certain embodiments, the tablet is a bilayer tablet, with the Compound of Formula I in one layer and emtricitabine and tenofovir alafenamide in the other layer. In certain embodiments, the subject is fasted. In other embodiments, the subject is fed.

[0270] In one embodiment, a composition is provided including a compound of Formula I (e.g., a compound of Formula II), tenofovir alafenamide, and emtricitabine, wherein the mean C_{max} of each component following a single dose is from about 99,000 h-ng/mL to about 135,000 h-ng/mL of the compound of Formula I, from about 8,700 h-ng/mL to about 13,000 h-ng/mL of emtricitabine, and from about 200 h-ng/mL to about 300 h-ng/mL of tenofovir alafenamide. In certain embodiments, the composition is administered to the human in a fasted state. In certain embodiments, the composition

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is a tablet. In certain embodiments, the tablet is a bilayer tablet. In certain embodiments, the tablet is a bilayer tablet, with the Compound of Formula I in one layer and emtricitabine and tenofovir alafenamide in the other layer. In certain embodiments, the subject is fasted. In other embodiments, the subject is fed.

[0271] In one embodiment, a composition is provided including a compound of Formula I, or a pharmaceutically acceptable salt thereof (e.g., a compound of Formula II), tenofovir alafenamide, or a pharmaceutically acceptable salt thereof, and emtricitabine, or a pharmaceutically acceptable salt thereof, wherein the mean C_{max} of each component following a single dose administered to a human is from about 4200 ng/mL to about 8000 ng/mL of the compound of Formula I, from about 1770 ng/mL to about 2800 ng/mL of emtricitabine, and from about 185 ng/mL to about 315 ng/mL of tenofovir alafenamide. In certain embodiments, the composition is administered to the human in a fasted state. In certain embodiments, the composition is a tablet. In certain embodiments, the tablet is a bilayer tablet. In certain embodiments, the tablet is a bilayer tablet, with the Compound of Formula I in one layer and emtricitabine and tenofovir alafenamide in the other layer. In certain embodiments, the subject is fasted. In other embodiments, the subject is fed.

[0272] In one embodiment, a composition is provided including a compound of Formula I, or a pharmaceutically acceptable salt thereof (e.g., a compound of Formula II), tenofovir alafenamide, or a pharmaceutically acceptable salt thereof, and emtricitabine, or a pharmaceutically acceptable salt thereof, wherein the mean C_{max} of each component following a single dose is from about 4700 ng/mL to about 5300 ng/mL of the compound of Formula I, from about 2000 ng/mL to about 2600 ng/mL of emtricitabine, and from about 200 ng/mL to about 300 ng/mL of tenofovir alafenamide. In certain embodiments, the composition is administered to the human in a fasted state. In certain embodiments, the composition is a tablet. In certain embodiments, the tablet is a bilayer tablet. In certain embodiments, the tablet is a bilayer tablet, with the Compound of Formula I in one layer and emtricitabine and tenofovir alafenamide in the other layer. In certain embodiments, the subject is fasted. In other embodiments, the subject is fed.

[0273] In one embodiment, a composition is provided including a compound of Formula I, or a pharmaceutically acceptable salt thereof (e.g., a compound of Formula II), tenofovir alafenamide, or a pharmaceutically acceptable salt thereof, and emtricitabine, or a pharmaceutically acceptable salt thereof, wherein the mean AUC_{last}, AUC_{inf}, and/or C_{max} of each component following a single dose administered to a human in the fed state is 80-125%, 80-120%, 85-115%, 90-110%, or 95-105% of the mean AUC_{last}, AUC_{inf}, and/or C_{max} of each component following a single dose administered to a human in the fasted state. In certain embodiments, the composition is a tablet. In certain embodiments, the tablet is a bilayer tablet. In certain embodiments, the tablet is a bilayer tablet, with the Compound of Formula I in one layer and emtricitabine and tenofovir alafenamide in the other layer. In certain embodiments, the subject is fasted. In other embodiments, the subject is fed.

[0274] In certain embodiments, the pharmacokinetic profile of the compositions described herein is within acceptable ranges, regardless of whether the subject has eaten prior to taking the medication. Accordingly, in certain embodiments, the compositions described herein can be taken without regard to food intake by the subject. In certain embodiments, food intake is a low fat, moderate fat, or high fat meal.

[0275] In one embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{last} of a single dose following administration to fed patients is within about 100% to about 160% of the mean AUC_{last} of a single dose following administration to fasted patients. In another embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{last} of a single dose following administration to fed patients is within about 100% to about 145% of the mean AUC_{last} of a single dose following administration to fasted patients. In a further embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{last} of a single dose following administration to fed patients is within about 100% to about 135% of the mean AUC_{last} of a single dose following administration to fasted patients. In another embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{last} of a single dose following administration to fed patients is within about 100% to about 125% of the mean AUC_{last} of a single dose following administration to fasted patients.

[0276] In certain embodiments, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{last} of a single dose following administration to fed patients is within 60% of the mean AUC_{last} of a single dose following administration to fasted patients. In another embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{last} of a single dose following administration to fed patients is within 45% of the mean AUC_{last} of a single dose following administration to fasted patients. In a further embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{last} of a single dose following administration to fed patients is within 35% of the mean AUC_{last} of a single dose following administration to fasted patients. In another embodiments a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{last} of a single dose following administration to fed patients is within 25% of the mean AUC_{last} of a single dose following administration to fasted patients.

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[0277] In one embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{inf} of a single dose following administration to fed patients is within about 100% to about 160% of the mean AUC_{inf} of a single dose following administration to fasted patients. In another embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{inf} of a single dose following administration to fed patients is within about 100% to about 150% of the mean AUC_{inf} of a single dose following administration to fasted patients. In a further embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{inf} of a single dose following administration to fed patients is within about 100% to about 135% of the mean AUC_{inf} of a single dose following administration to fasted patients. In another embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{inf} of a single dose following administration to fed patients is within about 100% to about 125% of the mean AUC_{inf} of a single dose following administration to fasted patients.

[0278] In certain embodiments, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{inf} of a single dose following administration to fed patients is within 60% of the mean AUC_{inf} of a single dose following administration to fasted patients. In another embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{inf} of a single dose following administration to fed patients is within 50% of the mean AUC_{inf} of a single dose following administration to fasted patients. In a further embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{inf} of a single dose following administration to fed patients is within 35% of the mean AUC_{inf} of a single dose following administration to fasted patients. In another embodiments a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{inf} of a single dose following administration to fed patients is within 25% of the mean AUC_{inf} of a single dose following administration to fasted patients.

[0279] In one embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean C_{max} of a single dose following administration to fed patients is within about 100% to about 160% of the mean C_{max} of a single dose following administration to fasted patients. In another embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean C_{max} of a single dose following administration to fed patients is within about 100% to about 130% of the mean C_{max} of a single dose following administration to fasted patients. In a further embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean C_{max} of a single dose following administration to fed patients is within about 100% to about 120% of the mean C_{max} of a single dose following administration to fasted patients. In another embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean C_{max} of a single dose following administration to fed patients is within about 100% to about 115% of the mean C_{max} of a single dose following administration to fasted patients.

[0280] In certain embodiments, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean C_{max} of a single dose following administration to fed patients is within 60% of the mean C_{max} of a single dose following administration to fasted patients. In another embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean C_{max} of a single dose following administration to fed patients is within 30% of the mean C_{max} of a single dose following administration to fasted patients. In a further embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean C_{max} of a single dose following administration to fed patients is within 20% of the mean C_{max} of a single dose following administration to fasted patients. In another embodiments a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean C_{max} of a single dose following administration to fed patients is within 15% of the mean C_{max} of a single dose following administration to fasted patients.

Manufacturing methods

[0281] Methods for producing the compositions and dosage forms (in particular tablets) disclosed herein are also provided. In some embodiments, the method comprises (a) compressing the compound of Formula I or a pharmaceutically acceptable salt thereof as a first layer, and (b) compressing the tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof as a second layer. For example, in some embodiments, the method comprises (a) compressing the compound of Formula I or a pharmaceutically acceptable salt thereof as a first layer, followed by (b) compressing the tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof as a second layer. In other embodiments, the method comprises (a) compressing the tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof followed by (b) compressing the compound of Formula I or a

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pharmaceutically acceptable salt thereof as another layer. In other embodiments, the method comprises (a) compressing the compound of Formula I or a pharmaceutically acceptable salt thereof as one layer followed by (b) compressing the tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof as another layer. The first layer and second layer may be compressed separately and subsequently combined. However, more typically, a first layer is formed by compression and subsequently a second layer is compressed onto the first layer. In certain embodiments, the choice of layer order in the tableting of multilayer tablets may have an impact on the properties of the tablets (e.g. the adhesion of the layers within the tablet).

[0282] In some embodiments, a tablet is provided wherein the first layer is obtainable by a method of (a) compressing the compound of Formula I or a pharmaceutically acceptable salt thereof as a first layer, and (b) compressing the tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof as a second layer. In other embodiments, a tablet is provided wherein the second layer is obtainable by a method of (a) compressing the compound of Formula I or a pharmaceutically acceptable salt thereof as a first layer, and (b) compressing the tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof as a first layer.

[0283] In certain embodiments, the methods will include a step of coating the tablet cores after compression, e.g. with a film coating as described above.

[0284] In general, tableting methods are well known in the art of pharmacy. Techniques and formulations generally are found in Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, PA).

[0285] A tablet can be made by compression or molding, optionally with one or more excipients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with excipients.

Therapeutic methods

[0286] The solid oral dosage forms (in particular tablets) disclosed herein are used for treatment of HIV infection (e.g. HIV-1 infection). In certain embodiments, the solid oral dosage forms (in particular tablets) disclosed herein are used for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1.

[0287] Accordingly, methods for treating a subject infected with HIV are provided, comprising administering a solid oral dosage form disclosed herein (in particular a tablet) to the subject. Similarly, a solid oral dosage form (in particular a tablet) is provided for use in such treatment methods. Also provided is the use of the compound of Formula I or a pharmaceutically acceptable salt thereof, tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and emtricitabine or a pharmaceutically acceptable salt thereof, in the manufacture of an oral dosage form disclosed herein (in particular a tablet) for treatment of HIV infection.

[0288] In certain embodiments, the solid oral dosage forms (in particular tablets) disclosed herein are used for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1. Accordingly, methods for preventing infection in a subject at risk of infection with HIV are provided, comprising administering a solid oral dosage form disclosed herein (in particular a tablet) to the subject. Similarly, a solid oral dosage form disclosed herein (in particular a tablet) is provided for use in such treatment methods.

[0289] In certain embodiments, a method of treating a subject with HIV with the compositions disclosed herein is provided, wherein the method does not increase the risk of a drug-drug interaction in the patient. In certain embodiments, a method of treating a subject with HIV with the compositions disclosed herein is provided, wherein the method decreases the risk of a drug-drug interaction in the patient. Exemplary drug-drug interactions include interactions between the compound of Formula I, tenofovir alafenamide, or emtricitabine with rifampin, metformin, one or more hormonal contraceptives or an HCV antiviral agent (e.g., one or more of sofosbuvir, ledipasvir, velpatasvir, voxilaprevir, grazoprevir, boceprevir, elbasvir, dasabuvir, ombitasvir, paritaprevir, ABT-530, and ABT-493). In certain embodiments, a method of treating a subject with HIV is provided, wherein the subject is administered one or the compositions disclosed herein, wherein the subject is also being treated with rifampin, metformin, or an HCV antiviral agent (e.g., one or more of sofosbuvir, ledipasvir, velpatasvir, voxilaprevir, grazoprevir, boceprevir, elbasvir, dasabuvir, ombitasvir, paritaprevir, ABT-530, and ABT-493).

[0290] The methods involve administering an oral dosage form disclosed herein (in particular a tablet) to the subject, typically a human, and will generally involve repeated administrations, typically once daily. The treatment may be prophylactic or therapeutic treatment.

General

[0291] The term "fed" in relation to administration of a solid oral dosage form to a human subject means administration of the dosage form orally under fed conditions (moderate fat meal) e.g. administration within about 30 minutes of the human consuming a standardized meal of about 300 to 600 calories and about 10 to about 15 grams of fat. In some

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embodiments, "fed" refers to administration within about 30 minutes of the human consuming a high fat meal.

[0292] The term "substantially free" in relation to the presence of a given component within e.g. a composition means that less than 5% by weight of the composition (e.g. less than 1% by weight of the composition) is that given component. The word "substantially" does not exclude "completely" e.g. a composition which is "substantially free" from Y may be completely free from Y. Where necessary, the word "substantially" may be omitted from the definition of the invention.

[0293] The term "segregated" as used in relation to certain components (e.g. A and B) within a tablet means that those components are physically discrete such that the presence of one component (e.g. A) does not substantially affect the stability in storage of the other component(s) (e.g. B) from which it is segregated. Typically, when components are segregated in a tablet then they will be present in separate layers in a multilayer tablet. By way of example, components A and B may be present in separate layers in a multilayer tablet, wherein (a) the layer containing component A is substantially free of component B and (b) the layer containing component B is substantially free of component A. The separate layers may be in contact with each other or may be separated e.g. by one or more additional layers.

[0294] The term "comprise" and variations thereof, such as "comprises" and "comprising", are to be construed in an open, inclusive sense, that is as "including, but not limited to".

[0295] The term "between" with reference to two values includes those two values e.g. the range "between" 10 mg and 20 mg encompasses e.g. 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 20 mg.

[0296] The term "about" used in connection with a quantity is inclusive of the stated value and has the meaning dictated by the context (e.g., includes the degree of error associated with measurement of the particular quantity). For example, in certain nonlimiting example the term "about" in relation to a numerical value x refers to $x \pm 10\%$, $x \pm 5\%$, or $x \pm 1\%$.

[0297] "% w/w" means the weight of a component as a percentage of the total weight of e.g. a layer or dosage form in which the component is present. For example, a composition comprising "5% w/w X" refers to a composition in which the weight of component X is 5% of the total weight of the composition.

[0298] Reference throughout this specification to "one embodiment" or "an embodiment" means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment provided herein. Thus, the appearances of the phrases "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily all referring to the same embodiment. Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments.

[0299] The term "pharmaceutically acceptable" with respect to a substance refers to that substance which is generally regarded as safe and suitable for use without undue toxicity, irritation, and/or allergic response, commensurate with a reasonable benefit/risk ratio. "Pharmaceutically acceptable" with regard to excipients includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier which has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

[0300] "Pharmaceutically acceptable salt" refers to a salt of a compound that is pharmaceutically acceptable and that possesses (or can be converted to a form that possesses) the desired pharmacological activity of the parent compound. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, or phosphoric acid; or formed with organic acids such as acetic acid, benzenesulfonic acid, benzoic acid, camphorsulfonic acid, citric acid, ethanesulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, lactic acid, maleic acid, malonic acid, mandelic acid, methanesulfonic acid, 2-naphthalenesulfonic acid, oleic acid, palmitic acid, propionic acid, stearic acid, succinic acid, tartaric acid, p-toluenesulfonic acid, or trimethylacetic acid, and salts formed when an acidic proton present in the parent compound is replaced by either a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as diethanolamine, triethanolamine, or N-methylglucamine. Also included in this definition are ammonium and substituted or quaternized ammonium salts. Representative non-limiting lists of pharmaceutically acceptable salts can be found in S.M. Berge et al., J. Pharma Sci., 66(1), 1-19 (1977), and Remington: The Science and Practice of Pharmacy, R. Hendrickson, ed., 21st edition, Lippincott, Williams & Wilkins, Philadelphia, PA. (2005), at p. 732, Table 38-5.

[0301] As used herein, the term "salts" includes co-crystals. The term "co-crystal" refers to a crystalline compound comprising two or more molecular components, e.g. wherein proton transfer between the molecular components is partial or incomplete.

[0302] The term "solvate" means a molecular complex comprising a compound and one or more pharmaceutically acceptable solvent molecules. Examples of solvent molecules include water and C_{1-6} alcohols, e.g. ethanol. When the solvate is water, the term "hydrate" may be used.

[0303] "Treating" and "treatment" of a disease include the following:

(1) preventing or reducing the risk of developing the disease, i.e. causing the clinical symptoms of the disease not to develop in a subject that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease.

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(2) inhibiting the disease, *i.e.* arresting or reducing the development of the disease or its clinical symptoms, and

(3) relieving the disease, *i.e.* causing regression of the disease or its clinical symptoms.

[0304] The term "effective amount" refers to an amount that may be effective to elicit the desired biological or medical response, including the amount of a compound that, when administered to a subject for treating a disease, is sufficient to effect such treatment for the disease. The effective amount will vary depending on the compound, the disease and its severity and the age, weight, *etc.* of the subject to be treated. The effective amount can include a range of amounts.

EXAMPLES

[0305] The following examples are provided for purposes of illustration, not limitation. Examples 1, 2, 2a, 3, 4, 5, and tablet formulation F6 of Example 7 are provided as reference examples.

Example 1 - Compound of Formula II single agent tablets

[0306] A formulation (tablet F1) of the compound of Formula II was prepared by dry granulation. Figure 5 is a flow diagram illustrating the preparation of this formulation. The composition of the single agent formulation is shown in the table below:

	Tablet Formulation F1	
Component	**Mass (mg/tablet)**	**% w/w/ tablet**
Compound of Formula II	78.7*	26.2
Microcrystalline cellulose	120	40
Lactose monohydrate	75.8	25.3
Crospovidone	21	7
Sodium Stearyl Fumarate**	4.5	1.5
Total Weight	**300**	
*Equivalent to 75 mg of the Compound of Formula I ** Intergranular:2.25 mg (0.75%; Extragranular: 2.25 mg (0.75%)		

[0307] In the pharmacokinetic studies of Example 3, the tablets of Formulation F1 were film coated with 12 mg Opadry II Yellow 85F92259. The total weight of the film coated tablets was 312 mg.

[0308] The Compound of Formula II was blended with intergranular excipients (lactose, microcrystalline cellulose, and crospovidone), further blended with the intergranular portion of the sodium stearyl fumarate), roller compacted, milled, and final blended with the sodium stearyl fumarate to yield a final powder blend for compression. The final powder blend had a mean particle size of 347 µm with a compressibility index of 21%. The final powder blend was compressed into tablet cores, which were film-coated as described above to a target weight gain of 4%.

Example 2 - Compound of Formula II/ emtricitabine / tenofovir alafenamide bilayer tablets

[0309] A bilayer formulation (tablet F2) of the compound of Formula II, emtricitabine, and tenofovir alafenamide hemifumarate was prepared using the method described in Example 8. Figure 6 is a flow diagram illustrating the preparation of bilayer tablets. The composition of the formulation is summarized in the table below:

Ingredient	Bilayer tablet F2 (mg/tablet)	
	Compound of Formula II Layer	Emtricitabine/tenofovir alafenamide hemifumarate Layer
Compound of Formula II	78.7*	
Emtricitabine		200

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(continued)

Ingredient	Bilayer tablet F2 (mg/tablet)	
	Compound of Formula II Layer	Emtricitabine/tenofovir alafenamide hemifumarate Layer
Tenofovir alafenamide hemifumarate		28.1**
Microcrystalline cellulose	247.8***	113.1
Croscarmellose sodium	21.2	30.2
Magnesium Stearate	5.3†	5.7††
Layer Weight	353	377
Tablet Core Weight	**730**	

*Equivalent to 75 mg of the Compound of Formula I
**Equivalent to 25 mg tenofovir alafenamide
***Intergranular: 212.5 mg (29.1%); Extragranular: 2.65 mg (0.4%)
†Intergranular: 2.65 mg (0.4%); Extragranular: 2.65 mg (0.4%)
††Intergranular: 2.83 mg (0.4%); Extragranular: 2.83 mg (0.4%)

[0310] In the pharmacokinetic studies of Example 3, the tablets of Formulation F2 were film coated with 21.9 mg Opadry II Yellow 85F92259 (represented 3% weight gain). The total weight of the film coated tablets was 752 mg.

[0311] The tablets were manufactured using a dry granulation by roller compaction process. An emtricitabine / tenofovir alafenamide final powder blend was manufactured by dry granulation of emtricitabine and tenofovir alafenamide with excipients (microcrystalline cellulose, croscarmellose sodium, intergranular magnesium stearate), followed by blending with extragranular lubricant (extragranular magnesium stearate). The final powder blend of the Compound of Formula I was manufactured by dry granulation of the active component with excipients (microcrystalline cellulose, croscarmellose sodium, intergranular magnesium stearate) followed by blending with the extragranular filler and lubricant (microcrystalline cellulose and extragranular magnesium stearate). In this study, the emtricitabine/tenofovir alafenamide final powder blend was compressed as layer 1 and the final powder blend of the Compound of Formula I was compressed as layer 2 to give a final bilayer tablet core. The core was film coated as described above.

Example 2A Emtricitabine /tenofovir alafenamide tablets

[0312] The composition of the emtricitabine / tenofovir alafenamide (F/TAF) fixed dose combination tablets used in subsequent studies is shown in the following table:

Component	Tablet Formulation F3 Emtricitabine/tenofovir alafenamide 200/25 mg (mg/tablet)
Intergranular	
Emtricitabine	200
Tenofovir Alafenamide Hemifumarate	28.0
Microcrystalline Cellulose	88.7
Croscarmellose Sodium	28.0
Magnesium Stearate	2.6
Extragranular	
Magnesium Stearate	2.6
Total Tablet Core Weight	**350**
Film-Coating	
Opadry II Blue 85F105057	10.5

[0313] Emtricitabine and tenofovir alafenamide hemifumarate were co-blended with microcrystalline cellulose and croscarmellose sodium, followed by lubrication with magnesium stearate. The roller compaction pre-blend was then roller compacted and milled using an oscillating mill. The resultant granules were lubricated with magnesium stearate and compressed into 350 mg tablet cores which that were subsequently film coated.

Example 3 - Pharmacokinetic Studies

[0314] Studies were carried out to assess the pharmacokinetic profiles of the formulations F1, F2, and F3 of Examples 1, 2, and 2A. A randomized, open-label, multiple-period, fixed-sequence, crossover study was performed to evaluate the relative bioavailability of bilayer tablet formulation F2 compared with that of single agent tablet formulation F1 co-administered simultaneously with a fixed-dose combination tablet containing emtricitabine and tenofovir alafenamide (tablet formulation F3). The bioavailability was evaluated in healthy subjects.

Study Design and Duration of Treatment

[0315] Three single doses of the following tablet formulations were administered orally during up to 21 days total study duration:

(a) a fixed dosed combination tablet containing emtricitabine and tenofovir alafenamide (200/25 mg - Tablet F3) and a single agent tablet containing the compound of Formula I (75 mg - Tablet F1) administered simultaneously, under fasted conditions (dosed on day 1; days 2-8 washout);

(b) a fixed dose combination tablet containing the compound of Formula I, emtricitabine, and tenofovir alafenamide (75/200/25 mg - Tablet F2) administered under fasted conditions (dosed on day 9; days 10-16 washout); and

(c) a fixed dose combination tablet containing the compound of Formula I, emtricitabine, and tenofovir alafenamide (75/200/25 mg - Tablet F2) administered under fed conditions with a high-fat meal (dosed on day 17; day 21 discharge).

Criteria for Evaluation

[0316] The following plasma pharmacokinetic parameters were calculated: C_{max}, AUC_{last}, and AUC_{inf}.

Statistical Methods

[0317] Pharmacokinetics: Plasma concentrations and PK parameters were listed and summarized by analyte and treatment group using descriptive statistics. In addition, a parametric analysis of variance using a mixed-effects model appropriate for a crossover design was fitted to the natural logarithmic transformation of the PK parameters (AUC_{inf}, AUC_{last}, and C_{max}). Two-sided 90% confidence intervals (CIs) were constructed for the ratio of geometric least-squares means (GLSMs) of each PK parameter for the compound of Formula I, emtricitabine, and tenofovir alafenamide.

Results

Subject Disposition and Demographics

[0318] A total of 28 subjects were randomized and received at least 1 dose of study drug.

[0319] The results for the first cohort of the clinical study are summarized in the table below. This

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table presents the mean (%CV) values, Geometric Least Squares Mean (GLSM) ratios, and 90% CI values of the plasma PK parameters AUC_{last}, AUC_{inf}, and C_{max} for each active ingredient, following administration of bilayer tablet formulation F2 or the single agent tablet formulation F1, co-administered with a fixed dose combination of emtricitabine and tenofovir alafenamide under fasted conditions.

PK Parameter	Mean (%CV)		% GLSM Ratio (90% CI)
	Compound of Formula I /F/TAF (75/200/25 mg) (Test) (N = 28)	Compound of Formula I (75 mg) + F/TAF (200/25 mg) (Reference) (N = 28)	
Compound of Formula I			
AUC_{last} (h•ng/mL)	151,844.0 (26.9)	119,619.4 (26.6)	126.76 (117.82, 136.37)
AUC_{inf} (h•ng/mL)	156,637.5 (27.5)	123,174.0 (26.6)	126.82 (117.87, 136.45)
C_{max} (ng/mL)	7123.9 (21.8)	5693.9 (31.0)	130.72 (119.95, 142.45)
FTC			
AUC_{last} (h•ng/mL)	11,412.3 (13.5)	11,199.3 (13.7)	101.89 (99.59, 104.33)
AUC_{inf} (h•ng/mL)	11,842.8 (13.2)	11,636.4 (13.2)	101.78 (99.45, 104.16)
C_{max} (ng/mL)	2264.3 (22.7)	2153.6 (21.5)	104.86 (97.73, 112.50)
TAF			
AUC_{last} (h•ng/mL)	205.5 (45.5)	223.6 (45.2)	91.62 (82.13, 102.21)
AUC_{inf} (h•ng/mL)	206.8 (45.2)	225.1 (45.0)	91.56 (82.27, 101.91)
C_{max} (ng/mL)	253.3 (44.2)	276.7 (51.7)	95.47 (79.88, 114.10)

[0320] The total exposure of the compound of Formula I, under fasted conditions, was approximately 30% higher when dosed in the bilayer tablet formulation F2, containing two additional therapeutic agents (TAF and FTC), compared to single agent tablet formulation F1, co-dosed with a fixed dose combination tablet containing TAF and FTC (F3). Under fasted conditions, the AUC_{inf} and C_{max} of the compound of Formula I were 27% and 31% higher, respectively, following administration of bilayer tablet formulation F2 than following administration of single-agent tablet formulation F1 with the F/TAF fixed dose combination (F3, 200/25 mg). Emtricitabine and tenofovir alafenamide exposure was similar following administration of bilayer tablet formulation F2 or single-agent tablet formulation F1 with the F/TAF FDC (F3, 200/25 mg).

[0321] Based on the data from this study, a new fixed dose formulation of the compound of Formula I, emtricitabine, and tenofovir alafenamide was developed.

[0322] The effect of food on the pharmacokinetics of the compound of Formula I was also examined in a non-randomized, open label, crossover, 2 period, fixed sequence, and single dose cohort consisting of 8 unique subjects. In this study, a single dose of the compound of Formula I was administered in two periods with fixed sequence under fasted and fed conditions respectively. A washout of at least five half-lives was required between fasted and fed sequences.

[0323] The compound of Formula I was prepared according to percent weight of the tablet formulation of Example 1, a dose equivalent to 100 mg of the compound of Formula I and excipient amounts adjusted accordingly to arrive at the designated weight percentages (100 mg/tablet). A single tablet containing the compound of Formula I (100 mg/tablet) was administered with approximately 240 mL water after an overnight fast (no food or drink, except water, for at least 10 hours) on Day 1. Subjects continued to fast until 4 hours post dose or until collection of the 4-hour postdose blood sample. On Day 9, A single tablet containing the compound of Formula I (100 mg/tablet) was administered with approximately 240 mL water after an overnight fast (no food or drink, except water, for at least 10 hours) and within 5 minutes of the subjects finishing a standard high-fat breakfast (approximately 800 calories with 50% of calories from fat).

[0324] The evaluation of the effect of food on compound of Formula I was obtained by comparing AUC_{inf}, AUC_{0-last}, and C_{max} on Days 1 and 9 under fed and fasted conditions. The natural log-transformed PK parameters (i.e., AUC_{inf},

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$AUC_{0\text{-}last}$, and C_{max}) were evaluated using a mixed-effects model with food as a fixed effect and subject as a random effect. The 90% CI for the geometric least square mean (GLSM) ratios for fast versus fed was constructed. The statistical comparison of the pharmacokinetic parameters of the compound of Formula I following single dose administration of this tablet formulation in fed and fasted states is presented in the table below.

Compound of Formula I PK Parameter	Mean (%CV)		% GLSM Ratio (90% CI)
	Test Compound of Formula I 100 mg Fed (n=8)	Reference Compound of Formula I 100 mg Fasted (n=8)	
AUC_{inf} (hr*ng/mL)	214,146.3 (15.9)	117,777.1 (23.3)	183.97 (152.05, 222.59)
AUC_{last} (hr*ng/mL)	209,259.9 (15.1)	115,681.7 (24.0)	183.58 (151.91, 221.86)
C_{max} (ng/mL)	11,268.8 (15.1)	5885.0 (34.9)	200.89 (165.93, 242.74)

[0325] The Table above presents the GLSM ratios and associated 90% confidence intervals (CIs) for the test (fed) versus reference (fasted) treatments for the primary plasma PK parameters of the compound of Formula I. Administration of a single dose of the compound of Formula I 100 mg with food (high-calorie/high-fat breakfast) increased the GLSM values of C_{max} and AUC_{inf} 101% (90% CI of GLSM ratio 165.93% to 242.74%) and 84% (90% CI of GLSM ratio 152.05% to 222.59%), respectively. There were no apparent changes in clearance and $t_{1/2}$ following administration with food, indicating that food enhanced the bioavailability of the compound of Formula I by improving its solubility and/or absorption.

[0326] The effect of food on the PK of the compound of formula I, emtricitabine, and tenofovir alafenamide when administered as the tablet formulation F2 tablet was evaluated in the clinical study described above (The randomized, open-label, multiple-period, fixed-sequence, crossover study involving 28 subjects comparing bilayer tablet formulation F2 with that of single agent tablet formulation F1 co-administered simultaneously with a fixed-dose combination tablet containing emtricitabine and tenofovir alafenamide (tablet formulation F3).

[0327] The mean (%CV) values, GLSM ratios, and 90% CI values of the plasma for PK parameters AUC_{last}, AUC_{inf}, and C_{max} for the compound of Formula I, emtricitabine, and tenofovir alafenamide following administration of tablet formulation F1 under fasted conditions or with a high-fat meal are presented in the following table.

PK Parameter	Mean (%CV)		%GLSM Ratio (90% CI)
	Compound of Formula I /F/TAF (75/200/25 mg) (High-Fat Meal; Test) (N = 28)	Compound of Formula I /F/TAF (75/200/25 mg) (Fasted; Reference) (N = 28)	
Compound of Formula I			
AUC_{last} (h*ng/mL)	216,733.1 (23.4)	151,844.0 (26.9)	144.45 (134.26, 155.40)
AUC_{inf} (h*ng/mL)	226,142.1 (24.9)	156,637.5 (27.5)	145.88 (135.58, 156.95)
C_{max} (ng/mL)	8941.1 (16.9)	7123.9 (21.6)	126.74 (116.30, 138.12)
FTC			
AUC_{last} (h*ng/mL)	11,483.0 (15.7)	11,412.3 (13.5)	100.34 (97.99, 102.75)
AUC_{inf} (h*ng/mL)	11,706.4 (15.6)	11,641.6 (13.2)	100.25 (97.96, 102.59)

(continued)

FTC			
C_{max} (ng/mL)	1872.5 (20.1)	2264.3 (22.7)	83.18 (77.53, 89.25)
TAF			
AUC_{last} (h•ng/mL)	315.3 (44.0)	205.5 (45.5)	166.81 (140.57, 174.94)
AUC_{inf} (h•ng/mL)	319.7 (43.1)	206.8 (45.2)	158.20 (142.14, 176.08)
C_{max} (ng/mL)	212.2 (49.4)	253.3 (44.2)	83.22 (69.63, 99.46)

[0328] Compared with administration under fasted conditions, administration of the tablet formulation F2 with a high-fat meal resulted in a 46% higher AUC_{inf} and a 27% higher C_{max} for the compound of Formula I. The impact of food on emtricitabine and tenofovir alafenamide exposure was similar to that previously observed.

[0329] The data presented in the two tables above also demonstrate that the effect of food on the total exposure of the compound of Formula I is reduced in bilayer tablet formulation F2, relative to the single agent tablet formulation F1. The geometric mean ratio of AUC_{inf} for the compound of Formula I in single agent tablet formulation F1 was 1.84, while the geometric mean ratio of AUC_{inf} for the compound of Formula I in bilayer tablet formulation F2 was 1.46. In comparison the geometric mean ratio of AUC_{inf} for emtricitabine in to 0.91 and 1.00 for emtricitabine and 1.75 and 1.58 for tenofovir alafenamide in each formulation respectively (comparing the emtricitabine and tenofovir alafenamide exposures of the tablet formulation F2 with that of tablet formulation F1 codosed with the tablet formulation F3). The geometric mean ratio of C_{max} for single agent tablet formulation F1 was 2.01, while the geometric mean ratio of C_{max} for bilayer tablet formulation F2 was 1.27. In comparison, the geometric mean ratios of C_{max} for emtricitabine and tenofovir alafenamide in tablet formulations F1 and F2 were 0.85 and 0.83, respectively. These data indicate that a fixed dosed combination tablet formulation of the compound of Formula I, emtricitabine, and tenofovir alafenamide may be taken without regard to food.

Example 4 -Dissolution Studies

[0330] Studies were carried out to assess the dissolution profiles of tablets F1, F2, and F3-A. Dissolution of the compound of Formula II was measured using USP Apparatus II, in 250 mL of pH 6.5 fasted state simulated intestinal fluid (FaSSIF), at 37 °C and paddle speed of 100 rpm. FaSSIF was prepared by adding simulated intestinal fluid (SIF) powder (Biorelevant.com) to pH 6.5 phosphate buffer at approximately 4.48 g/L. Once the powder was dissolved, the volume of the resulting solution was doubled. In the case of the single agent tablet formulation F1, dissolution of the compound of Formula II was measured in the presence of the fixed dose combination tablet formulation F3 of Example 2A containing emtricitabine and tenofovir alafenamide hemifumarate. The results are shown in Figure 1. These data show that the bilayer formulation (tablet F2) exhibited enhanced dissolution of the compound of Formula II, compared to the single agent formulation (tablet F1 codosed with F3). Tablet formulation F3-A was prepared as a single agent formulation according to the process described in Example 1 according to the table below.

Ingredient	Tablet F3-A (mg/tablet)
	Compound of Formula II Layer
Compound of Formula II	78.7*
Emtricitabine	
Tenofovir alafenamide hemifumarate	
Microcrystalline cellulose	247.8***
Croscarmellose sodium	21.2
Magnesium Stearate	5.3†

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(continued)

Ingredient	Tablet F3-A (mg/tablet)
	Compound of Formula II Layer
Tablet Core Weight	353
*Equivalent to 75 mg of the Compound of Formula I ***Intergranular: 212.5 mg (29.1%); Extragranular: 2.65 mg (0.4%) †Intergranular: 2.65 mg (0.4%); Extragranular: 2.65 mg (0.4%)	

[0331] As shown above, Tablet F3-A used the composition (excipient selection and quantities) of the Compound of Formula II Layer of Example 2 (F2). Figure 1 further demonstrates that Tablet formulation F2 exhibited enhanced dissolution of the compound of Formula II compared to Tablet formulations F1 and F3-A. The total percentage of the compound of Formula II dissolved from formulation F1 and F3-A was comparable at approximately 60%. The total amount of the compound of Formula II dissolved from formulation F2 was approximately 10% higher.

[0332] In a second study, dissolution of the compound of Formula II was measured using fed state simulated intestinal fluid (FeSSIF) as dissolution medium. FeSSIF was prepared by adding simulated intestinal fluid (SIF) powder (Biorelevant.com) to pH 5.0 phosphate buffer at approximately 22.405 g/L. Once the power was dissolved, the volume of the resulting solution was doubled. In this study, dissolution of the compound of Formula II was measured using USP Apparatus II, in 250 mL of pH 5.5 fed simulated intestinal fluid, at 37 °C and paddle speed of 100 rpm. As in the previous study using fasted simulated intestinal fluid, the single agent tablet formulation F1 was tested in the presence of a second tablet formulation containing emtricitabine and tenofovir alafenamide hemifumarate (tablet F3). The results are shown in Figure 2. These data also show that the bilayer formulation (tablet F2) exhibited enhanced dissolution of the compound of Formula II, compared to the single agent formulation (tablet F1).

Example 5 - Excipient Studies

[0333] To further assess the effect of specific excipients on dissolution of the compound of Formula I, three additional bilayer tablet formulations were prepared, F4, F5, and F6. Tablet formulation F4 is similar to tablet formulation F2, with croscarmellose sodium being replaced with crospovidone. Likewise, tablet formulation F5 is similar to tablet formulation F2, with magnesium stearate being replaced with sodium stearyl fumarate. Finally, tablet formulation F6 is similar to tablet formulation F2, with both croscarmellose sodium and magnesium stearate being replaced with crospovidone and sodium stearyl fumarate, respectively. Tablets F4, F5, and F6 were prepared using the method described in Example 8.

Ingredient		Bilayer tablet F4	Bilayer tablet F5	Bilayer tablet F6
	Emtricitabine/ tenofovir alafenamide hmifumarate Layer (mg/tablet)	Compound of Formula I Layer (mg/tablet)		
Emtricitabine	200			
Tenofovir alafenamide hemifumarate	28.1			
Compound of Formula II		78.7	78.7	78.7
Microcrystalline cellulose	113	244	248	244
Croscarmellose sodium	30.2		21.2	
Crospovidone		24.7		24.7
Magnesium Stearate	5.7	5.3		
Sodium Stearyl Fumarate			5.3	5.3
Layer Weight	377	353	353	353

(continued)

Ingredient		Bilayer tablet F4	Bilayer tablet F5	Bilayer tablet F6
	Emtricitabine/ tenofovir alafenamide hmifumarate Layer (mg/tablet)	Compound of Formula I Layer (mg/tablet)		
Tablet Core Weight		730	730	730

[0334] Figure 3 shows the results of dissolution studies performed on tablet formulations F4, F5, and F6, as well as tablet formulation F1 and F2. These data demonstrate that the substitution of each excipient enhances the dissolution of the compound of Formula I.

Example 6 - Compound of Formula I / emtricitabine / tenofovir alafenamide bilayer tablets - 50 mg dose

[0335] As a result of the higher *in vivo* exposure of the compound of Formula I that was observed in the pharmacokinetic studies, a bilayer formulation (tablet F7) of the compound of Formula II, emtricitabine, and tenofovir alafenamide hemifumarate was prepared incorporating a lower dose of the compound of Formula I. Tablet formulation F7 was prepared as described previously, *i.e.*, using the method described in Example 8. The composition of the formulation is summarized in the table below:

Ingredient	Bilayer tablet F7 (mg/tablet)	
	Compound of Formula II Layer	Emtricitabine/ tenofovir alafenamide hemifumarate Layer
Compound of Formula II	52.5*	
Emtricitabine		200
Tenofovir alafenamide hemifumarate		28**
Microcrystalline cellulose	246.3	113.2
Croscarmellose sodium	19.4	30.2
Magnesium Stearate	4.9	5.7
Layer Weight	323	377
Tablet Core Weight	**700**	
Opadry II Brown 85F165072	21	
Film Coated Tablet	**721**	
*Equivalent to 50 mg of the Compound of Formula I **Equivalent to 25 mg tenofovir alafenamide		

Example 7 - Compound of Formula I single agent tablets (50 mg)

[0336] Dissolution studies were performed comparing the 50 mg dose bilayer tablet F7 with a 50 mg single agent tablet.

[0337] A 50 mg formulation (tablet F8) of the compound of Formula II was prepared in a similar manner as tablet formulation F1 of Example 1. The composition of the single agent formulation is shown in the table below:

	Tablet Formulation F8	
Component	Mass (mg/tablet)	% w/w/ tablet
Compound of Formula II	52.5	26.2
Microcrystalline cellulose	80	40
Lactose	50.5	25.3

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(continued)

	Tablet Formulation F8	
Component	Mass (mg/tablet)	% w/w/ tablet
Crospovidone	14	7
Sodium Stearyl Fumarate	3	1.5
Total Weight	200	

[0338] Figure 4 shows the dissolution of 50 mg bilayer tablet formulation (fixed dose combination) F7 and 50 mg single agent tablet formulation F8. Dissolution of the compound of Formula II was measured using USP Apparatus II, in 333 mL of pH 6.5 FaSSIF, at 37 °C and paddle speed of 100 rpm. Two tablets of each tablet formulation, F7 and F8 were tested. As in Example 3, in the case of the single agent tablet formulation F8, dissolution of the compound of Formula II was measured in the presence of the fixed dose combination tablet formulation of Example 2A containing emtricitabine and tenofovir alafenamide hemifumarate. These data show that the 50 mg bilayer formulation (tablet F7) exhibited enhanced dissolution of the compound of Formula II, compared to the single agent formulation (tablet F8).

Example 8 - manufacturing process

[0339] The manufacturing/packaging procedure for the compound of Formula II/emtricitabine/tenofovir alafenamide hemifumarate tablets is divided into five unit processes:

1. mixing of the compound of Formula II drug substance with intergranular excipients, roller compaction or slugging, milling, and blending with extragranular excipients to yield the final powder blend for the compound of Formula II;
2. mixing of emtricitabine and tenofovir alafenamide hemifumarate drug substances with intergranular excipients, dry granulation, milling, and blending with extragranular excipients to yield emtricitabine/tenofovir alafenamide hemifumarate final powder blend;
3. tablet compression to yield bilayer tablet cores;
4. tablet film-coating to yield film-coated tablets; and
5. packaging.

[0340] The manufacturing process steps to produce the final drug product are detailed below.

Final Powder Blend for the Compound of Formula II (Dispensing, Blending, Dry Granulation, Milling, Final Blending)

[0341]

1. Weigh the compound of Formula II and the excipients (microcrystalline cellulose and croscarmellose sodium). Correct the weight of the compound of Formula II based on the drug content factor (DCF), with a concomitant reduction in the weight of microcrystalline cellulose.
2. Blend in intergranular portion of magnesium stearate to the tumble blender and blend.
3. Dry granulate the resulting blend using a roller compactor or slug the resulting blend and mill.
4. Add extragranular microcrystalline cellulose and magnesium stearate and blend.

Emtricitabine/tenofovir alafenamide hemifumarate Final Powder Blend (Dispensing, Blending, Dry Granulation, Milling, Final Blending)

[0342]

5. Weigh emtricitabine and tenofovir alafenamide hemifumarate drug substances and excipients (microcrystalline cellulose and croscarmellose sodium). Adjust the weight of emtricitabine and tenofovir alafenamide hemifumarate drug substances based on their corresponding DCF, with a concomitant adjustment to the weight of microcrystalline cellulose.
6. Blend in emtricitabine and tenofovir alafenamide hemifumarate drug substance, microcrystalline cellulose, and croscarmellose sodium to a tumble blender and blend.
7. Blend in intergranular portion of magnesium stearate to the tumble blender and blend.
8. Dry granulate the resulting blend using a roller compactor or slug the resulting blend and mill.

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9. Blend in the extragranular portion of magnesium stearate.

Tableting

[0343] 10. Compress the final powder blend of the compound of Formula II as the first layer and the emtricitabine/tenofovir alafenamide hemifumarate final powder blend as the second layer, with an appropriate main compression force to achieve a target hardness of 17 kP (range: 14 to 20 kP). For tablet formulations containing 50 mg of the compound of Formula II, the final powder blend is compressed to a target layer weight of 323 mg using a target total tablet weight of 700 mg. For tablet formulations containing 75 mg of the compound of Formula II, the final powder blend is compressed to a target layer weight of 353 mg using a target total tablet weight of 730 mg.

Film-coating

[0344] 11. Prepare a suspension of Opadry® II Brown 85F165072 (for tablets containing 50 mg compound of Formula I) or Opadry® II Yellow 85F92259 (for tablets containing 75 mg compound of Formula I). Film-coat the tablet cores to achieve the target tablet weight gain of 3% (range 2-4%). Dry film-coated tablets prior to cooling and discharge.

Example 9 - Pharmacokinetic Studies - Cohort 2

[0345] The pharmacokinetic study of Example 3 was continued with a second treatment group (cohort) to assess the pharmacokinetic profile of formulation F7 of Example 7 compared with that of formulation F2.

Study Design and Duration of Treatment

[0346] Four single doses of the following tablet formulations were administered once per day orally during 36 days total study duration:

(a) a fixed dosed combination tablet containing emtricitabine and tenofovir alafenamide (200/25 mg - Tablet F3) and a single agent tablet containing the compound of Formula I (75 mg - Tablet F1) administered simultaneously, under fasted conditions (Treatment A) (dosed on day 1; days 2-8 washout);

(b) a fixed dose combination tablet containing the compound of Formula I, emtricitabine, and tenofovir alafenamide (50/200/25 mg - Tablet F2) administered under fasted conditions (Treatment D) (dosed on day 9; days 10-16 washout); and

(b) a fixed dose combination tablet containing the compound of Formula I, emtricitabine, and tenofovir alafenamide (50/200/25 mg - Tablet F2) administered under fed conditions with a high-fat meal (Treatment E) (dosed on day 17; days 18-24 washout);

(c) a fixed dose combination tablet containing the compound of Formula I, emtricitabine, and tenofovir alafenamide (50/200/25 mg - Tablet F2) administered under fed conditions with a moderate-fat meal (Treatment F) (dosed on day 25; day 29 discharge).

Criteria for Evaluation

[0347] The following plasma pharmacokinetic parameters were calculated: AUC_{last}, AUC_{inf}, $\%AUC_{exp}$, C_{max}, C_{last}, T_{max}, T_{last}, CL/F, V_z/F, and $t_{1/2}$.

Statistical Methods

[0348] Pharmacokinetics: Individual subject concentration data and individual subject PK parameters for each analyte (compound of Formula 1, FTC, and TAF) were listed and summarized using descriptive statistics by treatment group (cohort) and treatment. Summary statistics were determined for both individual subject concentration data by time point, cohort, and treatment and individual subject PK parameters by cohort and treatment. Also, the geometric mean, 95% confidence interval (CI), and the mean, and standard deviation (SD) of the natural log-transformed values were presented for individual subject PK parameter data. The sample size for each time point was based on the number of subjects with nonmissing concentration data at that time point. The number of subjects with concentration below the level of quantitation (BLQ) was presented for each time point.

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[0349] Statistical comparisons of the natural log-transformed PK parameters for each analyte and treatment comparison of interest were performed. The statistical modelling was based on the PK Analysis set for the analyte under evaluation. For each analyte, all subjects with available data for the PK parameter under evaluation were included in the modelling. The statistical comparisons using Treatment A as a reference only used data from this cohort, not from the earlier cohort of Example 3 (i.e., Treatment A was not pooled).

For each analyte and each PK parameter, a parametric (normal theory) mixed-effects ANOVA model was fitted to the natural log-transformed values of the PK parameter under evaluation. The statistical model included treatment as a fixed effect and subject as a random effect.

[0350] A total of 27 subjects completed the second treatement group of the study.

Results

[0351] Plasma pharmacokinetic parameters for each analyte are presented below. This table presents the mean (%CV) values, Geometric Least Squares Mean (GLSM) ratios, and 90% CI values of the plasma PK parameters AUC_{last}, AUC_{inf}, and C_{max} for each active ingredient, following administration of bilayer tablet formulation F7 and monolayer tablet formulation F1 coadministered with F/TAF formulation F3, under fasted conditions.

	Mean (%CV)		%GLSM Ratio (90% CI) (Test/ Reference)
	Formulation F7 Compound of Formula I/F/TAF (50/200/25 mg), fasted (Test) (N = 27)	Formulation F1 + F3 Compound of Formula (75 mg) + F/TAF (200/25 mg)), fasted (Reference) (N = 28)	
Compound of Formula I PK Parameter			
AUC_{last} (hr•ng/mL)	109,361.4 (21.0)	142,396.6 (30.5)	78.46 (73.38, 83.89)
AUC_{inf} (hr•ng/mL)	112,619.6 (21.9)	146,931.6 (31.1)	78.56 (73.44, 84.04)
C_{max} (ng/mL)	5228.1 (16.9)	6791.1 (26.4)	78.07 (73.41, 83.01)
FTC PK Parameter			
AUC_{last} (hr•ng/mL)	10,652.9 (13.6)	11,035.5 (14.4)	96.52 (93.95, 99.15)
AUC_{inf} (hr•ng/mL)	10,873.9 (13.6)	11,234.6 (14.2)	96.76 (94.22, 99.37)
C_{max} (ng/mL)	2220.4 (30.1)	2166.4 (27.0)	102.36 (93.85, 111.64)
TAF PK Parameter[a]			
AUC_{last} (hr•ng/mL)	207.1 (46.5)	236.7 (45.3)	85.37 (75.24, 96.85)
AUC_{inf} (hr•ng/mL)	208.8 (46.3)	238.3 (45.0)	85.48 (75.33, 97.00)
C_{max} (ng/mL)	249.2 (51.6)	291.9 (55.4)	84.17 (67.59, 104.81)

[0352] In particular, these data confirmed that the exposure of the compound of Formula I in Formulation F7 was proportionally lower than that observed in Formulation F2 and were consistent with predicted exposures for the revised dose. These data were consistent with the modelling of earlier clinical data confirming that these exposures provided anti-HIV antiviral efficacy. FTC and TAF exposure were similar between Formulation F7 and Formulation F2 coadministered with F3; TAF Cmax was slightly lower (by approximately 16%) for Formulation F7 than for the coadministration of F2 and F3.

[0353] The effect of food on the pharmacokinetics of the compound of Formula I, emtricitabine and tenofovir alafenamide when administered in formulation F7 was also examined in a further treatment group of the above described clinical study.

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[0354] The mean (%CV) values, GLSM ratios, and 90% CI values of the plasma for PK parameters AUC_{last}, AUC_{inf}, and C_{max} for the compound of Formula I, emtricitabine, and tenofovir alafenamide following administration of tablet formulation F7 under fasted conditions or with a high-fat meal and with a moderate-fat meal are presented in the following table.

	Mean (%CV)		
	Compound of Formula I/F/TAF (50/200/25 mg) high fat meal (Test) (N = 27)	Compound of Formula I/F/TAF (50/200/25 mg) fasted (Reference) (N = 27)	%GLSM Ratio (90% CI) (Test/Reference)
Compound of Formula I PK Parameter			
AUC_{last} (hr•ng/mL)	135,117.3 (21.1)	109,061.4 (21.0)	123.96 (115.91, 132.57)
AUC_{inf} (hr•ng/mL)	140,032.4 (21.8)	112,619.6 (21.9)	124.41 (116.27, 133.11)
C_{max} (ng/mL)	5936.3 (18.3)	5228.1 (16.9)	113.23 (106.45, 120.43)
FTC PK Parameter			
AUC_{last} (hr•ng/mL)	10,213.0 (12.0)	10,652.9 (13.6)	96.02 (93.47, 98.65)
AUC_{inf} (hr•ng/mL)	10,467.0 (11.9)	10,873.9 (13.6)	96.41 (93.88, 99.02)
C_{max} (ng/mL)	1881.1 (24.2)	2220.4 (30.1)	85.52 (78.37, 93.31)
TAF PK Parameter[a]			
AUC_{last} (hr•ng/mL)	310.3 (34.9)	207.1 (46.5)	162.62 (143.10, 184.80)
AUC_{inf} (hr•ng/mL)	318.4 (32.8)	208.6 (46.3)	166.55 (146.54, 189.29)
C_{max} (ng/mL)	236.6 (55.1)	249.2 (51.6)	91.71 (73.46, 114.49)

	Mean (%CV)		%GLSM Ratio (90% CI) (Test/Reference)
	Compound of Formula I/F/TAF (50/200/25 mg) moderate fat meal (Test) (N = 27)	Compound of Formula I/F/TAF (50/200/25 mg) fasted (Reference) (N = 27)	
Compound of Formula IPK Parameter			
AUC_{last} (hr•ng/mL)	135,217.3 (22.9)	109,061.4 (21.0)	123.56 (115.53, 132.14)
AUC_{inf} (hr•ng/mL)	140,197.7 (23.6)	112,619.6 (21.9)	124.06 (115.95, 132.74)
C_{max} (ng/mL)	6279.6 (18.3)	5228.1 (16.9)	119.90 (112.72, 127.53)
FTC PK Parameter			
AUC_{last} (hr•ng/mL)	10,738.3 (9.8)	10,652.9 (13.6)	101.17 (98.48, 103.94)
AUC_{inf} (hr•ng/mL)	10,973.3 (9.5)	10,873.9 (13.6)	101.33 (98.66, 104.06)

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(continued)

FTC PK Parameter			
C_{max} (ng/mL)	1998.9 (18.4)	2220.4 (30.1)	91.64 (84.17, 100.21)
TAF PK Parameter[a]			
AUC_{last} (hr•ng/mL)	290.6 (41.3)	207.1 (46.5)	148.20 (130.41, 168.41)
AUC_{inf} (hr•ng/mL)	293.1 (40.9)	208.8 (46.3)	148.23 (130.42, 168.47)
C_{max} (ng/mL)	251.1 (66.7)	249.2 (51.6)	99.04 (79.33, 123.65)
a N = 28 for the Reference group			

[0355] Compared with administration under fasted conditions, administration of the tablet formulation F7 with a high-fat meal resulted in a 24% higher AUC_{inf} and a 13% higher C_{max} for the compound of Formula I. Administration of a moderate fat meal, resulted in a 24% higher AUC_{inf} and a 20% higher C_{max} for the compound of Formula I. The impact of food on emtricitabine and tenofovir alafenamide exposure was similar to that previously observed.

[0356] These data confirm that a fixed dosed combination tablet formulation of the compound of Formula I, emtricitabine, and tenofovir alafenamide may be taken without regard to food.

Example 10 - Compression Studies

[0357] To further investigate the properties of the compositions, the following studies investigated blend compressibility and layer adhesion.

[0358] First, various final blend compositions including the Compound of Formula I (as a sodium salt, i.e., the Compound of Formula II) were prepared with varying levels of intergranular or extragranular lactose is shown in the table below.

Compound of Formula II: Final Powder Blends Containing Lactose

	Tablet Formulation					
Components	**F9**	**F10**	**F11**	**F12**	**F13**	**F14**
Intergranular % w/w						
Compound of Formula II	16.24	16.24	16.24	16.24	14.86	14.86
Microcrystalline Cellulose	46.25	56.25	56.25	56.25	69.12	60.53
Lactose	20.00	NA	NA	NA	0.00	8.50
Croscarmellose Sodium	6.00	6.00	6.00	6.00	5.49	5.49
Magnesium Stearate	0.75	0.75	0.75	0.75	0.69	0.69
Extragranular % w/w						
Microcrystalline Cellulose	10.00	10.00	5.00	15.00	9.15	9.15
Lactose	NA	10.00	15.00	5.00	NA	NA
Magnesium Stearate	0.75	0.75	0.75	0.75	0.69	0.69
Layer weight (mg)	323	323	323	323	353	353

[0359] Next, final blend compositions of the Compound of Formula II with varying amounts of magnesium stearate ranging from 0.75% to 0.5% were prepared as shown on the following table:

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Compound of Formula I: Final Powder Blends with Varying Levels of Magnesium Stearate

Components	Tablet Formulation					
	F15	F16	F17	F18	F19	F20
Intergranular %w/w						
Compound of Formula II	16.24	16.24	16.24	16.24	16.24	16.24
Microcrystalline Cellulose	66.25	66.30	66.40	66.40	66.50	66.75
Croscarmellose Sodium	6.00	6.00	6.00	6.00	6.00	6.00
Magnesium Stearate	0.75	0.70	0.60	0.60	0.50	0.50
Extragranular %w/w						
Microcrystalline Cellulose	10.00	10.00	10.00	10.00	10.00	10.00
Magnesium Stearate	0.75	0.75	0.75	0.75	0.75	0.5
Layer weight (mg)	323	323	323	323	323	323

[0360] Finally, final blend compositions containing emtricitabine and tenofovir alafenamide were prepared with varying amounts of magnesium stearate ranging from 0.75% to 0.5% as shown in the table below:

Quantitative Compositions of F/TAF Final Powder Blends

Components	Tablet Formulation			
	F21	F22	F23	F24
Intergranular %w/w				
Tenofovir Alafenamide Hemifumarate	7.5	7.5	7.5	7.5
Emtricitabine	53.1	53.1	53.1	53.1
Microcrystalline Cellulose	29.9	30.4	30	30.2
Croscarmellose Sodium	8.0	8.0	8.0	8.0
Magnesium Stearate	0.75	0.50	0.70	0.60
Extragranular % w/w				
Magnesium Stearate	0.75	0.50	0.70	0.60
Layer Weight (mg)	377	377	377	377

[0361] Altering magnesium stearate content was studied to evaluate the impact on the compound of Formula I and emtricitabine / tenofovir alafenamide blend compressibility and layer adhesion. Formulations were also monitored for punch filming and sticking.

[0362] Fourteen combinations of the final powder blends described in the above tables were prepared as summarized in the table below. Critical tamp force was determined for all fourteen combinations.

Compression Study Critical Layer 1 Tamp Force Results

Formulation Combination	Tablet Formulation Layer 1	Tablet Formulation Layer 2	Critical Tamp Force (kN)	Observation
A*	F21	F15	1.0	Layers adhered
B*	F21	F9	<1.5	Delamination
C*	F21	F10	<1.5	Delamination
D*	F21	F11	<1.5	Delamination
E*	F21	F12	<1.5	Delamination

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(continued)

Formulation Combination	Tablet Formulation Layer 1	Tablet Formulation Layer 2	Critical Tamp Force (kN)	Observation
F*	F21	F13	<1.5	Delamination
G*	F21	F14	<1.5	Delamination
H	F15	F21	1.5	Delamination
I	F15	F22	2.0	Layers adhered
J	F16	F23	2.0	Layers adhered
K	F17	F24	1.5	Layers adhered
L	F18	F22	2.0	Layers adhered
M	F19	F22	2.5	Layers adhered, sticking
N	F20	F22	2.5	Layers adhered, sticking
* Note F/TAF as layer 1 and Compound of Formula I as layer 2 IG: Intergranular EG: Extragranular MgSt Magnesium Stearate				

[0363] Combination A represents layer order and composition used as baseline for comparison of other compositions. The tablet formulation of each layer corresponds to the corresponding layer of tablet formulation F7.One objective was to investigate whether it was possible to improve on the critical tamp force of 1.0 kN observed for Combination A.

[0364] Combinations B - G represent studies in which lactose was included in the layer including the Compound of Formula I to investigate evaluate layer adhesion. Combination G included 20% lactose in the intergranular portion, with none in the extragranular portion. The ratio of lactose to microcrystalline cellulose ranged from 1:1, 3:1, 1:3 in Combinations C, D, and E, respectively. Combination G included 20 mg lactose in the intergranular portion. Delamination was observed at 1.5kN for Combinations B - G. As a result, lower tamp forces were not further investigated. When layer order was reversed (Combination H), delamination did not occur at 1.0 kN but was observed at 1.5 kN using the layer compositions of Combination A.

[0365] In Combinations I - N, varying the amount of magnesium stearate in each layer was investigated to determine the effect on compressibility and layer adhesion. Intergranular magnesium stearate was 0.75%, 0.70% and 0.60% in the Compound of Formula I layer of Combinations I, J, and K, respectively. Total magnesium stearate content in the F/TAF layer of each of Combinations I, J, and K was 1.0 %, 1.4% and 1.2%%, respectively. Intergranular magnesium stearate was 0.6% and 0.5% in the Compound of Formula I layer of Combinations L and M, respectively (with 0.75% extragranular magnesium stearate in each). Combination N has the lowest overall level of magnesium stearate in both layers (1.0% in each layer).

[0366] It was found that reducing magnesium stearate from 0.75% to 0.5% in each of the intergranular and extragranular portions the emtricitabine / tenofovir alafenamide layer increased critical tamp force to 2.0 kN (combination I). Critical tamp force could be further improved to 2.5 kN when magnesium stearate was reduced to 0.5% extragranular and/or intergranular in the layer containing the Compound of Formula I (combinations M and N). However, despite gaining an increase in critical tamp force, decreasing magnesium stearate to 0.5% in each component of the powder blend containing the Compound of Formula 1 had a negative effect on sticking. Intermediate changes in magnesium stearate (Combinations J - L) had no further improvement over combination 1. As a result, magnesium stearate level was decreased in the emtricitabine/tenofovir alafenamide layer only (formulation combination I). A critical layer 1 tamp force of 1377 N was ultimately determined. The table below summarizes the composition of Formulation I.

[0367] Thus, the addition of intergranular or extragranular lactose to the layer containing the Compound of Formula I had little to one effect on layer adhesion. Decreasing magnesium stearate from each of final powder blends improved compressibility.

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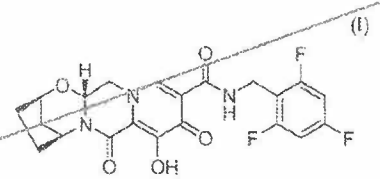
Quantitative Composition of Combination Formulation I

Components	Quantity per Tablet (mg)	w/w (%)
Compound of Formula I Layer		
Compound of Formula II[a]	52.5[a, b]	7.5
Microcrystalline Cellulose	246.3	35.2
Croscarmellose Sodium	19.4	2.8
Magnesium Stearate	4.9	0.7
Subtotal	323	46.1
F/TAF Layer		
Emtricitabine[c]	200.0[c]	28.6
Tenofovir Alafenamide Fumarate[c]	28.0[c, d]	4.0
Microcrystalline Cellulose	115.0	16.4
Croscarmellose Sodium	30.2	4.3
Magnesium Stearate	3.8	0.5
Subtotal	377	53.9
Total Bilayer Tablet Core Weight	700	100
Film Coat		
Opadry II Brown 85F165072[e]	21[f]	3[f]
Purified Water[g]	---[g]	---[g]

a The quantity used is adjusted on the basis of the purity of each batch of Compound of Formula II with a concomitant adjustment of the quantity of microcrystalline cellulose.
b Equivalent to 50 mg of Compound of Formula I free acid.
c The quantity used is adjusted on the basis of the purity of each batch of emtricitabine and tenofovir alafenamide hemifumarate with a concomitant adjustment of the quantity of microcrystalline cellulose.
d Equivalent to 25 mg of tenofovir alafenamide free base.
e Opadry II Brown 85F165072 contains polyvinyl alcohol, USP (40.0% w/w); titanium dioxide, USP (22.0% w/w); polyethylene glycol, NF (20.2% w/w); talc, USP (14.6% w/w); iron oxide red, NF (2.4% w/w); iron oxide black, NF (0.6% w/w).
f Represents a theoretical weight gain of 3% w/w (range 2% to 4% w/w) onto the tablet core weight.
g Sufficient purified water is used for film coating and is removed during the process

Claims

1. A tablet comprising 50 mg of the compound of Formula I:



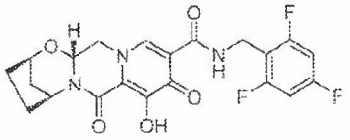
(I)

or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof.

Auxiliary Request 1 (August 2022):

1. A tablet comprising 50 mg of the compound of Formula I:

(I)



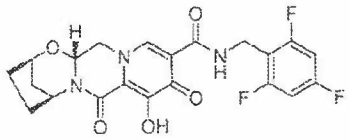
or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, wherein the tablet comprises 50 mg of the compound of Formula I as a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide as a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine.

2. The tablet of claim 1, wherein the tablet comprises 52 mg of the sodium salt of the compound of Formula I and 28 mg tenofovir alafenamide hemifumarate.

3. The tablet of claim 1 or claim 2, wherein the tablet has a total weight of:
(i) less than 800 mg; or
(ii) less than 730 mg.

4. A tablet comprising 50 mg of the compound of Formula I:

(I)



or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, wherein the tablet is a coated tablet.

5. The tablet of any one of the preceding claims, wherein the tablet contains less than 15% of the compound of Formula I or a pharmaceutically acceptable salt thereof.

6. The tablet of any one of the preceding claims, wherein the tablet contains less than 11% of the compound of Formula I or a pharmaceutically acceptable salt thereof.

7. A tablet according to any one of the preceding claims for use in the therapeutic treatment of an HIV infection.

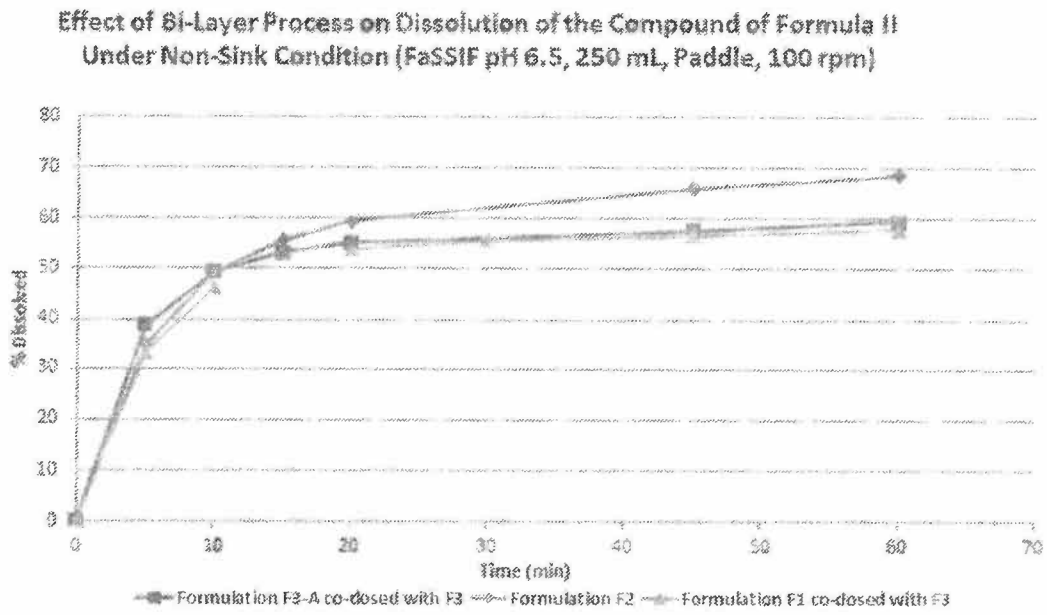

Effect of Bi-Layer Process on Dissolution of the Compound of Formula II
Under Non-Sink Condition (FaSSIF pH 6.5, 250 mL, Paddle, 100 rpm)
% Dissolved
Time (min)
0
10
20
30
40
50
60
70
80
Formulation F3-A co-dosed with F3
Formulation F2
Formulation F1 co-dosed with F3

FIGURE 1

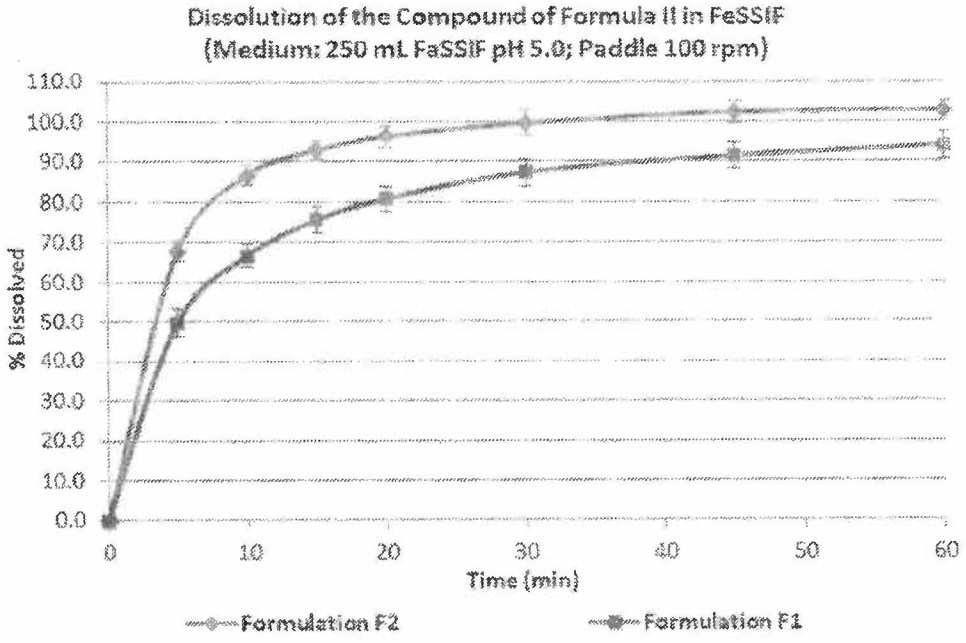

Dissolution of the Compound of Formula II in FeSSIF
(Medium: 250 mL FaSSIF pH 5.0; Paddle 100 rpm)
% Dissolved
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0
10
20
30
40
50
60
Time (min)
Formulation F2
Formulation F1

FIGURE 2

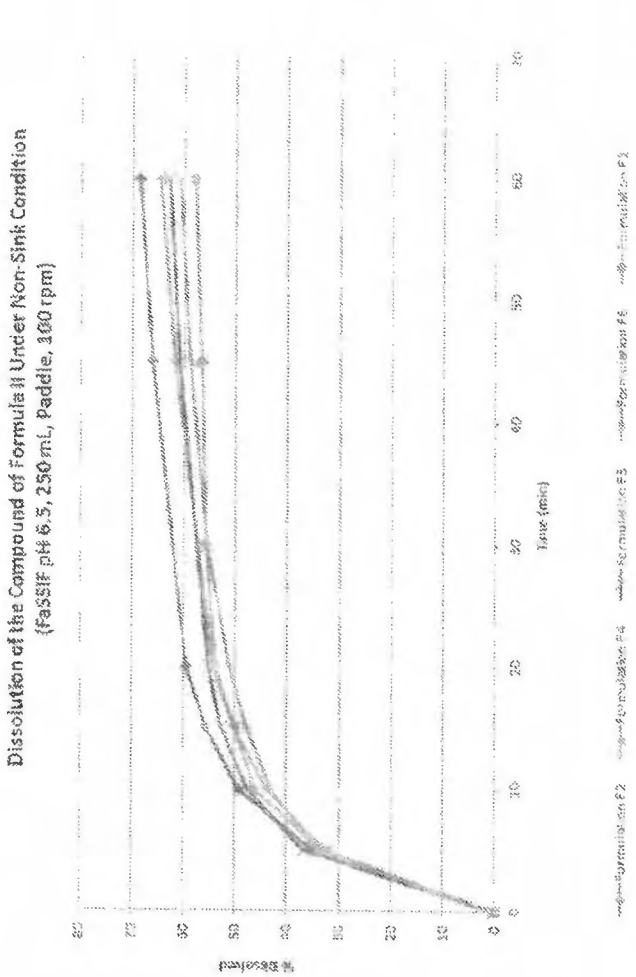

Dissolution of the Compound of Formula II Under Non-Sink Condition
(FaSSIF pH 6.5, 250 mL, Paddle, 100 rpm)
% Released
Time (min)

FIGURE 3

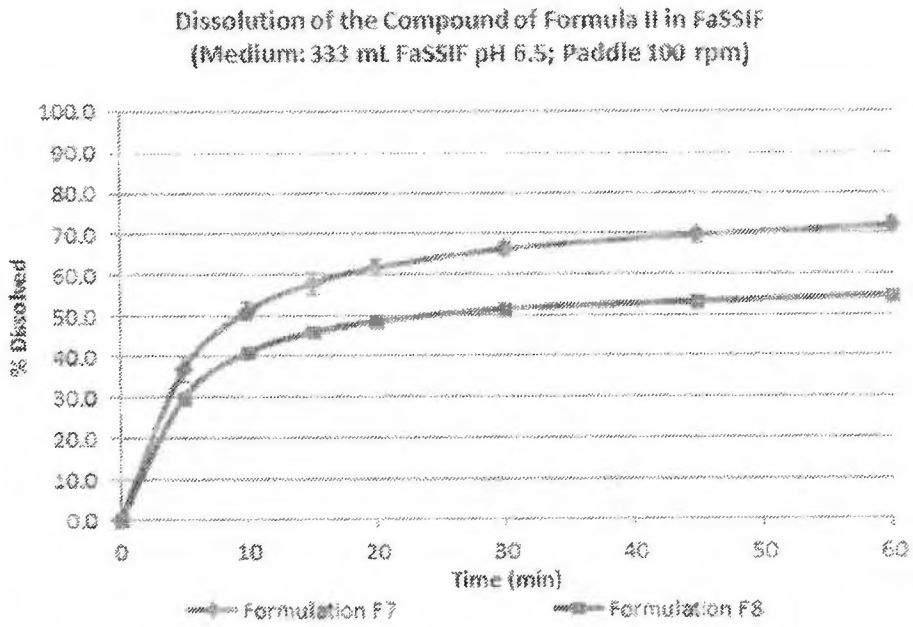

Dissolution of the Compound of Formula II in FaSSIF
(Medium: 333 mL FaSSIF pH 6.5; Paddle 100 rpm)
% Dissolved
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0
10
20
30
40
50
60
Time (min)
Formulation F7
Formulation F8

FIGURE 4

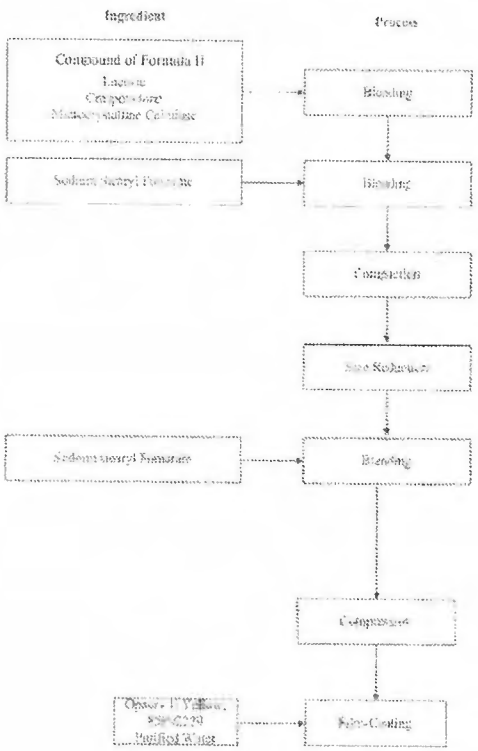

Ingredient
Process
Compound of Formula II
Blending
Blending
Compaction
Blending
Compression
Film-Coating

FIGURE 5

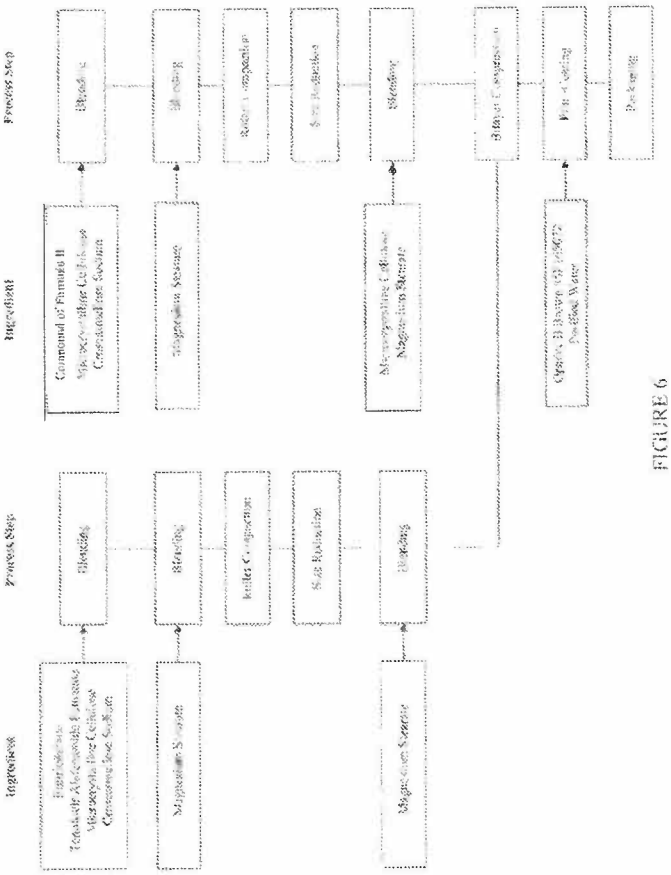


FIGURE 6

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Carpmaels & Ransford LLP
One Southampton Row
London WC1B 5HA
ROYAUME-UNI

Formalities Officer
Name: Penney, Karen
Tel: +49 89 2399 - 7914
or call
+31 (0)70 340 45 00

Application No. / Patent No	Ref	Date
16 798 063.0 - 1112 / 3 346 995 /	O009281EP:CJH/ PAK/HEB	23.12.2022
Proprietor Gilead Sciences, Inc.		

Provision of a copy of the minutes in accordance with Rule 124(4) EPC

The attached copy of the minutes of the oral proceedings is sent to you in accordance with Rule 124(4) EPC.

Europäisches Patentamt · European Patent Office · Office européen des brevets

Penney, Karen
Formalities Officer
Tel. No.: +49 89 2399 - 7914

Enclosure(s): Copy of the minutes (Form 2309)

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Application No.: 16 798 063.0

Patent No.: EP-B-3 346 995

Minutes of the oral proceedings before the OPPOSITION DIVISION

The proceedings were public.

Proceedings opened on 27.10.2022 at 09:08 hours

Present as members of the opposition division:

Chairman:	Büttner, Ulf
1st member:	Trifilieff, Sylvie
2nd member:	Collura, Alessandra
Minute writer:	Collura, Alessandra

Present as or for the party or parties:

- For the Proprietor(s): Gilead Sciences, Inc.

  Mr Hoggett as representative of the Proprietor, accompanied by Mr Kaufman as additional representative and Ms Braun, Mr. Marquart, Ms Yang, Mr Kessel, Ms Gressler, Ms Edward and Ms Horwitz

- For the Opponent 1: Teva Pharmaceutical Industries Ltd.

  Mr Fachini, as representative of Opponent 1

- For the Opponent 2: Cooke, Richard

  Mr Cooke

- For the Opponent 3: Sandoz GmbH

  Ms Müller, as representative of Opponent 3, accompanied by Ms Eben

The identity of the person/s (as well as, if applicable, that of the witness or witnesses) and, where necessary, the authorisation to represent/authority to act were checked.

Essentials of the oral proceedings and relevant statements of the parties:

1. The oral proceedings were opened at 9:08.

2. The chairman stated that no recordings of the oral proceedings were to be made.

3. The representative of the patent proprietor (PP), Mr Hoggett, was accompanied by Mr Kaufman, as a further representative, Ms Braun, Mr. Marquart, Ms Yang, Mr Kessel, Ms Gressler, Ms Edward and Ms Horwitz.

The representative of opponent 1 (O1) was Mr Fachini.

The representative of opponent 2 (O2) was Mr Cooke.

The representative of opponent 3 (O3), Ms Müller, was accompanied by Ms Ehen.

All representatives could be identified.

The representatives confirmed the receipt of the contact data of the members of the examining division (ED).

4. The representatives of the opponents confirmed their requests, these being the revocation of the patent in its entirety based on Article 100(a) EPC, because of lack of novelty (O2 and O3) and lack of inventive step (O1, O2 and O3), and on Article 100(c) EPC, because of added matter *vis à vis* the application as filed (O1, O2 and O3).

The representative of the patentee confirmed their requests, these being the maintenance of the patent based on the main request or auxiliary requests 1-10 filed on 26.08.2022. The PP also requested that if D41 and D42 were not to be allowed to support inventive step and if the patent was to be revoked because of lack of inventive step, then the procedure had be stayed to wait for the publication of decision G2/21.

5. **Main request**

5.1 **Article 123(2) EPC**

5.1.1 The chairman expressed the preliminary and non-binding opinion of the opposition division that the subject-matter of claim 1 of the main request did not appear to find basis in the application as filed.

5.1.2 The PP referred to the Guidelines H-V, 3,2,1 which indicated two conditions to be met to justify an allowable intermediate generalisation from the subject-matter of original claim 7 to arrive at the subject-matter of claim 1, these conditions being

(i) the feature was not related or inextricably linked to the other features of that

embodiment: claim 7 referred to a coated tablet; however the coating was physically separated from the active agents and some embodiments did not present one (see original claims 1, 6, and 9 and paragraphs 10 and 16 of the application as filed);

(ii) the overall disclosure justified the generalising isolation of the feature and its introduction into the claim: paragraph 71 of the application as filed made clear that the coating was an optional feature.

5.1.3 The opponents argued that the original application was directed to a number of different and independent embodiments, whose features could not be freely combined with each other. Moreover, Fig 6 relating to the process of production made clear that the coating had to be present.

In order to meet th requirements of Article 123(2) EPC, the deletion of a feature had to satisfy the "gold standard".

5.1.4 After an interruption of the oral proceedings between 9:42 and 9:56, the chairman announced the conclusion of the opposition division that the claims of the main request did not fulfil the requirements of Article 123(2) EPC.

6. Auxiliary request 1

Asked by the chairman, the PP indicated that he wished to proceed the discussion of auxiliary request 1 (AR1).

6.1 Rule 80 EPC and Article 84 EPC

6.1.1 O1 pointed out that AR1 included a new independent claim 4 to replace dependent claim 5 as granted; this amendment was not caused by any ground for opposition and led to the presence of two independent claims in the same category.

6.1.2 PP explained that the amendment was a reaction to the objection under Article 123(2) EPC and referred to the Guidelines H-II, 3.1, last sentence and to the Case Law, 10th Ed., IV-C, 5,1,6.

6.2 Article 123(2) EPC

6.2.1 None of the opponents raised any objections under Article 123(2) EPC for AR1.

6.3 After an interruption of the proceedings between 10:04 and 10:10, the chairman announced that the opposition division considered the AR1 to meet the requirements of Rule 80 EPC and of Articles 84 and 123(2) EPC.

6.3. Priority

None of the opponents contested the priority of the AR1 and the chairman announced that the priority was assumed to be validly claimed.

6.4. **Article 54 EPC**

6.4.1 The opponents contested the novelty of the claim 1 of the AR1 *vis à vis* the disclosure of D1, claim 1 (relating to bictegravir), claim 19 (relating to the other components in the composition), claim 21 (relating to a tablet), and paragraph 96 on page 32, second to last sentence (relating to the doses of the ingredients in the composition).

6.4.2 The PP pointed out that: (a) D1 did not disclose a tablet with all three compounds and their doses according with claim 1 of the AR1, (b) the embodiments disclosed in D1 were all equally preferred so that more than one selection had to be carried out to arrive at the subject-matter of the claim, and (c) the amounts given in paragraph 96 referred to the salts of bictegravir while the AR1 of the patent in suit clearly indicated that the amount was the one of the free acid.

6.4.3 After an interruption between 10:46 and 10:55, the chairman announced that the opposition division considered the claims of the AR1 to be novel.

6.5. **Article 56 EPC**

6.5.1 The opponents considered D5, passage bridging pages 19 and 20, as the closest prior art to the subject-matter of the claims of the AR1, since it disclosed a composition comprising 50 mg dolutegravir, 200 mg emtricitabine and 25 mg tenofovir, in particular tenofovir alafenamide.

Reference was made to D7 (p. 13), teaching that the combination of emtricitabine and tenofovir represented a backbone for HIV treatment to which a further ingredient such as dolutegravir could be added, and to D8 (p. 557, bottom of right-hand column), teaching the doses of dolutegravir.

The difference between the subject-matter of claim 1 of AR1 lied in the fact that bictegravir was used instead of dolutegravir.

Since no technical effect had been shown in the application as filed, the objective technical problem to be solved had to be considered the provision of a mere alternative treatment for HIV.

In order to solve the problem posed, the skilled person would have turned to D3 (page 3, lines 11-12, Table 4, example 107, claims 32 and 36) disclosing bictegravir as an integrase inhibitor, i.e. the same mechanism as dolutegravir. Page 35, line 22 of D3 disclosed the dosage of bictegravir. In any case, the determination of the optimum dosage of a compound was considered by the boards of appeal not to lead to any exercise of an inventive step.

D18 and D28 could also be used instead of D3 to be combined with D5 for solving the problem posed.

The post-published documents D41 and D42 filed by the PP could not be considered relevant because they related to effects not shown in the application.

The opponents also pointed out that the examples presented in the patent in suit related to compositions that differed not only in the amount of bictegravir in the composition but also in the type of excipients: this led to an impact on the dissolution and bioavailability independently on the amount of the active agent.

6.5.2 The proceedings were interrupted between 11:56 and 13:00 for the lunch break.

6.5.3 The PP argued that the subject-matter of the claims of the AR1 differed from the disclosure of D5 in (i) the integrase inhibitor, (ii) in its dosage, and (iii) in the form, i.e. a tablet, to be chosen.

The objective technical problem had to be considered the provision of an effective combination therapy for treating of HIV with improved effects, these being:

- Effectiveness, as shown at paragraph 352 of the patent in suit and confirmed by D36 (post-published).
- Minimization of the food effect: 50 mg of bictegravir in the claimed composition displayed lower food effect compared to a composition comprising 75 mg of the active agent as shown in examples 3 and 9 of the patent in suit. Reference was made to the summary on pages 10-11 of response of the applicant to the notices of opposition.
- Improved resistance profile as shown in the post-published document D41.
- Improved effect even in case of forgiveness as shown in the post-published document D42.

Reference was made to T1193/18 and T1442/18 both stating that any effect should be taken into account in the definition of the technical problem even if the effect did not lead to an improvement *vis à vis* the prior art, and to T2015/20, T1306/18, in which the identification of the dosage of the active agent was found inventive.

By referring to D45, the PP argued that the skilled person would have chosen a dose of bictegravir of 75 mg in the claimed composition in analogy to the study carried out to select the dose od dolutegravir.

Only with hindsight could the skilled person have arrived at the claimed invention, since neither in D3 nor in D18/D28 was bictegravir indicated as the preferred compound.

Concerning the effect of the excipients on dissolution/bioavailability, the burden was on the opponents to show that some embodiments in the scope of the claims did not work.

6.5.4 The discussion on inventive step was carried on and the parties exchanged their arguments; moreover the the following documents/issues were discussed:

- D36, page 73, bottom, page 75, page 77 and figure 9 in relation to the fact that the studies conducted were "non-inferiority" studies;

- D21b, middle of abstract, in relation to the fact that dolutegravir already belonged to the next generation of integrase inhibitors as bictegravir,

- D35 (page 2 in the middle) relating to the clinical trial on bictegravir,

- D21a in relation to the dosages of anti-HIV compounds,

- D41 (fig 1) and D21 in relation to the structures of bictegravir and dolutegravir,

- D29 in relation to the synergy of a triple combination,

- D40 (example 2) showing that the dissolution of bictegravir was influenced by excipients,

- the influence of the dissolution on the bioavailability,

- the formulation of the objective technical problem as an alternative or an optimised treatment for HIV.

6.5.5 During the discussion the oral proceedings were interrupted between 14:10 and 14:35 and between 15:57 and 16:17 to allow the parties to organise their arguments.

7. After an interruption between 17:21 and 17:45, the chairman announced that the AR1 was considered to meet the requirements of Article 56 EPC.

Asked by the chairman, the PP stated that all requests on file were maintained.

The opponents did not express any opinion on the adaptation of the description.

The parties confirmed that the oral proceedings had run smoothly from a technical point of view.

8. **Decision**

The chairman announced the decision of the opposition division that taking into consideration the amendments made by the proprietor of the European patent during the opposition proceedings, the patent and the invention to which it relates were considered to meet the requirements of the EPC and the patent was maintained in amended form based on the claims of the auxiliary request 1 and the description as granted.

9. The oral proceedings were closed at 17:50.

After deliberation of the opposition division,

- the chairman announced the following **decision** :

"Account being taken of the amendments made by the patent proprietor during the opposition proceedings, the patent and the invention to which it relates are found to meet the requirements of the European Patent Convention. The currently valid documents are those according to the first auxiliary request ."

Regarding the reasons for the decision, the chairman referred to:

Article 101(3)(a)EPC: Account being taken of the amendments made by the patent proprietor during the opposition proceedings, the patent and the invention to which it relates are found to meet the requirements of the European Patent Convention.Patent is maintained as amended.

The chairman **closed the oral proceedings** on 27.10.2022 at 17:50 hours.

signed:

Büttner, Ulf

.....

Chairman

signed:

Collura, Alessandra

.....

Minute Writer

Enclosure(s):
Form 2339.4

Documents for the maintenance of the patent as amended

Auxiliary Request 1

In the text for the Contracting States:
AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR

Description, Paragraphs

1-367 of the patent specification

Claims, Numbers

1-7 filed in electronic form on 26-08-2022

Drawings, Sheets

1/6-6/6 of the patent specification

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/738,803	04/05/2023 08:00:12 PM ET	1147-US-P2C2DC

Title of Invention

THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	2232	FILED BY	Frances Tsai
PATENT CENTER #	61871032	FILING DATE	05/06/2022
CUSTOMER #	25000	FIRST NAMED INVENTOR	Benjamin Micah Collman
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Donna Gressler

Documents

TOTAL DOCUMENTS: 40

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
1147-US-P2C2DC_TD.pdf		1	Terminal Disclaimer Filed	22 KB
1147-US-P2C2DC_POA.pdf		2	Power of Attorney	39 KB
1147-US-P2C2DC_IDS.pdf		15	-	228 KB
1147-US-P2C2DC_IDS-TRAN.LET.pdf	(1-2)	2	Transmittal Letter	26 KB
1147-US-P2C2DC_IDS-IDS.pdf	(3-15)	13	Information Disclosure Statement (IDS) Form (SB08)	183 KB
NPL_ClinicalTrials_2014_Phase1b.pdf		3	Non Patent Literature	106 KB

NPL_ClinicalTrials_2015_Phase2.pdf	4	Non Patent Literature	111 KB
NPL_Acosta_2021.pdf	1	Non Patent Literature	116 KB
NPL_Chamberlain_2021.pdf	3	Non Patent Literature	165 KB
NPL_Eron_2009.pdf	6	Non Patent Literature	120 KB
NPL_EMA_2015_Genvoya.pdf	20	Non Patent Literature	2708 KB
NPL_Kommavarapu_2015.pdf	10	Non Patent Literature	8750 KB
NPL_EMA_2018_Biktarvy.pdf	104	Non Patent Literature	11477 KB
NPL_Lozan_2020.pdf	4	Non Patent Literature	324 KB
NPL_OA_2021-03-24_1147-AU-P2D.pdf	5	Non Patent Literature	117 KB
NPL_OA_2022-11-23_1147-CA-P2.pdf	5	Non Patent Literature	204 KB
NPL_OA_2021-12-23_1147-KR-P2D.pdf	4	Non Patent Literature	576 KB
NPL_OA_2022-08-18_1147-KR-P2D_T.pdf	7	Non Patent Literature	847 KB
NPL_OA_2023-01-31_1147-KR-P2D_T.pdf	8	Non Patent Literature	734 KB
NPL_OA_2023-03-23_1147-KR-P2D2.pdf	4	Non Patent Literature	569 KB
NPL_OA_2022-07-27_1147-CN-P2D_T.pdf	18	Non Patent Literature	1438 KB

NPL_OA_2022-05-24_1147-TW-P2D_T.pdf	23	Non Patent Literature	2861 KB
NPL_OPP-O1-SUB_2022-08-25_1147-EP-P2.0.pdf	10	Non Patent Literature	91 KB
NPL_OPP-O2-SUB_2022-08-26_1147-EP-P2.0.pdf	6	Non Patent Literature	789 KB
NPL_OPP-O2-SUB_2021-03-09_1147-EP-P2.0.pdf	6	Non Patent Literature	572 KB
NPL_OPP-O3-SUB_2021-03-24_1147-EP-P2.0.pdf	12	Non Patent Literature	1587 KB
NPL_OPP-O3-SUB_2021-12-23_1147-EP-P2.0.pdf	6	Non Patent Literature	833 KB
NPL_OPP-O1-SUB_2021-03-26_1147-EP-P2.0.pdf	10	Non Patent Literature	1202 KB
NPL_OPP-O3-SUB_2022-08-26_1147-EP-P2.0.pdf	3	Non Patent Literature	415 KB
NPL_OPP-P-RES_2021-01-11_1147-EP-P2.0.pdf	24	Non Patent Literature	804 KB
NPL_OPP-P-RES_2022-01-24_1147-EP-P2.0.pdf	12	Non Patent Literature	314 KB
NPL_OPP-P-RES_2022-08-26_1147-EP-P2.0.pdf	5	Non Patent Literature	256 KB
NPL_OPP-SUM_2021-06-24_1147-EP-P2.0.pdf	19	Non Patent Literature	2300 KB
NPL_OPP-DEC_2022-12-23_1147-EP-P2.0.pdf	101	Non Patent Literature	12114 KB
NPL_OPP-SUM_2022-04-	18	Non Patent Literature	12671 KB

05_1147-EP-P2.0.pdf

NPL_Song_2009.pdf		1	Non Patent Literature	92 KB
NPL_Ziga_2021.pdf		8	Non Patent Literature	1723 KB
NPL_Smith_ 2018.pdf		18	Non Patent Literature	5034 KB
1147-US-P2C2DC_ResponseNfOA.pdf		6	-	44 KB
1147-US-P2C2DC_ResponseNfOA-A....pdf	(1-1)	1	Amendment/Request for Reconsideration-After Non-Final Rejection	23 KB
1147-US-P2C2DC_ResponseNfOA-CLM.pdf	(2-3)	2	Claims	28 KB
1147-US-P2C2DC_ResponseNfOA-REM.pdf	(4-6)	3	Applicant Arguments/Remarks Made in an Amendment	29 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
1147-US-P2C2DC_TD.pdf	80CEF22AC8455F5CB9364DEB60302DAF158492AA84F429393 1CFFB344DFD9B15AB002921FE75BE06D507CAD9544F5A8D88 97A61DE8D9C390199D48F38B1569BC
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1147-US-P2C2DC_ResponseNfOA.pdf	20911153B160B2A625C8DDD99ABD62DF849FAA34175E11DA53F3C7509A9DED4299882AC47DFD0ECA724822398B111F4C3B684419A2C1572966731ED25DF36B89
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This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/AIA/26 (04-14)
Approved for use through 05/31/2024. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	Docket Number (Optional) 1147-US-P2C2DC

In re Application of: Benjamin Micah Collman et al.

Application No.: 17/738,803

Filed: May 6, 2022

For: THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS

The applicant, Gilead Sciences, Inc., owner of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of **prior patent** No. 10,548,846 as the term of said **prior patent** is presently shortened by any terminal disclaimer. The applicant hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the applicant does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the **prior patent**, "as the term of said **prior patent** is presently shortened by any terminal disclaimer," in the event that said **prior patent** later:

expires for failure to pay a maintenance fee;
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is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

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I hereby acknowledge that any willful false statements made are punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

2. ☒ The undersigned is an attorney or agent of record. Reg. No. 45,544

/Donna Johnson Gressler/ — Signature
April 5, 2023 — Date

Donna Johnson Gressler — Typed or printed name

Agent for Applicant — Title
(650) 574-3000 — Telephone Number

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Dated: April 5, 2023 — Electronic Signature for Donna Johnson Gressler: /Donna Johnson Gressler/

#5006078v1

CARPMAELS & RANSFORD

European Patent Office
80298 Munich
Germany

Chartered Patent Attorneys
European Patent Attorneys
Chartered Trade Mark Attorneys
Solicitors

Carpmaels & Ransford LLP
One Southampton Row
London WC1B 5HA
United Kingdom
T +44 20 7242 8692
F +44 20 7405 4166
E email@carpmaels.com
www.carpmaels.com

Your Ref 16798063.0
Our Ref 0008281EP:CJH/PAK/HEB
Date 24th January 2022

Re: European Patent No. 3346995
GILEAD SCIENCES, INC.

We write in reply to the summons and preliminary opinion dated 24 June 2021.

I will represent the patentee at the oral proceedings, alongside Paul Kaufman and Hannah Brown of Carpmaels & Ransford LLP. We will speak in English (the language of the proceedings) and request simultaneous interpretation into English should any party intend to use a language other than English. The patentee's party will also include Tim Marquart, Andrew Kessel and Liuchun Yang (all of Gilead Sciences).

Contact information for the EPO to communicate the connection details to the patentee's party is provided in the attached annex, which I request is treated as confidential and is excluded from file inspection.

Contact information for our IT support team is set out below:

Contact Person: Gregory Judd
Email address: helpdesk@carpmaels.com
Telephone number: +44 20 3310 2418

Comments on the issues to be discussed at the oral proceedings

At the oral proceedings scheduled for 24 and 25 March 2022, we look forward to discussing the issues mentioned in the preliminary opinion. We provide some further comments below on the various issues, in response to the preliminary opinion and further submissions of the opponents.

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Added matter

In the preliminary opinion, the Division concludes that claim 1 of the main request contravenes Article 123(2) EPC. However, the concerns which the Division appears to have can be readily addressed, as discussed below.

Firstly, it is not necessary for the application to provide a single sentence which reproduces each and every feature of granted claim 1. As set out in the Guidelines (H-IV, 2.2), "*Literal support is, however, not required by the wording of Art. 123(2). […] When assessing the conformity of the amended claims with the requirements of Art. 123(2), the focus is placed on what is really disclosed to the skilled person by the documents as filed as directed to a technical audience. In particular, the examining division needs to avoid disproportionally focusing on the structure of the claims as filed to the detriment of the subject-matter that the skilled person would directly and unambiguously derive from the application as a whole*". It is thus appropriate for the Division to consider how the various passages which provide basis for claim 1 would be considered by a skilled person, in the context of the application as a whole, rather than by assessing each passage individually.

Secondly, both of the features in claim 1 which the Division objects to under Article 123(2) EPC have basis throughout the application as filed.

As a starting point in the preliminary opinion, the Division notes that [0008] discloses the features of granted claim 1 except that emtricitabine can be in the form of a **salt** and the dosage form is a **tablet**.

With respect to the feature in claim 1 that emtricitabine may be present in pharmaceutically acceptable **salt** form, the Division appears to have overlooked the fact that the first sentence of [0008] expressly states that emtricitabine can be present in salt form. Similarly, [0030] states that emtricitabine may be in free or pharmaceutically acceptable salt form in dosage forms of the disclosure, as does [0048]. These are general passages teaching that emtricitabine may be in free base or pharmaceutically acceptable salt form in dosage forms of the invention, and so the application provides general basis for dosage forms comprising emtricitabine or a pharmaceutically acceptable salt thereof.

This general basis is supported by the large number of other passages which refer to the use of emtricitabine, optionally as a pharmaceutically acceptable salt, including [0010], [0012], [0016], [0018], [0020], [0021], [0048], [0050], [0053], [0055]-[0058], [0116]-[0119], [0122]-[0124], [0277]-[0278], [0283]-[0284], and claims 1, 7-9, 11, 16-20, 31, 36. Of these, the following passages specifically disclose the use of **200 mg** emtricitabine or a pharmaceutically acceptable salt form: [0010], [0012], [0016], [0048], [0050], [0053], and claims 7-9. Plainly, specifying that the tablet can contain 200 mg of emtricitabine or a pharmaceutically acceptable salt does not present the skilled person with new technical information (G2/10).

The Division also refers to [0050] but appears to have misunderstood its meaning. This paragraph teaches that a reference in the application to a 200 mg amount of a pharmaceutically acceptable salt of emtricitabine means an amount of that salt which provides 200 mg of emtricitabine free base. The same disclosure is provided in relation to BIC and TAF at paragraphs [0036]-[0038] and [0042]-[0044], such that references to 25 mg of a pharmaceutically acceptable salt of TAF mean an amount

of a salt of TAF which provides 25 mg of TAF free acid and references to 50 mg of a pharmaceutically acceptable salt of BIC mean an amount of a salt of BIC which provides 50 mg BIC free acid. These sorts of passages are standard in patent applications and reflect the fact that salts are typically dosed according to the amount of free acid/base because the free acid/base is the pharmacologically active component of a salt. The granted claims are consistent with these passages, too. See, e.g. granted claim 3 which refers to 52 mg of the sodium salt of BIC and 28 mg of TAF hemifumarate (which provide 50 mg BIC free acid and 25 mg TAF free acid respectively). Thus, when a salt of emtricitabine is present, the total weight of the salt (in absolute terms) will be more than 200 mg, to account for the weight of the counterion. As a result, contrary to the comment in the preliminary opinion, the amount of emtricitabine salt used in the tablets of the invention is always equivalent (in the sense that it provides the same amount of emtricitabine) to 200 mg emtricitabine free base.

With respect to the feature in claim 1 that the dosage form is a **tablet**, the Division acknowledges that this feature can be found in the application as filed, but appears concerned that it is linked in some passages with other specific features which are not present in granted claim 1.

However, tablets are undoubtedly the preferred dosage forms in the application: they are discussed in detail throughout and are the only type of dosage form exemplified.

Indeed, the application as filed discloses tablets generally, and does not require the inclusion of other specific features. For example, claim 6, [0020] third sentence, [0054] first sentence, and [0116] all disclose tablets at a general level. More specific disclosures of tablets are provided at various passages, including [0012]-[0014] and [0016]-[0022], the majority of paragraphs between [0053]-[0269], [0277]-[0284], [0286], [0289], the Examples, and in claims 7-31 and 36-39. Collectively, these passages provide a clear indication that tablets are the preferred dosage forms in the application as filed.

This general preference is not undermined by the fact that some (although not all) of these paragraphs disclose tablets comprising additional features not found in granted claim 1. Those additional features are not described as being essential and are not inextricably linked to the other features of the invention. When looking through the passages referred to in the preliminary opinion, it is clear that in each and every case there is clear teaching in the application confirming that those additional features are not required as part of the general invention in the application:

- [0010] specifies that the dosage form has a total weight of less than 850 mg and does not specify that the dosage form is a tablet, but it is clear from other paragraphs that the dosage form is preferably a tablet (see passages listed above) and that a total weight of less than 850 mg is not required when using particular dosages of the three ingredients (see, e.g. [0008] and [0012] which refer to dosage forms without a weight limitation).
- [0012] and original claim 7 state that the tablet is coated. However, tablets according to the invention may be coated or uncoated ([0071]) and there are many general and specific disclosures where the tablets are not limited to being coated (see, e.g. [0014], [0016] and [0221]).
- [0016] and original claim 9 state that BIC and TAF are segregated in the tablet. Again, there are many general and specific disclosures where the tablets are not limited to being segregated (see, e.g. [0008], [0014], and [0221]).

Therefore, the application is not restricted to tablets having a specific total weight, a coating, or being segregated. The fact that the application also discloses embodiments which contain these additional features does not undermine the clear preference provided by those paragraphs to the use of tablet dosage form comprising BIC, TAF and FTC, or their pharmaceutically acceptable salts, at the claimed doses.

Thirdly, the Division notes that [0077]-[0085], [0090]-[0098] and [0103]-[0111] refer to "*a pharmaceutical composition comprising a tablet*". We are unsure why the Division has highlighted these words. A tablet *is* a pharmaceutical composition, and so these words are superfluous and add no new technical teaching compared to claim 1. In any event, the additional wording "*pharmaceutical composition comprising*" does not change the fact that these paragraphs all disclose tablets containing 50 mg BIC or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, 25 mg TAF or a pharmaceutically acceptable salt thereof.

Finally, we note that the Opposition Division's concerns are addressed by the amendments made in the auxiliary requests. In particular, the option for emtricitabine to be present as a "pharmaceutically acceptable salt" is deleted from auxiliary requests 5 and 9-15, and at least auxiliary requests 16 onwards are believed to be unaffected by the concerns raised in the preliminary opinion.

Priority

The Division has provided no detailed comments on priority, other than to note that the same observations apply as those made in relation to added matter. We agree that added matter and priority are linked and therefore our comments above apply equally to priority.

Novelty

As the Opposition Division's preliminary opinion is that the claims are novel over D1 and D2, we believe that no further comments in relation to this ground are necessary at this stage.

Inventive step

In its preliminary opinion, the Opposition Division invited us to consider the problem-solution approach starting from D5 or D31 as the closest prior art. We therefore provide additional comments on these documents below, taking into account the opponents' further submissions and the issues raised in the Opposition Division's preliminary opinion. To support these comments, we enclose:

- D41 Smith (2018)
- D42 Acosta (October 2021).

Problem solution analysis starting from D5

If D5 is selected as the closest prior art, the claimed solution is inventive as explained in section 5.58-5.81 of our response to the oppositions.

Specifically, we maintain that the opponents have selected a starting point within D5 using hindsight knowledge of the invention. In their recent submissions, O1 and O2 argue that the disclosure of D5 is not limited to compositions in which the weight ratio of dolutegravir and emtricitabine is from 1:1 to 1:3. Even if that were true, the opponents cannot dispute that the weight ratio of dolutegravir and emtricitabine of from 1:1 to 1:3 is a key teaching in D5 relating to the preferred doses of active ingredients that should be used. The importance of this ratio is highlighted throughout D5 and would not simply be ignored by the skilled person when choosing a starting point within the document. Instead, the skilled person would be guided towards compositions which satisfy the preferred ratio. The particular combination chosen by the opponents (50mg DTG, 200mg FTC, 25mg TAF) does not satisfy this ratio and is therefore not a realistic starting point within D5 that the skilled person would have chosen.

In addition, D5 does not contain any data to show that the particular combination comprising DTG (50mg), FTC (200mg) and TAF (25mg) chosen by the opponents is actually effective or has any beneficial properties. It is therefore inappropriate for the opponents to focus on that particular combination, which has been selected arbitrarily by the opponents on the basis of hindsight knowledge of the invention.

Establishing the objective technical problem

In relation to the objective technical problem, the opponents argue that no improvements have been demonstrated relative to the combination comprising 50mg DTG, 200mg FTC and 25mg TAF and therefore the objective technical problem is simply the provision of an alternative pharmaceutical composition for the treatment of HIV.

The opponents' formulation of the objective technical problem is incorrect. As mentioned above, there is no data in D5 demonstrating that tablets comprising 50 mg DTG, 200 mg FTC and 25 mg TAF could be prepared, are actually effective, would provide concentrations of active ingredients *in vivo* that would be clinically meaningful, would provide near maximal virologic response or would possess acceptable food effects. The skilled person therefore has no knowledge as to which, if any, combinations in D5 would possess these effects. In contrast, the claimed combination is useful *in vivo* for the treatment of HIV in humans, provides near-maximal virologic response, can be formulated as a single tablet, and provides acceptable food effects which are in fact reduced compared to higher BIC doses. Even in the absence of a direct comparison with a composition in D5, these are properties of the present invention which cannot be ignored and therefore must be taken into account when formulating the objective technical problem (see e.g. T1193/18 and T1442/18[1]).

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[1] T1193/18, r.9.2-9.3: "As previously noted, none of the numerous stability tests performed allows for a comparison between on the one hand the process of D3 and on the other hand solutions obtained following the process of D3 and only further differing therefrom in that the presently claimed pH variations are performed. (...) Hence, even if there is no evidence of an improvement over D3, the achievement of a good storage stability remains a property of the present process which cannot be ignored. It follows that, starting from D3, the objective technical problem to be solved by the process of claim 1 of auxiliary request 1B lies in the provision of an alternative process for the preparation of oral levothyroxine compositions having good storage stability."

T1442/18, r.19, English machine translation: "The appellant argued that [...] the respondents had not compared the claimed

In any event, contrary to the views of the opponents, there are many effects resulting from the differences between the claimed composition containing BIC and the composition of D5 containing DTG. As the opponents have specifically requested in their recent submissions that we provide evidence of a direct comparison, and insist that the closest prior art is D5, we provide this comparison below.

(a) Improved resistance profile

The enclosed **D41** (Smith 2018) demonstrates that BIC has an unexpectedly improved resistance profile compared to DTG and that BIC is improved versus DTG in its ability to inhibit a broad range of integrase mutations:

> *"BIC was more effective than DTG against several INSTI-resistant mutants. Overall, in terms of their ability to inhibit a broad range of INSTI-resistant IN mutants, BIC was superior to DTG."*[2]

The mutant strains that BIC was improved against include the DTG-resistant integrase mutant R263K (which is considered in the examples in D5), and well as integrase mutants G118R and H51Y/R263K[3]. As a result, D41 concludes that:

> *"BIC retained potency against several of the INSTI-resistant mutants that caused a decrease in susceptibility to DTG"*[4]

Therefore, BIC has a better resistance profile compared to DTG, and in particular is improved against mutants that cause a decrease in susceptibility to DTG.

(b) Reduced viral breakthrough and improved barrier to resistance at suboptimal adherence

The enclosed **D42** (Acosta 2021) provides the results of *in vitro* studies simulating the outcome of therapeutic regimens – including BIC+FTC+TAF (50/200/25 mg) as claimed with DTG+FTC+TAF (50/200/25 mg) as in D5 – after doses were missed. In particular, these studies evaluated the emergence of resistant strains and the ability to maintain viral suppression despite suboptimal adherence (known as "forgiveness").

Figure 3 shows that BIC+FTC+TAF (50/200/25 mg) had a higher forgiveness and barrier to resistance than DTG+FTC+TAF (50/200/25 mg) in the setting of suboptimal adherence (i.e. after

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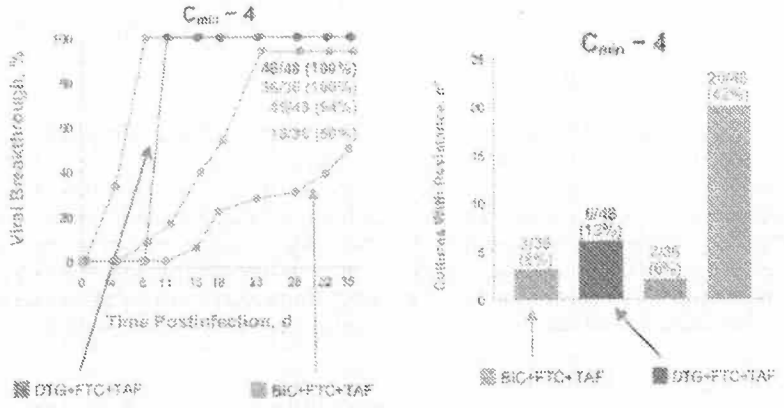
form A of afatinib dimaleate with the anhydrous free base of afatinib disclosed in D1, that, accordingly, no technical effect is apparent and that the objective technical problem is to be seen in the provision of only an alternative, and that the solution to this problem could not be inventive. The Board cannot follow suit. Even if there is no comparison between the now claimed form A of afatinib dimaleate and the (supposedly) anhydrous free base of afatinib disclosed in D1, it must nevertheless be taken into account that the respondents demonstrated the extremely low hygroscopicity of the claimed form A of afatinib dimaleate in their submission of 22 December 2017 (see above). Thus, even if one assumes in favour of the appellant that the free base of afatinib disclosed in D1 also has an extremely low hygroscopicity, the objective technical problem would still be to be seen in the provision of another physiologically acceptable compound with extremely low hygroscopicity and not merely in the provision of a physiologically acceptable compound."

[2] D41, abstract, results and conclusions sections.

[3] D41, page 3, left hand column, lines 17-20

[4] D41, abstract, conclusions section.

missed doses). For clarity, we have reproduced the final line graph and bar chart in Figure 3 below and have added legends indicating the different regimens.



These graphs show that with in vitro drug concentrations simulating four missed daily doses of antiretroviral regimens, all DTG+FTC+TAF cultures had viral breakthrough (i.e. HIV-1-induced cytopathic effect) by Day 12 while BIC+FTC+TAF had only 50% viral breakthrough by Day 35. While emergent drug resistance was seen for all regimens, the frequency was higher for DTG+FTC+TAF (13% of cultures) compared to BIC+FTC+TAF (8% of cultures).

Therefore, replacing DTG with BIC provides an improved composition with reduced viral breakthrough and improved barrier to resistance at suboptimal adherence.

The above advantageous effects are very important to HIV therapy. A drug's resistance profile is important because the usefulness of most antiretroviral drugs, including integrase inhibitors, is limited by the emergence of drug resistant strains (D21a, page 1207, right column, end of penultimate paragraph; D41, page 2, left column, second paragraph). Prevention of viral replication and emergence of resistance is necessary to maintain lifelong viral suppression, particularly in the real world where drug adherence is often suboptimal (D42 Acosta, final bullet under "Conclusions").

Thus, the objective technical problem starting from D5 is the provision of an effective combination therapy for the treatment of HIV in humans, which provides near-maximal virologic response, can be formulated as a single tablet, provides minimised food effects, and which has an improved resistance profile and improved forgiveness and barrier to resistance in a real world setting (i.e. under conditions of suboptimal adherence).

Non-obviousness

The opponents argue that, starting from D5, a skilled person would have had an incentive to replace DTG with another integrase inhibitor, then to select BIC as the integrase inhibitor, and then to use

the same amount (i.e. 50 mg) of BIC. However, there was no incentive in the art for the skilled person to make any of those selections when seeking to solve the objective technical problem.

First, there is no teaching in D5 to guide the skilled person to change the integrase inhibitor. The whole of D5 relates to DTG and it is only the prodrug of tenofovir which can be varied within D5. Therefore, the skilled person would not be motivated to change the integrase inhibitor when seeking to solve the objective technical problem.

Second, as discussed in paragraphs 5.68-5.70 of our opposition response, there is no guidance to select BIC when seeking to solve the objective technical problem. O1 argues that BIC is disclosed in D3 "*as a preferred HIV integrase inhibitor out of merely eight compounds*" on the basis that claim 32 of D3 lists eight integrase inhibitors, and thus that BIC was an obvious choice to combine with FTC and TAF.[5] This is plainly inconsistent with O1's argumentation in relation to D5 that "*What is claimed is essentially within the discretion of the applicant. This, however, does not justify that the disclosure of a prior art document is reduced to what is claimed.*"[6] The opponent cannot ignore preferences within the closest prior art document (i.e. ignoring the key weight ratio which forms the core of the invention in D5), only to argue that the skilled person is bound by preferences within other documents. D3 discloses 103 examples, but even if the skilled person were to consider only the eight compounds listed in claim 32, there is still no pointer to select BIC in particular, and certainly not with the expectation of providing the effects detailed above.

In relation to the 50 mg dose, while the opponents' argument may appear superficially attractive, the underlying science pointed away from using 50 mg BIC. In particular, the empirical data at the time would have suggested the claimed formulation would not work because it would not provide adequate BIC concentrations *in vivo*.

In particular, selection of an appropriate BIC dose to accompany FTC and TAF in a single tablet regimen was challenging and would have led away from 50 mg.

As discussed in our reply to the oppositions, by the priority date 75 mg BIC had been chosen as the optimum dose to be progressed in further clinical trials because it was predicted to provide near-maximal virologic response across a wide range of patients based on paIC$_{95}$. This is discussed in D36 (Biktarvy EPAR):

Based on PK/PD analysis, exposure associated with a 75 mg dose of single agent BIC is expected to provide near-maximal virologic response, with a predicted paIC95 of approximately 2h, providing considerable coverage above the target concentration of 167 ng/mL (adjusted).

(page 71)

The skilled person would have reached the same conclusion as the patentee and would have selected 75 mg rather than 50 mg, as claimed. Contrary to the way in which the opponents describe it, dose selection is not based on guesswork or on extrapolation of doses from other active

[5] O1 submissions dated 31st March 2021, paragraph 2.5.2.
[6] O1 submissions dated 31st March 2021, paragraph 2.3.5.

ingredients. Dose selection is based on pharmacokinetic (PK) and pharmacodynamic (PD) studies that involve numerous parameters, including trough concentrations and IC_{50}.

In further detail, the PK/PD analyses that would have been carried out by the skilled person at the priority date during Phase 1 trials are those that were, in fact, carried out by the patentee. These involved administration of doses of BIC to patients in four different treatment groups, each group receiving a once-daily 5 mg, 25 mg, 50 mg or 100 mg dose of BIC over a period of 10 days. The PK-PD response relationship established in these treatment groups is depicted below in Figure 1.

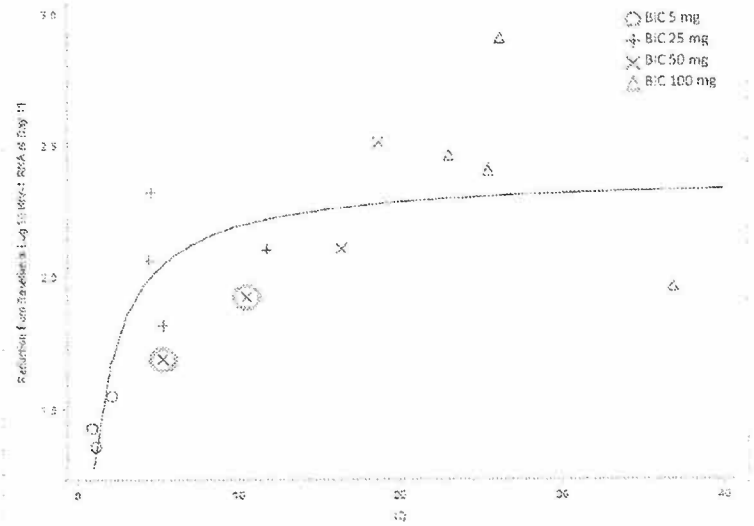


Figure 1: Relationship between BIC IQ and reduction of plasma HIV-1 RNA from baseline

This graph plots the relationship between BIC inhibitory quotient (IQ) – which is a measure of systemic exposure taking into account pharmacokinetic and pharmacodynamic properties as well as inhibitory concentrations – against the reduction from baseline in HIV-1 RNA viral load in patients at day 11, at different BIC doses.[7] The flat portion of this graph represents the maximum reduction from baseline in viral load. The data points for the optimum dose based on this PK-PD relationship often lie on the flat portion of the curve, somewhere distant from the inflection point but not significantly far to the right of the curve. Data points lying close to the inflection point could indicate potential "underdosing" of a patient, in other words a dose that is not high enough to achieve a near-maximal virologic response. Data points lying significantly far to the right of the curve could indicate potential

[7] IC (Inhibitory Quotient) is estimated by dividing predose concentration on Day 11 of the study (C_{trough}) by the in vitro protein-adjusted concentration that results in a 95% inhibition of integrase (paIC$_{95}$, 162 ng/mL).

over exposure of a patient, in other words a dose that is higher than is required to achieve a near-maximal response.

As can be seen from Figure 1, two of the four data points (i.e. 50% of the data points) from patients receiving a 50 mg dose lie around the inflection point (circled above), indicating that 50 mg BIC had the potential to result in "underdosing" of a patient, in other words that 50 mg BIC was not believed to be a high enough dose to achieve a near-maximal virologic response. For this reason, the 50 mg BIC dose was not taken forward to Phase II studies.

Similarly, data points from patients receiving a 100 mg BIC dose lie to the right of the flat portion of the curve, indicating that 100 mg BIC would result in over exposure of a patient, in other words that 100 mg BIC is a dose that is higher than is required to achieve a near-maximal response. For this reason, the 100 mg BIC dose was not taken forward to future studies.

Instead, 75 mg BIC was chosen as the optimal dose because it was expected to provide a middle ground between 50 mg and 100 mg.

These results cannot be dismissed simply because they were not in the prior art. As mentioned above, these results reflect the results that the skilled person would have obtained at the priority date. In exactly the same way as the patentee, the skilled person would instead have selected 75mg BIC over 50mg BIC.

Therefore, the claimed invention involves an inventive step.

There is also no logic to O1's argument that "*a skilled person looking for an alternative fixed dose combination would have had incentive to use the same amount of another HIV integrase inhibitor such as BIC.*"[6] Every compound has different properties which affect the dose which should be used. As we explained in our reply to the oppositions, integrase inhibitors on the market at the priority date varied from 20mg for DTG (D5, page 16, lines 15-16) to up to 1600 mg for raltegravir – an 80-fold difference. There was thus no "incentive" in the prior art to use 50mg as the dose for BIC. In fact, as established above, the underlying science pointed away from using 50mg BIC.

The opponents are also wrong to characterise the present invention as involving only routine dose optimisation, and further to assert that inventions based on new doses automatically lack an inventive step under Article 56 EPC. Firstly, we reject the notion that the present invention relates to routine dose optimisation, particularly if the closest prior art is indeed D5 as the opponents suggest. D5 does not mention BIC at all, so the invention involves more than optimising the dose of an already disclosed combination. In any event, there is no blanket prohibition on patents directed to new (optimised) doses, and the Boards find patents relating to dose optimisation to be inventive. For example, in T2015/20, the Board found that the claimed solution to the technical problem of "*providing an optimized dose with respect to efficacy and side effects for treatment of asthma*" was inventive, even though in that case (contrary to the present one) the closest prior art disclosed the

[6] Page. 10
O1 submissions dated 31st March 2021, paragraph 2.5.4

same drug as was being claimed and specified a range of suitable dosages encompassing the dosage that was claimed. The specific facts and circumstances of each particular case must be taken into account, as must the unexpected results and the surprising technical effects observed by the inventors. In the present case, these factors clearly indicate an inventive step.

O1 also argues that Gilead's products such as Odefsey and Genvoya illustrate that APIs from different BSC classes can be formulated in a fixed dose combination and so there would have been a reasonable expectation for successfully formulating BIC, FTC and TAF as a fixed dose combination.[9] This is an oversimplification of the complex factors which need to be considered when providing a fixed dose combination tablet. The fact that other fixed dose combination tablets have been successfully formulated – using the skill and expertise of Gilead's scientists – does not provide any reasonable expectation that a completely different combination of drugs could be formulated, and does not teach how they should be co-formulated.

Inventive step starting from D31

The Opposition Division also invited us to consider inventive step starting from D31. However, D31 is not a suitable closest prior art document because it was published after the priority date and so is not prior art against most of the claim requests.

The only claims which are not entitled to priority are those of auxiliary requests 27-29, which focus on the example compositions in the patent. AR29 particularly relates to the Tablet of Example 10.

ARs 27-29 are inventive over D31 because D31 does not suggest how BIC, FTC and TAF should be formulated at all. As such, D31 does not suggest the particular combination of excipients claimed in the specified amounts. The particular formulations claimed have several advantages, similarly to those discussed above for the main request, namely a desirable PK profile providing a near-maximal virologic response, and a reduced food effect. Starting from D31, it was not obvious for the skilled person to arrive at the particular formulations claimed when seeking to provide these advantageous effects.

O3's experiments in D40

We are still considering the opponent's new experimental report submitted in D40, but as an initial comment it does not appear to cast doubt on the numerous improved effects of the invention as discussed above and in our opposition response, which include clinical benefits relating to bioavailability, virologic effect, food effects, and barrier to resistance. To the extent that the opponent is somehow implying that the results of the 75mg BIC experiments performed in Examples 3 and 4 of the patent may be an effect of variability amongst BIC batches used by Gilead, we confirm that the BIC used in these experiments was all from the same batch.

[9] O1 submissions dated 31st March 2021, paragraph 2.5.3.

CARPMAELS & RANSFORD

Yours faithfully,

// ELECTRONICALLY SIGNED AND SUBMITTED //

HOGGETT, Christopher James
Carpmaels & Ransford LLP Professional Association No. 182

Encl. Confidential annex
D41
D42

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100020

北京市朝阳区东三环中路 1 号环球金融中心办公楼东楼 20 层 北京市金杜律师事务所

陈文平(010-58785037) 侯宝光(010-58785390)

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申请人或专利权人：吉利德科学公司

发明创造名称：治疗人免疫缺陷病毒的治疗组合物

第 一 次 审 查 意 见 通 知 书

1. ☒应申请人提出的实质审查请求，根据专利法第 35 条第 1 款的规定，国家知识产权局对上述发明专利申请进行实质审查。

☐根据专利法第 35 条第 2 款的规定，国家知识产权局决定自行对上述发明专利申请进行审查。

2. ☒申请人要求以其在：

US 专利局的申请日 2015 年 11 月 09 日为优先权日，

US 专利局的申请日 2016 年 09 月 26 日为优先权日。

☒申请人已经提交了经原受理机构证明的第一次提出的在先申请文件的副本。

☐申请人尚未提交经原受理机构证明的第一次提出的在先申请文件的副本，根据专利法第 30 条的规定视为未要求优先权要求。

3. ☐经审查，申请人于_____提交的修改文件，不符合专利法实施细则第 51 条第 1 款的规定，不予接受。

4. 审查针对的申请文件：

☐原始申请文件。☐分案申请递交日提交的文件。☒下列申请文件：

分案申请递交日提交的摘要附图、权利要求第 1-51 项、说明书第 1-660 段、说明书附图；

2021 年 9 月 18 日提交的说明书摘要。

5. ☐本通知书是在未进行检索的情况下作出的。

☒本通知书是在进行了检索的情况下作出的。

☒本通知书引用下列对比文件(其编号在今后的审查过程中继续沿用)：

编号	文 件 号 或 名 称	公开日期
1	US 20142213564A1	20140807
2	CN 103491948A	20140101

6. 审查的结论性意见：

关于说明书：

☐申请的内容属于专利法第 5 条规定的不授予专利权的范围。

☐说明书不符合专利法第 26 条第 3 款的规定。

☐说明书不符合专利法第 33 条的规定。

☐说明书的撰写不符合专利法实施细则第 17 条的规定。

☐_____

关于权利要求书：

☐权利要求_____不符合专利法第 2 条第 2 款的规定。

☐权利要求_____不符合专利法第 9 条第 1 款的规定。

☒权利要求 35 不具备专利法第 22 条第 2 款规定的新颖性。

☒权利要求 1-34、36-42 不具备专利法第 22 条第 3 款规定的创造性。

☐权利要求_____不具备专利法第 22 条第 4 款规定的实用性。

☒权利要求 39 属于专利法第 25 条规定的不授予专利权的范围。

☒权利要求 42-51 不符合专利法第 26 条第 4 款的规定。

☐权利要求_____不符合专利法第 31 条第 1 款的规定。

☐权利要求_____不符合专利法第 33 条的规定。

☐权利要求_____不符合专利法实施细则第 19 条的规定。

☐权利要求_____不符合专利法实施细则第 20 条的规定。

☐权利要求_____不符合专利法实施细则第 21 条的规定。

☐权利要求_____不符合专利法实施细则第 22 条的规定。

☐_____

☐申请不符合专利法第 26 条第 5 款或者实施细则第 26 条的规定。

☐申请不符合专利法第 19 条第 1 款的规定。

☐分案申请不符合专利法实施细则第 43 条第 1 款的规定。

上述结论性意见的具体分析见本通知书的正文部分。

7. 基于上述结论性意见，审查员认为：

☐申请人应当按照通知书正文部分提出的要求，对申请文件进行修改。

☐申请人应当在意见陈述书中论述其专利申请可以被授予专利权的理由，并对通知书正文部分中指出的不符合规定之处进行修改，否则将不能授予专利权。

☒专利申请中没有可以被授予专利权的实质性内容，如果申请人没有陈述理由或者陈述理由不充分，其申请将被驳回。

☐_____

8. 申请人应注意下列事项：

(1) 根据专利法第 37 条的规定，申请人应在收到本通知书之日起的 4 个月内陈述意见，如果申请人无正当理由逾期不答复，其申请被视为撤回。

(2) 申请人对其申请的修改应当符合专利法第 33 条的规定，不得超出原说明书和权利要求书记载的范围，同时申请人对专利申请文件进行的修改应当符合专利法实施细则第 51 条第 3 款的规定，按照本通知书的要求进行修改。

(3) 申请人的意见陈述书和/或修改文本应邮寄或递交国家知识产权局专利局受理处，凡未邮寄或递交给受理处的文件不具备法律效力。

(4) 未经预约，申请人和/或代理人不得前来国家知识产权局专利局与审查员举行会晤。

(5) 对进入实质审查阶段的发明专利申请，在第一次审查意见通知书答复期限届满前（已提交答复意见的除外），主动申请撤回的，可以请求退还 50%的专利申请实质审查费。

9. 本通知书正文部分共有 4 页，并附有下述附件：

☐引用的对比文件的复印件共_____份_____页。

☐_____

审查员：杨琪　　联系电话：027-59182839　　审查部门：专利审查协作湖北中心化学发明审查部

第一次审查意见通知书

申请号：202110669916

本申请涉及治疗人免疫缺陷病毒的治疗组合物。经审查，现提出如下审查意见。

一、权利要求1-34、36-42不符合专利法第22条第3款有关创造性的规定，权利要求35不符合专利法第22条第2款有关新颖性的规定，权利要求39属于专利法第25条第1款第（3）项规定的不授予专利权的客体。

1. 权利要求1请求保护固体口服剂型。对比文件1（US 20140221356A1，20140807）公开了：化合物42，45（即权利要求1的式1的化合物）。一种治疗或预防患有HIV感染或处于感染风险中的人的HIV感染的方法，其包括向人施用治疗有效量的本文公开的化合物或其药学上可接受的盐与治疗有效量的一种或多种另外的治疗剂的组合。另外的治疗剂选自以下中的一种或多种：（3）逆转录酶的HIV核苷抑制剂，其选自齐多夫定、恩曲他滨、去羟肌苷、司他夫定、扎西他滨、拉米夫定、阿巴卡韦、氨多索韦、艾夫他滨、阿洛夫定、MIV-210、±-FTC、D-d4FC、恩曲他滨、磷喃、福齐夫定替多酯尔、阿立他滨(AVX754)、KP-1461、GS-9131(Gilead Sciences)和福沙夫定替多酯尔（以前为HDP 99.0003）；(4)HIV逆转录酶核苷酸抑制剂，选自替诺福韦、替诺福韦地索普西富马酸盐、替诺福韦艾拉酚胺富马酸盐（Gilead Sciences）、GS-7340(Gilead Sciences)、GS-9148(Gilead Sciences)、阿德福韦、阿德福韦地匹伏酯、CMX-001(Chimerix)或CMX-157(Chimerix)（参见说明书第0312、0323段，说明书第0159、0162、0163段）。

权利要求1与对比文件1的区别在于：权利要求1限定了化合物与替诺福韦艾拉酚胺或其药学上可接受的盐以及恩曲他滨或其药学上可接受的盐的组合。

本申请说明书中声称：固定剂量组合(例如多层片剂)的使用可影响剂型内的一种或多种活性成分的溶出曲线，因此可能影响剂型的体内药代动力学（参见说明书第0070段）。同时，说明书实施例中给出了含有化合物与替诺福韦艾拉酚胺以及恩曲他滨三组分的双层片剂F2、F4-F7与单组份或双组份片剂在药代动力学、溶出度等方面的差异。但是只有特定的各层组分、特定含量下制成的两层片剂，才有所述的效果，而权利要求1中既没有限定具体的层数，也没有限定各层具体组分和含量，使得任意层数的片剂，是否均能用于本发明并达到与之相同或相似的效果，是本领域技术人员难以预测得到的。基于此，权利要求1实际解决的技术问题是：如何提供一种类似的药物组合。

对于上述区别技术特征，对比文件1已经公开了治疗剂的组合，并具体教导了另外的治疗剂的种类选自恩曲他滨、替诺福韦艾拉酚胺富马酸盐等逆转录酶的HIV核苷抑制剂和HIV逆转录酶核苷酸抑制剂，根据对比文件1的教导，本领域技术人员有动机将式I化合物与恩曲他滨、替诺福韦艾拉酚胺来组合使用，至于其药用盐也是活性物质常规使用形式。

综上，在对比文件1的基础上结合上述说理得到权利要求请求保护的技术方案对于本领域技术人员而言是显而易见的，权利要求1不具备突出的实质性特点和显著的进步，不符合专利法第22条第3款有关创造性的规定。

2. 权利要求2-6为从属权利要求，参见权利要求1的评述，各组分的含量本领域技术人员根据需要通过有限的实验即可得到，片剂是常规的药物剂型。因此，在引用的权利要求不具备创造性的基础上，权利要求2-6不具备专利法第22条第3款规定的创造性。

纸件申请，回函请寄：100088 北京市海淀区蓟门桥西土城路6号 国家知识产权局专利局受理处收
电子申请，应当通过电子专利申请系统以电子文件形式提交相关文件。除另有规定外，以纸件等其他形式提交的文件视为未提交。

3. 权利要求7请求保护包衣片剂。包衣片剂是本领域的普通使用剂型，包衣是包衣片剂的主要辅料之一。各组分的含量本领域技术人员根据需要通过有限的实验即可得到。综上，在对比文件1的基础上结合上述说理得到权利要求请求保护的技术方案对于本领域技术人员而言是显而易见的，权利要求7不具备突出的实质性特点和显著的进步，不符合专利法第22条第3款有关创造性的规定。

4. 权利要求8请求保护片剂。参见权利要求1的评述，各组分的含量本领域技术人员根据需要通过有限的实验即可得到，片剂是常规的药物剂型。综上，在对比文件1的基础上结合上述说理得到权利要求请求保护的技术方案对于本领域技术人员而言是显而易见的，权利要求8不具备突出的实质性特点和显著的进步，不符合专利法第22条第3款有关创造性的规定。

5. 权利要求9请求保护片剂。参见权利要求1的评述，各组分的含量本领域技术人员根据需要通过有限的实验即可得到，片剂是常规的药物剂型。参见权利要求1的评述，只有特定的各层组分、特定含量下制成的两层片剂，才有所述的效果。对比文件2（CN 103491948A，20140101）公开了片剂，可用于治疗HIV。其包含第一层和第二层，其中a)第一层包含利匹韦林HCl且基本上不含富马酸替诺福韦酯；b)第二层包含富马酸替诺福韦酯且基本上不含利匹韦林HCl；以及c)该片剂还包含恩曲他滨。第一层不含恩曲他滨，第二层包含恩曲他滨。其中第一层包含：

成分	片剂的单位配方 (毫克/片)
利匹韦林 HCl	27.5 ± 1.4
微晶纤维素	60.0 ± 3
聚山梨醇酯 20	0.4 ± 0.02
交联羧甲基纤维素钠	16.1 ± 0.8

且第二层包含：

成分	片剂的单位配方 (毫克/片)
恩曲他滨	200 ± 10
富马酸替诺福韦酯	300 ± 15
微晶纤维素	150 ± 7.5
交联羧甲基纤维素钠	60 ± 3.

（参见权利要求22）。对比文件2教导了将片剂中不同活性成分分离在不同层的技术启示，本领域技术人员有动机将化合物与替诺福韦、恩曲他滨分离，并对各组分的含量和片剂总重量进行具体限定。综上，在对比文件1的基础上结合对比文件2和上述说理得到权利要求请求保护的技术方案对于本领域技术人员而言是显而易见的，权利要求9不具备突出的实质性特点和显著的进步，不符合专利法第22条第3款有关创造性的规定。

6. 权利要求10为从属权利要求，参见权利要求1的评述，只有特定的各层组分、特定含量下制成的两

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层片剂，才有所述的效果。本领域技术人员有动机根据需要结合有限的试验对各层分离情况进行具体限定。因此，在引用的权利要求不具备创造性的基础上，权利要求 10 不具备专利法第 22 条第 3 款规定的创造性。

7. 权利要求 11 请求保护一种片剂，权利要求 12-15 为其从属权利要求。各组分的含量本领域技术人员根据需要通过有限的实验即可得到，片剂是常规的药物剂型。根据片剂性能的实际需求，本领域技术人员有动机对片剂的赋形剂种类进行限定。综上，在对比文件 1 的基础上结合上述说理得到权利要求请求保护的技术方案对于本领域技术人员而言是显而易见的，权利要求 11-15 不具备突出的实质性特点和显著的进步，不符合专利法第 22 条第 3 款有关创造性的规定。

8. 权利要求 16 请求保护一种多层片剂，权利要求 17-30 为其从属权利要求。参见权利要求 9-10 的评述，本领域技术人员有动机对各层组成和含量进行具体限定。在片剂组成确定的情况下，药物的溶出释放情况是由其组成决定的固有属性，药物溶出释放的限定对剂型或片剂自身不具备限定作用。综上，在对比文件 1 的基础上结合对比文件 2 和上述说理得到权利要求请求保护的技术方案对于本领域技术人员而言是显而易见的，权利要求 16-30 不具备突出的实质性特点和显著的进步，不符合专利法第 22 条第 3 款有关创造性的规定。

9. 权利要求 31 请求保护一种生产前述权利要求中任一项所述的片剂的方法，权利要求 32-33 为从属权利要求。分别压缩后合并或将第二层压缩到第一层上是本领域制备多层片剂的常规实验手段。综上，在对比文件 1 的基础上结合对比文件 2 和上述说理得到权利要求请求保护的技术方案对于本领域技术人员而言是显而易见的，权利要求 31-33 不具备突出的实质性特点和显著的进步，不符合专利法第 22 条第 3 款有关创造性的规定。

10. 权利要求 34 请求保护通过权利要求 31 所述的方法可获得的第二层。将药物通过压制成片剂是本领域的常规实验手段。综上，在对比文件 1 的基础上上述说理得到权利要求请求保护的技术方案对于本领域技术人员而言是显而易见的，权利要求 34 不具备突出的实质性特点和显著的进步，不符合专利法第 22 条第 3 款有关创造性的规定。

11. 权利要求 35 请求保护通过权利要求 31 所述的方法可获得的第二层。对比文件 2 还公开了：恩曲他滨/富马酸替诺福韦酯掺合物的研磨和掺合 14)通过用于粒径减小的研磨机转移干燥的颗粒和颗粒外赋形剂(交联羧甲基纤维素钠)。15)掺合该混合物。16)向该混合物中加入硬脂酸镁，掺合。压片 17)用双层片压片机将恩曲他滨/富马酸替诺福韦酯最终粉末掺合物，然后将利匹韦林最终粉末掺合物压制成目标重量和硬度（参见说明书第 0182-0187 段）。可见，对比文件 2 公开了权利要求 35 的全部技术特征，权利要求 35 与对比文件 2 属于相同的技术领域，二者能够解决相同的技术问题，达到相同的技术效果。因此，权利要求 35 不具备专利法第 22 条第 2 款规定的新颖性。

12. 权利要求 36 请求保护试剂盒，权利要求 37-38 为从属权利要求。参见在前的评述。试剂盒是本领域的常规产品形式，干燥剂是试剂盒中的常规成分，硅胶是常用的干燥剂。试剂盒的用途是由试剂盒本身的组成的固有属性决定的，对试剂盒用途的限定对产品本身不具备限定作用。综上，在对比文件 1 的基础上上述说理得到权利要求请求保护的技术方案对于本领域技术人员而言是显而易见的，权利要求 36-38 不具备突出的实质性特点和显著的进步，不符合专利法第 22 条第 3 款有关创造性的规定。

13. 权利要求 39 请求保护一种治疗性治疗 HIV 感染的方法。该用途包含了以有生命的人体或动物体为直接实施对象，其目的是治疗疾病。因此，权利要求 35 请求保护的技术方案属于专利法第 25 条第 1 款第（3）

项规定的疾病的治疗方法，不能被授予专利权。

假设权利要求 39 请求保护一种产品在制备治疗 HIV 感染的药物中的用途。参见在前的评述，在对比文件 1 的基础上上述说理得到权利要求请求保护的技术方案对于本领域技术人员而言是显而易见的，权利要求 39 不具备突出的实质性特点和显著的进步，不符合专利法第 22 条第 3 款有关创造性的规定。

14. 权利要求 40 请求保护一种组合物。对比文件 1 公开的内容参见在前的评述，权利要求 40 与对比文件 1 的区别技术特征在于：权利要求 40 加入了赋形剂微晶纤维素和交联羧甲基纤维素钠，限定了各组分的用量。微晶纤维素和交联羧甲基纤维素钠是本领域的常规赋形剂，本领域技术人员有动机根据剂型的实际需求加入合适的赋形剂，并对用量进行限定。综上，在对比文件 1 的基础上上述说理得到权利要求请求保护的技术方案对于本领域技术人员而言是显而易见的，权利要求 40 不具备突出的实质性特点和显著的进步，不符合专利法第 22 条第 3 款有关创造性的规定。

15. 权利要求 41 为从属权利要求。对比文件 2 公开的内容参见在前的评述，本领域技术人员有动机结合对比文件 2 的教导将药物制成多层片剂，并对各层中的活性成分和辅料组成作具体限定。因此，在引用的权利要求不具备创造性的基础上，权利要求 41 不具备专利法第 22 条第 3 款规定的创造性。

二、权利要求 42-51 不符合专利法第 26 条第 4 款的规定

1. 权利要求 42 在权利要求 41 的基础上对各层组分作了进一步的限定。根据说明书的记载：在禁食条件下式 I 化合物以含有两种另外的治疗剂（TAF 和 FTC）的双层片剂制剂 F2 施用时的总暴露量比与含有 TAF 和 FTC（T3）的固定剂量组合片剂共施用的单剂片剂制剂 F1 高约 30%（参见说明书第 0544 页），并且在本申请说明书实施例 1-2 部分，均对 F1 制剂、F2 制剂、F3 制剂的各组分和含量，特别是两层片剂 F2 的各层具体组分和含量进行了明确的限定，只有在两层片剂的各层特定组分、特定含量下制成的两层片剂（F2），才有所述的效果，并且根据实施例 5 和图 3 的记载，使用种类不同的赋形剂来替换 F2 的赋形剂会降低化合物 I 的溶出度，也在此证明片剂的特定组成决定了其性能。而权利要求 42 并没有完整限定各层具体组分和含量，使得限定范围内的任意含量组成的片剂，是否均能用于本发明并达到与之相同或相似的效果，是本领域技术人员难以预测得到的，所以权利要求 42 未以说明书为依据，得不到说明书的支持，不符合专利法第 26 条第 4 款的规定。

同理，权利要求 43-45 都不符合专利法第 26 条第 4 款的规定。

2. 权利要求 46 请求保护一种组合物，其特征部分包含了功能限定的技术特征，参见权利要求 42 的评述，其限定的功能是通过说明书中记载的特定组成、特定含量的双层片剂完成的，本领域技术人员不能明了通过采用说明书中未提到的其他替代方式也能达到类似的药代动力学效果。因此，权利要求 46 未以说明书为依据，得不到说明书的支持，不符合专利法第 26 条第 4 款的规定。

同理，权利要求 47-51 都不符合专利法第 26 条第 4 款的规定。

基于上述理由，本申请目前不能被授予专利权。

如对审查意见有疑问，可通过以下方式进行反馈：（1）本案审查员电话 027-59182839；（2）中心质量监督邮箱 hbzxywzx@cnipa.gov.cn；（3）中心审查业务咨询电话 027-59371999。通过质量监督邮箱反馈的意见陈述书和/或修改文本不具备法律效力，不能代替正式答复。

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审查员姓名:杨琪
审查员代码:216531

2:0401
2021.6

纸件申请，回函请寄：100088 北京市海淀区蓟门桥西土城路 6 号 国家知识产权局专利局受理处收
电子申请，应当通过电子专利申请系统以电子文件形式提交相关文件。除另有规定外，以纸件等其他形式提交的文件视为未提交。

国家知识产权局

检索报告

申请号：202110669916	申请日：20161108	首次检索
申请人：吉利德科学公司	最早的优先权日：20151109	
权利要求项数：51	说明书页数：66040	

申请总体分类号：A61K9/24,A61K9/30,A61K31/5365,A61K31/675,A61P31/18*A61K31/513

检索记录信息：US20142213556A1: 739 ENTXT, (tenofovir alafenamide or TAF) and (emtricitabine or FTC), 语义检索,语义基准:202110669916

CN103491948A: CNTXT 语义检索,语义基准:202110669916

CN102070629A: CNTXT 语义检索,语义基准:202110669916

CN104995198A: 1 ENTXT, WO2014100323/PN

WO2014100323A1: 1 ENTXT, WO2014100323/PN

US20150218359A1: 739 ENTXT, (tenofovir alafenamide or TAF) and (emtricitabine or FTC), 语义检索,语义基准:202110669916

相关专利文献

类型	国别以及代码[31] 检出的文献号	代码[43]或[45] 检出的日期	IPC分类号	相关的段落和/或附图	涉及的权利要求
X	US20142213556A1	20140807	A61K31/4468	说明书第0312、0323段；说明书第0159、0162、0163段	1-8、11-15、34-35、35-08、40

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Y	US20140221356A1	20140807	A61K31/498	说明书第0312、0323段、说明书第0159、0162、0163段	9-10、16-33、41
Y	CN103491948A	20140101	A61K9/20	权利要求 22	9-10、16-33、41
A	CN102670629A	20120919	A61K31/675	全文	1-51
A	CN104995168A	20151021	C07D498/14	全文	1-51
A	WO2014003325A2	20140626	C07D471/06	全文	1-51
A	US20150183789A1	20150115	C07D471/18	全文	1-51

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2016.9

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相关非专利文献

类型	书名（包括版本号和卷号） 期刊或文献名称 （包括卷号和期号）	出版日期 发布日期	作者姓名和工作单位 作者姓名和文献来源	相关页数 相关页数	涉及的权利要求 涉及的权利要求

表单填写说明事项：

1. 应首先检索该申请的IPC分类号或者填写到大组和/或小组层级的分类位置。
2. 期刊或其它资源类载体的名称可使用符合一般公认的国际通用缩写规则的名称。
3. 相关文件的类型说明：
   X：一篇文件单独评价发明的新颖性或进步性；
   Y：与A组合中的另外的1篇文件组合评价发明的进步性；
   A：背景技术文件；
   E：任何单位或个人提申请日同专利局提交的、属于同样的发明创造的专利或专利申请文件；
   P：中间文件，其公开日在申请的申请日与所要求的优先权日之间的文件；
   D：提交申请。

审查员：杨琪
2022年07月19日

审查部门：专利审查协作湖北中心纪律监察审查部

310401
2019.3

TEXT OF THE FIRST OFFICE ACTION

(PCT Application Entering the National Phase)

Application No.: 202110669316

The present application relates to therapeutic compositions for treatment of human immunodeficiency virus. The following examination opinions are provided upon examination.

I. Claims 1-34 and 36-42 do not possess inventiveness under Article 22.3 of the Chinese Patent Law, claim 35 does not possess novelty under Article 22.2 of the Chinese Patent Law, and claim 39 belongs to a non-patentable subject matter under Article 25.1(3) of the Chinese Patent Law.

1. Claim 1 is directed to a solid oral dosage form. **D1 (US2014221356 A1, published on August 7, 2014)** discloses the following: **compounds 42 and 45 (i.e., compounds of Formula I in claim 1)**; and a method of treating or preventing an HIV infection in a human having or at risk of having the infection by administering to the human a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents. The additional therapeutic agent is selected from one or more of: (3) HIV nucleoside inhibitors of reverse transcriptase selected from the group consisting of zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, ±-FTC, D-d4FC, **emtricitabine**, phosphazide, fozivudine tidoxil, apricitibine (AVX754), KP-1461, GS-9131 (Gilead Sciences) and fosalvudine tidoxil (formerly HDP 99.0003); (4) HIV nucleotide inhibitors of reverse transcriptase selected from the group consisting of tenofovir, tenofovir disoproxil fumarate, **tenofovir alafenamide** fumarate (Gilead Sciences), GS-7340 (Gilead Sciences), GS-9148 (Gilead Sciences), adefovir, adefovir dipivoxil, CMX-001 (Chimerix) or CMX-157 (Chimerix). (See the description of D1, paragraphs [0312], [0323], [0159], [0162] and [0163].)

Claim 1 differs from D1 in that claim 1 defines the combination of the compound with tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and with emtricitabine or a pharmaceutically acceptable salt thereof.

As disclosed in the instant description, the use of a fixed dose combinations, e.g., multilayer tablets, may affect the dissolution profile of one or more of the active ingredients within the dosage form, and is therefore likely to have an impact on the in vivo pharmacokinetics of the dosage form (see the description, paragraph [0070]). Also, the examples in the description show the differences in terms of the pharmacokinetics, dissolution and so on between the double-layer tablets F2, F4-F7 containing three components including the compound, tenofovir alafenamide and emtricitabine and the single-component or two-component tablets. However, only the two-layer tablets of specific components of each layer and specific content have said effect. However, claim 1 neither defines the specific number of layers nor defines the specific components and content of each layer, so it is difficult for those skilled in the art to expect whether a tablet of any number of layers can be used in the present invention and achieve the same or similar effect. Based on this, the technical problem actually solved by claim 1 is how to provide a similar pharmaceutical combination.

With regard to the above distinguishing technical features, D1 has disclosed a combination of therapeutic agents, and specifically teaches that the additional therapeutic agent is selected from one or more of: HIV nucleoside inhibitors of reverse transcriptase selected from the group consisting of emtricitabine, and HIV nucleotide inhibitors of reverse transcriptase selected from the group consisting of tenofovir alafenamide fumarate. According to the teaching of D1, those skilled in the art would be motivated to combine the compound of formula I with emtricitabine, and tenofovir alafenamide. As to the pharmaceutically acceptable salt thereof, it is also a conventional used form of the active substance.

In conclusion, it would be obvious for those skilled in the art to arrive at the technical solution of claim 1 based on D1 in combination with the above reasoning. Claim 1 neither has prominent substantive features nor represents notable progress, and therefore does not possess inventiveness under Article 22.3 of the Chinese Patent Law.

2. Claims 2-6 are dependent claims. With reference to the comments on claim 1, the content of each component can be obtained by those skilled in the art through a limited number of experiments as required. A tablet is a conventional pharmaceutical dosage form. Thus, on condition that the preceding claims do not possess inventiveness, dependent claims 2-6 do not possess inventiveness under Article 22.3 of the Chinese Patent Law, either.

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3. Claim 7 is directed to a coated tablet. Coated tablet is a commonly used dosage form in the art. The coating is one of the main excipients of coated tablets. The content of each component can be obtained by those skilled in the art through a limited number of experiments as required. In conclusion, it would be obvious for those skilled in the art to arrive at the technical solution of claim 7 based on D1 in combination with the above reasoning. Claim 7 neither has prominent substantive features nor represents notable progress, and therefore does not possess inventiveness under Article 22.3 of the Chinese Patent Law.

4. Claim 8 is directed to a tablet. With reference to the comments on claim 1, the content of each component can be obtained by those skilled in the art through a limited number of experiments as required. A tablet is a conventional pharmaceutical dosage form. In conclusion, it would be obvious for those skilled in the art to arrive at the technical solution of claim 8 based on D1 in combination with the above reasoning. Claim 8 neither has prominent substantive features nor represents notable progress, and therefore does not possess inventiveness under Article 22.3 of the Chinese Patent Law.

5. Claim 9 is directed to a tablet. With reference to the comments on claim 1, the content of each component can be obtained by those skilled in the art through a limited number of experiments as required. A tablet is a conventional pharmaceutical dosage form. With reference to the comments on claim 1, only a two-layer tablet of a specific composition of each layer and a specific content will have said effect. D2 (CN103491948 A, published on January 1, 2014, also published as WO2012068535) discloses a tablet, which can be used for treating HIV, comprising a first layer and a second layer wherein a) the first layer comprises rilpivirine HCl and is substantially free of tenofovir disoproxil fumarate; b) the second layer comprises tenofovir disoproxil fumarate and is substantially free of rilpivirine HCl; and c) the tablet further comprises emtricitabine. The first layer does not comprise emtricitabine. The second layer comprises emtricitabine. The first layer therein comprises the following:

Ingredient	Unit Formula for Tablets (mg/tablet)
Rilpivirine HCl	27.5 ± 1.4
Microcrystalline Cellulose	60.0 ± 3
Polysorbate 20	0.4 ± 0.02
Croscarmellose Sodium	16.1 ± 0.8

And the second layer comprises the following:

Ingredient	Unit Formula for Tablets (mg/tablet)
Emtricitabine	200 ± 10
Tenofovir disoproxil fumarate	300 ± 15
Microcrystalline Cellulose	150 ± 7.5
Croscarmellose Sodium	60 ± 3.

(See D2, claim 22; corresponding to WO2012068535, claims 1-22.)

D2 provides the technical suggestion of separating different active ingredients in a tablet into different layers. Those skilled in the art would be motivated to separate the compound from tenofovir and emtricitabine, and specifically define the content of each component and the total weight of the tablet. In conclusion, it would be obvious for those skilled in the art to arrive at the technical solution of claim 9 based on D1 in combination with D2 and the above reasoning. Claim 9 neither has prominent substantive features nor represents notable progress, and therefore does not possess inventiveness under Article 22.3 of the Chinese Patent Law.

6. Claim 10 is a dependent claim. With reference to the comments on claim 1, only a two-layer tablet of a specific composition of each layer and a specific content will have said effect. Those skilled in the art would be motivated to specifically define the separation conditions of each layer according to requirements in combination with a limited number of experiments. Hence, on condition that the preceding claim does not possess inventiveness, dependent claim 10 does not possess inventiveness under Article 22.3 of the Chinese Patent Law.

7. Claim 11 is directed to a tablet, and claims 12-15 are dependent claims. The content of each component can be obtained by those skilled in the art through a limited number of experiments as required. A tablet is a conventional pharmaceutical dosage form. Those skilled in the art would be motivated to define the types of excipients for a tablet according to the actual requirements for tablet performance. In conclusion, it would be obvious for those skilled in the art to arrive at the technical solutions of claims 11-15 based on D1 in combination with the above reasoning. Claims 11-15 neither have prominent substantive features nor represent a notable progress, and therefore do not possess inventiveness under Article 22.3 of the Chinese Patent Law.

8. Claim 16 is directed to a multi-layer tablet, and claims 17-30 are dependent claims. With reference to the comments on claims 9 and 10, those skilled in the art would be motivated to specifically define the composition and content of each layer. Where the composition of the tablet is determined, the dissolution release of the drug is an intrinsic property determined by its composition. The definition on the dissolution release of the drug does not have a limiting effect on the dosage form or the tablet itself. In conclusion, it would be obvious for those skilled in the art to arrive at the technical solution of claim 1 based on D1 in combination with D2 and the above reasoning. Claims 16-30 neither have prominent substantive features nor represent a notable progress, and therefore do not possess inventiveness under Article 22.3 of the Chinese Patent Law.

9. Claim 31 is directed to a method of producing a tablet of any one of the preceding claims. Claims 32 and 33 are dependent claims. It is a conventional experimental means in the art to prepare a multi-layer tablet to compress respectively and combine the two layers, or to compress the first layer the second layer onto the first layer. In view of the above, it would be obvious for those skilled in the art to arrive at the technical solution of claims 31-33 based on D1 in combination with D2 and the above reasoning. Claims 31-33 neither have prominent substantive features nor represent a notable progress, and therefore do not possess inventiveness under Article 22.3 of the Chinese Patent Law.

10. Claim 34 is directed to the first layer obtainable by the method of claim 31. It is a conventional experimental means in the art to compress a drug into a tablet. In conclusion, it would be obvious for those skilled in the art to arrive at the technical solution of claim 34 based on D1. Claim 34 neither has prominent substantive features nor represents notable

progress, and therefore does not possess inventiveness under Article 22.3 of the Chinese Patent Law.

11. Claim 35 is directed to the second layer obtainable by the method of claim 31. D2 also discloses the following:

> *Milling and Blending of Emtricitabine/Tenofovir DF Blend*
> *14) Transfer the dried granules and the extragranular excipient (croscarmellose sodium) through a mill for particle size reduction.*
> *15) Blend the mixture.*
> *16) Add magnesium stearate to the mixture and blend. Tableting*
> *17) Compress the emtricitabine/tenofovir DF final powder blend followed by the rilpivirine final powder blend to target weight and hardness on a bilayer tablet press.*

(See the description of D2, paragraphs [0182]-[0187], corresponding to WO2012068535, page 25, paragraph 1.) Accordingly, D2 discloses all the technical features of claim 35. Claim 35 and D2 fall within the same technical field, and both can solve the same technical problem and achieve the same technical effect. Hence, claim 35 does not possess novelty underArticle 22.2 of the Chinese Patent Law.

12. Claim 36 is directed to a kit. Claims 37 and 38 are dependent claims. See previous comments. The kit is a conventional product form in the art, the desiccant is a conventional component in the kit, and the silica gel is a common desiccant. The use of the kit is determined by the inherent properties of the composition of the kit itself. The definition on the use of the kit does not limit the product itself. In conclusion, it would be obvious for those skilled in the art to arrive at the technical solutions of the claims based on D1 by the above reasoning. Claims 36-38 neither have prominent substantive features nor represent a notable progress, and therefore do not possess inventiveness under Article 22.3 of the Chinese Patent Law.

13. Claim 39 is directed to a method of therapeutic treatment of an HIV infection. The use takes a living human or animal body as the direct administration subject for the purpose of treating a disease. Hence, the technical solution of claim 39 is a method for treatment of a disease, which is non-patentable under Article 25.1 (3) of the Chinese Patent Law.

It is assumed that claim 39 is directed to use of a product in the manufacture of a medicament for treating HIV infection. With reference to the comments above, it would be obvious for those skilled in the art to arrive at the technical solution of the claim based on D1. Claim 39 neither has prominent substantive features nor represents notable progress, and therefore does not possess inventiveness under Article 22.3 of the Chinese Patent Law.

14. Claim 40 is directed to a composition. Please refer to the comments for the disclosure of D1. The distinguishing technical features between claim 40 and D1 are as follows: in claim 40, excipients microcrystalline cellulose and croscarmellose sodium are added, and claim 40 defines the amount of each component. The microcrystalline cellulose and croscarmellose sodium are conventional excipients in the art. Those skilled in the art would be motivated to add suitable excipients according to the actual requirements of the dosage form and define the amount thereof. In conclusion, it would be obvious for those skilled in the art to arrive at the technical solution of claim 1 based on D1 and the above reasoning. Claim 40 neither has prominent substantive features nor represents notable progress, and therefore does not possess inventiveness under Article 22.3 of the Chinese Patent Law.

15. Claim 41 is a dependent claim. See the above comments for disclosure of D2. With reference to the teaching of D2, those skilled in the art would be motivated to prepare the drug into a multi-layer tablet, and specifically define the composition of the active ingredient and auxiliary materials in each layer. Hence, on condition that the preceding claim does not possess inventiveness, claim 41 does not possess inventiveness under Article 22.3 of the Chinese Patent Law.

II. Claims 42-51 do not comply with Article 26.4 of the Chinese Patent Law.

1. Claim 42 further defines the composition of each layer on the basis of claim 41. According to the disclosure in the description, the total exposure of the compound of Formula I, under fasted conditions, was approximately 30% higher when dosed in the bilayer tablet formulation F2, containing two additional therapeutic agents (TAF and FTC), compared to single agent tablet formulation F1, co-dosed with a fixed dose combination tablet containing TAF and FTC (F3) (see the description, page 0544). Also, in Examples 1-2 of the instant description, each component and content of the F1 formulation, the F2 formulation and the F3 formulation, especially the specific components and contents of each layer of the two-layer tablet F2 are clearly defined. Only the two-layer tablet (F2) of the specific components of each layer and

specific content would have the stated effect. Also, according to Example 5 and Figure 3, the use of a different kind of excipient to replace the excipient of F2 would reduce the dissolution of Compound I, which also demonstrates that the specific composition of the tablet determines its performance. Claim 42 does not completely define the specific components and content of each layer. Accordingly, it would be difficult for those skilled in the art to predict whether a tablet of any composition and any content in the defined range can be used in the present invention to achieve the same or similar effect. Accordingly, claim 42 is not supported by the description under Article 26.4 of the Chinese Patent Law.

By the same reasoning, claims 43-45 do not comply with Article 26.4 of the Chinese Patent Law.

2. Claim 46 is directed to a composition. The characterizing portion thereof includes a technical feature of functional definition. With reference to the comments on claim 42, the function defined therein is achieved by using a double-layer tablet with a specific composition and a specific content disclosed in the description. Those skilled in the art would not be able to understand that a similar pharmacokinetic effect can also be achieved by using other alternative ways not mentioned in the description. Hence, claim 46 is not supported by the description under Article 26.4 of the Chinese Patent Law.

By the same reasoning, claims 47-51 do not comply with Article 26.4 of the Chinese Patent Law.

Based on the above reasoning, the present application cannot be granted a patent right based on the current documents.

If there are any questions about the examination opinions, the following methods may be used for feedback: (1) call the Examiner of this case at 027-59182839; (2) Center Quality Supervision Email hbzxywzx@cnipa.gov.cn; (3) Center Examination Business Consultation Number 027-59371999. Observations and/or amended documents sent to the Quality Supervision Emailbox have no legal effect and cannot replace formal response.

Examiner's Name: YANG Qi

Examiner's Code: 216531

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발송번호: 9-5-2023-027546139
발송일자: 2023.03.23.
제출기일: 2023.05.23.

수신 서울특별시 종로구 사직로8길 39, 세양빌딩 (내자동) 5층(김.장법률사무소)
양영준 귀하(귀중)

03170

특 허 청
의견제출통지서

출원인	성명	길리애드 사이언시즈, 인코포레이티드 (특허고객번호: 519990290219)
	주소	미국 캘리포니아 94404 포스터 시티 레이크사이드 드라이브 333
대리인	성명	양영준 외 1 명
	주소	서울특별시 종로구 사직로8길 39, 세양빌딩 (내자동) 5층(김.장법률사무소)
발명자	성명	홀, 레이
	주소	미국 94404 캘리포니아주 포스터 시티 레이크사이드 드라이브 333 길리애드 사이언시즈, 인코포레이티드 내
발명자	성명	클랜, 벤자민, 미카
	주소	미국 94404 캘리포니아주 포스터 시티 레이크사이드 드라이브 333 길리애드 사이언시즈, 인코포레이티드 내
발명자	성명	코지아라, 조안나 엠.
	주소	미국 94404 캘리포니아주 포스터 시티 레이크사이드 드라이브 333 길리애드 사이언시즈, 인코포레이티드 내
출원번호		10-2023-7001933
출원일자		2023.01.17.
발명의 명칭		인간 면역결핍 바이러스의 치료를 위한 치료 조성물

1. 이 출원에 대한 심사결과 다음과 같은 거절이유가 있어 특허법 제63조에 따라 이를 통지하오니 의견이 있거나 보정이 필요할 경우에는 상기 제출기일(2023.05.23.)까지 의견(답변, 소명)서[특허법시행규칙 별지 제24호서식] 또는/및 보정서[특허법시행규칙 별지 제9호서식]를 제출하여 주시기 바랍니다.

2. 상기 제출기일(2023.05.23.)을 연장하려는 경우에는 지정기간연장신청을 통해 그 제출기일을 4개월까지 연장할 수 있습니다. 이 경우 연장신청은 1개월 단위로 해야 하며, 필요 시 4개월을 초과하지 않는 범위에서 2개월 이상을 일괄하여 연장신청할 수 있습니다. 불가피한 사유의 발생(하단의 안내참조)으로 4개월을 초과하여 지정기간을 연장받고자 하는 때에는 그 사유를 기재한 소명서를 추가로 첨부해서 연장신청을 해야 합니다.

[심사결과]

☐ 심사 대상 청구항 : 제1항

☐ 이 출원의 거절이유가 있는 부분과 관련 법조항

순번	거절이유가 있는 부분	관련 법조항

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1	청구항 전항	특허법 제29조제2항

[구체적인 거절이유]

1. 이 출원의 청구범위의 청구항 전항에 기재된 발명은 아래와 같이 그 출원 전에 이 발명이 속하는 기술분야에서 통상의 지식을 가진 사람이 쉽게 발명할 수 있는 것이므로 특허법 제29조제2항에 따라 특허를 받을 수 없습니다.

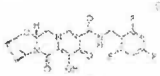
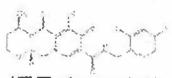
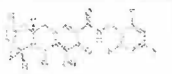
- 아 래 -

특허요건판단 기준일: 2015.11.09.

인용발명 1 : 국제공개공보 WO2015/022351(2015.02.19.)
인용발명 2 : 국제공개공보 WO2014/100323(2014.06.26.)
인용발명 3 : J. Acquir. Immune Defic. Syndr., Vol. 67, No. 1, pp52-58 (2014.09.01.)

1-1. 제1항은 '제약상 허용되는 염으로서, 50 mg의 화학식 I의 화합물; 제약상 허용되는 염으로서, 25 mg의 테노포비르 알라페나미드, 및 200 mg의 엠트리시타빈 또는 그의 제약상 허용되는 염을 포함하는 정제'입니다.

제1항을 인용발명 1 내지 3과 대비하면 다음과 같습니다.

구분	제1항	인용발명 1	인용발명 2	인용발명 3
활성 성분	 의 염	 (돌루테그라비르)	 화합물 42	엘비테그라비르
	테노포비르 알라페나미드의 염	테노포비르 디소프록실 푸마레이트	(-)	테노포비르 알라페나미드 푸마레이트
	엠트리시타빈	엠트리시타빈	(-)	엠트리시타빈
제형	정제	정제	(-)	정제

먼저, 제1항을 인용발명 1과 대비하면, 인테그라아제 억제 활성을 가지는 HIV 억제용 물질, 테노포비르의 전구체 및 엠트리시타빈을 함유하는 정제인 점이 같습니다.
다만, 제1항은 인테그라아제 억제 활성 물질이 ①화학식 I의 화합물인 점, ②테노포비르 전구체로 테노포비르 알라페나미드를 사용하는 점, ③각 활성성분의 함량을 특정한 점에서 인용발명 1과 차이가 있습니다.

①그런데, 인용발명 2에 화학식 I의 화합물이 인테그라아제 억제 물질로 게시되어(화합물 42 참조) 있어 살펴보면, 위 물질이 우수한 HIV 억제 활성, 낮은 세포독성, 양호한 생체 이용률 등 의약품 개발에 적절한 성질을 가지는 물질이라는 것을 알 수 있으므로(표 1 내지 4 등 참조), 이 기술분야에서 통상의 지식을 가진 자(이하 '통상의 기술자'라

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함)가 화학식 I 화합물을 선택하여 인용발명 1의 톨루테그라비르를 치환하는 것에 어려움이 없다고 판단됩니다.

②또한, 인용발명 3에도 인테그라아제 억제 물질인 엘비테그라비르, 테노포비르 전구체 및 엠트리시타빈을 함유하는 정제가 개시되어 있는데, 그 정제는 테노포비르 디소프록실 푸마레이트에 비하여 안전하고 효과적인 테노포비르 알라페나이드 푸마레이트(TAF)를 포함하고 있고, 흡수촉진제인 코비시스타트가 부가될 때 10 mg의 TAF는 25mg의 TAF와 동등하다고 기재되어 있으므로(제53면, 좌측열 단락 2 내지 4 참조), 통상의 기술자가 인용발명 1의 테노포비르 디소프록실 푸마레이트를 TAF로 쉽게 치환할 수 있습니다.

③그리고, 약리효과를 고려하여 단순 반복적인 시험을 통해 그 함량을 도출해 보는 것 또한 이 기술분야에서 통상적으로 시도되는 기술상식입니다.

그리고 제1항의 효과를 살펴보아도, 발명의 설명으로부터 세 종류의 약물을 단일 정제로 제조할 수 있다는 것을 알 수 있을 뿐이고, 통상의 기술자가 인용발명 1 내지 3으로부터 예측하기 어려운 현저히 우수한 항-HIV 효과 등을 나타낸다고 인정할 근거가 없습니다.

따라서 **제1항**은 통상의 기술자가 인용발명 1 내지 3으로부터 쉽게 발명할 수 있는 것입니다.

[첨 부]

첨부1 국제공개공보 WO2015/022351(2015.02.19.) 1부.

첨부2 국제공개공보 WO2014/100323(2014.06.26.) 1부.

첨부3 J. Acquir. Immune Defic. Syndr.. Vol. 67, No. 1, pp52-58 (2014.09.01.) 1부. 끝.

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1. 지정기간연장 인내 : 연장기능기간(4개월)을 초과하여 지정기간을 연장하고자 소멸시킬 특허에 지정기간연장신청서를 제출한 경우 심사관은 아래의 사유에 해당되는지를 판단하여 지정기간연장의 승인 여부 및 연장할 수 있는 기간을 정하여 통지합니다.

【4개월을 초과하여 지정기간을 연장할 수 있는 사유】

① 기간만료일 전 1개월 이내에 출원인변경신고서를 제출한 경우

② 기간만료일 전 1개월 이내에 심사결과통보를 받은 경우(이 경우 심사결과서 등 심사결과를 보정서에 의한 보정기간 허용 2개월 이내에 심사관에게 제출)

추출위 사본도 같이 제출해야 함)

④ 외국정부지사의 출원(1개월 이상 지연된 경우(1개월 추가 연장 가능)

⑤ 질병출산 또는 분쟁출원이 심판이나 소송에 계류 중인 경우

⑥ 기술이유와 관련된 시험 및 결과분석에 기간이 더 필요한 경우

⑦ 기타 불가피하게 기간연장이 필요하다고 인정되는 경우

단, 제3자가 심사청구한 때에는 ①~⑤의 경우만도 불송함

※ 심사청구료 및 발명 인내 : 자동으로 특허청에서 인건재료비지사의 의견서제출기한 만료 전까지 출원을 취하(또는 포기)하는 경우 출원인은 심사청구료의 3분의 1에 해당하는 금액을 반환신청할 수 있습니다.(2021.11.18.부터 시행)

※ 위에서 안내한 후속 절차 및 심층 서식 등에 관한 사항은 특허고객상담센터 ☎1544-8080로, 이 통지서 내용에 대한 사항은 특허청 약품화학심사과 ☎042-481-5490(대표번호)로 문의하시기 바랍니다.

※ 특허로(www.patent.go.kr) 또는 특허청(www.kipo.go.kr) 홈페이지를 방문하시면 심사 심판, 서류 제출 및 절차에 관한 보다 많은 정보를 제공받을 수 있습니다.

(특허청) 우 35208 대전광역시 서구 청사로 189, 4층 (둔산동, 정부대전청사)

2023.03.23.

특허청 화학생명기술심사국

약품화학심사과 심사관 박희진

<< 안내 >>

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Carpmaels & Ransford LLP
One Southampton Row
London WC1B 5HA
ROYAUME UNI

Formalities officer
Thornton, Jean

Date 15-03-2021

Reference	Application No./Patent No.
P072824EP	16798063.0 - 1112 / 3346995
Applicant/Proprietor: Gilead Sciences, Inc.	

BRIEF COMMUNICATION

Subject:
- ☐ Your letter of
- ☐ Our telephone conversation of
- ☐ Communication of
- ☐

Enclosure(s):
- ☐ Letter from the proprietor of the patent of
- ☒ Letter from the opponent O2 of 9.3.21
- ☐ Copy (copies)

Communication:

☐ The documents specified as patent documents and as non-patent literature in this letter are available for inspection via the European Patent Register at **www.epo.org/register.** Should you wish to receive these documents in paper format, they will be supplied to you free of charge if specifically requested on receipt of this communication (OJ EPO 2020, A105).

☐

For the Opposition Division

Europäisches Patentamt • European Patent Office • Office européen des brevets

☒ Registered letter

E+F

ELKINGTON + FIFE

European patent no. 3 346 995
(application no. 16798063.0)
Gilead Sciences, Inc.
Opponent: Dr Richard Cooke

Further submissions

1. Introduction and requests

(01) We are writing in reply to the patentee's response to the notices of opposition. For completeness, we maintain our requests for revocation of the patent in its entirety and for oral proceedings.

(02) All arguments raised in our statement of opposition are maintained, but we will restrict the present submissions to added subject-matter and inventive step.

2. Added subject-matter (Articles 100(c) and 123(2) EPC)

2.1 Claim 1

(03) The patentee apparently accepts that there is no single disclosure in the application that discloses a tablet wherein all the active ingredients are present at the defined doses as pharmaceutically acceptable salts.

(04) According to the patentee, the claim has basis considering the "application as a whole", because other passages disclose compositions including the particular amounts of salts.

(05) However, none of these passages provide a basis for the tablet of claim 1:

- [0010]: defines a particular mass of the dosage form;
- [0012]: defines a coated tablet;
- [0016]: defines a segregated tablet having a particular mass;
- [0048]/[0050]: only refers to emtricitabine;
- [0053]: defines a particular mass of the dosage form;
- [0077]-[0085], [0090]-[0098], [0103]-[0111] and [0264]: define particular plasma concentrations;
- Claim 7: defines coated tablet;
- Claim 8: does not define pharmaceutically acceptable salts of each active ingredient; and
- Claim 9: defines a segregated tablet having a particular mass.

(06) The patentee's arguments that the amounts of the particular salts can be extracted from these disclosures is not in accordance with the gold standard.

(07) Further, these passages do not indicate a general preference for the amounts of the particular salts. On the contrary, the skilled person would understand from the above passages that the application disclosed the particular amounts of pharmaceutically acceptable salts only in combination with additional features, and not at the level of generality defined by the patent as granted.

2.2 Claims 6 and 7

(08) We do not agree with the patentee that claim 16 would not be viewed by the skilled person as an independent embodiment. On the contrary, an independent claim is an independent embodiment.

(09) There is no basis to combine this independent embodiment with the passages of the description referred to by the patentee.

3. Lack of inventive step over D5 (Articles 56 and 100(a) EPC)

3.1 The closest prior art

(10) The patent relates to a fixed-dose tablet comprising:

- 25 mg tenofovir alafenamide or pharmaceutically acceptable salt thereof;
- 200 mg emtricitabine or a pharmaceutically acceptable salt thereof; and
- 50 mg of bictegravir a pharmaceutically acceptable salt thereof.

(11) The patentee argues that the closest prior art can only be a document disclosing the same three active ingredients in a non-fixed dose combination (D37), and cannot be a document relating to a fixed-dose combination in which one of the active ingredients is different (D5).

(12) The patentee is incorrect. The purpose or effect of the patent is to provide a treatment of HIV. D5 has the same purpose or effect, and therefore is a feasible starting point (e.g. T 1742/12, T 967/97 and T 21/06).

(13) Essentially, the patentee's position is that, for a claim directed to a combination of active ingredients, the closest prior art must be a document disclosing that same combination. Again, the patentee is incorrect. It is entirely standard for the closest prior art document to relate to a different combination for the treatment of the same disease.

(14) Therefore, D5 is a possible starting point for the assessment of inventive step and can be taken as the closest prior art.

3.2 The distinguishing feature

(15) As explained in our statement of opposition, the closest embodiment to the claimed invention in D5 is a pharmaceutical composition comprising 50 mg dolutegravir, 200 mg

emtricitabine and 25 mg tenofovir alafenamide (page 19 to 20), which can be combined with D5's most preferred dosage form which is a tablet (page 23).

(16) The patentee argues that this disclosure falls "outside the invention of D5", because D5 requires a specific ratio of dolutegravir to emtricitabine which excludes this composition.

(17) However, the ratio is not an essential feature of D5, which discloses compositions including active ingredient in particular ratios but also in particular amounts (page 1):

> "The present invention concerns a pharmaceutical combination comprising (a) dolutegravir, (b) emtricitabine and (c) tenofovir or a prodrug thereof, wherein preferably the compounds are present in a specific weight ratio and/or in specific amounts, for use as a medicament, preferably in treatment of viral infection/disease such as an HIV infection. Further, the present invention relates to a pharmaceutical composition comprising the pharmaceutical combination and optionally further pharmaceutical excipient(s)." (Emphasis added.)

(18) The preferred embodiment at page 19 is an example of a composition including "specific amounts" of the compounds, and therefore does not fall outside the teaching of D5.

(19) The patentee is also incorrect to argue that the above analysis involves the "stitching together of different passages" (part 5.59 of the patentee's reply). The starting point is the specific "preferred" pharmaceutical composition at page 20, which can be combined with the disclosure of the tablet at page 23 because that is the most preferred dosage form in D5.

(20) Contrary to the arguments of the patentee, the disclosure of the tablet being the preferred dosage form is not restricted to the specific pharmaceutical composition in the preceding paragraph. Rather, this passage makes a general disclosure that the preferred type of composition is a tablet (page 23):

> The pharmaceutical composition of the present invention can be preferably a solid oral dosage form. It is further preferred that the dosage form of the invention is a capsule or a tablet, in particular a tablet.

(21) Therefore, the distinguishing feature is the use of 50 mg bictegravir instead of 50 mg dolutegravir.

3.3 The objective technical problem

(22) The patentee argues that the difficulty with starting from (inter alia) D5 is that this document does not "relate to the same or similar purpose as the patent because they do not relate to a combination of BIC, FTC and TAF". Therefore, according to the patentee, "no relevant objective technical problem can be formulated without appropriate hindsight" (part 5.36 of the patentee's reply).

(23) The patentee's first argument conflates the purpose or effect of the patent with the solution to the objective technical problem. The solution claimed by the patent is the particular combination of tenofovir alafenamide, emtricitabine and bictegravir. The purpose or effect is the provision of a treatment of HIV. Therefore, the test set by the passage of the Case Law book referred to by the patentee (I.D.3.3), which requires that the closest prior relates to the same or a similar problem, is met in the present case because D5 also relates to treatments of HIV.

(24) The patentee's second argument, that no relevant objective technical problem can be defined without hindsight, is also incorrect. The distinguishing feature is the use of 50 mg bictegravir instead of 50 mg dolutegravir. The objective technical problem is defined by determining the effect of changing the integrase inhibitor. The issue of hindsight has no relevance.

(25) The patentee does not have any evidence to demonstrate any effect in changing the integrase inhibitor from dolutegravir to bictegravir, which of course is why the patentee seeks to avoid use of D5 as the closest prior art. However, the fact that the patentee does not have comparative data does not mean that no relevant objective technical problem can be defined, in the sense that it is logically impossible. Rather, it just means that no ambitious problem can be defined because the patentee has not provided any evidence.

(26) Accordingly, the objective technical problem can only be the provision of an alternative pharmaceutical composition for treating HIV.

3.4 Obviousness of the solution

3.4.1 Bictegravir is an obvious alternative HIV integrase inhibitor

(27) We agree with the patentee that the skilled person could also change the other components of the composition. However, this does not detract from the obviousness of changing the integrase inhibitor, and one known integrase inhibitor was bictegravir.

(28) As explained in our statement of opposition, the selection of one from several obvious solutions does not involve an inventive step (Case Law, I.D.9.19.8, 261).

3.4.2 The dose of bictegravir

(29) The patentee argues that the skilled person would not merely use the same dose of bictegravir as was used for dolutegravir in the closest prior art.

(30) Even if this is true, optimising a dose involves routine experimentation (see T 237/15, r 4.6.1).

(31) The patentee argues that this case could be distinguished because the present case relates to a combination and the optimum dose had already been determined.

(32) We do not agree that there is any difference. The appropriate dose of an active ingredient must be determined in the context of a particular formulation, and therefore the skilled person would need to determine the optimum dose for the fixed dose. Even if the skilled person used a higher dose initially, they would reduce that dose without invention until the desired exposure was obtained. Thus, the same routine experimentation would lead to that appropriate dose, as it would in the case of a monoproduct.

4. The auxiliary requests

(33) The patentee accepts that AR1-AR16 do not change issues for inventive step.

(34) AR17 is limited to tenofovir alafenamide hemifumarate which is the preferred form in D5 (page 13, lines 16 to 18) and the sodium salt of bictegravir which is one option for the salt disclosed in D3 (page 14).

(35) AR18 is limited to a coated tablet which is a standard option (D15, page 412).

(36) AR19 to AR25 are limited to multilayer tablets which is a standard option (D15, page 412).

(37) AR26 to AR29 are limited to compositions including arbitrary amounts of standard excipients.

Dr Richard Cooke
European Patent Attorney
Elkington and Fife LLP (ref R79369OP)
04 March 2021

PATENTEE'S RESPONSE TO OPPOSITIONS

EUROPEAN PATENT 3 346 995 B1

GILEAD SCIENCES, INC. | TEVA | RICHARD COOKE | SANDOZ

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1 INTRODUCTION AND REQUESTS

1.1 EP 3 346 995 B1 ("the patent") has been opposed by Teva Pharmaceutical Industries Ltd (O1), Dr Richard Cooke (O2) and Sandoz AG (O3).

1.2 The patent relates to a tablet comprising 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof. The compound of Formula I used to be known by its codename GS-9883 and is now known by its INN, bictegravir.

1.3 The tablets of the invention have been proven to be clinically effective: a representative tablet of claim 1 has been approved in Europe as Biktarvy®, indicated for the treatment of human immunodeficiency virus-1 (HIV-1) in adults. Biktarvy is an orally administered single tablet regimen (STR) containing the combination of 50 mg bictegravir ("BIC") (as bictegravir sodium), 25 mg tenofovir alafenamide ("TAF") (as tenofovir alafenamide hemifumarate) and 200 mg emtricitabine ("FTC").

1.4 The opponents object that the patent adds matter over the application as filed, and lacks novelty and inventive step. All of these objections should be rejected as explained in detail below.

1.5 The patentee's main request is for the oppositions to be dismissed in their entirety and for the patent to be maintained as granted. Oral proceedings are requested if the opposition division intends any other outcome.

1.6 The patentee also encloses auxiliary requests 1-29, and requests permission to make further amendments to the claims (e.g. to delete claims) and/or submit auxiliary requests in response to points raised by the opposition division or the opponents during the proceedings.

1.7 The consolidated numbering provided by the EPO is adopted in this response. The following documents are newly filed by the patentee:

- D35 Phase I study into the potency, safety and pharmacokinetics of multiple doses of BIC
- D36: Biktarvy EPAR Scientific Discussion
- D37: Phase II study comparing BIC (75 mg) + FTC/TAF (200/25 mg) vs DTG (50 mg) + FTC/TAF (200/25 mg)

2 ADDED MATTER

2.1 All opponents argues that the claims of the patent as granted add matter relative to the application as filed. O1 objects to granted claims 1 and 6-10, O2 objects to granted claims 1, 4, 6 and 7, and O3 objects to granted claims 5-7. However, all of the granted claims have basis in the application as filed.

2.2 The granted claims have basis in at least the following parts of the application as filed:

Claim	Basis in application as filed
1	[0008], [0010], [0012], [0016], [0034], [0037], [0048], [0050], [0053], [0077]-[0085], [0090]-[0098], [0103]-[0111], [0264], claims 6-9
2	[0008], claims 2 and 6
3	[0008], [0014], [0034], [0053], [0128], claims 3, 6, 8
4	[0010]-[0011], [0052]-[0053], claims 4-6
5	[0012], [0071], [0210]-[0211], [0279], claim 7
6	[0016], [0020], [0054], [0055], [0117]-[0118], [0126], [0128]-[0262], claims 9-10, 16
7	[0055], claim 17
8	Claim 26
9	Claim 27
10	[0001], [0007], [0282]-[0283], claims 38-39

Claim 1

2.3 Opponents O1 and O2 object that the application as filed does not disclose the doses of BIC, FTC and TAF in a tablet described at the level of generality of granted claim 1. They point out that certain passages of the application as filed (such as claim 2) which include the 50 mg BIC, 200 mg FTC and 25 mg TAF doses also contain additional limitations which are not present in granted claim 1.

2.4 However, it is clear from the application as a whole, in particular the passages cited in the table above, that 50 mg BIC, 200 mg FTC and 25 mg TAF, are disclosed and preferred doses of the APIs in the solid oral dosage forms of the invention, regardless of other limitations to the tablet (e.g. regardless of whether the compounds are present in a pharmaceutically acceptable salt or free base form, and regardless of the specific weight of the tablet).

2.5 Paragraph [0008] is a general teaching of 50 mg BIC or a pharmaceutically acceptable salt, 25 mg TAF or a pharmaceutically acceptable salt and 200 mg FTC. While salts of FTC appear to have been omitted here, the use of 200 mg of salts of FTC together with 50 mg BIC or a pharmaceutically acceptable salt and 25 mg TAF or a pharmaceutically acceptable salt is disclosed throughout the application as filed (see, e.g. [0010], [0012], [0016], [0048], [0050], [0053], [0077]-[0085], [0090]-[0098], [0103]-[0111], [0264], claim 7-9).

2.6 It is irrelevant that some of the passages relied upon for basis comprise additional limitations such as coatings or a particular tablet weight, because together all of these passages show

that the overall teaching of the application as filed is that these are preferred doses of BIC, FTC, TAF, and their pharmaceutically acceptable salts.

2.7 Contrary to the arguments of the opponents, the subject-matter of granted claim 1 is not an unallowable intermediate generalisation because the application as filed clearly does not describe an inextricable link between the doses of the APIs and the other limitations which the opponents focus on. For example, while [0010] refers to a specific total weight but does not refer to a coating, [0012] refers to coating but does not refer to a total weight. It follows that the doses of the APIs are not tied to either the weight or to the presence of a coating. The same logic follows for the other passages relied upon for basis.

2.8 Therefore, claim 1 does not add matter.

Claim 5

2.9 O3 does not deny that the application as filed provides basis for the coated tablets of claim 5 comprising 50 mg BIC or a pharmaceutically acceptable salt, 25 mg TAF or a pharmaceutically acceptable salt and 200 mg FTC or a pharmaceutically acceptable salt.

2.10 However, O3 objects to claim 5 insofar as it depends on claims 3 and 4 on the ground that the application presents coated tablets as an "independent aspect/embodiment" and provides "no link between this aspect/embodiment and any amounts of the sodium salt of bictegravir and tenofovir alafenamide hemifumarate and/or the total weight of the tablet".

2.11 The opponent is taking an overly formalistic view, which focusses on the structure of the claims and their dependencies, rather than the overall disclosure of the application as filed.[1] It is clear from the application as filed, e.g. [0071] and [0279] that tablets of the invention *in general* may be coated and indeed will usually be provided as coated tablets for clinical use. This general teaching is reflected in the example section, in which all the tablets were coated.

2.12 Clearly, coated tablets associated with the subject-matter of original claims 3 and 8, which provide the doses of the sodium salt of BIC and TAF hemifumarate, and original claims 4 and 5 which provide tablet weights, are directly and unambiguously derivable from the application as filed. And as discussed above, the particular dosages of BIC, FTC and TAF and their salts are generally disclosed and preferred throughout the application. The same is true of the particular salt forms of BIC and TAF (see, e.g. [0008], [0014], [0034], [0053], [0128], claims 3, 6, 8).

Claims 6 and 7

2.13 The opponents again place all of their focus on the structure of the claims of the original application at the expense of understanding the actual technical teaching of the application as filed.

[1] See, in particular, EPO Guidelines H-IV, 2: "When assessing the conformity of the amended claims with the requirements of Art. 123(2), the focus should be placed on what is really disclosed to the skilled person by the documents as filed as directed to a technical audience. In particular, the examining division should avoid disproportionally focusing on the structure of the claims as filed to the detriment of the subject-matter that the skilled person would directly and unambiguously derive from the application as a whole. Furthermore, the assessment of the requirements of Art. 123(2) should be made from the standpoint of the skilled person on a technical and reasonable basis, avoiding artificial and semantic constructions (T 99/13)."

2.14 While it is true that original claim 16 (relating to multilayer tablets) was formally independent, the opponents are wrong to argue that this aspect of the invention cannot be combined with other aspects.

2.15 Multilayer tablets are described as generally preferred throughout the application. For example, [0020] states that "a multilayer tablet as a particular type of fixed dose combination may also provide pharmacokinetic and/or stability benefits […]. Accordingly, multilayer tablet comprising […] is provided". Thus, the application provides general teaching regarding the use of multilayer tablets. Further general disclosures are provided at [0054], [0055], [0117], etc, and the discussion regarding multilayer tablets extends until at least [0262]. At paragraph [0126], there is a general disclosure of the use of the specific doses of the three APIs as a multilayer tablet, and at claim 10 there is a clear disclosure of a multilayer tablet containing the doses of APIs found in granted claim 6.

2.16 In view of the general and specific teaching in the application, the multilayer tablet of original claim 16 would not be viewed as an "independent" embodiment, and would instead be directly and unambiguously combined with the particular preferred doses of the three APIs disclosed in the application as filed, as well as the other features claimed in granted claims 2-5. In particular, the specific salts of granted claim 3 are provided at [0128] as a multilayer tablet, a coated tablet of granted claim 5 is provided at [0210] and [0211] as a multilayer tablet.

2.17 Therefore, claims 6 and 7 have basis in the application as filed.

Claims 4 and 8-10

2.18 Claims 4 and 8-10 are objected to only to due to their dependency on claim 1. As there is no added matter in claim 1, there is no added matter in these claims either.

3 PRIORITY

3.1 O2 objects that claims 6-10 as granted are not entitled to priority from P1, while O3 objects that claims 1, 4-7 and 10 as granted are not entitled to priority from P1. However, all of the granted claims are entitled to the P1 priority date.

3.2 The granted claims have basis in at least the following parts of P1:

Claim	Basis in P1
1	[0007], [0009], [0011], [0015], [0033], [0036], [0042], [0048], [0051], [0092], and claims 1, 2, 6, 7 and 9
2	[0007], claim 2
3	[0007], [0013], [0033], [0051], [0094], claim 3
4	(i) [0050], [0051]; (ii) [0009], [0051], claim 4; (iii) [0009], claim 5
5	[0011], [0067], [0183], claim 7
6	[0015], [0019], [0052], [0053], [0085]-[0180] in particular [0085], [0092] and [0094], claim 16
7	[0015], [0053], [0092], [0094], claim 17

8	Claim 26
9	Claim 27
10	[0001], [0006], [0186]-[0187], claims 39, 40

Claim 1

3.3 O3 objects that the doses in claim 1 are intermediate generalisations from P1 because claim 2 and [0007] of P1 are limited to pharmaceutically acceptable salts of BIC, FTC and TAF. However, the patentee explained above in relation to added matter that this is wrong. In particular, it is clear from P1 as a whole that 50 mg BIC, 200 mg FTC and 25 mg TAF, are disclosed and preferred doses of the APIs in the solid oral dosage forms of the invention, regardless of whether the compounds are present in a pharmaceutically acceptable salt or free base form. See, for example, [0009], [0011], [0015], [0033], [0036], [0042], [0048], [0051], [0092], and claims 7 and 9. It is not relevant that some of these passages comprise additional limitations such as coatings or a particular tablet weight, because together these passages show that the overall teaching of P1 is that these doses are preferred for the APIs in free base or salt form in general. Therefore, claim 1 does not represent an unallowable intermediate generalisation of P1.

Claims 4-7 and 10

3.4 Claim 4 was objected to by O3 on the basis that P1 does not disclose a tablet weight of less than 1.0 g, but O3 appears to have overlooked [0050] and [0051].

3.5 O3 objects to claims 5-7 because they are derived from independent claims 7 and 16 of P1, which do not refer back to earlier claims. Similarly, O2 objects to claim 6 by focussing in on original claim 10 without considering other parts of P1. In the same way as discussed above in relation to added matter, the opponents are taking an overly formalistic view which focusses on the structure of the claims and their dependencies, rather than the overall disclosure of P1.

3.6 The claims have priority for the same reasons as they have basis. In particular, in relation to claim 5, it is clear from P1, e.g. [0067] that tablets of the invention will usually be provided as coated tablets (and this is reflected in the fact that the tablets of the examples were all coated). In relation to claims 6 and 7, it is clear from the passages of P1 mentioned above, in particular [0019], [0052]-[0053] and claim 16 that tablets of the invention may generally be provided as multilayer tablets. As noted above, 50 mg BIC, 200 mg FTC and 25 mg TAF, are disclosed and preferred doses of the APIs in all solid oral dosage forms of the invention, regardless of whether the compounds are present in a pharmaceutically acceptable salt or free base form. It is thus wrong for the opponents to argue that there is "no link" between coatings or multilayer tablets, and the doses/tablets of the invention. Indeed, the compositions of the examples provide support for the use of coated tablets and multilayer tablets.

3.7 O2 and O3 also object to claims 7-10 by virtue of their dependency on claim 1 and/or 6. As claims 1 and 6 are entitled to priority, so too are claims 7-10.

D1, D2, D31 and D32 are not prior art under Article 54(2) EPC

3.8 In view of the above, the claims are entitled to the P1 priority date of 9 November 2015.

3.9 As a result, D1 (WO 2015/196116 A1) and D2 (WO 2015/196137 A1) – both of which have an earliest priority date of 20 June 2014 and a publication date of 23 December 2015 – are novelty-only prior art under Article 54(3) EPC.

3.10 D31 (EudraCT number 2015-003988-10) dated 19 November 2015 and D32 (USAN statement) dated 24 February 2016 cited by O3 are not prior art.

4 NOVELTY

4.1 O2 objects that claims 1 and 2 lack novelty over D1, while O3 objects that claims 1, 2 and 10 as granted lack novelty over D1 and D2.

4.2 However, the opponents have not provided a direct and unambiguous disclosure of the tablet of granted claim 1 or 2, in particular comprising 50 mg BIC or a pharmaceutically acceptable salt thereof, 25 mg TAF or a pharmaceutically acceptable salt thereof, and 200 mg FTC or a pharmaceutically acceptable salt thereof, or the use of that particular tablet in treating HIV according to granted claim 10. The combination partners TAF and FTC and their doses have been selected from a range of options (D1 paragraphs 72-97, D2 paragraphs 196-219), the dose of 50 mg BIC has been selected from a range (D1 paragraph 96, D2 paragraph 218) and combined with the disclosure of a tablet (D1 paragraph 65, D2 paragraph 187). Therefore, claims 1 and 2 are not anticipated by D1 and D2.

4.3 None of the opponents objected to granted claims 3-9.

4.4 Therefore, the claims are novel.

5 INVENTIVE STEP

The invention

5.1 The present invention provides a single tablet regimen combining three anti-HIV medicines at safe and effective doses – 50 mg bictegravir (BIC), 25 mg tenofovir alafenamide (TAF), 200 mg emtricitabine (FTC) – that can be administered once daily for the treatment of HIV.

5.2 Realising suitable fixed dose combinations of multiple active pharmaceutical ingredients (APIs) is not straightforward. For example, it is well known that different APIs can be unsuitable for co-formulation due to physicochemical issues. It also well-known that APIs can trigger unexpected interactions with each other when provided together in combination. This means that formulation scientists often face unexpected – and sometimes unsurmountable – difficulties when attempting to provide single tablet regimens.

5.3 The inventors faced these challenges when attempting to provide a combination regimen involving BIC, FTC and TAF. During clinical development, the inventors surprisingly found that the physicochemical and pharmacokinetic properties of BIC are uniquely susceptible to significant and unpredictable changes when in proximity with TAF and FTC in a single tablet.

5.4 BIC was first disclosed in the patentee's patent application D3 alongside many other integrase inhibitors (see compound 42). The patentee identified BIC as a promising candidate

and this compound was then moved forward into development for treatment of HIV-1 in adults.

5.5 During Phase I clinical trials, the potency, safety and pharmacokinetics of multiple doses of BIC were investigated (D35). The completion of this Phase I dose finding study led to the selection of **75 mg BIC** as the optimum dose to be progressed in further clinical trials. This dose was predicted to provide near-maximal virologic response. See, e.g. D36 (Biktarvy EPAR):

> Based on PK/PD analyses, exposure associated with a 75 mg dose of single agent BIC is expected to provide near-maximal virologic response, with a predicted gaiPBS of approximately 20, providing considerable coverage above the target concentration of 162 ng/mL (naIC95).

(page 71)

5.6 Thus, at the priority date, the 75 mg dose of BIC was being tested in Phase II trials as part of a study comparing the efficacy of (i) a combination therapy of **75 mg** BIC (formulated as a single agent tablet) co-administered with a tablet comprising FTC/TAF (200/25 mg) against (ii) a combination therapy of **50 mg** DTG (dolutegravir, another HIV integrase inhibitor) co-administered with FTC/TAF (200/25 mg) (D37). A 50 mg dose of DTG was administered because this was an approved adult dose of DTG at the priority date.

5.7 The real-life situation facing the skilled person at the priority date was the completion of this Phase II trial. Successful completion of this Phase II study would have cemented the selection of the 75 mg dose as the optimal course for development. This is confirmed in, e.g. D36:

> Based on this study, a BIC dose at 75 mg was selected. (page 72)

5.8 Therefore, at the priority date, dose optimisation had resulted in the identification of 75 mg BIC as the most promising candidate for co-administration with FTC/TAF (200/25 mg) and as the most suitable comparator for DTG (50 mg) + FTC/TAF (200/25 mg). Therefore, following the guidance from the prior art, the skilled person would have continued with a 75 mg BIC dose.

Unexpected increase in BIC exposure

5.9 Subsequently, Gilead compared the bioavailability of a fixed dose combination tablet of BIC/FTC/TAF (75/200/25 mg) relative to a 75 mg BIC single agent tablet co-administered with FTC/TAF (200/25 mg). The results from this comparison demonstrated that BIC plasma exposure following administration of the fixed dose combination tablet of BIC/FTC/TAF (75/200/25 mg) was unexpectedly enhanced relative to co-administration of a BIC single agent tablet (75 mg) with F/TAF. It is believed that this unexpected enhancement arose as a result of an unpredicted and unique interaction between BIC and FTC when present in close proximity in a fixed dose combination tablet.

5.10 The above results are provided in the first part of Example 3 of the patent (paragraphs [0319]-[0320]). Formulating 75 mg BIC with TAF and FTC in a single tablet resulted in an unexpected increase in the bioavailability of BIC of around 30% under fasted conditions (see

[0320]).[2] Specifically, a 27% increase in AUC_{inf} and a 31% increase in C_{max} was observed when the three APIs were combined into a single tablet.[3] The exposures of FTC and TAF, on the other hand, were similar between the fixed dose combination tablet and single agent BIC co-administered with FTC/TAF.

5.11 As explained in the patent (paragraph [0321]), based on these surprising results, an unusual step was taken to deviate from the findings of the dose finding clinical study and lower the BIC dose in the fixed dose combination tablet from 75 mg to 50 mg. This was not a routine step since the 50 mg BIC dose had previously been considered but discounted in favour of the 75 mg dose in the dose finding clinical study. Reconsidering the lower 50 mg dose was an anomaly bought about by the unexpected pharmacokinetic behaviour of BIC when in proximity to the other APIs FTC and TAF in the fixed dose combination tablet.

5.12 A new BIC/FTC/TAF tablet with the lower 50 mg dose of BIC was therefore developed. When the bioavailability of this tablet was evaluated against a 75 mg single agent BIC tablet co-administered with FTC/TAF, similar exposures of BIC, FTC and TAF were observed.

5.13 The underlying results are presented in Example 9 of the patent (paragraphs [0351]-[0352]). These results show that the pharmacokinetic properties of the 50 mg BIC fixed dose combination tablet are shown to be equivalent to the higher dose 75 mg BIC single agent tablet co-administered with FTC/TAF.[4] In particular, AUC_{last}, AUC_{inf} and C_{max} %GLSM ratios and 90% CIs for BIC were within the protocol-defined boundary of equivalence. These data were consistent with the modelling of earlier clinical data confirming that these exposures provided anti-HIV antiviral efficacy (patent, [0352]).

5.14 The conclusions discussed above are found in D36:

> Bictegravir AUC_{inf} and C_{max}, for single-dose administration of the B/F/TAF (75/200/25 mg) FDC were approximately 29% and 31% higher, respectively, relative to BIC 75 mg + F/TAF (200/25 mg). Therefore, another FDC formulation was developed that contained BIC 50 mg, FTC 200 mg, and TAF 25 mg. Upon single-dose administration of the B/F/TAF (50/200/25 mg) FDC or BIC 75 mg + F/TAF (200/25 mg) under fasted conditions (also in Study GS-US-141-1233), the geometric least-squares mean ratio and their 90% CIs for the BIC primary PK parameters of AUC_{last}, AUC_{inf}, and C_{max} were 78.46% (73.38, 83.89), 78.56% (73.44, 84.04), and 78.07% (73.41, 83.01), respectively, and were considered by the Applicant as within the protocol-defined boundary of PK equivalence (70% to 143%). Based on these data, the B/F/TAF 50/200/25 mg FDC was chosen for further evaluation in Phase 3 studies.
>
> (page 48)

> Relative bioavailability study GS-US-141-1233 showed higher than expected BIC exposures when BIC was administered as the B/F/TAF 75/200/25 mg FDC (BIC AUC and Cmax increased by 1.27 and 1.31 fold, out of the 80-125 acceptance range for the confidence interval). The dose of BIC was therefore reduced from 75 mg to 50 mg and a new B/F/TAF 50/200/25 mg FDC tablet was developed, showing lower BIC exposures (BIC AUC and Cmax decreased by 0.78 fold as compared to the 75 mg BIC + FTC/TAF) but within the confidence interval that was enlarged (70-143%) to take into account the different BIC doses. An enlarged CI could be accepted given the lack of lower boundary of BIC therapeutic window and the clinical efficacy results.
>
> (page 67)

[2] The pharmacokinetic properties relate to a BIC/FTC/TAF (75/200/25 mg) fixed dose combination tablet (tablet F2) with a 75 mg BIC single agent tablet (tablet F1) co-administered with FTC/TAF (200/25 mg) (tablet F3). The formulations of tablets F1, F2 and F3 are shown in Examples 1, 2 and 2A respectively.
[3] This is reflected in the reported % GLSM ratios for AUC_{inf} and C_{max} of ~127% and ~131% respectively in the table on page 54 of the patent. GLSM = geometric least squares means.
[4] The pharmacokinetic properties relate to a BIC/FTC/TAF (50/200/25 mg) fixed dose combination tablet (tablet F2) compared with a 75 mg BIC single agent tablet (tablet F1) co-administered with FTC/TAF (200/25 mg) (tablet F3). The formulations of tablets F1 and F3 are shown in Examples 1 and 2A respectively; the formulation of tablet F7 is shown in Example 6.

The initial bioavailability study GS-US-141-1233 evaluated two FDC tablet formulations (B/F/TAF (50/200/25 mg) FDC and B/F/TAF (75/200/25 mg) FDC) compared with BIC 75 mg + F/TAF (200/25 mg). According to these results, the FDC containing BIC 50 mg instead of BIC 75 mg was selected for further evaluation in Phase 3 studies, in order to achieve equivalent BIC exposure than with BIC 75 mg single components. (page 72)

5.15 Co-formulating BIC in a fixed dose combination tablet with FTC and TAF therefore allowed a much lower dose of BIC to be used, which as such has the potential to be safer, whilst achieving equivalent bioavailability to the higher dose single agent tablet which was expected to provide near-maximal virologic response. Thus, by lowering the dose of BIC by a third, a more bioequivalent tablet could be obtained without compromising efficacy. This allows for the provision of a **smaller tablet** to patients with the potential to be safer, which in turn improves patient convenience and thus compliance (patent, [0057]).

Unexpected improvement in dissolution

5.16 Studies into the dissolution of BIC *in vitro* indicate that a key driver for the surprising enhancement of bioavailability of BIC from a fixed dose combination tablet comprising BIC, FTC and TAF is the presence of these APIs together in a single tablet formulation.

5.17 Example 4 of the patent compares the BIC dissolution from (i) the BIC/FTC/TAF (75/200/25 mg) fixed dose combination tablet (F2), (ii) a 75 mg BIC single agent tablet (F1) in the presence of FTC/TAF (200/25 mg) (F3), and (iii) a different 75 mg BIC single agent tablet (F3-A), with the same formulation as the BIC layer of the BIC/FTC/TAF bilayer tablet (F2), in the presence of FTC/TAF (F3).

5.18 The results are presented in Figure 1 of the patent and are described in paragraph [0331]. A comparison of the dissolution profiles for the single agent BIC tablet F1 and F3-A (in the presence of FTC/TAF) shows that changing the excipients had little effect on the dissolution of BIC in these experiments. The total percentage dissolution was comparable at ~60% for each experiment (patent, [0331]). Similarly, a comparison of the dissolution profiles of the fixed dose combination tablet F2 and single agent tablet F3-A shows that combining the three APIs into a single tablet F2 surprisingly increased dissolution by approximately 10%. The excipients were kept constant between the BIC single agent tablet F3-A and the BIC layer of the tablet F2. Therefore, in this experiment, the increase in dissolution of F2 appears to have resulted from the presence of all three APIs in a single tablet.

5.19 Example 7 of the patent investigates the dissolution of the 50 mg fixed dose combination tablet (F7), compared to a 50 mg BIC single agent tablet (F8), in the presence of FTC/TAF (200/25 mg) (F3). The results of this experiment are presented in Figure 4. Comparing the dissolution profiles shown in Figure 4, the 50 mg fixed dose combination tablet F7 shows enhanced dissolution of BIC of ~15% compared to the single agent tablet F8.

Unexpected improvement in food effect

5.20 Surprisingly, the BIC/FTC/TAF **50**/200/25 mg tablets of the invention have a **lower food effect** compared to BIC/FTC/TAF **75**/200/25 mg fixed dose combination tablets.

5.21 Food effect bioavailability studies are performed to assess the effects of food on the rate and extent of absorption of a drug when the drug product is administered shortly after a meal (fed conditions), as compared to administration under fasting conditions. The impact of food on

bioavailability is unpredictable. Ideally, variability in exposure after food should be minimised to ensure the patient receives consistent, optimal drug exposure.

5.22 The second part of Example 3 of the patent presents data on the effect of food on the pharmacokinetics of BIC from a 75 mg fixed dose combination tablet. Subjects were administered the BIC/FTC/TAF 75/200/25 mg fixed dose combination tablet (F2) under both fed and fasted conditions. A comparison of the pharmacokinetic parameters AUC_{inf}, AUC_{last} and C_{max} of BIC under these conditions is reported in the table at paragraph [0327] of the patent. Administration of F2 with a high fat meal increased the GLSM values of C_{max} and AUC_{inf} by 27% and 46% respectively, which is reflected in the reported % GLSM ratios of 127% for C_{max} and 146% for AUC_{inf}.

5.23 The bioavailability of the reduced dose BIC/TAF/FTC (50/200/25 mg) fixed dose combination tablet (F7) relative to a 75 mg single agent BIC tablet (tablet F1) co-administered with an FTC/TAF tablet (F3) under fasted conditions is presented in Example 9. The formulation of tablet F7 is shown in Example 6.

5.24 Example 9 presents data showing the effect of food on the pharmacokinetic properties of BIC from a 50 mg fixed dose combination tablet. Subjects were administered the BIC/FTC/TAF 50/200/25 mg fixed dose combination tablet (F7) under both fed and fasted conditions. Two comparisons with fasted conditions were made under two different fed conditions, one in which subjects consumed a high fat meal and one in which subjects consumed a moderate fat meal prior to administration. The results of the comparison of the pharmacokinetic parameters AUC_{inf}, AUC_{last} and C_{max} of BIC under these three conditions are reported in the table in paragraph [0354] of the patent. Compared with administration under fasted conditions, administration of fixed dose combination tablet F7 with a high fat meal increased C_{max} and AUC_{inf} by 13% and 24% respectively (high fat meal) or 20% and 24% respectively (moderate fat meal).[5]

5.25 The tablet below summarises the GLSM ratio (fed/fasted) for C_{max} and AUC_{inf} for the 75 mg and the 50 mg fixed dose combination tablets. It is clear from this table that reducing the dose of BIC from 75 mg to 50 mg reduces the effect of food on the pharmacokinetic properties of BIC: AUC_{inf} GLSM ratio is reduced from 1.46 to 1.27 and C_{max} GLSM ratio is reduced from 1.24 to 1.14.

BIC PK parameter	GLSM Ratio (fed/fasted)
BIC/FTC/TAF 75/200/25 mg (F2)	
AUC_{inf}	1.46
C_{max}	1.27
BIC/FTC/TAF 50/200/25 mg (F7)	

[5] This is reflected in the reported % GLSM ratios of 113% for C_{max} and 124% for AUC_{inf} (high fat meal) or 120% for C_{max} and 124% for AUC_{inf} (moderate fat meal).

AUC_{inf}	1.24
C_{max}	1.14

Therefore, the effect of food on the pharmacokinetic properties of BIC for the 50 mg fixed dose combination tablet is surprisingly reduced compared to the higher dose 75 mg fixed dose combination tablet. This result is also confirmed in D36:

Food effect

GS-US-141-1233 showed that after a high-fat meal, BIC AUC and Cmax were increased by 1.24 and 1.14 fold, and after a moderate-fat meal, BIC AUC and C_{max} were increased by 1.24 and 1.28 fold. This food effect was larger with the 75 mg FDC (1.45 fold increase in AUC and 1.27 fold increase in Cmax).

(pages 49 and 67)

Summary

5.26 In view of the unexpected increase in bioavailability and solubility of BIC when co-formulated with TAF and FTC, the inventors took the unusual step of decreasing the 75 mg dose of BIC that had been identified earlier in development by a third to 50 mg. This allowed the inventors to achieve a **smaller** single tablet regimen **having a desirable PK profile** showing bioequivalence of the three APIs to the 75 mg BIC single agent tablet co-administered with FTC/TAF (200/25 mg) thereby providing near-maximal virologic response, **improved food effects**, and the potential to be safer, which is embodied in the patentee's commercial product Biktarvy®.

5.27 There is simply no teaching in the prior art that would have led the skilled person to the present invention and its improved properties.

5.28 In their oppositions, the opponents have largely overlooked the fact that drugs are formulated on a case-by-case basis, taking into account the relevant information known about the particular APIs. Instead they have pursued hindsight-driven approaches based on combinations of APIs other than the present combination and have made technical assumptions that fail to consider the properties of the specific APIs of the invention. The opponents have also ignored the unexpected findings set out in detail in the patent. As a result, none of the opponents' arguments prejudice the maintenance of the patent.

Closest prior art

5.29 In accordance with the EPO's problem-solution approach, the first step is to identify the closest prior art document. The closest prior art document is "*... that which in one single reference discloses the combination of features which constitutes the most promising starting point for a development leading to the invention.*" (Guidelines, G-VII, 5.1). The primary consideration in selecting the closest prior art is that it should be "*... directed to a similar purpose or effect as the invention ...*" (Guidelines, G-VII, 5.1).

5.30 According to the patent, the purpose of the invention is to provide pharmaceutical formulations suitable for treating viral infections such as HIV including BIC, FTC and TAF ([0001], [0016]) etc.).

5.31 The opponents have proposed various documents as the closest prior art that do not relate to combinations of these three APIs. Given that the skilled person would always start from the specific APIs in question, none of these proposed options are suitable starting points.

5.32 All opponents put forward D5 (WO 2015/022351) as a closest prior art document. However, D5 does not disclose BIC, its structure or any of its properties. Instead D5 exclusively relates to pharmaceutical compositions comprising dolutegravir (DTG), FTC and tenofovir or a prodrug thereof (including TAF). DTG is a different compound to BIC, having a different chemical structure and different properties. Moreover, D5 does not actually disclose any specific formulations comprising DTG, FTC and TAF – it remains entirely general throughout and even the example section remains silent as to the structure of any specific formulation. In the absence of any teaching relating to the combination of BIC, FTC and TAF, and any specific guidance regarding combination tablets, the skilled person would not consider such a document as a promising starting point towards the invention.

5.33 O2 also proposes D10, D12 and D14 as closest prior art documents. These are Business Wire press releases publicising completion of certain steps in the regulatory pathway for three different combination therapies in development by the patentee at the priority date.

5.34 D10 relates to FDA approval of the single tablet regimen Genvoya® (elvitegravir 150 mg / cobicistat 150 mg / emtricitabine 200 mg / tenofovir alafenamide 10 mg). D12 relates to submission of a New Drug Application to the FDA for a single tablet regimen comprising rilpivirine 25 mg / emtricitabine 200 mg / tenofovir alafenamide 25 mg (now known as Odefsey®). D14 relates to EMA validation of a Marketing Authorization Application for a fixed-dose combination of emtricitabine 200 mg / tenofovir alafenamide 10 mg and for emtricitabine 200 mg / tenofovir alafenamide 25 mg (now known as Descovy®).

5.35 Not only do none of D10, D12 and D14 relate to BIC in any way, none provides any concrete formulation details beyond the reference to "single tablet regimen". Again, there is no reason for a skilled person to start from any of these documents as a closest prior art when seeking to arrive at a combination of BIC, FTC and TAF.

5.36 The difficulty in starting with any of D5, D10, D12 or D14 as closest prior art for the problem-solution approach is that they do not relate to the same or similar purpose as the patent because they do not relate to a combination of BIC, FTC and TAF. Following the established practice of the Boards, this means that no relevant technical problem can be formulated without inappropriate hindsight, because without such hindsight any attempt to establish a logical chain of considerations which might lead to the claimed invention inevitably runs into difficulties at the start, for want of a relevant identifiable goal or object. If the relevant problem is not derivable from the alleged closest prior art, the measures for its solution were *a fortiori* not derivable. In other words, the invention is not obvious in the light of such art.[6]

[6] See Case Law of the Boards of Appeal, ninth English language edition ("CLBA"), I.D.3.3 (page 182), in particular the passages referring to:
(a) T686/91 "not mentioning a technical problem which is at least related to that derivable from the patent specification does not normally qualify as the closest prior art for inventive step purposes, however many technical features it may have in common with the subject-matter of the patent concerned";

5.37 Therefore, regardless of whether D5, D10, D12 or D14 is selected as the closest prior art, the invention involves an inventive step.

5.38 As an alternative, O2 also proposes D1 as closest prior art, while O3 also proposes D31 as closest prior art. However, as discussed above, these documents are not prior art under Article 54(2) EPC and so are not citable for inventive step.

5.39 A more realistic starting point is D37, which describes a Phase II clinical trial comparing BIC (75 mg) + FTC/TAF (200/25 mg) against dolutegravir ("DTG") (50 mg) + FTC/TAF (200/25 mg). It relates to a combination therapy involving co-administration of BIC, FTC and TAF and therefore has a similar purpose to the patent.

The claims are inventive over D37

5.40 D37 discloses the Phase II clinical study mentioned above comparing the clinical safety and efficacy of BIC (75 mg) + FTC/TAF (200/25 mg) with DTG (50 mg) + FTC/TAF (200/25 mg). In each arm of the study, the integrase inhibitor (BIC or DTG) was co-administered with a separate tablet comprising FTC/TAF (200/25 mg).

5.41 Compared to D37, the invention differs in that it provides a substantially reduced dose of BIC as part of a single fixed dose combination tablet with 200 mg FTC and 25 mg TAF.

Technical effects and objective technical problem

5.42 As set out above, the invention provides a **smaller** single tablet regimen **having a desirable PK profile, improved food effects** and the potential to be safer. In particular, the invention provides a single tablet regimen with a 50 mg dose of BIC that achieves:

- an effective exposure of BIC, FTC and TAF *in vivo* that is bioequivalent to a higher dose 75 mg single agent tablet co-administered with F/TAF (200/25 mg) thereby providing near-maximal virologic response,
- the potential for improved safety due to the reduced dose of BIC,
- improved patient compliance, resulting from the ability to prepare a smaller tablet due to the lower dose of BIC,
- improved food effects relative to the higher dose 75 mg single tablet regimen (75/200/25 mg) meaning that the bioavailability of BIC from the 50 mg single tablet

(b) T644/97 "a technical problem arising from a "closest prior art" disclosure which was irrelevant to the claimed subject-matter (in the sense that it did not mention a problem that was at least related to that derivable from the patent specification) had a form such that its solution could practically never be obvious, because any attempt by the skilled person to establish a chain of considerations leading in an obvious way to the claimed subject-matter was bound to fail"; and
(c) T835/00 "It was a fatal defect that a prior art disclosure from which no relevant technical problem could be formulated without inappropriate hindsight had been chosen as a starting point for the application of the problem and solution approach, because without such hindsight any attempt to establish a logical chain of considerations which might lead to the claimed invention inevitably ran into difficulties at the start, for want of a relevant identifiable goal or object. If the relevant problem was not derivable from the alleged closest prior art, the measures for its solution were a fortiori not derivable. In other words, the invention was not obvious in the light of such art".

regimen (50/200/25 mg) is less dependent on the consumption of food by a patient, thereby improving the consistency of BIC exposure.

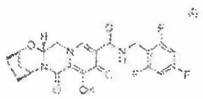
5.43 The objective technical problem is therefore the provision of an effective BIC, FTC, TAF combination therapy which has improved patient compliance, has the potential to be safer, has a desirable PK profile and bioequivalence of the three APIs to a 75 mg single agent BIC tablet co-administered with FTC/TAF (200/25 mg), thereby providing near-maximal virologic response, as well as a reduced food effect.

Non-obviousness

5.44 The relevant consideration is how would – not could – the skilled person have modified the closest prior art in view of the prior art.

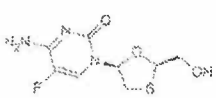
5.45 The prior art did not teach that it would be possible to successfully co-formulate BIC, FTC and TAF into one single tablet. When considering whether it is possible to achieve a pharmaceutically acceptable single tablet regimen, the properties of the APIs in question are particularly pertinent.

5.46 BIC is a potent HIV integrase inhibitor with *in vitro* activity against wild-type HIV-1. It has the following formula:



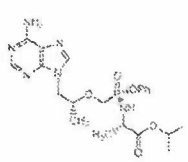
5.47 As discussed in the patent ([0035]-[0036]), BIC is a weak acid with pKa of 8.6. The aqueous solubility of BIC free acid is pH-dependent, with solubility increasing with increasing pH, with a maximum at pH 10.5.The chemical stability of BIC is also pH dependent, with maximum stability at pH 4. Under the Biopharmaceutics Classification System ("BCS"), BIC is a **BCS Class II compound, with low solubility but high permeability**. The preferred form of BIC for use in pharmaceutical formulations of the invention is the sodium salt.

5.48 Emtricitabine is a potent HIV nucleoside reverse transcriptase inhibitor having the following formula:



5.49 FTC is a **BCS class I** compound exhibiting high solubility and high permeability, and degrades by hydrolysis in aqueous solution and to a much smaller degree, in the solid phase.

5.50 TAF is a nucleotide reverse transcriptase inhibitor having the following formula:



5.51 TAF is a **BCS class III** compound exhibiting high solubility but low permeability. The preferred form of TAF for use in pharmaceutical formulations of the invention is TAF hemifumarate.

5.52 One of the most striking aspects of the properties of the three APIs is that each belongs to a different BCS class. BCS classes are used as a tool for design of pharmaceutical formulations, and each different class specifies properties – solubility and permeability – that have different implications for formulation. Given that each API is in a different class, it follows that the APIs have competing characteristics that each imply different, and in some cases conflicting, formulation challenges. In the absence of teaching in the art that it was even possible to make a fixed dose combination tablet of BIC, FTC and TAF, the skilled person would not have a reasonable expectation of successfully solving the objective technical problem.

5.53 Moreover, faced with D37, the skilled person would have attempted to complete the Phase II study comparing BIC (75 mg) + FTC/TAF (200/25 mg) with DTG (50 mg) + FTC/TAF (200/25 mg). The skilled person would know that this trial commenced on the basis of pre-clinical testing and would require authority approval which takes ethical and economical considerations into account (cf T239/16, r. 6.5-6) and would have sought to complete this study.

5.54 Indeed, the results of this trial (from after the priority date) show that the study was successful – BIC (75 mg) + FTC/TAF (200/25 mg) showed similar antiviral effect compared to DTG (50 mg) + FTC/TAF (200/25 mg). Therefore the obvious path for the skilled person would be to continue with 75 mg of BIC. This is reflected in D36:

> For each of the subgroups analysed (age, race, baseline HIV-1 RNA, baseline CD4 cell count, and study drug adherence), there was no difference between the 3 treatment groups in the percentages of subjects with HIV-1 RNA < 50 copies/mL.
>
> At Week 48, mean changes from baseline in HIV-1 RNA and CD4 cell count were similar in both groups.
>
> Based on this study, a BIC dose of 75 mg was selected. (page 72)

5.55 The art provided no reason for the skilled person to consider changing this dose to 50 mg. In particular, there was no pointer in the art to suggest that 75 mg BIC would have higher *in vivo* exposure than expected when co-formulated with FTC and TAF and therefore no teaching that the BIC dose could be reduced without compromising antiviral efficacy.

5.56 There was also no teaching in the art that food effects could be reduced by lowering the BIC dose by a third, and the skilled person could not have predicted this result. Therefore, the skilled person would not know how to solve the objective technical problem starting from D37.

5.57 Therefore, the skilled person seeking to solve the objective technical problem would not have arrived at the claimed solution starting from D37 without an inventive step.

The opponents' attacks starting from D5

5.58 The opponents' attacks in view of D5 as closest prior art are fundamentally flawed. As discussed above, D5 is an inappropriate starting point for assessment of inventive step.

5.59 Rather than relying on a concrete starting point, the opponents have created an artificial starting point within D5 by stitching together disparate passages.[7] Contrary to the assertions of the opponents, D5 does not disclose a single tablet formulation comprising DTG/FTC/TAF (50/200/25 mg).

5.60 D5 generally discloses a "pharmaceutical combination comprising dolutegravir, emtricitabine and tenofovir or a prodrug thereof, wherein preferably the compounds are present in a specific weight ratio and/or in specific amounts, for use as a medicament, preferably in treatment of viral infection/disease such as an HIV infection" (p1, first paragraph).

5.61 The weight ratio of dolutegravir (DTG) and FTC is "1:1 to 1:3" (p2, lines 18-20; p27, claim 1). This specific weight ratio of 1:1 to 1:3 provides the basis for the alleged invention in D5, which requires the amount of FTC being reduced such that the DTG:FTC weight ratio falls within 1:1 to 1:3. Page 3 lines 8-11 of D5 explain that the object of the invention has been solved by a combination "having a specific weight ratio of (a) dolutegravir to emtricitabine (b)".

5.62 The opponents seek to rely on the doses of 50 mg DTG, 200 mg FTC and 25 mg TAF from the list of doses on pages 19-20 of D5. In doing so, they make a hindsight driven selection which ignores the fact that this dose combination contains a DTG:FTC weight ratio of 1:4 and thus falls outside the invention of D5, which is limited to pharmaceutical combinations wherein the weight ratio of dolutegravir to emtricitabine is from 1:1 to 1:3 (see p2, lines 18-20; p15, lines 18-20; p27, claim 1). The skilled person would not consider a hypothetical (*i.e.* not exemplified) embodiment found outside of the core teaching of a prior art document as a promising starting point.

5.63 The opponents then seek to combine the above doses with the disclosure of a "tablet" (p23, lines 7-8, claim 14) to argue that D5 discloses a single tablet comprising 50 mg DTG, 200 mg FTC and 25 mg TAF as a single embodiment.

5.64 However, there is no single embodiment in D5 disclosing a tablet comprising 50 mg DTG, 200 mg FTC and 25 mg TAF. The reference to "tablets" at page 23 lines 7-8 follows on from the previous paragraph (bridging pages 22-23) disclosing a "unit dosage form" of the invention. That unit dosage form is thus limited to particular weights of DTG, FTC and tenofovir or a prodrug thereof, and in particular requires 50-150 mg FTC, i.e. it excludes the use of 200 mg FTC. This interpretation is confirmed by claim 14 of D5, which is similarly limited to the use of 50-150 mg FTC by its dependency on claim 13.

5.65 Therefore, whereas D5 generally provides combinations of DTG, FTC and tenofovir or a prodrug thereof such as TAF (and where the weight ratio of DTG and FTC is 1:1 to 1:3) – or at best a combination of 50 mg DTG, 200 mg FTC and 25 mg TAF – the present invention specifically relates to a fixed dose combination tablet comprising 50 mg BIC or a

[7] In T1194/00, r. 3.1, the Board stated (emphasis added) that the closest prior art must be a concrete disclosure: "The Board is of the opinion that an objective assessment of inventive step starting from the closest prior art implies that the latter has been positively identified and considered (see for example decision T 248/85, OJ EPO 1986, 261). The closest prior art must be unequivocally and clearly defined, at least for the features which are essential for the claimed subject-matter with which said closest prior art is being compared." [...] "The closest prior art should be an entity i.e. a concrete piece of prior art and not a puzzle of features chosen with knowledge of the invention in a catalog of features and assembled together in a post facto approach in order to constitute the most promising starting point to arrive at the claimed invention."

pharmaceutically acceptable salt thereof, 25 mg TAF or a pharmaceutically acceptable salt thereof, and 200 mg FTC or a pharmaceutically acceptable salt thereof.

5.66 The objective technical problem starting from D5 is the provision of a safe and effective anti-HIV combination therapy which can be provided as a single tablet regimen.

5.67 Starting from the 50 mg DTG, 200 mg FTC and 25 mg TAF combination in D5, the skilled person would have attempted to solve the objective technical problem by co-formulating that particular combination into a single tablet.

5.68 There is no suggestion in D5 that the invention in that document extends to compounds other than DTG, FTC and TAF. Even if the skilled person considered changing one or more of these APIs, there is no teaching in D5 that would have led the skilled person to develop a new combination therapy by replacing DTG with another integrase inhibitor, rather than e.g. replacing FTC with a different nucleoside reverse transcriptase inhibitor or replacing tenofovir with a different tenofovir prodrug or a different nucleotide reverse transcriptase inhibitor, or even adding a fourth agent to the composition of D5.

5.69 There is no pointer in D5 towards selecting an integrase inhibitor disclosed in D3, let alone BIC specifically. It is only with unallowable hindsight knowledge of the invention that the opponents argue that the skilled person would select BIC from D3. In particular, O3's suggestion that the skilled person would "search the prior art" for an alternative integrase inhibitor is fundamentally incompatible with the problem-solution approach, which relies on the skilled person taking rational steps on the basis of specific pointers in the prior art, not venturing aimlessly into a research project.

5.70 Based on the BHIVA Guidelines (D7), the opponents argue that the skilled person would have included FTC and TAF in the combination therapy because these are recommended backbone agents. Following the same logic, even if the skilled person had considered replacing DTG with a different integrase inhibitor, they would have selected a recommended agent from D7. According to D7, preferred third agents to accompany tenofovir and emtricitabine are atazanavir, darunavir, dolutegravir, elvitegravir, raltegravir and rilpivirine. Of these, dolutegravir, elvitegravir and raltegravir are integrase inhibitors; BIC is not listed. Therefore, following the BHIVA guidelines, the skilled person looking to replace DTG with a different integrase inhibitor would have used either raltegravir or elvitegravir, not BIC. The opponents cannot pick and choose the parts of the BHIVA Guidelines they wish to rely on (i.e. the use of emtricitabine and tenofovir) while ignoring the parts that do not support their case (i.e. the identity of the third agent).

5.71 In relation to the dose of BIC, the opponents' assertion that the skilled person would simply switch 50 mg DTG for 50 mg BIC is unrealistic.

5.72 The development of a new therapy does not begin with a post-hoc amalgamation of dosages and formulation features known for a different API. Rather, it begins with a consideration of the properties of the particular API being developed.

5.73 In particular, the selection of a suitable dose for an API begins with a consideration of that API's pharmacokinetic and pharmacodynamic properties. The skilled person would not be able to predict these properties and would not be able to extrapolate those properties from one API to another (even if they belonged to the same class of agents). Similarly, arriving at a

suitable formulation of an API begins with consideration of that particular active ingredients' physical and chemical properties. Again, the skilled person would not be able to predict these properties and would not be able to extrapolate them from one API to another (even if they belonged to the same class of agents).

5.74 These steps can be particularly complex for combination therapies. Active ingredients may interact with each other, and with the body, in unexpected ways leading to challenges when establishing suitable dosages and suitable formulations. It is clearly wrong for the opponents to argue that the skilled person would have selected the same dose of BIC as DTG simply because they are both HIV integrase inhibitors.

5.75 As discussed above, it was observed that BIC dissolution and exposure were surprisingly increased when co-administered with FTC and TAF. Ultimately this provided the opportunity to lower the BIC dose in order to provide a smaller tablet, which as such has the potential to be safer, which was bioequivalent to the single agent 75 mg BIC tablet and which had reduced food effects.

5.76 There is, however, no suggestion in D5 of any similar observations when DTG, FTC and TAF are co-administered. On the contrary, D5 states that "The combination of the present invention preferably does not show any significant pharmacokinetic interaction of dolutegravir, emtricitabine and tenofovir" (paragraph bridging p14-15). In view of this teaching, the observed pharmacokinetic changes associated with the present invention would have been highly unexpected to the skilled person at the priority date.

5.77 O3 argues that 50 mg BIC would have been used because the prior art taught the skilled person to use "50 mg of an integrase inhibitor". The opponent bases this on an assertion that "at the priority date the current daily dose of dolutegravir, elvitegravir and raltegravir was 50 mg". This is wrong. The daily dose of elvitegravir was 85 or 150 mg depending on co-administered agents (D21a, p1203, LHC; see also D10), and the daily dose of raltegravir was 800 mg or 1600 mg again depending on co-administered agents (D21a, p1195, RHC). The dose of INSTI therefore differs from as low as 20 mg for DTG in D5 (page 16, lines 15-16) to up to 1600 mg for raltegravir – an 80-fold difference. Therefore, the skilled person knew that the specific dose of an agent (in particular an integrase inhibitor) was highly dependent on the agent used. It cannot simply be extrapolated from one integrase inhibitor to another in the way that the opponents suggest.

5.78 As described above, D37 teaches a Phase II clinical trial in which 75 mg BIC co-administered with FTC/TAF (200/25 mg) is compared against 50 mg DTG co-administered with FTC/TAF (200/25 mg). Therefore, even if the skilled person starting from D5 had considered switching DTG to BIC, they would have selected a 75 mg BIC dose in view of D37.

5.79 O2 relies on T237/15 (r 4.6.1) to argue that dose optimisation involves routine experimentation. However, the present case is distinct from T237/15.

5.80 Unlike T237/15, the present case relates to a combination therapy, which involves more complex dosing challenges than when considering a single active agent. Furthermore, by the priority date, the optimal dose had already been determined in human clinical trials as 75 mg BIC and this dose had been progressed into later stage clinical trials. The inventors'

surprising discovery that the dose could be reduced to 50 mg came later, and was derived from the highly unexpected increase in BIC exposure when co-formulated with FTC and TAF.

5.81 In view of the above, the claims are inventive over D5.

The opponents attacks starting from D10, D12 and D14

5.82 As discussed above, D10, D12 and D14 are press releases relating to fixed dose combination tablets containing TAF and FTC. They do not constitute valid starting points for the assessment of inventive step because they do not relate to BIC, whereas the skilled person seeking to provide a combination dosage form would start from the individual APIs being considered – which necessarily includes BIC in this case – for the reasons discussed above.

5.83 In any event, the claims are inventive starting from any of D10, D12 and D14.

5.84 The objective technical problem starting from D10, D12 or D14 would be the provision of a safe and effective anti-HIV combination therapy which can be provided as a single tablet regimen.

5.85 The solution to this problem is inventive for all the reasons already discussed above.

5.86 Given that D10, D12 and D14 do not provide a specific pointer towards BIC, they certainly do not point towards the addition BIC at a 50 mg dose.

5.87 Indeed, as discussed above, at the priority date D37 taught that the dose of BIC that should be used is 75 mg. Therefore, the skilled person would not have used a lower dose of 50 mg.

5.88 Furthermore, D10, D12 and D14 do not provide any pointer or guidance as to whether it is even possible to achieve a fixed dose combination tablet comprising BIC, FTC and TAF which is pharmaceutically acceptable. They do not even provide any technical details of the tablets which they relate to beyond the doses of the actives and that they are "single tablet regimens", and so the skilled person cannot take any relevant guidance from these documents.

5.89 For all the reasons discussed above in relation to the other closest prior art documents, the claims are inventive over D10, D12 and D14.

O3's criticisms of the Examples in the patent should be rejected

5.90 O3 argues that D27 supports its view that the increased dissolution observed in Example 7 of the patent is not a direct result of the use of a bilayer tablet.

5.91 First, it is noted that the experiment in D27 shows highly variable results which have not been rationalised by the opponent. The dissolution of BIC from both tablets in the first graph on page 5 of D27 reaches about 90%, whereas the dissolution of BIC from both tablets in the second graph on page 5 of D27 only reaches about 80%. This variability is surprising given that the same tablets are allegedly being measured in each experiment. There is no explanation in D27 as to why this variation was observed, and in the absence of such an explanation the relevance of the data in D27 must be seriously questioned.

5.92 Second, even if the results in D27 are taken at face value, they make the patentee's observations that allowed the dose to be reduced from 75 mg to 50 mg even more surprising and unusual. Unlike the opponent's experiment in D27 for a 50 mg tablet, the patentee observed that the dissolution of BIC from the 75 mg fixed dose combination tablet (BIC/FTC/TAF 75/200/25 mg) was higher than a 75 mg BIC single agent tablet, even when the excipients remained essentially constant, and that the bioavailability of BIC from the 75 mg tablet co-administered with FTC/TAF (200/25 mg) was higher than a 75 mg BIC single agent tablet.

5.93 Third, D27 is an *in vitro* result and does not impact on the results in the patent relating to *in vivo* food effect.

5.94 Finally, the exercise performed by O3 in D27 is not a true reflection of how the skilled person would have proceeded in view of the prior art. The experiment is an *ex post facto* dissection of the patentee's commercial bilayer formulation, which the opponent only has knowledge of as a result of the invention described in the patent. It is not the situation that faced the skilled person at the priority date, and therefore it cannot cast doubt on the inventiveness of the claimed dosage form.

6 AUXILIARY REQUESTS

6.1 If the Opposition Division is unable to maintain the patent as granted, it is requested to maintain the patent in the form of one of the enclosed auxiliary claim requests. These amendments address the added matter, priority, novelty, and inventive step objections raised by the opponents.

6.2 The amendments made in the auxiliary requests are summarised below:

#	Key amendment	Intended to address at least the following objections
AR1	Claim 5 made dependent on claim 1 only	Added matter, priority
AR2	Claim 6 made dependent on claim 1 or 3	Added matter, priority
AR3	Claim 6 made dependent on claim 3 only	Added matter, priority
AR4	Claim 6 made dependent on claim 1 only	Added matter, priority
AR5	Salts of emtricitabine deleted from claims 1 and 6	Added matter, priority
AR6	AR1 + AR2	Added matter, priority
AR7	AR1 + AR3	Added matter, priority

AR8	AR1 + AR4	Added matter, priority
AR9	AR1 + AR5	Added matter, priority
AR10	AR1 + AR2 + AR5	Added matter, priority
AR11	AR1 + AR3 + AR5	Added matter, priority
AR12	AR1 + AR4 + AR5	Added matter, priority
AR13	AR2 + AR5	Added matter, priority
AR14	AR3 + AR5	Added matter, priority
AR15	AR4 + AR5	Added matter, priority
AR16	Claim 1 has been amended to introduce the feature of claim 2. As a consequence of this amendment, claims 5 and 6 are made independent	Added matter, priority
AR17	Claim 1 has been amended to introduce the limitation of granted claim 3. As a consequence of this amendment, claims 5 and 6 are made independent	Added matter, priority, novelty, inventive step
AR18	Claim 1 has been amended to introduce the limitation of granted claim 5. As a consequence of this amendment, claim 4 is deleted, and claim 6 is made independent	Added matter, priority, novelty, inventive step
AR19	Claim 1 has been amended to introduce the limitation of granted claim 6	Added matter, priority, novelty, inventive step
AR20	Claim 1 has been amended to introduce the limitation of granted claim 6, claims 4-5 are deleted.	Added matter, priority, novelty, inventive step
AR21	Claim 1 has been amended to introduce the limitation of original claim 10 (claim 10 of P1)	Added matter, priority, novelty, inventive step
AR22	Claim 1 has been amended based on [0124] ([0090] of P1)	Priority, novelty, inventive step
AR23	Claim 1 has been amended based on [0124]-[0126] ([0090]-[0092] of P1)	Priority, novelty, inventive step

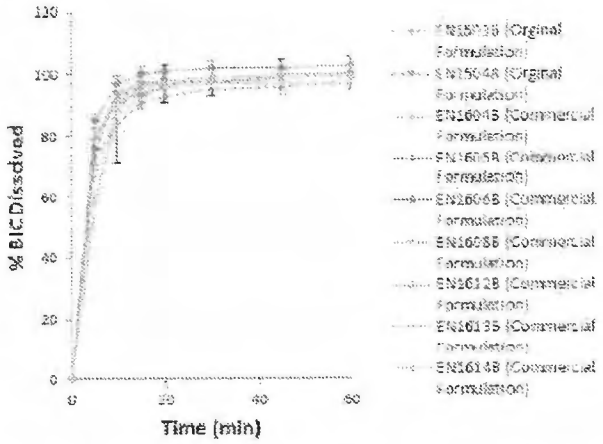
AR24	Claim 1 has been amended based on [0124]-[0126] and [0128] ([0090]-[0092] and [0094] of P1)	Priority, novelty, inventive step
AR25	Claim 1 has been amended to introduce the limitations of granted claims 3 and 6 based on [0128] ([0094] of P1)	Priority, novelty, inventive step
AR26	Claim 1 has been amended based on [0221] ([0169] of P1)	Priority, novelty, inventive step
AR27	Claim 1 has been amended based on [0229]	Novelty, inventive step
AR28	Claim 1 has been amended based on [0234]	Novelty, inventive step
AR29	Claim 1 has been amended based on [0261]	Novelty, inventive step

6.3 To the extent not mentioned in the table above, basis in the application as filed and P1 for the above amendments are already discussed in relation to added matter and priority above. The P1 date is not relied on for AR27-29.

6.4 The features of the independent claims of AR1-29 are not found in D1, D2 or other novelty citations. AR17-29 particularly address the objections made by the opponents in relation to inventive step, in particular to the breadth of the claims, by focussing in on the example compositions.

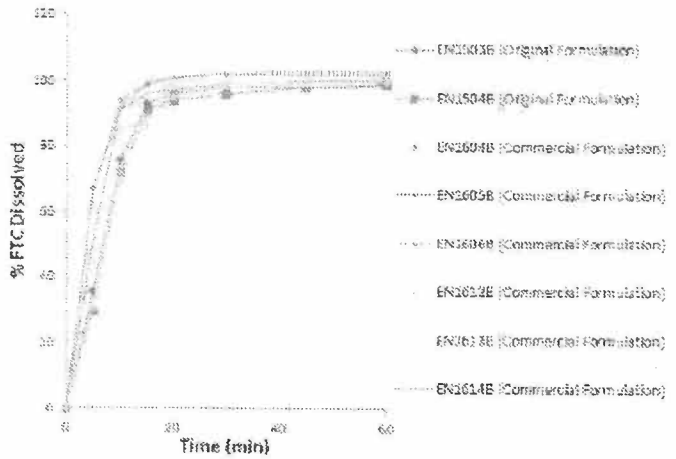
6.5 AR29 particularly relates to the tablet of Example 10, which has an almost identical composition to the tablet of Example 6 (reduction in magnesium stearate content in the FTC/TAF layer from 1.5% w/w to 1.0% w/w). As shown in the dissolution data below, the tablet of Example 10 ("Commercial Formulation" lots in the figures below) and the tablet of Example 6 ("Original Formulation" lots in the figures below) demonstrate similar performance. In particular, BIC, FTC and TAF were found to dissolve rapidly, with ≥85% dissolved at 15 minutes, for all lots manufactured. The dissolution of BIC, FTC and TAF was therefore considered similar without the need for further statistical analysis (in accordance with the European Medicines Agency Guidelines on the Investigation of Bioequivalence).

Figure 1: Dissolution of BIC from B/F/TAF Clinical Tablet Lots as a Function of Formulation



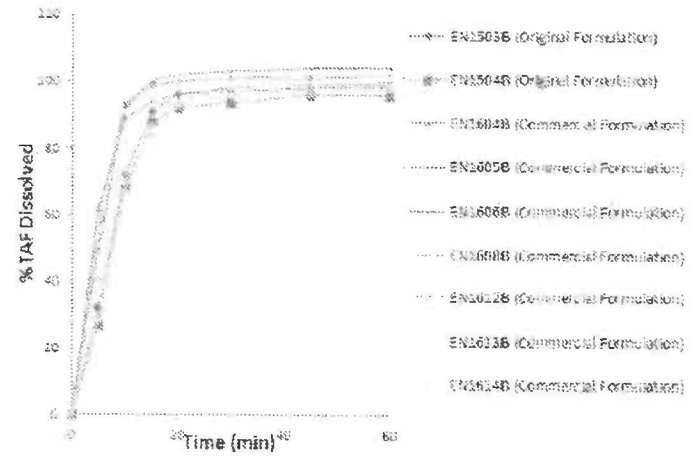
Dissolution method: USP Apparatus II (paddle), 900 mL of 50 mM sodium citrate buffer, pH 3.5, containing 0.25% (w/v) sodium dodecyl sulfate maintained at 37 °C with a paddle speed of 75 rpm.

Figure 2: Dissolution of FTC from B/F/TAF Clinical Tablet Lots as a Function of Formulation



Dissolution method: USP Apparatus II (paddle), 900 mL of 50 mM sodium citrate buffer, pH 5.5, containing 0.25% (w/v) sodium dodecyl sulfate maintained at 37 °C with a paddle speed of 75 rpm.

Figure 3: Dissolution of TAF from B/F/TAF Clinical Tablet Lots as a Function of Formulation



Dissolution method: USP Apparatus II (paddle), 900 mL of 50 mM sodium acetate, pH 5.5, containing 0.25% (w/v) sodium dodecyl sulfate maintained at 37 °C with a paddle speed of 75 rpm.

CARPMAELS & RANSFORD

Chartered Patent Attorneys
European Patent Attorneys
Chartered Trade Mark Attorneys
Solicitors

Carpmaels & Ransford LLP
One Southampton Row
London WC1B 5HA
United Kingdom
T +44 20 7242 8692
F +44 20 7405 4166
E email@carpmaels.com
www.carpmaels.com

European Patent Office
80298 Munich
Germany

Electronically submitted

Your Ref 16798063.0
Our Ref O008281EP
Date 26th August 2022

Re: European Patent No. 3346995
GILEAD SCIENCES, INC.

We write in reply to the summons dated 5th April 2022, and provide our written submissions under Rule 116 EPC ahead of the oral proceedings scheduled for 27-28th October 2022.

I will represent the patentee at the oral proceedings, alongside Paul Kaufman and Hannah Brown of Carpmaels & Ransford LLP. We will speak in English (the language of the proceedings) and request simultaneous interpretation into English should any party intend to use a language other than English.

Requests

Although the patentee does not agree with the arguments of the opponents relating to added matter and priority, we enclose a new set of claim requests.

These requests are being filed purely to streamline the upcoming oral proceedings and to simplify the issues for discussion arising under Articles 123(2) and 87 EPC so that the parties can focus on the key remaining points in dispute. As summarised in the table, each of the new requests corresponds directly to a previous request, with a small number of additional amendments consisting entirely of straightforward deletions of dependent claims/embodiments to address added matter and priority objections. These amendments do not raise new issues. Instead, they reduce the number of issues and requests to be discussed at the oral proceedings.

Provided these requests are admitted, we withdraw the previous requests.

Enclosed request	Correspondence with previous request
Main request	Previous AR1, with deletion of claims 4(i), 6 and 7.
AR1	Previous AR16, with deletion of claims 3(i), 5 and 6.

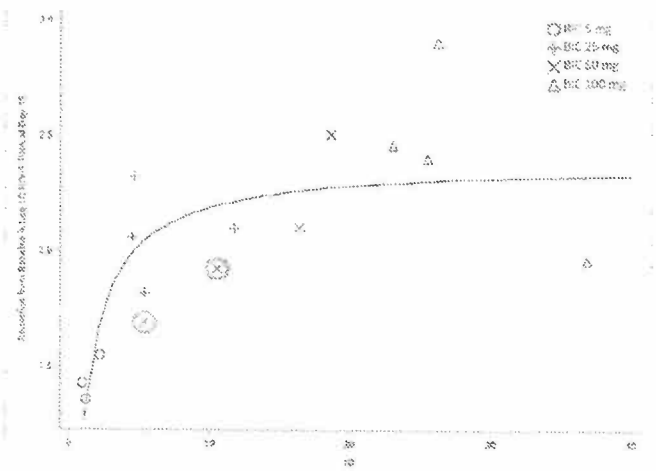
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AR2	Previous AR17, with deletion of claims 2, 4 and 5.
AR3	Previous AR18, with deletion of claims 2-5.
AR4	Previous AR21, with deletion of claims 2-5.
AR5	Previous AR24, with deletion of claims 2-5.
AR6	Previous AR25, with deletion of claims 2-5.
AR7	Previous AR26.
AR8	Previous AR27, with deletion of claims 2 and 3.
AR9	Previous AR28.
AR10	Previous AR29.

Inventive step

In our submission of 24th January 2022, we considered the problem-solution approach starting from D5 as the closest prior art as requested by the Opposition Division in its preliminary opinion. As we explained, there are various reasons why the skilled person would not have arrived at the claimed combination comprising 50 mg bictegravir (BIC), 200 mg emtricitabine (FTC) and 25 mg tenofovir alafenamide (TAF), starting from D5, when trying to solve the objective technical problem.

In particular, we explained on pages 8-10 of our submission that the skilled person would have approached dose selection at the priority date using PK/PD analyses based on early dose ranging studies, and specifically by considering where various doses lie on an exposure-response curve (or "Emax curve"). In the case of bictegravir (BIC), the curve that the skilled person would have obtained (reproduced from our previous submission below) showed that the 50 mg BIC dose lies around the inflection point, indicating potential "underdosing" of a patient, i.e. that the dose was not considered high enough to consistently achieve an optimal virologic response. To safely avoid the inflection point and ensure a near-maximal virologic response, the skilled person would have increased the BIC dose above 50 mg, e.g. to 75 mg.



In view of the opponents' continued reliance on D5 as the closest prior art, which requires comparisons to be made with a different integrase inhibitor dolutegravir (DTG), we enclose D43 and

D44. These documents explain how the 50 mg dose was selected for DTG and thereby provide further confirmation of the way in which the skilled person would have selected integrase inhibitor doses at the priority date.

D43 is a poster presented at the 5th International AIDS (IAS) Conference, one of the world's most influential meetings on HIV research, held on 19-22 July 2009[1]. D44 is a report from the same conference, commenting on the "most important" results presented at the conference, which included the results in D43. These documents relate to the compound having the codename S/GSK1349572 and, as explained in D5 and as was well-known by the priority date, this codename refers to DTG.[2]

D43 explains that the developers of DTG followed the dose selection step set out above, i.e. by performing PK/PD analyses based on data obtained from a dose ranging study. As an important part of these analyses, the exposure-response relationship of DTG at various doses (2 mg, 10 mg, 50 mg) was investigated, as shown in Figure 2 of D43 (reproduced below).

Figure 2. Exposure-Response Relationship of S/GSK1349572

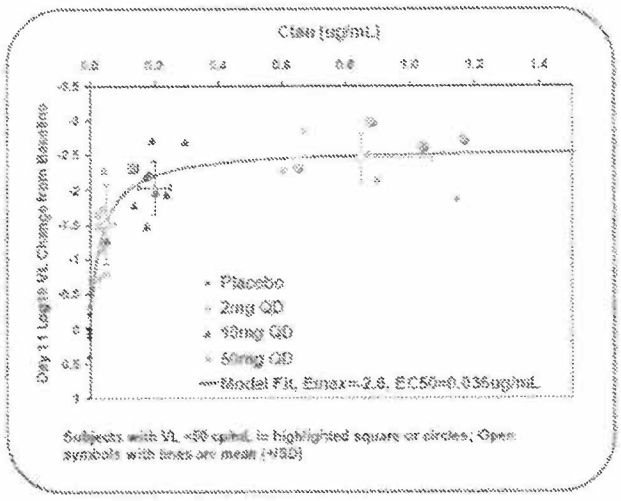


Figure 2 shows that the 2 mg and 10 mg doses fell around the inflection point of the exposure-response curve, implying potential "underdosing" of a patient, in other words these doses were not high enough to achieve a consistent exposure and robust virologic response. The 50 mg dose,

[1] It is possible that the clarity of the poster will be poor once it is scanned and uploaded to the EPO Register. We will happily supply a high-quality version of this document by email to the Opposition Division or the other parties. Please send any requests by email to hannah.brown@carpmaels.com.

[2] See, for example, D5 top of p4: "dolutegravir, also known as S/GSK1349572", D21 p397 middle of right column: "Dolutegravir (DTG)(S/GSK1349572, brand name TIVICAY)" and D21b p505 middle of right column: "The second-generation INSTI dolutegravir (S/GSK1349572)".

however, lay on the flat portion of the curve, implying a maximal virologic response and providing confidence to researchers that the 50 mg DTG dose should be selected.

The critical importance of the position of the 50 mg DTG dose on the exposure-response curve is highlighted in D44 (p1, second paragraph, emphasis added):

> *Importantly the concentration response curve (or Emax curve) in HIV-1 infected patients showed encouraging pharmacodynamics. The 50 mg daily dose was on the flat part of the Emax curve meaning that this dose was likely to give the maximum response possible in patients with integrase-susceptible virus and that there was substantial security at that dose as concentrations achieved were well past the inflection point where activity decreased as concentrations fell.*

D43 and D44 thus confirm the importance of the exposure-response curve in the integrase inhibitor dose selection process.

By extension, D43 and D44 also support our position that the opponents are simply wrong to argue that the skilled person would have selected 50 mg as the appropriate BIC dose based on the fact that D5 disclosed a 50 mg DTG dose. As the exposure-response curves for BIC and DTG reveal, the PK/PD relationship of BIC and DTG are considerably different. For example, as explained above, while 50 mg DTG falls on the flat part of the curve away from the inflection point and was therefore progressed to the next stage of development, 50 mg BIC falls on the inflection point and would therefore not have been taken forward by the skilled person because this could indicate potential "underdosing".

Indeed, D43 is clear that "*Antiviral activity for INIs* [integrase inhibitors] *is exposure driven*" (see Conclusions section), so the skilled person would undoubtedly have placed great weight on the exposure-response curve when selecting an integrase inhibitor dose. Therefore, to avoid potential underexposure and to ensure a consistent exposure and robust virologic response, the skilled person would have increased the BIC dose, e.g. to 75 mg, to ensure that it fell beyond the inflection point on the exposure-response curve (and this is exactly what Gilead did, as explained in D36 at p71).

Therefore, the skilled person would not have selected the 50 mg BIC dose, and would have been surprised that the BIC dose could, in fact, be lowered to 50 mg when combined with 200 mg FTC and 25 mg TAF while maintaining near-maximal virologic response to BIC. The skilled person would also have had no expectation that the use of this dose of BIC in the claimed tablet would result in a dosage form that provides minimised food effects, and which has an improved resistance profile and improved forgiveness and barrier to resistance in a real-world setting (i.e. under conditions of suboptimal adherence). For these reasons, and for the further reasons set out in our previous submissions, the claimed invention involves an inventive step.

Yours faithfully,

// ELECTRONICALLY SIGNED AND SUBMITTED //

HOGGETT, Christopher James
Carpmaels & Ransford LLP Professional Association No. 182

Encl. Amended requests
D43 and D44

발송번호: 9-5-2021-100512211
발송일자: 2021.12.23.
제출기일: 2022.02.23.

수신 서울특별시 종로구 사직로8길 39, 세양빌딩 (내자동) 5층(김.장법률사무소)
양영준 귀하(귀중)

03170

특 허 청

의견제출통지서

출원인	성명	길리애드 사이언시즈, 인코포레이티드 (특허고객번호: 519990290219)
	주소	미국 캘리포니아 94404 포스터 시티 레이크사이드 드라이브 333
대리인	성명	양영준 외 1명
	주소	서울특별시 종로구 사직로8길 39, 세양빌딩 (내자동) 5층(김.장법률사무소)
발명자	성명	홈, 레이
	주소	미국 94404 캘리포니아주 포스터 시티 레이크사이드 드라이브 333 길리애드 사이언시즈, 인코포레이티드 내
발명자	성명	콜맨, 벤자민, 미카
	주소	미국 94404 캘리포니아주 포스터 시티 레이크사이드 드라이브 333 길리애드 사이언시즈, 인코포레이티드 내
발명자	성명	코지아라, 조안나 엠.
	주소	미국 94404 캘리포니아주 포스터 시티 레이크사이드 드라이브 333 길리애드 사이언시즈, 인코포레이티드 내
출원번호		10-2020-7025458
출원일자		2020.09.03.
발명의 명칭		인간 면역결핍 바이러스의 치료를 위한 치료 조성물

1. 이 출원에 대한 심사결과 다음과 같은 거절이유가 있어 특허법 제63조에 따라 이를 통지하오니 의견이 있거나 보정이 필요할 경우에는 상기 제출기일(2022.02.23.)까지 의견(답변, 소명)서[특허법시행규칙 별지 제24호서식] 또는/및 보정서[특허법시행규칙 별지 제9호서식]를 제출하여 주시기 바랍니다.

2. 상기 제출기일(2022.02.23.)을 연장하려는 경우에는 지정기간연장신청을 통해 그 제출기일을 4개월까지 연장할 수 있습니다. 이 경우 연장신청은 1개월 단위로 해야 하며, 필요 시 4개월을 초과하지 않는 범위에서 2개월 이상을 일괄하여 연장신청할 수 있습니다. 불가피한 사유의 발생(하단의 안내참조)으로 4개월을 초과하여 지정기간을 연장받고자 하는 때에는, 그 사유를 기재한 소명서를 추가로 첨부해서 연장신청을 해야 합니다.

[심사결과]

☐ 심사 대상 청구항 : 제1항

☐ 이 출원의 거절이유가 있는 부분과 관련 법조항

순번	거절이유가 있는 부분	관련 법조항

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1	청구항 제1항	특허법 제29조제2항
2	청구항 제1항	특허법 제42조제4항제2호

[구체적인 거절이유]

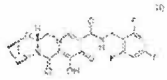
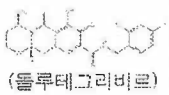
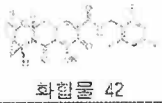
1. 이 출원의 청구범위의 청구항 제1항에 기재된 발명은 아래와 같이 그 출원 전에 이 발명이 속하는 기술분야에서 통상의 지식을 가진 사람이 쉽게 발명할 수 있는 것이므로 특허법 제29조제2항에 따라 특허를 받을 수 없습니다.

- 아 래 -

인용발명 1 : 국제공개공보 WO2015/022351(2015.02.19.)
인용발명 2 : 국제공개공보 WO2014/100323(2014.06.26.)
인용발명 3 : J. Acquir. Immune Defic. Syndr., Vol. 67, No. 1, pp52-58 (2014.09.01.)

1-1. 제1항은 '화학식 I의 화합물 또는 그의 제약상 허용되는 염', '테노포비르 알라페나미드 또는 그의 제약상 허용되는 염' 및 '엠트리시타빈 또는 그의 제약상 허용되는 염'을 포함하는 '고체 경구 투여 형태의 용도'입니다.

제1항을 인용발명 1 내지 3과 대비하면 다음과 같습니다.

구분	제1항	인용발명 1	인용발명 2	인용발명 3
활성 성분		 (돌루테그라비르)	 화합물 42	엠비테그라비르
	테노포비르 알라페나미드의 염	테노포비르 디소프록실 푸마레이트	(-)	테노포비르 알라페나미드 푸마레이트
	엠트리시타빈	엠트리시타빈	(-)	엠트리시타빈
제형	고체 경구 투여 형태	정제	(-)	정제

먼저, 제1항을 인용발명 1과 대비하면, 인테그라아제 억제 활성을 가지는 HIV 억제용 물질, 테노포비르의 전구체 및 엠트리시타빈을 함유하는 제형인 점이 동일합니다.
다만, 제1항은 인테그라아제 억제 활성 물질이 화학식 I의 화합물인 점 및 테노포비르 전구체로 테노포비르 알라페나미드를 사용하는 점에서 인용발명 1과 차이가 있습니다.

그런데, 인용발명 2에 화학식 I의 화합물이 인테그라아제 억제 물질로 개시되어(화합물 42 참조) 있어 살펴보면, 위 물질이 우수한 HIV 억제 활성, 낮은 세포독성, 양호한 생체 이용률 등 의약품 개발에 적절한 성질을 가지는 물질이라는 것을 알 수 있으므로(표 1 내지 4 등 참조), 이 기술분야에서 통상의 지식을 가진 자(이하 '통상의 기술자'라 함)가 화학식 I 화합물을 선택하여 인용발명 1의 돌루테그라비르를 치환하는 것에 어려움이 없다고 판단됩니다.

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또한, 인용발명 3에도 인테그라이제 억제 물질인 엘비테그라비르, 테노포비르 전구체 및 엠트리시타빈을 함유하는 정제가 게시되어 있는데, 그 정제는 테노포비르 디소프록실 푸마레이트에 비하여 안전하고 효과적인 테노포비르 알라페나이드 푸마레이트(TAF)를 포함하고 있고, 흡수촉진제인 코비시스타트가 부기될 때 10 mg의 TAF는 25mg의 TAF와 동등하다고 기재되어 있으므로(제53면, 좌측열 단락 2 내지 4 참조), 통상의 기술자가 인용발명 1의 테노포비르 디소프록실 푸마레이트를 TAF로 쉽게 치환할 수 있습니다.

그리고 제1항의 효과를 살펴보아도, 발명의 설명으로부터 세 종류의 약물을 단일 정제로 제조할 수 있다는 것을 알 수 있을 뿐이고, 통상의 기술자가 인용발명 1 내지 3으로부터 예측하기 어려운 현저히 우수한 항-HIV 효과 등을 나타낸다고 인정할 근거가 없습니다.

따라서 제1항은 통상의 기술자가 인용발명 1 내지 3으로부터 쉽게 발명할 수 있는 것입니다.

2. 이 출원은 청구범위의 청구항 제1항의 기재가 아래에 지적한 바와 같이 불비하여 특허법 제42조제4항제2호에 따른 요건을 충족하지 못하므로 특허를 받을 수 없습니다.

- 아 래 -

제1항은 청구항의 말미를 '용도'로 기재하고 있어서 특허법제2조에서 정의하고 있는 발명의 종류인 물건, 방법, 제조방법의 발명 중 어느 것에도 해당하지 않아서 발명이 보호받고자 하는 사항을 명확하고 간결하게 기재하지 않은 것입니다('의약용도'를 청구하는 경우에는 이 기술분야에서 통상적으로 사용되는 ' ~ 를 유효성분으로 포함하는, ~를 치료하기 위한 약학적 조성물'과 같이 기재하여야 합니다).

[첨 부]
첨부1 국제공개공보 WO2015/022351(2015.02.19.) 1부.
첨부2 국제공개공보 WO2014/100323(2014.06.26.) 1부.
첨부3 J. Acquir. Immune Defic. Syndr., Vol. 67, No. 1, pp52-58 (2014.09.01.) 1부.
끝.

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1002
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2021.12.23.

특허청 화학생명기술심사국

약품화학심사과 심사관 곽희찬 곽희찬

<< 안내 >>

1. 지정기간연장 안내 : 연장가능기간(4개월)을 초과하여 지정기간을 연장하고자 소명서를 첨부하여 지정기간연장신청서를 제출한 경우 심사관은 아래의 사유에 해당되는지를 판단하여 지정기간연장의 승인 여부 및 연장할 수 있는 기간을 정하여 통지합니다.
【4개월을 초과하여 지정기간연장을 할 수 있는 사유】
① 기간만료 전 1개월 이내에 최초로 대리인을 선임하거나 선임된 대리인 모두를 해임·변경한 경우
② 기간만료 전 1개월 이내에 출원인변경신고서를 제출한 경우
③ 기간만료 전 2개월 이내에 외국특허청의 심사결과를 받은 경우로서 동 심사결과를 보정서에 반영하고자 하는 경우(이 경우 신청서 제출 시 해당 심사결과 사본 및 그 기초가 된 청구범위 사본도 같이 제출해야 함)
④ 의견제출통지서의 송달이 1개월 이상 지연된 경우(1개월 추가 연장 가능)
⑤ 원출원 또는 분할출원이 심판이나 소송에 계류 중인 경우
⑥ 거절이유와 관련된 시험 및 결과측정에 기간이 더 필요한 경우
⑦ 기타 불가피하게 기간연장이 필요하다고 인정되는 경우
단, 제3자가 심사청구한 때에는 ①~⑤의 경우라도 불승인

※ 심사청구료 일부 반환 안내 : 처음으로 통지되는 의견제출통지서의 의견서제출기한 만료 전까지 출원을 취하(또는 포기)하는 경우 출원인은 심사청구료의 3분의 1에 해당하는 금액을 반환신청할 수 있습니다.(2021.11.18.부터 시행)

※ 위에서 안내한 후속 절차 또는 신청 서식 등에 관한 사항은 특허고객상담센터 ☎1544-8080로, 이 통지서 내용에 대한 사항은 특허청 ☎042-481-3327(담당심사관 곽희찬)로 문의하시기 바랍니다.

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(특허청) 우 35208 대전광역시 서구 청사로 189, 4동 (둔산동, 정부대전청사)

TER MEER STEINMEISTER & PARTNER PATENTANWÄLTE mbB

GERMAN & EUROPEAN
PATENT ATTORNEYS
Dipl.-Chem. Dr. Christian Hollatz
Dipl.-Ing. Jörg Riemann
Dipl.-Chem. Dr. Bernd Aechter
Dipl.-Phys. Dr. Julia Meil
Dipl.-Chem. Dr. Luigi Rumi
Dipl.-Ing. (FH) Stefan Manzer, M.Sc.
Dipl.-Chem. Dr. Ingo Ortel
Apothekerin Dr. Veronika Müller
Dipl.-Biochem. Dr. Markus Ackermann
Dr. Jonas Tholemann, M.Sc.
Claudia Schwartzkopff, M.Sc.
Dipl.-Phys. Frank Müller*
Dipl.-Phys. Dr. Wolfgang Söker*

EUROPEAN PATENT ATTORNEY
Abhishek Tewary, M.Sc.

Consultants:
Dipl.-Ing. Gebhard Merkle
Manfred Wiebusch*

Ter Meer · Steinmeister & Partner · Nymphenburger Straße 4 · 80335 München

Nymphenburger Straße 4
Zugang Dachauer Straße 63
80335 MÜNCHEN

Telefon: (089) 72 98 960-0
Telefax: (089) 72 98 960-20
www.termeer.de
Registergericht: AG München PR1207
VAT Reg. No: DE 130 747 219
St.-Nr./ Tax No: 143/573/60894

European Patent Office
Bob-van-Benthem-Platz 1
80469 München

Opposition against EP 3 346 995 (16 798 063.0)
"Therapeutic compositions for treatment of Human Immunodeficiency Virus"
Patentee: Gilead Sciences, Inc.
Opponent: Sandoz GmbH

23.12.2021
Ae/VM/vb
aechter@termeer.de

In response to the preliminary opinion dated June 24, 2021, as well as patentee's response to the oppositions dated January 11, 2021, the following is submitted.

1. Introduction

The present submission is not intended to comprehensively address all issues of the case. Instead, in reply to the proprietor's submission dated January 11, 2021, and the preliminary opinion of the Opposition Division dated June 24, 2021, present submission merely emphasises some issues of particular relevance for the preparation of the oral proceedings.

To the extent that objections raised previously are not discussed herein, they are expressly maintained. In addition, the present opponent reserves the right to comment on all grounds for opposition, in particular during the oral proceedings.

2. Requests

The opponent's requests currently on file are maintained. In particular, revocation of the opposed patent in its entirety is requested.

* Büro Bielefeld: Artur-Ladebeck-Str. 51, 33617 BIELEFELD
Telefon: (0521) 914 940 Telefax: (0521) 914 94 20

3. Documents

The following additional document is referred to in this submission in order to address specific issues in reply to the preliminary opinions or patentee's arguments:

D40 Experimental Report dated December 22, 2021

Experimental report D40 addresses patentee's allegation that the dissolution of BIC from a 75 mg fixed dose combination (FDC) tablet was higher than from a 75 mg BIC single agent tablet and the consideration that the amount of bictegravir was to be linked to an unexpected technical effect (patentee's submission dated January 11, 2021, para. 5.92 and preliminary opinion of the OD dated June 24, 2021, p. 12, 2nd para.).

2. Patentee's Obtained Enhanced BIC Dissolution Does NOT Have its Origin in Its Formulation as a BIC, FTC and TAF FDC-Tablet

2.1 The Allegation of the Patentee

In its reply to the notices of oppositions, the patentee states that when the excipients remain essentially constant, then the dissolution of BIC from a 75 mg triple agent FDC tablet is supposedly higher than from a 75 mg BIC single agent tablet. This finding would be surprising and unusual, in particular, as the experiments of D27 show that there is no difference in BIC dissolution of 50 mg triple agent FDC tablet and 50 mg BIC single agent tablet (patentee's submission dated January 11, 2021, para. 5.92).

2.2 There is No Difference in BIC Dissolution of 75 mg FDC-tablet and a 75 mg BIC-Monolayer Tablet

In order to verify the allegation of the patentee, the following experiment was carried out as summarized in the experimental report (D40):

First of all, the FDC/bilayer formulation F2 according to example 2 of the opposed patent was prepared and labelled as 031X-T02 (D40, section 1.1). In addition, a BIC single agent tablet was prepared, wherein the composition of the tablet corresponds to the composition of the BIC-layer of F2 which in turn corresponds to tablet formulation F3-A of example 4 of the opposed patent. The single agent BIC tablet was labelled as 028X-T02 (D40, section 1.2). Further, a FTC/TAF tablet was prepared, wherein the composition of the tablet corresponds to the composition of the FTC/TAF layer of F3 according to example 2A of the opposed patent. The FTC/TAF tablet was labelled as 026X-T01 (D40, section 1.5).

The compositions of 031X-T02, 028X-T02 and 026X-T01 are depicted in the table below:

Ingredient	031X-T02 (Bilayer)		028X-T02 (single BIC)	026X-T01 (FTC/TAF)
	Na-BIC-Layer	FTC/TAF-Layer	Na-BIC	FTC/TAF
Na-Bictegravir	78.7		78.7	
Emtricitabine (FTC)		200		200
Tenofovir Alafenamide Hemifumarate (TAF)		28.1		28
MCC (intra-granular + extra-granular)	247.8 (212.5+35.3)	113.1 (113.1+0)	247.8 (212.5+35.3)	88.7 (88.7+0)
Croscarmellose Sodium	21.2	30.2	21.2	28.0
Magnesium Stearate (intra-granular + extra-granular)	5.3 (2.65+2.65)	5.7 (2.83+2.83)	5.3 (2.65+2.65)	5.2 (2.6+2.6)
Layer Weight	353	377.06	353	349.90
Tablet Total Weight	**730.06**		**353**	**377.1**

As apparent from the table above, the evaluated tablets only differ in a FDC bilayer formulation comprising BIC/FTC/TAF (031X-T02) versus a monolayer formulation comprising the active agents BIC (028X-T02) and FTC/TAF (026X-T01).

In a second step, the dissolution of BIC of 031X-T02 was compared with 028X-T02 in the presence of 026X-T01, measured using USP Apparatus II, in 250 mL of pH 6.5 FaSSIF at 37°C and paddle speed of 100 rpm (D40, section 2).

The results of the BIC dissolution are depicted in the following figure (**Figure 1**):

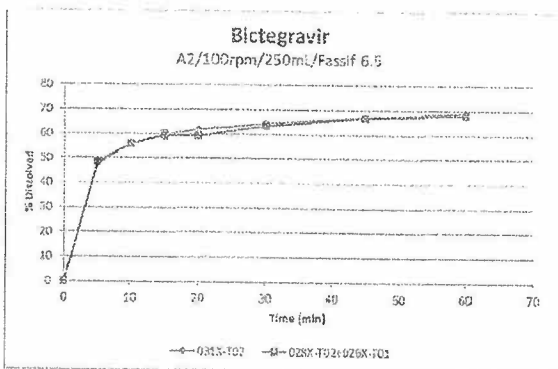


Figure 1: Drug release profiles for bictegravir from samples 031X-T02 and 028X-T02+026X-T01 in 250 ml FaSSIF pH 6.5 by using Apparatus II and 100 rpm.

Figure 1 clearly shows that the dissolution of BIC from 031X-T02 and 028C-T02 in the presence of 026X-T01 is the same (D40, p. 5, Figure 2).

Hence, D40 contradicts by verifiable facts patentee's assumed surprising finding of an enhanced BIC dissolution of the FDC/bilayer formulation F2 compared to a single agent BIC tablet. In fact, D40 verifies the data of D27 in that the dissolution of BIC from an FDC tablet is the same as from a BIC monolayer tablet and in particular, is not influenced by the use of an FDC/bilayer formulation as suggested in the opposed patent (opposed patent, [0029], [0058]).

2.3 BIC Dissolution is at Least Influenced by the Used BIC and Formulation

In order to clarify whether there are any factors influencing BIC dissolution, the following experiment was carried out:

Three different samples of BIC single layer tablets were prepared: two samples correspond to the composition of the BIC monolayer tablet of F2/F3-A but differ in the utilized bictegravir, i.e. bictegravir from different batches was used. The samples were labelled as 028X-T02 and 029-T02 (D40, sections 1.2 and 1.3). Further, a BIC monolayer tablet was prepared, wherein the composition of the tablet corresponds to the composition of F1 according to example 1 of the opposed patent. This BIC-monolayer tablet was labelled as 030X-T02 (D40, section 1.4). The compositions of 028X-T02, 029X-T02 and 030X-T02 are depicted in the table below:

Ingredient	**028X-T02** (single BIC)	**029X-T02** (single BIC)	**030X-T02** (single BIC)
	Na-BIC	**Na-BIC**	**Na-BIC**
Na-Bictegravir (batch number)	78.7 (S-BIC-1-144-02)	78.7 (S-BIC-1-129-02)	78.7 (S-BIC-1-129-02)
MCC (intra-granular + extra-granular)	247.8 (212.5+35.3)	247.8 (212.5+35.3)	120.0 (120.0+0)
Lactose monohydrate	-	-	75.8
Croscarmellose Sodium	21.2	21.2	-
Crospovidone			21.0
Magnesium Stearate (intra-granular + extra-granular)	5.3 (2.65+2.65)	5.3 (2.65+2.65)	-
Sodium stearyl fumarate (intra-granular + extra-granular)	-	-	4.5 (2.25+2.25)
Tablet Total Weight	**353**	**353**	**353**

Secondly, the dissolution of BIC of 028X-T02, 029-T02 and 030x-T02 were compared in the presence of 026X-T01, measured using USP Apparatus II, in 250 mL of pH 6.5 FaSSIF at 37°C and paddle speed of 100 rpm (D40, section 2).

The results of the BIC dissolution are depicted in the following figures (**Figure 2** and **Figure 3**):

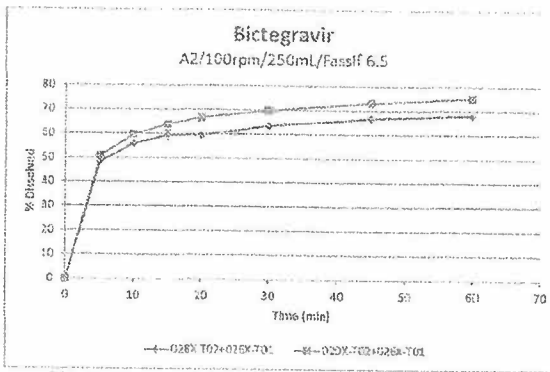


Figure 2: Drug release profiles for bictegravir from samples 028X-T02+026X-T01 and 029X-T02+026X-T01 in 250 ml FaSSIF pH 6.5 by using Apparatus II and 100 rpm.

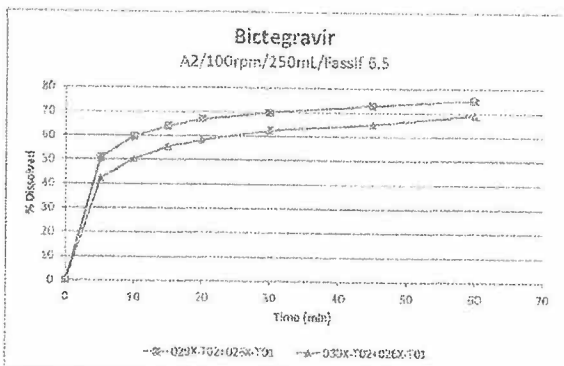


Figure 3: Drug release profiles for bictegravir from samples 029X-T02+026X-T01 and 030X-T02+026C-T01 in 250 ml FaSSIF pH 6.5 by using Apparatus II and 100 rpm.

From the figures shown above, it is apparent that the dissolution of BIC is influenced by two aspects, namely:

a) the used batch of bictegravir (Figure 2), and
b) the formulation (Figure 3).

Hence, the results provide verifiable facts that BIC dissolution is influenced/enhanced at least by the choice of bictegravir batches and formulation.

In addition, and as shown by the figure below (**Figure 4**), the comparison of the dissolution profiles for 028X-T02, 029X-T02 and 031X-092 reveals that the used batch of bictegravir has a stronger impact on the dissolution profile than the formulation aspect.

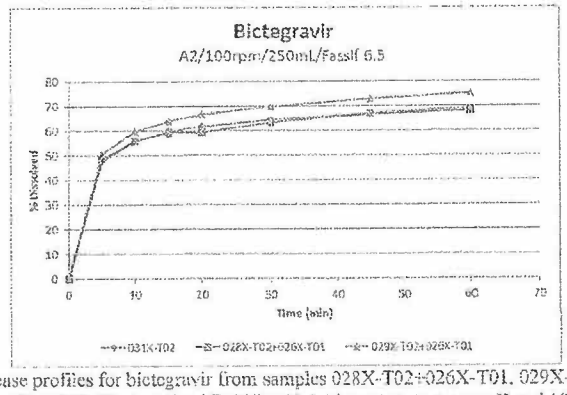


Figure 4: Drug release profiles for bictegravir from samples 028X-T02+026X-T01, 029X-T02+026X-T01 and 031X-T02+026X-T01 in 250 ml FaSSIF pH 6.5 by using Apparatus II and 100 rpm.

Thus, D40 provides further verifiable facts in form of experimental data that combining the three APIs, BIC, FTC and TAF, in a triple agent FDC tablet formulation does NOT change the dissolution of BIC compared to its dissolution out of a BIC single agent tablet.

Therefore, it is maintained, as already outlined in our grounds for opposition, that patentee's obtained enhanced BIC dissolution of the FDC/bilayer formulation does not have its origin in the feature FDC/bilayer formulation.

8. Conclusion

As evident from the above, the technical effect in form of enhanced dissolution accompanied by improved bioavailability does not have its origin in the presence of BIC, FTC and TAF together in a single tablet formulation.

Dr. Bernd Aechter
European Patent Attorney
Association No. 6

Dr. Veronika Müller
European Patent Attorney
Association No. 6

Enclosure: D40

TER MEER STEINMEISTER & PARTNER PATENTANWÄLTE mbB

GERMAN & EUROPEAN
PATENT ATTORNEYS
Dipl.-Chem. Dr. Christian Hollatz
Dipl.-Ing. Jörg Riemann
Dipl.-Chem. Dr. Bernd Aechter
Dipl.-Phys. Dr. Julia Matl
Dipl.-Chem. Dr. Luigi Rumi
Dipl.-Ing. (FH) Stefan Menzer, M.Sc.
Dipl.-Chem. Dr. Ingo Orlé
Apothekerin Dr. Veronika Müller
Dipl.-Biochem. Dr. Markus Ackermann
Claudia Schwartzkopff, M.Sc.
Dipl.-Ing. Dr. Moritz Herbrich
Dipl.-Biochem. Dr. Susanne Greser
Dipl.-Phys. Frank Müller*
Dipl.-Phys. Dr. Wolfgang Säker*

EUROPEAN PATENT ATTORNEY
Abhishek Tewary, M.Sc.

Consultants:
Dipl.-Ing. Gebhard Merkle
Manfred Wiebusch*

Nymphenburger Straße 4
Zugang Dachauer Straße 63
80335 MÜNCHEN

Telefon: (089) 72 98 960-0
Telefax: (089) 72 98 960-20
www.termeer.de
Registergericht: AG München PR1207
VAT Reg. No: DE 130 747 219
St.-Nr./ Tax No: 143/573/30694

ter Meer · Steinmeister & Partner · Nymphenburger Straße 4 · 80335 München

European Patent Office
Bob-van-Benthem-Platz 1
80469 München

Opposition against EP 3 346 995 (16 798 063.0)
"Therapeutic compositions for treatment of Human Immunodeficiency Virus"
Patentee: Gilead Sciences, Inc.
Opponent: Sandoz GmbH

26.08.2022
Ac/VM/vh
acchter@termeer.de

In response to patentee's further submission of January 24, 2022, the following is submitted.

1. Introduction

The present submission is not intended to comprehensively address all issues of the case. Instead, in reply to the proprietor's submission dated January 24, 2022 the present submission merely emphasises the issue of objective technical problem for the preparation of the oral proceedings.

To the extent that objections raised previously are not discussed, they are expressly maintained. In addition, the present opponent reserves the right to comment on all grounds for opposition, in particular during the oral proceedings.

* Büro Bielefeld: Artur-Ladebeck-Str. 51, 33617 BIELEFELD
Telefon: (0521) 914 940 Telefax: (0521) 914 94 20

2. Requests

The opponent's requests currently on file are maintained. In particular, revocation of the opposed patent in its entirety is requested.

3. The Objective Technical Problem

3.1 The Alleged Technical Effects

In its latest submission, the patentee firstly alleges that there are many effects resulting from the differences between the claimed composition containing BIC and the composition of D5 containing DTG (patentee's submission dated 24 January 2022, p. 6, 1st para.).

Secondly, the patentee specifically mentioned two effects, namely

- "improved resistance profile", and
- "*reduced viral breakthrough and improved barrier to resistance at suboptimal adherence*".

Regarding these effects, the patentee relied on the newly submitted documents D41 and D42, which are both post-published (patentee's submission dated 24 January 2022, p. 6, 2nd para. and the following).

Based on these effects, the patentee formulated the objective technical problem starting from D5 as the provision of an effective combination therapy for the treatment of HIV in humans which provides a near-maximal virologic response, can be formulated as a single tablet, provides minimised food effects, and which has an improved resistance profile and improved forgiveness and barrier to resistance in a real world setting (patentee's submission dated January 24, 2022, p. 7, penultimate para.).

3.2 Legal Technical Background

According to the established jurisprudence of the Boards of Appeal, the assessment of inventive step is to be made at the effective date of the patent on the basis of the information in the patent together with the common general knowledge then available to the skilled person. Moreover, there can only be an invention if the application makes it at least plausible that its teaching indeed solves the problem it purports to solve. In this respect, the Boards of Appeal have established that the verification of whether or not the claimed solution actually solves the problem, i.e. whether the claimed subject-matter actually provides the desired effect, must be based on the data in the application. Post-

published evidence to support that the claimed subject-matter solves the problem to be solved is taken into account if it is already credible from the disclosure in the patent that the problem is indeed solved (Case Law of the Boards of Appeal, 9th ed., I.D.4.6).

3.3 From the Disclosure it is NOT Credible that the Problem is Indeed Solved

As outlined in the grounds for opposition, the opposed patent does not disclose any technical effect concerning the differences between the claimed composition containing BIC and the composition of D5 containing DTG (grounds for opposition, p. 22, section 8.2).

In particular, and as also outlined in the grounds for opposition, the examples of the opposed patent solely concern different tablet formulations of Na-BIC, FTC/TAF and their dissolution characteristics and/or pharmacokinetic profiles (grounds for opposition, p. 22, section 7).

Moreover, the opposed patent neither addresses any resistance profiles nor viral breakthroughs and/or barriers to resistance at suboptimal adherence.

Thus, the opposed patent is completely silent whether the claimed combination therapy solves the problem formulated by the patentee.

In such cases, it is established case law that post-published evidence as done by the patentee has not to be taken into account for the assessment of inventive step.

Consequently, the alleged technical effect of the claimed subject-matter has "*to be disregarded when determining the objective problem underlying the invention and thus when assessing inventive step*" (Case Law of the Boards of Appeal, 9th ed., I.D.9.8.3).

3.4 Conclusion

In view of the above, it is therefore maintained that starting from D5 as the closest prior art the technical problem can only be seen in the provision of a fixed-dose combination in form of a tablet comprising an alternative INSTI, emtricitabine and tenofovir alafenamide.

Dr. Veronika Müller
European Patent Attorney
Association No. 6

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European Patent Office
80298 MUNICH
GERMANY

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Formalities officer
Pepper-Cane, Emmanuel

Carpmaels & Ransford LLP
One Southampton Row
London WC1B 5HA
ROYAUME UNI

Date: 05.04.2022

Reference	Application No./Patent No.
O008281EP:CJH/PAK/HEB	16796063.0 - 1112 / 3346995
Applicant/Proprietor: Gilead Sciences, Inc.	

EPA/EPO/OEB Formblatt/Form/Formulaire : 2310

Empfangsbescheinigung über den Zugang des vorstehend bezeichneten Schriftstücks
Acknowledgement of receipt of the document specified above
Récépissé du document spécifié ci-dessus

Unter Bezugnahme auf die Mitteilung im ABl EPA 7/2010, 377 wird gebeten, die Empfangsbescheinigung mit Empfangsdatum und Unterschrift zu versehen und **umgehend** an das EPA zurückzusenden:

With reference to the Notice in OJ EPO 7/2010, 377, you are requested to date and sign the acknowledgement of receipt and return it to the EPO **immediately**:

Conformément au communiqué paru au JO OEB 7/2010, 377, vous êtes prié d'indiquer sur le récépissé la date de réception du document, de signer le récépissé et de le renvoyer **sans délai** à l'OEB:

- **über die Online-Dienste des EPA** (als Anlage zu EPA Form 1038) / **through EPO Online Services** (as annex to EPO Form 1038) / **par les services en ligne de l'OEB** (en tant que pièce jointe au formulaire OEB 1038),
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Pepper Cano, Emmanuel

Carpmaels & Ransford LLP
One Southampton Row
London WC1B 5HA
ROYAUME UNI

Date
05.04.2022

Reference	Application No./Patent No.
O006281EP:CJH/PAK/HEB	16798063.0 - 1112 / 3346995
Applicant/Proprietor: Gilead Sciences, Inc.	

Summons to attend oral proceedings pursuant to Rule 115(1) EPC

You are hereby summoned to attend oral proceedings arranged in connection with the above-mentioned European patent.

The matters to be discussed are set out in the communication accompanying this summons (EPO Form 2906).

The oral proceedings, which will be public, will take place before the opposition division

on 27/28.10.2022 at 09.00 hrs *

No changes to the date of the oral proceedings can be made, except on serious grounds (see OJ EPO 1/2009, 68). If you do not appear as summoned, the oral proceedings may continue without you (R. 115(2) EPC).

Your attention is drawn to Rule 4 EPC, regarding the language of the oral proceedings, and to the Special edition No. 3 OJ EPO 2007, 128, concerning the filing of authorisations for company employees and lawyers acting as representatives before the EPO.

The final date for making written submissions and/or amendments (R. 116 EPC) is 26.08.22.

* The parties will be informed on the form of oral proceedings nearer to the scheduled date.

1st Examiner:
Triffileff, Sylvie

2nd Examiner:
Collura, Alessandra

Chairman:
Büthner, Ulf

For the Opposition Division

Annexes:
Confirmation of receipt (Form 2936)
Rule 4 EPC (EPC Form 2043)
Communication (EPO Form 2906)

Registered Letter

1. European patent 3 346 995 having the title "THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS " is based upon European patent application No.16 798 063.0 filed on 08-11-2016. It claims priority of US 201562253042 filed on 09-11-2015 and US 201662399999 filed on 26-09-2016.

The mention of the grant of the patent has been published in the European Patent Bulletin of28-08-2019 . Proprietor of the patent (hereinafter P) is
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
US.

2. Notices of opposition has/have been filed by
Opponent 1 (hereinafter O1):
Teva Pharmaceutical Industries Ltd
5 Basel Street
49131 Petach-Tikva
IL
on 27-05-2020

Opponent 2 (hereinafter O2):
Cooke, Richard
Elkington and Fife LLP
Patents Department
3-4 Holborn Circus
London EC1N 2HA
GB
on 28-05-2020

Opponent 3 (hereinafter O3):
Sandoz GmbH
Biochemiestrasse 10
6250 Kundl
AT
on 28-05-2020 .

The opponents request revocation of the patent in its entirety on the following grounds:

. the granted subject-matter extends beyond the content of the application as originally filed (A. 100(c) and A. 123(2) EPC): O1, O2 and O3.

. the granted subject-matter lacks novelty (A. 100(a); A. 54 EPC): O2 and O3.

. the granted subject-matter lacks inventive step (A. 100(a); A. 56 EPC): O1, O2 and O3.

. O2 and O3 further dispute the validity of the priority.

All opponents request oral proceedings as an auxiliary measure.

3. With the submission dated 11-01-2021, P requests that the oppositions be dismissed and that the patent be maintained as granted or on the basis of one of the 29 auxiliary requests (AR1 to AR29) filed with the same submission.

P requests oral proceedings as an auxiliary measure.

4. The opponents react as follows:

O2 submits further arguments on 04-03-2021.

O3 submits further arguments on 24-03-2021.

O1 submits D38 and D39 together with further arguments on 26-03-2021.

5. Oral proceedings are hereby summoned.

6. The present communication represents the provisional and non binding opinion of the opposition division (hereinafter OD) on the above topics.

The documents cited by the parties are:

		P	O1	O2	O3
PRIO1	US 2015/62253042				TM1
PRIO2	US 2016/62399999				TM2
D1	WO 2015/196116			D1	TM14

D1a	Evidence of D1 entry to European Regional phase			D1a	
D2	WO 2015/196137			D2	TM15
D3	WO 2014/100323		D1	D3	TM3
D4	WO 2013/116720		D3	D4	
D5	WO 2015/022351		D2	D5	TM17
D6	Gilead Sciences Finalizes Agreement with Tibotec Pharmaceuticals to Develop and Commercialize a Single-Tablet Regimen of Prezista® with Emtriva®, GS 7340 and Cobicistat, 15 November 2011			D6	
D7	British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy, 2015, pages 13-14			D7	
D8	BNF 2015, Emtricitabine with tenofovir, pages 557-558 and 566			D8	
D9	Fernando, S., Butterworth, A., Choices, choices: the rapidly evolving HIV treatment landscape, pmlive.com, 15 March 2015			D9	
D10	Business Wire, 5 November 2015, "U.S. Food and Drug Administration Approves Gilead's Single Tablet Regimen Genvoya® (Elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide) for treatment of HIV-1 infection"			D10	
D11	Centre for Drug Evaluation and Research, first page of approval package, Odefsey®			D11	

D12	Business Wire, 1 July 2015, "Gilead Submits New Drug Application to U.S. Food and Drug Administration for Single Tablet Regimen for HIV Containing Rilpivirine, Emtricitabine and Tenofovir Alafenamide (R/F/TAF)"			D12	
D13	Business Wire, 4 April 2016, "U.S. Food and Drug Administration Approves Descovy® (Emtricitabine, Tenofovir Alafenamide), Gilead's Third TAF-Based HIV Therapy			D13	
D14	Business Wire, 28 May 2015, "European Medicines Agency Validates Gilead's Marketing Application for Fixed-dose Combination of Emtricitabine and Tenofovir Alafenamide for HIV treatment"			D14	
D15	Aulton, Pharmaceutics: The Science of Dosage Form Design, 2nd Edition, 2002, pages 411-412			D15	
D16	P. Shende et al., "Multi-layer Tablet: Current scenario and recent advances", International Journal of Drug Delivery 4 (2012) 418-426;		D4		
D17	WO 2017/083304 A1		D5		
D18	WHO Drug Information 29(2), July 2015				TM4
D18a	Publication date of TM4				TM4a
D19	Guidance on the establishment of new INN stems, 2007				TM5
D20	WHO, The use of stems in the selection of International Nonproprietary Names (INN) for pharmaceutical substances, 2013				TM6
D20a	WHO, Pre-Stems: Suffixes used in the selection of INN, 2012				TM6a

D20b	WHO, Pre-Stems: Suffixes used in the selection of INN, June 2014				TM6b
D21	Yoshinaga et al., Antiviral Characteristics of GSK1265744, an HIV Integrase Inhibitor Dosed Orally or by Long-Acting Injection, Antimicrobial Agents and Chemotherapy, January 2015, Vol. 51, Nr. 1, p. 397-406				TM7
D21a	Park et al., Review of integrase strand transfer inhibitors for the treatment of human immunodeficiency virus infection, Expert Rev. Anti Infect. Ther. 13(10), 2015				TM7a
D21b	Shah et al., Dolutegravir: A New Integrase Strand Transfer Inhibitor for the Treatment of HIV, Pharmacotherapy, Vol. 34, No. 5, 2014				TM7b
D22	WO 02/08241 A2				TM8
D23	Clayden et al., 2015 Pipeline Report, HCV, HCV, TB, July 2015				TM9
D24	FDA, Drug Approval Package Viread				TM10
D25	EMA, Viread, Authorization details				TM11
D26	Press Release Gilead dated November 5, 2015				TM12
D27	Experimental Report dated May 15, 2020				TM16
D28	US 2014/0221356 A1				TM18
D28a	Submission in the Examination Proceedings of TM18 dated August 26, 2015				TM18a
D29	Kulkarni et al., The Combined Anti-HIV-1 Activities of Emtricitabine and Tenofovir plus the Integrase Inhibitor Elvitegravir or Raltegravir Show High Levels of Synergy In				TM19

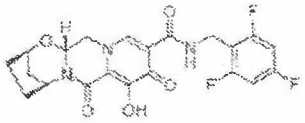
	Vitro, Antimicrobial Agents and Chemotherapy, October 2014, Vol. 58, Nr. 10, p. 6145-6150				
D30	Analyzing Gilead Sciences' Research and Development in 3Q15, October 23, 2015				TM20
D31	EudraCT number 2015-003988-10 dated November 19, 2015				TM21
D32	USAN statement dated February 24, 2016				TM22
D33	WO 2010/091197 A2				TM23
D34	WO 2013/115916 A1				TM24
D35	Phase I study into the potency, safety and pharmacokinetics of multiple doses of BIC	D35			
D36	Biktarvy EPAR Scientific Discussion	D36			
D37	Phase II study comparing BIC (75 mg) + FTC/TAF (200/25 mg) vs DTG (50 mg) + FTC/TAF (200/25 mg)	D37			
D38	P. Kommavarapu et al., "Preparation and characterization of rilpivirine solid dispersions with the application of enhanced solubility and dissolution rate", Beni-Suef University Journal of Basic and Applied Sciences 4 (2015) 71-79.		D38		
D39	European Medicines Agency, Assessment report "Genvoya", 24 September 2015, extract (pp.1-20).		D39		

6. MAIN REQUEST (patent as granted):

The patent comprises two independent claims 1 and 10 which read:

1. A tablet comprising 50 mg of the compound of Formula I:

(I)



or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof.

10. A tablet according to any one of the preceding claims for use in the therapeutic treatment of an HIV infection.

It is noted that the non proprietary name of the compound of Formula I is bictegravir.

6.1 Extension of the subject-matter beyond the content of the original application (A. 100 (c) and A. 123(2) EPC):

According to O1 and O2 the application as filed does not disclose the tablet of granted claim 1. Such a specific tablet would neither be disclosed in the claims nor in the description of the original application. The passages of the original application (claims and/or description) which could be relied upon for basis would comprise additional limitations such as coatings or a particular tablet weight which are not present in granted claim 1.

O3 raises the objection for granted claim 5 which would comprise combinations which would be artificially created from separate embodiments of the original application.

The opponents extend the objection to the dependent claims 4 to 10.

P answers that the claims have the following basis in the application as filed:

claim 1: § 8, 10, 12, 16, 34, 37, 48, 50, 53, 77 to 85, 90 to 98, 103 to 111, 264, claims 6 to 9

claim 2: § 8, claims 2 and 6

claim 3: § 8, 14, 34, 53, 128, claims 3, 6 and 8

claim 4: § 10, 11, 52, 53, claims 4 to 6

claim 5: § 12, 71, 210, 211, 279, claim 7

claim 6: § 16, 20, 54, 55, 117, 118, 126, 128 to 262, claims 9, 10 and 16

claim 7: § 55, claim 17

claim 8: claim 26

claim 9: claim 27

claim 10: § 1, 7, 282, 283, claims 38 and 39

In particular, granted claim 1 would be described in §008 combined with the teaching found throughout the application stating that emtricitabine is present either as such or as a pharmaceutically acceptable salt (paragraphs mentioned in the table).

P also argues that the subject-matter of granted claim 1 is not an unallowable intermediate generalisation because the application as filed would not describe an inextricable link between the doses of the active compounds and the other limitations found in the different paragraphs of the original application such as total weight of the tablet or presence of a coating.

O3's objection concerning claim 5 would result from an over formalistic view which would only take into account the the structure of the original claims and their dependencies rather than the overall original disclosure.

This would also be the case for claims 4 and 6 to 10.

Reading §008 of the original application, the OD notes that it describes a solid oral dosage form (1st sentence) which in certain embodiments (2nd sentence) comprises 50 mg of the compound of formula I or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine.

This passage does neither specify that the dosage form is a tablet nor that emtricitabine can be in the form of a salt.

§010 of the original application recites a solid oral dosage form which comprises 50 mg of the compound of formula I or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof. This passage however further specifies that this oral dosage form has a total weight of less than 850 mg and does not specify that the dosage form is a tablet.

The feature of granted claim 1 relating to the "tablet" specific form can indeed be found in some of the different paragraphs mentioned as basis in the above table. It appears however to be linked with other specific technical features of the dosage form which are

not present in granted claim 1 such as the fact that the tablet is coated (§012 and original claim 7) or the fact that bictegravir and tenofovir alafenamide are segregated in the tablet (§016 and original claim 9).

As for the feature relating to the "emtricitabine salt", §0048 mentions that "solid oral dosage forms disclosed herein include emtricitabine, optionally as a pharmaceutically acceptable salt" and §0050 that "a reference to '200 mg emtricitabine or a pharmaceutically acceptable salt and/or solvate thereof' means an amount of emtricitabine or a pharmaceutically acceptable salt and/or solvate thereof which provides the same amount of emtricitabine as 200 mg of emtricitabine free base". It would hence seem that 200 mg emtricitabine would not be equivalent to 200 mg of a salt of emtricitabine.

Further, §0077 to §0085, §0090 to §0098 and §0103 to §0111 do not describe a tablet as depicted in granted claim 1 but a **pharmaceutical composition comprising** a tablet **containing** 50 mg of bictegravir or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof.

The OD is thus of the provisional opinion that the subject-matter of granted claim 1 extends beyond the content of the original application.

6.2. Validity of the priority rights (A. 87 EPC):

O2 objects that granted claims 6 to 10 are not entitled to the first priority of 09-11-2015 (P1) and O3 raises the same objection against granted claims 1, 4 to 7 and 10.

P answers that the granted claims are described in P1 as follows:

Claim 1: § 7, 9, 11, 15, 33, 36, 42, 48, 51, 92 and claims 1, 2, 6, 7 and 9

claim 2: § 17, claim 2

claim 3: § 7, 13, 33, 51, 94, claim 3

claim 4: (i) § 50, 51; (ii) § 9, 51, claim 4; (iii) § 9, claim 5

claim 5: § 11, 67, 183, claim 7

claim 6: § 15, 19, 52. 53, 85 to 180 in particular § 85, 92 and 94, claim 16

claim 7: § 15, 53, 92, 94, claim 17

claim 8: claim 26

claim 9: claim 27

claim 10: § 1, 6, 186, 187, claims 39 and 40

and that they are entitled to the date of P1.

Reading the passages recited in the table above, it would seem that the same observations as those made under point 6.1. above by the OD would apply.

Hence it would appear that the claims would not be entitled to the priority date of 09-11-2015.

6.3. Novelty (A. 100(a) and A. 54 EPC):

O2 objects that claims 1 and 2 lack novelty over D1 while D3 objects that claims 1, 2 and 10 lack novelty over D1 and D2.

D1 was filed on 10-06-2015 and validly entered the European regional phase so that it would be relevant for consideration of novelty regardless of whether P1 is validly claimed.

The same would apply to D2 filed on 19-06-2015 and published on 23-12-2015.

Both opponents contend that D1 §96 teaches a combination of 50 to 500 mg of sodium bictegravir with 25 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate or tenofovir alafenamide and 200 mg emtricitabine. D1 would further disclose that tablets are preferred pharmaceutical compositions (§65 and claim 21). D1 would hence anticipate the subject-matter of granted claim 1.

D1 would also describe that the most preferred form of bictegravir would be the sodium salt, the most preferred from of emtricitabine would be the free base and the most preferred form of tenofovir alafenamide would be the hemifumarate salt (claim 19 D1). Thus also granted claim 2 would lack novelty over D1.

The objection would apply to granted claim 10 in view of §69 and claims 22-25 of D1.

O3 raises similar objections with respect to D2 taking into consideration §6, 21, 23, 218 , 187, 191 and claims 49 to 52.

P answers that none of the documents actually describes a tablet such as that of granted claim 1 and that the conclusions of O2 and O3 are based on combinations selected from different ranges of options.

The OD is of the preliminary opinion that none of D1 and D2 describes a specific tablet as that depicted in granted claim 1.

6.4. Inventive step (A. 100(a) and A. 56 EPC):

In relation to the issue of validity of the priority date of P1 and since the opinion expressed under item 6.2 above is only preliminary it would seem appropriate to distinguish between the situation where P1 would be valid and the one where it would not.

6.4.1. The date of P1 would be validly claimed:

The opponents regard D5 as the closest prior art document.

D5 would disclose a composition comprising 50 mg dolutegravir (which is an integrase inhibitor), 200 mg emtricitabine and 25 mg tenofovir alafenamide (p. 19-20). The most preferred composition would be a tablet (p. 23).

The distinguishing feature between this teaching and the subject-matter of granted claim 1 would be the use of 50 mg bictegravir as integrase inhibitor instead of 50 mg of dolutegravir.

The patent would not disclose any technical effect linked to this difference.

Hence the problem would be the provision of a fixed-dose combination in form of a tablet comprising an alternative integrase inhibitor, emtricitabine and tenofovir alafenamide.

Bictegravir would be an obvious alternative to dolutegravir since its effect as integrase inhibitor is disclosed in different prior art documents such as D3, D18, D28 and D28a (D3 and D28a would even indicate that bictegravir is one of the preferred integrase inhibitors disclosed in D28).

The opponents conclude that the subject-matter of granted claim 1 would not meet the requirements for inventive step.

They extend the objection to all dependent claims, as well as to claim 10, referring to further prior art documents (D4, D16, D15, D7, D8, D33, D34) and/or to general knowledge and/or to routine methodology.

Other reasonings are made (O2), starting from D10, D12 or D4 as closest prior art combined with D3, D5 or D7.

P regards D37 as closest prior art because it would be the only prior art document which would describe a combination comprising exactly the same three compounds as the composition of granted claim 1.

The difference would lie in the amount of bictegravir used and would be linked to unexpected technical effects shown in the patent so that inventive step would be present.

Reasoning with D5 as closest prior art, P asserts that it would not actually describe a composition comprising 50 mg dolutegravir (which is an integrase inhibitor), 200 mg emtricitabine and 25 mg tenofovir alafenamide because this would contravene some statements of D5 concerning ratios between dolutegravir and emtricitabine.

The problem with respect to D5 would be the provision of a safe and effective anti-HIV combination therapy which could be provided as a single tablet.

There would be no reason for the skilled person to specifically replace the integrase inhibitor (i.e. dolutegravir) rather than the other two active agents. Even if the skilled person had considered doing so, the prior art (e.g. D7) would not have suggested bictegravir. As for the dose of 50 mg, it would not have been obvious to simply switch 50 mg of dolutegravir for 50 mg of bictegravir.

Hence the granted subject-matter would be inventive.

The same reasoning would apply starting from D10, D12 or D14.

Regarding the choice of the closest prior art document, the OD notes that D37 does not mention bictegravir as such but only the code name GS-9883. The only available document which draws a link between GS-9883 and bictegravir is D32 published on 24-02-2016.

Hence would P1 be valid, GS-9883 in D37 could not simply be read as "bictegravir" but would remain a compound of unknown structure and mechanism.

Accordingly D5 would seem more adequate than D37 as starting point for assessing inventive step.

6.4.2. The date of P1 would not be validly claimed:

O2 reasons that starting from D1, the subject-matter of claims 6 and 7 would lack an inventive step.

O3 starts from D31 (completed with D32) which describes a phase 3 clinical trial in which the safety and efficacy of a fixed dose combination of bictegravir/emtricitabine/ tenofovir alafenamide is compared to a treatment with dolutegravir and emtricitabine/ tenofovir alafenamide to treat HIV.

According to O3, this teaching would render the subject-matter of claims 1 and 10 obvious. The objection would apply to all dependent claims 2 to 9.

No counter argument is presented by P. P is however invited to take into consideration the above approaches, particularly the one starting from D31.

The matter of inventive step will have to be discussed at the oral proceedings. Whatever conclusion is made on the validity of the claimed priority date, the first step will have to select the closest prior art document.

D5 would seem appropriate if the date of P1 is acknowledged as being valid.

If not, D31 might be the most appropriate document.

7. AUXILIARY REQUESTS:

7.1 Extension of the subject-matter beyond the content of the original application (A. 100 (c) and A. 123(2) EPC):

The preliminary opinion expressed under point 6.1. above for the main request applies to AR1 to AR4, AR6 to AR8.

In view of the great number of auxiliary requests it does not seem appropriate to express any further preliminary opinion other than the one above for the moment.

Europäisches Patentamt
European Patent Office
Office européen des brevets

Wichtige Hinweise zur mündlichen Verhandlung	Important information concerning oral proceedings	Très important Procédure orale
Das Europäische Patentamt verfügt über keine eigenen Dolmetscher. Diese müssen im Bedarfsfall von außerhalb, teilweise sogar aus anderen Ländern, beigezogen werden, was mit einem hohen Aufwand an Kosten und organisatorischen Vorbereitungen verbunden ist. Muss ein Verhandlungstermin kurzfristig abberaumt werden, können Kosten für bestellte Dolmetscher nicht mehr vermieden werden.	The European Patent Office has no interpreters of its own. When interpreters are needed they have to be brought in from outside, sometimes even from other countries, which is costly and involves considerable organisation. If oral proceedings have to be cancelled at short notice, the cost of interpreters already engaged still has to be borne.	L'Office européen des brevets ne dispose pas de son propre service d'interprètes. Aussi faut-il faire appel le cas échéant à des interprètes de l'extérieur, qui viennent même parfois de l'étranger, ce qui occasionne des frais élevés et demande un grand travail d'organisation. Si la date d'une procédure orale doit être annulée au dernier moment, il n'est plus possible d'éviter les frais d'interprètes.
Es wird daher gebeten, eine Simultanübersetzung nur bei wirklichem Bedarf in Anspruch zu nehmen. Es wäre wünschenswert, wenn sich die Beteiligten (zweckmäßigerweise gleichzeitig mit der Terminabstimmung) auf die Benutzung einer Amtssprache einigen könnten. Bei Verständigungsschwierigkeiten sind die Mitglieder der Einspruchsabteilung bereit zu helfen.	Please therefore make use of simultaneous interpreting facilities only where strictly necessary. If possible the parties should agree on an official language for the proceedings, preferably at the time when they arrange a date. The members of the Opposition Division will be willing to help should any communication problems arise.	Les parties à une procédure sont donc priées de ne demander une traduction simultanée qu'en cas de réel besoin. Il serait souhaitable qu'elles puissent se mettre d'accord en même temps qu'elles conviennent de la date sur l'utilisation d'une langue officielle comme langue des débats. Si les parties éprouvent des difficultés de compréhension lors des débats, les membres de la division d'opposition sont disposés à leur prêter leur assistance.
Nachstehend führen wir den Zeitpunkt auf, bis zu dem die Verfahrensbeteiligten aus organisatorischen Gründen gebeten werden, ihre bevorzugte (abgestimmte) Verhandlungssprache mitzuteilen. Bis dahin bitten wir auch bei Bedarf eine Simultanübersetzung zu beantragen. Regel 4 (1) EPÜ bleibt hiervon unberührt.	For organisational reasons, we ask parties to inform us by the date specified below of their preferred (agreed) language for the oral proceedings. We also ask them to request any simultaneous interpreting required by the same date. This does not affect application of Rule 4(1) EPC.	Est indiquée ci-dessous la date jusqu'à laquelle, pour des raisons d'organisation, les parties sont priées de communiquer leur langue préférée (sur laquelle elles se sont préalablement mises d'accord). Les parties sont également priées, le cas échéant, de demander une interprétation simultanée avant cette date. La règle 4(1) CBE ne s'en trouve pas affectée.
☐ Verfahrenssprache ist: **Deutsch**	☒ Language of the proceedings is: **English**	☐ La langue de la procédure est le **français**
Von der/dem/den Einsprechenden wurde	The language used by the opponent/s was	La langue utilisée par l'opposant/les opposants était
☐ Englisch	☒ German	☐ l'allemand
☐ Französisch benutzt.	☐ French.	☐ l'anglais.
Es wird um eilige Mitteilung, möglichst per Online Filing (OLF), gebeten.	**Please inform us urgently, where possible by Online Filing (OLF).**	**Prière d'indiquer d'urgence par dépôt en ligne (OLF) si possible.**
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Datum: 26.08.22	Date 26.08.22	Date 26.08.22

1. welche Sprache(n) Sie in der mündlichen Verhandlung verwenden (**Sprechen**)	1. which language(s) you intend to use during the oral proceedings (**Speaking**)	1. quelle(s) langue(s) vous utiliserez au cours de la procédure orale (**pour parler**)
2. aus welcher Sprache Sie eine Simultanübersetzung benötigen (**Hören**).	2. from which language you need simultaneous interpretation (**Listening**).	2. à partir de quelle langue vous aurez besoin d'une traduction simultanée (**pour écouter**).

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Sollten Sie Ihren Antrag auf mündliche Verhandlung zurückziehen oder zum anberaumten Verhandlungstermin nicht erscheinen wollen bzw. aus wichtigem Grund daran gehindert sein, werden Sie gebeten,

- **unverzüglich das Amt - möglichst per Online Filing (OLF) - davon zu benachrichtigen, wobei das Schriftstück mit einem deutlichen Vermerk "Dringend, mündliche Verhandlung am..." oder sinngemäß gekennzeichnet sein sollte**
- **in dringenden Fällen** (weniger als 1 Monat vor dem Verhandlungstermin) zusätzlich **auch dem/die anderen Verfahrensbeteiligten** bzw. ihre(n) Vertreter auf schnellstem Weg **direkt zu unterrichten.**

In jedem solchen Fall obliegt der Einspruchsabteilung die Entscheidung, ob die Verhandlung durchgeführt oder abberaumt wird. Es wird jedoch darauf hingewiesen, dass einem Verfahrensbeteiligten, der eine nicht rechtzeitige oder unterbliebene Benachrichtigung zu verantworten hat, die dadurch den anderen Beteiligten verursachten Kosten auferlegt werden können (Art. 104 EPÜ).

Hinweis auf Regel 4 EPÜ

Regel 4
Sprache im mündlichen Verfahren

(1) Jeder an einem mündlichen Verfahren vor dem Europäischen Patentamt Beteiligte kann sich anstelle der Verfahrenssprache einer anderen Amtssprache des Europäischen Patentamts bedienen, sofern er dies dem Europäischen Patentamt spätestens einen Monat vor dem angesetzten Termin mitgeteilt hat oder selbst für die Übersetzung in die Verfahrenssprache sorgt. Jeder Beteiligte kann sich einer Amtssprache eines Vertragsstaats bedienen, sofern er selbst für die Übersetzung in die Verfahrenssprache sorgt. Von diesen Vorschriften kann das Europäische Patentamt Ausnahmen zulassen.

Should you decide to withdraw your request for oral proceedings or not wish to attend on the date set, or if for some special reason you are unable to do so, you are requested

- **to notify the EPO immediately, where possible by Online Filing (OLF), marking the document clearly with the words "Urgent, oral proceedings on ..." or similar**
- **in urgent cases** (less than one month before the date set for the proceedings), additionally to **notify the other party/parties** and/or their representative(s) **direct as rapidly as possible.**

In all such cases the Opposition Division will decide whether the proceedings are to go ahead or be cancelled. You should however note that costs incurred by the other parties may be charged to a party who either fails to notify them or does not do so in good time (Article 104 EPC).

Attention is drawn to Rule 4 EPC

Rule 4
Language in oral proceedings

(1) Any party to oral proceedings before the European Patent Office may use an official language of the European Patent Office other than the language of the proceedings, if such party gives notice to the European Patent Office at least one month before the date of such oral proceedings or provides for interpretation into the language of the proceedings. Any party may use an official language of a Contracting State, if he provides for interpretation into the language of the proceedings. The European Patent Office may permit derogations from these provisions.

Si vous retirez votre requête tendant à recourir à la procédure orale ou si vous ne souhaitez pas vous présenter à la date fixée pour la procédure orale ou ne pouvez vous y présenter pour une raison sérieuse, veuillez

- **en faire avis sans retard à l'Office, par dépôt en ligne (OLF) si possible, en portant sur votre communication clairement la mention "Urgent, procédure orale le..." ou une indication similaire;**
- **dans les cas urgents** (moins d'un mois avant la date fixée pour la procédure orale) **en faire avis également directement** par la voie la plus rapide à **autre/aux autres partie(s)** ou bien à son/leurs mandataire(s).

Il appartient alors à la division d'opposition de décider si la procédure orale aura lieu ou non. Il est néanmoins souligné que les frais causés aux autres parties par une partie qui est responsable de l'omission d'un tel avis ou de ce que cet avis n'a pas été fait en temps utile peuvent être mis à la charge de cette partie (art. 104 CBE).

Rappel de la Règle 4 CBE

Règle 4
Langues admissibles lors de la procédure orale

(1) Toute partie à une procédure orale devant l'Office européen des brevets peut utiliser une langue officielle de l'Office européen des brevets autre que la langue de la procédure, à condition soit d'en aviser l'Office européen des brevets un mois au moins avant la date de la procédure orale, soit d'assurer l'interprétation dans la langue de la procédure. Toute partie peut utiliser une langue officielle de l'un des Etats contractants à condition d'assurer l'interprétation dans la langue de la procédure. L'Office européen des brevets peut autoriser des dérogations aux présentes dispositions.

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1002
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(2) Die Bediensteten des Europäischen Patentamts können sich im mündlichen Verfahren anstelle der Verfahrenssprache einer anderen Amtssprache des Europäischen Patentamts bedienen.

(2) In the course of oral proceedings, employees of the European Patent Office may use an official language of the European Patent Office other than the language of the proceedings

(2) Au cours de la procédure orale, les agents de l'Office européen des brevets peuvent utiliser une langue officielle de l'Office européen des brevets autre que la langue de la procédure.

(3) In der Beweisaufnahme können sich die zu vernehmenden Beteiligten, Zeugen oder Sachverständigen, die sich in einer Amtssprache des Europäischen Patentamts oder eines Vertragsstaats nicht hinlänglich ausdrücken können, einer anderen Sprache bedienen. Erfolgt die Beweisaufnahme auf Antrag eines Beteiligten, so werden die Beteiligten, Zeugen oder Sachverständigen mit Erklärungen, die sie in einer anderen Sprache als in einer Amtssprache des Europäischen Patentamts abgeben, nur gehört, sofern dieser Beteiligte selbst für die Übersetzung in die Verfahrenssprache sorgt. Das Europäische Patentamt kann jedoch die Übersetzung in eine seiner anderen Amtssprachen zulassen.

(3) Where evidence is taken, any party, witness or expert to be heard who is unable to express himself adequately in an official language of the European Patent Office or of a Contracting State may use another language. Where evidence is taken upon request of a party, parties, witnesses or experts expressing themselves in a language other than an official language of the European Patent Office shall be heard only if that party provides for interpretation into the language of the proceedings. The European Patent Office may, however, permit interpretation into one of its other official languages.

(3) Lors de l'instruction, les parties, témoins ou experts appelés à être entendus, qui ne possèdent pas une maîtrise suffisante d'une langue officielle de l'Office européen des brevets ou d'un Etat contractant, peuvent utiliser une autre langue. Si la mesure d'instruction est ordonnée sur requête d'une partie, les parties, témoins ou experts qui s'expriment dans une langue autre qu'une langue officielle de l'Office européen des brevets ne sont entendus que si cette partie assure l'interprétation dans la langue de la procédure. L'Office européen des brevets peut toutefois autoriser l'interprétation dans l'une de ses autres langues officielles.

(4) Mit Einverständnis aller Beteiligten und des Europäischen Patentamts kann jede Sprache verwendet werden.

(4) If the parties and the European Patent Office agree, any language may be used.

(4) Sous réserve de l'accord des parties et de l'Office européen des brevets, toute langue peut être utilisée.

(5) Das Europäische Patentamt übernimmt, soweit erforderlich, auf seine Kosten die Übersetzung in die Verfahrenssprache und gegebenenfalls in seine anderen Amtssprachen, sofern ein Beteiligter nicht selbst für die Übersetzung zu sorgen hat.

(5) The European Patent Office shall, if necessary, provide at its own expense interpretation into the language of the proceedings, or, where appropriate, into its other official languages, unless such interpretation is the responsibility of one of the parties.

(5) L'Office européen des brevets assure à ses frais, en tant que de besoin, l'interprétation dans la langue de la procédure, ou, le cas échéant, dans ses autres langues officielles, à moins que cette interprétation ne doive être assurée par l'une des parties.

(6) Erklärungen von Bediensteten des Europäischen Patentamts, Beteiligten, Zeugen und Sachverständigen, die in einer Amtssprache des Europäischen Patentamts abgegeben werden, werden in dieser Sprache in die Niederschrift aufgenommen. Erklärungen in einer anderen Sprache werden in der Amtssprache aufgenommen, in die sie übersetzt worden sind. Änderungen einer europäischen Patentanmeldung oder eines europäischen Patents werden in der Verfahrenssprache in die Niederschrift aufgenommen.

(6) Statements by employees of the European Patent Office, parties, witnesses or experts, made in an official language of the European Patent Office, shall be entered in the minutes in that language. Statements made in any other language shall be entered in the official language into which they are translated. Amendments to a European patent application or European patent shall be entered in the minutes in the language of the proceedings.

(6) Les interventions des agents de l'Office européen des brevets, des parties, témoins et experts faites dans une langue officielle de l'Office européen des brevets sont consignées au procès-verbal dans cette langue. Les interventions faites dans une autre langue sont consignées dans la langue officielle dans laquelle elles sont traduites. Les modifications apportées à une demande de brevet européen ou à un brevet européen sont consignées au procès verbal dans la langue de la procédure.

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Dated: April 5, 2023
Electronic Signature for Frances Tsai: /Frances Tsai/

Docket No.: 1147-US-P2C2DC
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Benjamin Micah Collman et al.

Application No.: 17/738,803

Confirmation No.: 2232

Filed: May 6, 2022

Art Unit: 1615

For: THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS

Examiner: J. N. Worsham

INFORMATION DISCLOSURE STATEMENT (IDS)

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

Pursuant to 37 C.F.R. §§ 1.56, 1.97, and 1.98, the attention of the United States Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of the above-identified application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Information Disclosure Statement is filed more than three months after the filing date of this application, OR more than three months after the date of entry of the national stage in the international application, AND after the mailing date of a first Office Action on the merits, but before the mailing date of any of a Final Action under 37 C.F.R. § 1.113, a Notice of Allowance under 37 C.F.R. § 1.311 or an action that otherwise closes prosecution in this application (37 C.F.R. § 1.97(c)).

In accordance with 37 C.F.R. § 1.98(a)(2)(ii), copies of U.S. patents and U.S. patent application publications are not submitted. Submitted herewith are copies of foreign patents and non-patent literature in accordance with 37 C.F.R. § 1.98(a)(2).

#5030514v1

A translation of the non-English language references is attached.

In accordance with 37 C.F.R. § 1.98(d)(1) and as noted by a double-asterisk next to the Cite No. on the attached PTO/SB/08, the following references are not supplied because they were previously cited by or submitted to the Office in prior application numbers 16/987,081 filed August 6, 2020, and 15/346335 filed November 8, 2016 and relied on in the above-identified application for an earlier effective filing date under 35 U.S.C. § 120.

In accordance with 37 C.F.R. § 1.97(g), the filing of this Information Disclosure Statement shall not be construed as a representation that a search has been made. In accordance with 37 C.F.R. § 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that the information cited in this Information Disclosure Statement is, or is considered to be, material to patentability as defined in 37 C.F.R. § 1.56(b).

It is submitted that the Information Disclosure Statement is in compliance with 37 C.F.R. § 1.98, and the Examiner is respectfully requested to consider the listed references.

Please charge our Deposit Account No. 07-1250 in the amount of $260.00 covering the fee set forth in 37 C.F.R. § 1.17(p). The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 07-1250, under Order No. 1147-US-P2C2DC.

Dated: April 5, 2023

Respectfully submitted,

Electronic signature: /Donna Johnson Gressler/
Donna Johnson Gressler
Registration No.: 45,544
GILEAD SCIENCES, INC.
Correspondence Customer Number: 25000
(650) 574-3000
Agent For Applicant

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 13

	Complete if Known
Application Number	17/738,803
Filing Date	May 6, 2022
First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	J. N. Worsham
Attorney Docket Number	1147-US-P2C2DC

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	AA	US-2002-0119443-A1	08-29-2002	Becker et al.	
	AB	US-2003-0219727-A1	11-27-2003	Becker et al.	
	AC	US-2005-0124583-A1	06-09-2005	Becker et al.	
	AD	US-2005-0124584-A1	06-09-2005	Becker et al.	
	AE	US-2005-0124585-A1	06-09-2005	Becker et al.	
	AF	US-2006-0024659-A1	02-02-2006	Becker et al.	
	AG	US-20070099902-A1	05-03-2007	Dahl et al.	
	AH	US-2007/0219243-A1	09-20-2007	Kearney et al.	
	AI	US-2008/0200435-A1	08-21-2008	Stoffels	
	AJ	US-20100285122-A1	11-11-2010	Oliyai et al.	
	AK	US-2013/0243857-A1	09-19-2013	Oliyai et al.	
	AL	US-2014/0142070-A1	05-22-2014	Delaet et al.	
	AM	US-2014/0213556-A1	07-31-2014	DAHL et al.	
	AN	US-2014/0221355-A1	08-07-2014	Lazerwith et al.	
	AO	US-2014/0349971-A1	11-27-2014	Janssen R & D Ireland	
	AP	US-2015/0111856-A1	04-23-2015	Dahl et al.	
	AQ	US-2015/0150810-A1	06-04-2015	OLIYAI et al.	
	AR	US-2015/0283135-A1	10-08-2015	Janssen R & D Ireland	
	AS	US-2016/0016973-A1	01-21-2016	Carra et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	BA**	WO-2004024078-A2	03-25-2004	Merck & Co., Inc		
	BB**	WO-2006030807-A1	03-23-2006	Shionogi & Co., Ltd		
	BC**	WO-2006116764-A1	11-02-2006	Shionogi & Co., Ltd		
	BD**	WO-2008/043829-A2	04-17-2008	Boehringer Ingelheim Int		
	BE**	WO-2013/116720-A1	08-08-2013	Gilead Sciences, Inc		
	BF**	WO-2013/115916-A1	08-08-2013	Gilead Sciences, Inc		

Examiner Signature		Date Considered	

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Dated: April 5, 2023 Electronic Signature for Donna Johnson Gressler: /Donna Johnson Gressler/

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Sheet 2 of 13

Complete if Known	
Application Number	17/738,803
Filing Date	May 6, 2022
First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	J. N. Worsham
Attorney Docket Number	1147-US-P2C2DC

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	AT	US-2016/0194335-A1	07-07-2016	Jin et al.	
	AU	US-2017/0000807-A1	01-05-2017	Koziara et al.	
	AV	US-2017/0027967-A1	02-02-2017	Koziara et al.	
	AW	US-2017/0079999-A1	03-23-2017	DAHL et al.	
	AX	US-2017/0114074-A1	04-27-2017	Jin et al.	
	AY	US-2017/0197985-A1	07-13-2017	Carra et al.	
	AZ	US-2018/0022757-A1	01-25-2018	Chiu et al.	
	AA1	US-2018-0065986-A1	03-08-2018	Carra et al.	
	AB1	US-2018-0215769-A1	08-02-2018	Jin et al.	
	AC1	US-2019-0015420-A1	01-17-2019	Carra et al.	
	AD1	US-7,390,791	06-24-2008	Becker et al.	
	AE1	US-7,803,788	09-28-2010	Becker et al.	
	AF1	US-8,592,397	11-26-2013	Dahl et al.	
	AG1	US-8,598,185	12-03-2013	Dahl et al.	
	AH1	US-8,716,264	05-06-2014	Dahl et al.	
	AI1	US-8,754,065	06-17-2014	Liu et al.	
	AJ1	US-8,841,310	09-23-2014	Janssen R & D Ireland	
	AK1	US-9,018,192	04-28-2015	Dahl et al.	
	AL1	US-9,216,996	12-22-2015	Jin et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	BG**	WO-2014100323-A1	06-26-2014	Gilead Sciences, Inc		
	BH**	WO-2015/022351-A1	02-19-2015	Ratiopharm Gmbh		
	BI**	WO-2015039348-A1	03-26-2015	Merck Sharp & Dohme		
	BJ**	WO-2015/196116-A1	12-23-2015	Gilead Sciences, Inc		
	BK**	WO-2015/196137-A1	12-23-2015	Gilead Sciences, Inc		
	BL**	WO-2017/083304-A1	05-18-2017	Gilead Sciences, Inc		

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 3 of 13

Complete if Known	
Application Number	17/738,803
Filing Date	May 6, 2022
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Art Unit	1615
Examiner Name	J. N. Worsham
Attorney Docket Number	1147-US-P2C2DC

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	AM1	US-9,296,769	03-29-2016	Liu et al.	
	AN1	US-9,457,036	10-04-2016	Dahl et al.	
	AO1	US-9,545,414	01-17-2017	Dahl et al.	
	AP1	US-9,663,528	05-30-2017	Desai et al.	
	AQ1	US-9,682,084	06-20-2017	Carra et al.	
	AR1	US-9,708,342	07-18-2017	Carra et al.	
	AS1	US-9,732,092	08-15-2017	Jin et al.	
	AT1	US-10,035,809	07-31-2018	Bacon et al.	
	AU1	US-10,098,886	10-16-2018	Carra et al.	
	AV1	US-10,385,067	08-20-2019	Carra et al.	
	AW1	US-2015/0018359-A1	01-15-2015	DESAI et al.	
	AX1	US-10,548,846-B2	02-04-2020	Collman et al.	
	AY1	US-2017/0189337-A1	07-06-2017	Collman et al.	
	AZ1	US-2021/0052502-A1	02-25-2021	Collman et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	BM**	WO-2020/091197-A1	05-07-2020	Ulsan Nat Inst Science & Tech Unist		

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Sheet 4 of 13

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First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	J. N. Worsham
Attorney Docket Number	1147-US-P2C2DC

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CA**	AHMED, N. et al. (2015) "BHIVA Guidelines for the Treatment of HIV-1-Positive Adults With Antiretroviral Therapy 2015" *British HIV Association* 1-5.	
	CB**	AULTON, M.E. (1988) "Tablets and Compaction" *Pharmaceutics: The Science of Dosage Form Design* 27(2):410-412.	
	CC**	British Medical Association and Royal Pharmaceutical Society of Great Britain (2016) "British National Formulary" 557-566.	
	CD**	Business Wire (2015) "European Medicines Agency Validates Gilead's Marketing Application for Fixed-Dose Combination of Emtricitabine and Tenofovir Alafenamide for HIV Treatment" 1-2.	
	CE**	Business Wire (2015) "Gilead Submits New Drug Application to U.S. Food and Drug Administration for Single Tablet Regimen for HIV Containing Rilpivirine, Emtricitabine and Tenofovir Alafenamide (R/F/TAF) 1-3.	
	CF**	Business Wire (2016) "U.S. Food and Drug Administration Approves Descovy (Emtricitabine, Tenofovir Alafenamide), Gilead's Third TAF-Based HIV Therapy" 1-4.	
	CG**	CLAYDEN, P. et al. (2015) "HIV, Hepatitis C Virus (HCV), And Tuberculosis (TB) Drugs, Diagnostics, Vaccines, Preventive Technologies, Research Toward a Cure, and Immune-Based and Gene Therapies in Development" *2015 Pipeline Report* 1-183.	
	CH**	EMA Viread Authorization (2017) "Product Details" *European Medicines Agency*.	
	CI**	Eron, Joe et al. (2016) "Retesting of suspected low-level HIV-1 viral load blips: A new paradigm to prevent extra clinic visits and unnecessary patient anxiety" Abstract, 10/28/2016 New Orleans	
	CJ**	EU Clinical Trials Reigster (2020) "A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of GS-9883/Emtricitabine/Tenofovir Alafenamide Versus Dolutegravir + Emtricitabine/Tenofovir Alafenamide in HIV-1 Infected, Antiretroviral Treatment-Naive Adults"	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 5 of 13

Complete if Known	
Application Number	17/738,803
Filing Date	May 6, 2022
First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	J. N. Worsham
Attorney Docket Number	1147-US-P2C2DC

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	CK**	Examination Report dated 2018-08-15 for New Zealand Appl. No. 741957.	
	CL**	Examination Report dated 2019-11-05 for Australian Appl. No. 2016354007.	
	CM**	Extended European Search Report dated 2020-03-11 for European Appl. No. 19186760.5.	
	CN**	Gallant Joel et al. (2016) Abstract "Novel INSTI GS-9883 10 Day Monotherapy in HIV-1 Infected Subjects " ASM2016	
	CO**	Gallant, Joel et al. (2016) "Novel Integrase Strand Transfer Inhibitor Bictegravir 10 Day Monotherapy in HIV-1-Infected Patients" ASMMicrobe2016	
	CP**	JERAJ, Z. (2020) "Experimental Report" 1-5.	
	CQ**	JOHNSON, L. (2015) "Gilead's New Four-in-One HIV Pill, Genvoya, Wins US Approval" *Medical Xpress.*	
	CR**	Jones, Gregg et al. (2016) Poster #413 "Bictegravir (GS-9883), a Novel HIV-1 Integrase Strand Transfer Inhibitor (INSTI) with Optimized In Vitro Resistance Profile"	
	CS**	KULKARNI, R. et al. (2014) "The Combined Anti-HIV-1 Activies of Emtricitabine and Tenofovir plus the Integrase Inhibitor Elvitegravir or Raltegravir Show High Levels of Synergy In Vitro" *Antimicrobial Agents and Chemotherapy* 58(10):6145-6150.	
	CT**	Lazerwith, Scott E. (2016) Poster #414 "Discovery of Bictegravir (GS-9883), a Novel, Unboosted, Once-Daily HIV-1 Integrase Strand Transfer Inhibitor (INSTI) with Improved Pharmacokinetics and In Vitro Resistance Profile"	

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Sheet 6 of 13

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	CU**	Lazerwith, Scott E. et al. Abstract "Discovery of GS-9883, an HIV-1 Integrase Strand Transfer Inhibitor (INSTI) with Improved Pharmacokinetics and In Vitro Resistance Profile "	
	CV**	Moss et al. (2012) Divalent metals and pH alter raltegravir disposition *in vitro*." American Society for Microbiology doi:10.1128/AAC.05407-11	
	CW**	Notice of Final Rejection dated 2020-03-19 for Korean Appl. No. 10-2018-7015929.	
	CX**	Notice of Opposition dated 2020-05-27 for European Patent No. 3346995 (Dr. Richard Cooke).	
	CY**	Notice of Opposition dated 2020-05-27 for European Patent No. 3346995 (Teva Pharmaceutical Industries Ltd.).	
	CZ**	Notice of Opposition dated 2020-05-28 for European Patent No. 3346995 (Sandoz GmbH).	
	CA1**	Notice of Preliminary Rejection dated 2019-09-04 for Korean Appl. No. 10-2018-7015929.	√
	CB1**	ODEFSEY Approval Package (2016) "Center for Drug Evaluation and Research"	
	CC1**	Office Action dated 2018-09-18 for Bolivian Appl. No. SP260-2016.	√
	CD1**	Office Action dated 2018-10-03 for Panamanian Appl. No. 92163.	√

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	CE1**	Office Action dated 2018-11-13 for Pakistani Appl. No. 696/2016.	
	CF1**	Office Action dated 2019-01-21 for European Appl. No. 16798063.0.	
	CG1**	Office Action dated 2019-03-25 for Bolivian Appl. No. SP260-2016	
	CH1**	Office Action dated 2019-09-22 for Gulf Cooperation Council Appl. No. 2016-32320.	
	CI1**	Office Action dated 2020-03-27 for Chinese Appl. No. 201680065167.3.	
	CJ1**	Office Action received 2019-05-27 for El Salvadorian Appl. No. 2018005682	
	CK1**	Office Action received 2019-07-01 for Eurasian Appl. No. 201890654	
	CL1**	Opposition dated 2017-06-20 for Colombian Appl. No. 15-265.717	√
	CM1**	PARK, T. et al. (2015) "Review of Integrase Strand Transfer Inhibitors for the Treatment of Human Immunodeficiency Virus Infection" *Expert Rev. Anti Infect. Ther.* 13(10):1195-1212.	
	CN1**	Patel, Parul et al. (2014) "Relative bioavailability of a paediatric granule formulation of the HIV intergrase inhibitor dolutegravir in healthy adult subjects." Antiviral Therapy (19):229-233	

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	CO1**	PATRICK, M. (2015) "Analyzing Gilead Sciences' Research and Development in 3Q15" *Market Realist* 1-2.	
	CP1**	Sax, P. et al. (2014) "Tenofovir Alafenamide Vs. Tenofovir Disoproxil Fumarate in Single Tablet Regimens for Initial HIV-1 Therapy: A Randomized Phase 2 Study" *J Acquir Immune Defic Syndr* 67(1):52-58.	
	CQ1**	Sax, Paul E. (2016) "Randomized Trial of Bictegravir or Dolutegravir with FTC/TAF for Initial HIV Therapy" CROI BIC 09/08/2016	
	CR1**	Search Report - Intl Search Report - Written Opinion dated January 24, 2007 for PCT/US2016/060989	
	CS1**	SHAH, B. et al. (2014) "Dolutegravir: A new Integrase Strand Transfer Inhibitor for the Treatment of HIV" *Pharmacotherapy* 34(5):506-520.	
	CT1**	SHENDE, P. et al. (2012) "Multi-layer Tablet: Current Scenario and Recent Advances" *International Journal of Drug Delivery* 4(4):418-426.	
	CU1**	Thomson Reuters Drug News (2011) "Gilead and Tibotec finalize agreement on single-tablet HIV regimen" http://drugnews.thomson-pharma.com/ddn/article.do?id=113441&source=Company Communication&section=AIDS#	
	CV1**	TIVICAY Product Label (Revised September 2018) GlaxoSmithKline, 44 Pages.	
	CW1**	TRIUMEQ Product Label (Revised November 2017) GlaxoSmithKline, 48 Pages.	
	CX1**	Tsiang, M. et al. "Antiviral Activity of GS-9883, a Potent Next Generation HIV-1 Integrase Strand Transfer Inhibitor" (ASMMicrobe20161)	

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Sheet	9	of	13

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Art Unit	1615
Examiner Name	J. N. Worsham
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	CY1**	Tsiang, M. et al. "GS-9883, a Novel HIV-1 Integrase Strand Transfer Inhibitor (INSTI) with Optimized In Vitro Resistance Profile" (ASMMicrobe20162)	
	CZ1**	Tsiang, M. et al. (2016) Poster #416 "Antiviral Activity of Bictegravir (GS-9883), a Potent Next Generation HIV-1 Integrase Strand Transfer Inhibitor"	
	CA2**	U.S. National Library of Medicine (2019) "Safety and Efficacy of Switching to a FDC of GS-9883/F/TAF From E/C/F/TAF, E/C/F/TDF, or ATV+RTV+FTC/TDF in Virologically Supressed HIV-1 Infected Women" ClinicalTrials.gov. 1-8.	
	CB2**	USAN (2016) "Statement on a Nonproprietary Name Adopted by the USAN Council"	
	CC2**	Viread Draft Labeling (2001) Center for Drug Evaluation and Research 1-26.	
	CD2**	White, Kristen et al. (2016) "Potent Activity of Bictegravir (BIC; GS-9883), a Novel Unboosted; HIV-1 Integrase Strand Transfer Inhibitor (INSTI), Against Patient Isolates; with INSTI-Resistance" EU Workshop HIV Hepatitis;	
	CE2**	White, Kristen et al. (2016) Poster "The Integrase Strand Transfer Inhibitor Bictegravir has; a Long Integrase/DNA Dissociation Half-life" ;	
	CF2**	White, Kristen et al. (2016) The Integrase Strand Transfer Inhibitor Bictegravir has a Long Integrase/DNA Dissociation Half-life	
	CG2**	White, Kritsten et al. (2017) "Bictegravir Dissociation Half-life from HIV-1 G140S+Q148H Integrase/DNA Complexes " CROI BIC	
	CH2**	World Health Organization (2007) "Guidance on the Establishment of New INN Stems" 1-2.	

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Sheet 10 of 13

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Art Unit	1615
Examiner Name	J. N. Worsham
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	CI2**	World Health Organization (2013) "The Use of Stems in the Selection of International Nonproprietary Names (INN) for Pharmaceutical Substances" 1-192.	
	CJ2**	World Health Organization Drug Information (2015) "International Nonproprietary Names for Pharmacuetical Substances (INN)" 29(2):1-107.	
	CK2**	YOSHINAGA, T. et al. (2015) "Antivrial Characteristics of GSK1265744, an HIV Integrase Inhibitor Dosed Orally or by Long-Acting Injection" *Antimicrobial Agents and Chemotherapy* 59(1):397-406.	
	CL2**	Zhang et al. (2017) "Clinical Pharmacology of the HIV Integrase Strand Transfer Inhibitor Bictegravir " CROI BIC 09/26/2016	
	CM2	ClinicalTrials.gov Archive. (2014) "A Phase 1b Randomized, Double-Blinded, Sequential Cohort Placebo-Controlled Study of the Safety, Pharmacokinetics, and Antiviral Activity of GS-9883 in HIV-1 Infected Subjects", https://clinicaltrials.gov/archive/NCT02275065/2014_10_26, 3 pages.	
	CN2	European Medicines Agency, Committee for Medicinal Products for Human Use. (2018) "Assessment report - Biktarvy". 104 pages.	
	CO2	ClinicalTrials.gov Archive. (2015) "A Phase 2, Randomized, Double-Blinded Study of the Safety and Efficacy of GS-9883 + Emtricitabine/Tenofovir Alafenamide Versus Dolutegravir + Emtricitabine/Tenofovir Alafenamide in HIV-1 Infected, Antiretroviral Treatment-Naive Adults", https://clinicaltrials.gov/archive/NCT02397694/2015_03_24, 4 pages.	
	CP2**	Exam Report dated 2019-07-26 for Indian Appl. No. 201817013772.	
	CQ2	Examination Report dated 2021-03-24 for Australian Appl. No. 2020200995, 5 pages.	
	CR2	KOMMAVAPARU, P. et al. (2015) "Preparation and characterization of rilpivirine solid dispersions with the application of enhanced solubility and dissolution rate", Beni-Suef University Journal of Basic and Applied Sciences 4, pp. 71-79.	

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	CT2	ZIGA. (2021) Experimental Report, Sandoz GmbH, 8 pages.	
	CU2	SMITH, S. et al. (2018) "Efficacies of Cabotegravir and Bictegravir against drug-resistant HIV-1 integrase mutant", Retrovirology 15(37), 18 pages.	
	CV2	ACOSTA, R. et al. (2021) "*In Vitro* Forgiveness of Oral and Long-Acting INSTI-Containing Regiments at Drug Concentrations Simulating Variable Adherence", 18th European AIDS Conference, 1 page.	
	CW2	LOZANO, A. et al. (2020) "Failure to bictegravir and development of resistance mutations in an antiretroviral-experienced patient", Antiviral Research 179, 104717, pp. 1-4.	
	CX2	CHAMBERLAIN N. et al. (2021) "Case Report: Emergent Resistance in a Treatment-Naïve Person With Human Immunodeficiency Virus Under Bictegravir-Based Therapy", Open Forum Infectious Diseases, pp. 1-3.	
	CY2	SONG I. et al. (2009) Poster - Pharmacokinetic (PK) and Pharmacodynamic (PD) Relationship of S/GSK1349572, a Next Generation Integrase Inhibitor (INI), in HIV-1 Infected Patients, 5th International AIDS (IAS) Conference on HIV Pathogenesis, Treatment and Prevention, 1 page.	
	CZ2	ERON. (2009) Report - New Drugs, New strategies, 5th International AIDS (IAS) Conference on HIV Pathogenesis, Treatment and Prevention, 5 pages.	
	CA3	Notice of Preliminary Rejection dated 2021-12-23 for Korean Appl. No. 10-2020-7025458, 4 pages.	
	CB3	Office Action dated 2022-05-24 for Taiwanese Appl. No. 110129951, 23 pages.	√

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	CD3	Office Action and Search Report dated 2022-07-27 for Chinese Appl. No. 202110669391.6, 18 pages.	√
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	CG3	Notice of Preliminary Rejection dated 2023-03-23 for Korean Appl. No. 10-2023-7001933, 4 pages.	
	CH3	Patentee's Response to Oppositions dated 2021-01-11 for European Patent No. EP3346995, 24 pages.	
	CI3	Brief Communication and Further Submissions from Opponent Dr. Richard Cooke dated 2021-03-09 for European Patent No. EP3346995, 6 pages.	
	CJ3	Brief Communication and Further Submissions from Opponent Sandoz GmbH dated 2021-03-24 for European Patent No. EP3346995, 12 pages.	
	CK3	Brief Communication and Further Submissions from Opponent Teva Pharmaceutical Industries Ltd. dated 2021-03-26 for European Patent No. EP3346995, 10 pages.	
	CL3	Summons to Attend Oral Proceedings and Preliminary Opinion dated 2021-06-24 for European Patent No. EP3346995, 19 pages.	

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	CP3	Further Submissions and Response to Preliminary Opinion from Opponent Teva Pharmaceutical Industries Ltd. dated 2022-08-25 for European Patent No. EP3346995, 10 pages.	
	CQ3	Further Submissions from Opponent Dr. Richard Cooke dated 2022-08-26 for European Patent No. EP3346995, 6 pages.	
	CR3	Further Submissions from Opponent Sandoz GmbH dated 2022-08-26 for European Patent No. EP3346995, 3 pages.	
	CS3	Patentee's Response to Summons and Written Submissions dated 2022-08-26 for European Patent No. EP3346995, 5 pages.	
	CT3	Interlocutory Decision and Minutes of the Oral Proceedings dated 2022-12-23 for European Patent No. EP3346995, 101 pages.	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

#5030513V1

ClinicalTrials.gov archive
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← History of this study | Current version of this study

View of NCT02397694 on 2015_03_24

ClinicalTrials Identifier: NCT02397694
Updated: 2015_03_24

Descriptive Information

Brief title	Safety and Efficacy of GS-9883 + Emtricitabine/Tenofovir Alafenamide Versus Dolutegravir + Emtricitabine/Tenofovir Alafenamide in HIV-1 Infected, Antiretroviral Treatment-Naive Adults
Official title	A Phase 2, Randomized, Double-Blinded Study of the Safety and Efficacy of GS-9883 + Emtricitabine/Tenofovir Alafenamide Versus Dolutegravir + Emtricitabine/Tenofovir Alafenamide in HIV-1 Infected, Antiretroviral Treatment-Naive Adults

Brief summary

This study will evaluate the efficacy, safety and tolerability of GS-9883 + emtricitabine/tenofovir alafenamide (FTC/TAF) fixed dose combination (FDC) versus dolutegravir (DTG) + FTC/TAF in HIV-1 Infected, antiretroviral treatment-naive adults. This study will also evaluate the pharmacokinetic (PK) profile of GS-9883, FTC and TAF.

Detailed description

Phase	Phase 2
Study type	Interventional
Study design	Treatment
Study design	Randomized
Study design	Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Study design	Parallel Assignment
Study design	Efficacy Study
Primary outcome	Measure: Percentage of participants with HIV-1 RNA < 50 copies/mL as determined by the FDA-defined snapshot algorithm. Time Frame: Week 24 Safety Issue? No
Secondary outcome	Measure: Percentage of participants with HIV-1 RNA < 50 copies/mL as determined by the FDA-defined snapshot algorithm. Time Frame: Week 12 Safety Issue? No
Secondary outcome	Measure: Percentage of participants with HIV-1 RNA < 50 copies/mL as determined by the FDA-defined snapshot algorithm. Time Frame: Week 48 Safety Issue? No

Secondary outcome	Measure: The change from baseline in log10 HIV-1 RNA and in CD4+ cell count Time Frame: Weeks 12, 24 and 48 Safety Issue? No
Secondary outcome	Measure: The incidence of treatment-emergent adverse events (AEs) and treatment-emergent laboratory abnormalities. Time Frame: Up to 1 year Safety Issue? No
Secondary outcome	Measure: Maximum observed plasma concentration (Cmax) of GS-9883, FTC, and TAF Time Frame: Week 4 or 8 Safety Issue? No Description: For a subset of participants who enroll in the PK substudy.
Secondary outcome	Measure: Time to maximum observed plasma concentration (Tmax) of GS-9883, FTC, and TAF Time Frame: Week 4 or 8 Safety Issue? No Description: For a subset of participants who enroll in the PK substudy.
Secondary outcome	Measure: Observed drug concentration at the end of the dosing interval (Ctau) for GS-9883, FTC, and TAF Time Frame: Week 4 or 8 Safety Issue? No Description: For a subset of participants who enroll in the PK substudy.
Secondary outcome	Measure: Area under the concentration-time curve over the dosing interval (AUCtau) for GS-9883, FTC, and TAF Time Frame: Week 4 or 8 Safety Issue? No Description: For a subset of participants who enroll in the PK substudy. AUCtau is defined as concentration of drug over time.
Secondary outcome	Measure: Estimate of the terminal elimination half-life (t1/2) of GS-9883, FTC, and TAF Time Frame: Week 4 or 8 Safety Issue? No Description: For a subset of participants who enroll in the PK substudy.
Secondary outcome	Measure: Trough plasma concentrations for GS-9883, FTC, and TAF Time Frame: Weeks 4, 8, 12 and 24 Safety Issue? No Description: This endpoint will measure the plasma concentrations of GS-9883, FTC, and TAF.
Enrollment	75 (Anticipated)

Condition	HIV-1 Infection
Arm/Group	Arm Label: Treatment Arm 1 Experimental - Participants will receive GS-9883 + FTC/TAF FDC + placebo to match DTG once daily for 48 weeks. - Following Week 48, participants will continue to take their blinded treatment and attend visits every 12 weeks until treatment assignments have been unblinded. Participants will return for an unblinding visit and be given the option to participate in an open-label rollover extension and receive GS-9883 + FTC/TAF until it becomes commercially available, or until Gilead Sciences elects to terminate the development of GS-9883 or FTC/TAF.
Arm/Group	Arm Label: Treatment Arm 2 Active Comparator - Participants will receive DTG + FTC/TAF FDC + placebo to match GS-9883 once daily for 48 weeks. - Following Week 48, participants will continue to take their blinded treatment and attend visits every 12 weeks until treatment assignments have been unblinded. Participants will return for an unblinding visit and be given the option to participate in an open-label rollover extension and receive GS-9883 + FTC/TAF until it becomes commercially available, or until Gilead Sciences elects to terminate the development of GS-9883 or FTC/TAF.
Intervention	Drug: FTC/TAF Arm Label: Treatment Arm 1 Emtricitabine/Tenofovir Alafenamide (FTC/TAF) 200 mg/25 mg tablet administered orally
Intervention	Drug: GS-9883 Arm Label: Treatment Arm 1 GS-9883 75 mg tablet administered orally
Intervention	Drug: DTG Arm Label: Treatment Arm 2 Dolutegravir (DTG) 50 mg tablet administered orally
Intervention	Drug: Placebo to match GS-9883 Arm Label: Treatment Arm 2 Tablet administered orally
Intervention	Drug: Placebo to match DTG Arm Label: Treatment Arm 1 Tablet administered orally

Recruitment Information

Status	Recruiting
Start date	2015-03
Last follow-up date	2016-05 (Anticipated)
Primary completion date	2015-12 (Anticipated)
Criteria	

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Inclusion Criteria:
- Antiretroviral naive (≤ 10 days of prior therapy with any antiretroviral agent following a
diagnosis of HIV-1 infection) except the use for pre-exposure prophylaxis (PREP) or post-exposure prophylaxis (PEP), up to one month prior to screening.
- Plasma HIV-1 RNA levels ≥ 1,000 copies/mL at screening.
- Screening genotype report provided by Gilead Sciences must show sensitivity to tenofovir (TFV) and
FTC.
- Adequate renal function as measured by estimated glomerular filtration rate ≥ 50 mL/min according to the Cockcroft-Gault formula
- CD4+ cell count > 50 cells/μL at screening.

Exclusion Criteria:
- A new AIDS-defining condition diagnosed within the 30 days prior to screening as defined in the study protocol
- Chronic Hepatitis B Virus (HBV) infection
- Hepatitis C infection (individuals who are hepatitis C virus (HCV) Ab positive, but have a documented negative
HCV RNA, are eligible)
- Active, serious infections (other than HIV-1 infection) requiring parenteral antibiotic or
antifungal therapy within 30 days prior to Baseline
- Participation in any other clinical trial without prior approval from the sponsor is prohibited
while participating in this trial

Gender	Both
Minimum age	18 Years
Healthy volunteers	No

Administrative Data

Organization name	Gilead Sciences
Organization study ID	GS-US-141-1475
Sponsor	Gilead Sciences
Health Authority	United States: Food and Drug Administration

Australian Government
IP Australia

24 March 2021

Examination report No. 1 for standard patent application

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Davies Collison Cave Pty Ltd
Level 15
1 Nicholson Street
MELBOURNE VIC 3000
Australia

Your reference	35538924/MJC/GDB/VZS
Application number	2020200995
Applicant name	Gilead Sciences, Inc.
Earliest priority date	09 November 2015

Final date for acceptance:	**24 March 2022**
Date of this report:	24 March 2021
Examination request date:	14 April 2020

Dear Davies Collison Cave Pty Ltd,

Your application has been examined under *section 45 of the Patents Act 1990*. I consider that this application does not meet the requirements of the Act because there are issues with the application that are explained in the report details.

You have **12 months** from the date of this report to overcome all my objection(s) otherwise this application will lapse.

You will also need to pay any annual continuation fees that apply. Your next continuation fee is due on **8 November 2021**.

NOTE: There is a current postponement of acceptance in place. If you overcome all other objections before the expiration of that postponement, the Commissioner will only accept the application at that time if you have filed a clear and unambiguous statement requesting the withdrawal of that postponement. Otherwise, a further adverse report will be issued.

Your reference	35538924/MJC/GDB/VZS
Application number	2020200995

Details of this patent application can be viewed on AusPat, our Australian patent search database.

Yours sincerely,

Thomas Case
Section: CHEM 5 - PHARMACEUTICALS
Phone: (612) 6283 2656

Supervisor: Catherine Downes
Phone: (612) 6283 2527

IP Australia recognises that many of our customers may be struggling with the impacts of COVID-19. We remain open for business and our staff are working from home to ensure that our services can continue. We are committed to supporting you and we are here to help you through these difficult times. We have put in place a streamlined process for extension of time requests and associated fee waivers or refunds to assist customers impacted by the COVID-19 outbreak. Please visit our website (www.ipaustralia.gov.au) for guidance and Frequently Asked Questions (FAQs) related to your IP Right. If you would like to discuss your particular circumstances, please contact us directly. We will continue to update our website and FAQs with the latest information.

Report details

Basis of the report

In examining this application I have considered:

- the specification as filed
- allowed and/or proposed amendment/s under S104 up to and including amendment item number 3, filed on 22 April 2020.

Summary of novelty, inventive step and patentable subject matter

	Satisfy requirements?	*Claim numbers*
Novelty/inventive step	**Yes**	NONE
	No	1-14
Patentable subject matter	**Yes**	1-14
	No	NONE

Detailed objections on issues that have been identified

Documents cited or considered relevant

D1 : WO 2015/196116 A1 (GILEAD SCIENCES, INC) 23 December 2015 [1]
Category: **P,X** Claims: 1, 4, 7 and 9

D2 : WO 2015/196137 A1 (GILEAD SCIENCES, INC) 23 December 2015 [1]
Category: **P,X** Claims: 1, 4, 7 and 9

D3 : WO 2014/100323 A1 (GILEAD SCIENCES, INC) 26 June 2014 [1]
Category: **X** Claims: 7
Category: **Y** Claims: 1-14

D4 : WO 2013/116720 A1 (GILEAD SCIENCES, INC) 08 August 2013 [1]
Category: **X** Claims: 7
Category: **Y** Claims: 1-14

D5 : WO 2015/022351 A1 (RATIOPHARM GMBH) 19 February 2015 [1]
Category: **Y** Claims: 1-14

[1] Cited in EP 19 186 760.5

Special categories of cited documents:

X: The claimed invention cannot be considered novel under subsection 7(1) in light of the document and/or cannot be considered to involve an inventive step under subsection 7(2) of the Act in light of the common general knowledge considered together with the document.

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Y: The claimed invention cannot be considered to involve an inventive step under subsection 7(2) of the Act in light of the common general knowledge when considered together with a combination of the document and one or more other such documents.
P: Document published prior to the filing date but on or after the priority date claimed

Novelty and inventive step

1 Claims 1, 4, 7 and 9 are not novel when compared with D1.

-Although it was published later than the priority date of the present claims its information has an earlier priority date than the present claims.

D1 discloses compositions comprising compounds of Formula I and II (the sodium salt thereof) ([0002]) for the treatment of HIV ([0008-0014]). D1 discloses compositions comprising 25-100 mg Formula II, 5-30 mg tenofovir alafenamide and 200 mg emtricitabine ([0058, 0096]; claims 12-18). D1 discloses pharmaceutical compositions that are solid oral dosage forms such as tablets and capsules ([0065]). D1 discloses compositions comprising microcrystalline cellulose and croscarmellose sodium as excipients ([0145]).

A similar objection also applies with D2.

2 Claim 7 is not novel or inventive in light of D3 or D4.

Note that this claim is directed to the specific layer (i) or (ii) and does not comprise the other layer of the tablet. A single dosage form is within the scope of these claims.

D3 discloses single dosage forms comprising compounds of Formula I (see page 40; example 42). D4 discloses a monolayer and bilayer tablet comprising in one single layer tenofovir alafenamide and emtricitabine compressed together.

3 Claims 1-14 are not inventive in light of D3 when combined with anyone of D4 or D5.

D3 discloses compounds of Formula I and II in the treatment of HIV (see abstract, example 42) and suggests combination therapy with other anti-HIV agents such as emtricitabine and tenofovir alafenamide (page 38).

D3 does not directly disclose the solid dosage form as defined in the present claims comprising compounds of Formula I, emtricitabine and tenofovir alafenamide. D4 and D5 both disclose compositions comprising combinations of emtricitabine and tenofovir alafenamide.

It is noted that the application has not described any unexpected or surprising effect such as synergy resulting from the specific combination of Formula I, emtricitabine and tenofovir alafenamide. It does not involve an inventive step to combine multiple agents known for treating the same condition into one composition. Therefore, it would be obvious to the person skilled in the art to combine the known anti-HIV drugs of Formulas I/II (D3) with other known anti-HIV drugs emtricitabine and tenofovir alafenamide (D4, D5) into one formulation.

Claim features relating to specific formulation options such: as coated tablets; multilayered tablets; specific excipients including croscarmellose sodium, magnesium stearate, microcrystalline cellulose; and particular concentrations of active ingredients are not considered to provide an inventive step over the prior art. Such features are obvious to the person skilled in the art as they relate to routine or standard pharmaceutical formulation

options known in the art. It would not be inventive to package such a composition in a kit with desiccants.

END OF REPORT

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Antiviral Research 179 (2020) 104717

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/antiviral

Failure to bictegravir and development of resistance mutations in an antiretroviral-experienced patient

Ana Belén Lozano[a], Natalia Chueca[b,c], Adolfo de Salazar[b,c], Elisa Fernández-Fuertes[a], Antonio Collado[d], Juan Manuel Fernández[a], Marta Álvarez[b,c], Federico García[b,c,*]

[a] Hospital de Poniente, El Ejido, Almería, Spain
[b] Hospital Clínico Universitario San Cecilio, Granada, Spain
[c] Instituto de Investigación Biosanitaria ibs, Granada, Spain
[d] Hospital Torrecárdenas, Almería, Spain

ARTICLE INFO

Keywords:
Bictegravir
Virological failure
R263K

ABSTRACT

We present here one of the first cases of virological failure during treatment with bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF). On March 2019, an antiretroviral-experienced HIV-infected patient was admitted to hospital because of cerebral toxoplasmosis. After undergoing treatment with sulfadiazine-pyrimethamine for two weeks, the patient initiated a BIC/FTC/TAF treatment, with 6.01 HIV RNA Log copies/mL, and 37 CD4 cells/μL. After two months under antiretroviral therapy (ART), acute neurologic deterioration with epilepsy, right hemiparesis and dysphagia occurred, leading to nasogastric nutrition and treatment. After several weeks, virological failure was confirmed with 4.61 HIV RNA Log copies/mL and R263K and M184V resistance mutations were detected.

Bictegravir is a novel, potent integrase strand inhibitor (INSTI) with a high barrier to resistance, a favorable pharmacokinetic profile and very few drug-drug interactions. Bictegravir has recently been approved as a single tablet regimen with emtricitabine and tenofovir alafenamide as a once daily regimen (BIC/FTC/TAF) for the treatment of HIV infection. BIC/FTC/TAF safety and efficacy has been demonstrated in controlled clinical trials in treatment-naïve adults (Gallant et al., 2017; Sax et al., 2017; Wohl et al., 2019; Stellbrink et al., 2019), suppressed switch adults (Daar et al., 2018; Molina et al., 2018), adolescents and children. BIC/FTC/TAF has also proved its efficacy in patients with both archived M184V/I mutation (Andreatta et al., 2019), and/or patients with known or suspected resistance to nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors (PIs), and/or non-NRTIs (NNRTIs), but no documented INSTI resistance or confirmed virologic failure on an INSTI-containing regimen. No treatment-emergent resistance or breakthrough has been detected in any treatment-naïve or virologically suppressed participant in the clinical trials of BIC/FTC/TAF.

Bictegravir has shown a potent antiviral activity *in vitro* against multiple integrase mutants, including raltegravir-resistant double mutant G140S/Q148H and dolutegravir-resistant integrase mutants G118R, R263K, and H51Y/R263K (Tsiang et al., 2016; Hightower et al., 2017; Smith et al., 2018). *In vitro* experiments have also shown how R263K mutation conferred low-level resistance to bictegravir (< 3-fold) after serial passages at weeks 36–46 (Oliveira et al., 2018). The R263K integrase mutation is a substitution diminishing HIV DNA integration and viral fitness (Mesplède et al., 2017).

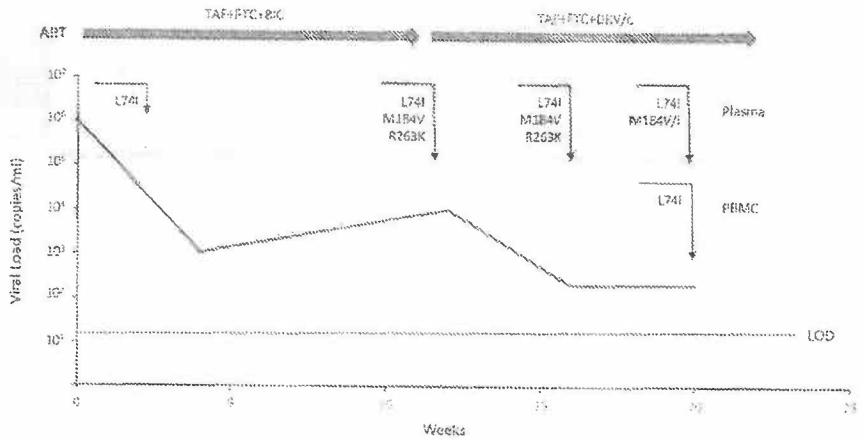
Here, we present a case of a virological failure during treatment with BIC/FTC/TAF, with resistance mutations at position M184V in the reverse transcriptase (RT) and at position R263K in the integrase.

The study was approved by the Ethics Committee of El Ejido & Torrecárdenas Hospitals (Almería), having the patient's informed consent for the study.

A 39-year-old woman from Nigeria, living in Spain, was diagnosed with HIV-1 infection in 2011. At diagnosis, the patient suffered from pulmonary tuberculosis, she was immunosuppressed (129 CD4 cells/μL) and she had 2,398,832 HIV RNA copies/mL. The patient started lopinavir$_{ritonavir}$/tenofovir difumarate/emtricitabine therapy. The patient was lost to follow-up on August 2012. She returned to the hospital on February 2013 and started on raltegravir/abacavir/emtricitabine therapy with 2,700,000 HIV RNA copies/mL, and 86 CD4 cells/μL. Patient was lost to follow-up again on February 2014 until she returned to the hospital once more on April 2017. Raltegravir/abacavir/emtricitabine was then re-initiated until the patient was lost to follow-up again on June 2017. The patient was admitted to the hospital on March 2019 because of cerebral toxoplasmosis. After two weeks under

* Corresponding author. Hospital Universitario San Cecilio, Avenida de la Ilustración S/n, 18016, Granada, Spain.
E-mail address: fegarcia@ugr.es (F. García).

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Mutation	Wk 0	Wk 12	Wk 16	Wk 20 (Plasma)	Wk 20 (Cells)
		% Prevalence; copies/ml			
M184V	0%; 0	5%; 511	25%; 51	29%; 59*	0%
L74I	52%; 540372	97%; 9925	97%; 198	83%; 169	93%
R263K	0%; 0	96%; 9822	33%; 67	0%; 0	0%

* 8% M184I: 16 copies/mL

Fig. 1. Virological evolution of the patient since initiation of Biktarvy ®.
TAF: tenofovir alafenamide; FTC: emtricitabine; BIC: bictegravir; DRV/c: darunavir, cobicistat. Viral load is expressed as HIV RNA copies/mL; LOD: Limit of detection.

treatment with sulfadiazine-pyrimethamine, a viral load of 1,023,292 HIV RNA copies/mL, and 37 CD4 cells/μL, and a CRF02_AG wild-type virus in the integrase, protease, and reverse transcriptase (RT) were found and the patient initiated a BIC/FTC/TAF treatment. For resistance testing we used the Illumina MiSeq platform for deep sequencing of HIV amplicons, obtained with the DeepChek®-HIV INT Genotyping Assay and the DeepChek®-HIV RT/PR Genotyping Assay (Advanced Biological Laboratories -ABL SA-, Luxembourg).

After 4 weeks under treatment, viral load was 1,084 copies/mL and CD4 count was 134 cells/μL. Following two months under ART, acute neurologic deterioration with epilepsy, right hemiparesis and dysphagia occurred due to the development of a progressive multifocal leukoencephalopathy-immune reconstitution syndrome. Nasogastric nutrition was started and BIC/FTC/TAF was then crushed and administered as a solution through the nasogastric tube. After 12 weeks of starting BIC/FTC/TAF treatment, viral load was 10,232 copies/mL and a resistance test was ordered, finding a protease wild-type virus, M184V mutation (5% prevalence: 511 copies/mL) in RT, and L74I mutation (97%, 9,925 copies/mL) and R263K mutation (96%, 9,822 copies/mL) in the integrase gene. The median genetic divergence of the viral lineages, estimated using DIVERN (Deng et al., 2019), from April 2019 (before BIC/FTC/TAF) to July 2019 (after BIC/FTC/TAF), and the viral genetic divergence between the two time points were 0.04743254 and 0.00304879 respectively.

Then, ART was changed to emtricitabine and tenofovir alafenamide and darunavir 600 mg/12h + ritonavir 100 mg/12h. One month later, viral load was reduced to 204 copies/mL, finding again M184V (25%, 51 copies/mL) in RT, and L74I (97%, 198 copies/mL) and R263K (33%, 67 copies/mL) in the integrase. Two months after starting the darunavir-based treatment, viral load remained at 204 copies/mL and resistance mutations were investigated in plasma, where the integrase R263K mutation was cleared while M184V remained stable. No mutations were found in RT and protease of proviral DNA from peripheral blood mononuclear cells, and only the L74I mutation (97%) was found in the integrase. Viral load, and resistance findings are shown in Fig. 1.

We present a case of virological failure to BIC/FTC/TAF, with the development of R263K mutation in the integrase and M184V in RT. A severely immunosuppressed patient with a past history of ART failed to BIC/FTC/TAF treatment after its administration through a feeding tube for 6 weeks.

BIC/FTC/TAF is currently recommended as one of the initial regimens for most people with HIV (Panel on antiretroviral g, 2019) and it may be used for switching strategies in patients who are virologically-suppressed on a stable antiretroviral regimen for at least 3 months with no history of treatment failure and no known substitutions associated with resistance to its individual components.

In contrast to other regimens based on second-generation INSTIs, such as dolutegravir, BIC/FTC/TAF is not approved for treating ART-experienced patients because there are no clinical trials demonstrating its efficacy in this population. For dolutegravir-based regimens, virological failure in experienced- and antiretroviral-naïve patients remains very low. Only a few cases of virological failure with the development of R263K mutation, the signature mutation for both bictegravir and dolutegravir, have been reported to date. In general, selection of this mutation was linked to low blood levels of the drug due to drug-drug interactions with rifampin (Pena et al., 2019) or rifabutin (Lübke et al., 2019). In our case report, although we could not test the levels of bictegravir in the blood of our patient, we hypothesize that a dosage of 50 mg of bictegravir every 24 h for the treatment of an antiretroviral-experienced patient (who had been under a first-generation INSTI, such as Raltegravir), administered as

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crushed tablets for liquid administration, have been certainly responsible for inadequate blood levels of the drug that led to the R263K mutation selection. BIC/FTC/TAF is not intended to be administered through a nasogastric tube because crushing BIC/FTC/TAF tablets into a liquid medium is not recommended by the manufacturer. No studies evaluating the pharmacokinetics of a crushed BIC/FTC/TAF tablet dispersed into a liquid medium compared to a whole tablet are available to date. Bictegravir is practically insoluble (solubility of 0.1 mg/mL) in water at 20 °C (https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210251s000lbl.pdf). Non-adherence and prior frequent treatment interruptions with the lower genetic barrier integrase inhibitor raltegravir led to a higher probability of development of resistance mutations, despite they had been ruled out using a 1% cutoff next generation sequencing assay prior to initiating therapy with BIC/FTC/TAF. As virological failure was promptly detected, we believe there was no time for viral evolution that could have compensated the fitness cost on viral replication of R263K, and the mutation was cleared rapidly when bictegravir was replaced with darunavir.

Two additional reports on failure to BIC/FTC/TAF have been recently presented at the 17th European AIDS Conference in November 2019. Vanig et al. (Unpublished results) reported on an antiretroviral experienced patient that fails after three months of treatment; the patient had previously failed TDF/FTC/EVGc with mutations in RT (M184V) and integrase (M50I + N155H), and adds R138K, S147G and R263K in the integrase after failing BIC/FTC/TAF. Andre-Garnier et al. (Unpublished results) reported on a patient infected by HIV-1 subtype B that fails BIC/FTC/TAF after switching from abacavir/lamivudine/dolutegravir, with the addition of A256V in the integrase, a novel mutation that has not been previously described. The patient in our study, was infected by a non-B Subtype (CRF02_AG); although we cannot rule out a potential role of the non-B background on resistance to bictegravir, in vitro studies (Tsiang et al., 2016; Neogi et al., 2017) have demonstrated the activity of bictegravir, as well as other second-generation integrase inhibitors, on non-B subtypes.

As previous exposure to raltegravir and the development of resistance mutations in the integrase may had driven failure to bictegravir, we believe that an important limitation of our study is that we did not have any information on resistance after failure/discontinuation of the raltegravir based regimen. Although we tested for integrase resistance mutations in April 2019, both the facts of the very high viral load (1,023,292 HIV RNA copies/mL) and the prolonged period (22 months) free of antiretroviral therapy may contribute to the finding of a wild-type virus. Also interesting is the finding that both L74I and R263K became dominant (> 95% of the quasispecies population) very early after exposure to bictegravir, and that after 20 weeks on FTC the M184V mutation remained detectable at low levels (below 20% of the viral population). As R263K exerts a great impact on viral fitness, this mutation disappeared very quickly after removing bictegravir from the regimen, while keeping FTC in the new regime may explain why M184V was detectable at low levels.

In summary, after ruling out other possibilities, such as main drug-to-drug interactions, we believe that under-expected concentrations of bictegravir, due to an unintended misuse, are probably responsible for the virological failure and the subsequent development of resistance mutations. We also believe that the interest of this case relies on highlighting that although bictegravir has a high genetic barrier to resistance and a high antiviral activity, standard bictegravir doses may lead to resistance development under stringent conditions, so clinicians must be aware that bictegravir cannot be used under any circumstance outside those recommended by currently available guidelines.

Funding

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Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgment

We acknowledge Nutraceutical Translations for English language editing of this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.antiviral.2020.104717.

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ClinicalTrials.gov archive
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History of this study | Current version of this study

View of NCT02275065 on 2014_10_26

ClinicalTrials Identifier: NCT02275065
Updated: 2014_10_26

Descriptive Information

Brief title	Safety, Pharmacokinetics, and Antiviral Activity of GS-9883 in HIV-1 Infected Subjects
Official title	A Phase 1b Randomized, Double-Blinded, Sequential Cohort Placebo-Controlled Study of the Safety, Pharmacokinetics, and Antiviral Activity of GS-9883 in HIV-1 Infected Subjects

Brief summary

This study will investigate the short-term antiviral potency, safety, plasma pharmacokinetics (PK), and the PK/pharmacodynamic (PD) relationship (the dose-response relationship) of GS-9883 at multiple doses in antiretroviral (ART) treatment-naive adult subjects and subjects who are ART-experienced but are currently off of ART therapy. Up to 32 participants will be enrolled in the study.

Detailed description

Phase	Phase 1
Study type	Interventional
Study design	Treatment
Study design	Randomized
Study design	Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Study design	Parallel Assignment
Study design	Safety/Efficacy Study
Primary outcome	Measure: DAVG11 in plasma HIV-1 RNA (log10 copies/mL) Time Frame: Up to 11 days Safety Issue? No Description: DAVG11: time-weighted average between the first postbaseline value and the last available value up to Day 11 minus the baseline value.
Secondary outcome	Measure: Incidence of adverse events and graded laboratory abnormalities Time Frame: Up to 11 days Safety Issue? No Description: Overall safety profile will be characterized by number of participants experiencing adverse events or laboratory abnormalities.

Secondary outcome	Measure: Maximum reduction from baseline through Day 11 in plasma HIV-1 RNA (log10 copies/mL) Time Frame: Up to 11 Days Safety Issue? No Description: The maximum reduction will be calculated as the lowest up to Day 11 postbaseline value minus the baseline value.
Secondary outcome	Measure: PK parameters of GS-9883 following single- and multiple-dose administration, and the correlation between AUCtau of GS-9883 and DAVG11 in plasma HIV-1 RNA Time Frame: Predose and postdose on Days 1 and 10 Safety Issue? No Description: DAVG11: time-weighted average between the first postbaseline value and the last available value up to Day 11 minus the baseline value. AUCtau: concentration of drug over time - PK measurements will include: AUCinf, AUC0-last, and Cmax for single-dose administration; and AUCtau, Cmax, and Ctau for multiple-dose administration. - PK/PD measurements will include Pearson correlation between AUCtau of GS-9883 and DAVG11 in plasma HIV-1 RNA
Secondary outcome	Measure: Initial viral decay slope in plasma HIV-1 RNA (copies/mL) Time Frame: Up to 11 days Safety Issue? No Description: The ratio of the mean slopes between treatment pairs of interest will be calculated.
Enrollment	32 (Anticipated)
Condition	HIV-1 Infection
Arm/Group	Arm Label: Cohort 1 Experimental GS-9883 1 × 25 mg tablet (or placebo to match) for 10 days.
Arm/Group	Arm Label: Cohort 2 Experimental GS-9883 1 × 100 mg (or placebo to match) for 10 days.
Arm/Group	Arm Label: Cohort 3 Experimental GS-9883 5 mg or 10 mg (1 × 5 or 2 × 5 mg tablet) (or placebo to match) for 10 days.
Arm/Group	Arm Label: Cohort 4 Experimental GS-9883 50 mg or 75 mg (2 × 25 or 3 × 25 mg tablet) (or placebo to match) for 10 days.
Intervention	Drug: GS-9883 Arm Label: Cohort 1 GS-9883 tablet(s) administered orally once daily

Intervention	Drug: GS-9883 Placebo Arm Label: Cohort 1 Placebo to match GS-9883 administered orally once daily

Recruitment Information

Status	Not yet recruiting
Start date	2014-10
Last follow-up date	2015-01 (Anticipated)
Primary completion date	2015-01 (Anticipated)

Criteria

Inclusion Criteria:

- No current or prior anti-HIV treatment, including antiretroviral medications received for prevention (preexposure prophylaxis [PrEP]), or postexposure prophylaxis (PEP) within 12 weeks of screening
- Must be between 18 and 65 years of age, inclusive on the date of the screening visit
- Plasma HIV-1 RNA ≥ 10,000 copies/mL but ≤ 400,000 copies/mL at screening
- CD4+ cell count > 200 cells/mm^3

Exclusion Criteria:

- Anticipated to start HIV-1 therapy during the study period
- Active participation in another study of investigational or approved antiretroviral agents
- A new AIDS-defining condition diagnosed within the 30 days prior to screening
- Subjects with positive hepatitis C antibody at screening
- Chronic hepatitis B virus (HBV) infection
- Active, serious infections (other than HIV-1 infection) requiring parenteral antibiotic or antifungal therapy within 42 days prior to Day 1 (baseline)

Gender	Both
Minimum age	18 Years
Maximum age	65 Years
Healthy volunteers	No

Administrative Data

Organization name	Gilead Sciences
Organization study ID	GS-US-141-1219
Sponsor	Gilead Sciences
Health Authority	United States: Food and Drug Administration

23 November 2022 (23-11-2022)

ROBIC
opic.brevets@robic.com

Application No.	:	**2,948,021**
Owner	:	GILEAD SCIENCES, INC.
Title	:	**PHARMACEUTICAL FORMULATIONS**
Classification	:	A61K 31/675 (2006.01)
Your File No.	:	**003613-0242**
Examiner	:	Orysia Zaporozan

YOU ARE HEREBY NOTIFIED OF A REQUISITION BY THE EXAMINER IN ACCORDANCE WITH SUBSECTION 86(2) OF THE *PATENT RULES*. IN ORDER TO AVOID ABANDONMENT UNDER PARAGRAPH 73(1)(*a*) OF THE *PATENT ACT*, A WRITTEN REPLY MUST BE RECEIVED WITHIN **FOUR (4)** MONTHS AFTER THE ABOVE DATE.

This application has been examined as originally filed.

The number of claims in this application is 51.

Documents Cited:

D1:*	WO 2014/100323 A1	Jin et al.	26 June 2014 (26-06-2014)
D2:*	WO 2013/116720 A1	Ramanathan Srinivasan	8 August 2013 (08-08-2013)

* document cited by a foreign patent office

D1 discloses a tablet comprising a compound of formula (I) (compound 42 and 45). The compound is useful in the treatment of HIV.

D2 discloses a composition comprising tenofovir alafenamide and emtricitabine. The composition is useful for the treatment of viral infections including HIV. (claim 21, 29)

The examiner has identified the following defects in the application:

1 Claims 34, 35 encompass subject-matter that was disclosed in D1 and D2 before the one-year period immediately preceding the filing date or, if the claim date is before that period, before the claim date and do not comply with paragraph 28.2(1)(*a*) of the *Patent Act*.

2 The claims on file do not comply with section 28.3 of the *Patent Act* because they define an aggregation of elements known before the claim date. Each element performs its function independently of the others, and the elements fail to cooperate with each other to achieve a unitary result that is other than merely the sum of the results of the individual elements. These

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individual elements can be found in D1 and D2. It would have been obvious to the person skilled in the art to combine the composition comprising the compound of Formula I in D1 that is known to be effective in the treatment of HIV, with tenofovir alafenamide and emtricitabine which are known from D2 to be effective in the treatment of HIV and other viral infections, to treat an HIV infection and to provide the compounds in a solid dosage form as defined in the claims. Therefore, the claims do not involve an inventive step.

3 Claim 10 is indefinite and does not comply with subsection 27(4) of the *Patent Act*. The expression "wherein (a) and (b) are within separate layers in a multilayer tablet" causes ambiguity. It is unclear what is meant by this expression. Furthermore, claim 9 defines that (a) and (b) are segregated, which would imply that they are in separate layers.

4 Claims 13-15 are indefinite and do not comply with subsection 27(4) of the *Patent Act*. The preamble of a dependent claim should be consistent with the preamble of the claim or claims to which it refers. Claims 1-6 are directed to a solid oral dosage form.

5 Claim 17 is a dependent claim that does not include all of the limitations contained in the claim to which it refers, and does not comply with subsection 63(4) of the *Patent Rules*. Specifically, claim 16 defines that the tablet comprises all three of a) the compound of formula I, b) tenofovir alafenamide and c) emtricitabine.

6 Claim 18 is indefinite and does not comply with subsection 27(4) of the *Patent Act*. The expression "further comprises emtricitabine" causes ambiguity. It is unclear what further comprises emtricitabine, the tablet, or one of the first or second layers. Also, since claim 16 defines that the tablet comprises emtricitabine and does not define that it is optional, this expression causes ambiguity.

7 Claims 28-30 are indefinite and do not comply with subsection 27(4) of the *Patent Act*. The inclusion of "at least about" causes ambiguity. The applicant attempts to set distinct lower limits by the use of the expression "at least", whereas the inclusion of the term "about" attempts to set indefinite values.

8 Claims 30, 31, 38, 39 are indefinite and do not comply with subsection 27(4) of the *Patent Act*. For clarity, the preamble "[t]he solid oral dosage form or tablet of any one of claims 1 to 29" should be replaced with the preamble "[t]he solid oral dosage form of any one of claims 1 to 6 or the tablet of any one of claims 7 to 29". Furthermore, the term "the tablet" should be replaced with "the solid oral dosage form or tablet releases".

9 Claims 30, 31 are indefinite and do not comply with subsection 27(4) of the *Patent Act*. Claims 8, 12-15 do not define that the tablet comprises a compound of Formula I. These claims define the compound of Formula II.

10 Claims 34, 35 are indefinite and do not comply with subsection 27(4) of the *Patent Act*. The inclusion of "obtainable" causes ambiguity. Said term implies that the layer may be obtained by other methods than the one claimed, thus rendering the scope of the protection sought by the applicant unclear. The use of "obtained" would be more appropriate. Furthermore, it is unclear how 1) the claims can be directed to a part of a multilayer tablet, that being one of the layers, since it can only be defined as a layer within the context of being a part of the tablet and 2) a layer can be obtained by a method for producing a tablet, and not a layer.

11 Claims 38, 39 are indefinite and do not comply with subsection 27(4) of the *Patent Act*. The expression "therapeutic treatment" causes ambiguity. Treatment would necessarily have a therapeutic aspect.

12 Claims 40, 43, 44 are indefinite and do not comply with subsection 27(4) of the *Patent Act*. The term "compound of Formula I" has no antecedent.

13 Claims 40, 43, 44, 46, 49-51 are indefinite and do not comply with subsection 27(4) of the *Patent Act*. The compound of Formula I or II is not defined in these claims.

14 Claim 42 is indefinite and does not comply with subsection 27(4) of the *Patent Act*. The expression "wherein the composition further comprises a second layer" causes ambiguity. Claim 41 defines that the composition is a first layer of a multilayer tablet, therefore it is unclear how the composition can be both a first layer and a second layer.

15 Claim 44 is indefinite and does not comply with subsection 27(4) of the *Patent Act*. It is unclear how a tablet composition differs from a tablet.

16 Claim 45 is indefinite and does not comply with subsection 27(4) of the *Patent Act*. The preamble of a dependent claim should be consistent with the preamble of the claim or claims to which it refers. Claim 43 is directed to a tablet and claim 44 is directed to a tablet composition.

17 Claim 46 is indefinite and does not comply with subsection 27(4) of the *Patent Act*. The use of the subjective expression "e.g.", appears to direct the claim simultaneously to both broad and narrow embodiments, causing a lack of clarity as to the intended scope of this claim. Furthermore, the inclusion of a feature in parentheses raises uncertainty as to whether this feature is optional or always present.

18 The description contains statements that incorporate by reference other documents and does not comply with subsection 57(1) of the *Patent Rules*. Such statements are found at paragraphs [0281], [0297], [0361] and should be removed.

19 The title of the invention is not precise and does not comply with paragraph 56(1)(a) of the *Patent Rules*. The title should assist a searcher in determining the subject matter of the invention and should be descriptive of the invention, not merely of the field of the invention (see section 14.06 of the *Manual of Patent Office Practice*).

In view of the foregoing defects, the applicant is requisitioned, under subsection 86(2) of the *Patent Rules*, to amend the application in order to comply with the *Patent Act* and the *Patent Rules* or to provide arguments as to why the application does comply.

Under section 102 of the *Patent Rules*, any amendment made in response to this requisition must be accompanied by a statement explaining the purpose of the amendment and identifying the differences between the new page and the replaced page.

Orysia Zaporozan
Patent Examiner
819-639-9424

As per CIPO Client Service Standards, a response to a telephone enquiry or voice mail should be provided by the end of the next business day. In the event that attempts to reach the examiner are unsuccessful, the examiner's Section Head, Okemona Oke, can be reached at 819-639-9352.

For general inquiries: 1-866-997-1936 or for more options see http://www.ic.gc.ca/eic/site/cipointernet-internetopic.nsf/eng/wr00006.html.

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The Examination Search Report is provided for reference only and is not part of any requisition made by the examiner in accordance with the *Patent Act* or *Rules*. The applicant is not required to respond to the information contained in the Examination Search Report.

Examination Search Report

Box I: General Information			
Application No.	2,948,021	Search Report Date	2022-11-05
Title	PHARMACEUTICAL FORMULATIONS		
Examiner	Orysia Zaporozan	Search Conducted?	Yes

Box II: Family Prosecution		
Family Member	File Wrapper Reviewed	Status of Prosecution
US10548846B2	2022-11-05	Completed
US2021052502A1	2022-11-05	Abandoned
EP3346995B1	2022-11-05	In opposition
EP3632415A1	2022-11-05	In Progress
WO2017083304A8	2022-11-05	Completed

Box III: Search History			
Claims Searched	1-51	Date of Search	2022-11-05
Type of Search Conducted (select all that apply):			
Canadian first to file search	■	Supplemental/top up search	☐
Inventor/applicant search	■	Non laid open search	☐
Comprehensive search	☐	In-house searcher	☐

Search History from Databases Consulted:

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##### CANADIAN PATENT DATABASE/INTELLECT ##########

inventor:("COLLMAN BENJAMIN MICAH"~3 OR "HONG LEI"~3 OR "KOZIARA JOANNA
M."~3)  10

filing-date:[2011-11-08 TO 2018-01-23] AND ipc:(A61K\ 31/675 OR A61K\ 9/24 OR
A61K\ 9/28 OR A61K\ 31/513 OR A61K\ 31/537 OR A61P\ 31/18)  873
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Carpmaels & Ransford LLP
One Southampton Row
London WC1B 5HA
ROYAUME UNI

Formalities officer
Ambroa, Jose Ramon

Date
31-03-2021

Reference	Application No./Patent No.
P072824EP	16798063.0 - 1112 / 3346995
Applicant/Proprietor: Gilead Sciences, Inc.	

BRIEF COMMUNICATION

Subject:
- ☐ Your letter of
- ☐ Our telephone conversation of
- ☐ Communication of
- ☐

Enclosure(s):
- ☐ Letter from the proprietor of the patent of
- ☒ Letter from the opponent O1 of 26.03.21
- ☐ Copy (copies)

Communication:

☐ The documents specified as patent documents and as non-patent literature in this letter are available for inspection via the European Patent Register at **www.epo.org/register.** Should you wish to receive these documents in paper format, they will be supplied to you free of charge if specifically requested on receipt of this communication (OJ EPO 2020, A105).

☐

For the Opposition Division

Europäisches Patentamt • European Patent Office • Office européen des brevets

☒ **Registered letter**

LEDERER & KELLER
Patentanwälte Partnerschaft mbB
European Patent Attorneys

DR. FRANZ LEDERER
(1963 – 2012)
DR. GÜNTER KELLER
Dipl.-Biol.
DR. MICHAEL BEST
Dipl.-Chem.
DR. STEPHAN TEIPEL
Dipl.-Chem.
DR. GEORG KALHAMMER
Dipl.-Biochem.
DR. JÖRG-THOMAS BINDER
Dipl.-Chem.
DOTT. MARCO FACHINI
Laurea in Chimica

80538 MÜNCHEN
Unsöldstraße 2
Telefon +49 89 21 23 99 0
Telefax +49 89 21 23 99 22
E-Mail info@lederer-keller.de

European Patent Office

80298 Munich

Your reference

Our reference
ESP00476TEV

26 March 2021
Be/Bi/sh/Lo

Re.: European Patent No. 3 346 995
European Patent Application No. 16798063.0
Patentee: Gilead Sciences, Inc.
Opponent: Teva Pharmaceutical Industries Ltd.

In response to patentee's petition dated January 11, 2021:

1. **Requests**

1.1 The requests as per the notice of opposition, i.e. to revoke the European patent no. 3 346 995 in total and to summon to oral proceedings should the Opposition Division not be in a position to do so on the basis of opponent's written submissions, are maintained.

1.2 In addition to documents D1 to D37 as presently on file, the following further documents are filed herewith:

D38: P. Kommavarapu et al., "Preparation and characterization of rilpivirine solid dispersions with the application of enhanced solubility and dissolution rate", Beni-Suef University Journal of Basic and Applied Sciences 4 (2015) 71-79.

D39: European Medicines Agency, Assessment report "Genvoya", 24 September 2015, extract (pp.1-20).

Both documents are pre-published and will be discussed in connection with lack of inventive step of the contested patent.

1.3 In the following, opponent will provide his comments on patentee's response to the oppositions filed. Arguments presented in the notice of opposition are maintained even if they are not explicitly reiterated herein below.

2. Lack of inventive step

2.1 Preliminary remarks

In accordance with patentee's petition, the following abbreviations will be used herein below:

BIC = bictegravir;
FTC = emtricitabine;
TAF = tenofovir alafenamide;
DTG = dolutegravir.

2.2 Document D37 as the closest prior art

2.2.1 Patentee considers document D37 as the closest prior art. According to patentee, document D37 discloses a phase II clinical study comparing the clinical safety and efficacy of BIC (75 mg) + FTC/TAF (200/25 mg) with DTG (50 mg) + FTC/TAF (200/25 mg). Document D37 would be a more realistic starting point than document D5 as it relates to a combination therapy involving co-administration of BIC, FTC and TAF which has a similar purpose as the patent (patentee's petition, item 5.39).

Patentee's interpretation of document D37 is misleading.

2.2.2 Contrary to what patentee attempts to suggest, document D37 does not disclose a combination therapy involving BIC, FTC and TAF. Rather, document D37 discloses an investigational combination therapy involving, besides FTC/TAF, a compound which is only characterized by its lab-code "GS-9883".

Document D37 does not disclose what "GS-9883" is, let alone that it is bictegravir. This is only known from post-published documents, such as document D36 filed by patentee or document D32 filed by opponent 3.

2.2.3 In such a situation, it is the general practice of the EPO that the disclosure of the lab-code is not accepted as a disclosure of the compound per se. The disclosure of document D37, to the extent that it relates to the combination of GS-9883 + FTC/TAF, is accordingly not the disclosure of a specific combination and therefore cannot constitute the closest prior art for the contested patent.

2.3 Document D5 as the closest prior art

2.3.1 With respect to document D5 as the closest prior art, the patentee raises criticism, which, however, is unfounded.

2.3.2 The first criticism of patentee concerns the embodiment disclosed on page 20, lines 1/2 of document D5 regarding a pharmaceutical composition comprising about 50 mg dolutegravir, about 200 mg emtricitabine and about 25 mg tenofovir. According to patentee, this embodiment falls outside the invention of document D5, which would be limited to pharmaceutical combinations wherein the weight ratio of dolutegravir to emtricitabine is from 1:1 to 1:3. In this regard, patentee refers *inter alia* to the disclosure on page 3, lines 18-20 and claim 1 of document D5 (patentee's petition, items 5.60-5.62).

2.3.3 According to the Guidelines for Examination (Part G-VII-5.1):

> "*The closest prior art is that which in one single reference discloses the combination of features which constitutes the most promising starting point for a development leading to the invention. In selecting the closest prior art, the first consideration is that it must be directed to a similar purpose or effect as the invention or at least belong to the same or a closely related technical field as the claimed invention. In practice, the closest prior art is generally that which corresponds to a similar use and requires the minimum of structural and functional modifications to arrive at the claimed invention (see T 606/89).*" (emphasis added).

It is the purpose of the contested patent to provide (contested patent, paragraph [0001]):

> "*Pharmaceutical formulations suitable for treating viral infections such as HIV [...], in particular solid oral dosage forms including the compound of Formula I, emtricitabine and tenofovir alafenamide*" (emphasis added).

2.3.4 Document D5 discloses on page 1, lines 3-8:

> "*The present invention concerns a pharmaceutical combination comprising (a) doluteoravir, (b) emtricitabine and (c) lenofovir or a prodrug thereof, wherein preferably the compounds are present in a specific weight ratio and/or in specific amounts, for use as a medicament, preferably in treatment of viral infection/disease such as an HIV infection.*" (emphasis added).

Document D5 further discloses on page 3, lines 15/16:

> "*This invention provides a pharmaceutical combination comprising (a) dolutegravir, (b) emtricitabine and (c) tenofovir for use as a medicament.*" (emphasis added)

The passage following this passage (D5, page 3, lines 18-20), to which patentee *inter alia* refers to reads:

> "*This invention also provides a pharmaceutical composition comprising (a) dolutegravir, (b) emtricitabine and (c) tenofovir, wherein the weight ratio of (a) dolutegravir and (b) emtricitabine is from 1 : 1 to 1 : 3.*" (emphasis added).

From the above citations, it can clearly be derived that contrary to patentee's position, the disclosure of document D5 is not limited to pharmaceutical compositions, wherein the weight ratio of (a) dolutegravir and (b) emtricitabine is from 1:1 to 1:3. Rather, the invention according to document D5 also concerns pharmaceutical compositions comprising dolutegravir, emtricitabine and tenofovir in specific amounts, and the embodiment disclosed on page 20, lines 1/2 wherein the pharmaceutical composition comprises about 50 mg dolutegravir, about 100 mg emtricitabine and about 25 mg tenofovir is covered by this generic disclosure.

2.3.5 The fact that claim 1 of document D5 is limited to an embodiment, wherein the weight ratio of dolutegravir and emtricitabine is from 1:1 to 1:3, is not a reason to disregard the overall disclosure of document D5. What is claimed is essentially within the discretion of the applicant. This, however, does not justify that the disclosure of a prior art document is reduced to what is claimed.

The Guidelines for Examination are also silent as to such an interpretation of a prior art document. Rather, as it has been set out in the above citation of the Guidelines, the first consideration is that the closest prior art must be directed to a similar purpose of the present invention. It is readily apparent that the purpose of the contested patent and document D5 is the same (compare contested patent, paragraph [0001] with document D5, page 1, lines 3-8).

namely to provide a combination therapy comprising emtricitabine and tenofovir and another HIV integrase inhibitor, which is dolutegravir in case of document D5 and bictegravir in case of the contested patent.

Already for this reason, document D5 constitutes a suitable closest prior art, with the distinguishing feature being the HIV integrase inhibitor.

2.3.6 Patentee further criticizes that there would be no single embodiment in D5 disclosing a tablet comprising 50 mg DTG, 200 mg FTC and 25 mg TAF. According to patentee, the disclosure on page 23, lines 7-8 of document D5 would follow on from the previous paragraph (bridging pages 22 and 23) disclosing a "unit dosage form" of the invention, which comprises 50 to 150 mg FTC, i.e. it excludes the use of 200 mg FTC. This would also be confirmed by claim 14 of document D5 referring back to claim 13 (patentee's petition, items 5.59, 5.63, 5.64).

The whole section (D5, page 22, lines 31/32 to page 23, lines 1-8) reads as follows:

> *"In a preferred embodiment the pharmaceutical composition of the present invention can be considered as a unit dosage form comprising*
>
> *(i) 20 to 75 mg dolutegravir*
> *(ii) 50 to 150 mg emtricitabine,*
> *(iii) 0.5 to 400 mg tenofovir or a prodrug thereof and optionally*
> *(iv) pharmaceutical excipient(s).*
>
> *The pharmaceutical composition of the present invention can be preferably a solid or a dosage form. It is further preferred that the dosage form of the invention is a capsule or a tablet, in particular a tablet."* (emphasis added).

It is not apparent why the paragraph on page 23, lines 7/8 should only refer to the preferred pharmaceutical composition of the previous paragraph. To the contrary, the passage refers to the "pharmaceutical composition of the present invention", which includes the preferred embodiment disclosed on pages 19, lines 30/31 to page 20, lines 1/2:

> *"In an alternatively preferred embodiment the pharmaceutical composition of the present invention comprises about 50 mg dolutegravir, about 200 mg emtricitabine and about 25 mg tenofovir (c), in particular tenofovir alafenamide."* (emphasis added).

it cannot be seen why a pharmaceutical composition comprising 50 mg DTG, 200 mg FTC, and 25 mg TAF should be excluded from the provision in form of a tablet.

The fact that claim 14 of document D5 refers back to claim 13, which claims an embodiment comprising up to 150 mg emtricitabine, is not a reason that an embodiment comprising 200 mg FTC is not disclosed in form of a tablet. Again, what is claimed is within the discretion of the applicant, but this does not limit the disclosure of a prior art document as a whole.

2.3.7 With respect to the question of the closest prior art, the following is accordingly to be held.

The disclosure of document D37 to the extent that it concerns a combination of "GS-9883" (75 mg) + FTC/TAF (200/25 mg) is not enabling, because at the priority date of the contested patent, the skilled person was not aware that "GS-9883" stands for BIC.

The criticism of patentee regarding document D5 as the closest prior art is unjustified for the reasons discussed above. In fact, document D37 serves as a pointer towards the combination of DTG (50 mg), FTC (200 mg) and TAF (25 mg) as the starting point for further development of the HIV combination therapy comprising an HIV integrase inhibitor and FTC/TAF (200/25 mg) because the investigational combination comprising "GS-9883" + FTC/TAF was compared with a combination of DTG (50 mg) + FTC/TAF (200/25 mg).

However, since a single tablet as disclosed in document D5 requires the minimum of structural and functional modifications in order to arrive at the claimed invention (Guidelines for Examination, Part G-VII-5.1, passage cited above), not the embodiment disclosed in document D37, i.e. DTG (50 mg) + FTC/TAF (200/25 mg), but rather the single tablet combination DTG/FTC/TAF (50/200/25 mg) constitutes the closest prior art for the contested patent.

2.3.8 The claimed single tablet combination differs from the known combination only in terms of the HIV integrase inhibitor.

2.4 The objective technical problem

2.4.1 Patentee in his petition comes to the conclusion that the claimed single tablet regimen of BIC/FTC/TAF (50/200/25 mg) would impose several unexpected and improved properties, including a desirable PK profile achieved with a smaller tablet, reduced food effects, the

potential for improved safety and patient compliance (patentee's petition, e.g. items 5.26, 5.42, 5.43).

2.4.2 However, such effects have not been shown comparing the claimed combination with the combination that forms the closest prior art, i.e. a combination comprising DTG (50 mg), FTC (200 mg) and TAF (25 mg). A comparison of the claimed combination with this prior art combination has not been provided by patentee, and effects resulting from such a comparison are also not discussed in patentee's petition.

2.4.3 Hence, the objective technical problem in view of the closest prior art can only be seen in the provision of an alternative pharmaceutical composition for the treatment of HIV.

2.5 Obviousness

2.5.1 The solution as suggested by the contested patent to this problem is obvious in view of the prior art on file.

2.5.2 Bictegravir is disclosed in document D3 as a preferred HIV integrase inhibitor out of merely eight compounds (D3, page 3, lines 11/12; claim 32, first entry). Furthermore, document D3 suggests combination therapies involving emtricitabine (D3, page 38, lines 13/16) and tenofovir alafenamide (D3, page 38, lines 18-20).

Taking this into consideration, bictegravir is one obvious choice to replace the HIV integrase inhibitor dolutegravir in the combination with emtricitabine and tenofovir alafenamide in order to solve the problem of providing an alternative pharmaceutical composition for the treatment of HIV.

2.5.3 Patentee argues that the prior art did not teach that it would be possible to successfully co-formulate BIC, FTC and TAF into one single tablet. According to patentee, it would be challenging to formulate APIs from different classes in a fixed dose combination (patentee's petition, items 5.45-5.52).

However, as discussed by opponent 2 in his notice of opposition under section 6.3.3, single tablet regimens was the standard practice for treating HIV at the priority date of the contested patent. From patentee's own products such as Odefsey® and Genvoya® referred to by opponent 2 in his notice of opposition illustrate that it is standard to formulate APIs from different BCS classes in a fixed dose combination tablet.

Odefsey® comprises emtricitabine, rilpivirine and tenofovir alafenamide as single tablet formulation (200/25/25 mg). Emtricitabine and tenofovir alafenamide represent BCS class I and BCS class III agents, as set out in patentee's petition. Rilpivirine, represents a BCS class II compound (D38, page 72, left-hand column, second paragraph), similar to bictegravir. The single tablet according to this product is prior art, as evidenced by D12, first paragraph.

Likewise, the compound "cobicistat" in the commercial product Genvoya® of patentee, which further comprises emtricitabine and tenofovir alafenamide, is considered as a BCS class II compound (D39, page 18, 4th paragraph under "Description of the product ..."). The single tablet formulation according to the Genvoya® product is also prior art, as evidenced by document D10.

Hence, there was a reasonable expectation for successfully formulating a combination of BIC/FTC/TAF (50/200/25 mg) as a fixed dose combination tablet.

2.5.4 Patentee further argued in his petition that clinical trials of phase I had shown that 75 mg of BIC would be the best dose for administering BIC in a combination treatment with FTC and TAF and it would have been surprising that 50 mg of BIC would be sufficient if BIC, FTC and TAF are formulated into a single tablet. As evidence patentee referred to the phase II trials according to document D37.

However, the closest prior art is already a single tablet containing FTC, TAF and an HIV integrase inhibitor (DTG in case of document D5) and thus a fixed dose combination of these components. Therefore, what dose of the HIV integrase inhibitor a skilled person might have used in clinical trials with a non-fixed dose combination of BIC, FTC and TAF such as disclosed in document D37 is irrelevant for the problem and solution approach.

Since the fixed dose combination of DTG (the HIV integrase inhibitor) with FTC and TAF of the closest prior art contained the HIV integrase inhibitor already in an amount of 50 mg, a skilled person looking for an alternative fixed dose combination would have had incentive to use the same amount of another HIV integrase inhibitor such as BIC. In fact, 50 mg BIC is already disclosed as a suitable dose in document D3 (D3, page 35, line 22).

Thus, patentee's arguments relying on document D37 are irrelevant if the problem and solution approach is correctly applied in the present case.

Dr Michael Best

Encl:
D38, D39

Pharmacokinetic (PK) and Pharmacodynamic (PD) Relationship of S/GSK1349572, a Next Generation Integrase Inhibitor (INI), in HIV-1 Infected Patients

by [illegible], Margaret Chen[1], Yu Leach, Julie Bottorff[1], Teresa Fujiwara[1], Samuel Piscitelli[1], Brenda Min[1],
[illegible] NC, USA, [1]Shionogi & Co., Ltd., Osaka, Japan

Abstract

Background: S/GSK1349572 is a next generation integrase inhibitor (INI) that demonstrated PK supporting once daily dosing and great antiviral activity in a dose ranging, placebo-controlled 10-day monotherapy study in HIV-1 infected subjects.

Methods: 35 treatment naïve subjects were randomized to dose of 2mg, 10mg, 50mg, or placebo once daily for 10 days. Serial HIV-1 RNA and PK samples were collected pre-dose. Study S/GSK1265[illegible] was analyzed using a validated LC/MS/MS assay. PK parameters were calculated by non-compartmental methods. Relationship between PK (AUC0-24hr, Cmax, and C24) and change in HIV-1 RNA (log10 copies/mL) from baseline to Day 11 was explored using Emax and linear models. Model selection was based on Akaike Information Criteria values and R-sqrd.

Results: [illegible] subjects were enrolled. [illegible] subjects received study drug and had evaluable PK and virology data. Mean baseline HIV-1 RNA was [illegible] log10 copies/mL. Mean change from baseline in HIV-1 RNA at Day 11 was [illegible] log10 copies/mL for placebo, [illegible] log10 copies/mL for 2mg QD, [illegible] log10 copies/mL for 10mg QD, and [illegible] log10 copies/mL for 50mg QD. [illegible] subjects with virologic failure were identified. Mean AUC0-24hr, Cmax, and C24 increased [illegible]-fold, [illegible]-fold, and [illegible]-fold, respectively, between 2mg QD and 50mg QD. [illegible] subjects with virologic failure had lower exposures than those without virologic failure. The relationship between C24 and [illegible] was best described by an Emax model with [illegible] = [illegible] log10 copies/mL, [illegible] = [illegible] mg, and [illegible] = [illegible] ng/mL (r²=[illegible]).

Conclusions: S/GSK1349572 demonstrated low PK variability and predictable, well characterized exposure-response relationship. Antiviral activity for INIs is exposure driven. S/GSK1349572 achieved greater antiviral activity than RAL and ELV after 10-day monotherapy. The PK parameter that best predicts S/GSK1349572 efficacy is C24, therefore achieving a high IC will lead to increased clinical outcomes.

Introduction

- The long-standing Shionogi-GSK Joint Venture has made considerable progress in developing next generation integrase inhibitors
- S/GSK1349572 is the only once daily, unboosted integrase inhibitor currently in development with unprecedented potency, activity and a superior resistance profile
- To date, the PK/PD relationship for INIs has not been well characterized. There has been a lack of PK/PD relationship demonstrated for raltegravir (RAL) and can partly be attributed to high RAL PK variability. Elvitegravir (GS-9137, another INI currently in Phase III clinical development) has demonstrated exposure-dependent antiviral activity.
- S/GSK1349572 demonstrates low PK variability which provides a good foundation for understanding the PK-PD relationship of this drug, and can also be applied to better understanding the class.
- A dose ranging, placebo-controlled 10-day monotherapy study of S/GSK1349572 in NAÏVE infected subjects showed a mean 2.5 log decrease from baseline in plasma HIV RNA with the 50mg dose, and a clear dose-response relationship.
- The design and dose selection of this study provided data to better understand the PK-PD relationship of this compound and provide inference across all INIs.

Methods

- 35 subjects were randomized to dose of 2mg, 10mg, 50mg, or placebo once daily (QD) for 10 days
- Serial HIV-1 RNA and PK samples were collected during the study. S/GSK1349572 concentrations were analyzed using a validated LC/MS/MS assay.
- S/GSK1349572 PK parameters were calculated by non-compartmental methods. Relationship between PK and HIV response (change in HIV-1 RNA) was assessed using various Emax and linear models. Model selection was based on Akaike Information Criteria value and R-sqrd.
- PK measures: AUC0, Cmax, and C24 on Day 10
- PD measures: reduction in $\log_{10}$ copies HIV-1 RNA on Day 11 from baseline (pre-dose on Day 1), reduction in $\log_{10}$ copies HIV-1 RNA from baseline to the on treatment nadir
- Log-linear models: $PD = \alpha + \beta \log_{10}(PK)$
- Sigmoid Emax models: $y = E_0 + \frac{E_{max} * PK^{\gamma}}{EC_{50}^{\gamma} + PK^{\gamma}}$

where PK measure is either original or log-transformed; Emax was either pre-set to 0 or fixed to 2.5, 2.7, or 2.9 to help model converge; γ was either estimated or fixed to 1

Results

Figure 1. Mean (±SD) S/GSK1349572 Concentration-Time Profiles by Dose

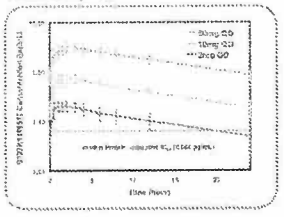


Table 1. Summary of S/GSK1349572 PK Parameters and Mean HIV-1 RNA Reduction from Baseline by Dose

	AUC0-24hr (µg*hr/mL)	Cmax (µg/mL)	C24 (µg/mL)	IC	ΔLog10 HIV-1 RNA
2mg QD (n=9)	3.98 (20%)	0.22 (25%)	0.04 (50%)	0.5	-1.51
10mg QD (n=7)	10.1 (25%)	0.85 (23%)	0.12 (75%)	2	-2.63*
50mg QD (n=18)	41.4 (25%)	3.34 (16%)	0.62 (95%)	15	-3.46

Geometric mean (CV%) for C0=C24hr, mean (CV%) for all other PK parameters

- Dose-proportional PK and steady state is achieved by 7 days of dosing
- PK supports once daily dosing without boosting
- Robust antiviral responses across the low dose cohorts
- Very low inter- and intra-subject variability provides foundation for understanding PK/PD relationship and is key in defining therapeutic target

Figure 2. Exposure-Response for Antiviral Activity

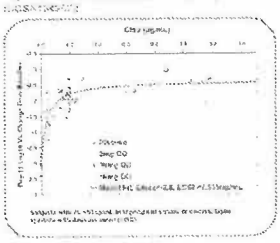
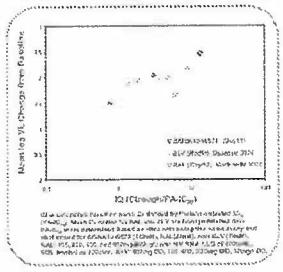


Table 2. S/G Results of Sigmoid Emax Models of Antiviral Response to [illegible] and Parameter Estimates after Day 10 of 10-Day Monotherapy

Model	AUC0-24hr	Cmax	C24
[illegible]	14.6	17.1	13.6
[illegible]	39.1	39.0	33.6
[illegible]	39.4	45.4	46.3
[illegible]	38.8	39.2	33.7
[illegible]	39.7	42.1	31.5

- The relationship between S/GSK1349572 exposure and reduction in $\log_{10}$ HIV-1 RNA on Day 11 can be best described by an Emax model with PK measures on the original scale. Emax fixed to 2.5 $\log_{10}$ and γ fixed to 1.
- C24 concentration at end of dosing interval was the PK parameter that best predicted Day 11 plasma viral load reduction from baseline or maximum observed viral load reduction from baseline.
- It should be noted that this study was not designed to differentiate these PK predictions as all doses were given QD and all PK parameters are correlated.

Figure 3. PK-PD Relationship of S/GSK1349572, RAL, and ELV in 10-day Monotherapy (Protocol 0[illegible])



Discussions

- The pooled data from S/GSK1349572 and ELV in 10-day monotherapy shows a PK-PD relationship for the integrase inhibitors as a class, in that higher exposure drives higher antiviral activity.
- IC2 (calculated by Shionogi PA-IC_{90}) is a good predictor of antiviral activity for short-term monotherapy for S/GSK1349572.
- S/GSK1349572 50mg QD demonstrated unprecedented antiviral activity, anticipated to maximize IC2 achieved.
- RAL failed to show PK-PD relationship in 10-day monotherapy due to the narrow dose range studied and unpredictable PK.
- In contrast, the Phase 3b study of S/GSK1349572 studied a wide dose range, allowing in-depth understanding of the PK-PD relationship.
- The clear PK-PD relationship observed for S/GSK1349572 supports integrated drug-disease modeling and dose selection in currently ongoing Phase 2b clinical trials across all [illegible] patient populations and the confidence in chronic dosing of S/GSK1349572 in HIV-infected patients.

Conclusions

- S/GSK1349572 demonstrated low PK variability and is clear, predictable, and well characterized exposure-response relationship.
- Antiviral activity for INIs is exposure driven.
- S/GSK1349572 achieved greater antiviral activity than RAL and ELV after 10-day monotherapy.
- The PK parameter that best predicts S/GSK1349572 efficacy is C24, therefore achieving a high IC will lead to increased clinical outcomes.

Acknowledgements

[illegible] thank the study participants and the investigators for their participation and contribution to this study.

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Experimental Report

Ljubljana, December 22, 2021

Preamble

My name is Žiga Jeraj and I am a leading scientist working in the Sandoz development center at Lek Pharmaceuticals d.d. in Ljubljana. I have almost 8 years of professional experience in the science and technology of dosage forms with special expertise in the development of solid oral dosage forms including biopharmaceutics of orally administered drugs.

I was asked to reproduce the bilayer tablet F2 according to EP 3 346 995 B1. In addition, I was asked to produce three monolayer tablet formulations, namely

a) tablet comprising sodium bictegravir (Na-BIC) and exhibiting the same composition as the Na-BIC layer of F2. Two tablet with same composition were produced, differing in the batch number of Na-BIC used;
b) tablet comprising sodium bictegravir (Na-BIC) and exhibiting the same composition as the Na-BIC tablet F1, and
c) tablet comprising emtricitabine/tenofovir alefenamide hemifumarate (FTC/TAF) and exhibiting the same composition as FTC/TAF tablet F3.

Beyond that, I was asked to compare the dissolution of Na-BIC of the produced tablets.

I confirm that I carried out all the experiments with great care and to the best of my knowledge.

Sincerely,

X Jeraj Ziga

Žiga Jeraj

1. Preparation of the Tablets

1.1 Bilayer Tablet (031X-T02) According to F2 of EP 3 346 995 B1

The Bilayer tablets 031X-T02 were prepared as follows:

1. Preparation of the Na-BIC-Layer
   1.1. Na-BIC (B.N.: S-BIC-1-144-02) was mixed with the excipients intra-granular microcrystalline cellulose and croscarmellose sodium and blended,
   1.2. Inter-granular magnesium stearate was added and blended,
   1.3. a dry granulate was prepared using a roller compactor or slug the resulting blend followed by milling,
   1.4. Extra-granular microcrystalline cellulose and extra-granular magnesium stearate was added and blended to a final powder blend.

2. Preparation of the FTC/TAF-Layer
   2.1. FTC was mixed with TAF and the excipients intra-granular microcrystalline cellulose and croscarmellose sodium and blended,
   2.2. Inter-granular magnesium stearate was added and blended,
   2.3. a dry granulate was prepared using a roller compactor or slug the resulting blend followed by milling,
   2.4. Extra-granular magnesium stearate was added and blended to a final powder blend.

3. Tabletting of 031X-T02
   3.1 compressing 353 mg of the final powder blend from step 1.4 to receive the first layer, and
   3.2 compressing 377.1 mg of the final powder blend from step 2.4 to the first layer,
   3.3 obtaining bilayer tablets.

1.2 Na-BIC tablet (028X-T02) According to NA-BIC Layer of F2 or tablet F3-A

The Na-BIC tablets 028X-T02 were prepared as follows:

1. Na-BIC (B.N.: S-BIC-1-144-02) was mixed with the excipients intra-granular microcrystalline cellulose and croscarmellose sodium and blended.
2. Inter-granular magnesium stearate was added and blended,
3. a dry granulate was prepared using a roller compactor or slug the resulting blend followed by milling,
4. Extra-granular microcrystalline cellulose and extra-granular magnesium stearate was added and blended to a final powder blend, and
5. compressing the final powder blend into tablets.

1.3 Na-BIC tablet (029X-T02) According to NA-BIC Layer of F2 or tablet F3-A

The Na-BIC tablets 029X were prepared as follows:

1. Na-BIC (B.N.: (S-BIC-1-129-02) was mixed with the excipients intra-granular microcrystalline cellulose and croscarmellose sodium and blended,
2. Inter-granular magnesium stearate was added and blended,
3. a dry granulate was prepared using a roller compactor or slug the resulting blend followed by milling,
4. Extra-granular microcrystalline cellulose and extra-granular magnesium stearate was added and blended to a final powder blend, and
5. compressing the final powder blend into tablets.

1.4 Na-BIC tablet (030X-T02) According to single agent tablet of F1

The Na-BIC tablets 030X were prepared as follows:

1. Na-BIC (B.N.: (S-BIC-1-129-02) was mixed with the excipients intra-granular microcrystalline cellulose and croscarmellose sodium and blended,
2. Inter-granular magnesium stearate was added and blended,
3. a dry granulate was prepared using a roller compactor or slug the resulting blend followed by milling,
4. Extra-granular microcrystalline cellulose and extra-granular magnesium stearate was added and blended to a final powder blend, and
5. compressing the final powder blend into tablets.

1.5 FTC/TAF tablet (026X-T01) According to FTC/TAF tablet of F3

The FTC/TAF tablets 026X-T01 were prepared as follows:

1. FTC was mixed with TAF and the excipients intra-granular microcrystalline cellulose and croscarmellose sodium and blended,
2. Inter-granular magnesium stearate was added and blended,
3. a dry granulate was prepared using a roller compactor or slug the resulting blend followed by milling,
4. Extra-granular magnesium stearate was added and blended to a final powder blend, and
5. compressing the final powder blend into tablets.

1.4 Overview of the Tablet Compositions

For ease of comparison, the tablets compositions 031X-T02, 028X-T02 and 026X-T01 are depicted in the following table and 028X-T02, 029X-T02 and 030X-T02 in the second table.

Ingredient	031X-T02 (Bilayer)		028X-T02 (single BIC)	026X-T01 (FTC/TAF)
	Na-BIC-Layer	FTC/TAF-Layer	Na-BIC	FTC/TAF
Na-Bictegravir	78.7		78.7	-
Emtricitabine (FTC)	-	200	-	200
Tenovofir Alafenamide Hemifumarate (TAF)	-	28.1	-	28
MCC (intra-granular + extra-granular)	247.8 (212.5+35.3)	113.1 (113.1+0)	247.8 (212.5+35.3)	88.7 (88.7+0)
Croscarmellose Sodium	21.2	30.2	21.2	28.0
Magnesium Stearate (intra-granular + extra-granular)	5.3 (2.65+2.65)	5.7 (2.83+2.83)	5.3 (2.65+2.65)	5.2 (2.6+2.6)
Layer Weight	353	377.06	353	349.90
Tablet Total Weight	**730.06**		**353**	**377.1**

Ingredient	028X-T02 (single BIC)	029X-T02 (single BIC)	030X-T02 (single BIC)
	Na-BIC	Na-BIC	Na-BIC
Na-Bictegravir (batch number)	78.7 (S-BIC-1-144-02)	78.7 (S-BIC-1-129-02)	78.7 (S-BIC-1-129-02)
MCC (intra-granular + extra-granular)	247.8 (212.5+35.3)	247.8 (212.5+35.3)	120.0 (120.0+0)
Lactose monohydrate	-	-	75.8
Croscarmellose Sodium	21.2	21.2	-
Crospovidone			21.0
Magnesium Stearate (intra-granular + extra-granular)	5.3 (2.65+2.65)	5.3 (2.65+2.65)	-
Sodium stearyl fumarate (intra-granular + extra-granular)	-	-	4.5 (2.25+2.25)
Tablet Total Weight	**353**	**353**	**353**

2. **Dissolution Studies**

The dissolution of Na-BIC of the samples presented above was measured using USP Apparatus II, in 250 mL of pH 6.5 FaSSIF at 37°C and paddle speed of 100rpm

The results of the Na-BIC-dissolution are depicted in the following figures:

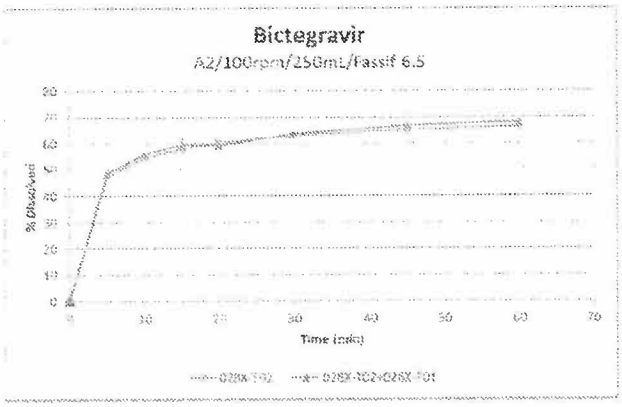


Figure 1: Drug release profiles for bictegravir from sample 028X-T02 and 028X-T02+026X-T01 in 250 ml FaSSIF pH 6.5 by using Apparatus II and 100 rpm.

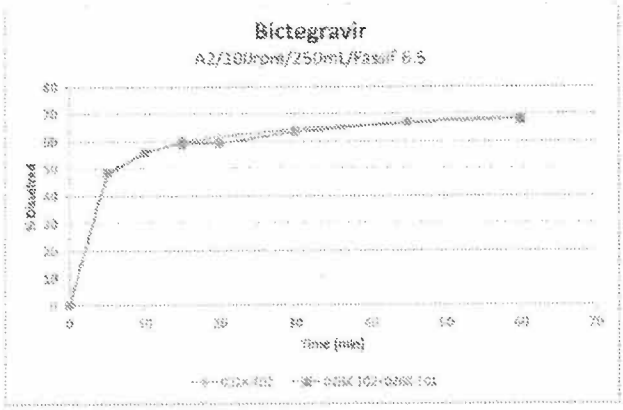


Figure 2: Drug release profiles for bictegravir from samples 031X-T02 and 028X-T02+026X-T01 in 250 ml FaSSIF pH 6.5 by using Apparatus II and 100 rpm.

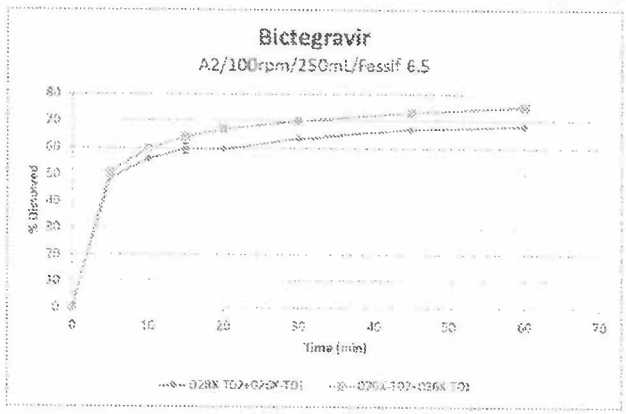


Figure 3: Drug release profiles for bictegravir from samples 028X-T02+026X-T01 and 029X-T02+026X-T01 in 250 ml FaSSIF pH 6.5 by using Apparatus II and 100 rpm.

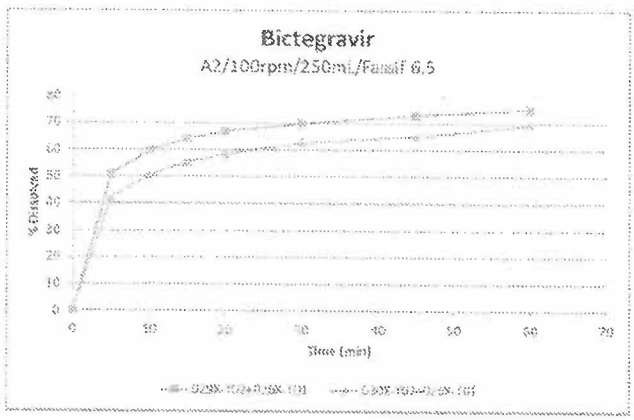


Figure 3: Drug release profiles for bictegravir from samples 029X-T02+026X-T01 and 030X-T02+026C-T01 in 250 ml FaSSIF pH 6.5 by using Apparatus II and 100 rpm.

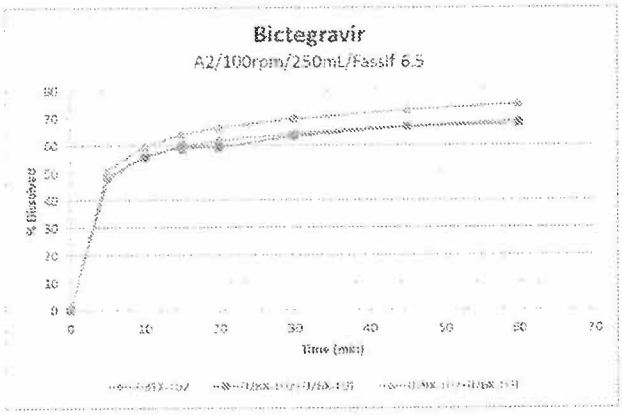


Figure 5: Drug release profiles for bictegravir from samples 028X-T02+026X-T01, 029X-T02+026X-T01 and 031X-T02+026X-T01 in 250 ml FaSSIF pH 6.5 by using Apparatus II and 100 rpm.

The figures show that the dissolution of Na-BIC from 031X-T02 and 028X-T02 either alone or in the presence of 026X-T01 is the same (see Figures 1 and 2).

In addition, figures 3 and 4 show that the dissolution of Na-BIC is influenced by the following two aspects, namely:

a) the used batch of bictegravir (028X-T02+026X-T01 and 029X-T02+026C-T01), and

b) the formulation (029X-T02+026X-T01 and 030X-T02+026C-T01).

Further, figure 5 shows that the used batch of bictegravir has a stronger impact on the dissolution profile than the formulation aspect

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Retrovirology

RESEARCH Open Access

Efficacies of Cabotegravir and Bictegravir against drug-resistant HIV-1 integrase mutants

Steven J. Smith[1], Xue Zhi Zhao[2], Terrence R. Burke Jr.[2] and Stephen H. Hughes[1*]

Abstract

Background: Integrase strand transfer inhibitors (INSTIs) are the class of antiretroviral (ARV) drugs most recently approved by the FDA for the treatment of HIV-1 infections. INSTIs block the strand transfer reaction catalyzed by HIV-1 integrase (IN) and have been shown to potently inhibit infection by wild-type HIV-1. Of the three current FDA-approved INSTIs, Dolutegravir (DTG), has been the most effective, in part because treatment does not readily select for resistant mutants. However, recent studies showed that when INSTI experienced patients are put on a DTG salvage therapy, they have reduced response rates. Two new INSTIs, Cabotegravir (CAB) and Bictegravir (BIC), are currently in late-stage clinical trials.

Results: Both CAB and BIC had much broader antiviral profiles than RAL and EVG against the INSTI-resistant single, double, and triple HIV-1 mutants used in this study. BIC was more effective than DTG against several INSTI-resistant mutants. Overall, in terms of their ability to inhibit a broad range of INSTI-resistant IN mutants, BIC was superior to DTG, and DTG was superior to CAB. Modeling the binding of CAB, BIC, and DTG within the active site of IN suggested that the "left side" of the INSTI pharmacophore (the side away from the viral DNA) was important in determining the ability of the compound to inhibit the IN mutants we tested.

Conclusions: Of the two INSTIs in late stage clinical trials, BIC appears to be better able to inhibit the replication of a broad range of IN mutants. BIC retained potency against several of the INSTI resistant mutants that caused a decrease in susceptibility to DTG.

Keywords: HIV-1, Integrase, Infectivity, Potency, Susceptibility, Modeling, Resistance

Background

INSTIs are the class of antiretroviral (ARV) drugs most recently approved by the FDA to treat HIV-1 infections. INSTIs target the second reaction performed by HIV-1 integrase (IN), strand transfer (ST), in which IN catalyzes the integration of the viral DNA into the cellular genome [1, 2]. INSTIs have a centralized pharmacophore, which contains a chelating functionality that interacts with the two catalytic Mg^{2+} ions at the IN active site [3, 4]. This central pharmacophore is joined to a halogenated benzyl moiety that interacts with the penultimate base at the 3′ end of the viral DNA [5]. Thus, INSTIs interact with both the enzyme and its nucleic acid substrate. The combination of these interactions allows the INSTIs to target and potently inhibit HIV-1 IN. Raltegravir (RAL) and Elvitegravir (EVG) are the first and second FDA-approved INSTIs, respectively. They potently inhibit WT HIV-1; however, resistant mutants can develop relatively quickly (Fig. 1). A partial list of the well-defined primary resistance mutations includes: Y143R, N155H, G140S/Q148H, T66I, and E92Q. Other mutations that confer resistance to RAL and EVG have been identified. In many cases, mutations selected by either RAL or EVG reduce the susceptibility of IN to the other INSTI, showing that RAL and EVG have overlapping resistance profiles [6–8].

In 2013, Dolutegravir (DTG) was approved by the FDA and it quickly became a preferred drug for combination antiretroviral therapy (cART) [9–12]. DTG differs from the first generation INSTIs in that its chelating motif is located on a tri-cyclic scaffold [13, 14]. In addition, the structural component that connects the central chelating

*Correspondence: hughes@ncifcrf.gov
[1] HIV Dynamics and Replication Program, National Cancer Institute-Frederick, National Institutes of Health, Frederick, MD, USA
Full list of author information is available at the end of the article

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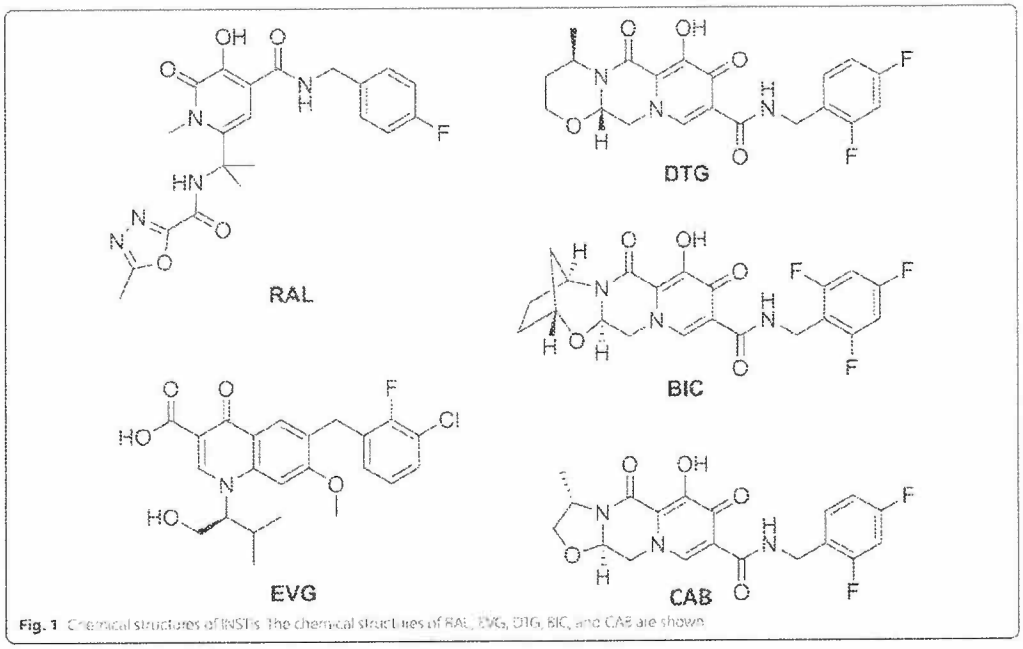


Fig. 1 Chemical structures of INSTIs. The chemical structures of RAL, EVG, DTG, BIC, and CAB are shown

moiety to the halogenated benzyl group is longer than it is in either RAL or EVG (Fig. 1) [15]. Not only do these structural differences allow DTG to be highly effective against WT HIV-1, but DTG is much more potent against IN mutants that confer resistance to the first generation INSTIs. Moreover, it has been difficult to select for DTG resistant mutants in cell culture and the treatment of HIV-1 patients using DTG has been, generally speaking, quite successful [16–21].

The usefulness of most ARV drugs is limited by the emergence of resistant mutants, and DTG will not be an exception. Recent in vitro selection studies with DTG have uncovered resistance mutations [22–24]. In clinical trials with INSTI-experienced subjects [25, 26] whose viruses had INSTI resistance mutations at the primary position Q148 plus at least one additional mutation at any of the secondary positions, L74, E138, G140, or G163, patients were put on a salvage regimen that included DTG. This change in therapy failed to lower HIV-1 below 50 copies/mL. Analysis of the virus present in the patients after the trial showed that additional mutations were selected in IN. These results showed that mutations that confer resistance to DTG can be selected in viruses that carry preexisting resistance mutations.

Recently, two new INSTIs, Cabotegravir (CAB) and Bictegravir (BIC), have been developed and these are currently in late phase clinical trials [13, 27, 28]. BIC and CAB, which are structurally similar to DTG, (both have tri-cyclic central pharmacophores), could offer therapeutic alternatives to HIV-1 patients (Fig. 1). Here, we describe evaluation of the antiviral potency of CAB and BIC against broad panels of well-characterized INSTI-resistant single and double mutants, and against the INSTI-resistant triple mutants identified in the VIKING clinical trials. Our objective was to determine how well these new INSTIs performed compared to DTG, the current standard of care.

Results

Initial screening of CAB and BIC against primary INSTI resistant mutants

The abilities of CAB and BIC to inhibit the replication of WT HIV-1 and INSTI-resistant mutants were determined in single-round viral replication assays. We initially screened CAB and BIC against a panel of primary INSTI-resistant mutants, which included: Y143R, N155H, G140S/Q148H, T66I, E92Q, H51Y, G118R, R263K, H51Y/R263K, and E138K/E263K. Y143R, N155H, and G140S/Q148H (Fig. 2; see also Additional file 1: Table S1A) were chosen because they have been selected in patients by treatment with RAL [29–31]; the T66I and E92Q mutants were selected by treatment with EVG

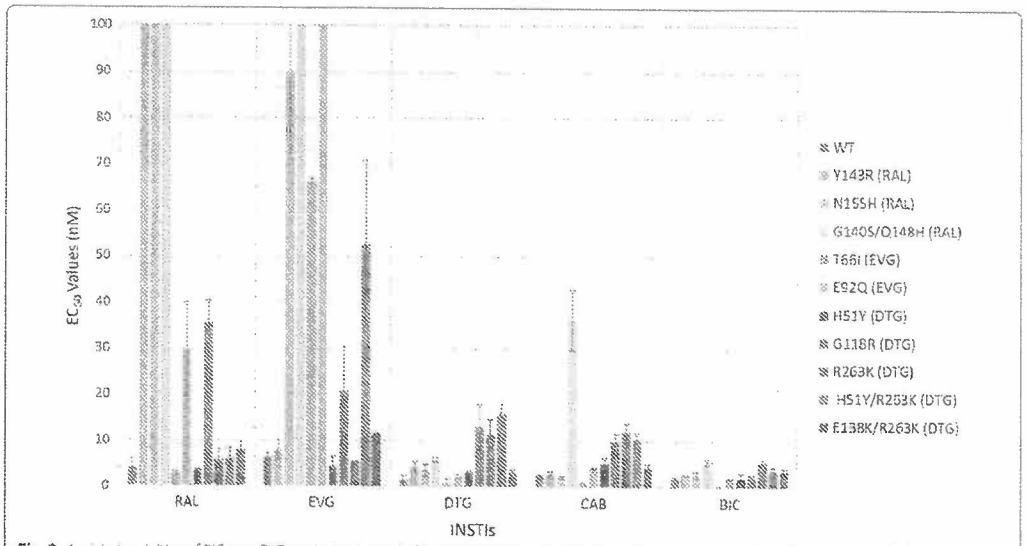


Fig. 2 Antiviral activities of BIC and CAB against primary INSTI-resistant mutants. The EC_{50} values were determined, in single round infection assays, using vectors that carry the INSTI-resistant IN mutants. Error bars represent the standard deviations in the data from independent experiments ($n = 4$). The EC_{50} values shown in the figure have a maximum of 100 nM. The EC_{50} values of RAL against Y143R, N155H and G140S/Q148H, EVG versus G140S/Q148H, and E92Q primary INSTI-resistant mutants were all > 100 nM

[32–34]. The IN mutations H51Y, G118R, R263K, H51Y/R263K, E138K/R263K mutants have been selected with DTG in cell culture [22–24]. The R263K mutation has been selected in several treatment-experienced, INSTI-naïve patients undergoing DTG therapy [16]. Both CAB and BIC potently inhibited the infection of WT HIV-1 with EC_{50} values equivalent to the FDA-approved INSTIs (< 3 nM). Moreover, CAB and BIC were minimally toxic in cell culture assays with CC_{50} values > 250 μM (data not shown), which is similar to the FDA-approved INSTIs. This demonstrates that these INSTIs have very favorable therapeutic indexes in cultured cells. Additionally, both CAB and BIC potently inhibited the RAL-resistant mutants Y143R and N155H; the EVG-resistant IN mutants T66I and E92Q, and the DTG-resistant IN mutant H51Y and E138K/R263K with EC_{50} values < 5 nM. However, only BIC potently inhibited the well-known RAL-resistant IN double mutant G140S/Q148H and the DTG-resistant IN mutants G118R, R263K, and H51Y/R263K with EC_{50} values ≤ 5 nM. The RAL-resistant IN mutant G140S/Q148H caused a substantial loss of CAB potency (36.3 ± 6.5 nM), while there was a smaller but still modest loss of potency against the DTG-resistant IN mutants G118R (12.1 ± 1.9 nM), R263K (13.4 ± 1.3 nM), and H51Y/R263K (10.4 ± 1.5 nM). These antiviral data were compared to previous screens, in which the antiviral potencies of RAL, EVG, and DTG were measured against the same INSTI-resistant primary mutants [35, 36]. When the antiviral profiles of the second generation INSTIs, DTG, CAB and BIC were compared to the FDA-approved INSTIs for WT HIV-1 and the RAL- and EVG-resistant mutants, all of the second generation INSTIs had antiviral profiles that were obviously superior to RAL and EVG. The differences were sufficiently clear cut that the comparisons between the first and second generation INSTIs were not subjected to statistical analysis. The more important question was whether either CAB or BIC was better than DTG, in terms of their ability to inhibit the IN mutants. To make the comparison objective, the statistical significance of the EC_{50} data for CAB, BIC, and DTG were analyzed using the Student's *t* test. The EC_{50} values for WT HIV for DTG, CAB and BIC were similar, which allowed us to compare the EC_{50} values for the mutants directly. In the initial screen, which included ten INSTI-resistant primary mutants, BIC was significantly better than CAB for seven of these ten primary mutants (four p values < 0.01 and three p values < 0.001; see Fig. 2 and Additional file 1: Table S1B). In addition, BIC was better than DTG against three of the primary mutants. In contrast, CAB was significantly better than DTG for one primary mutant and DTG was better than CAB for three of the primary mutants.

Antiviral activities of CAB and BIC against other common INSTI-resistant single mutants

We determined the antiviral profiles of CAB and BIC, as well as the FDA-approved INSTIs, against a second panel of additional INSTI-resistant single mutants to compare the strengths and weaknesses of the two new INSTIs and the FDA-approved INSTIs [37–39]. This panel of INSTI-resistant single mutants included: M50I, L74M, T97A, S119R, E138K, G140S, Q146L, Q146P, Q148H, Q148K, Q148R, and S153Y (Fig. 4; Additional file 1: Table S2A). BIC potently inhibited this entire panel of INSTI-resistant mutants with EC_{50} values below 5 nM, which was comparable to DTG. CAB also inhibited the majority of mutants in this panel. However, it lost some potency against the INSTI-resistant single mutants E138K (12.9 ± 1.0 nM), Q146P (10.3 ± 2.1 nM), and Q148H (6.8 ± 1.5 nM). Most of the INSTI-resistant single mutants in this panel caused significant drops in susceptibility to the first generation INSTIs, RAL and EVG, with the Q148H/K/R mutants having the greatest effect on the EC_{50} values. Based on the data obtained with the mutants in this panel, DTG was better than CAB and BIC (Fig. 3; Additional file 1: Table S2B). DTG was significantly better than CAB against six of the mutants and better than BIC against four mutants (two p values < 0.001). Conversely, BIC was better than CAB against five of these mutants.

Antiviral activities of CAB and BIC against a panel of INSTI-resistant double mutants having a primary mutation at position Q148

We next tested CAB, BIC, and the FDA-approved INSTIs against a panel of INSTI-resistant double mutants that included either one of the primary mutations at position Q148 (H/K/R), or Y143R or N155H. These primary mutations were combined with a secondary mutation at positions E138 (A/K) or G140 (A/C/S) (Fig. 5; Additional file 1: Table S3A). BIC potently inhibited (EC_{50} < 5 nM) the INSTI-resistant double mutants G140A/Q148H, Y143R/Q148H, Q148H/N155H, G140S/Q148K, E138A/Q148R, E138K/Q148R, and Q148R/N155H. Conversely, the INSTI-resistant double mutants G140A/Q148R (10 ± 2.5 nM), G140C/Q148R (6.4 ± 1.4 nM), G140S/Q148R (6.1 ± 1.3 nM) caused small losses in susceptibility to BIC, whereas the double mutants E138K/Q148K (59.3 ± 4.9 nM) and G140A/Q148K (137.1 ± 5.0 nM) resulted in substantial reductions in susceptibility to BIC. However, there was a large reduction in CAB potency against most of the double mutants in the panel. The double mutants Y143R/Q148H (6.0 ± 0.4 nM), E138A/Q148R (25.6 ± 0.8 nM), E138K/Q148R (24.1 ± 0.1 nM), and G140A/Q148R (13.7 ± 2.7 nM) caused a minimal loss in susceptibility to CAB, whereas E138K/Q148K (772.1 ± 72.2 nM), G140A/Q148K (393.1 ± 51.1 nM), G140S/Q148K (87.3 ± 7.6 nM), G140C/Q148R (66.6 ± 8.1 nM), and Q148R/N155H (50.5 ± 6.5 nM) caused large reductions in susceptibility to CAB. DTG was very effective across this panel of INSTI-resistant double mutants. However, it sustained a moderate loss in potency against the INSTI-resistant double mutant E138K/Q148K (25.0 ± 2.1 nM) and significant loss in potency against the INSTI-resistant double mutant G140A/Q148K (450.7 ± 58.8 nM). The first generation INSTIs RAL and EVG exhibited considerable loss of potency against all of the mutants in this panel of INSTI-resistant double mutants. BIC was significantly better than DTG against five of these double mutants (four p values < 0.01; Fig. 3; Additional file 1: Table S3B); however, DTG was better than BIC for four of the mutants (two p values < 0.001). CAB was not significantly better than either DTG or BIC against any double mutants.

Antiviral activities of CAB and BIC against a panel of INSTI-resistant double mutants that included the primary mutations T66I and N155H and additional mutations at other positions

We determined the antiviral profiles of CAB, BIC, and the FDA-approved INSTIs against the EVG-resistant double mutant T66I/E157Q and a panel of INSTI-resistant double mutants with a primary mutation at N155H and one of the following secondary mutations: E92Q, G140S, Y143H/R, or G163R (Fig. 6; Additional file 1: Table S4A). BIC, CAB, and DTG retained potency against the INSTI-resistant double mutant T66I/E157Q and the other INSTI-resistant double mutants (EC_{50} < 5 nM). The first generation INSTIs, RAL and EVG, failed to potently inhibit any of these double mutants. Based on this panel of mutants, the antiviral profiles of the three second generation INSTIs were similar to each other. CAB was significantly better than BIC against two of these double mutants (one p value < 0.001; see Figs. 3 and 7 and Additional file 1: Table S4B). DTG had better activity against one of the double mutants than CAB and BIC (p value < 0.01).

(See figure on next page.)

Fig. 3 Statistical significance of the antiviral data among DTG, CAB, and BIC. The Student's t test was used to calculate the statistical significance of the differences in the antiviral activities of the INSTIs. Because of multiple comparisons, p values < 0.025 were considered statistically significant when comparing the efficacies among DTG, CAB, and BIC

Figure and Supplementary Table	p-Value < 0.025	p-Value < 0.01	p-Value < 0.001	Overall Comparison among INSTIs for Table	
Figure 2 Antiviral Data and Supplementary Table 1	BIC - DTG (R263K)	DTG – CAB (G140S/Q148H) BIC – CAB (G140S/Q148H) BIC – CAB (T66I) DTG – CAB (E92Q) DTG – CAB (H51Y) BIC - DTG (H51Y) BIC - CAB (H51Y) BIC - CAB (G118R) CAB - DTG (H51Y/R263K)	BIC - CAB (E92Q) BIC - CAB (R263K) BIC - DTG (H51Y/R263K) BIC - CAB (H51Y/R263K)	BIC > CAB BIC > DTG DTG > CAB DTG > BIC CAB > BIC CAB > DTG	7 3 3 0 0 1
Figure 3 Antiviral Data and Supplementary Table 2	DTG - CAB (Q148R)	CAB - DTG (L74M) DTG – CAB (T97A) DTG – BIC (Q148L) DTG – CAB (Q148P) BIC - CAB (Q148P) DTG – CAB (Q148H) DTG – BIC (Q148H) BIC - CAB (Q148H) DTG - CAB (Q148K) BIC - CAB (Q148K) BIC - CAB (Q148R)	CAB – BIC (M50I) DTG – CAB (E138K) DTG – BIC (E138K) BIC - CAB (E138K) DTG – BIC (Q148P)	BIC > CAB BIC > DTG DTG > CAB DTG > BIC CAB > BIC CAB > DTG	5 0 6 4 1 1
Figure 4 Antiviral Data and Supplementary Table 3	BIC - DTG (Y143R/Q148H) DTG – BIC (G140A/Q148R)	BIC - DTG (G140A/Q148H) BIC - CAB (G140A/Q148H) DTG - CAB (Q148H/N155H) BIC - CAB (Q148H/N155H) BIC - DTG (G140A/Q148K) BIC - CAB (G140A/Q148K) DTG – CAB (G140A/Q148R) DTG – BIC (G140C/Q148R) BIC - DTG (G140S/Q148R) BIC - DTG (Q148R/N155H)	DTG – CAB (Y143R/Q148H) BIC - CAB (Y143R/Q148H) DTG – CAB (E138K/Q148K) DTG – BIC (E138K/Q148K) BIC - CAB (E138K/Q148K) DTG - CAB (G140S/Q148K) DTG – BIC (G140S/Q148K) BIC - CAB (G140S/Q148K) DTG - CAB (E138A/Q148R) BIC - CAB (E138A/Q148R) DTG - CAB (E138K/Q148R) BIC - CAB (E138K/Q148R) DTG - CAB (G140C/Q148R) BIC - CAB (G140C/Q148R) DTG - CAB (G140S/Q148R) BIC - CAB (G140S/Q148R) DTG - CAB (Q148R/N155H) BIC - CAB (Q148R/N155H)	BIC > CAB BIC > DTG DTG > CAB DTG > BIC CAB > BIC CAB > DTG	11 5 16 4 0 0
Figure 5 Antiviral Data and Supplementary Table 4		DTG – BIC (T66I/E157Q) DTG - CAB (G140S/N155H) CAB – BIC (Y143R/N155H)	CAB – BIC (T66I/E157Q) BIC - CAB (G140S/N155H)	BIC > CAB BIC > DTG DTG > CAB DTG > BIC CAB > BIC CAB > DTG	1 0 1 1 2 0
Figure 6 Antiviral Data and Supplementary Table 5	BIC - DTG (E138A/S147G/Q148R)	DTG - CAB (L74M/G140A/Q148R) BIC - CAB (L74M/G140A/Q148R) DTG - CAB (L74M/G140C/Q148R) BIC - DTG (L74M/G140C/Q148R) BIC - CAB (L74M/G140C/Q148R) DTG - BIC (E138K/G140C/Q148R)	DTG - CAB (T97A/Y143R/Q148H) BIC - CAB (T97A/Y143R/Q148H) DTG - CAB (E138K/G140A/Q148K) BIC - CAB (E138K/G140A/Q148K) DTG - CAB (E138K/G140C/Q148R) BIC - CAB (E138K/G140C/Q148R) BIC - CAB (E138A/S147G/Q148R)	BIC > CAB BIC > DTG DTG > CAB DTG > BIC CAB > BIC CAB > DTG	6 2 5 1 0 0
Figure 7 Antiviral Data and Supplementary Table 6	BIC - CAB (T66I/T97A/E157Q)	DTG - CAB (T66I/T97A/E157Q) DTG - CAB (G140S/Y143R/N155H) BIC - CAB (G140S/Y143R/N155H) BIC - DTG (E92Q/N155H/G163R)	DTG - CAB (T97A/Y143R/N155H) BIC - CAB (T97A/Y143R/N155H)	BIC > CAB BIC > DTG DTG > CAB DTG > BIC CAB > BIC CAB > DTG	3 1 3 0 0 0
Figure 8 Antiviral Data and Supplementary Table 7		CAB - DTG (T97A/G140S/Q148H) BIC - CAB (T97A/G140S/Q148H) DTG - CAB (E138K/G140S/Q148H) DTG - CAB (G140S/Y143R/Q148H) BIC - CAB (G140S/Y143R/Q148H) DTG - CAB (G140S/Q148H/N155H) BIC - CAB (G140S/Q148H/N155H) DTG - CAB (G140S/Q148H/G163K)	BIC - DTG (T97A/G140S/Q148H) DTG - CAB (E138A/G140S/Q148H) BIC - CAB (E138A/G140S/Q148H) BIC - DTG (E138K/G140S/Q148H) BIC - CAB (E138K/G140S/Q148H) BIC - DTG (G140S/Q148H/G163K) BIC -CAB (G140S/Q148H/G163K)	BIC > CAB BIC > DTG DTG > CAB DTG > BIC CAB > BIC CAB > DTG	6 3 5 0 0 1

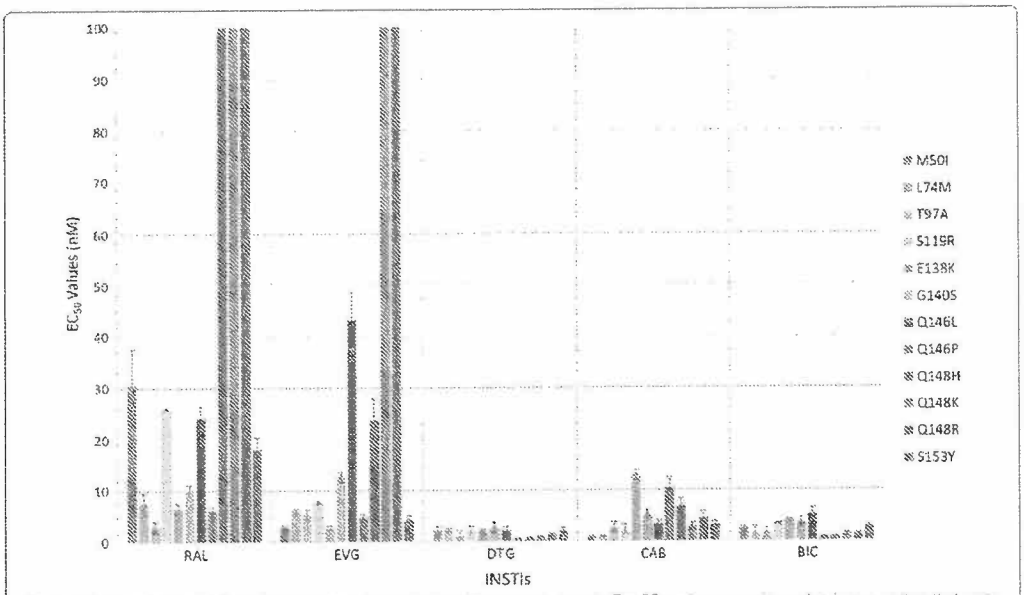


Fig. 4 Antiviral activities of BIC and CAB against common INSTI-resistant single mutants. The EC_{50} values were determined using vectors that carry the INSTI-resistant IN double mutants in single round infection assays. Error bars represent the standard deviations in the data from independent experiments ($n = 4$). The EC_{50} values shown in the figure have a maximum of 100 nM. The EC_{50} values of RAL against Q148H, Q148K, and Q148R and EVG versus Q148K and Q148R INSTI-resistant mutants were all > 100 nM

Antiviral activities of CAB and BIC against a panel INSTI-resistant triple mutants that included a primary mutation (Q148H/K/R) and two additional mutations

We determined the antiviral activities of CAB, BIC, and the FDA-approved INSTIs against a panel of INSTI-resistant triple mutants that included a primary mutation at Q148 (H/K/R) with two additional mutations at primary or secondary positions. The panel of INSTI-resistant triple mutants included: T97A/Y143R/Q148H, T97A/Q148H/N155H, E138K/G140A/Q148K, L74M/G140A/Q148R, L74M/G140C/Q148R, E138K/G140C/Q148R, and E138A/S147G/Q148R (Fig. 8; Additional file 1: Table S5A). Overall, DTG and BIC showed similar antiviral profiles against these triple mutants, and in some cases, CAB also retained potency. DTG, BIC, and CAB potently inhibited (EC_{50}s ≤ 5 nM) the T97A/Y143R/Q148H and E138A/S147G/Q148R INSTI-resistant triple mutants. The E138K/G140C/Q148R INSTI-resistant mutant caused only a small loss of potency to DTG (5.3 ± 1.0 nM) and BIC (8.2 ± 1.1 nM). This mutant showed a significant reduction in susceptibility to CAB (134.2 ± 0.3 nM). The L74M/G140C/Q148R triple mutant was moderately susceptible to BIC (6.1 ± 0.9 nM) and DTG (10.2 ± 1.3 nM). However, this mutant caused a massive loss in susceptibility to CAB (220.3 ± 41.2 nM). The L74M/G140A/Q148R triple mutant with a different mutation at position G140, caused a modest loss of susceptibility to both DTG (12.0 ± 2.1 nM) and BIC (11.7 ± 1.3 nM); however, this also caused a substantial loss in susceptibility to CAB (53.2 ± 14.8 nM). Finally, DTG, BIC, and CAB failed to retain potency against the E138K/G140A/Q148K INSTI-resistant triple mutant (EC_{50}s > 200 nM). The first generation INSTIs, RAL and EVG failed to retain potency against the entire panel of INSTI-resistant triple mutants, except for T97A/Y143R/Q148H, against which EVG showed modest inhibition, with an EC_{50} value of 41.6 ± 3.0 nM. BIC had significantly higher potencies against two of the INSTI-triple mutants than DTG (one p value < 0.01, see Fig. 3 and Additional file 1: Table S5B), compared to one for DTG versus BIC against the triple mutants in this panel. Both BIC and DTG were more effective than CAB. BIC had better efficacies than CAB against six of the triple mutants (four p values < 0.001); DTG was better than CAB for five of the mutants in this panel (three p values < 0.001).

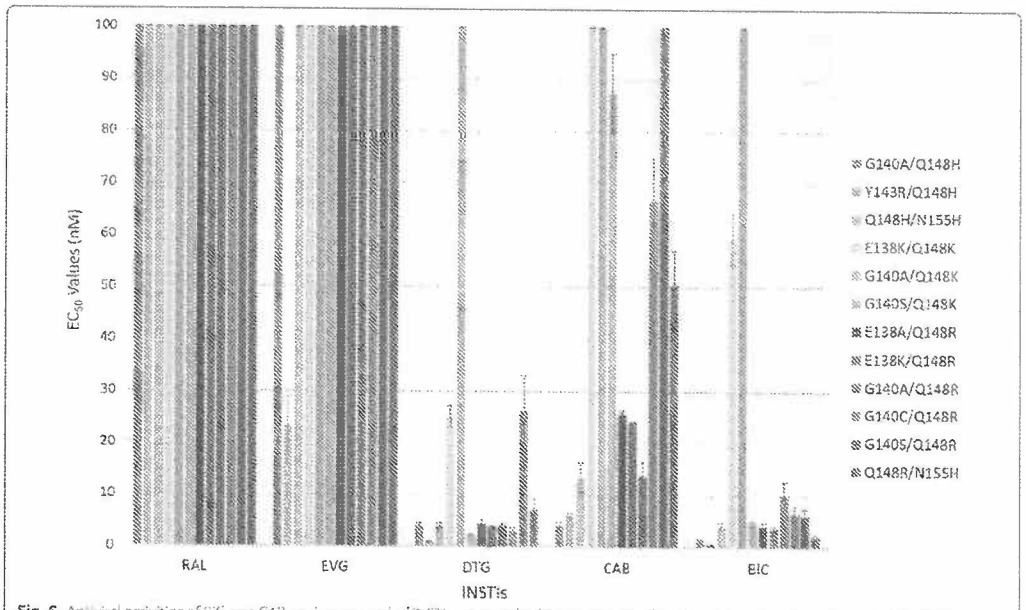


Fig. 5 Antiviral activities of BIC and CAB against a panel of INSTI-resistant double mutants that have a primary mutation at position Q148. The EC_{50} values were determined using vectors that carry the INSTI-resistant double mutants in single round infection assays. Error bars represent the standard deviations in the data from independent experiments ($n = 4$). The EC_{50} values shown in the figure have a maximum of 100 nM. The EC_{50} values of RAL and EVG against this entire panel (except for EVG versus Y143R/Q148H) were all > 100 nM. The EC_{50} values of DTG against G140A/Q148K, CAB versus E138K/Q148K, G140A/Q148K, G140S/Q148R, and BIC against G140A/Q148K were all > 100 nM

Antiviral activities of CAB and BIC versus a panel of INSTI-resistant triple mutants that consists of a primary mutation at T66I and N155H with additional secondary mutations

We examined CAB, BIC, and the FDA-approved INSTIs, against a panel of INSTI-triple mutants that included T66I/T97A/E157Q, T97A/Y143R/N155H, G140S/Y143R/N155H, and E92Q/N155H/G163R (Fig. 6; Additional file 1: Table S6A). The triple mutant T66I/T97A/E157Q is an EVG-resistant mutant and, as expected, this mutant showed a substantial decrease in potency to EVG (69.4 ± 11.8 nM) and a lesser loss of potency to RAL (33.5 ± 8.7 nM). In contrast, DTG (0.5 ± 0.1 nM), BIC (0.4 ± 0.2 nM), and CAB (0.8 ± 0.1 nM) retained full potency against this triple mutant. Additionally, DTG, BIC, and CAB retained high antiviral potencies against the E92Q/N155H/G163R INSTI-resistant triple mutant (EC_{50} < 5 nM). The G140S/Y143R/N155H triple mutant was susceptible to both DTG (2.6 ± 0.3 nM) and BIC (2.1 ± 0.1 nM), but it caused a moderate loss in potency to CAB (20.0 ± 3.5 nM). Both DTG and BIC retained significant potency against the T97A/Y143R/N155H triple mutant, 8.5 ± 1.5 nM and 8.2 ± 1.7 nM, respectively, whereas CAB lost substantial potency (142.2 ± 8.3 nM). RAL and EVG both failed to potently inhibit the T97A/Y143R/N155H, G140S/Y143R/N155H, and E92Q/N155H/G163R INSTI-resistant triple mutants (EC_{50}s > 90 nM). Both DTG and BIC were more effective than CAB; each one had a significantly higher potency than CAB against 3 of the triple mutants in this panel (at least one p value < 0.001; see Fig. 3 and Additional file 1: Table S6B). BIC was significantly better than DTG against one of the triple mutants (p value < 0.01).

Antiviral activities of CAB and BIC against a panel of INSTI-resistant triple mutants that include the well-characterized RAL-resistant double mutant G140S/Q148H and an additional secondary mutation

We tested the antiviral potencies of CAB, BIC, and the FDA-approved INSTIs against a panel of INSTI-resistant triple mutants that included the RAL-resistant G140S/Q148H double mutations with an additional mutation: T97A, E138A/K, Y143R, N155H, or G163K (Fig. 10; Additional file 1: Table S7A). As expected, both of the first generation INSTIs, RAL and EVG, were ineffective against this panel of six INSTI-resistant triple mutants

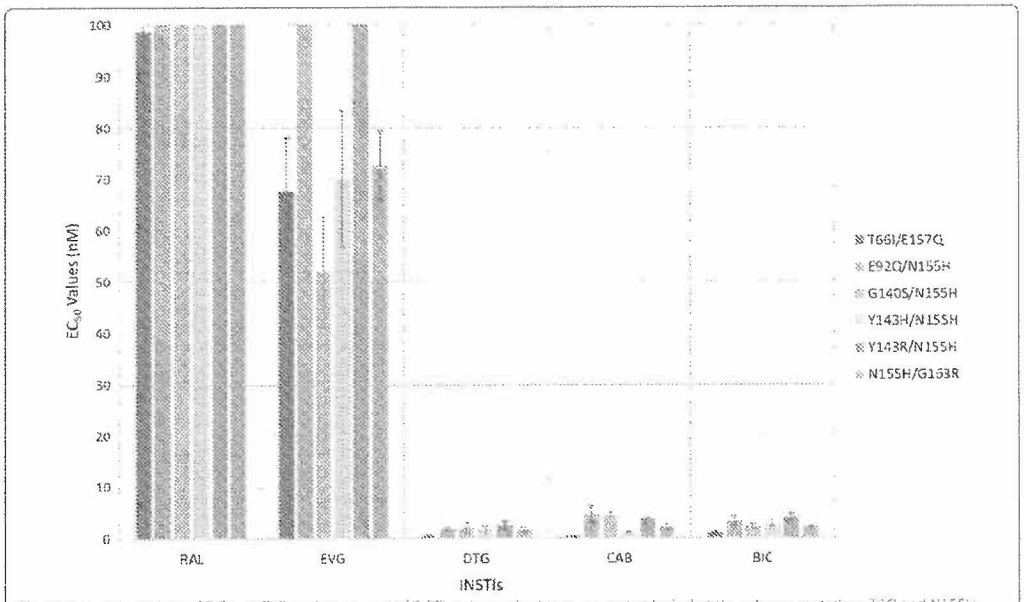


Fig. 6 Antiviral activities of BIC and CAB against a panel of INSTI-resistant double mutants that included the primary mutations T66I and N155H with additional mutations at other positions. The EC_{50} values were determined using vectors that carry the INSTI-resistant double mutants in single round infection assays. Error bars represent the standard deviations in the data from independent experiments ($n = 4$). The EC_{50} values shown in the figure have a maximum of 100 nM. The EC_{50} values of RAL against this entire panel of INSTI-resistant double mutants were all > 100 nM. The EC_{50} values of EVG against E92Q/N155H and Y143R/N155H were all > 100 nM

(EC_{50}s > 5000 nM). In addition, DTG, which potently inhibited the G140S/Q148H INSTI-resistant double mutant ($EC_{50} < 5$ nM) showed a loss of potency against the INSTI-resistant triple mutants. The E138A/G140S/Q148H, G140S/Y143R/Q148H, and G140S/Q148H/G163K triple mutants caused modest drops in potency, from 13.8 ± 4.8 nM, to 7.7 ± 2.0 nM, and 24.3 ± 1.1 nM, respectively. However, the INSTI-resistant triple mutants T97A/G140S/Q148H, E138K/G140S/Q148H, and G140S/Q148H/N155H caused substantial reductions in potency (EC_5s ≥ 55 nM). CAB was not broadly active against these INSTI-resistant triple mutants; most of the mutants caused significant drops in susceptibility to CAB. Conversely, for this panel of mutants, BIC was more effective than DTG in retaining potency. BIC showed at most a modest loss in potency against E138A/G140S/Q148H, E138K/G140S/Q148H, G140S/Y143R/Q148H, and G140S/Q148H/G163K (EC_{50}s < 10 nM. However, the INSTI-resistant triple mutant T97A/G140S/Q148H caused a larger reduction in susceptibility to BIC (29.5 ± 4.4 nM). Thus, BIC was superior to the other INSTIs in terms of its ability to retain antiviral activity against this set of triple mutants. BIC was the superior INSTI against this panel of triple mutants, as it had significantly better potencies against five INSTI-resistant triple mutants than CAB (2 p values < 0.01 and 3 p values < 0.001, see Fig. 3 and Additional file 1: S7B) and three triple mutants than DTG (p values < 0.001). DTG was a better INSTI than CAB as it had higher efficacies against five triple mutants than CAB.

Homology modeling of the binding of BIC and CAB into the HIV-1 IN active site using PFV intasome structural data

Using the previously reported crystal structure of the PFV intasome with DTG bound at the catalytic site (PDB ID: 3S3M) [15] and the structure of the HIV-1 IN strand transfer complex (STC) solved by electron microscopy as a template (PDB ID: 5U1C) [40], homology models were prepared of BIC and CAB bound to the HIV-1 intasome (Fig. 1, panels B and C). Modeling allowed us (1) to understand better how BIC and CAB bind in the HIV-1 IN active site and (2) to identify structural features that may help (or hinder) these INSTIs in overcoming INSTI-resistant mutants. The chelating motifs of BIC and CAB aligned similarly to

Overall Comparison	BIC > CAB	39
	BIC > DTG	14
	DTG > CAB	33
	DTG > BIC	10
	CAB > BIC	3
	CAB > DTG	3
***p*-Value < 0.025**	BIC > CAB	1
	BIC > DTG	3
	DTG > CAB	1
	DTG > BIC	1
	CAB > BIC	0
	CAB > DTG	0
***p*-Value < 0.01**	BIC > CAB	17
	BIC > DTG	7
	DTG > CAB	18
	DTG > BIC	5
	CAB > BIC	1
	CAB > DTG	3
***p*-Value < 0.001**	BIC > CAB	21
	BIC > DTG	4
	DTG > CAB	14
	DTG > BIC	4
	CAB > BIC	2
	CAB > DTG	0

Fig. 7 Overall Comparison of the statistical significance of the antiviral data among DTG, CAB, and BIC. The Student's *t* test was used to calculate the statistical significance of the differences in the antiviral activities of the INSTIs. The *p* values < 0.025, < 0.01, and < 0.001 between DTG, CAB, and BIC were used to decide which INSTIs were more broadly efficacious against the mutants

DTG (Fig. 11, panel D), as did the halobenzyl moieties, which have π–π hydrophobic stacking interactions with the penultimate cytosine on the 3′ ends of the viral DNA. However, it is the "left" side of the tricyclic ring system of BIC, which is the portion of the INSTI that is distal to the end of the viral DNA, and has an oxazepine ring which features a methylene bridge and lacks a methyl group, that appears to distinguish BIC from DTG. This cyclic modification can, in the model, adopt and maintain a different configuration from the components on the left side of DTG and CAB. Both the methyl-modified oxazine ring of DTG and the methyl-modified oxazole ring of CAB appear to be more constrained than the oxazepine ring of BIC. The greater flexibility of the oxazepane ring allows it to bend backwards or forwards, depending on the exact geometry of the active site, which can be modified by nearby mutations. Thus, the apparent greater conformational flexibility of the oxazepine ring could allow BIC to bind tightly to the various INSTI-resistant mutants, such as G118R and S119R, which affect the periphery of the IN active site, and limit the modifications that can be added to the "left" side of the INSTI scaffold distal to the end of the viral DNA (unpublished observations). Conversely, the oxazole ring of CAB is pointed out and away from the position occupied by the corresponding oxazine ring of DTG (Fig. 11, panel B), and its methyl group does not appear to be in a position to make an important contribution to binding, which is in good agreement with the data of Yoshinaga et al. [41], which appeared when this manuscript was in review. This could account for the fact that, although CAB and DTG adopt similar spatial orientations when bound to the IN active site, DTG is much more broadly effective against INSTI-resistant mutants (see "Discussion").

Discussion

The relatively recent development of INSTIs as potent and effective HIV-1 inhibitors permits improved treatment strategies for HIV-1 infected patients. In general, INSTIs are minimally toxic and work well in combination with other ARV drug classes [20, 42–44]. In addition, DTG appears not to readily select for resistance mutations. DTG is now widely used in therapies for the treatment of both naïve and experienced patients [11, 12, 16, 18, 19]. However, patients in advanced clinical trials that were previously on a RAL-based therapy, who switched to a DTG-based salvage therapy, have shown signs of virological failure. In some cases, additional resistance mutations were selected [25, 26]. Therefore, there is a need for new INSTIs that can overcome emerging INSTI-resistant mutants.

BIC and CAB are now in late stage clinical trials [45–48]. Based on our antiviral analysis of the ability of these new INSTIs to inhibit previously identified INSTI-resistant single, double, and triple mutants in a single round replication assay, it appears that both BIC and CAB are both more broadly effective than either of the first generation INSTIs, RAL and EVG. However, in terms of their ability to inhibit the fifty-seven INSTI-resistant mutants we tested, BIC was significantly better than DTG against fourteen out of the mutants (Fig. 7; seven featured p values < 0.01, whereas four had p values < 0.001). BIC was also better than CAB against thirty-nine of the mutants (twenty-one had p values < 0.001). Conversely, DTG was better than BIC against ten of the mutants tested (four with p values < 0.001) and better than CAB

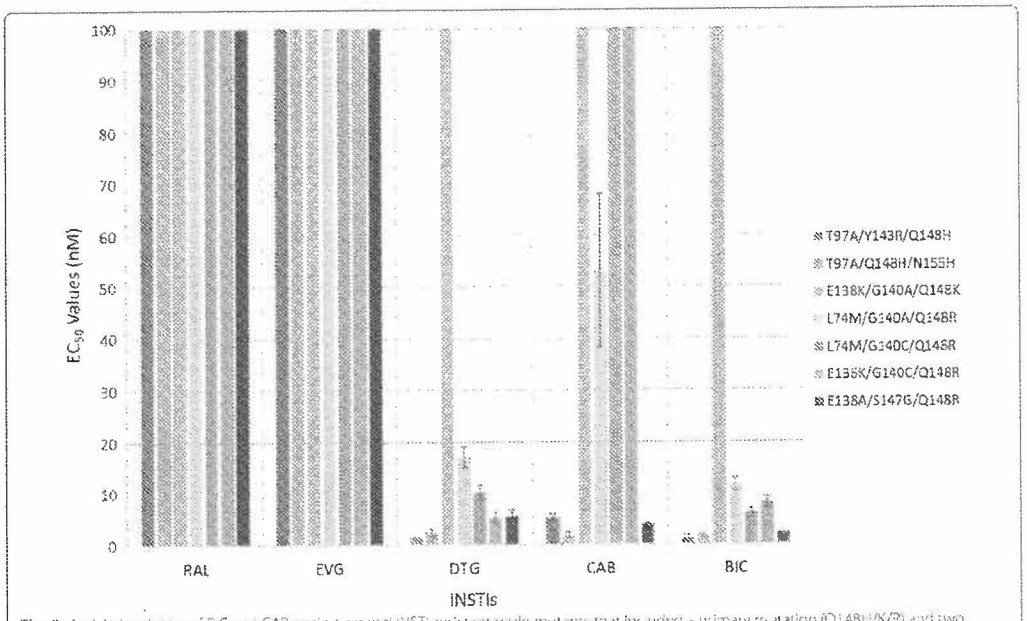


Fig. 8 Antiviral activities of BIC and CAB against a panel INSTI-resistant triple mutants that included a primary mutation (Q148H/K/R) and two additional mutations. The EC_{50} values were determined using vectors that carry the INSTI-resistant triple mutants in single round infection assays. Error bars represent the standard deviations in the data from independent experiments ($n = 4$). The EC_{50} values shown in the figure have a maximum of 100 nM. The EC_{50} values of RAL and EVG versus this entire panel of INSTI-resistant triple mutants were all > 100 nM. The EC_{50} values of DTG against E138K/G140A/Q148K, CAB versus E138K/G140A/Q148K, L74M/G140C/Q148R, and E138K/G140C/Q148R, and BIC against E138K/G140A/Q148K were all > 100 nM

for thirty-three of the mutants (fourteen with p values < 0.001). CAB was better than BIC and DTG for three mutants each (all three p values < 0.01 for DTG and two p values < 0.001 for BIC). Overall, our conclusions concerning the relative efficacies of the new INSTIs against mutants are in good agreement with the data of Yoshinaga et al. [41] and Neogi et al. [49], which appeared when this manuscript was in review.

Given the complexities of pharmacology, a significant difference in the behavior of a drug against a particular mutant (or mutants) may or may not translate directly into a desirable clinical outcome. However, given the problems that arise with drug resistance, it is likely that, among related compounds, those that are more broadly effective against resistant viruses will have an advantage in the clinic. In addition, in comparing the potencies of the compounds, the single round assay allows us to directly compare the efficacies of the new INSTIs against INSTI-resistant mutants in a reproducible and accurate manner. The single round assay avoids the issue of the effects of the mutations on the replication capacity, which, in turn, affects the number of viral life cycles in assays done with replication competent viruses, and by extension, can affect the EC_{50}s.

Having a better understanding of how INSTIs bind to HIV-1 IN is an important part of developing more effective new drugs. However, superpositioning the available PFV and HIV IN structures has revealed differences in the PFV and HIV-1 IN active sites [15, 40]. Notably, the β4α2 loops are in different positions relative to the IN active site and there are differences in the structures and locations of the C-terminal domains (CTDs) near the IN active site. Thus, the contacts and interactions between INSTIs and the PFV intasome might not correspond exactly to the related contacts in the HIV-1 intasome. Until the structure of the HIV-1 intasome with these INSTIs bound is solved, HIV-1 IN models based on the structures of the PFV template with bound INSTIs and the available HIV-1 strand transfer (STC) structures can be used to predict how new INSTIs will bind to the HIV-1 intasome. DTG, BIC, and CAB are similar chemically and structurally. Not surprisingly, based on the model we built using the available structural information, all three compounds adopt similar configurations within

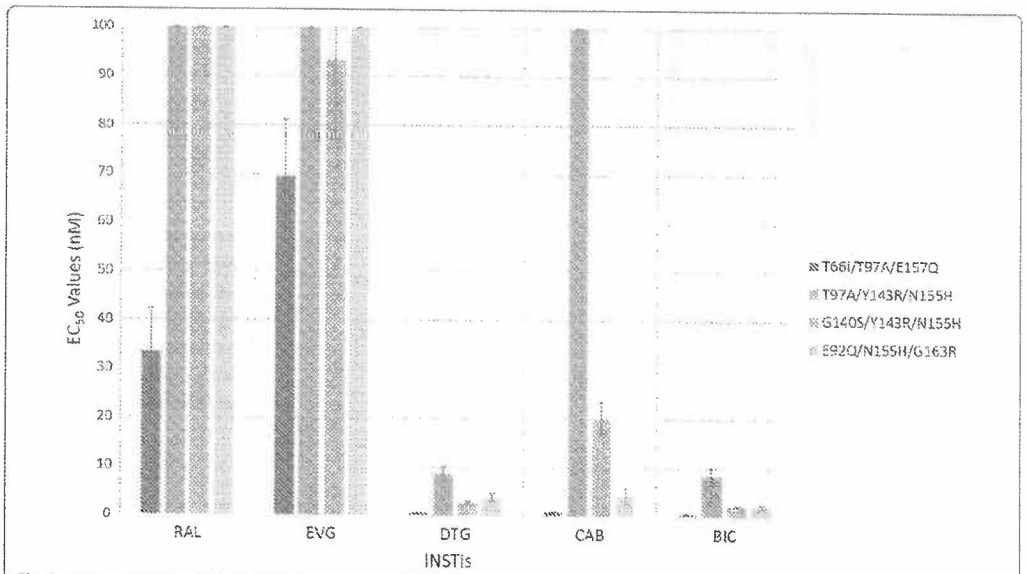


Fig. 9 Antiviral activities of BIC and CAB versus a panel of INSTI-resistant triple mutants that consists of a primary mutation at T66I and N155H with additional secondary mutations. The EC_{50} values were determined using vectors that carry the INSTI-resistant triple mutants in single round infection assays. Error bars represent the standard deviations of the data from independent experiments (n = 4). The EC_{50} value shown in the figure have a maximum of 100 nM. The EC_{50} values of RAL against T97A/Y143R/N155H, G140S/Y143R/N155H, and E92Q/N155H/G163R were all > 100 nM. The EC_{50} values of EVG versus T97A/Y143R/N155H and E92Q/N155H/G163R and CAB against T97A/Y143R/N155H were all > 100 nM

the active site of HIV-1 IN. It appears that the structural differences on the "left side" of these INSTIs, the part of the pharmacophore away from the 3′ end of the viral DNA, are largely responsible for their different resistance profiles.

Although there are similarities, as noted above, BIC is better than DTG, and DTG is better than CAB, in terms of their respective abilities to broadly inhibit the known IN mutants. We think it is likely that BIC is more broadly effective in its ability to inhibit a range of INSTI-resistant mutants, because it is better able to adjust its conformation, in response to the changes in the shape of the active site caused by the various resistance mutations. Thus, as has been proposed for the binding of non-nucleoside reverse transcriptase inhibitors (NNRTIs) to HIV-1 RT [50–53], the most broadly potent compounds are those that are able to adjust their binding mode and/or their configuration in response to changes in and around the IN active site. As briefly discussed earlier, BIC has an oxazepine ring with a methylene bridge appended to its chelating scaffold, which differs from the oxazine ring of DTG. It appears, based on the models, that the oxazepine ring of BIC is more flexible, which would allow it to be more conformationally adaptable. The introduction of resistance mutations in residues in and around the IN active site may cause alterations in the active site geometry. These changes could potentially affect the binding of relatively rigid compounds, giving rise to resistance. The greater flexibility of the extended ring system of BIC may help it adapt to changes in the geometry in the IN active site, allowing BIC to overcome many of the known IN resistance mutations. However, the details of the binding of BIC, particularly to the INSTI-resistant forms of HIV-1 IN, will require additional high resolution structural data. Conversely, the methyl-modified oxazole ring of CAB does not appear to be in a favorable position to interact with WT IN. In addition, it does not appear to be conformationally adaptable. As a consequence, CAB may have difficulty overcoming the changes in the geometry of the active site of HIV IN caused by resistance mutants.

Generally speaking, the second generation INSTIs (DTG, BIC, and CAB) are much more proficient at inhibiting these INSTI-resistant mutants than RAL and EVG. Based on the data from our panel of mutants, DTG and BIC are more broadly effective against the mutants than CAB (Fig. 3). The potency of the second generation INSTIs can be affected by triple mutants which arise when mutations at G140 (A/C/S) and Q148 (H/R) are

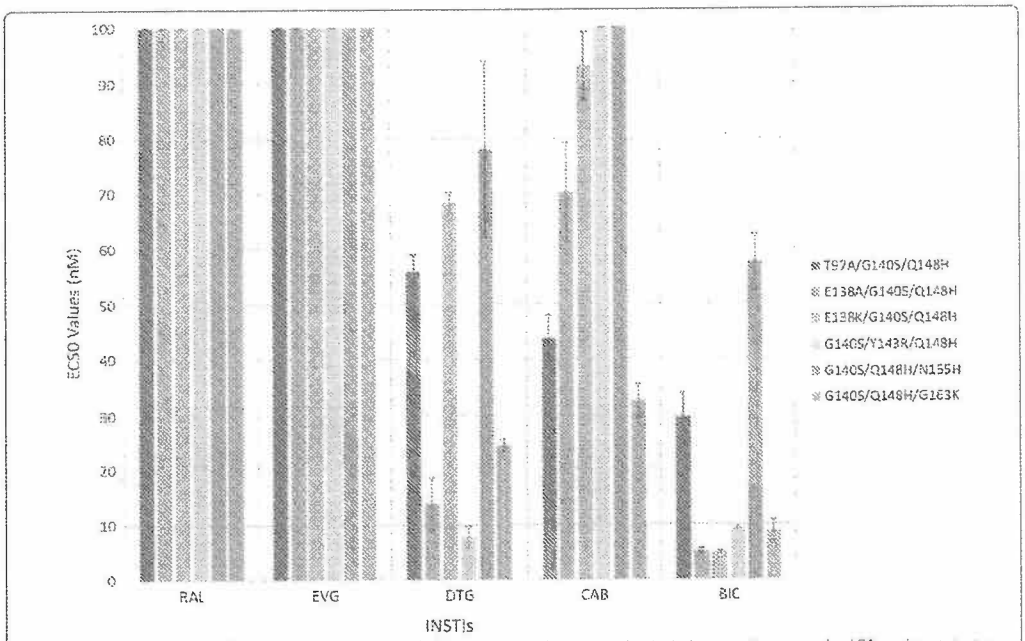


Fig. 10 Antiviral activities of CAB and BIC against a panel of INSTI-resistant triple mutants that include the well-characterized RAL-resistant double mutant G140S/Q148H plus an additional secondary mutation. The EC_{50} values were determined using vectors that carry the INSTI-resistant triple mutants in single-round infection assays. Error bars represent the standard deviations in the data from independent experiments ($n = 4$). The EC_{50} values shown in the figure have a maximum of 100 nM. The EC_{50} values of RAL and EVG against this entire panel of INSTI-resistant triple mutants were all > 100 nM. The EC_{50} values of CAB against G140S/Y143R/Q148H and G140S/Q148H/N155H were all > 100 nM

combined with the polymorphic mutation at L74M or T97A. Although it is not entirely clear how frequently L74M and T97A occur in either B or non-B HIV-1 subtypes in INSTI-naïve patients, it is possible that, when these polymorphisms are present, that they could affect the development of resistance.

Conclusions

Based on these results, BIC appears to be a very promising INSTI. CAB has obvious disadvantages in terms of its breadth of antiviral potency relative to both BIC and DTG. However, CAB may have other advantages; it can be formulated as a long-acting compound that can be injected into patients once every 2–3 months [46, 47]. Nonetheless, based on experience with previous ARV drugs, in the long-term, resistant viruses will emerge. Thus, it is likely that at least some of the compounds that are broadly effective against the known mutants will be successful. This idea is underscored by the fact that, currently, in Washington DC, where the levels of HIV infection is still high, approximately 20% of new cases involve a HIV strain that has at least one drug resistance mutation [54].

Methods

INSTI synthesis

Acquisition of RAL, EVG, and DTG was previously described [18, 55, 56]. BIC was obtained from PharmaBlock (Cat. No. PBLJ8958) and CAB was obtained from AbovChem LLC (Cat. No. HY-15592).

Cell-based assays

Single-round viral infectivity assays, using HIV-1 vectors that express either WT or mutant forms of IN, were used to determine antiviral potencies (EC_{50} values) of the compounds as previously described [57]. The Student's *t* test was used to calculate the *p* values used to determine statistical significance.

Vector constructs

The vector pNLNgoMIVR-ΔENV.LUC has been described previously [36]. To produce the new IN mutants used in this study, the IN open reading frame

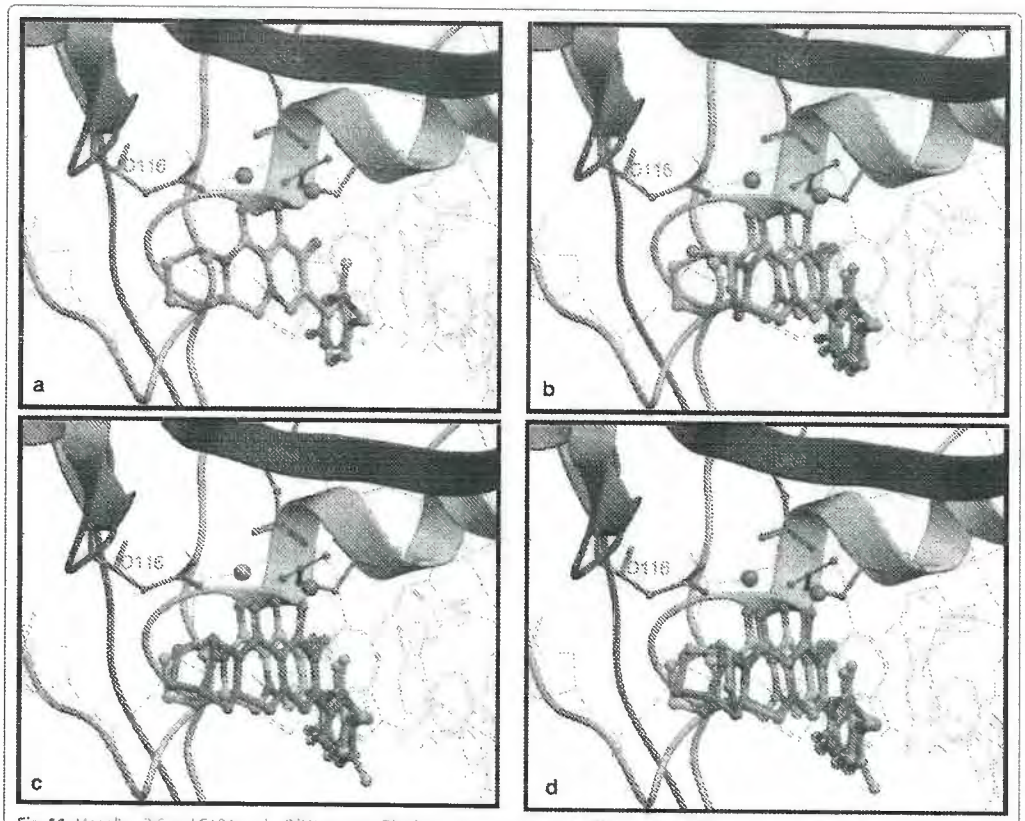


Fig. 11 Modeling BIC and CAB into the PFV intasome. The four panels show models of DTG, CAB, or BIC bound in the active site of HIV-1 IN. The upper left panel **a** shows a model of DTG (cyan) bound to HIV-1 IN. The upper right panel **b** shows a model of CAB (green) bound to the active site of the HIV-1 IN using DTG (cyan) as the template. The lower left panel **c** shows a model of BIC (magenta) bound to the active site of HIV-1 IN using DTG (cyan) as the template. The lower right panel **d** shows an overlay of the binding of DTG (cyan), BIC (magenta), and CAB (green) to HIV-1 IN, specifically showing how the "left-side" of these three INSTIs, the part of pharmacophores that interact with HIV-1 IN. All four panels show the Mg^{2+} cofactors rendered in space-filling format (slate gray) interacting with the chelating motifs of each of the INSTIs. HIV-1 IN is depicted in multi-colored ribbons with active site residues D64, D116, and E152 labeled in red and rendered in dark gray ball and stick format

was removed from pNLNgoMIVR-ΔENV.LUC by digestion with KpnI and SalI and resulting fragment was inserted between the KpnI and SalI sites of pBluescript KS+. Using that construct as the wild-type template, we prepared the following HIV-1 IN mutants using the QuikChange II XL site directed mutagenesis kit (Agilent Technologies, Santa Clara, CA) protocol: M50I, L74M, T97A, S119R, E138K, G140S, Q146L, Q146P, Q148H, Q148K, Q148R, S153Y, T66I/E157Q, E92Q/N155H, T124A/153Y, E138A/Q148R, E138K/Q148K, E138K/Q148R, E138K/263K, G140A/Q148H, G140A/Q148K, G140A/Q148R, G140C/Q148R, G140S/Q148K, G140S/Q148R, G140S/N155H, Y143H/N155H, Y143R/Q148H, Y143R/N155H, Q148H/N155H, Q148R/N155H, N155H/G163R, T66I/T97A/E157Q, L74M/G140A/Q148R, L74M/G140C/Q148R, E92Q/N155H/G163R, T97A/G140S/Q148H, T97A/Y143R/Q148H, T97A/Y143R/N155H, T97A/Q148H/N155H, E138A/G140S/Q148H, E138A/S147G/Q148R, E138K/G140A/Q148K, E138K/G140C/Q148R, E138K/G140S/Q148H, G140S/Y143R/Q148H, G140S/Y143R/N155H, G140S/Q148H/N155H, and G140S/Q148H/G163K. The following sense oligonucleotides were used with matching cognate antisense oligonucleotides (not shown) (Integrated DNA Technologies, Coralville, IA) in the mutagenesis: M50I, 5′-CAG CTAAAAGGGGAAGCCATTCATGGACAAGTAGAC

TGT-3′; T66I, 5′- ATATGGCAGCTAGATTGTATT CATTTAGAAGGAAAAGTT-3′; L74M, 5′- TTAGAA GGAAAAGTTATCATGGTAGCAGTTCATGTAGCC-3′; E92Q, 5′- GCAGAAGTAATTCCAGCACAAACA GGGCAAGAAACAGCA-3′; T97A, 5′- GCAGAGACA GGGCAAGAAGCTGCATACTTCCTCTTAAAA-3′; S119R, 5′- GTACATACAGACAATGGCCGTAATTTC ACCAGTACTACA-3′; E138A, 5′- TGGGCGGGGATC AAGCAGGCTTTTGGCATTCCCTACAAT-3′; E138K, 5′- TGGGCGGGGATCAAGCAGAAATTTGGCATT CCCTACAAT-3′; G140A, 5′- GGGATCAAGCAGGAA TTTGCTATTCCCTACAATCCCCAA-3′; G140C, 5′-GGGATCAAGCAGGAATTTTGTATTCCCTACAAT CCCCAA-3′; G140S, 5′-GGGATCAAGCAGGAATTT TCCATTCCCTACAATCCCCAA-3′; Y143H, 5′- CAG GAATTTGGCATTCCCCATAATCCCCAAAGTCAA GGA-3′; Y143R, 5′-CAGGAATTTGGCATTCCCAGA AATCCCCAAAGTCAAGGA-3′; Q146L, 5′- GGCATT CCCTACAATCCCTTAAGTCAAGGAGTAATAGAA-3′; Q148H, 5′-TACAATCCCCAAAGTCACGGAGTA ATAGAATCT-3′; Q148K, 5′- CCCTACAATCCCCAA AGTAAAGGAGTAATAGAATCTATG-3′; Q148R, 5′-CCCTACAATCCCCAAAGTCGTGGAGTAATAGAA TCTATG-3′; S153Y, 5′- AGTCAAGGAGTAATAGAA TATATGAATAAAGAATTAAAG-3′; N155H, 5′-GGA GTAATAGAATCTATGCATAAAGAATTAAAGAAA ATT-3′; 5′-E157Q, 5′-ATAGAATCTATGAATAAACAA TTAAAGAAAATTATAGGA-3′; G163K, 5′- GAATTA AAGAAAATTATAAAACAGGTAAGAGATCAGGCT -3′, G163R, 5′ -GAATTAAAGAAAATTATACGTCAG GTAAGAGATCAGGCT -3′, E138K for G140S/Q148H, 5′- TGGTGGGCGGGGATCAAGCAGAAATTTTCC ATTCCCTACAATCCC-3′; S147G for E138A/Q148R, 5′-ATTCCCTACAATCCCCAAGGTCGTGGAGTAATA GAATCT-3′; E138K for G140C/Q148R, 5′- TGGGCG GGGATCAAGCAGAAATTTTGTATTCCCTACAAT-3′; E138K for G140A/Q148K, 5′- TGGGCGGGGATC AAGCAGAAATTTGCTATTCCCTACAAT-3′; E138A for G140S/Q148H, 5′- TGGGCGGGGATCAAGCAG GCATTTTCCATTCCCTACAAT-3′; Y143R for Y143R/Q148H, 5′-CAGGAATTTGGCATTCCCAGAAAT CCCCAAAGTCACGGA-3′; Y143R for G140S/Q148H, 5′-CAGGAATTTTCCATTCCCAGAAATCCCCAA AGTCACGGA-3′; Y143R for G140S/N155H, 5′-CAG GAATTTTCCATTCCCAGAAATCCCCAAAGTCAA GGA-3′.

The following IN mutants from Fig. 2 (Additional file 1: Tables S1A and S1B), H51Y, T66I, E92Q, G118R, Y143R, N155H, R263K, H51Y/R263K, and G140S/Q148H have been described [35]. The remaining E138K/R263K double mutant was made using the previously constructed E138K mutant and the appropriate listed R263K oligonucleotides, which were used to add the second mutation.

The IN mutants from Fig. 4 (Additional file 1: Tables S2A and S2B), which includes M50I, L74M, T97A, S119R, E138K, G140S, Q146L, Q146P, Q148H, Q148K, Q148R, and S153Y, were constructed as described above using the appropriate listed oligonucleotides.

The IN mutants from Fig. 5 (Additional file 1: Tables S3A and S3B), were made as followed. The E138A/Q148R and E138K/Q148R double mutants were made using the previously generated Q148R mutant and the E138A and E138K oligonucleotides, respectively, to add the second mutation. The E138K/Q148K double mutant was constructed using the previously made E138K mutant and the appropriate Q148K oligonucleotides, which were used to add the second mutation. The G140A/Q148H and G140A/Q148K double mutants were made with the previously constructed G140A mutant and the appropriate oligonucleotides for the second mutation either Q148H or Q148K, respectively. The double mutants G140A/Q148R and G140C/Q148R were made with the previously generated Q148R mutant and the oligonucleotides for the second mutation, either G140A or G140C, respectively. The double mutants G140S/Q148K and G140S/Q148R were made using the previously generated G140S mutant and appropriate oligonucleotides for the second mutation, either Q148K or Q148R, respectively. The double mutants Q148H/N155H and Q148R/N155H were made using the previously generated N155H mutant and appropriate oligonucleotides for the second mutation, either Q148H or Q148R, respectively. The double mutant Y143R/Q148H was made using the previously generated Q148H mutant and appropriate oligonucleotides to introduce the second mutationY143R.

The IN mutants from Fig. 6 (Additional file 1: Tables S4A and S4B), were made as followed. The T66I/E157Q double mutant was made using the previously generated T66I mutant and the appropriate E157Q oligonucleotides to add the second mutation. The double mutants E92Q/N155H, G140S/N155H, Y143H/N155H, Y143R/N155H, and N155H/G163R were made using the previously generated N155H mutant and appropriate oligonucleotides for the second mutation, either E92Q, G140S, Y143H, Y143R, or G163R, respectively.

The IN mutants from Fig. 8 (Additional file 1: Tables S5A and S5B), were constructed as followed. The L74M/G140A/Q148R triple mutant was made using the previously generated G140A/Q148R double mutant and the oligonucleotides for the third mutation, L74M. The triple mutant L74M/G140C/Q148R was made with the previously generated G140C/Q148R double mutant and the oligonucleotides for the third mutation, L74M. The triple mutant T97A/Y143R/Q148H was constructed using the previously generated Y143R/Q148H double mutant and the appropriate oligonucleotides for the third mutation,

T97A. The triple mutant E138K/G140C/Q148R was made using the previously generated G140C/Q148R double mutant and the appropriate oligonucleotides to create the third mutation, E138K. The triple mutant T97A/Q148H/N155H was made using the previously constructed Q148H/N155H double mutant and the appropriate oligonucleotides for the third mutation, T97A. The triple mutant E138A/S147G/Q148R was made with the previously generated E138A/Q148R double mutant and oligonucleotides to make the third mutation, S147G. The triple mutant E138K/G140A/Q148K was made using the previously constructed double mutant G140A/Q148K double mutant and the appropriate oligonucleotides to make the third mutation, E138K.

The IN mutants from Fig. 9 (Additional file 1: Tables S6A and S6B) were made as followed. The T66I/T97A/E157Q triple mutant was made using the previously generated T66I/E157Q double mutant and the oligonucleotides for the third mutation, T97A. The E92Q/N155H/G163R triple mutant was made using the previously generated E92Q/N155H double mutant and the oligonucleotides for the third mutation, G163R. The triple mutant G140S/Y143R/N155H was made using the previously constructed G140S/N155H double mutant and the correct oligonucleotides to create the third mutation, Y143R. The triple mutant T97A/Y143R/N155H was made with the previously generated Y143R/N155H double mutant and the appropriate oligonucleotides for the third mutation, T97A.

The IN mutants from Fig. 10 (Additional file 1: Tables S7A and S7B), were constructed as followed. The triple mutants T97A/G140S/Q148H, G140S/Q148H/N155H, and G140S/Q148H/G163K were each made with the previously generated G140S/Q148H double mutant and the appropriate oligonucleotides for the third mutation, either T97A, N155H, or G163K, respectively. The triple mutant was E138A/G140S/Q148H was made using the previously constructed G140S/Q148H double mutant and oligonucleotides to make the third mutation E138A. The triple mutant E138K/G140S/Q148H was made using the previously generated G140S/Q148H double mutant and the correct oligonucleotides to make the third mutation, E138K. The triple mutant G140S/Y143R/Q148H was made using the previously constructed G140S/Q148H double mutant and the appropriate oligonucleotides to make the third mutation Y143R.

The DNA sequence of each construct was verified independently by DNA sequence determination. The mutated IN coding sequences from pBluescript KS+ were then subcloned into pNLNgoMIVR-ΔEnv.LUC (between the KpnI and SalI sites) to produce mutant HIV-1 constructs; the sequence of the final construct was checked by DNA sequencing.

Computer modeling

All modeling was conducted using MOE 2016.0802 (Chemical computing group, Montreal, Quebec, Canada). The sequences and structures of DTG bound in the PFV intasome (PDB ID: 3S3M) and HIV-1 IN (PDB ID: 5U1C) served as the structural templates to construct a HIV-1 IN model with DTG bound in the active site. First, the N-terminal portions of the NTD, CCD, and CTD domains of the PFV and HIV-1 IN were used to align the domains properly. Next the sequences and structures of HIV-1 and PFV INs were aligned so that the HIV IN sequence was matched to superpose the HIV-1 and PFV IN. The coordinates of the HIV-1 IN structure (PDB ID: 5U1C) from the aforementioned alignment were used as the IN template to construct the HIV-1 IN model. This structure was modified to fit the structural coordinates of DTG, Mg^{2+} cofactors, and the viral DNA from the PFV intasome (PDB ID: 3S3M). The model of the HIV-1 intasome with DTG bound was energy minimized using a PFROSST forcefield with relative field solvation as recommended by the manufacturer. The new HIV-1 IN model was then aligned (structure only) with the HIV-1 IN structure (PDB ID: 5U1C) from the aforementioned alignment with PFV IN (PDB ID: 3S3M) and aligned to a RMSD value of 0.82 Å. Additionally, the new HIV-1 IN model was aligned with the previously solved HIV-1 IN structure (PDB ID: 5U1C) and aligned to a RMSD value of 1.12 Å. The surface (Van der Waals) of DTG was determined to locate possible steric clashes with the active site residues in the model. To identify potential contacts with CAB and BIC, both INSTIs were docked using DTG as the template. CAB or BIC were placed using the triangle matcher method and scored with London dG with approximately 30 poses and then the putative ligand poses were further refined using the rigid receptor method in MOE and scored with the GBVI/WSA dG function. If the expected ligand poses were not created, a pharmacophore editor tool in the docking function was used to add certain features that made the appropriate docking of CAB or BIC to DTG easier to view and the resulting structures were refined in the manner described above. The poses with the best docking scores were selected based on how well the bound compounds overlay with the DTG scaffold, bound to Mg^{2+}, and how well their halogenated benzyl moiety interacted hydrophobically through π–π stacking with the penultimate cytosine on the 3′ end of the bound viral DNA. Docking poses images were refined using MolSoft ICM Pro software version 3.8-5 (MolSoft LLC, San Diego, CA).

Additional file

Additional file 1. Two sets of supplementary tables are provided for Figs. 2, 4, 5, 6, 8, 9, and 10. One set of tables (**A**) shows the antiviral activities of the INSTIs against HIV resistant mutants and the other set of tables (**B**) shows the statistical significance (p values) when comparing antiviral activities against INSTI-resistant mutants among the INSTIs.

Abbreviations

INSTI: integrase strand transfer inhibitor; ARV, antiretroviral; STC: strand transfer complex; HIV: human immunodeficiency virus; PFV: prototype foamy virus; NNRTI: non nucleoside reverse transcriptase inhibitors; FDA: Food and Drug Administration; EC_{50}: half maximal inhibitory concentration.

Author details

[1] HIV Dynamics and Replication Program, National Cancer Institute-Frederick, National Institutes of Health, Frederick, MD, USA. [2] Chemical Biology Laboratory, National Cancer Institute-Frederick, National Institutes of Health, Frederick, MD, USA.

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Authors' contributions

ES performed the experiments. SS and SH designed the experiments. ES, XZ, FB, and SH analyzed the data. XZ and FB contributed with compounds and imaging software. SS and SH drafted the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Not applicable.

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Title of Invention

THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	2232	FILED BY	Frances Tsai
PATENT CENTER #	61871032	AUTHORIZED BY	Donna Gressler
CUSTOMER #	25000	FILING DATE	05/06/2022
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Benjamin Micah Collman

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 071250	E202345K01396200	Frances Tsai

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
1251	EXTENSION FOR RESPONSE WITHIN FIRST MONTH	220.00	1	220.00
1806	SUBMISSION OF AN INFORMATION DISCLOSURE STATEMENT	260.00	1	260.00
1814	STATUTORY DISCLAIMER, INCLUDING TERMINAL DISCLAIMER	170.00	1	170.00
			TOTAL AMOUNT:	$650.00

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If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

正本

檔　　號：
保存年限：

經濟部智慧財產局　審查意見通知函

機關地址：臺北市大安區辛亥路2段185號3樓
聯 絡 人：陳世芹
聯絡電話：(02)23765352
電子郵件：
傳　　真：(02)23779875

受文者：美商基利科學股份有限公司（代理人：陳長文　專利代理人）

發文日期：中華民國111年5月20日
發文字號：（111）智專二（五）01319字第11120501620號
速　　別：
密等及解密條件或保密期限：
附　　件：如文

111205016 20

主旨：第110129951號專利申請案經審查有說明一所述情事，請於文到次日起3個月內提出申復說明或修正。屆期未申復說明或修正者，依專利法第46條第2項規定將不予專利，請查照。

說明：

一、本案經審查認為：

(一)本案「用於治療人類免疫缺乏病毒之治療組合物」，係原申請案第105136333號之分割案，曾於111年2月14日提出申請專利範圍修正本到局，經查修正內容未超出申請時說明書、申請專利範圍、圖式所揭露之範圍，本案依該修正及申請時所提資料進行審查，其請求項共計10項，其中第1-7、9-10項為獨立項，其餘為附屬項。

(二)本案主張之第一優先權 US 62/253042(2015年11月9日)，經查本案請求項 5、7-10 內容並未記載於該第一

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發收時間 111/05/24(2022/05/24) 09:19:23

優先權文件，且依據專利審查基準第五章 1.4.1 記載「後申請案申請專利範圍中所載之發明與優先權基礎案所揭露之發明之間若屬下列二種情事之一者，應判斷為『相同發明』：a. 兩發明之記載形式及實質內容完全相同。b. 兩發明之差異僅在於文字的記載形式、或差異僅在於部分相對應之技術特徵，係該發明所屬技術領域中具有通常知識者基於優先權基礎案所揭露之發明形式上明確記載的技術內容，即能直接且無歧異得知其實質上單獨隱含或整體隱含申請專利之發明中相對應的技術特徵，而不會得知其他技術特徵者」，惟本案請求項所請之特定含量或 AUC、CMax 等數據之組合物非該發明所屬技術領域中具有通常知識者基於優先權基礎案所揭露之發明形式上明確記載的技術內容即能直接且無歧異得知之所請特定化合物範圍之技術特徵，故請求項 5、7-10 請求項比對基準日，以本案第二優先權日 US 62/399999(2016 年 9 月 26 日)為之。

(三)本案請求項 5-10，不符專利法第 26 條第 2 項之規定。

本案請求項 5-10，本項所載「式 I 化合物」、「式 II 化合物」未界定代表結構為何，所請不明確。

(四)依據引證 1-2 揭示內容，本案請求項 2-6 不符專利法第 22 條第 2 項之規定；依據引證 3 揭示內容，本案請求項 5、7-10 不符專利法第 22 條第 2 項之規定。

1、本案請求項 2-6，引證 1【說明書第 3-4、15-20 頁，實施例段落】揭示將 dolutegravir、泰諾福韋艾拉酚胺與恩曲他濱製備為一種口服劑型，其中 dolutegravir 為 HIV 整合酶抑制劑，引證 1【第 19-

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20 頁】揭示藥物組合物包含 50 mg dolutegravir、200 mg 恩曲他濱、25mg 泰諾福韋艾拉酚胺；引證 1 與本案所請之差異在於引證 1 未揭示所請式 I 化合物；惟引證 2【說明書第 3-7 頁，Example 42、45、說明書第 212-221 頁】揭示所請式 I 化合物為 HIV 整合酶抑制劑，並揭示其可用於治療 HIV 感染，由於引證 1-2 所揭示之發明均屬於治療 HIV 感染技術領域，均具有「結構相近之 HIV 整合酶抑制劑」功能或作用之相關性，該發明所屬技術領域中具有通常知識者具有動機結合引證 1-2 之技術內容，能輕易推知將引證 2 揭示之所請式 I 化合物與恩曲他濱、泰諾福韋艾拉酚胺組合製作錠劑，且以一般例行性工作之普通手段即能輕易選擇調整醫藥上可接受之鹽形式、成分含量、製作為多層錠劑及壓縮第一層、第二層之製造方法、其他習知賦形劑種類及含量等；且查本案說明書僅揭示特定含量之成分之錠劑，相較於以「式 I 化合物調配物」與「泰諾福韋艾拉酚胺與恩曲他濱調配物」分開使用之情況下具有較佳式 I 化合物 AUC、Cmax、溶解度等功效，如說明書實施例所揭示特定含量成分之錠劑為 50mg 式 I 化合物、25mg 泰諾福韋艾拉酚胺及 200mg 恩曲他濱之錠劑等，故本案說明書並未證實所請僅以重量百分比率或未界定特定成分含量之錠劑或組合物皆具有較佳功效，故本項係所屬技術領域中具有通常知識者於參酌先前技術所能輕易完成，請求項 2-6 不具進步性。

2、本案請求項 5、7-10，經查本案優先權文件並未記載

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請求項 5、7-10 內容，故有關上述請求項比對基準日，以第二優先權日 2016 年 9 月 26 日為之。引證 3【全文】揭示一種錠劑包含 GS-9883/F/TAF(50/200/25 mg)，其中 GS-9883/F/TAF 為 GS-9883/emtricitabine/tenofovir alafenamide，GS-9883 即為所請之式 I 化合物(參酌作為參考文獻之引證 4【Figure 2】揭示 Bictegravir(GS-9883)即為所請式 I 化合物)，故本案請求項 5、7-10 所請之錠劑或組合物係該發明所屬技術領域中具有通常知識者具有動機結合引證 3 內容所能輕易推知，並能以一般例行性工作之普通手段即能輕易選擇調整醫藥上可接受之鹽形式、藥物成分及習知賦形劑種類及含量百分比、並測試藥物動力學 AUC、Cmax 等數值，故本項係所屬技術領域中具有通常知識者於參酌先前技術所能輕易完成，請求項 5、7-10 不具進步性。

(五)本案請求項 1 於現在時點並未發現不予專利理由，如有發現新的不予專利理由時，會再通知不予專利理由。

(六)引證文件：

1、WO 2015/022351 A1。

2、WO 2014/100323 A1。

3、History of Changes for Study: NCT02652624, Safety and Efficacy of Switching to a FDC of GS-9883/F/TAF From E/C/F/TAF, E/C/F/TDF, or ATV+RTV+FTC/TDF in Virologically Suppressed HIV-1 Infected Women. Submitted Date: August 22, 2016 (v7)

4、ASM Microbe，Discovery of bictegravir (GS-9883), a novel, unboosted, once-daily HIV-1 integrase strand

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transfer inhibitor (INSTI) with improved pharmacokinetics and in vitro resistance profile.(June 16-20, 2016)

二、本案如有修正、訂正，應依專利法第 43 條、第 44 條第 3 項、專利法施行細則第 36 條至第 38 條之規定辦理，並請依專利修正申請書、專利誤譯訂正申請書之規定撰寫。

三、若需當面示範或說明者，請以「面詢申請書」敘明面詢所依據之版本、面詢事項及說明並繳交規費新台幣 1 千元，本局認為有必要時，將另行通知面詢地點及時間。

四、檢送本案檢索報告 1 份。本案檢索報告如附有引證用之非專利文獻，僅供專利申請人個人參考之用，如涉及其他利用該著作之行為(如：列印紙本對公眾散布、將檔案上傳網路等)，仍應取得著作財產權人之同意或授權，以避免侵權。

正本：美商基利科學股份有限公司（代理人：陳長文　專利代理人）
副本：

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HIV Articles

Back »

Discovery of Bictegravir (GS-9883), a Novel, Unboosted, Once-Daily HIV-1 Integrase Strand Transfer Inhibitor (INSTI) with Improved Pharmacokinetics and In Vitro Resistance Profile

Reported by Jules Levin

ASM Microbe, June 16-20, 2016, Boston, MA

SE Lazerwith, R Cai, X Chen, G Chin, MC Desai, S Eng, R Jacques, M Ji, G Jones, H Martin, C McMahon, M Mish, P Morganelli, J Mwangi, H-J Pyun, U Schmitz, G Stepan, J Szwarcberg, J Tang, M Tsiang, J Wang, K Wang, K White, L Wiser, J Zack, H JinGilead Sciences, Foster City, CA

Conclusions

- To discover higher potency INSTIs, a series of oxo-pyridones with larger, three-dimensional A-rings were synthesized.
- SAR studies of these A-ring analogs led to the discovery of bicyclic A-ring systems which showed very low PXR activation, and specific [3.2.1] oxaza A-rings that showed high protein binding and long mean residence times in animals.
- SAR studies of the D-ring resulted in the 2,4,6-trifluorophenyl group, which improved solubility and resistance profile.
- Simultaneous incorporation of novel A- and D-rings gives bictegravir (BIC, GS-9883).
- BIC shows high potency against wild-type HIV-1and improved potency against many integrase resistant mutants compared with EVG, RAL and DTG.3
- BIC shows longer mean residence times in both rat and dog compared with DTG.
- BIC exhibits reduced in vitro PXR activation and lower OCT-2 inhibition compared with DTG.
- In human POC study, BIC has an average human $t_{1/2}$ of approximately 19 h, confirming once-daily dosing potential.8
- In summary, an extensive SAR study led to the discovery of bictegravir, a novel, potent, once-daily, INSTI with an improved resistance profile. BIC is currently being studied in clinical trials as a single tablet regimen combination with FTC and TAF.

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Introduction

- Currently approved integrase strand-transfer inhibitor (INSTI) based treatments comprise 5 of 8 DHHS recommended regimens for HIV-1 infection.[1] Limitations of early INSTIs include twice-daily dosing (raltegravir, RAL) and the need for a pharmacokinetic enhancer (elvitegravir, EVG). Dolutegravir (DTG) is a more recently-approved INSTI that exhibits an improved resistance profile compared to RAL and EVG, and is dosed once-daily in most naive patients.[2] Limitations of DTG include the need for twice-daily dosing for integrase experienced patients due to non-linear pharmacokinetics when dosing >50 mg once-daily,[2] as well as reduced susceptibility to many integrase double and triple mutants.[3] In addition, DTG shows moderate activation of PXR, raising the risk of DDIs with other agents,[4] and modest increases in patients' serum creatinine, likely due to inhibition of OCT-2.[5]

Figure 1. Structures of Currently Approved INSTIs

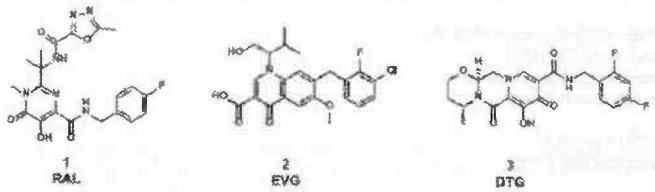
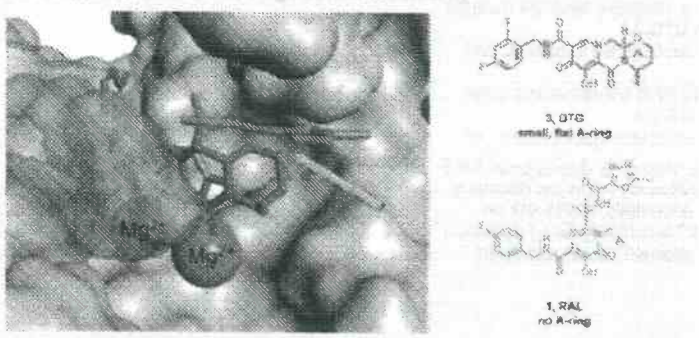


Figure 2. INSTIs Bind at the Integrase-vDNA Interface[6]



- Little binding to hydrophobic surface near the A-ring of INSTIs (green arrow).
- Hypothesis: Larger, three-dimensional A-rings may improve INSTI potency.

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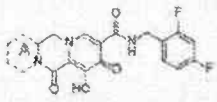
Methods

- Antiviral potency and cytotoxicity were assessed in MT-4 and MT-2 T-cell lines.
- Metabolic stability with pooled hepatic microsomal fractions was determined using the in vitro half-life method. Cofactors were NADPH (as a regenerating system) and UDP-glucuronic acid. Incubations were at 37°C and disappearance of substrate was monitored by sequential removal of aliquots over 60 min followed by analysis by LC-MS/MS. In vitro half- life values were determined and then scaled to predicted hepatic metabolic clearance using the well-stirred liver model.
- Protein binding was determined by equilibrium dialysis with a Dianorm device (Harvard Apparatus, Holliston MA) with a semipermeable membrane (10 kDa cut-off) separating two 1 mL PTFE half-cells.[7] For free fraction studies, dialysis was against isotonic phosphate buffer.
- Kinetic solubility studies were carried out by adding compound dissolved in DMSO to phosphate-buffered saline (pH 7.4) to a target concentration of 100 µM (final DMSO concentration 1.0%). After shaking for 1 hr, non-dissolved material was removed by centrifugation and the equilibrium concentration remaining in the supernatant determined by LC-UV analysis.
- Thermodynamic solubility studies were carried out by adding compound (1 mg) to aqueous media (1 mL). This mixture was sonicated briefly and stirred for a minimum of 12 hours. The suspension was centrifuged and the supernatant was analyzed by UPLC.
- Activation of PXR was assessed via a reporter gene assay in a stably transformed tumor cell line (DPX2) at six concentrations. %Emax is determined relative to 10 µM rifampicin.
- Animal PK: test compounds were dosed in rats or dogs via 30-min IV infusion or oral administration. Serial blood samples were collected and LC/MS/MS methods were used to measure the concentrations of test compounds in plasma. Non-compartmental pharmacokinetic analysis was performed on the plasma concentration-time data to generate the PK parameters.

Results

Table 1. SAR of the A-ring: Diaza-Bridging Bicycles

	A Ring	EC_{50} (nM)	Human MS $t_{1/2}$ (min)	%free (human plasma)	PXR (%Emax, 15µM)	G140S/Q148R fold shift
3 (DTG)		2.0	>395	5.7	51	4.8
4		14.8	202	21	3	--
5		5.3	278	1.8	0	11
6		3.3	>395	20	2	599
7		2.8	212	3.0	2	24

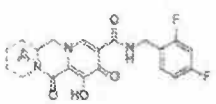


- Bicyclic diaza A-rings did not provide potency increase
- Bicyclic diaza A-rings show markedly lower PXR activation compared with monocyclic 3.
- Microsomal stability and G140S/Q148R potency is often compromised.
- Free fraction in human plasma higher than desired.

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Table 2. SAR of the A-ring: Oxaza-Bridging Bicycles

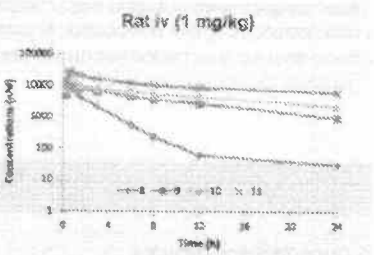
	A Ring	EC_{95} (nM)	Human MS $t_{1/2}$ (min)	%free (human plasma)	PXR (%Emax, 10μM)	G140S/ Q148R fold shift
3 (DTG)		1.7	>395	0.7	51	4.9
9		3.5	>395	5.8	7	4.5
9		2.5	>395	4.7	7	3.2
10		2.0	>395	0.75	8	4.2
11		2.2	>395	0.28	5	3.4
12		2.3	>395	1.3	7	1.3



- Bicyclic oxaza A-rings maintain but do not improve potency compared with monocyclic 3.
- Bicyclic oxaza A-rings also show much lower PXR activation than monocycle 3.
- High metabolic stability is seen in all bicyclic oxaza A-rings.
- [3.2.1] bicyclic A-rings 10 and 11 display favorably low levels of free fraction in human plasma.

Table 3. Rat PK of Bicyclic A-Ring Analogs Show Higher Protein Binding Leading to Longer Mean Residence Times

	MS (rat) $t_{1/2}$ (min)	%free (rat plasma)	Mean Residence Time (rat)
8	395	0.32	3 h
9	395	0.06	11 h
10	395	0.03	18 h
11	395	0.016	30 h

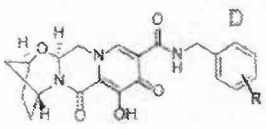


- For stable and highly protein bound compounds, mean residence times in rat correlate strongly with plasma protein binding.

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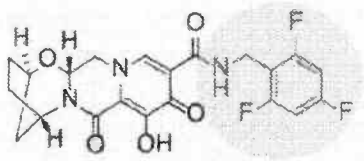
Table 4. SAR Study Suggests Advantages of 2,4,6-Trifluorophenyl as the D-ring substituent

	D Ring	EC_{50} (nM)	Human MS $t_{1/2}$ (min)	%free (human plasma)	Solubility (pH 1 / 7)	G140S/ Q148R fold shift
10		2.0	385	0.75	34 / 53	18
13		1.9	379	4.6	6 / 4	--
14		1.8	221	2.9	21 / 22	--
15		2.0	175	1.2	16 / 12	44
16		4.0	314	1.3	92 / 81	67
17		2.2	385	1.2	87 / 85	6
18		38	--	--	--	--



- Using A-ring 10, a study of D-ring substituents was performed.
- Most analogs showed reduced metabolic stability.
- 2,4,6-trifluorophenyl analog 17, shows improved solubility and higher potency against G140S/Q148R mutant compared with difluorophenyl analog 16.

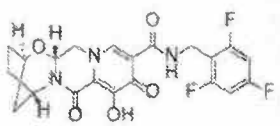
Figure 2. Simultaneous Incorporation of Novel A- and D-rings Gives Bictegravir



Bictegravir (GS-9883)
wt EC_{50} = 1.9 nM
G140S/Q148R
fold-shift = 2.0

Table 5. In Vitro Profile of Bictegravir Compared with RAL, EVG and DTG

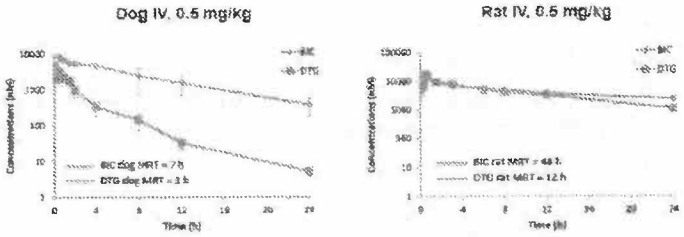
	RAL	EVG	DTG	BIC
EC_{50} (nM, MT-4)	0.9	1.8	1.7	1.9
Plasma Adjusted EC_{95} (nM, MT-4)	21	43	47	83
human liver microsomal Cl (L/h/kg)	0.34	0.43	0.15	0.17
%free human plasma	12.2	0.5	0.7	0.59
OCT-2 IC_{50} (μM)			0.13	0.49
PXR %Emax@ 15μM			51	18
Solubility (pH = 7, μg/mL)	1906	2	53	119
G140S/Q148R fold shift	34	207	4.8	2.9



- BIC shows improved G140S/Q148R potency compared to previous agents.
- BIC shows reduced OCT-2 inhibition, reduced PXR activation, and higher solubility compared with DTG
- BIC shows low human microsomal clearance, high plasma protein binding and was predicted to have a long human $t_{1/2}$.

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Figure 3. Bictegravir Exhibits an Excellent Preclinical PK Profile



Species	Formulation (dose)	3 (DTG)	BIC
%F rat	Solution (0.5 mg/kg)	52	50
%F dog	Suspension (1 mg/kg)	17	28

- Bictegravir shows longer half-lives in intravenous PK studies and higher exposure from solid oral dosing studies than DTG in pre-clinical species

References

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2. Kandel, C. E.; Walmsley, S. L. *Drug Des. Devel. Ther.* 2015, 9, 3547-3555.
3. See (a) Tsiang, M., et al. *ASM Microbe 2016*, Poster #416, and (b) White, K.; Ciriar, T.; Miller, M. D. *14th European Workshop on HIV & Hepatitis*, 2016, Abstract O-01.
4. Chu, V.; Einolf, H. J.; Evers, R.; Kumar, G.; Moore, D.; Sipp, S.; Silva, J.; Sinha, V.; Sinz, M.; Skerjanec, A. *Drug Metabolism and Disposition*, 2009, 37, 1339-1354.
5. Lepist, E. -I.; Murray, B. P.; Tong, L.; Roy, A.; Bannister, R.; Ray, A. S. *Antimicrobial Agents and Chemotherapy (ICAAC)*, 2011, Poster #A1-1724.
6. Figure made by the overlay of DTG and RAL bound in the active site of prototype foamy virus (PFV) described in: Hare, S., et al. *Mol Pharmacol.* 2011, 80, 565-572.
7. Weber, H. G.; Schildknecht, J.; Kesselring, P. *Amer Lab*, 3, 17-21.
8. Gallant, J. et al. *ASM Microbe 2016*, Poster #415.

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History of Changes for Study: NCT02652624

Safety and Efficacy of Switching to a FDC of GS-9883/F/TAF From E/C/F/TAF, E/C/F/TDF, or ATV+RTV+FTC/TDF in Virologically Suppressed HIV-1 Infected Women

Latest version submitted February 10, 2020 on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol Section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in red.
- Study additions are displayed in green.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	January 6, 2016	None (earliest version on record)
2	○	○	February 26, 2016	Recruitment Status, Study Status and Contacts/Locations
3	○	○	March 15, 2016	Study Status and Contacts/Locations
4	○	○	April 28, 2016	Study Status and Contacts/Locations
5	○	○	June 2, 2016	Study Status and Contacts/Locations
6	○	○	July 12, 2016	Study Status, Outcome Measures, Contacts/Locations and Eligibility
7	●	●	August 22, 2016	Contacts/Locations, Outcome Measures, Study Status and Eligibility
8	○	○	October 7, 2016	Arms and Interventions, Study Status, Contacts/Locations, Study Description and Study Identification
9	○	○	December 23, 2016	Arms and Interventions, Contacts/Locations, Outcome Measures, Study Status, Eligibility, Study Design, Study Description and Study Identification
10	○	○	February 1, 2017	Recruitment Status, Study Status, Contacts/Locations, Study Design and Oversight
11	○	○	April 7, 2017	Arms and Interventions, Study Status and Eligibility
12	○	○	September 5, 2017	Study Status and Contacts/Locations
13	○	○	February 23, 2018	Study Status, Contacts/Locations and Arms and Interventions
14	○	○	October 2, 2018	Study Status, Outcome Measures, Arms and Interventions, Document Section, Results, Eligibility, Study Design and Study Description
15	○	○	January 7, 2019	Recruitment Status, Study Status and IPDSharing
16	○	○	November 14, 2019	Adverse Events, Participant Flow, Document Section, Baseline Characteristics, Study Status and Outcome Measures
17	○	○	February 10, 2020	IPDSharing and Study Status

Compare Comparison Format: ● Merged ○ Side-by-Side

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Study NCT02652624

Submitted Date: August 22, 2016 (v7)

Study Identification

Unique Protocol ID: GS-US-380-1961

Brief Title: Safety and Efficacy of Switching to a FDC of GS-9883/F/TAF From E/C/F/TAF, E/C/F/TDF, or ATV+RTV+FTC/TDF in Virologically Suppressed HIV-1 Infected Women

Official Title: A Phase 3, Randomized, Open Label Study to Evaluate the Safety and Efficacy of Switching to a Fixed Dose Combination (FDC) of GS-9883/Emtricitabine/Tenofovir Alafenamide (GS-9883/F/TAF) From Elvitegravir/Cobicistat/Emtricitabine/ Tenofovir Alafenamide (E/C/F/TAF), Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate (E/C/F/TDF) or Atazanavir + Ritonavir + Emtricitabine/Tenofovir Disoproxil Fumarate (ATV+RTV+FTC/TDF) in Virologically Suppressed HIV-1 Infected Women

Secondary IDs:

Study Status

Record Verification: August 2016

Overall Status: Recruiting

Study Start: February 2016

Primary Completion: September 2017 [Anticipated]

Study Completion: August 2018 [Anticipated]

First Submitted: January 8, 2016

First Submitted that Met QC Criteria: January 8, 2016

First Posted: January 12, 2016 [Estimate]

Last Update Submitted that Met QC Criteria: August 22, 2016

Last Update Posted: August 23, 2016 [Estimate]

Sponsor/Collaborators

Sponsor: Gilead Sciences

Responsible Party: Sponsor

Collaborators:

Oversight

U.S. FDA-regulated Drug:

U.S. FDA-regulated Device:

Data Monitoring: Yes

Study Description

Brief Summary: This study will evaluate the efficacy of switching to a fixed-dose combination (FDC) of GS-9883/emtricitabine/tenofovir alafenamide (GS-9883/F/TAF) versus continuing on a regimen consisting of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF), elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (E/C/F/TDF), or atazanavir (ATV) + ritonavir (RTV) + emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in virologically suppressed HIV-1 infected women.

Detailed Description:

Conditions

Conditions: HIV-1 Infection

Keywords:

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▼ Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	None (Open Label)
Allocation:	Randomized
Enrollment:	400 [Anticipated]

▼ Arms and Interventions

Arms	Assigned Interventions
Experimental: GS-9883/F/TAF Participants will switch to E/C/F/TAF FDC and receive treatment for 48 weeks. Following Week 48, participants in countries where GS-9883/F/TAF is not available may have the option to receive GS-9883/F/TAF for up to 48 additional weeks.	Drug: GS-9883/F/TAF GS-9883/F/TAF (50/200/25 mg) FDC tablet administered orally once daily without regard to food
Active Comparator: Baseline Regimen Participants will remain on their baseline regimen of E/C/F/TAF, E/C/F/TDF, or ATV+RTV+FTC/TDF for 48 weeks. Following Week 48, participants in countries where GS-9883/F/TAF is not available may have the option to receive GS-9883/F/TAF for up to 48 additional weeks.	Drug: E/C/F/TAF E/C/F/TAF (150/150/200/10 mg) FDC tablet administered orally once daily Other Names: • Genvoya® Drug: E/C/F/TDF E/C/F/TDF (150/150/200/300 mg) FDC administered orally once daily with food Other Names: • Stribild® Drug: ATV ATV 300 mg capsules administered orally once daily Other Names: • Reyataz® Drug: RTV RTV 100 mg tablets administered orally once daily Other Names: • Norvir® Drug: FTC/TDF FTC/TDF (200/300 mg) tablet administered orally once daily Other Names: • Truvada® Drug: GS-9883/F/TAF GS-9883/F/TAF (50/200/25 mg) FDC tablet administered orally once daily without regard to food

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Outcome Measures

Primary Outcome Measures:

1. Proportion of Participants With Virologic Failure (HIV-1 RNA ≥ 50 copies/mL) at Week 48 as Defined by the Modified FDA Snapshot Algorithm
[Time Frame: Week 48]

Secondary Outcome Measures:

1. Proportion of Participants With HIV-1 RNA < 50 copies/mL at Week 48 as Defined by the US FDA Snapshot Algorithm
[Time Frame: Week 48]

2. Change From Baseline in CD4+ Cell Count at Week 48
[Time Frame: Baseline; Week 48]

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: Female

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Medically stable HIV-1 infected women who meet the following criteria:

- Completion of the Week 48 open-label extension (OLE) visit or any post Week 48 OLE visits in Gilead-sponsored study GS US 236 0128, or Completion of the Week 96 visit or any post Week 96 visits in Gilead-sponsored study GS US-292-0109
- Currently on a stable antiretroviral regimen consisting of E/C/F/TAF, E/C/F/TDF, or ATV+RTV+FTC/TDF continuously for ≥ 12 consecutive weeks preceding the screening visit
- Documented plasma HIV-1 RNA levels < 50 copies/mL for ≥ 12 weeks preceding the Screening visit. After reaching HIV-1 RNA < 50 copies/mL, single values of HIV-1 RNA

  ≥ 50 copies/mL followed by re-suppression to < 50 copies/mL is allowed

- HIV-1 RNA <50 copies/mL at screening
- Estimated glomerular filtration rate (eGFR) ≥ 50 mL/min according to the Cockcroft-Gault formula at the screening visit

Contacts/Locations

Central Contact Person: Gilead Study Team
Email: GS-US-380-1961@gilead.com

Study Officials: Huyen Cao, MD
Study Director
Gilead Sciences

Locations: **United States, California**

[Recruiting]
Sacramento, California, United States, 95817

United States, Connecticut

[Recruiting]
Stamford, Connecticut, United States, 6902

United States, District of Columbia

[Recruiting]
Washington, District of Columbia, United States, 20009

[Recruiting]
Washington, District of Columbia, United States, 20037

United States, Florida

[Recruiting]
Fort Pierce, Florida, United States, 34982

[Recruiting]
Ft. Lauderdale, Florida, United States, 33308

[Recruiting]
Miami, Florida, United States, 33133

[Recruiting]
Miami, Florida, United States, 33136

[Recruiting]
Orlando, Florida, United States, 32803-1851

[Recruiting]
Tampa, Florida, United States, 33607

[Recruiting]
Tampa, Florida, United States, 33614

[Recruiting]
West Palm Beach, Florida, United States, 33401

United States, Georgia

[Recruiting]
Atlanta, Georgia, United States, 30308

[Recruiting]
Decatur, Georgia, United States, 30033

[Recruiting]
Macon, Georgia, United States, 31201

[Recruiting]
Savannah, Georgia, United States, 31401

United States, Massachusetts

[Recruiting]
Springfield, Massachusetts, United States, 01105

United States, Missouri

[Recruiting]
St. Louis, Missouri, United States, 63110

United States, New Jersey

[Recruiting]
Newark, New Jersey, United States, 07102

United States, New York

[Recruiting]
Bronx, New York, United States, 10467

[Recruiting]
Great Neck, New York, United States, 11021

[Withdrawn]
Mt. Vernon, New York, United States, 10550

United States, North Carolina

[Recruiting]
Charlotte, North Carolina, United States, 28207

[Recruiting]
Durham, North Carolina, United States, 27710

[Recruiting]
Huntersville, North Carolina, United States, 28078

United States, Texas

[Recruiting]
Bellaire, Texas, United States, 77401

[Recruiting]
Dallas, Texas, United States, 75208

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[Recruiting]
Dallas, Texas, United States, 75219

[Recruiting]
Fort Worth, Texas, United States, 76104

[Recruiting]
Harlingen, Texas, United States, 78550

[Recruiting]
Houston, Texas, United States, 77004

Dominican Republic

[Recruiting]
Santo Domingo, Dominican Republic, 10514

[Recruiting]
Santo Domingo, Dominican Republic

Puerto Rico

[Recruiting]
San Juan, Puerto Rico, 00909-1711

Thailand

[Recruiting]
Bangkok, Thailand, 10330

[Recruiting]
Khon Kaen, Thailand, 40002

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[Recruiting]
Kampala, Uganda

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附件

第110129951號專利申請案檢索報告

1.申 請 日：	105年11月8日
2.優先權日：	2015年11月9日、2016年9月26日
3.本案國際專利分類號(IPC)：	***A61K31/5365*** (2006.01) ， ***A61K31/675*** (2006.01) ***A01K31/513*** (2006.01) ， ***A61K9/24*** (2006.01) ***A61K9/30*** (2006.01) ， ***A61P31/18*** (2006.01)
4.檢索國際專利分類號(IPC)範圍：	A61K/31/5365, A61K/31/675, A61K/31/513, A61K/9/24, A61K/9/30, A61P/31/18 A61K31/5365 (2006.01), A61K31/675 (2006.01), A61K31/513 (2006.01), A61K9/24 (2006.01), A61K9/30 (2006.01), A61P31/18 (2006.01)
5.檢索使用資料庫名稱：(關鍵詞)	STN、Google、TIPO全球/全域專利資料庫、國內外專利資料庫全域系統

關聯性代碼	引用文獻資料與相關段落處	相關聯請求項
Y	1. WO 2015/022351 A1 2015/02/19 說明書第3-4、15-20頁，實施例段落	2-6
Y	2. WO 2014/100323 A1 2014/06/26 說明書第3-7頁、Example 42、45、說明書第212-221頁	2-6
P,X	3. 網路文獻 3. History of Changes for Study: NCT02652624, Safety and Efficacy of Switching to a FDC of GS-9883/F/TAF From E/C/F/TAF, E/C/F/TDF, or ATV+RTV+FTC/TDF in Virologically Suppressed HIV-1 Infected Women. Submitted Date: August 22, 2016 (v7) 全文	5、7-10
P,A	4. 期刊 Lazerwith, S. E., et al. "Discovery of bictegravir (GS-9883), a novel, unboosted, once-daily HIV-1 integrase strand transfer inhibitor (INSTI) with improved pharmacokinetics and in vitro resistance profile." ASM Microbe . (2016) . Figure 2	5、7-10

關聯性代碼說明：

X：單獨引用即足以否定發明新穎性或進步性之特別相關的文獻。

Y：結合一或多篇其他文獻後足以否定發明進步性之特別相關的文獻。

A：一般技術水準之參考文獻。

D：說明書已記載之文獻。

E：申請在前，公開/公告在後之專利文獻。

O：公開使用、販賣或展覽陳列之文件。

P：申請日與優先權日間公開之文獻。

L：其他理由引用之文獻。

完成日： 111年5月13日

1112050162O

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OFFICE ACTION OF THE INTELLECTUAL PROPERTY OFFICE

(Translation)

Receipt Date: 24 May 2022

I. Applicant: GILEAD SCIENCES, INC.

II. Attorney: C. V. Chen
Address: 8F, No. 555, Sec. 4, Zhongxiao E. Rd., Taipei

SUMMARY:

After examination, the Intellectual Property Office (IPO) considers that ROC (Taiwan) Patent Application No. 110129951 has the defects indicated in EXPLANATION (A). The applicant is required to file a response or amendment within three months from the day after receipt of this office action. If a response or amendment is not submitted by the deadline, the subject application will be rejected in view of the Patent Act, Article 46, Paragraph 2.

EXPLANATION:

(A) Upon examination, the IPO notes the following:

(1) The subject application, for an invention titled "THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS," is a divisional application of Patent Application No. 105136333. The applicant submitted amended claims on 14 February 2022, which do not exceed the scope of the disclosure in the specification, claims and drawings originally filed. The subject application was examined based on the amendment and the documents submitted at the time of filing. The subject application has 10 claims. Claims 1 to 7, 9 and 10 are independent claims and the rest are dependent claims.

(2) The subject application claims the first priority to USSN 62/253,042 (filed on 9 November 2015). It was found that the contents of Claims 5 and 7 to 10 of the subject application are not disclosed in the first priority application. According to the Patent Examination Guidelines, Chapter 5, Section 1.4.1, "the invention claimed in a later-filed application is deemed 'the same invention' as the invention disclosed in the priority application only if one of the following two conditions is met: a. the two inventions are substantially identical; b. the difference between the two inventions only lies in the literal description or part of the corresponding technical features, and a person of ordinary skill in the art can directly and unambiguously infer from the disclosure of the priority application that the explicitly described technical content alone or as a whole implies the corresponding technical features of the claimed invention, not any other technical features." However, the specific contents or data such as AUC and C_{Max} of the claimed composition of the subject application cannot be directly and unambiguously inferred from the technical content explicitly disclosed in the priority application. Therefore, the date based on which the comparison of prior art and the invention of Claims 5 and 7 to 10 is

the filing date of the second priority application USSN 62/399,999 (26 September 2016).

(3) Claims 5 to 10 do not conform to the Patent Act, Article 26, Paragraph 2.

Claims 5 to 10 refer to "the compound of Formula I" and "the compound of Formula II" without depicting their structures. Therefore, the claims are indefinite.

(4) In view of Citations 1 and 2, Claims 2 to 6 do not comply with the Patent Act, Article 22, Paragraph 2. In view of Citation 3, Claims 5 and 7 to 10 do not comply with the Patent Act, Article 22, Paragraph 2.

(a) Claims 2 to 6

Citation 1 discloses on pages 3, 4 and 15 to 20 and in the examples the preparation of an oral dosage form with dolutegravir, tenofovir alafenamide and emtricitabine, wherein dolutegravir is an HIV integrase inhibitor. Citation 1 discloses on pages 19 and 20 that the pharmaceutical composition contains 50 mg of dolutegravir, 200 mg of emtricitabine and 25 mg of tenofovir alafenamide. The difference between Citation 1 and the claimed invention lies in that Citation 1 does not disclose the compound of Formula I as claimed. However, Citation 2 discloses on pages 3 to 7 and 212 to 221 and in Examples 42 and 45 that the compound of formula I is an HIV integrase inhibitor and may be used in treating HIV infection. Since Citations 1 and 2 pertain to the same technical field relating to the treatment of HIV infection, and have the commonality in the function or action of "structurally similar HIV integrase inhibitors," a person of ordinary skill in the art would have motivation to combine Citation 1 with Citation 2 and could easily infer that the compound of Formula I disclosed in Citation 2 can be combined with emtricitabine and tenofovir alafenamide to prepare a tablet. In addition, the pharmaceutically acceptable salt forms, the amount of each ingredient, the preparation of a multilayer tablet, the preparation method of compressing a first layer and a second layer, and the species and amounts of other conventional excipients can be easily selected and adjusted by a person of ordinary skill in the art through ordinary means in routine work. In addition, the specification only discloses in the examples that the tablet having specific ingredients and amounts thereof, such as a tablet comprising 50 mg of the compound of Formula I, 25 mg of tenofovir alafenamide and 200 mg of emtricitabine" can achieve better efficacies, such as AUC, C_{Max} and solubility of the compound of Formula I, as compared to the efficacies achieved by separately administering "a formulation comprising the compound of Formula I" and "a formulation comprising tenofovir alafenamide and emtricitabine." Therefore, the specification does not prove that the tablet or composition comprising ingredients specified with weight percentage or unspecified amounts could achieve the claimed better efficacy. Therefore, the claimed invention can be easily achieved by a person of ordinary skill in the art in view of the prior art reference, and Claims 2 to 6 lack an inventive step.

(b) Claims 5 and 7 to 10

It was found the priority document does not disclose the contents of Claims 5 and 7 to 10, so the examination of Claims 5 and 7 to 10 is based on the filing date of the second priority application, 26 September 2016. Citation 3 discloses in the whole document a tablet comprising GS-9883/F/TAF (50/200/25mg), wherein GS-9883/F/TAF stands for GS-9883/emtricitabine/tenofovir alafenamide, and GS-9883 is the compound of Formula I as claimed (please refer to Citation 4 which discloses in Figure 2 that bictegravir (GS-9883) is the compound of Formula I as claimed). Therefore, a person of ordinary skill in the art would have motivation to refer to Citation 3 and could easily infer the tablet or composition as claimed in Claims 5 and 7 to 10. In addition, a person of ordinary skill in the art can easily select and adjust the pharmaceutically acceptable salt forms, the pharmaceutical ingredients and the species and amounts of conventional excipients, and perform tests to obtain pharmacokinetic data such as AUC and C_{Max}. Therefore, the claimed invention can be easily achieved by a person of ordinary skill in the art in view of the prior art reference, and Claims 5 and 7 to 10 lack an inventive step.

(5) Reasons for rejecting/objecting to Claim 1 are not found at present. The applicant will be further notified if any new reason for objection/rejection is found.

(6) Cited documents:

Citation 1: WO 2015/022351 A1
Citation 2: WO 2014/100323 A1
Citation 3: History of Changes for Study: NCT02652624, Safety and Efficacy of Switching to a FDC of GS-9883/F/TAF From E/C/F/TAF, E/C/F/TDF, or ATV+RTV+FTC/TDF in Virologically Suppressed HIV-1 Infected Women. Submitted Date: August 22, 2016 (v7)
Citation 4: ASM Microbe, Discovery of bictegravir (GS-9883), a novel, unboosted, once-daily HIV-1 integrase strand transfer inhibitor (INSTI) with improved pharmacokinetics and in vitro resistance profile. (June 16-20, 2016)

(B) If any amendments and/or corrections are to be made to the subject application, such amendments and/or corrections should be made according to the provisions of Article 43 and Paragraph 3 of Article 44 of the Patent Act and Articles 36 to 38 of the Enforcement Rules of the Patent Act; the application form(s) should be completed according to the regulations for amending and/or correcting patent applications.

(C) If the applicant wishes to appear before the IPO for a face-to-face demonstration or explanation, please submit the "Interview Request Form" and indicate therein the version of the patent documents and the issues to be discussed with relevant explanations and effect payment of a government fee of NT$1,000. The time and place of the interview will be arranged if the IPO considers an interview necessary.

(D) Attached is a search report for the subject application. Please note that a non-patent document attached to the search report for citation, if any, is only for the applicant's reference. If such document is to be used in other manners, such as printing and publishing, uploading to the internet, etc., it is still required that consent or authorization be obtained from the author/copyright owner so as to avoid infringement.

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Formalities officer
Helm, Patrick

Carpmaels & Ransford LLP
One Southampton Row
London WC1B 5HA
ROYAUME UNI

Date: 29.03.2021

Reference	Application No./Patent No.
P072824EP	16798063.0 - 1112 / 3346995

Applicant/Proprietor:
Gilead Sciences, Inc.

BRIEF COMMUNICATION

Subject:
- ☐ Your letter of
- ☐ Our telephone conversation of
- ☐ Communication of
- ☐

Enclosure(s):
- ☐ Letter from the proprietor of the patent of
- ☒ Letter from the opponent O3 of 24.3.2021
- ☐ Copy (copies)

Communication:

☐ The documents specified as patent documents and as non-patent literature in this letter are available for inspection via the European Patent Register at **www.epo.org/register.** Should you wish to receive these documents in paper format, they will be supplied to you free of charge if specifically requested on receipt of this communication (OJ EPO 2020, A105).

☐

For the Opposition Division

Europäisches Patentamt • European Patent Office • Office européen des brevets

☐ **Registered letter**

TER MEER STEINMEISTER & PARTNER PATENTANWÄLTE mbB

ter Meer Steinmeister & Partner · Nymphenburger Straße 4 · 80335 München

GERMAN & EUROPEAN
PATENT ATTORNEYS
Dipl.-Chem. Dr. Christian Hollatz
Dipl.-Ing. Jörg Klemann
Dipl.-Chem. Dr. Bernd Aechter
Dipl.-Phys. Dr. Julia Matl
Dipl.-Chem. Dr. Luigi Rumi
Dipl.-Ing. (FH) Stefan Menzer, M.Sc.
Dipl.-Chem. Dr. Ingo Ortel
Apothekerin Dr. Veronika Müller
Dipl.-Ing. Matthias Überreiter
Dipl.-Biochem. Dr. Markus Ackermann
Dipl.-Phys. Frank Möller*
Dipl.-Phys. Dr. Wolfgang Säker*

GERMAN PATENT ATTORNEYS
Dr. Jonas Thelemann, M.Sc.
Claudia Schwartzkopff, M.Sc.

EUROPEAN PATENT ATTORNEY
Abhishek Tewary, M.Sc.

Consultants:
Dipl.-Ing. Gebhard Merkle
Manfred Wiebusch*

Nymphenburger Straße 4
Zugang Dachauer Straße 63
80335 MÜNCHEN

Telefon: (089) 72 98 960-0
Telefax: (089) 72 98 960-20
www.termeer.de
Registergericht: AG München PR1207
VAT Reg. No: DE 130 747 219
St.-Nr./ Tax No: 143/573/80694

European Patent Office
Bob-van-Benthem-Platz 1
80469 München

Opposition against EP 3 346 995 (16 798 063.0)
"Therapeutic compositions for treatment of Human Immunodeficiency Virus"
Patentee: Gilead Sciences, Inc.
Opponent: Sandoz GmbH

24.03.2021
Ae/VM/vb
aechter@termeer.de

In response to the reply of the patent proprietor to the notice of opposition dated January 11, 2021, the following is submitted.

1. Introduction

The present submission is not intended to comprehensively address all issues of the case. In fact, we maintain our requests for revocation of the patent in its entirety and for oral proceedings as well our right to submit further arguments, if required.

All arguments raised in our grounds for opposition are maintained. In reply to the proprietor's submission dated January 11, 2021, however, two points are addressed below which seem to be of high relevance for the current proceedings, namely the selection of the closest prior art and the experimental data depicted in D27.

* Büro Bielefeld: Artur-Ladebeck-Str. 51, 33617 BIELEFELD
Telefon: (0521) 914 940 Telefax: (0521) 914 94 20

2. The Selection of the Closest Prior Art

2.1 Introduction

With their grounds for opposition, all opponents unanimously considered D5 as closest prior art document. The patentee counter argued that D37 would be a more realistic starting point (reply to the notices of opposition, p. 13, para. 5.39).

In the following it will be shown that in dependence on the entitlement of the 1st priority date, different documents have to be considered as closest prior art. Irrespective of whether the 1st priority is validly claimed or not, however, D37 does not qualify as closest prior art.

2.2 1st Priority is Invalidly Claimed: D31 Represents the Closest Prior Art

As outlined in our grounds for opposition, the 1st priority is not validly claimed resulting in the effective date of September 26, 2016. Consequently, D31 and D32 dated November 19, 2015 (D21) and February 24, 2016 (D22), respectively, represent prior art documents under Article 54(2) EPC (grounds for opposition dated May 28, 2020, sections 5 and 8.5).

In such case, D31 represents a more promising springboard than D37. Both D31 and D37 describe clinical trials regarding an agent designated as GS-9883. The clinical trial of D31 evaluates a fixed dose combination (FDC) in form of a film-coated tablet comprising 50 mg GS-9883, 200 mg emtricitabine (FTC) and 25 mg tenofovir alafenamide (TAF) (D31, D.3.4, D.3.8, D.3.10.1 and D.3.10.3). In contrast, D37 concerns a clinical trial in which 75 mg GS-9883 single agent tablet is co-administered with a separate FDC-tablet comprising 200 mg FTC and 25 mg TAF (D37, p. 1, summary in combination with p. 3, intervention). Neither D31 nor D37 disclose that GS-9883 represents the code designation of the active agent bictegravir (BIC). However, the link between GS-9883 and BIC is disclosed in its USAN statement (D32).

Hence, at the effective date of September 26, 2016 as reflected by D32, it was apparent that D31 describes a FDC-tablet comprising 50 mg BIC, 200 mg FTC and 25 mg, while D37 only discloses co-administration of a 75 mg BIC single agent tablet with a FDC-tablet comprising 200 mg FTC and 25 mg TAF.

Thus, D31 has more features in common with the subject-matter of the opposed patent than D37. Consequently, in case non-entitlement to the 1st priority date is considered, D31 and not D37 constitutes the most promising starting point for an obvious development in the direction of the claimed subject-matter.

2.3 Priority is Validly Claimed: D37 Does Not Qualify as Closest Prior Art

If, for the sake of argument only, the Opposition Division regards the 1st priority as validly claimed, D37 still does not qualify as closest prior art.

In the following it will be shown that

a) D37 only refers to the code designation GS-9883,
b) at the priority date it was not known that GS-9883 is linked to BIC, and that
c) therefore, the alleged technical effects of improved exposure, dissolution and food effect are completely irrelevant.

a) D37 Only Discloses the Code Designation GS-9883

As a matter of fact, D37 does not disclose the INN name bictegravir (BIC) or the structural formula of BIC. Instead, D37 only refers to an active ingredient designated according to a code as GS-9883.

Consequently, D37 merely describes a clinical trial, in which the efficacy, safety and tolerability of an undisclosed compound (named GS-9883) co-administered with a separate FDC-tablet comprising FTC/TAF is compared against co-administered dolutegravir (DTG) (50 mg) (D37, p. 1, official title brief summary)

From the disclosure of D37 alone, therefore, it is not possible to conclude that GS-9883 refers to BIC.

b) At the Priority Date It Was Not Known that GS-9883 Refers to BIC

In his reply to the notices of oppositions, the patentee stated the following in view of D37:

> *"5.39 ... D37, which describes a Phase II clinical trial comparing BIC (75 mg) + FTC/TAF (200/25 mg) ...*
>
> *5.40 ... comparing the clinical safety and efficacy of BIC (75 mg) + FTC/TAF (200/25 mg)..." (patentee's reply to the notices of opposition, p. 5.39 and 5.40).*

This conclusion of the patentee is disputed. As outlined above, D37 only refers to GS-9883.

Further, the link between GS-9883 and BIC was not commonly known in the art before the first priority date, as it has been established in February 2016 as shown by its USAN statement (D32).

Thus, the patentee apparently has overlooked (or ignored) the fact that D37 merely discloses a combination therapy involving co-administration of an active agent labelled as GS-9883 with FTC and TAF. In other words, D37 does not disclose BIC.

Patentee's assumption that D37 would be a realistic starting point for the assessment of inventive step, is therefore a hindsight-driven approach and wrong. At the priority date, there was no reason for the skilled person to choose D37 as most promising springboard when seeking to arrive at fixed dose combination of BIC, FTC and TAF.

c) The Alleged Technical Effects of Improved Exposure, Dissolution and Food Effect are Irrelevant for the Assessment of Inventive Step

In his reply to the notices of opposition, the patentee outlined under reference to D35 that a phase I dose finding study led to the selection of 75 mg BIC as the optimum dose to be progressed in further clinical trials (reply to the notice of opposition, p. 7, para. 5.5).

Like D37, document D35 only refers to the code designation GS-9883 (D35). The patentee again ignored the fact that, at the priority date, it was not known at all to which agent the designation GS-9883 belongs to.

Hence, the assumption of the patentee that at the priority date dose optimisation had resulted in the identification of 75 mg BIC as the most promising candidate for co-administration with FTC/TAF (200/25 mg) is irrelevant, because that assumption was not part of the state of the art. Instead, it's a hindsight-driven assumption (reply to the notice of opposition, p. 7, para. 5.8).

Based on this approach, the patentee also wrongly concluded that the claimed subject-matter would differ from D37 in a substantially reduced dose of BIC as part of a single FDC-tablet with FTC and TAF (reply to the notice of opposition, p. 13, para. 5.41).

In fact, the subject-matter of granted claim 1 *inter alia* differs from the disclosure of D37 in that 50 mg BIC is used instead of 75 mg of GS-9883. In the absence of any link between GS-9883 and BIC, the assumption of a reduced dose of BIC is completely false.

Thus, any technical effect accompanied by the reduction of the BIC-dose, such as the alleged unexpected increase in BIC exposure and dissolution as well as the supposed food effect, is irrelevant for the assessment of inventive step.

Consequently, the arguments presented by the patentee in paragraphs 5.9 to 5.28 as well as 5.40 to 5.57 of his reply to the notices of opposition have to be ignored for the inventive step discussion.

2.4 D5 as Closest Prior Art

2.4.1 Introduction

In his reply to the notices of oppositions, the patentee objected D5 as an inappropriate starting point for assessment of inventive step. In particular, the patentee criticised that D5 does not disclose BIC, its structure or any of its properties (reply to the notices of oppositions, p. 12, para. 32 and p. 15, para. 5.58). However, this criticism is flawed since it applies mutatis mutandis to D37.

In the following it will be shown, that in line with the jurisprudence of the Boards of Appeal, D5 is a suitable starting point for the assessment of inventive step and qualifies as closest prior art.

2.4.2 Legal Background

It is established jurisprudence that the closest prior art for assessing inventive step is normally a prior art document disclosing subject-matter conceived

i. for the same purpose or effect,
ii. similarity of the technical problem,
iii. having the most relevant technical features in common, i.e. requiring the minimum of structural modifications.

In addition, the Boards of Appeal further established that if the skilled person had a choice of several workable routes, i.e. routes starting from different documents, which might lead to the invention, the rationale of the problem and solution approach required that the invention be assessed relative to all these possible routes, before an inventive step could be acknowledged. Conversely, if the invention was obvious to the skilled person in respect of at least one of these routes, then an inventive step was lacking (Case Law of the Boards of Appeal, I. D., 3).

2.4.3 D5 Qualifies as Closest Prior Art

D5 concerns the same purpose or effect as the opposed patent, namely pharmaceutical combinations for use in the treatment of viral infection/disease such as an HIV infection (D5, p. 1, ll., 1-7).

As outlined in great detail in our notice of opposition, D5 addresses a similar technical problem, namely the provision of a fixed-dose combination (FDC).

In particular, D5 discloses pharmaceutical compositions comprising about 50 mg DTG, about 200 mg FTC and about 25 mg TAF, wherein the amount of TAF is based of tenofovir alafenamide free base or tenofovir alafenamide hemifumarate (D5, p. 20, li. 3-4). In addition, D5 further discloses that the preferred dosage form of the composition is an oral dosage form in form of a tablet (D5, p. 23, ll. 6-8).

As outlined in great detail in our notice of opposition, at the priority date it was known that active agents containing the common stem *"-tegravir"* belong to the same class of antiviral agents, namely integrase strand transfer inhibitors (INSTI) (see our grounds for opposition, section 3.2.2).

Thus, D5 relates to the same technical problem as the opposed patent, namely to the provision of a FDC in form of a tablet comprising an INSTI, 200 mg FTC and 25 mg TAF.

Finally, the subject-matter of granted claim 1 and D5 only differs in that the FDC of the opposed patent comprises the INSTI BIC instead of DTG.

Consequently, starting from D5 as closest prior art, a minimum of one structural modification (replacing the INSTI) has to be made to arrive at the claimed subject-matter.

As evident from the above, D5 clearly qualifies as closest prior art.

3. The Data of D27 are Not Questionable but of High Relevance

3.1 Introduction

In the reply to the notices of oppositions, the patentee raised the objection that the experiments in D27 would allegedly show highly variable results. In this respect, the patentee estimated that the dissolution of BIC from both tablets in the first graph supposedly reaches about 90%, whereas the dissolution of BIC from both tablets in the second graph allegedly

only ended up at about 80%. According to the patentee, such a variability would be surprising, which was why the data in D27 were seriously questioned (patentee's reply, p. 19, para. 5.91).

Contrary to the assumption of the patentee, the data in D27 are scientifically sound and have to be taken into account for the assessment of inventive step.

In the following it will be shown that:

a) the patentee inaccurately estimated the dissolution percentages of BIC in D27 and
b) overlooked that formulation 010X can be regarded as an internal standard in the described experiments.

In addition, it will be explained that:

c) the data of D27 clearly show that combining BIC, FTC and TAF in a single tablet does NOT increase dissolution compared to a BIC single agent tablet and that
d) therefore, the data provide verifiable facts that the improvement in dissolution does NOT have its origin in the presence of these APIs together in a single tablet formulation.

3.2 The Patentee Inaccurately Estimated the Dissolution Percentages of BIC in D27

The patentee estimated a dissolution percentage of BIC of about 90% and 80% of the tablet formulations in the first and second graphs of D27, respectively. Based on this, the patentee mentions that there would be a "*surprising variability*" given that the same tablet formulation is measured in each dissolution test (patentee's reply, p. 19, para. 5.91).

As will be shown by the individual data points underlying the graphs depicted in D27, the patentee wrongly estimated the dissolution percentages in each dissolution test resulting in such an untenable assumption.

The first and second graphs of D27 represent the results of two individual dissolution tests performed separately from each other. The data points of the individual dissolution tests underlying graphs 1 and 2 are depicted in the following tables:

Dissolution test 1 - Graph 1

Time (min)	007X-T02			010X-T02		
	mean	RSD	n	mean	RSD	n
5	62.5	2.1	3	63.7	1.5	3
10	73.8	0.9	3	73.8	1.0	3
15	77.8	1.2	3	79.3	1.3	3
20	79.6	1.2	3	81.4	0.9	3
30	83.6	1.6	3	84.8	1.0	3
45	85.7	1.3	3	86.7	0.6	3
60	87.0	0.5	3	88.4	0.1	3

Dissolution test 2 - Graph 2

Time (min)	007X-T02+006X-T02			010X-T02		
	mean	RSD	n	mean	RSD	n
5	59.0	2.6	3	58.2	0.4	3
10	65.3	1.3	3	65.3	0.5	3
15	71.2	1.3	3	70.3	1.2	3
20	74.2	0.6	3	74.1	0.8	3
30	76.6	0.8	3	76.6	1.2	3
45	80.3	1.6	3	80.0	1.2	3
60	82.2	1.3	3	81.5	0.8	3

For each dissolution test, three tablets (n=3) of the same tablet formulation were evaluated. The results are given in the mean dissolution percentage including its relative standard deviation (RSD).

The RSDs show that the variability of one time point within the same dissolution test of each tested formulation ranges between 0.4 and 2.6%. Hence, a very low variability for all time points within one dissolution test was observed.

In addition, the results show that the dissolution percentage of BIC at the final time point is

- 87.0 ± 0.5 % (007X alone) and 88.4 ± 0.1 (010X) in dissolution test 1, and
- 82.2 ± 1.3 % (007X + 006X) and 81.5 ± 0.8 % (010X) in dissolution test 2.

Hence, at the final time point the dissolution percentage of BIC of dissolution test 1 differs by only 4.8% for 007X and 7.1% for 010X from dissolution test 2.

Thus, patentee's estimations of dissolution percentages of BIC of about 90% and about 80% in the first and second graphs of D27, respectively, is inaccurate. Due to this the patentee falsely assumed a variability of about 10% between the dissolution tests, instead of only 4.8% to 7.1%.

A variability of 4.8% to 7.1%, however, lies within common acceptable differences between two separately conducted dissolution tests.

3.3 The Patentee Overlooked that 010X Can Be Regarded as an Internal Standard

In each dissolution test, the dissolution of BIC from formulation 010X is evaluated for the reasons set out below (see section c) below). Formulation 010X, thereby, can be regarded as an internal standard to which 007X is compared within the same dissolution test.

It is evident from the data points depicted above and represented in graphs 1 and 2 of D27 that formulation 007X shows a similar dissolution profile to the internal standard 010X in both dissolution tests.

Utilizing the dissolution profile of 010X as an internal standard to which the dissolution profile of 007X is normalised shows that the dissolution profile of formulation 007X is comparable in both dissolution tests.

Thus, the parallel evaluation of formulation 010X in each dissolution test confirms that the dissolution profile of 007X is comparable in both tests.

3.4 The Data of D27 Show that Combining BIC, FTC and TAF in a Single Tablet Formulation Does NOT Enhance Dissolution

As outlined in our grounds for opposition, formulation 010X corresponds to the BIC/FTC/TAF (50/200/25 mg) fixed-dose combination tablet (F7) according to Example 6 of the opposed patent.

The experiment of D27 compares the BIC dissolution from

(i) the BIC/FTC/TAF (50/200/25 mg) fixed-dose combination tablet (010X) with
(ii) a 50 mg BIC single agent tablet (007X) and with
(iii) a 50 mg BIC single agent tablet (007X) in the presence of an FTC/TAF (200/25 mg) (006X).

The formulation of the BIC single agent tablet is the same as that of the BIC layer of the BIC/FTC/TAF bilayer tablet. Similarly, the formulation of the FTC/TAF tablet is the same as that of the FTC/TAF layer of the BIC/FTC/TAF bilayer tablet (see our grounds of opposition, section 7.2.4).

The dissolution results are depicted in the figures of D27. A comparison of the dissolution profiles shows that the total percentage dissolution of BIC from a BIC/FTC/TAF combination tablet (010X) is identical to the total percentage dissolution of BIC from

- a BIC single agent tablet (007X), and
- a BIC single agent tablet (007X) in the presence of FTC/TAF (006X).

Hence, dissolution of BIC from a BIC/FTC/TAF combination tablet (010X) is not changed at all in comparison to a BIC single agent tablet alone (dissolution test 1) or in the presence of an FTC/TAF tablet (dissolution test 2).

Thus, combining the three APIs BIC, FTC and TAF in a single tablet formulation (010X) does NOT enhance dissolution of BIC compared to its dissolution out of a BIC single agent tablet (007X).

3.5 D27 Provides Verifiable Facts that Improvement of BIC-Dissolution Does NOT Have its Origin in its Formulation as a Triple Agent Tablet

It belongs to established jurisprudence that a surprising effect (advantageous effect or feature) can be demonstrated in a comparative test. However, if comparative tests are chosen to demonstrate an inventive step on the basis of an improved effect, the nature of the comparison with the closest state of the art must be such that the alleged advantage or effect is convincingly shown to have its origin in the distinguishing feature (Case Law of the Boards of Appeal, 9th ed., I., D. 10.9).

In D27 the formulation of the BIC single agent tablet 007X and the formulation of the FTC/TAF tablet 006X is the same as the BIC layer and FTC/TAF layer of the BIC/FTC/TAF combination tablet (010X) (see section 2. c)).

Dissolution test 2 of D27 evaluated BIC dissolution from a BIC/FTC/TAF combination tablet (010X) in comparison to BIC dissolution from a BIC single agent tablet (007X) in the presence of an FTC/TAF tablet (006X).

Hence, the nature of dissolution test 2 is such that the mere distinguishing feature is the presence of all APIs together in a single tablet formulation.

As shown above, BIC dissolution from a BIC/FTC/TAF combination tablet (010X) corresponds to BIC dissolution from a BIC single agent tablet (007X) in the presence of a FTC/TAF tablet (006X).

Thus, D27 provides verifiable facts in form of experimental data that combining the three APIs, BIC, FTC and TAF, in a single tablet formulation does NOT change dissolution of BIC compared to its dissolution out of a BIC single agent tablet.

4. Conclusion

As evident from the above, if the priority is considered as invalidly claimed, D31 has more technical features in common than D37, and therefore, represents the closest prior art. If, however, priority is acknowledged to be validly claimed then it follows that D5 is the closest prior art. Contrary, D37 does not qualify as a promising starting point as it only refers to an unknown agent labelled as GS-9883. The alleged technical effects presented by the patentee are, therefore, completely irrelevant and have to be ignored for the inventive step discussion.

For the sake of completeness, however, it is noted that an alleged technical effect in form of enhanced dissolution accompanied by improved bioavailability does not have its origin in the presence of BIC, FTC and TAF together in a single tablet formulation as shown by the data of D27.

Dr. Bernd Aechter
European Patent Attorney
Association No. 6

Dr. Veronika Müller
European Patent Attorney
Association No. 6

5th IAS Conference on HIV Pathogenesis,
Treatment and Prevention
July 19th-22nd 2009
Capetown, South Africa

Back »

New Drugs, New strategies

Summary for IAS in Cape Town 2009

Joe Eron, MD, Univeristy of North Carolina

Back in the Game

The most important new drug presentation at IAS this year came from an old warrior in the HIV drug development game, GlaxoSmithKline. After many disappointments including an early integrase inhibitor, a CCR5 inhibitor, a promising second generation NNRTI and darunavir-like protease inhibitor, all which went belly-up in early clinical development either due to issues with activity or toxicity, GSK presented the first clinical activity of their new integrase inhibitor, S/GSK1349572 or "572", developed in a full joint venture with Shionogi [1]. This compound has multiple characteristics that may make it stand out amongst the integrase inhibitors that have reached clinical development to date. First off 572 seems to have remarkable in vivo potency. Three doses, 2, 10 and 50 mg once daily were tested over 10 days in integrase-inhibitor naive patients who had been off therapy or were treatment naive. At the highest dose, 50 mg daily, the peak decline in viral load was 2.5 log10 copies per mL (300 fold), which is the largest decline in viral load we have seen in a short term monotherapy study with any agent in any class. Of the 10 HIV infected subject who received this dose, seven had their plasma HIV RNA fall to < 50 c/mL so the peak decline may have been even greater. The 10 mg dose reached a maximum VL decline of ~ 2.0 log10 copies/mL and even the individuals receiving the 2 mg dose had a peak decline of ~ 1.5 log10 copies/mL. In this short study the drug also seemed well tolerated and no major side effects were observed.

A second characteristic of the integrase inhibitor was very consistent and therefore predictable pharmacokinetics across the doses tested in this first in HIV-infected patients [2] and in uninfected volunteers. Concentrations increased in a predictable way with dose, the inter-subject variability in drug concentrations at a given dose was small and the concentrations were similar when the medication was given with or without food. Importantly the concentration response curve (or Emax curve) in HIV-infected patients showed encouraging pharmacodynamics. The 50 mg daily dose was on the flat part of the Emax curve meaning that this dose was likely to give the maximum response possible in patients with integrase-susceptible virus and that there was substantial security at that dose as concentrations achieved were well past the inflection point where activity decreased as concentrations fell.

Laboratory studies of resistance of this compound were also encouraging. In vitro selection of resistance to 572 was difficult[3]. In studies performed by Shionogi, high level resistance to elvitegravir occurred after 56 days in culture and high level resistance to raltegravir emerged after 84 days. Mutations seen were consistent with in vitro or in vivo resistance mutations to these integrase inhibitors. On the other hand even after 112 days in culture, clear high level resistance to 572 had not emerged (FC 1.2 to 4.1). Several mutations were seen but these mutations conferred minimal resistance to 572 and at least one of the mutations was a polymorphism. These studies suggest that 572 may have a higher barrier to resistance than either elvitegravir or raltegravir. We know raltegravir and elvitegravir are potent with approximately 2 log10 activity in short term studies [4, 5], however if there is virologic rebound in the context

of combination therapy resistance will emerge in a substantial proportion of patients[6, 7]. In vitro selection studies do not always mirror what occurs in the clinic, so while promising, the selection studies with 572 should be interpreted with caution. No resistance mutations emerged in the short term monotherapy study in integrase naïve patients just presented at IAS [1] but resistance mutations were not selected for in the phase 2a studies of elvitegravir or raltegravir either [4, 5]. To date only the boosted protease inhibitor class has consistently shown a "high barrier to resistance" in longer term clinical studies and predominantly in studies conducted in previously treatment naïve patients.

Finally the issue of cross resistance between 572 and raltegravir and elvitegravir was examined. Cross resistance between viruses resistant to one of the two integrase inhibitors approved or in advanced clinical development, raltegravir and elvitegravir, is common [8] especially when resistance mutations selected in clinical studies of raltegravir are examined. In a poster presentation at IAS an array of viruses created in vitro by site directed mutagenesis with elvitegravir and raltegravir associated mutations remained susceptible to 572 [3]. These viruses included mutations from the common pathways seen in raltegravir failures in the clinic including the 155, 140-148 and 143 pathways. However, when clinical isolates were examined the story was slightly different [9]. Viruses with 155H mutation and with 143 mutations appeared to retain full susceptibility to 572. The results were mixed in viruses with the combination of mutations at the 140 and 148 codons. Many of these viruses conveyed little alteration in fold change to 572 however some showed an increase in fold change greater than 10. The relationship of fold change with specific 140-148 codon substitutions was not completely clear though some viruses with 140S and 148H appeared to have the highest fold change. These viruses were clinical isolates obtained from patients failing raltegravir and the full integrase sequence was not yet known. Mutations or polymorphisms at other sites within integrase may explain some of the variation in the level of decreased susceptibility. The question of whether 572 can rescue raltegravir failures will remain a very important one. Raltegravir resistance evolution is complex. Most viruses seen in early failure have the 155H mutation but over time the pattern evolves and in many patients, viruses with the 140-148 combination emerge. The in vitro data on cross resistance with 572 will stimulate further debate on whether patients failing raltegravir should have their raltegravir stopped as soon as failure is confirmed to avoid selection of complex resistance patterns. This strategy may make sense though advanced patients who have had a substantial CD4 gain might be put at risk of losing their CD4 increase. The success of 572 in patients with raltegravir failure may depend on pattern of mutations but will also likely depend on the strength of the partner agents (which may be very limited in some raltegravir failures) and on the barrier to further resistance with 572. In vitro selection experiments starting with raltegravir resistance viruses may be informative.

Overall the debut of 572 was impressive. Clearly the drug is very potent, has low milligram dose (desirable characteristic for co-formulation), is clearly once a day, has very predictable pharmacokinetics and pharmacodynamics, does not need boosting and in vitro assessments suggest a high barrier to resistance and the potential to have activity in patients with raltegravir resistant virus. Of course we are a long way from an approved medication or even expanded access. Tolerability and toxicity have only been assessed short term so the longer Phase IIB studies are anxiously anticipated. A pilot study to assess activity of 572 in patients with raltegravir resistant virus is also in the works. Having GSK/Shionogi back in the game with a drug in advanced clinical development is good for the field and the prospect of a 'second generation' integrase inhibitor will stimulate discussion among virologists and clinicians and hopefully will eventually benefit our patients.

Raltegravir as Initial Therapy

Recently the FDA approved raltegravir for use as initial therapy for HIV infected adults in combination with other antiretroviral medications. This approval was based on the 48 week results of STARTMRK trial, just published in the Lancet by Lennox and colleagues, which demonstrated that raltegravir plus tenofovir DF/emtricitabine was non inferior to efavirenz plus the same 2 NRTI in treatment naïve patients [10]. At 48 weeks 86.1% of the raltegravir treated patients and 81.9% of efavirenz treated patients had plasma HIV RNA levels < 50 c/mL.

At IAS we saw long term data on raltegravir as initial therapy. In a poster presentation the 144 week data from the Merck 004 study were presented [11]. This study was originally a dose finding study and 4 doses of raltegravir, 100, 200, 400, and 600 mg twice daily, were tested versus efavirenz at a dose of 600 mg daily, all in combination with TDF and lamivudine [12]. After 48 weeks when all doses had similar efficacy that compared to efavirenz all patients (N =160) on raltegravir were switched to the 400 mg twice daily dose that is now the approved dose of raltegravir. At 144 weeks, raltegravir plus TDF/3TC had sustained antiretroviral activity similar and to efavirenz with 78% vs 76% of patients having a plasma HIV RNA < 50 copies/mL. Drug related adverse events were less frequent in the raltegravir arm and over this almost 3 year study raltegravir had minimal effect on total choiesterol, LDL-C, and triglycerides and HDL rose by a mean of 6.6 mg/dL. Between 96 and 144 weeks 2 patients had viral rebound on the raltegravir arm and one patient rebounded on the efavirenz arm. Neither patient on the raltegravir arm had characteristic integrase resistance mutations.

These data are strong evidence of a sustained treatment response when raltegravir is used as initial therapy in combination with 2 NRTI. Though twice daily, raltegravir therapy is very well tolerated and has really no adverse effect on lipids. We don't yet know about long term effects on bone shape or bone density though DEXA analyses are planned for the 004 study. Resistance emergence does occur in patients who either fail to suppress or rebound on therapy but in the 004 study integrase resistance mutations occurred in less than half the patients (3 out of 8 virologic failures with genotypes). Raltegravir-based initial therapy is a very viable alternative to either efavirenz based or boosted PI-based treatment and may be the most tolerable of the three. A large trial on once daily raltegravir is ongoing and the results are anxiously awaited.

New or Novel Strategies

Several studies looked at new or alternative strategies for administering antiretroviral therapy to simplify therapy, avoid toxicity and/or increase convenience.

The ARIES study, presented by Kathleen Squires and sponsored by GSK, is a ritonavir sparing study[13]. The study consisted of two phases. During the first induction phase all subjects received abacavir/lamivudine (Epzicom) with atazanavir plus ritonavir at standard doses. Those patients who had confirmed plasma HIV RNA < 50 c/mL by week 36 then entered the randomized phase and at week 36 were randomized to either continue with the induction therapy or drop the ritonavir and increase their atazanavir to 400 mg daily. This is not really a simplification study as the pill number does not change. However, even low dose (100 mg) of ritonavir may have substantial adverse effects, which may be symptomatic (e.g. gastrointestinal) or asymptomatic (e.g. elevated triglycerides). Five hundred and fifteen subjects entered the study and 419 were randomized. Notably, over half the patients at baseline had HIV RNA levels > 100,000 c/mL. The results were pretty straightforward. At 84 weeks (48 weeks after randomization) the proportion of patients who remained on therapy and suppressed (ITT - TLOVR analysis) was similar 86% on abacavir/lamivudine and atazanavir and 81% on the arm that continued with atazanavir plus ritonavir. 3% more patients dropped out of the atazanavir/ritonavir arm for a wide variety of reasons that hinted at tolerability (patient decision, lost to follow-up, adverse event etc). There was no difference in suppression rates by baseline HIV RNA with 85% and 87% remaining suppressed and on therapy on the atazanavir arm with baseline VL < 100,000 c/mL and > 100,000 c/mL respectively. There were actually more virologic failures on the atazanavir/ritonavir arm (7 total vs. 1) though there were no new major PI mutations in any of the failures. Again, this finding may suggest tolerability and adherence issues. Important, though not surprising, was the decrease in triglycerides and total cholesterol when ritonavir was dropped from the regimen. LDL-c also seemed to decrease slightly while HDL-c remained stable and up from baseline. The proportion of patients with hyperbilirubinemia also decreased. No myocardial infarctions were observed during the study (mean age at randomization was 39 years and 85% of the participants were men). These results clearly show that dropping RTV once suppressed is feasible, tolerable and maintains HIV suppression. The strategy fits with abacavir/lamivudine (Epzicom) and not TDF/emtricitabine (Truvada) because of the effect of tenofovir on atazanavir that requires maintaining ritonavir with that NRTI combination. The ARIES study was designed and enrolled prior to the D.A.D. results

that demonstrated an association of abacavir with myocardial infarction and was clearly designed to show a lipid (and therefore an implied cardiovascular) advantage to dropping ritonavir. The D.A.D. results made this study less appealing. However, now that there are studies that raise some question about the abacavir-MI association, the ARIES study strategy may be considered by clinicians especially in those patients that have difficulty tolerating even a low dose of ritonavir.

Metabolic Complications of HIV infection Update form the 5th IAS Conference in Cape Town - Pablo Tebas MD, University of Pennsylvania - (07/30/09)

Abacavir Not Associated with MIs, 2 Studies Report at IAS - (07/23/09)

Old Strategy, New Drug

Protease inhibitor monotherapy as a simplification strategy has been tested in the past with lopinavir/ritonavir and with atazanavir with ritonavir [14-17]. While generally successful there were suggestions that either boosted PI monotherapy was just not quite as good as continuing therapy with the boosted PI with nucleosides. There were greater numbers of patients with low level viremia, occasional selection of PI resistant virus and the question of whether virus remains suppressed in all compartments [18]. At IAS Arribas and colleagues presented the results of the MONET study, which tested the boosted PI simplification strategy with boosted darunavir[19]. The study design was straightforward. Subjects had to be suppressed < 50 c/mL for more than 6 months on 2 NRTI and either a boosted PI or NNRTI. They had to be naive to darunavir and have no history of virologic failure. Two hundred fifty six patients were randomized 1:1 to continue NRTI and switch to once daily darunavir/ritonavir (800/100) or switch to once daily darunavir/ritonavir alone. Primary endpoint included virologic rebound (2 consecutive values > 50 c/mL), discontinuation of darunavir, addition of NRTI in the monotherapy arm or discontinuation of NRTI in the NRTI arm. The study population was typical; mostly men, mostly white, median age 43 and a high baseline CD4. The mean duration of previous antiretroviral therapy was remarkably long; 6.4 years and 7.4 years in the triple therapy and monotherapy arms respectively. Suppression rates were very similar. In the per protocol analysis 87.8 and 86.2% were suppressed < 50 c/mL at 48 weeks in tripie therapy and monotherapy respectively and 85.3 and 84.3% in the intent to treat analysis. If patients who switched therapy but remained suppressed were included as successes then 95.1 vs. 93.5% remained suppressed < 50 c/mL at 48 weeks. All of these analyses demonstrated non-inferiority, which was defined as 95% CI of -12%. The investigators presented data on all patients at 48 weeks and almost all (97%) were suppressed < 50 though some had switched therapy and others had rebounded to > 50 c/mL but then suppressed again without changing therapy. Still there were hints of a little more viremia on the monotherapy arm. 11 vs. 7 patients met criteria for virologic rebound and 22 patients on the monotherapy arm had genotypes performed compared to 13 patients who remained on triple therapy (major PI mutations were observed in only one patient on each arm). Adverse events also didn't really improve. In fact, though likely not significant, there were numerically more clinical and laboratory adverse events in the monotherapy arm.

So where does this well-done study leave us? Is this a strategy that clinicians are likely to adopt? The arguments in favor are 1) simpler therapy in some instances though if switching from an NNRTI based regimen the pill number might actually increase, 2) preservation of the NRTI class (especially FTC or 3TC) 3) avoidance of NRTI toxicity and 4) decreased cost. The arguments against are pragmatic put perhaps compelling; 1) why mess with success? 2) boosted PI monotherapy isn't really much simpler 3) adverse events aren't really improved, at least over the observation period and 4) the gnawing concern that virologic suppression is just not quite as good. My guess is that there isn't going to be a great rush to darunavir/ritonavir monotherapy just as lopinavir/ritonavir and atazanavir monotherapy never really caught on. This may be an alternative for some patients, for example a patient suppressed on a boosted PI who was having renal dysfunction and had high cardiovascular risk such that avoiding both TDF and abacavir made sense? In general I suspect most patients and their clinicians will stick with their "nucs".

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Application Number	17/738,803
Filing Date	May 6, 2022
First Named Inventor	Benjamin Micah Collman
Title	THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS
Art Unit	1615
Examiner Name	J. N. Worsham
Attorney Docket Number	1147-US-P2C2DC

SIGNATURE of Applicant or Patent Practitioner

Signature	/Donna Johnson Gressler/	Date (Optional)	April 5, 2023
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Open Forum Infectious Diseases

Case Report: Emergent Resistance in a Treatment-Naive Person With Human Immunodeficiency Virus Under Bictegravir-Based Therapy

Nicholas Chamberlain,[1] Leandro Mena,[2] and James Benjamin Brock[1]

[1]Division of Infectious Diseases, Department of Medicine, University of Mississippi Medical Center, Jackson, Mississippi, USA, and [2]Department of Population Health Science, University of Mississippi Medical Center, Jackson, Mississippi, USA

Few instances of treatment-emergent resistance to bictegravir have been reported in the literature. We describe a case of treatment-emergent resistance to bictegravir in a person recently diagnosed with human immunodeficiency virus who developed M184V and R263K mutations while on therapy.

Keywords. bictegravir; HIV; R263K; resistance.

Current human immunodeficiency virus (HIV) guidelines for initial therapy in most treatment-naive individuals recommend therapy with an integrase inhibitor (INI) in combination with at least 1, but generally 2, nucleoside reverse transcriptase (RT) inhibitors [1]. Bictegravir (BIC)/emtricitabine (FTC)/tenofovir alafenamide (TAF) is a once-daily, single-tablet option for treatment-naive individuals, and this medication has high potency, low potential for drug–drug interactions, and a high barrier to resistance [2]. It demonstrated noninferiority to active comparators in treatment-naive and treatment-experienced individuals, and there have been no cases of treatment-emergent resistance documented in treatment-naive or treatment-experienced individuals in clinical trials of BIC/FTC/TAF [3]. BIC/FTC/TAF has also been proven efficacious in sustaining viral suppression in individuals with documented M184V/I mutations [4]. As of the time of this brief report, only a few instances of treatment-emergent resistance to BIC have been identified in the literature [5, 6]. We describe a case of treatment-emergent resistance to BIC in a person recently diagnosed with HIV who developed M184V (RT) and R263K (INI) mutations while on BIC therapy.

CASE REPORT

A 51-year-old man was diagnosed with advanced HIV infection complicated by cryptococcal meningitis. Baseline laboratory tests revealed an absolute CD4 count of 16 cells/mm^3 (3%) with a viral load of 3 700 000 copies/mL. A pretreatment genotype, which included INI testing, revealed an HIV-1 subtype B along with an L74I (RT) mutation conferring high-level resistance to didanosine and intermediate-level resistance to abacavir. The pretreatment L74I (RT) mutation was not present 27 days earlier on genotype with integrase testing performed at the time of HIV diagnosis at an outside health center. The person was started on BIC/FTC/TAF around 40 days after HIV diagnosis once he had completed 2 weeks of induction therapy with intravenous (IV) amphotericin B lipid complex (5 mg/kg daily) and oral flucytosine (25 mg/kg every 6 hours) followed by 4 weeks of consolidation therapy with oral fluconazole (400 mg daily) for his cryptococcal infection.

After 4 weeks of therapy, his viral load was 30 000 copies/mL, and after 11 weeks, his viral load was 319 copies/mL. The absolute CD4 count increased from 11 cells/mm^3 (3%) pretreatment to 160 cells/mm^3 (8%) after 11 weeks of therapy. He reported to providers that he was "mostly" taking his medications. At week 13, he was admitted to the hospital for acute encephalopathy with concerns for recurrent cryptococcal meningitis. According to his family, he had been off antiretroviral therapy (ART) and antifungal therapy for "several weeks" at that time. A repeat viral load was 98 000 copies/mL, and an updated genotype revealed an M184V (RT) mutation conferring resistance to lamivudine and FTC in addition to the previously seen L74I (RT) mutation. Given his poor adherence and recurrent central nervous system (CNS) infection, ART was not restarted until he had completed an additional 2-week course of IV amphotericin B lipid complex (5 mg/kg daily) and oral flucytosine (25 mg/kg every 6 hours) induction therapy and was transitioned to oral fluconazole (400 mg daily) for the consolidation phase of treatment for his CNS infection.

At week 20, BIC/FTC/TAF was restarted but later withheld at week 23 due to poor medication adherence resulting from untreated mental illness complicated by substance abuse, followed by a prolonged hospitalization for inpatient psychiatric care. After 8 weeks of inpatient psychiatric care, he was released and BIC/FTC/TAF was resumed at week 31. At follow-up the next month (week 37), he had an HIV RNA load of 14 095 copies/mL and a newly acquired R263K mutation (conferring low-level resistance to BIC) along with the previously documented M184V

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Correspondence: Nicholas Chamberlain, MD, University of Mississippi Medical Center, Department of Medicine, Division of Infectious Diseases, 2500 N State St, Jackson, MS 39216, USA (nchamberlain@umc.edu)

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(RT) and L74I (RT) mutations. ART was adjusted to darunavir/cobicistat and FTC/rilpivirine/TAF. At multiple subsequent follow-up visits, he continued to report inconsistent medication adherence with documented persistent viremia in the range of 400–13 000 copies/mL. Figure 1 provides an illustration of his viral loads, CD4 cell counts, and resistance mutations developed over time in response to ART exposure while on BIC/FTC/TAF.

DISCUSSION

Integrase strand transfer inhibitors (INSTIs), which include raltegravir (RAL), elvitegravir (EVG), dolutegravir (DTG), and BIC, are the one of the newest classes of antiretroviral drugs to be approved for treatment of HIV and inhibit the HIV protein integrase from inserting the viral DNA genome into the host cell [7, 8]. Resistance to RAL and EVG has been well-characterized in the literature with the accumulation of primary resistance substitutions along several pathways including the N155H, Q148, and G140A/G148R/H/Q pathways conferring high-level cross-resistance to RAL and EVG [2]. However, second-generation INSTIs like DTG and BIC have demonstrated higher barriers to resistance and maintain potency against primary mutations that confer resistance to RAL or EVG [2, 7, 8].

Treatment-emergent resistance to second-generation INIs is uncommon but has been documented [9]. One mutation of particular interest is the R263K (INI) mutation, which confers low-level (<3-fold reduced susceptibility) resistance to DTG and BIC and is associated with diminished HIV DNA integration and viral fitness [2, 8, 9]. In treatment-naive individuals, the R263K (INI) mutation is very rare and has most commonly been observed by ultra-deep sequencing [8]. Most cases of treatment failure with development of R263K (INI) mutations have been documented in the context of DTG administration, with failure most often linked to low serum drug levels from drug–drug interactions with rifampin or rifabutin [9]. However, a recent 2020 case report did document treatment-emergent resistance in a treatment-experienced individual who had received crushed BIC/FTC/TAF tablets through a nasogastric tube, which the authors speculate may have resulted in inadequate blood levels of the drug that led to the R263K mutation [8].

To the best of our knowledge, this case represents one of very few instances of documented treatment-emergent resistance to BIC in a person with no prior HIV treatment history. Prior to treatment initiation, he had 2 genotypes with integrase testing performed: one at diagnosis revealing a wild-type virus and the other 4 weeks later revealing an L74I (RT) mutation. He experienced an initial (albeit suboptimal) response to ART followed by prolonged viremia in the setting of frequent treatment interruptions and suboptimal adherence due to recurrent CNS infections requiring ART to be held, inpatient treatment for poorly controlled mental health issues, and ongoing alcohol and substance use disorder. Despite suboptimal viral

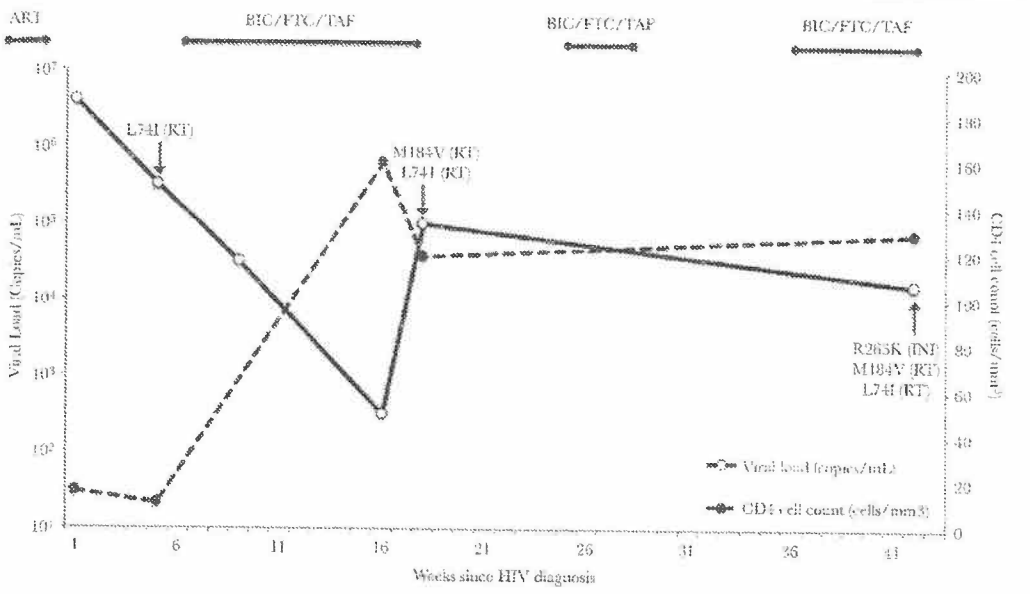


Figure 1. Viral loads, CD4 cell counts, antiretroviral therapy, and detected mutations over time. Abbreviations: ART, antiretroviral therapy; BIC, bictegravir; FTC, emtricitabine; HIV, human immunodeficiency virus; INI, integrase inhibitor; RT, reverse transcriptase; TAF, tenofovir alafenamide.

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suppression, he experienced a significant CD4 cell reconstitution as denoted by the increase of his CD4 cell count from 11 cells/mm^3 to 160 cells/mm^3 and 129 cells/mm^3 after 11 and 37 weeks of therapy, respectively. The M184V (RT) mutation was detected after 17 weeks of therapy, and at week 57 the R263KR (INI) mutation was detected via bulk sequencing (Viracor Lab, Missouri) necessitating a change in ART. Neither the M184V (RT) mutation nor the R263KR (INI) mutation was observed in the 2 pretreatment genotypes, suggesting that these were treatment-emergent mutations and were not transmitted or present at baseline. This combination of mutations has been shown to decrease viral infectiousness and replicative capacity in vitro when compared to the effects of either individual substitution alone, suggesting that this combination of substitutions has a strong effect on viral load; however, these findings have not been evaluated in clinical settings [10]. Two other reported cases of the R263KR (INI) mutation have been in individuals with non–subtype B HIV type 1, both with advanced HIV disease, one in a treatment-experienced individual and another under first-line treatment with BIC/FTC/TAF [5, 6].

Identifying individuals at highest risk for treatment failure and utilizing strategies to prevent treatment-emergent resistance from developing are paramount to HIV management. As treatment-emergent resistance is heavily linked to ART exposure, barriers to optimal ART adherence must be considered when prescribing a regimen, which include (1) regimen characteristics (ie, pill size and number, frequency, requirement of ingestion with food, and side effects) and (2) unaddressed mental health and substance use issues that may complicate an individual's ability to adhere to medications [11]. This individual's treatment course was made difficult by suspected recurrent cryptococcal meningitis that prevented reinitiation of ART due to the potentially devastating long-term neurological consequences. Another consideration given the person's robust CD4 cell count recovery was immune reconstitution inflammatory syndrome, which is managed by continuing both ART and antifungal therapy and reducing elevated intracranial pressure, if present [11]. Finally, this person's poorly managed mental health issues and struggles with substance abuse further complicated his care. Substance use disorders are prevalent among people with HIV and contribute to poor medication adherence and poor health outcomes. Second-generation INIs (DTG and BIC) and protease inhibitors provide a higher genetic barrier to resistance and should be given consideration when starting ART in individuals who may have poor adherence [1]. In this case, the better side-effect profile and fewer drug–drug interactions of the INIs were favored given this person's advanced HIV disease.

A holistic approach to HIV management should include not only ART, but also social support; screening for mental health and substance use disorders; counseling; and, when needed, evidence-based pharmacotherapy, psychiatric treatment, and even rehabilitation to address psychosocial factors that, when controlled, may result in better health outcomes. Individuals starting ART may benefit from more frequent follow-up and laboratory monitoring of viral loads and genotypes (when applicable) until they reach viral suppression. In this case, there were several months during which this individual had no recorded visits or laboratory work that might have allowed for earlier recognition of his adherence challenges and impending development of HIV drug resistance.

Notes

Patient consent statement. This case report does not include factors necessitating patient consent.

Potential conflicts of interest. L. M. reports grants from Gilead Sciences, GSK/ViiV Healthcare, Janssen, MSD, Visby Medical, ThaiMed, Evofem Biosciences, Prosofi Clinical, SpeedDx Pty Ltd, and Lupin Pharmaceuticals, and personal fees from Gilead Sciences, GSK/ViiV Healthcare, and MSD, outside the submitted work. All other authors report no potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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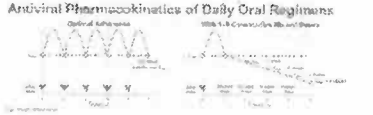
In Vitro Forgiveness of Oral and Long-Acting INSTI-Containing Regimens at Drug Concentrations Simulating Variable Adherence

Rima K. Acosta, Michelle L. D'Antoni, Andrew Mulato, Stephen R. Vant, Tomas Cihlar, Kirsten White — Gilead Sciences, Inc. Foster City, California, USA

Introduction

- EACS guidelines for initial treatment of HIV-1 infection recommend daily oral regimens anchored by an INSTI plus 1 or 2 NRTIs, including the STR of BIC/FTC/TAF, the combination of DTG+FTC/TAF, and the STR of DTG/3TC[1]
- The 2-drug daily oral STR of DTG/RPV is approved for PWH switching ARV regimens
- Recently, the LA INJ regimen CAB+RPV was approved for monthly and 2-month dosing in some countries
- Lapses in adherence to daily ARV drugs can lead to virologic failure and development of drug resistance, but regimens will have distinct thresholds of "forgiveness" (avoiding viral rebound and resistance in the setting of suboptimal adherence)
  - Long-acting regimens may be beneficial for those who want alternative to daily oral medications, but they cannot be self-administered and there is potential for resistance development associated with low drug exposure, inconsistent dosing, preexisting drug resistance, or HIV-1 subtype[2]
  - Previous *in vitro* studies have shown that when using an inoculum of wild-type or M184V virus, BIC+FTC+TAF was better at preventing viral breakthrough and emergent drug resistance than DTG+3TC[3]
    - *In vitro* viral breakthrough experiments should be analyzed comparatively; clinical trials assessing the impact of missed doses of these ARV combinations have not been conducted

Antiviral Pharmacokinetics of Daily Oral Regimens



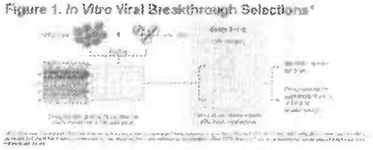
- Missing daily oral ARV doses results in a predictable decrease of systemic exposures to each drug in the regimen based on its established plasma half-life ($t_{1/2}$)

Objectives

- To understand relative time to *in vitro* viral breakthrough and resistance barrier using simulated human drug exposures at either full or suboptimal treatment adherence to BIC+FTC+TAF, DTG+FTC+TAF, DTG+3TC, DTG+RPV and CAB+RPV LA INJ

Methods

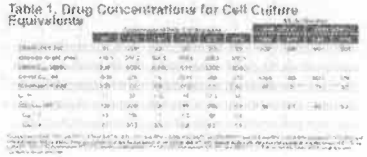
Figure 1. *In Vitro* Viral Breakthrough Selections[4]



- Simulation of drug C_{min} *in vitro*:
  - To simulate clinical C_{min} pharmacokinetic data from participants in clinical trials were used and corrected for human plasma protein binding for BIC, DTG, RPV and CAB
  - For the NRTIs FTC, 3TC, and TAF, intracellular active metabolite considerations were used
- Simulation of missed daily oral doses:
  - To simulate 2 and 4 consecutive missed doses (C_{min} -2 and C_{min} -4, respectively), drug concentrations were adjusted by plasma $t_{1/2}$ for BIC, DTG, and RPV, and by intracellular $t_{1/2}$ for NRTIs (TAF, FTC, and 3TC)
  - C_{min} doses were determined as C_{min}×0.5[5,6]
- Genotypic analyses:
  - Each viral breakthrough supernatant was sequenced by next-generation sequencing (NGS; R Core 4.0; Co.KG, Kaiserslautern, Germany) and mutations were reported if present at ≥2%
    - A bioinformatic filter was used to remove ARTEMIS mediated errors by paired-read sequences
  - Mutations were observed between 2.1% and 99.3% per culture

Results

Table 1. Drug Concentrations for Cell Culture Equivalents

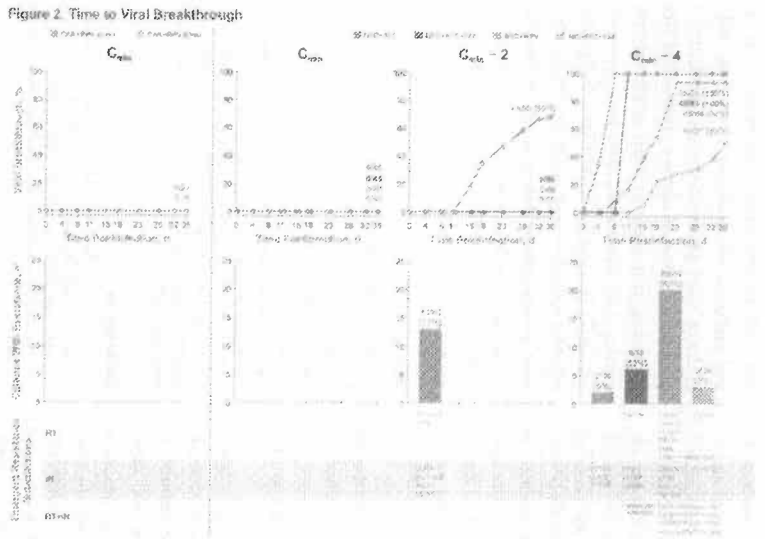


- BIC, DTG, RPV, and CAB concentrations were calculated using their human plasma clinical C_{min} according to their prescribing information and adjusted for human plasma protein binding (Table 1)[5,6]
- TAF C_{min} used the active metabolite TFV-DP at its physiologic concentration in peripheral blood mononuclear cells from TAF-treated individuals[5,6]
- FTC and 3TC concentrations were set at their human plasma-free adjusted C_{min}[5,6]

Table 2. Mechanisms of Forgiveness and Barriers to Resistance for Daily Oral Combinations



Figure 2. Time to Viral Breakthrough



- The LA INJ combination CAB+RPV prevented viral breakthrough at drug C_{min}, monthly and 2-month dosing. Fig 2.

Conclusions

- The INSTI-containing combinations of BIC+FTC+TAF, DTG+FTC+TAF, DTG+3TC, and DTG+RPV had no viral breakthrough with concentrations simulating high adherence
  - Regimen differentiation occurred when multiple missed doses were simulated *in vitro*. BIC+FTC+TAF had the highest forgiveness and barrier to resistance
    - *In vitro* viral breakthrough experiments should be analyzed comparatively; controlled clinical trials assessing the impact of missed doses of these ARV combinations have not been conducted
- The long-acting injectable combination of CAB+RPV had no viral breakthrough at concentrations simulating C_{min} for both monthly and 2-month dosing. Further studies with CAB+RPV are needed to understand forgiveness during the pharmacokinetic tail of this regimen

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수신 서울특별시 종로구 사직로8길 39, 세양빌딩 (내자동) 5층(김.장법률사무소)
양영준 귀하(귀중)

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특 허 청

특허거절결정서

출 원 인 성 명 길리애드 사이언시즈, 인코포레이티드 (특허고객번호: 519990290219)
주 소 미국 캘리포니아 94404 포스터 시티 레이크사이드 드라이브 333
대 리 인 성 명 양영준 외 1 명
주 소 서울특별시 종로구 사직로8길 39, 세양빌딩 (내자동) 5층(김.장법률사무소)

출 원 번 호 10-2020-7025458
발 명 의 명 칭 인간 면역결핍 바이러스의 치료를 위한 치료 조성물

2022.05.20.자 정수된 [명세서등 보정]보정서 및 [거절이유 등 통지에 따른 의견]의견서·답변서·소명서에 의하여 다시 심사한바 2021.12.23.자 거절이유를 해소하지 못하였으므로 이 출원에 대하여 특허법 제62조에 따라 거절결정합니다.

[다시 심사한 결과]

☐ 심사 대상 청구항 : 제1-11항

☐ 이 출원의 거절이유가 해소되지 않은 부분과 관련 법조항

순번	거절이유가 해소되지 않은 부분	관련 법조항
1	청구항 제1항	특허법 제29조제2항

[거절결정의 이유]

1. 이 출원의 청구범위의 청구항 제1항에 기재된 발명은 아래와 같이 그 출원 전에 이 발명이 속하는 기술분야에서 통상의 지식을 가진 사람이 쉽게 발명할 수 있는 것이므로 특허법 제29조제2항에 따라 특허를 받을 수 없습니다.

- 아 래 -

인용발명 1 : 국제공개공보 WO2015/022351(2015.02.19.)
인용발명 2 : 국제공개공보 WO2014/100323(2014.06.26.)
인용발명 3 : J. Acquir. Immune Defic. Syndr., Vol. 67, No. 1, pp52-58 (2014.09.01.)

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※ 기 통지된 거절이유는 청구항 전항의 발명이 인용발명 1 내지 3으로부터 쉽게 발명할 수 있는 것이므로 특허법 제29조제2항의 규정에 의해 특허를 받을 수 없다는 것이었습니다.

(1) 보정사항 및 의견서 내용

1) 보정사항

출원인은 제1항에 보정 전의 '고체 경구 투여 형태의 용도'를 '코팅된 정제'로 변경하였고, 각 성분의 함량을 한정하여 보정하였으며, 이는 식별번호 [0015]를 근거로 한정한 것이므로 적법한 보정입니다.

2) 출원인 주장

출원인은 아래와 같은 이유로 진보성이 인정된다고 주장하고 있습니다.

① 이 출원은 화학식 I의 화합물(빅테그라비르), 테노포비르 알라페나이드 및 엠트리시타빈의 조합에 관한 것이고, 세 가지 유효성분을 모두 포함하는 단일 정제를 제조한 경우 허용 가능한 약동학적 프로파일을 달성하는데 필요한 부형제의 총량을 감소시키면서 제약상 허용되는 고체 경구 투여 형태를 제제화 하는 것이 가능함을 밝혀낸 것에 기술적 특징이 있습니다. 그러나 인용발명 1 내지 3에는 이 출원 제제의 유효성분 조합이 기재되어 있지 않고, '단일 정제'가 병또 투여에 비해 현저히 우수한 효과를 나타낸다는 점을 쉽게 도출해낼 수 없습니다.

② 이 출원의 명세서에는 정제의 우수한 효과가 데이터로 뒷받침되어 있습니다. 정제 F7은 이중층 제제이고, 실시예의 조합으로 정제를 제조하여 환자에 투여시, 음식물에 관계없이 우수한 생체이용률을 나타냅니다.

(2) 의견내용 검토

(보정사항) '용도'를 '정제'로 변경하고 있으나, 결과적으로 청구범위의 구성을 한정한 것으로 보고, 제제에 '코팅'을 부가한 것과 유효성분 함량을 한정한 것을 검토합니다.

'코팅'과 관련하여 제제의 안정성이나 복용의 편의성 등을 고려하여 부가할 수 있는 것이므로 특별한 기술적 특징으로 볼 수 없습니다. 유효성분의 함량과 관련하여 인용발명 1 내지 3에 엠트리시타빈의 용량을 200mg으로 기재하고 있으며, 인용발명 3에는 테노포비르 알라페나이드를 25mg으로 기재하고 있습니다. 또한, 유효성분의 함량을 결정하는 것은 제제를 개발하는 과정에서 필수적으로 고려하는 사항이고, 단순 반복적인 시험을 통해 최적화 가능한 것으로 판단되는 바, 상기 항의 한정사항에 특별한 기술적 특징이 있다고 볼 수 없습니다.

(출원인의 주장) 주장 ①, ②와 관련하여, 기 통지된 의견제출통지서에서 살펴본 바와 같이 인테그라제 저해제인 화학식 I의 화합물은 인용발명 2에 *우수한 항바이러스 효과와 약동력학 성질을 가지는 물질로 개시*된 것이어서(실시예 42, 표 1 내지 4 등 참조) 이 기술분야에서 통상의 지식을 가진 자가 위 화합물을 선택하여 인용발명 1 또는 3에 기재된 인테그라제 저해제에 치환하는 것에 어려움이 없고, 그 용량을 50 mg으로 한정한 것도 반복된 실험을 통하여 적절한 용량을 선택한 것에 불과합니다.

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*항-HIV 활성을 가지는 인테그라제들을 TAF 및 엠트리시타빈과 조합하여 투여하고 이를 단일 용량의 조합을 포함하는 제형으로 제조하는 것은 개발 중인 물질에까지 적용*되었던 정도로 이 출원발명의 우선일 당시 널리 알려진 기술이므로(2014. 10. 14. 공개된 Encyclopedia of AIDS, T. J. Hope et al. eds., Springer Science+Business Media New York. 참조), 인용발명 1 또는 3의 인테그라제 저해제를 인용발명 2의 물질로 치환하는 것에 어려움이 있다고 할 수 없고,

이 출원발명의 설명에 기재된 효과를 살펴볼 때, 조합제제인 이중층 정제 F2는 봉해제 크로스카르멜로스 소듐과 활택제 스테아르산마그네슘을 포함하고, 화학식 I 화합물을 포함하는 대조제제 F1은 크로스포비돈과 소듐 스테아릴푸마레이트를 함유하는데, 부형제의 차이에 따라 화학식 I 화합물의 용해도와 용출에 차이를 나타내는 것을 알 수 있으므로(실시예 5 식별번호 [0547] 및 도 3 참조), 이 출원의 병용 투여에 비하여 체내 노출이 증가된 효과는 그 부형제의 차이에 따라 용출이 증가된 것에 기인한 것이고, 조합 정제로 한 것에 따라 얻어진 효과라고 볼 수 없습니다.

그리고 약물의 함량은 그 효능과 약동력학 성질에 따라 통상의 기술자가 반복된 실험을 통하여 적의 선택하는 것이고, 약물의 용출을 개선하여 약효가 유지되는 범위에서 약물의 용량을 낮추는 것도 통상적인 제제학적 기술에 해당하므로, 제1항의 효과가 인용발명 1 내지 3에 비하여 현저히 우수하다고 할 수 없습니다.

따라서 제1항은 출원인의 주장을 반영하여 검토하더라도 인용발명 1 내지 3에 의해 진보성이 부정됩니다.

(3) 결론

제1항은 지난번 거절이유가 여전히 해소되지 않은 것으로 판단됩니다.

참고사항

※ 보정서의 제2항 내지 제11항은 신설된 청구항이므로 이전 의견제출통지서에서 특허가능 여부를 판단하지 않았으므로 본 거절결정서에 포함하지 않았습니다. 그러나 상기 항들은 일부 화합물의 함량범위를 달리하거나 정제의 형태를 한정하거나, 부가성분을 추가하여 함량을 한정하거나, 약동학 데이터를 한정하여 부가하는 정도이고, 이는 제제개발과정에서 통상적으로 알려진 제조방법을 적용하여 단순 반복적인 시험을 통해 부가성분을 가감하는 등, 특별한 기술적 어려움이 있다고 볼 수 없습니다. 다만, 앞서 살펴본 바와 같이 '이중층 정제' 의 경우 대조제제와의 부형제의 차이에 따라 용해도와 용출에 차이가 있음을 실험적으로 확인한 것으로 판단됩니다. 끝.

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2022.08.17.

특허청 화학생명기술심사국

약품화학심사과 심사관 곽희찬 곽희찬

<< 재심사 청구, 거절결정 불복심판 청구 및 분할출원 안내 >>

1. 출원인은 이 거절결정서를 송달받은 날부터 3개월 이내(심판 청구기간)에 보정을 하여 특허청(출원과)에 재심사를 청구하거나 특허심판원에 거절결정불복심판 청구서를 제출하여 보정 없이 심판을 청구할 수 있습니다. 또한, 심판 청구기간(재심사 청구 이후는 제외)에는 분할출원도 할 수 있습니다. 재심사 청구 시에는 특허법 제47조제2항 및 제3항에 따른 범위 내에서 보정할 수 있습니다.

2. 심판 청구기간(재심사 청구기간)은 특허법 제15조제1항에 따라 연장할 수 있습니다. 심판 청구기간을 연장하려는 경우에는 심판 청구기간 만료 전까지 법정기간 연장신청서(특허법 시행규칙 별지 제10호서식)를 특허청장에게 제출해 주시기 바랍니다.

3. 명세서 등의 보정은 반드시 특허법 시행규칙 별지 제8호서식을 이용해야 합니다:
(재심사 청구 시 반드시 '재심사청구 란'에 체크하시기 바랍니다.)

※ 위에서 안내한 후속 절차 또는 신청 서식 등에 관한 사항은 특허고객상담센터 ☎1544-8080로, 이 통지서 내용에 대한 사항은 특허청 ☎042-481-3327(담당심사관 곽희찬)로 문의하시기 바랍니다.

※ 특허로(www.patent.go.kr) 또는 특허청(www.kipo.go.kr) 홈페이지를 방문하시면 심사 진행상황, 서류제출 및 절차에 관한 보다 많은 정보를 제공받을 수 있습니다.
(특허청) 우 35208 대전광역시 서구 청사로 189, 4동 (둔산동, 정부대전청사)

KIPO's Notice of Final Rejection (Translation)

The present application has been re-examined based on the response (the response to a preliminary rejection, etc.) and the amendment (the amendment to the specification, etc.) filed on May 20, 2022. However, the Preliminary Rejection dated December 23, 2021 has not been overcome. Thus, this Final Rejection is being issued pursuant to Article 62 of the Korean Patent Act.

[Result of Examination]

- Examined Claims: Claims 1-11
- Rejected Portions and Relevant Provisions

No.	Rejected Portions	Relevant Provisions
1	Claim 1	Article 29(2) of the Korean Patent Act

[Examiner's Grounds for Final Rejection]

1. The present application cannot be allowed under Article 29(2) of the Korean Patent Act because Claim 1 lacks inventiveness, as set forth below.

Cited Reference 1: WO 2015/022351 (February 19, 2015)
Cited Reference 2: WO 2014/100323 (June 26, 2014)
Cited Reference 3: J. *Acquir. Immune Defic. Syndr.*, Vol. 67, No. 1, pp52-58 (September 1, 2014)

※ The previous rejection ground is that the present application cannot be allowed under Article 29(2) of the Korean Patent Act because all the claims lack inventiveness over Cited References 1 to 3.

(1) Summary of the amendment and the response

1) Amendments

The applicant amended the 'use of a solid oral dosage form' of **Claim 1** before amendment to 'a coated tablet' and limited the amount of each ingredient based on paragraph [0015]. Thus, these amendments are legitimate.

2) Applicant's arguments

The applicant argues that the present invention has inventiveness on the following grounds:
① The present invention relates to a combination of a compound of Formula I (bictegravir), tenofovir alafenamide, and emtricitabine, and is technically characterized by discovering that in the case where a single tablet comprising all the three active ingredients is produced, it is possible to formulate a solid oral dosage form that is pharmaceutically acceptable while reducing the total amount of excipients necessary to achieve an acceptable pharmacokinetic profile. However, Cited References 1 to 3 do not disclose a combination of the active ingredients that the claimed formulation comprises. Further, it cannot be easily conceived therefrom that 'a single tablet' exhibits remarkably superior effects compared to separate administration.
② The specification of the present invention provides data supporting the superior effects of the tablet. Tablet F7 is a bilayer formulation and the tablet made of the combination described in the example and administered to patients exhibits superior bioavailability regardless of food.

(2) **Review of the arguments**

(**Amendments**) The word 'use' has been amended to 'tablet.' However, this amendment is considered to have consequently limited the claimed feature. Accordingly, the addition of the characteristic of being 'coated' to the formulation and the limitation on the amounts of the active ingredients will be reviewed.
In relation to the characteristic of being 'coated,' it is not considered as a special technical characteristic because it can be added in consideration of the stability of the formulation, dosing convenience, etc. In relation to the amounts of the active ingredients, Cited References 1 to 3 disclose 200 mg emtricitabine, and Cited Reference 3 discloses 25 mg tenofovir alafenamide. In the course of developing a formulation, determining the amounts of active ingredients is essentially considered and can be optimized through simple and repetitive tests. Thus, it is not considered that the limitations of said claim have any special technical characteristic.

(**Applicant's arguments**) In relation to Arguments ① and ②, as mentioned in the previous Notice of Preliminary Rejection, a compound of Formula I which is an integrase inhibitor is disclosed in Cited Reference 2 as *a substance that has superior antiviral effects and pharmacokinetic properties* (*see* Example 42, Tables 1-4, etc.). Accordingly, a person of ordinary skill in the art would have had no difficulty in selecting this compound and substituting it with an integrase inhibitor disclosed in Cited Reference 1 or 3. With respect to its limited amount of 50 mg, an appropriate amount can be selected through repetitive experiments.

It was widely known as of the priority date of the present application that *integrases having anti-HIV activity can be administered in combination with TAF and emtricitabine and the preparation of formulations comprising combinations of single doses thereof can be applied even to the materials under development* (*see*

Encyclopedia of AIDS, T. J. Hope et al. eds., Springer Science+Business Media New York, published on October 14, 2014). Accordingly, there would have been no difficulty in replacing the integrase inhibitor of Cited Reference 1 or 3 with the material of Cited Reference 2.

Upon reviewing the effects described in the present specification, bilayer tablet F2 which is a combined formulation includes croscarmellose sodium as a disintegrant and magnesium stearate as a glidant, while control formulation F1 comprising a compound of Formula I includes crospovidone and sodium stearyl fumarate. It can be known that the solubility and elution of a compound of Formula I vary depending on the excipients (*see* Example 5, paragraph [0547], and Fig. 3). Given the above, the effect of increased *in vivo* exposure of the present invention compared to that of co-administration resulted from increased elution due to different excipients, not from the combined tablet.

Further, the dose of a drug could have been appropriately selected by a person of ordinary skill in the art through repetitive experiments according to the efficacy and pharmacokinetic properties of the drug, and reducing the dose of the drug within a range where the elution of the drug can be improved and the pharmacological efficacy can be maintained corresponds to a conventional formulation technique. Accordingly, it is not considered that Claim 1 has remarkably excellent effects compared to Cited References 1 to 3.

Thus, despite the applicant's arguments, **Claim 1** lacks inventiveness over Cited References 1 to 3.

(3) **Conclusion**

Claim 1 has not yet overcome the previous rejection ground.

Examiner's Remarks

※ **Claims 2-11** newly added by the amendment are not included in the rejected claims because their patentability has not been assessed in the previous Notice of Preliminary Rejection. However, said claims merely describe different amount ranges of some compounds, limit the form of the tablet, further comprise additional ingredients and limit their amounts, or limit pharmacokinetic data. It is not considered that there would be any special technical difficulty in adding or subtracting additional ingredients through simple and repetitive tests by applying a conventional preparation process in the course of developing a formulation. It was experimentally identified, as mentioned above, that the 'bilayer tablet' exhibits different solubility and elution from the control formulation depending on different excipients.

[==== End of Translation ====]

발송번호: 9-5-2023-010076805
발송일자: 2023.01.31.
제출기일: 2023.03.31.

수신 서울특별시 종로구 사직로8길 39, 세양빌딩 (내자동) 5층(김.장법률사무소)
양영준 귀하(귀중)

03170

최후통지

특 허 청

의견제출통지서

출원인	성명	길리애드 사이언시즈, 인코포레이티드
	주소	미국 캘리포니아 94404 포스터 시티 레이크사이드 드라이브 333
대리인	성명	양영준 외 1명
	주소	서울특별시 종로구 사직로8길 39, 세양빌딩 (내자동) 5층(김.장법률사무소)
발명자	성명	홍, 레이
	주소	미국 94404 캘리포니아주 포스터 시티 레이크사이드 드라이브 333 길리애드 사이언시즈, 인코포레이티드 내
발명자	성명	콜맨, 벤자민, 미카
	주소	미국 94404 캘리포니아주 포스터 시티 레이크사이드 드라이브 333 길리애드 사이언시즈, 인코포레이티드 내
발명자	성명	코지아리, 조안나 엠.
	주소	미국 94404 캘리포니아주 포스터 시티 레이크사이드 드라이브 333 길리애드 사이언시즈, 인코포레이티드 내
출원번호		10-2020-7025458
출원일자		2020.09.03.
발명의 명칭		인간 면역결핍 바이러스의 치료를 위한 치료 조성물

1. 이 출원에 대한 심사결과 특허법 제47조제1항제1호에 따른 보정에 의하여 발생한 아래와 같은 거절이유가 있어 특허법 제63조에 따라 이를 통지하오니 의견이 있거나 보정이 필요한 경우에는 상기 제출기일(2023.03.31.)까지 의견(답변, 소명)서[특허법시행규칙 별지 제24호서식] 또는/및 보정서[특허법시행규칙 별지 제9호서식]를 제출하여 주시기 바랍니다.

2. 상기 제출기일(2023.03.31.)을 연장하려는 경우에는 지정기간연장신청을 통해 그 제출기일을 4개월까지 연장할 수 있습니다. 이 경우 연장신청은 1개월 단위로 해야 하며, 필요 시 4개월을 초과하지 않는 범위에서 2개월 이상을 일괄하여 연장신청할 수 있습니다. 불가피한 사유의 발생(하단의 안내참조)으로 4개월을 초과하여 지정기간을 연장 받고자 하는 때에는 그 사유를 기재한 소명서를 추가로 첨부해서 연장신청을 해야 합니다.

[심사결과]

☐ 심사 대상 청구항 : 제1, 2, 3, 4, 5, 6, 7, 8, 9, 10항

☐ 이 출원의 거절이유가 있는 부분과 관련 법조항

순번	거절이유가 있는 부분	관련 법조항
1	청구항 제1항, 제3항, 제7항, 제8항, 제9항	특허법 제29조제2항

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2	청구항 제3항, 제5항	특허법 제42조제4항제2호

□ 특허 가능한 청구항 : 제2, 4, 6, 10항

※ 위 특허 가능한 청구항은 의견제출통지시점에서의 심사의견이며 추후 변경될 수 있습니다. 이 출원이 특허결정을 받기 위해서는 이 출원에 대해 지적된 거절이유가 모두 해소되어야 합니다.

[구체적인 거절이유]

1. 이 출원의 청구범위의 청구항 제1항, 제3항, 제7항, 제8항, 제9항에 기재된 발명은 아래와 같이 그 출원 전에 이 발명이 속하는 기술분야에서 통상의 지식을 가진 사람이 쉽게 발명할 수 있는 것이므로 특허법 제29조제2항에 따라 특허를 받을 수 없습니다.

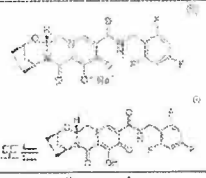
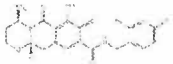
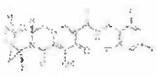
- 아 래 -

※ 보정하면서 '제2항 내지 제11항'을 신설하였고, 재심사를 청구하면서 보정 전의 '제1항'은 삭제하고, 보정 전의 '제2항 내지 제11항'을 '제1항 내지 제10항'으로 항정리하여 청구한 것이므로, 거절이유가 통지되지 않았던 항들(제1항 내지 제10항)에 대하여 본 의견제출통지서의 거절이유에 포함하였습니다.

인용발명 1 : 국제공개공보 WO2015/022351(2015.02.19.)
인용발명 2 : 국제공개공보 WO2014/100323(2014.06.26.)
인용발명 3 : J. Acquir. Immune Defic. Syndr., Vol. 67, No. 1, pp52-58 (2014.09.01.)

1-1. 제1항은 '52 mg의 화학식 II의 화합물; 28 mg의 테노포비르 알라페나미드 헤미푸마레이트, 및 200 mg의 엠트리시타빈 또는 그의 제약상 허용되는 염을 포함하는 정제'이고, 제3항은 '(A) 6.5 내지 11.0 % w/w의 화학식 I의 화합물 또는 그의 제약상 허용되는 염; 3.0 내지 4.5 % w/w의 테노포비르 알라페나미드 또는 그의 제약상 허용되는 염, 및 25 내지 30 % w/w의 엠트리시타빈 또는 그의 제약상 허용되는 염(이때 중량 백분율은 전체 정제의 비율을 표시하는 것임); 또는 (B) 7.0 내지 11.0 % w/w의 화학식 II의 화합물; 3.5 내지 4.1 % w/w의 테노포비르 알라페나미드 헤미푸마레이트, 및 25 내지 30 % w/w의 엠트리시타빈, (이때 중량 백분율은 전체 정제의 비율을 표시하는 것임)을 포함하는 정제'입니다.

제1항, 제3항을 인용발명 1 내지 3과 대비하면 다음과 같습니다.

구분	제1항, 제3항	인용발명 1	인용발명 2	인용발명 3
활성성분	 또는	 (둘루테그라비르)	 화합물 42	엘비테그라비르
	테노포비르 알라페나미드	테노포비르 디소프록실	(-)	테노포비르 알라페나미드

	헤미푸마레이트	푸마레이트		푸마레이트
	엠트리시타빈	엠트리시타빈	(-)	엠트리시타빈
제형	정제	정제	(-)	정제

먼저, 제1항, 제3항을 인용발명 1과 대비하면, 인테그라아제 억제 활성을 가지는 HIV 억제용 물질, 테노포비르의 전구체 및 엠트리시타빈을 함유하는 제형인 점이 동일합니다.
다만, 상기 항들은 인테그라아제 억제 활성 물질이 화학식 I의 화합물 또는 화학식 II의 화합물인 점 및 테노포비르 전구체로 테노포비르 알라페니아미드 헤미푸마레이트를 사용하는 점에서 인용발명 1과 차이가 있고, 각 구성성분들의 함량이나 함량비를 한정한 점에서 차이가 있습니다.

그런데, 인용발명 2에 화학식 I의 화합물이 인테그라아제 억제 물질로 개시되어(화합물 42 참조) 있어 살펴보면, 위 물질이 우수한 HIV 억제 활성, 낮은 세포독성, 양호한 생체 이용률 등 의약품 개발에 적절한 성질을 가지는 물질이라는 것을 알 수 있으므로(표 1 내지 4 등 참조), 이 기술분야에서 통상의 지식을 가진 자(이하 '통상의 기술자'라 함)가 화학식 I 화합물을 선택하여 인용발명 1의 돌루테그라비르를 치환하는 것에 어려움이 없다고 판단됩니다.
또한, 인용발명 3에도 인테그라아제 억제 물질인 엘비테그라비르, 테노포비르 전구체 및 엠트리시타빈을 함유하는 정제가 개시되어 있는데, 그 정제는 테노포비르 디소프록실 푸마레이트에 비하여 안전하고 효과적인 테노포비르 알라페나미드 푸마레이트(TAF)를 포함하고 있고, 흡수촉진제인 코비시스타트가 부가될 때 10 mg의 TAF는 25mg의 TAF와 동등하다고 기재되어 있으므로(제53면, 최측열 단락 2 내지 4 참조), 통상의 기술자가 인용발명 1의 테노포비르 디소프록실 푸마레이트를 TAF로 쉽게 치환할 수 있습니다.
또한, 각 구성성분의 함량을 한정한 것은 약리효과 또는 제제를 개발하는 과정에서 단순 반복적인 시험을 통해 최적화 가능한 것이므로, 이와같은 구성에 특별한 기술적 어려움이 있다고 볼 수 없습니다.

그리고 제1항, 제3항의 효과를 살펴보아도, 발명의 설명으로부터 세 종류의 약물을 단일 정제로 제조할 수 있다는 것을 알 수 있을 뿐이고, 통상의 기술자가 인용발명 1 내지 3으로부터 예측하기 어려운 현저히 우수한 항-HIV 효과 등을 나타낸다고 인정할 근거가 없습니다.

제7항 내지 제9항은 상기 항들과 동일한 유효성분을 포함하며, 일부 부가성분을 추가하거나, 약동학 데이터를 추가하는 것으로 한정하고 있으나, 이와같은 구성은 제제를 개발하는 과정에서 통상적으로 고려하는 것이므로 특별한 구성의 어려움이 없고, 이와같이 한정하여 현저한 효과가 있다고 인정할만한 근거도 없습니다.

따라서 **제1항, 제3항, 제7항 내지 제9항**은 통상의 기술자가 인용발명 **1** 내지 **3**으로부터 쉽게 발명할 수 있는 것입니다.

2. 이 출원은 청구범위의 청구항 제3항, 제5항의 기재가 아래에 지적한 바와 같이 불비하여 특허법 제42조제4항제2호에 따른 요건을 충족하지 못하므로 특허를 받을 수 없습니다.

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- 아 래 -

제3항은 '(이때 중량 백분율은 전체 정제의 비율을 표시한 것임)'과 같이 괄호를 기재하고 있습니다. 그러나 괄호 안의 구성이 포함되는 것인지 포함되지 않는 것인지 명확하지 않습니다. 따라서 상기 항 및 이를 인용하는 제5항은 발명이 보호받고자 하는 사항을 명확하고 간결하게 기재하지 않은 것입니다.

[첨 부]
첨부1 국제공개공보 WO2015/022351(2015.02.19.) 1부.
첨부2 국제공개공보 WO2014/100323(2014.06.26.) 1부.
첨부3 J. Acquir. Immune Defic. Syndr., Vol. 67, No. 1, pp52-58 (2014.09.01.) 1부.
끝.

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2023.01.31.

특허청 화학생명기술심사국

약품화학심사과 심사관 곽희찬 곽희찬

<< 안내 >>

1. 지정기간연장 안내 : 연장가능기간(4개월)을 초과하여 지정기간을 연장하고자 소명서를 첨부하여 지정기간연장신청서를 제출한 경우 심사관은 아래의 사유에 해당되는지를 판단하여 지정기간연장의 승인 여부 및 연장할 수 있는 기간을 정하여 통지합니다.

【4개월을 초과하여 지정기간연장을 할 수 있는 사유】

① 기간만료 전 1개월 이내에 최초로 대리인을 선임하거나 선임된 대리인 모두를 해임·변경한 경우

② 기간만료 전 1개월 이내에 출원인변경신고서를 제출한 경우(다만, 새로운 출원인이 추가된 경우에 한함)

③ 기간만료 전 2개월 이내에 외국특허청의 심사결과를 받은 후 이를 기간연장신청서와 함께 제출한 경우

④ 의견제출통지서의 송달이 1개월 이상 지연된 경우

⑤ 원출원 또는 후출원이 심판이나 소송에 계류 중인 경우(다만, 분리출원에 관한 기간연장인 경우에는 불승인)

⑥ 거절이유와 관련된 시험 및 결과측정에 기간이 더 필요한 경우

⑦ 기타 불가피하게 기간연장이 필요하다고 인정되는 경우

단, 제3자가 심사청구한 때에는 ①~⑥의 경우라도 불승인

※ 위에서 안내한 후속 절차 또는 신청 서식 등에 관한 사항은 특허고객상담센터 ☎1544-8080로, 이 통지서 내용에 대한 사항은 특허청 약품화학심사과 ☎042-481-5490(대표번호)로 문의하시기 바랍니다.

※ 특허로(www.patent.go.kr) 또는 특허청(www.kipo.go.kr) 홈페이지를 방문하시면 심사 진행상황, 서류 제출 및 열지에 관한 보다 많은 정보를 제공받을 수 있습니다.

(특허청) 우 35208 대전광역시 서구 청사로 189, 4동 (둔산동, 정부대전청사)

KIPO'S NOTICE OF PRELIMINARY REJECTION (ENGLISH TRANSLATION)

RESULTS OF KIPO EXAMINATION – SUMMARY

- Examined Claims: Claims 1-10
- Rejected Portions and Relevant Provisions

No.	Rejected Portions	Relevant Provisions - Grounds
1	Claims 1, 3, 7, 8, and 9	Article 29(2) – Inventiveness
2	Claims 3 and 5	Article 42(4)(ii) – Clarity

- Allowable Claims: Claims 2, 4, 6, and 10

* **NOTE:** The allowable claims above are based on the examination results rendered as of the date of this Notice. Another Notice of Preliminary Rejection may be issued later if new grounds of rejection are found. In addition, for the present application to be allowed, all the rejections outlined below must be overcome.

EXAMINER'S DETAILED GROUNDS FOR REJECTION

1. The present application cannot be allowed under Article 29(2) of the Korean Patent Act because Claims 1, 3, 7, 8, and 9 lack inventiveness, as set forth below.

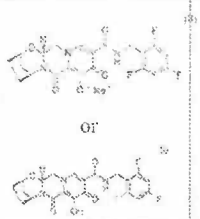
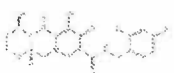
※ By filing an amendment, 'Claims 2-11' were newly added. Thereafter, upon filing a request for reconsideration, 'Claim 1' before amendment was deleted and 'Claims 2-11' before amendment were renumbered as 'Claims 1-10.' The claims (Claims 1-10) which have never been previously rejected are discussed in the rejection grounds of the present Notice of Preliminary Rejection.

Cited Reference 1: WO 2015/022351 (February 19, 2015)
Cited Reference 2: WO 2014/100323 (June 26, 2014)
Cited Reference 3: *J. Acquir. Immune Defic. Syndr.*, Vol. 67, No. 1, pp 52-58 (September 1, 2014)

1-1. **Claim 1** is directed to 'a tablet comprising 52 mg of the compound of Formula II, 28 mg tenofovir alafenamide hemifumarate, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof,' and **Claim 3** is directed to 'a tablet comprising (A) from 6.5-11.0 % w/w of the compound of Formula I or a pharmaceutically acceptable salt thereof, 3.0-4.5 % w/w tenofovir alafenamide or a

pharmaceutically acceptable salt thereof, and 25-30 % w/w emtricitabine or a pharmaceutically acceptable salt thereof, where the weight percentages denote a proportion of the whole tablet; or (B) from 7.0-11.0 % w/w of the compound of Formula II, 3.5-4.1 % w/w tenofovir alafenamide hemifumarate, and 25-30 % w/w emtricitabine, where the weight percentages denote a proportion of the whole tablet.'

Claims 1 and 3 can be compared with Cited References 1-3 as shown in the table below.

	Claims 1 and 3	Cited Reference 1	Cited Reference 2	Cited Reference 3
Active ingredients	 or	 (dolutegravir)	 Compound 42	Elvitegravir
	tenofovir alafenamide hemifumarate	tenofovir disoproxil fumarate	(-)	tenofovir alafenamide fumarate
	emtricitabine	emtricitabine	(-)	emtricitabine
Formulation	Tablet	Tablet	(-)	Tablet

First, upon comparison, Claims 1 and 3 are identical to Cited Reference 1 in that they relate to a formulation containing an HIV inhibitor having an integrase inhibitory activity, a tenofovir precursor, and emtricitabine.
Said claims are different from Cited Reference 1 in using a compound of Formula I or Formula II as an integrase inhibitory activity material and tenofovir alafenamide hemifumarate as a tenofovir precursor and in limiting the content or content ratio of the respective components.

However, Cited Reference 2 discloses a compound of Formula I as an integrase inhibitor (*see* Compound 42) and teaches that the inhibitor has properties suitable for drug development, such as excellent HIV inhibitory activity, low cytotoxicity, good bioavailability, and the like (*see* Tables 1-4, etc.). Accordingly, a person of ordinary skill in the art would not have had any difficulty in selecting a compound of Formula I and substituting the dolutegravir of Cited Reference 1 therewith.
Cited Reference 3 also discloses a tablet containing elvitegravir as an integrase inhibitor, a tenofovir precursor, and emtricitabine, and describes that the tablet comprises tenofovir alafenamide fumarate (TAF) which is more safe and effective than tenofovir disoproxil fumarate and 10 mg TAF in the presence of cobicistat which boosts absorption is equivalent to 25 mg TAF (*see* p.53, left column, paragraphs 2-4). Accordingly, a person of ordinary skill in the art could have easily

substituted the tenofovir disoproxil fumarate of Cited Reference 1 with 25 mg TAF. With regard to the limitation on the content of the respective components, since it is possible to optimize a content through simple and repetitive tests during the development of a pharmacological effect or a formulation, it is not considered that such a feature has any special technical difficulty.

Upon review of the effects of Claims 1 and 3, it can only be known from the specification that three types of drugs can be formulated into a single tablet, and there is no ground supporting that the tablet exhibits a remarkably excellent anti-HIV effect and the like that a person of ordinary skill in the art could not predict from Cited References 1 to 3.

Claims 7-9 comprise the same active ingredients as said claims and further comprise some additional ingredients or add pharmacodynamic data. However, since these features are generally considered during the development of a formulation, said claims do not have any particular constitutional difficulty. Further, there is no ground supporting that such limitations result in remarkable effects.

Thus, **Claims 1, 3, and 7-9** could have been easily conceived by a person of ordinary skill in the art in view of Cited References 1 to 3.

2. The present application cannot be allowed because Claims 3 and 5 fail to meet the requirements under Article 42(4)(ii) of the Korean Patent Act, as set forth below.

Claim 3 describes '(where the weight percentages denote a proportion of the whole tablet)' using parentheses. However, it is unclear whether the claim comprises the feature in the parentheses or not. Thus, said claim and **Claim 5** referring to said claim do not describe the subject matter to be protected by the invention clearly and concisely.

[Documents Annexed]

1. WO 2015/022351 (February 19, 2015)
2. WO 2014/100323 (June 26, 2014)
3. *J. Acquir. Immune Defic. Syndr.*, Vol. 67, No. 1, pp 52-58 (September 1, 2014)

[=== End of Translation ===]

LEDERER & KELLER
Patentanwälte Partnerschaft mbB
European Patent Attorneys

DR. GÜNTER KELLER
Dipl.-Biol.
DR. MICHAEL BEST
Dipl.-Chem.
DR. STEPHAN TEIPEL
Dipl.-Chem.
DR. GEORG KALHAMMER
Dipl.-Biochem.
DR. JÖRG-THOMAS BINDER
Dipl.-Chem.
DOTT. MARCO FACHINI
Laurea in Chimica
DR. JOHANNES STEINBAUER
M.Sc. Chem.

80538 MÜNCHEN
Unsöldstraße 2
Telefon +49 89 21 23 99 0
Telefax +49 89 21 23 99 22
E-Mail info@lederer-keller.de

European Patent Office

80298 Munich

Your reference	Our reference	25 August 2022
	ESP00476TEV	MF

Re.: European Patent No. 3 346 995
European Patent Application No. 16798063.0
Patentee: Gilead Sciences, Inc.
Opponent: Teva Pharmaceutical Industries Ltd. (opponent 1)

In response to the preliminary opinion of the Opposition Division dated 24th June 2021 and in preparation to the oral proceedings scheduled for 27th-28th October 2022:

1. Oral proceedings

We will speak English at the oral proceedings and kindly request simultaneous interpretation if French is spoken.

2. Cited documents

1.1 The following new documents are referred to hereinafter:

D43: Lozano, A.B. *et al.*, *Antivir. Res.* **2020**, 179, 104717;

D44: Chamberlain, N. *et al.*, *Open Forum Infect. Dis.* **2021**, 8(6).

1.2 The patentee filed with their latest petition dated 24th January 2022 documents D41 and D42 and argued for the first time that bictegravir has an improved resistance profile and higher forgiveness and barrier to resistance compared to dolutegravir.

1.3 We note that the patentee did not explain why they did not file these documents with their reply to the opposition,[1] nor why they should be admitted to the proceedings.

1.4 In the event that D41 and D42 are admitted to the proceedings, we are filing D43 and D44 as a direct reaction to their filing.

2. Added subject matter

2.1 We agree with the preliminary opinion of the Opposition Division that claim 1 of the main request does not fulfil the requirements of Article 123(2) EPC.

2.2 We also concur with the co-opponents that claim 6 of the main request does not meet the requirements of Article 123(2) EPC, since original paragraph [0126], on which the patentee relies as basis, only refers to emtricitabine free base, while claim 6 encompasses also the pharmaceutically acceptable salts thereof.

3. Lack of priority

3..1 We agree with the preliminary opinion of the Opposition Division that considerations similar to those made under Article 123(2) EPC apply to the priority entitlement. Therefore, the main request is not entitled to the first priority date of 9th November 2015. For this reason, documents D1, D2, D11, D13, D31 and D32 belong to the state of the art according to Article 54(2) EPC.

3.2 We also note that the first priority document is substantially shorter than the application as filed. Notably, the first priority document does not contain in paragraph [0007] a sentence corresponding to the one in paragraph [0008] on which the patentee heavily relies as basis for amendments (*"In certain embodiments, the dosage form comprises 50 mg of the compound of*

[1] We note for completeness' sake that also the reply of the oppositions was filed late, i.e., on 11.01.2021. The time limit under Rule 79(1) and its 2 month extension under Rule 132 EPC expired already on 29.12.2020 (including the 10 day period under Rule 126(2) EPC).

Formula I or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine").

3.3 Moreover, the first priority document does not contain paragraphs equivalent to paragraphs [0077], [0085], [0090], [0098] and [0103] to [0111] of the international application, which were also cited by the patentee as basis for amendments.

3.4 In conclusion, arguments in relation to added matter and priority entitlement are linked with each other, but this link is not reciprocal. A finding of lack of compliance with Article 123(2) has the necessary consequence that the claimed subject matter is not entitled to priority. However, should the Opposition Division deviate from their preliminary opinion and consider that the claimed subject matter meets the requirements of Article 123(2) EPC, the analysis of the priority entitlement should be repeated considering the above-mentioned differences.

3. Lack of novelty

3.1 Lack of novelty over D1 or D2

3.1.1 We concur with the co-opponents that the subject matter of at least claims 1 and 2 lacks novelty over either prior right D1 or D2, irrespective of the validity of the priority claim. As the arguments are substantially the same irrespective of the choice of the document, we will refer in the following only to D1.

3.1.2 We disagree with the preliminary opinion of the Opposition Division that none of D1 and D2 describes a specific tablet as that depicted in granted claim 1. We note that no reasoning is provided for this finding in the preliminary opinion.

3.1.3 Indeed, we cannot follow the argument of the patentee that combinations selected from different ranges of options are needed to arrive at the claimed subject matter. There cannot be doubts that bictegravir sodium is the most preferred compound of D1 (see, e.g., claim 1) and a tablet is the most preferred pharmaceutical composition of D1 (see, e.g., claim 21). The dosages of 25 mg tenofovir alafenamide (as fumarate, hemifumarate, or free base) and 200 mg emtricitabine are disclosed in combination with each other and a dosage of 50-500 mg of a compound of Formula II (bictegravir being the most preferred one) in paragraph [0096] of D1. The disclosure of the range 50-500 mg amounts to a specific disclosure of its endpoints.

Therefore, D1 discloses a tablet comprising 50 mg of bictegravir sodium, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine.

3.1.4 Hence, at least claims 1 and 2 of the main request lack novelty over D1 and D2 and thus do not meet the requirements of Article 54(2) EPC (if priority is invalid) or 54(3) EPC (if priority is valid).

3.2 Lack of novelty over D31 if the priority claim is invalid

3.2.1 Document D31 was published on 19th November 2015 and thus belongs to the state of the art for subject matter not entitled to the first priority date of 9th November 2015. It discloses the protocol of a phase 3 clinical trial on the safety and efficacy in the treatment of HIV infection of a fixed dose combination GS-9883 / emtricitabine / tenofovir alafenamide compared to the treatment with dolutegravir and emtricitabine / tenofovir alafenamide (D31, sections A.3 and A.3.1). The tested fixed dose combination is a film-coated tablet containing 50 mg GS-9883, 200 mg emtricitabine and 25 mg tenofovir alafenamide (D32, sections D.3.4, D.3.8, D.3.10.1 and D.3.10.3). D31 does not expiicitly disclose that the lab-code GS-9883 corresponds to bictegravir.

3.2.2 Document D32 was published on 24th February 2016, i.e., after the first priority date, but before the second priority date of 26th September 2016. D32 is a statement of the non-proprietary name bictegravir adopted by the USAN council. The United States Adopted Names (USAN) Council is responsible for selecting simple, informative and unique non-proprietary (generic) drug names. This document thus represents the general knowledge of the person skilled in the art.

3.2.3 The skilled person reading D31 immediately understands that the lab-code GS-9883 corresponds to bictegravir. This feature is thus implicitly disclosed in D31. Therefore, D31 discloses a film-coated tablet comprising 50 mg of bictegravir, 25 mg tenofovir alafenamide and 200 mg emtricitabine.

3.2.4 Hence, claim 1 of the main request lacks novelty over D31.

4. Lack of inventive step

4.1 The closest prior art for subject matter not entitled to priority

4.1.1 Should the Opposition Division consider that the identity of the lab-code GS-9883 is not even implicitly disclosed in D31, we agree with opponent 3 and the Opposition Division that document D31 qualifies as the closest prior art for subject matter not entitled to priority. We note that this is not contested by the patentee (see their letter of 24th January 2022, page 11).

4.1.2 The only difference between D31 and the claimed subject matter is therefore the identification of GS-9883 as bictegravir. This is easily done by consulting the USAN dictionary D32, which is a triviality for the skilled person.

4.1.3 Hence, claim 1 of the main request does not involve an inventive step over D31 in light of the common general knowledge (as evidenced by D32) and thus does not meet the requirements of Article 56 EPC.

4.1 The closest prior art for subject matter entitled to priority

4.1.1 All opponents and the Opposition Division agree that document D5, and in particular the embodiment bridging pages 19-20, represent the closest prior art for subject matter entitled to priority.

4.1.2 We note that the patentee dropped in their latest submission the position that D37 is the closest prior art instead, after having been made aware that D37 only discloses the lab-code GS-9883, whose identity was unknown before the first priority date. Should the patentee put forward yet another document as closest prior art, we note the following.

4.1.3 The patentee argued that the skilled person would not have started from the chosen embodiment, because the doses of emtricitabine and dolutegravir are not in line with the claims. First of all, the patentee disregards the fact that this embodiment of D5 has the most technical features in common with claim 1 of the main request.

4.1.4 Moreover, the skilled person would have considered this embodiment as a realistic starting point based on their general knowledge. As evidenced by guidelines D7, the combination of dolutegravir, tenofovir and emtricitabine was among the recommended combinations for the treatment of HIV (D7, page 4, table 5.1). Therefore, contrary to the

allegations of the patentee, it is immaterial that D5 does not disclose the efficacy of the triple combination, since this belonged already to the common general knowledge at the relevant date.

4.1.5 Moreover, also the standard doses of emtricitabine and dolutegravir belonged to the common general knowledge. Medical dictionary D8 shows on the bottom of page 557, right-hand column, that the standard dosage of dolutegravir is 50 mg once daily. It also shows on the middle of page 566, left-hand column, that the standard dosage of emtricitabine is 200 mg.

4.1.6 The skilled person reads the disclosure of a document with their general knowledge in mind. They would have thus considered the embodiment bridging pages 19-20 of D5, disclosing the standard dosages of dolutegravir and emtricitabine, as a very realistic and promising springboard for the development of the claimed fixed-dose combination. Hence, this embodiment of D5 constitutes the closest prior art.

4.2 The objective technical problem

4.2.1 As already explained, the distinguishing feature between D5 and the subject matter of claim 1 is the use of 50 mg bictegravir instead of 50 mg dolutegravir.

4.2.2 There are no data in the opposed patent comparing the claimed tablet with a tablet comprising 50 mg dolutegravir, 25 mg tenofovir alafenamide and 200 mg emtricitabine. Therefore, no technical effect is connected with the distinguishing feature.

4.2.3 The objective technical problem is therefore the provision of an alternative tablet for treating HIV.

4.2.4 In the hope of formulating a more ambitious problem, the patentee relied for the first time in their letter of 24th January 2022 on post-published evidence D41 and D42. Based on D41, the patentee argued that bictegravir has an improved resistance profile compared to dolutegravir. Based on D42, they argued that the combination of bictegravir, emtricitabine and tenofovir alafenamide has a higher forgiveness and barrier to resistance than the analogous combination with dolutegravir.

4.2.5 However, it is not permissible to take into consideration the results of D41 and D42 for the reformulation of the objective technical problem. There is not even a single hint in the original application that bictegravir can have better resistance against mutations or a higher

forgiveness for missed doses compared to dolutegravir. This is not surprising, considering that the opposed patent is a classical formulation patent and not a medical use patent. As a matter of fact, all examples relate to formulation studies and not to clinical trials.

4.2.6 Therefore, proof of the effect on which the patentee relies rests exclusively on post-published evidence. As we are all aware, the evaluation of the plausibility of a claimed technical effect is the object of the pending referral to the Enlarged Board of Appeal G 2/21. The present case is however independent from the outcome of this referral, since the post-published data of D41 and D42 cannot be taken into consideration in any case.

4.2.7 Based on the information in the original application and the common general knowledge, the skilled person would have considered the claimed effects not plausible at the relevant date (lack of ab initio plausibility). Moreover, the skilled person would have considered the claimed effect implausible (ab initio implausibility). As a matter of fact, no comparative data whatsoever on the activity of bictegravir and dolutegravir can be found in the original application or in any other prior art document. Only document D3 discloses the activity of bictegravir, but offers no comparison with dolutegravir. Moreover, D3 is a patent application and therefore cannot represent the common general knowledge.

4.2.8 Even if the post-published evidence were considered, it would not allow a reformulation of the objective technical problem. We shall expand.

4.1.9 Document D41 cannot show a superiority of the claimed combination for two reasons. First of all, this document compares bictegravir *per se* with dolutegravir *per se*, and not the two triple combinations with each other. Bictegravir was a known compound at the relevant date. Therefore, D41 can at most support the patentability of bictegravir as a compound and the grant of its product patent based on application D3.

4.2.10 Secondly, it is not true that bictegravir has an unexpectedly improved resistance profile compared to dolutegravir, as the patentee alleges. In figure 2 on page 3 of D41, the in vitro activity of raltegravir, elvitegravir, dolutegravir and bictegravir against wild type virus (WT) and 10 known mutants are compared. Each mutant is characterised by a mutation aimed at overcoming a particular drug: 3 are raltegravir mutants, 2 elvitegravir mutants and 5 dolutegravir mutants (see the legend on the right-hand side of the figure).

4.2.11 No bictegravir mutants were studied in D41. This is not surprising, because bictegravir was first launched in 2018, the publication year of D41. Dolutegravir was instead authorised 5

years earlier, in 2013. Until 2018, bictegravir had been tested only in clinical trials, which offer a controlled environment in which only selected patients are enrolled. Instead, mutations usually occur in patients with a severely compromised immune system and/or with poor adherence to therapy, i.e., once a drug is authorised and used in a variety of patients. Therefore, in 2018 there had not been enough chances for the virus to develop mutations to overcome the effect of bictegravir. Nevertheless, D41 warns that this will inevitably happen (D41, page 12, left-hand column, last paragraph).

4.2.12 By definition, the activity of a compound is reduced against its mutants. Since no bictegravir mutants have been studied in D41, this document cannot support a superiority of bictegravir over dolutegravir.

4.2.13 If we now look at D43 and D44, which were published in 2020 and in 2021, respectively, we note that indeed bictegravir mutants emerged as expected (D43, title; D44, title). These mutations, together with poor adherence to the therapy, led to virological failure. As the use of bictegravir spreads, bictegravir mutants will inevitably become more common.

4.2.14 As far as D42 is concerned, it is important to note that it is a poster funded by the patentee. Moreover, each and every one of its authors were employees of Gilead Science at its publication date, as it can be found with a quick Google or LinkedIn search. Therefore, they are not impartial.

4.2.15 Moreover, D42 only relates to an *in vitro* study. It is well-known that *in vitro* models have limitations. Indeed, a direct translation of simulated missed doses *in vitro* to *in vivo* missed doses is not possible. An *in vitro* system is more sensitive to missed doses than *in vivo*, where the immune system contributes to viral suppression and helps keeping HIV-1 in a latent state. Moreover, a major reason for poor adherence are side effects: although a drug combination may have high forgiveness or a high resistance barrier in an *in vitro* assay, the combination may have more side effects, which would lead to poorer clinical adherence. Hence, there is no evidence that the claimed combination allows for a greater forgiveness than the one of D5 in human patients.

4.2.16 In conclusion, there is no evidence in the opposed patent of any technical effect of the claimed combination over the one of the closest prior art. The post-published data recently filed by the patentee cannot cure this deficiency. Therefore, the objective technical problem can only be the provision of an alternative tablet for treating HIV.

4.2.17 As a matter of fact, D36, filed by the patentee, proves that this is the correct formulation of the objective technical problem. D36 shows that the claimed combination was authorised based on its mere non-inferiority compared to the standard of care, including the combination of D5.

4.2.18 D36 explains starting from page 73 that four phase 3 studies were performed with the claimed combination:

1. vs abacavir / dolutegravir / lamivudine in treatment naïve subjects
2. vs dolutegravir / emtricitabine / tenofovir alafenamide in treatment naïve adults (see page 74)
3. vs abacavir / dolutegravir / lamivudine in treatment experienced subjects
4. vs boosted atazanavir or darunavir + emtricitabine/tenofovir or abacavir/lamivudine

4.2.19 As it can be seen in the *"Hypothesis"* box of each of the tables relating to the four studies, the patentee planned all of them as non-inferiority studies. Therefore, the patentee was the first one not to believe in any superiority of the claimed combination.

4.2.20 If we then closely examine the subgroup analysis on figure 9 on page 77 of D36, we can see that the claimed combination is slightly worse than the one of D5 in all subgroups. Since the differences are not statistically significant, the claimed combination met the non-inferiority criteria and was eventually authorised by the regulatory authorities.

4.2.21 Summing up, D36 unequivocally shows that both the patentee and the regulatory authorities came to the conclusion that the claimed combination is non-inferior to the one of the closest prior art D5. This is far from being better, as the patentee alleges. It is therefore evident that a more ambitious formulation of the objective technical problem is not justified.

4.3 Obviousness

4.3.1 The solution to such a problem is obvious over D5 in combination with D3, disclosing bictegravir as a preferred HIV integrase inhibitor. In this respect, we refer to our notice of opposition, our submission dated 26th March 2022, as well as the notices of opposition and the submissions of the co-opponents.

4.3.2 Therefore, claim 1 of the main request does not fulfil the requirements of article 56 EPC.

5. Conclusion

It has been shown above and in the notice of opposition that the opposed patent is not in accordance with the requirements of Articles 54, 56 and 123(2) EPC. Therefore, the request to revoke EP 3 346 995 in its entirety is fully justified.

Marco Fachini

Enc.
Documents D43-D44

ELKINGTON + FIFE

London office
Thavies Inn House, 3-4 Holborn Circus, London EC1N 2HA
+44 (0)20 7936 8800 • elkfife@elkfife.com • www.elkfife.com

European Patent Office
D-80298 Munich
Germany

Our ref RSC/YZZ/R79369OP

26 August 2022

ONLINE FILING

Re: **European Patent No. 3346995 (Application No. 16798063.0)**
Gilead Sciences, Inc.
Opponent Dr Richard Cooke

We refer to the summons to attend oral proceedings on 27 and 28 October 2022 and enclose further submissions on behalf of the opponent.

We intend to use English at the oral proceedings. If any party intends to use a language other than English, simultaneous interpretation is requested.

Yours Sincerely.

Elkington and Fife LLP
Richard Cooke

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European patent no. 3 346 995
(application no. 16798063.0)
Gilead Sciences, Inc.
Opponent: Dr Richard Cooke

Further submissions

1. General

(01) We are writing to provide comments on Article 56 EPC, in response to the patentee's submissions dated 21 January 2022 enclosing post-published documents D41 and D42. These documents supposedly demonstrate a technical effect associated with the distinguishing feature and allow the objective technical problem to be defined ambitiously.

(02) As we will explain, post-published D41 and D42 should not be considered as they attempt to demonstrate an effect not made plausible by the application as filed. However, even if considered, they do not show that the alleged problems have been solved.

(03) Therefore, we do not think a stay in view of G 2/21 will be necessary in any circumstances, because the outcome of the present case does not "depend entirely" on the outcome of the referral. The objective technical problem remains the provision of an alternative tablet, whether-or-not D41 and D42 are considered.

2. Lack of inventive step over D5 (Articles 56 and 100(a) EPC)

2.1 The closest prior art and the distinguishing feature

(04) The patent relates to a fixed-dose tablet comprising 25 mg tenofovir alafenamide, 200 mg emtricitabine and 50 mg bictegravir.

(05) The most promising springboard to the invention is the tablet disclosed in D5, which differs only in that the composition includes 50 mg dolutegravir rather than 50 mg bictegravir.

(06) In their recent submissions, the patentee appears to accept, at least for the purposes of the argument, that D5 can be taken as the closest prior art. In case the patentee still contests this point, the patentee is incorrect. D5 relates to the same general purpose as the patent – the provision of triple combinations for the treatment of HIV – and therefore this document is plainly a "workable" route from which inventive step must be considered (Case Law, I.D.3.1).

(07) However, even to the extent that the patentee accepts D5 as the closest prior art, the patentee objects to the use of the above composition within that document as the starting point. According to the patentee, even if this composition falls within the scope of the broadest teaching of D5, the preferred compositions in that document include a ratio of from 1:1 to 1:3 of dolutegravir

to emtricitabine. In the patentee's view, the skilled person would therefore be "guided" to other compositions which satisfy this ratio, and would not select the above composition without hindsight.

(08) As an initial point, the use of hindsight is permissible, and in fact essential, when determining the closest prior art (T 1443/16, r 4.3.2):

> "Furthermore, the issue of hindsight is immaterial to the selection of the closest prior art. Given that the closest prior art is selected on the basis of its proximity to the invention, its selection necessarily requires the knowledge of the invention."

(09) This applies when selecting the most appropriate document, but also when choosing the closest embodiment within that document (T 72/18, r 3.9.2):

> "3.9.2 Within the context of the problem-and-solution approach, it is therefore both permissible and appropriate to select, within a piece of prior art used as the starting point (in this case, document D10), the embodiment closest to the subject-matter of the claim to be assessed (in this case, panobinostat). Panobinostat is simply the 'most promising springboard' among the various disclosures in D10. While certainly based on knowledge of the claimed subject-matter, this pre-selection of a disclosure in a document does not introduce inappropriate hindsight any more than the pre-selection of a closest-prior-art document does. It merely streamlines the process by avoiding the need to haphazardly try out all possible options in D10 (one of them being panobinostat anyway)." (Emphasis added.)

(10) The patentee's argument that the skilled person would be "guided" to other formulations is irrelevant. All realistic starting points in D5 are possible. The state of the art includes all embodiments in the closest prior art, and not only those which are indicated to be preferred (T 72/18, r 3.9.3):

> "3.9.3 Panobinostat is not just encompassed by the Markush formula (I) of D10. It is also disclosed as an individualised embodiment (compound 200, prepared according to Example P3, one of three individually listed options in claim 38). Selecting panobinostat as the starting point would thus be the appropriate choice even if this embodiment were not, moreover, characterised in D10 as one of three 'important' (i.e. preferred) compounds of formula (I) (see point 3.4 above and D10: page 17, fourth paragraph)." (Emphasis added.)

(11) The relevant composition is not made unrealistic by the absence of efficacy data for the specific combination within D5, because the effectiveness of the relevant compounds formed part of the common general knowledge and is shown for combinations in the examples of D5.

2.2 The objective technical problem

(12) As explained at the very start of the proceedings, the patent provides no evidence to show that changing the integrase inhibitor from 50 mg dolutegravir to 50 mg bictegravir solved any problem.

(13) In their last submissions, after their initial response to the notices of opposition and the preliminary opinion from the opposition division, the patentee filed D41 and D42.

(14) D41 compares dolutegravir and bictegravir monotherapies and supposedly shows that bictegravir has an improved resistance profile. D42 describes in vitro experiments using a combination of dolutegravir, emtricitabine and tenofovir, and the corresponding triple combination including bictegravir, and supposedly shows that the bictegravir triple combination has a higher barrier to resistance and less viral breakthrough.

2.2.1 The patentee cannot rely on post-published evidence to show these improvements

(15) The patentee cannot rely on post-published evidence, in the absence of any plausible disclosure of these specific effects in the application as filed (e.g. T 1329/04).

2.2.2 D41 and D42 do not show any technical effect

(16) Even if considered, D41 and D42 do not allow the objective technical problem to be defined ambitiously.

D41

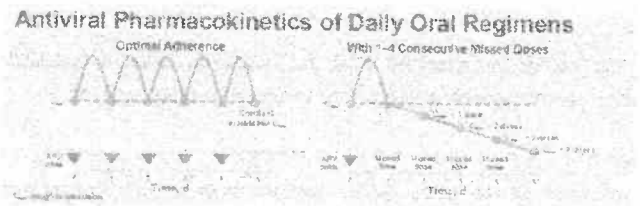
(17) D41 compares inter alia dolutegravir and bictegravir monotherapies. Comparative data are relevant only if the comparative example reflects the starting point in the prior art and the inventive example adequately represents the claimed subject-matter (T 712/13, r 3.8(a)). In the present case, the effects of the monotherapies do not reflect the specific triple combination therapy claimed or that disclosed in the closest prior art. The relative efficacy of two specific triple combinations cannot be inferred by comparing two of their constituent monotherapies.

D42

(18) D42 discloses in vitro tests which supposedly reflect in vivo conditions, and show how viral breakthrough and development of resistance varies depending on the level of patient adherence to the required dosage regimen.

(19) In D42, MT-2 cells infected with HIV-1 IIIb cells are exposed to different fixed concentrations of inter alia tenofovir alafenamide, emtricitabine and bictegravir (supposedly reflecting the claim) or tenofovir alafenamide, emtricitabine and dolutegravir (supposedly reflecting D5).

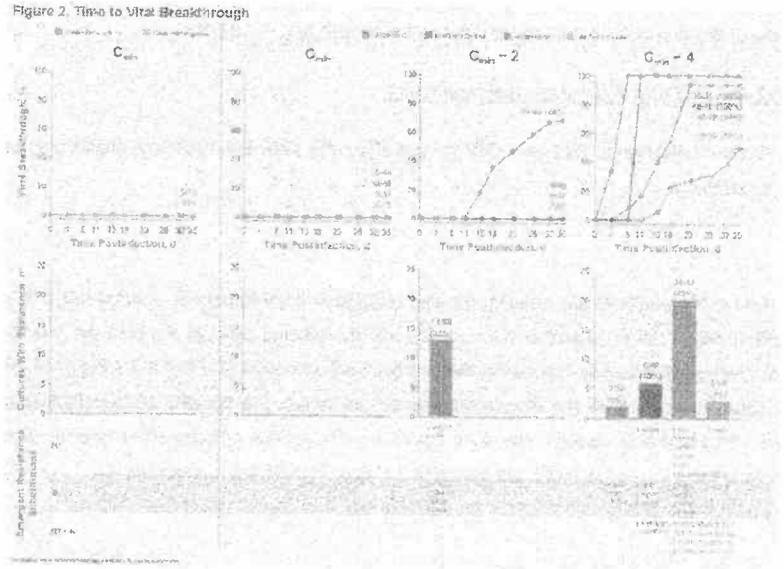
(20) The fixed in vitro concentrations are chosen to reflect the C_{min} (i) achieved by normal daily dosing (labelled "C_{min}") (ii) present after two days of no dosing (labelled "C_{min}-2"), and (iii) present after four days of no dosing (labelled "C_{min}-4"):



* Missing daily oral ARV doses results in a predictable decrease of systemic exposures to each drug in the regimen based on its established clinical half-life ($t_{1/2}$)

(21) D42 shows the levels of viral breakthrough and resistance to mutation which resulted using these three fixed in vitro doses (Figure 2):

Figure 2. Time to Viral Breakthrough



(22) "C_{min}", which as explained supposedly reflects the C_{min} provided by daily dosing, shows no difference between the bictegravir and dolutegravir triple combinations in either viral breakthrough or barrier to resistance.

(23) "C_{min}-2", which supposedly reflects the plasma concentration resulting after two days of no dosing, also shows no difference between the bictegravir and dolutegravir triple combinations in either viral breakthrough or barrier to resistance.[1]

[1] Using the black and white version on file, we are unsure which therapy shows viral breakthrough and viral resistance in the C_{min}-2 graph but we understand it to be the double combinations that are not relevant to the present case.

(24) For "C_{min}-4", which supposedly reflects the plasma concentration resulting after four days of no dosing, the patentee argues that the claimed bictegravir triple combination results in a higher barrier to resistance and less viral breakthrough then the dolutegravir triple combination.

(25) As mentioned above, comparative data are relevant only if the comparative example reflects the starting point in the prior art and the inventive example adequately represents the claimed subject-matter (T 712/13, r 3.8(a)). Furthermore, the comparative data must credibly show an effect over the entire scope claimed (T 712/13, r 3.8(c).

(26) D42 shows that there is no advantage using the C_{min} provided when the two combinations are administered once-daily, as recommended by the patent (see paragraph [0290]) and the prior art (see page 17, lines 27 to 29 D5). Therefore, the comparative examples do not reflect the invention or the closest prior art.

(27) We note that the following the teaching of the prior art, in fact higher average plasma concentrations would result because a fixed C_{min} does not reflect repeated daily dosing (see the figure illustrating dosing regimens above).

(28) Moreover, the comparative data do not show an effect across the whole scope of the claim, which is not limited to any particular dosing regimen. The only example in which an advantage is supposedly shown uses extreme conditions – wherein the plasma concentration that would result following four days of no dosing is maintained for 35 days.

(29) These conditions do not justify a claim not limited to any dosing regimen, in particular when D42 demonstrates that, when the patent and prior art are implemented in the standard manner using once-daily dosing, there is no advantage whatsoever.

2.2.3 Summary

(30) The objective technical problem is the provision of an alternative tablet. D41 and D42 should not be considered based on a lack of plausibility in the application as filed. However, even if considered, D41 and D42 do not allow the problem to be defined differently.

2.3 Obviousness of the solution

(31) We refer to our previous submissions. The exchange of one integrase inhibitor for another, in order to solve the problem of providing an alternative tablet, does not involve invention.

Dr Richard Cooke
European Patent Attorney
Elkington and Fife LLP (ref R79369OP)
26 August 2022

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Carpmaels & Ransford LLP
One Southampton Row
London WC1B 5HA
ROYAUME UNI

Date
24-06-2021

Reference	Application No./Patent No.
P072824EP	16798063.0 - 1112 / 3346995

Applicant/Proprietor
Gilead Sciences, Inc.

Summons to attend oral proceedings pursuant to Rule 115(1) EPC

You are hereby summoned to attend oral proceedings arranged in connection with the above-mentioned European patent.

The matters to be discussed are set out in the communication accompanying this summons (EPO Form 2906).

The oral proceedings, which will be public, will take place before the opposition division

on 18.-19.01.2022 (2 days) at 09:00 hrs as a video conference

No changes to the date of the oral proceedings can be made, except on serious grounds (see OJ EPO 1/2009, 68). If you do not appear as summoned, the oral proceedings may continue without you (R. 115(2) EPC).

Your attention is drawn to Rule 4 EPC, regarding the language of the oral proceedings, and to the Special edition No. 3 OJ EPO 2007, 128, concerning the filing of authorisations for company employees and lawyers acting as representatives before the EPO.

The final date for making written submissions and/or amendments (R. 116 EPC) is 18.11.21.

1st Examiner:
Trifilieff, Sylvie

2nd Examiner:
Collura, Alessandra

Chairman:
Büttner, Ulf

For the Opposition Division

Annexes:
Confirmation of receipt (Form 2936)
Rule 4 EPC (EPO Form 2043)
Communication (EPO Form 2906)

Registered letter
EPO Form 2310 07.19 (ORAL03=8888) (21/06/21)

ORAL4

to EPO postal service: 21.06.21
page 1 of 1

Europäisches Patentamt
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Wichtige Hinweise zur mündlichen Verhandlung

Das Europäische Patentamt verfügt über keine eigenen Dolmetscher. Diese müssen im Bedarfsfall von außerhalb, teilweise sogar aus anderen Ländern, beigezogen werden, was mit einem hohen Aufwand an Kosten und organisatorischen Vorbereitungen verbunden ist. Muss ein Verhandlungstermin kurzfristig abberaumt werden, können Kosten für bestellte Dolmetscher nicht mehr vermieden werden.

Es wird daher gebeten, eine Simultanübersetzung nur bei wirklichem Bedarf in Anspruch zu nehmen. Es wäre wünschenswert, wenn sich die Beteiligten (zweckmäßigerweise gleichzeitig mit der Terminabstimmung) auf die Benutzung einer Amtssprache einigen könnten. Bei Verständigungsschwierigkeiten sind die Mitglieder der Einspruchsabteilung bereit zu helfen.

Nachstehend führen wir den Zeitpunkt auf, bis zu dem die Verfahrensbeteiligten aus organisatorischen Gründen gebeten werden, ihre bevorzugte (abgestimmte) Verhandlungssprache mitzuteilen. Bis dahin bitten wir auch bei Bedarf eine Simultanübersetzung zu beantragen. Regel 4 (1) EPÜ bleibt hiervon unberührt.

☐ Verfahrenssprache ist **Deutsch**

Von der/dem/den Einsprechenden wurde

☐ Englisch

☐ Französisch benutzt.

Es wird um ollige Mitteilung, möglichst per Online Filing (OLF), gebeten.

möglichst bis

Datum **18.11.21**

1. welche Sprache(n) Sie in der mündlichen Verhandlung verwenden **(Sprechen)**
2. aus welcher Sprache Sie eine Simultanübersetzung benötigen **(Hören)**.

Important information concerning oral proceedings

The European Patent Office has no interpreters of its own. When interpreters are needed they have to be brought in from outside, sometimes even from other countries, which is costly and involves considerable organisation. If oral proceedings have to be cancelled at short notice, the cost of interpreters already engaged still has to be borne.

Please therefore make use of simultaneous interpreting facilities only where strictly necessary. If possible the parties should agree on an official language for the proceedings, preferably at the time when they arrange a date. The members of the Opposition Division will be willing to help should any communication problems arise.

For organisational reasons, we ask parties to inform us by the date specified below of their preferred (agreed) language for the oral proceedings. We also ask them to request any simultaneous interpreting required by the same date. This does not affect application of Rule 4(1) EPC.

☑ Language of the proceedings is **English**

The language used by the opponent/s was

☐ German ☒ English

☐ French.

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Date **18.11.21**

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Tres important Procédure orale

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si possible jusqu'au

Date **18.11.21**

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Il appartient alors à la division d'opposition de décider si la procédure orale aura lieu ou non. Il est néanmoins souligné que les frais causés aux autres parties par une partie qui est responsable de l'omission d'un tel avis ou de ce que cet avis n'a pas été fait en temps utile peuvent être mis à la charge de cette partie (art. 104 CBE).

Hinweis auf Regel 4 EPÜ

Regel 4
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(1) Jeder an einem mündlichen Verfahren vor dem Europäischen Patentamt Beteiligte kann sich anstelle der Verfahrenssprache einer anderen Amtssprache des Europäischen Patentamts bedienen, sofern er dies dem Europäischen Patentamt spätestens einen Monat vor dem angesetzten Termin mitgeteilt hat oder selbst für die Übersetzung in die Verfahrenssprache sorgt. Jeder Beteiligte kann sich einer Amtssprache eines Vertragsstaats bedienen, sofern er selbst für die Übersetzung in die Verfahrenssprache sorgt. Von diesen Vorschriften kann das Europäische Patentamt Ausnahmen zulassen.

Attention is drawn to Rule 4 EPC

Rule 4
Language in oral proceedings

(1) Any party to oral proceedings before the European Patent Office may use an official language of the European Patent Office other than the language of the proceedings, if such party gives notice to the European Patent Office at least one month before the date of such oral proceedings or provides for interpretation into the language of the proceedings. Any party may use an official language of a Contracting State, if he provides for interpretation into the language of the proceedings. The European Patent Office may permit derogations from these provisions.

Rappel de la Règle 4 CBE

Règle 4
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(1) Toute partie à une procédure orale devant l'Office européen des brevets peut utiliser une langue officielle de l'Office européen des brevets autre que la langue de la procédure, à condition soit d'en aviser l'Office européen des brevets un mois au moins avant la date de la procédure orale, soit d'assurer l'interprétation dans la langue de la procédure. Toute partie peut utiliser une langue officielle de l'un des Etats contractants à condition d'assurer l'interprétation dans la langue de la procédure. L'Office européen des brevets peut autoriser des dérogations aux présentes dispositions.

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(2) Die Bediensteten des Europäischen Patentamts können sich im mündlichen Verfahren anstelle der Verfahrenssprache einer anderen Amtssprache des Europäischen Patentamts bedienen.

(2) In the course of oral proceedings, employees of the European Patent Office may use an official language of the European Patent Office other than the language of the proceedings

(2) Au cours de la procédure orale, les agents de l'Office européen des brevets peuvent utiliser une langue officielle de l'Office européen des brevets autre que la langue de la procédure.

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(3) Where evidence is taken, any party, witness or expert to be heard who is unable to express himself adequately in an official language of the European Patent Office or of a Contracting State may use another language. Where evidence is taken upon request of a party, parties, witnesses or experts expressing themselves in a language other than an official language of the European Patent Office shall be heard only if that party provides for interpretation into the language of the proceedings. The European Patent Office may, however, permit interpretation into one of its other official languages.

(3) Lors de l'instruction, les parties, témoins ou experts appelés à être entendus, qui ne possèdent pas une maîtrise suffisante d'une langue officielle de l'Office européen des brevets ou d'un Etat contractant, peuvent utiliser une autre langue. Si la mesure d'instruction est ordonnée sur requête d'une partie, les parties, témoins ou experts qui s'expriment dans une langue autre qu'une langue officielle de l'Office européen des brevets ne sont entendus que si cette partie assure l'interprétation dans la langue de la procédure. L'Office européen des brevets peut toutefois autoriser l'interprétation dans l'une de ses autres langues officielles.

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(4) If the parties and the European Patent Office agree, any language may be used.

(4) Sous réserve de l'accord des parties et de l'Office européen des brevets, toute langue peut être utilisée.

(5) Das Europäische Patentamt übermittelt, soweit erforderlich, auf seine Kosten die Übersetzung in die Verfahrenssprache und gegebenenfalls in seine anderen Amtssprachen, sofern ein Beteiligter nicht selbst für die Übersetzung zu sorgen hat.

(5) The European Patent Office shall, if necessary, provide at its own expense interpretation into the language of the proceedings, or, where appropriate, into its other official languages, unless such interpretation is the responsibility of one of the parties.

(5) L'Office européen des brevets assure à ses frais, en tant que de besoin, l'interprétation dans la langue de la procédure, ou, le cas échéant, dans ses autres langues officielles, à moins que cette interprétation ne doive être assurée par l'une des parties.

(6) Erklärungen von Bediensteten des Europäischen Patentamts, Beteiligten, Zeugen und Sachverständigen, die in einer Amtssprache des Europäischen Patentamts abgegeben werden, werden in dieser Sprache in die Niederschrift aufgenommen. Erklärungen in einer anderen Sprache werden in der Amtssprache aufgenommen, in die sie übersetzt worden sind. Änderungen einer europäischen Patentanmeldung oder eines europäischen Patents werden in der Verfahrenssprache in die Niederschrift aufgenommen.

(6) Statements by employees of the European Patent Office, parties, witnesses or experts, made in an official language of the European Patent Office, shall be entered in the minutes in that language. Statements made in any other language shall be entered in the official language into which they are translated. Amendments to a European patent application or European patent shall be entered in the minutes in the language of the proceedings.

(6) Les interventions des agents de l'Office européen des brevets, des parties, témoins et experts faites dans une langue officielle de l'Office européen des brevets sont consignées au procès-verbal dans cette langue. Les interventions faites dans une autre langue sont consignées dans la langue officielle dans laquelle elles sont traduites. Les modifications apportées à une demande de brevet européen ou à un brevet européen sont consignées au procès verbal dans la langue de la procédure.

In accordance with the Decision of the President of the EPO of 14 May 2021, the oral proceedings in opposition in the above-mentioned case will be held by videoconference. The date and time of the oral proceedings remain unchanged.

For FAQs, please refer to https://www.epo.org/service-support/faq/procedure-law/oral-proceedings-by-videoconference.html.

The videoconference platform for the oral proceedings is Zoom.

Technical details
The EPO supports the following technologies for connecting to oral proceedings in opposition via Zoom:

- Zoom desktop client installation on Windows (version 5.2.1, i.e. 44052.0816 or higher), Mac OS (version 4.5.3261.0825 or higher)
- Zoom mobile app for iOS (version 4.5.0 [3261.0825] or higher) or Android (version 4.5.3261.0825 or higher)
- Zoom web client (Chromium Edge 80 or higher; Google Chrome 53.0.2785 or higher; Firefox 76 or higher; Internet Explorer 10 or higher; Safari 10.0.602.1.50 or higher) for oral proceedings **without** simultaneous interpretation.

Please note that

- **the Zoom web client cannot be used for oral proceedings involving simultaneous interpretation**
- the Zoom web client allows you to join a Zoom meeting or webinar without downloading any plugins or software. However, the web client has limited features (e.g. you will only be able to see the active speaker; see https://support.zoom.us/ for further information)
- you should inform the opposition division in advance if you intend to use the Zoom web client.

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Please DO NOT USE
Microphones built into a PC, wireless headsets connected to the computer via Bluetooth, phone earbuds (even if wired) or standard VICO room equipment with array microphones. None of these perform adequately for remote interpreting. They do not cover the frequency range of 125 Hz to 15000 Hz that simultaneous interpreters need to listen and speak at the same time; see ISO/PAS standard 24019.

Note that if two or more people are physically present in the same room and intend to speak during the proceedings, they MUST avoid echoes and MUST each have their own headset/microphone and camera. Preferably they should remove their mask while speaking.

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- the presentation of content is possible in both directions
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IMPORTANT
Please inform the EPO without delay if you have not received the videoconference connection details at least ten days before the scheduled date of the oral proceedings.

1. European patent 3 346 995 having the title "THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS " is based upon European patent application No.16 798 063.0 filed on 08-11-2016. It claims priority of US 201562253042 filed on 09-11-2015 and US 201662399999 filed on 26-09-2016.

The mention of the grant of the patent has been published in the European Patent Bulletin of28-08-2019 . Proprietor of the patent (hereinafter P) is
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
US.

2. Notices of opposition has/have been filed by
Opponent 1 (hereinafter O1):
Teva Pharmaceutical Industries Ltd
5 Basel Street
49131 Petach-Tikva
IL
on 27-05-2020

Opponent 2 (hereinafter O2):
Cooke, Richard
Elkington and Fife LLP
Patents Department
3-4 Holborn Circus
London EC1N 2HA
GB
on 28-05-2020

Opponent 3 (hereinafter O3):
Sandoz GmbH
Biochemiestrasse 10
6250 Kundl
AT
on 28-05-2020 .

The opponents request revocation of the patent in its entirety on the following grounds:

. the granted subject-matter extends beyond the content of the application as originally filed (A. 100(c) and A. 123(2) EPC): O1, O2 and O3.

. the granted subject-matter lacks novelty (A. 100(a); A. 54 EPC): O2 and O3.

. the granted subject-matter lacks inventive step (A. 100(a); A. 56 EPC): O1, O2 and O3.

. O2 and O3 further dispute the validity of the priority.

All opponents request oral proceedings as an auxiliary measure.

3. With the submission dated 11-01-2021, P requests that the oppositions be dismissed and that the patent be maintained as granted or on the basis of one of the 29 auxiliary requests (AR1 to AR29) filed with the same submission.

P requests oral proceedings as an auxiliary measure.

4. The opponents react as follows:

O2 submits further arguments on 04-03-2021.

O3 submits further arguments on 24-03-2021.

O1 submits D38 and D39 together with further arguments on 26-03-2021.

5. Oral proceedings are hereby summoned.

6. The present communication represents the provisional and non binding opinion of the opposition division (hereinafter OD) on the above topics.

The documents cited by the parties are:

		P	O1	O2	O3
PRIO1	US 2015/62253042				TM1
PRIO2	US 2016/62399999				TM2
D1	WO 2015/196116			D1	TM14

D1a	Evidence of D1 entry to European Regional phase			D1a	
D2	WO 2015/196137			D2	TM15
D3	WO 2014/100323		D1	D3	TM3
D4	WO 2013/116720		D3	D4	
D5	WO 2015/022351		D2	D5	TM17
D6	Gilead Sciences Finalizes Agreement with Tibotec Pharmaceuticals to Develop and Commercialize a Single-Tablet Regimen of Prezista® with Emtriva®, GS 7340 and Cobicistat, 15 November 2011			D6	
D7	British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy, 2015, pages 13-14			D7	
D8	BNF 2015, Emtricitabine with tenofovir, pages 557-558 and 566			D8	
D9	Fernando, S., Butterworth, A., Choices, choices: the rapidly evolving HIV treatment landscape, pmlive.com, 15 March 2015			D9	
D10	Business Wire, 5 November 2015, "U.S. Food and Drug Administration Approves Gilead's Single Tablet Regimen Genvoya® (Elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide) for treatment of HIV-1 infection"			D10	
D11	Centre for Drug Evaluation and Research, first page of approval package, Odefsey®			D11	

D12	Business Wire, 1 July 2015, "Gilead Submits New Drug Application to U.S. Food and Drug Administration for Single Tablet Regimen for HIV Containing Rilpivirine, Emtricitabine and Tenofovir Alafenamide (R/F/TAF)"			D12	
D13	Business Wire, 4 April 2016, "U.S. Food and Drug Administration Approves Descovy® (Emtricitabine, Tenofovir Alafenamide), Gilead's Third TAF-Based HIV Therapy			D13	
D14	Business Wire, 28 May 2015, "European Medicines Agency Validates Gilead's Marketing Application for Fixed-dose Combination of Emtricitabine and Tenofovir Alafenamide for HIV treatment"			D14	
D15	Aulton, Pharmaceutics: The Science of Dosage Form Design, 2nd Edition, 2002, pages 411-412			D15	
D16	P. Shende et al., "Multi-layer Tablet: Current scenario and recent advances", International Journal of Drug Delivery 4 (2012) 418-426;		D4		
D17	WO 2017/083304 A1		D5		
D18	WHO Drug Information 29(2), July 2015				TM4
D18a	Publication date of TM4				TM4a
D19	Guidance on the establishment of new INN stems, 2007				TM5
D20	WHO, The use of stems in the selection of International Nonproprietary Names (INN) for pharmaceutical substances, 2013				TM6
D20a	WHO, Pre-Stems: Suffixes used in the selection of INN, 2012				TM6a

D20b	WHO, Pre-Stems: Suffixes used in the selection of INN, June 2014				TM6b
D21	Yoshinaga et al., Antiviral Characteristics of GSK.1265744, an HIV Integrase Inhibitor Dosed Orally or by Long-Acting Injection, Antimicrobial Agents and Chemotherapy, January 2015, Vol. 51, Nr. 1, p. 397-406				TM7
D21a	Park et al., Review of integrase strand transfer inhibitors for the treatment of human immunodeficiency virus infection, Expert Rev. Anti Infect. Ther. 13(10), 2015				TM7a
D21b	Shah et al., Dolutegravir: A New Integrase Strand Transfer Inhibitor for the Treatment of HIV, Pharmacotherapy, Vol. 34, No. 5, 2014				TM7b
D22	WO 02/08241 A2				TM8
D23	Clayden et al., 2015 Pipeline Report, HCV, HCV, TB, July 2015				TM9
D24	FDA, Drug Approval Package Viread				TM10
D25	EMA, Viread, Authorization details				TM11
D26	Press Release Gilead dated November 5, 2015				TM12
D27	Experimental Report dated May 15, 2020				TM16
D28	US 2014/0221356 A1				TM18
D28a	Submission in the Examination Proceedings of TM18 dated August 26, 2015				TM18a
D29	Kulkarni et al., The Combined Anti-HIV-1 Activities of Emtricitabine and Tenofovir plus the Integrase Inhibitor Elvitegravir or Raltegravir Show High Levels of Synergy In				TM19

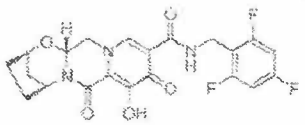
	Vitro, Antimicrobial Agents and Chemotherapy, October 2014, Vol. 58, Nr. 10, p. 6145-6150				
D30	Analyzing Gilead Sciences' Research and Development in 3Q15, October 23, 2015				TM20
D31	EudraCT number 2015-003988-10 dated November 19, 2015				TM21
D32	USAN statement dated February 24, 2016				TM22
D33	WO 2010/091197 A2				TM23
D34	WO 2013/115916 A1				TM24
D35	Phase I study into the potency, safety and pharmacokinetics of multiple doses of BIC	D35			
D36	Biktarvy EPAR Scientific Discussion	D36			
D37	Phase II study comparing BIC (75 mg) + FTC/TAF (200/25 mg) vs DTG (50 mg) + FTC/TAF (200/25 mg)	D37			
D38	P. Kommavarapu et al., "Preparation and characterization of rilpivirine solid dispersions with the application of enhanced solubility and dissolution rate", Beni-Suef University Journal of Basic and Applied Sciences 4 (2015) 71-79.		D38		
D39	European Medicines Agency, Assessment report "Genvoya", 24 September 2015, extract (pp.1-20).		D39		

6. MAIN REQUEST (patent as granted):

The patent comprises two independent claims 1 and 10 which read:

1. A tablet comprising 50 mg of the compound of Formula I:

(I)



or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof

10. A tablet according to any one of the preceding claims for use in the therapeutic treatment of an HIV infection.

It is noted that the non proprietary name of the compound of Formula I is bictegravir.

6.1 Extension of the subject-matter beyond the content of the original application (A. 100 (c) and A. 123(2) EPC):

According to O1 and O2 the application as filed does not disclose the tablet of granted claim 1. Such a specific tablet would neither be disclosed in the claims nor in the description of the original application. The passages of the original application (claims and/or description) which could be relied upon for basis would comprise additional limitations such as coatings or a particular tablet weight which are not present in granted claim 1.

O3 raises the objection for granted claim 5 which would comprise combinations which would be artificially created from separate embodiments of the original application.

The opponents extend the objection to the dependent claims 4 to 10.

P answers that the claims have the following basis in the application as filed:

claim 1: § 8, 10, 12, 16, 34, 37, 48, 50, 53, 77 to 85, 90 to 98, 103 to 111, 264, claims 6 to 9

claim 2: § 8, claims 2 and 6

claim 3: § 8, 14, 34, 53, 128, claims 3, 6 and 8

claim 4: § 10, 11, 52, 53, claims 4 to 6

claim 5: § 12, 71, 210, 211, 279, claim 7

claim 6: § 16, 20, 54, 55, 117, 118, 126, 128 to 262, claims 9, 10 and 16

claim 7: § 55, claim 17

claim 8: claim 26

claim 9: claim 27

claim 10: § 1, 7, 282, 283, claims 38 and 39

In particular, granted claim 1 would be described in §008 combined with the teaching found throughout the application stating that emtricitabine is present either as such or as a pharmaceutically acceptable salt (paragraphs mentioned in the table).

P also argues that the subject-matter of granted claim 1 is not an unallowable intermediate generalisation because the application as filed would not describe an inextricable link between the doses of the active compounds and the other limitations found in the different paragraphs of the original application such as total weight of the tablet or presence of a coating.

O3's objection concerning claim 5 would result from an over formalistic view which would only take into account the the structure of the original claims and their dependencies rather than the overall original disclosure.

This would also be the case for claims 4 and 6 to 10.

Reading §008 of the original application, the OD notes that it describes a solid oral dosage form (1st sentence) which in certain embodiments (2nd sentence) comprises 50 mg of the compound of formula I or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine.

This passage does neither specify that the dosage form is a tablet nor that emtricitabine can be in the form of a salt.

§010 of the original application recites a solid oral dosage form which comprises 50 mg of the compound of formula I or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof. This passage however further specifies that this oral dosage form has a total weight of less than 850 mg and does not specify that the dosage form is a tablet.

The feature of granted claim 1 relating to the "tablet" specific form can indeed be found in some of the different paragraphs mentioned as basis in the above table. It appears however to be linked with other specific technical features of the dosage form which are

not present in granted claim 1 such as the fact that the tablet is coated (§012 and original claim 7) or the fact that bictegravir and tenofovir alafenamide are segregated in the tablet (§016 and original claim 9).

As for the feature relating to the "emtricitabine salt", §0048 mentions that "solid oral dosage forms disclosed herein include emtricitabine, optionally as a pharmaceutically acceptable salt" and §0050 that "a reference to '200 mg emtricitabine or a pharmaceutically acceptable salt and/or solvate thereof' means an amount of emtricitabine or a pharmaceutically acceptable salt and/or solvate thereof which provides the same amount of emtricitabine as 200 mg of emtricitabine free base". It would hence seem that 200 mg emtricitabine would not be equivalent to 200 mg of a salt of emtricitabine.

Further, §0077 to §0085, §0090 to §0098 and §0103 to §0111 do not describe a tablet as depicted in granted claim 1 but a **pharmaceutical composition comprising** a tablet **containing** 50 mg of bictegravir or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof.

The OD is thus of the provisional opinion that the subject-matter of granted claim 1 extends beyond the content of the original application.

6.2. Validity of the priority rights (A. 87 EPC):

O2 objects that granted claims 6 to 10 are not entitled to the first priority of 09-11-2015 (P1) and O3 raises the same objection against granted claims 1, 4 to 7 and 10.

P answers that the granted claims are described in P1 as follows:

Claim 1: § 7, 9, 11, 15, 33, 36, 42, 48, 51, 92 and claims 1, 2, 6, 7 and 9

claim 2: § 17, claim 2

claim 3: § 7, 13, 33, 51, 94, claim 3

claim 4: (i) § 50, 51; (ii) § 9, 51, claim 4; (iii) § 9, claim 5

claim 5: § 11, 67, 183, claim 7

claim 6: § 15, 19, 52. 53, 85 to 180 in particular § 85, 92 and 94, claim 16

claim 7: § 15, 53, 92, 94, claim 17

claim 8: claim 26

claim 9: claim 27

claim 10: § 1, 6, 186, 187, claims 39 and 40

and that they are entitled to the date of P1.

Reading the passages recited in the table above, it would seem that the same observations as those made under point 6.1. above by the OD would apply.

Hence it would appear that the claims would not be entitled to the priority date of 09-11-2015.

6.3. Novelty (A. 100(a) and A. 54 EPC):

O2 objects that claims 1 and 2 lack novelty over D1 while D3 objects that claims 1, 2 and 10 lack novelty over D1 and D2.

D1 was filed on 10-06-2015 and validly entered the European regional phase so that it would be relevant for consideration of novelty regardless of whether P1 is validly claimed.

The same would apply to D2 filed on 19-06-2015 and published on 23-12-2015.

Both opponents contend that D1 §96 teaches a combination of 50 to 500 mg of sodium bictegravir with 25 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate or tenofovir alafenamide and 200 mg emtricitabine. D1 would further disclose that tablets are preferred pharmaceutical compositions (§65 and claim 21). D1 would hence anticipate the subject-matter of granted claim 1.

D1 would also describe that the most preferred form of bictegravir would be the sodium salt, the most preferred from of emtricitabine would be the free base and the most preferred form of tenofovir alafenamide would be the hemifumarate salt (claim 19 D1). Thus also granted claim 2 would lack novelty over D1.

The objection would apply to granted claim 10 in view of §69 and claims 22-25 of D1.

O3 raises similar objections with respect to D2 taking into consideration §6, 21, 23, 218 , 187, 191 and claims 49 to 52.

P answers that none of the documents actually describes a tablet such as that of granted claim 1 and that the conclusions of O2 and O3 are based on combinations selected from different ranges of options.

The OD is of the preliminary opinion that none of D1 and D2 describes a specific tablet as that depicted in granted claim 1.

6.4. Inventive step (A. 100(a) and A. 56 EPC):

In relation to the issue of validity of the priority date of P1 and since the opinion expressed under item 6.2 above is only preliminary it would seem appropriate to distinguish between the situation where P1 would be valid and the one where it would not.

6.4.1. The date of P1 would be validly claimed:

The opponents regard D5 as the closest prior art document.

D5 would disclose a composition comprising 50 mg dolutegravir (which is an integrase inhibitor), 200 mg emtricitabine and 25 mg tenofovir alafenamide (p. 19-20). The most preferred composition would be a tablet (p. 23).

The distinguishing feature between this teaching and the subject-matter of granted claim 1 would be the use of 50 mg bictegravir as integrase inhibitor instead of 50 mg of dolutegravir.

The patent would not disclose any technical effect linked to this difference.

Hence the problem would be the provision of a fixed-dose combination in form of a tablet comprising an alternative integrase inhibitor, emtricitabine and tenofovir alafenamide.

Bictegravir would be an obvious alternative to dolutegravir since its effect as integrase inhibitor is disclosed in different prior art documents such as D3, D18, D28 and D28a (D3 and D28a would even indicate that bictegravir is one of the preferred integrase inhibitors disclosed in D28).

The opponents conclude that the subject-matter of granted claim 1 would not meet the requirements for inventive step.

They extend the objection to all dependent claims, as well as to claim 10, referring to further prior art documents (D4, D16, D15, D7, D8, D33, D34) and/or to general knowledge and/or to routine methodology.

Other reasonings are made (O2), starting from D10, D12 or D4 as closest prior art combined with D3, D5 or D7.

P regards D37 as closest prior art because it would be the only prior art document which would describe a combination comprising exactly the same three compounds as the composition of granted claim 1.

The difference would lie in the amount of bictegravir used and would be linked to unexpected technical effects shown in the patent so that inventive step would be present.

Reasoning with D5 as closest prior art, P asserts that it would not actually describe a composition comprising 50 mg dolutegravir (which is an integrase inhibitor), 200 mg emtricitabine and 25 mg tenofovir alafenamide because this would contravene some statements of D5 concerning ratios between dolutegravir and emtricitabine.

The problem with respect to D5 would be the provision of a safe and effective anti-HIV combination therapy which could be provided as a single tablet.

There would be no reason for the skilled person to specifically replace the integrase inhibitor (i.e. dolutegravir) rather than the other two active agents. Even if the skilled person had considered doing so, the prior art (e.g. D7) would not have suggested bictegravir. As for the dose of 50 mg, it would not have been obvious to simply switch 50 mg of dolutegravir for 50 mg of bictegravir.

Hence the granted subject-matter would be inventive.

The same reasoning would apply starting from D10, D12 or D14.

Regarding the choice of the closest prior art document, the OD notes that D37 does not mention bictegravir as such but only the code name GS-9883. The only available document which draws a link between GS-9883 and bictegravir is D32 published on 24-02-2016.

Hence would P1 be valid, GS-9883 in D37 could not simply be read as "bictegravir" but would remain a compound of unknown structure and mechanism.

Accordingly D5 would seem more adequate than D37 as starting point for assessing inventive step.

6.4.2. The date of P1 would not be validly claimed:

O2 reasons that starting from D1, the subject-matter of claims 6 and 7 would lack an inventive step.

O3 starts from D31 (completed with D32) which describes a phase 3 clinical trial in which the safety and efficacy of a fixed dose combination of bictegravir/emtricitabine/ tenofovir alafenamide is compared to a treatment with dolutegravir and emtricitabine/ tenofovir alafenamide to treat HIV.

According to O3, this teaching would render the subject-matter of claims 1 and 10 obvious. The objection would apply to all dependent claims 2 to 9.

No counter argument is presented by P. P is however invited to take into consideration the above approaches, particularly the one starting from D31.

The matter of inventive step will have to be discussed at the oral proceedings. Whatever conclusion is made on the validity of the claimed priority date, the first step will have to select the closest prior art document.

D5 would seem appropriate if the date of P1 is acknowledged as being valid.

If not, D31 might be the most appropriate document.

7. AUXILIARY REQUESTS:

7.1 Extension of the subject-matter beyond the content of the original application (A. 100 (c) and A. 123(2) EPC):

The preliminary opinion expressed under point 6.1. above for the main request applies to AR1 to AR4, AR6 to AR8.

In view of the great number of auxiliary requests it does not seem appropriate to express any further preliminary opinion other than the one above for the moment.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 17/738,803	Filing Date 05/06/2022	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	13 minus 20 =	* 0		x $100 =	0
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	* 0		x $480 =	0
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	0

APPLICATION AS AMENDED - PART II

AMENDMENT	04/05/2023	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 20	Minus	** 20	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 3	Minus	*** 3	= 0		x $480 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/MARISSA R BLYTHER/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
* 17/738,803 *	17/738,803	Collman et al.	
	Examiner	Art Unit	
	WORSHAM, JESSICA N	1615	

Document Code - DISQ	Internal Document - DO NOT MAIL

TERMINAL DISCLAIMER	☑ APPROVED	☐ DISAPPROVED
Date Filed: 05 April 2023	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:

/PAMELA A YOUNG/

Technology Center: OPLC

Telephone: (571)272-3622

_____

UNITED STATES PATENT AND TRADEMARK OFFICE

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NOTICE OF ALLOWANCE AND FEE(S) DUE

25000 7590 04/17/2023

GILEAD SCIENCES, INC
333 LAKESIDE DR
FOSTER CITY, CA 94404

EXAMINER
WORSHAM, JESSICA N

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 04/17/2023

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/738,803	05/06/2022	Benjamin Micah Collman	1147-US-P2C2DC	2232

TITLE OF INVENTION: THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	07/17/2023

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PTOL-85 (Rev. 02/11)

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address, and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

25000 7590 04/17/2023
GILEAD SCIENCES, INC
333 LAKESIDE DR
FOSTER CITY, CA 94404

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)

(Signature)

(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/738,803	05/06/2022	Benjamin Micah Collman	1147-US-P2C2DC	2232

TITLE OF INVENTION: THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	07/17/2023

EXAMINER	ART UNIT	CLASS-SUBCLASS
WORSHAM, JESSICA N	1615	424-465000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. Fees submitted: ☐ Issue Fee ☐ Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

☐ Electronic Payment via Patent Center or EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29
NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

☐ Applicant asserting small entity status. See 37 CFR 1.27
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

☐ Applicant changing to regular undiscounted fee status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (08-18) Approved for use through 01/31/2020 OMB 0651-0033 U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1002**
770 of 1074

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/738,803	05/06/2022	Benjamin Micah Collman	1147-US-P2C2DC	2232

25000 7590 04/17/2023

GILEAD SCIENCES, INC
333 LAKESIDE DR
FOSTER CITY, CA 94404

EXAMINER	
WORSHAM, JESSICA N	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 04/17/2023

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 02/11)

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 17/738,803	Applicant(s) Collman et al.	
	Examiner JESSICA WORSHAM	Art Unit 1615	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to communication filed 5 April 2023.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 52-64 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov**.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 4/5/23.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☑ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/JESSICA WORSHAM/
Primary Examiner, Art Unit 1615

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16. 2013, is being examined under the first inventor to file provisions of the AIA.

Detailed Action

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on 5 April 2023 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner except where lined through. English translations of the lined through documents were not provided. See attached copy of PTO-1449.

Terminal Disclaimer

2. The terminal disclaimer filed on 5 April 2023 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of **U.S. Patent No. 10,548,846** has been reviewed and is accepted. The terminal disclaimer has been recorded.

Reasons for Allowance

3. The following is an examiner's statement of reasons for allowance: The closest prior art of Carra et al. (WO2015/196116, U.S. Patent Application Publication No. 2016/0016973, and U.S. Patent Nos. 10.098,886 and 10.385,067) were published after the effective filing date of the instant application and have a common assignee. The next closest prior art of WO2014/100323 comprises administering the compound of Formula I at a different time than additional drugs such as tenofovir or emtricitabine. The prior art does not teach all three drugs within the same tablet.

Applicants have shown a 30% higher exposure of bictegravir in a fixed dose combination of bictegravir, emtricitabine, and tenofovir alafenamide relative to its exposure when co-administered as a single agent of bictegravir with a fixed dose combination of emtricitabine and tenofovir alafenamide.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Correspondence

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to JESSICA WORSHAM whose telephone number is (571)270-7434. The examiner can normally be reached Monday-Friday (8-5).

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Wax can be reached on 571-272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov.

Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JESSICA WORSHAM/
Primary Examiner, Art Unit 1615

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/738,803	Collman et al.
	Examiner	Art Unit
	JESSICA WORSHAM	1615

CPC											
Symbol									Type	Version
A61K	/	9	/	209					F	2013-01-01
A61K	/	9	/	2054					I	2013-01-01
A61K	/	31	/	513					I	2013-01-01
A61K	/	31	/	675					I	2013-01-01
A61K	/	31	/	553					I	2013-01-01
A61K	/	9	/	2086					I	2013-01-01
A61P	/	31	/	18					I	2018-01-01
A61K	/	9	/	2027					I	2013-01-01
A61K	/	9	/	2833					I	2013-01-01
A61K	/	31	/	537					I	2013-01-01
A61K	/	9	/	0053					I	2013-01-01
A61K	/	9	/	2013					I	2013-01-01
A61K	/	9	/	2095					I	2013-01-01
A61K	/	9	/	28					I	2013-01-01
A61K	/	31	/	5365					I	2013-01-01

CPC Combination Sets							
Symbol					Type	Set	Ranking	Version
A61K	/	31	/	513	I	1	1	2013-01-01
A61K	/	2300	/	00	I	1	2	2013-01-01
A61K	/	31	/	553	I	2	1	2013-01-01
A61K	/	2300	/	00	I	2	2	2013-01-01
A61K	/	31	/	675	I	3	1	2013-01-01
A61K	/	2300	/	00	I	3	2	2013-01-01

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	13	
/JESSICA WORSHAM/ Primary Examiner, Art Unit 1615	12 April 2023	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office

Part of Paper No.: 20230410

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/738,803	Collman et al.
	Examiner	Art Unit
	JESSICA WORSHAM	1615

INTERNATIONAL CLASSIFICATION				
CLAIMED				
A61K	/	31	/	5365
NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	13	
/JESSICA WORSHAM/ Primary Examiner, Art Unit 1615	12 April 2023	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office

Part of Paper No.: 20230410

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1002
778 of 1074

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/738,803	Collman et al.
	Examiner	Art Unit
	JESSICA WORSHAM	1615

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1		10		19		28		37		46	4	55	13	64
	2		11		20		29		38		47	5	56		
	3		12		21		30		39		48	6	57		
	4		13		22		31		40		49	7	58		
	5		14		23		32		41		50	8	59		
	6		15		24		33		42		51	9	60		
	7		16		25		34		43	1	52	10	61		
	8		17		26		35		44	2	53	11	62		
	9		18		27		36		45	3	54	12	63		

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	13	
/JESSICA WORSHAM/ Primary Examiner, Art Unit 1615	12 April 2023	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office

Part of Paper No.: 20230410

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/738,803	Collman et al.
	Examiner	Art Unit
	JESSICA WORSHAM	1615

CPC - Searched*		
Symbol	Date	Examiner
(A61K9/209 or A61K9/0053 or A61K9/2013 or A61K9/2027 or A61K9/2054 or A61K9/2086 or A61K9/2095 or A61K9/28 or A61K9/2833 or A61K31/513 or A61K31/5365 or A61K31/537 or A61K31/553 or A61K31/675 or A61P31/18 or A61K9/282 or A61K9/20 or A61K2300/00).cpc.	04/12/2023	JW

CPC Combination Sets - Searched*		
Symbol	Date	Examiner
No classified search performed.		

US Classification - Searched*			
Class	Subclass	Date	Examiner
	No classified search performed.		

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
Inventor Search: PE2E, PALM	12/01/2022	JW
PE2E: See attached	12/01/2022	JW
SciFinder: See attached	12/01/2022	JW
PE2E: See attached	04/12/2023	JW

/JESSICA WORSHAM/ Primary Examiner, Art Unit 1615	

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1002
780 of 1074

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/738,803	Collman et al.
	Examiner	Art Unit
	JESSICA WORSHAM	1615

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
	(emtricitabine and tenofovir and tablet and bictegravir).clm.	04/12/2023	JW

/JESSICA WORSHAM/ Primary Examiner, Art Unit 1615	

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1002
781 of 1074

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 13

Complete if Known	
Application Number	17/738,803
Filing Date	May 6, 2022
First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	J. N. Worsham
Attorney Docket Number	1147-US-P2C2DC

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	AA	US-2002-0119443-A1	08-29-2002	Becker et al.	
	AB	US-2003-0219727-A1	11-27-2003	Becker et al.	
	AC	US-2005-0124583-A1	06-09-2005	Becker et al.	
	AD	US-2005-0124584-A1	06-09-2005	Becker et al.	
	AE	US-2005-0124585-A1	06-09-2005	Becker et al.	
	AF	US-2006-0024659-A1	02-02-2006	Becker et al.	
	AG	US-20070099902-A1	05-03-2007	Dahl et al.	
	AH	US-2007/0219243-A1	09-20-2007	Kearney et al.	
	AI	US-2008/0200435-A1	08-21-2008	Stoffels	
	AJ	US-20100285122-A1	11-11-2010	Oliyai et al.	
	AK	US-2013/0243857-A1	09-19-2013	Oliyai et al.	
	AL	US-2014/0142070-A1	05-22-2014	Delaet et al.	
	AM	US-2014/0213556-A1	07-31-2014	DAHL et al.	
	AN	US-2014/0221355-A1	08-07-2014	Lazerwith et al.	
	AO	US-2014/0349971-A1	11-27-2014	Janssen R & D Ireland	
	AP	US-2015/0111856-A1	04-23-2015	Dahl et al.	
	AQ	US-2015/0150810-A1	06-04-2015	OLIYAI et al.	
	AR	US-2015/0283135-A1	10-08-2015	Janssen R & D Ireland	
	AS	US-2016/0016973-A1	01-21-2016	Carra et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	BA**	WO-2004024078-A2	03-25-2004	Merck & Co., Inc		
	BB**	WO-2006030807-A1	03-23-2006	Shionogi & Co., Ltd		
	BC**	WO-2006116764-A1	11-02-2006	Shionogi & Co., Ltd		
	BD**	WO-2008/043829-A2	04-17-2008	Boehringer Ingelheim Int		
	BE**	WO-2013/116720-A1	08-08-2013	Gilead Sciences, Inc		
	BF**	WO-2013/115916-A1	08-08-2013	Gilead Sciences, Inc		

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: April 5, 2023 Electronic Signature for Donna Johnson Gressler: /Donna Johnson Gressler/

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.W/

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 13

Complete if Known	
Application Number	17/738,803
Filing Date	May 6, 2022
First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	J. N. Worsham
Attorney Docket Number	1147-US-P2C2DC

U. S. PATENT DOCUMENTS

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	AT	US-2016/0194335-A1	07-07-2016	Jin et al.	
	AU	US-2017/0000807-A1	01-05-2017	Koziara et al.	
	AV	US-2017/0027967-A1	02-02-2017	Koziara et al.	
	AW	US-2017/0079999-A1	03-23-2017	DAHL et al.	
	AX	US-2017/0114074-A1	04-27-2017	Jin et al.	
	AY	US-2017/0197985-A1	07-13-2017	Carra et al.	
	AZ	US-2018/0022757-A1	01-25-2018	Chiu et al.	
	AA1	US-2018-0065986-A1	03-08-2018	Carra et al.	
	AB1	US-2018-0215769-A1	08-02-2018	Jin et al.	
	AC1	US-2019-0015420-A1	01-17-2019	Carra et al.	
	AD1	US-7,390,791	06-24-2008	Becker et al.	
	AE1	US-7,803,788	09-28-2010	Becker et al.	
	AF1	US-8,592,397	11-26-2013	Dahl et al.	
	AG1	US-8,598,185	12-03-2013	Dahl et al.	
	AH1	US-8,716,264	05-06-2014	Dahl et al.	
	AI1	US-8,754,065	06-17-2014	Liu et al.	
	AJ1	US-8,841,310	09-23-2014	Janssen R & D Ireland	
	AK1	US-9,018,192	04-28-2015	Dahl et al.	
	AL1	US-9,216,996	12-22-2015	Jin et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	BG**	WO-2014100323-A1	06-26-2014	Gilead Sciences, Inc		
	BH**	WO-2015/022351-A1	02-19-2015	Ratiopharm Gmbh		
	BI**	WO-2015039348-A1	03-26-2015	Merck Sharp & Dohme		
	BJ**	WO-2015/196116-A1	12-23-2015	Gilead Sciences, Inc		
	BK**	WO-2015/196137-A1	12-23-2015	Gilead Sciences, Inc		
	BL**	WO-2017/083304-A1	05-18-2017	Gilead Sciences, Inc		

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the Indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.W/

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Sheet 3 of 13

Complete if Known	
Application Number	17/738,803
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Art Unit	1615
Examiner Name	J. N. Worsham
Attorney Docket Number	1147-US-P2C2DC

U. S. PATENT DOCUMENTS

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	AM1	US-9,296,769	03-29-2016	Liu et al.	
	AN1	US-9,457,036	10-04-2016	Dahl et al.	
	AO1	US-9,545,414	01-17-2017	Dahl et al.	
	AP1	US-9,663,528	05-30-2017	Desai et al.	
	AQ1	US-9,682,084	06-20-2017	Carra et al.	
	AR1	US-9,708,342	07-18-2017	Carra et al.	
	AS1	US-9,732,092	08-15-2017	Jin et al.	
	AT1	US-10,035,809	07-31-2018	Bacon et al.	
	AU1	US-10,098,886	10-16-2018	Carra et al.	
	AV1	US-10,385,067	08-20-2019	Carra et al.	
	AW1	US-2015/0018359-A1	01-15-2015	DESAI et al.	
	AX1	US-10,548,846-B2	02-04-2020	Collman et al.	
	AY1	US-2017/0189337-A1	07-06-2017	Collman et al.	
	AZ1	US-2021/0052502-A1	02-25-2021	Collman et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	BM**	WO-2020/091197-A1	05-07-2020	Ulsan Nat Inst Science & Tech Unist		

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

#5030513v1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.W/

PTO/SB/08b (07-09)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 4 of 13

Complete if Known	
Application Number	17/738,803
Filing Date	May 6, 2022
First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	J. N. Worsham
Attorney Docket Number	1147-US-P2C2DC

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CA**	AHMED, N. et al. (2015) "BHIVA Guidelines for the Treatment of HIV-1-Positive Adults With Antiretroviral Therapy 2015" *British HIV Association* 1-5.	
	CB**	AULTON, M.E. (1988) "Tablets and Compaction" *Pharmaceutics: The Science of Dosage Form Design* 27(2):410-412.	
	CC**	British Medical Association and Royal Pharmaceutical Society of Great Britain (2016) "British National Formulary" 557-566.	
	CD**	Business Wire (2015) "European Medicines Agency Validates Gilead's Marketing Application for Fixed-Dose Combination of Emtricitabine and Tenofovir Alafenamide for HIV Treatment" 1-2.	
	CE**	Business Wire (2015) "Gilead Submits New Drug Application to U.S. Food and Drug Administration for Single Tablet Regimen for HIV Containing Rilpivirine, Emtricitabine and Tenofovir Alafenamide (R/F/TAF) 1-3.	
	CF**	Business Wire (2016) "U.S. Food and Drug Administration Approves Descovy (Emtricitabine, Tenofovir Alafenamide), Gilead's Third TAF-Based HIV Therapy" 1-4.	
	CG**	CLAYDEN, P. et al. (2015) "HIV, Hepatitis C Virus (HCV), And Tuberculosis (TB) Drugs, Diagnostics, Vaccines, Preventive Technologies, Research Toward a Cure, and Immune-Based and Gene Therapies in Development" *2015 Pipeline Report* 1-183.	
	CH**	EMA Viread Authorization (2017) "Product Details" *European Medicines Agency.*	
	CI**	Eron, Joe et al. (2016) "Retesting of suspected low-level HIV-1 viral load blips: A new paradigm to prevent extra clinic visits and unnecessary patient anxiety" Abstract, 10/28/2016 New Orleans	
	CJ**	EU Clinical Trials Reigster (2020) "A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of GS-9883/Emtricitabine/Tenofovir Alafenamide Versus Dolutegravir + Emtricitabine/Tenofovir Alafenamide in HIV-1 Infected, Antiretroviral Treatment-Naive Adults"	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 5 of 13

Complete if Known	
Application Number	17/738,803
Filing Date	May 6, 2022
First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	J. N. Worsham
Attorney Docket Number	1147-US-P2C2DC

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CK**	Examination Report dated 2018-08-15 for New Zealand Appl. No. 741957.	
	CL**	Examination Report dated 2019-11-05 for Australian Appl. No. 2016354007.	
	CM**	Extended European Search Report dated 2020-03-11 for European Appl. No. 19186760.5.	
	CN**	Gallant Joel et al. (2016) Abstract "Novel INSTI GS-9883 10 Day Monotherapy in HIV-1 Infected Subjects " ASM2016	
	CO**	Gallant, Joel et al. (2016) "Novel Integrase Strand Transfer Inhibitor Bictegravir 10 Day Monotherapy in HIV-1-Infected Patients" ASMMicrobe2016	
	CP**	JERAJ, Z. (2020) "Experimental Report" 1-5.	
	CQ**	JOHNSON, L. (2015) "Gilead's New Four-in-One HIV Pill, Genvoya, Wins US Approval" *Medical Xpress*.	
	CR**	Jones, Gregg et al. (2016) Poster #413 "Bictegravir (GS-9883), a Novel HIV-1 Integrase Strand Transfer Inhibitor (INSTI) with Optimized In Vitro Resistance Profile"	
	CS**	KULKARNI, R. et al. (2014) "The Combined Anti-HIV-1 Activies of Emtricitabine and Tenofovir plus the Integrase Inhibitor Elvitegravir or Raltegravir Show High Levels of Synergy In Vitro" *Antimicrobial Agents and Chemotherapy* 58(10):6145-6150.	
	CT**	Lazerwith, Scott E. (2016) Poster #414 "Discovery of Bictegravir (GS-9883), a Novel, Unboosted, Once-Daily HIV-1 Integrase Strand Transfer Inhibitor (INSTI) with Improved Pharmacokinetics and In Vitro Resistance Profile"	

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Sheet	6	of	13

Complete if Known	
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	CU**	Lazerwith, Scott E. et al. Abstract "Discovery of GS-9883, an HIV-1 Integrase Strand Transfer Inhibitor (INSTI) with Improved Pharmacokinetics and In Vitro Resistance Profile "	
	CV**	Moss et al. (2012) Divalent metals and pH alter raltegravir disposition *in vitro*." American Society for Microbiology doi:10.1128/AAC.06407-11	
	CW**	Notice of Final Rejection dated 2020-03-19 for Korean Appl. No. 10-2018-7015929.	
	CX**	Notice of Opposition dated 2020-05-27 for European Patent No. 3346995 (Dr. Richard Cooke).	
	CY**	Notice of Opposition dated 2020-05-27 for European Patent No. 3346995 (Teva Pharmaceutical Industries Ltd.).	
	CZ**	Notice of Opposition dated 2020-05-28 for European Patent No. 3346995 (Sandoz GmbH).	
	CA1**	Notice of Preliminary Rejection dated 2019-09-04 for Korean Appl. No. 10-2018-7015929.	√
	CB1**	ODEFSEY Approval Package (2016) "Center for Drug Evaluation and Research"	
	CC1**	Office Action dated 2018-09-18 for Bolivian Appl. No. SP260-2016.	√
	CD1**	Office Action dated 2018-10-03 for Panamanian Appl. No. 92163.	√

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	CE1**	Office Action dated 2018-11-13 for Pakistani Appl. No. 696/2016.	
	CF1**	Office Action dated 2019-01-21 for European Appl. No. 16798063.0.	
	CG1**	Office Action dated 2019-03-25 for Bolivian Appl. No. SP260-2016	
	CH1**	Office Action dated 2019-09-22 for Gulf Cooperation Council Appl. No. 2016-32320.	
	CI1**	Office Action dated 2020-03-27 for Chinese Appl. No. 201680065167.3.	
	CJ1**	Office Action received 2019-05-27 for El Salvadorian Appl. No. 2018005682	
	CK1**	Office Action received 2019-07-01 for Eurasian Appl. No. 201890654	
	CL1**	Opposition dated 2017-06-20 for Colombian Appl. No. 15-265.717	√
	CM1**	PARK, T. et al. (2015) "Review of Integrase Strand Transfer Inhibitors for the Treatment of Human Immunodeficiency Virus Infection" *Expert Rev. Anti Infect. Ther.* 13(10):1195-1212.	
	CN1**	Patel, Parul et al. (2014) "Relative bioavailability of a paediatric granule formulation of the HIV intergrase inhibitor dolutegravir in healthy adult subjects." Antiviral Therapy (19):229-233	

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Sheet 8 of 13

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	CO1**	PATRICK, M. (2015) "Analyzing Gilead Sciences' Research and Development in 3Q15" *Market Realist* 1-2.	
	CP1**	Sax, P. et al. (2014) "Tenofovir Alafenamide Vs. Tenofovir Disoproxil Fumarate in Single Tablet Regimens for Initial HIV-1 Therapy: A Randomized Phase 2 Study" *J Acquir Immune Defic Syndr* 67(1):52-58.	
	CQ1**	Sax, Paul E. (2016) "Randomized Trial of Bictegravir or Dolutegravir with FTC/TAF for Initial HIV Therapy" CROI BIC 09/08/2016	
	CR1**	Search Report - Intl Search Report - Written Opinion dated January 24, 2007 for PCT/US2016/060989	
	CS1**	SHAH, B. et al. (2014) "Dolutegravir: A new Integrase Strand Transfer Inhibitor for the Treatment of HIV" *Pharmacotherapy* 34(5):506-520.	
	CT1**	SHENDE, P. et al. (2012) "Multi-layer Tablet: Current Scenario and Recent Advances" *International Journal of Drug Delivery* 4(4):418-426.	
	CU1**	Thomson Reuters Drug News (2011) "Gilead and Tibotec finalize agreement on single-tablet HIV regimen" http://drugnews.thomson-pharma.com/ddn/article.do?id=113441&source=Company Communication&section=AIDS#	
	CV1**	TIVICAY Product Label (Revised September 2018) GlaxoSmithKline, 44 Pages.	
	CW1**	TRIUMEQ Product Label (Revised November 2017) GlaxoSmithKline, 48 Pages.	
	CX1**	Tsiang, M. et al. "Antiviral Activity of GS-9883, a Potent Next Generation HIV-1 Integrase Strand Transfer Inhibitor" (ASMMicrobe20161)	

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Sheet	9	of	13

Complete if Known	
Application Number	17/738,803
Filing Date	May 6, 2022
First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	J. N. Worsham
Attorney Docket Number	1147-US-P2C2DC

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	CY1**	Tsiang, M. et al. "GS-9883, a Novel HIV-1 Integrase Strand Transfer Inhibitor (INSTI) with Optimized In Vitro Resistance Profile" (ASMMicrobe20162)	
	CZ1**	Tsiang, M. et al. (2016) Poster #416 "Antiviral Activity of Bictegravir (GS-9883), a Potent Next Generation HIV-1 Integrase Strand Transfer Inhibitor"	
	CA2**	U.S. National Library of Medicine (2019) "Safety and Efficacy of Switching to a FDC of GS-9883/F/TAF From E/C/F/TAF, E/C/F/TDF, or ATV+RTV+FTC/TDF in Virologically Supressed HIV-1 Infected Women" ClinicalTrials.gov. 1-8.	
	CB2**	USAN (2016) "Statement on a Nonproprietary Name Adopted by the USAN Council"	
	CC2**	Viread Draft Labeling (2001) Center for Drug Evaluation and Research 1-26.	
	CD2**	White, Kristen et al. (2016) "Potent Activity of Bictegravir (BIC; GS-9883), a Novel Unboosted; HIV-1 Integrase Strand Transfer Inhibitor (INSTI), Against Patient Isolates; with INSTI-Resistance" EU Workshop HIV Hepatitis;	
	CE2**	White, Kristen et al. (2016) Poster "The Integrase Strand Transfer Inhibitor Bictegravir has; a Long Integrase/DNA Dissociation Half-life" ;	
	CF2**	White, Kristen et al. (2016) The Integrase Strand Transfer Inhibitor Bictegravir has a Long Integrase/DNA Dissociation Half-life	
	CG2**	White, Kritsten et al. (2017) "Bictegravir Dissociation Half-life from HIV-1 G140S+Q148H Integrase/DNA Complexes " CROI BIC	
	CH2**	World Health Organization (2007) "Guidance on the Establishment of New INN Stems" 1-2.	

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Sheet 10 of 13

Complete if Known	
Application Number	17/738,803
Filing Date	May 6, 2022
First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	J. N. Worsham
Attorney Docket Number	1147-US-P2C2DC

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	CI2**	World Health Organization (2013) "The Use of Stems in the Selection of International Nonproprietary Names (INN) for Pharmaceutical Substances" 1-192.	
	CJ2**	World Health Organization Drug Information (2015) "International Nonproprietary Names for Pharmacuetical Substances (INN)" 29(2):1-107.	
	CK2**	YOSHINAGA, T. et al. (2015) "Antivrial Characteristics of GSK1265744, an HIV Integrase Inhibitor Dosed Orally or by Long-Acting Injection" *Antimicrobial Agents and Chemotherapy* 59(1):397-406.	
	CL2**	Zhang et al. (2017) "Clinical Pharmacology of the HIV Integrase Strand Transfer Inhibitor Bictegravir " CROI BIC 09/26/2016	
	CM2	ClinicalTrials.gov Archive. (2014) "A Phase 1b Randomized, Double-Blinded, Sequential Cohort Placebo-Controlled Study of the Safety, Pharmacokinetics, and Antiviral Activity of GS-9883 in HIV-1 Infected Subjects", https://clinicaltrials.gov/archive/NCT02275065/2014_10_26, 3 pages.	
	CN2	European Medicines Agency, Committee for Medicinal Products for Human Use. (2018) "Assessment report - Biktarvy", 104 pages.	
	CO2	ClinicalTrials.gov Archive. (2015) "A Phase 2, Randomized, Double-Blinded Study of the Safety and Efficacy of GS-9883 + Emtricitabine/Tenofovir Alafenamide Versus Dolutegravir + Emtricitabine/Tenofovir Alafenamide in HIV-1 Infected, Antiretroviral Treatment-Naive Adults", https://clinicaltrials.gov/archive/NCT02397694/2015_03_24, 4 pages.	
	CP2**	Exam Report dated 2019-07-26 for Indian Appl. No. 201817013772.	
	CQ2	Examination Report dated 2021-03-24 for Australian Appl. No. 2020200995, 5 pages.	
	CR2	KOMMAVAPARU, P. et al. (2015) "Preparation and characterization of rilpivirine solid dispersions with the application of enhanced solubility and dissolution rate", Beni-Suef University Journal of Basic and Applied Sciences 4, pp. 71-79.	

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Sheet	11	of	13		

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Application Number	17/738,803
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	CS2	European Medicines Agency, Committee for Medicinal Products for Human Use. (2015) "Assessment report - Genvoya", extract, pp.1-20.	
	CT2	ZIGA. (2021) Experimental Report, Sandoz GmbH, 8 pages.	
	CU2	SMITH, S. et al. (2018) "Efficacies of Cabotegravir and Bictegravir against drug-resistant HIV-1 integrase mutant", Retrovirology 15(37), 18 pages.	
	CV2	ACOSTA, R. et al. (2021) "*In Vitro* Forgiveness of Oral and Long-Acting INSTI-Containing Regiments at Drug Concentrations Simulating Variable Adherence", 18th European AIDS Conference, 1 page.	
	CW2	LOZANO, A. et al. (2020) "Failure to bictegravir and development of resistance mutations in an antiretroviral-experienced patient", Antiviral Research 179, 104717, pp. 1-4.	
	CX2	CHAMBERLAIN N. et al. (2021) "Case Report: Emergent Resistance in a Treatment-Naïve Person With Human Immunodeficiency Virus Under Bictegravir-Based Therapy", Open Forum Infectious Diseases, pp. 1-3.	
	CY2	SONG I. et al. (2009) Poster - Pharmacokinetic (PK) and Pharmacodynamic (PD) Relationship of S/GSK1349572, a Next Generation Integrase Inhibitor (INI), in HIV-1 Infected Patients, 5th International AIDS (IAS) Conference on HIV Pathogenesis, Treatment and Prevention, 1 page.	
	CZ2	ERON. (2009) Report - New Drugs, New strategies, 5th International AIDS (IAS) Conference on HIV Pathogenesis, Treatment and Prevention, 5 pages.	
	CA3	Notice of Preliminary Rejection dated 2021-12-23 for Korean Appl. No. 10-2020-7025458, 4 pages.	
	CB3	Office Action dated 2022-05-24 for Taiwanese Appl. No. 110129951, 23 pages.	√

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Sheet 12 of 13

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Art Unit	1615
Examiner Name	J. N. Worsham
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	CD3	Office Action and Search Report dated 2022-07-27 for Chinese Appl. No. 202110669391.6, 18 pages.	√
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	CF3	Office Action dated 2023-01-31 for Korean Appl. No. 10-2020-7025458, 8 pages.	√
	CG3	Notice of Preliminary Rejection dated 2023-03-23 for Korean Appl. No. 10-2023-7001933, 4 pages.	
	CH3	Patentee's Response to Oppositions dated 2021-01-11 for European Patent No. EP3346995, 24 pages.	
	CI3	Brief Communication and Further Submissions from Opponent Dr. Richard Cooke dated 2021-03-09 for European Patent No. EP3346995, 6 pages.	
	CJ3	Brief Communication and Further Submissions from Opponent Sandoz GmbH dated 2021-03-24 for European Patent No. EP3346995, 12 pages.	
	CK3	Brief Communication and Further Submissions from Opponent Teva Pharmaceutical Industries Ltd. dated 2021-03-26 for European Patent No. EP3346995, 10 pages.	
	CL3	Summons to Attend Oral Proceedings and Preliminary Opinion dated 2021-06-24 for European Patent No. EP3346995, 19 pages.	

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	CO3	Summons to Attend Oral Proceedings dated 2022-04-05 for European Patent No. EP3346995, 18 pages.	
	CP3	Further Submissions and Response to Preliminary Opinion from Opponent Teva Pharmaceutical Industries Ltd. dated 2022-08-25 for European Patent No. EP3346995, 10 pages.	
	CQ3	Further Submissions from Opponent Dr. Richard Cooke dated 2022-08-26 for European Patent No. EP3346995, 6 pages.	
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	CS3	Patentee's Response to Summons and Written Submissions dated 2022-08-26 for European Patent No. EP3346995, 5 pages.	
	CT3	Interlocutory Decision and Minutes of the Oral Proceedings dated 2022-12-23 for European Patent No. EP3346995, 101 pages.	

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PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	735	((("GILEAD") near3 ("SCIENCES") near3 ("INC"))).AS,AANM.	(USPAT)	OR	ON	ON	2022/12/01 01:36 PM
L2	127	((("COLLMAN") near3 ("Benjamin")) OR (("HONG") near3 ("Lei")) OR (("KOZIARA") near3 ("Joanna"))).INV.	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2022/12/01 01:37 PM
L3	2	"10548846".pn.	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2022/12/01 01:37 PM
L4	4491	tenofovir ADJ alafenamide	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/12/01 01:43 PM
L5	2629	L4 SAME emtricitabine	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/12/01 01:43 PM
L6	2067	L5 AND tablet	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO,	OR	ON	ON	2022/12/01 01:43 PM

			MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)				
L7	104	L5 AND pyrazino	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/12/01 01:43 PM
L9	1	2016/0016973	(US-PGPUB; USPAT)	OR	ON	ON	2022/12/01 02:07 PM
L10	2	"20160016973"	(US-PGPUB; USPAT)	OR	ON	ON	2022/12/01 02:07 PM
L11	22692	tenofovir SAME emtricitabine	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2023/04/12 10:17 AM
L12	831	L11 SAME bictegravir	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2023/04/12 10:18 AM
L13	97	L12 AND (multilayer OR	(US-PGPUB; USPAT;	OR	ON	ON	2023/04/12

		bilayer OR trilayer)	USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)				10:19 AM
L14	1266917	(A61K9/209 OR A61K9/0053 OR A61K9/2013 OR A61K9/2027 OR A61K9/2054 OR A61K9/2086 OR A61K9/2095 OR A61K9/28 OR A61K9/2833 OR A61K31/513 OR A61K31/5365 OR A61K31/537 OR A61K31/553 OR A61K31/675 OR A61P31/18 OR A61K9/282 OR A61K9/20 OR A61K2300/00).cpc.	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2023/04/12 10:20 AM
L15	19108	L14 AND tenofovir	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2023/04/12 10:20 AM
L16	12934	L15 AND emtricitabine	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO,	OR	ON	ON	2023/04/12 10:20 AM

			NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)				
L17	768	L16 AND bictegravir	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2023/04/12 10:20 AM
L18	57	L17 AND (multilayer OR bilayer OR trilayer)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2023/04/12 10:20 AM

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1002
798 of 1074

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United States Patent and Trademark Office
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
17/738,803	05/06/2022	Benjamin Micah Collman	1147-US-P2C2DC

CONFIRMATION NO. 2232

POA ACCEPTANCE LETTER

25000
GILEAD SCIENCES, INC
333 LAKESIDE DR
FOSTER CITY, CA 94404

OC000000137740583

Date Mailed: 04/14/2023

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 04/05/2023.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/byemane/

TO: IPDocketing@gilead.com,IPUS2@gilead.com
FROM: noreply@uspto.gov
CC: PatentCenter_eOfficeAction@uspto.gov
SUBJECT: USPTO: Patent Electronic System - Correspondence Notification for Customer Number 25000

Fri Apr 14 05:36:32 EDT 2023

Dear Patent Center Customer:

Correspondence Address:
GILEAD SCIENCES, INC
333 LAKESIDE DR
FOSTER CITY,CALIFORNIA,94404
UNITED STATES

This is a courtesy notification regarding the following USPTO patent application(s) associated with your Customer Number, 25000, that have new outgoing correspondence. This correspondence is now available for viewing in Patent Center.

The official date of notification of the outgoing correspondence will be indicated on the form (e.g., PTOL-90) accompanying the correspondence.

Disclaimer:
The list of documents shown below are provided as a courtesy and is not part of the official file wrapper. The content of the images shown in the Image File Wrapper is the official record.

Application	Document	Mailroom Date	Attorney Docket No.
17738803	N570	04/14/2023	1147-US-P2C2DC

To view your correspondence online, please sign in to Patent Center and then select Workbench/View correspondence. To update your email address(es), select Manage/Manage customer numbers.

If you have any questions, please contact the Patent Electronic Business Center (EBC) at ebc@uspto.gov or 866-217-9197 Monday – Friday, 6 a.m. to midnight ET.

Please do not reply to this email as it was sent from an unmonitored mailbox.

Sincerely,

The Patent Center Team

TO: IPDocketing@gilead.com,IPUS2@gilead.com
FROM: noreply@uspto.gov
CC: PatentCenter_eOfficeAction@uspto.gov
SUBJECT: USPTO: Patent Electronic System - Correspondence Notification for Customer Number 25000

Mon Apr 17 05:12:19 EDT 2023

Dear Patent Center Customer:

Correspondence Address:
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333 LAKESIDE DR
FOSTER CITY,CALIFORNIA,94404
UNITED STATES

This is a courtesy notification regarding the following USPTO patent application(s) associated with your Customer Number, 25000, that have new outgoing correspondence. This correspondence is now available for viewing in Patent Center.

The official date of notification of the outgoing correspondence will be indicated on the form (e.g., PTOL-90) accompanying the correspondence.

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Application	Document	Mailroom Date	Attorney Docket No.
17738803	NOA	04/17/2023	1147-US-P2C2DC
17738803	1449	04/17/2023	1147-US-P2C2DC

To view your correspondence online, please sign in to Patent Center and then select Workbench/View correspondence. To update your email address(es), select Manage/Manage customer numbers.

If you have any questions, please contact the Patent Electronic Business Center (EBC) at ebc@uspto.gov or 866-217-9197 Monday – Friday, 6 a.m. to midnight ET.

Please do not reply to this email as it was sent from an unmonitored mailbox.

Sincerely,

The Patent Center Team

Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (01-22)
Approved for use through 05/31/2024. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	17738803	Filing Date	2022-05-06	Docket Number (if applicable)	1147-US-P2C2DC	Art Unit	1615
First Named Inventor	Benjamin Micah Collman			Examiner Name	J. N. Worsham		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

☐ Other _____

☒ Enclosed

☐ Amendment/Reply

☒ Information Disclosure Statement (IDS)

☐ Affidavit(s)/ Declaration(s)

☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____
(Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

☒ **The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**
The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 071250

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

Applicant Signature

EFS - Web 2.1.16

PTO/SB/30EFS (01-22)
Approved for use through 05/31/2024. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Signature of Registered U.S. Patent Practitioner			
Signature	/Donna Johnson Gressler/	Date (YYYY-MM-DD)	2023-04-20
Name	Donna Johnson Gressler	Registration Number	45544

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/738,803	04/20/2023 03:34:36 PM ET	1147-US-P2C2DC

Title of Invention

THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	2232	FILED BY	Frances Tsai
PATENT CENTER #	61954880	AUTHORIZED BY	Donna Gressler
CUSTOMER #	25000	FILING DATE	05/06/2022
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Benjamin Micah Collman

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 071250	E20234JF35559135	Frances Tsai

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
1801	REQUEST FOR CONTINUED EXAMINATION (RCE) - 1ST REQUEST (SEE 37 CFR 1.114)	1360.00	1	1360.00
			TOTAL AMOUNT:	$1,360.00

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/738,803	**04/20/2023 03:34:36 PM ET**	**1147-US-P2C2DC**

Title of Invention

THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	2232	FILED BY	Frances Tsai
PATENT CENTER #	61954880	FILING DATE	05/06/2022
CUSTOMER #	25000	FIRST NAMED INVENTOR	Benjamin Micah Collman
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Donna Gressler

Documents

TOTAL DOCUMENTS: 5

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
1147-US-P2C2DC_IDS.pdf		4	-	66 KB
1147-US-P2C2DC_IDS-TRAN.LET.pdf	(1-2)	2	Transmittal Letter	25 KB
1147-US-P2C2DC_IDS-IDS.pdf	(3-4)	2	Information Disclosure Statement (IDS) Form (SB08)	36 KB
1147-US-P2C2DC_RCE.pdf		3	Request for Continued Examination (RCE)	1628 KB
NPL_OA_2021-12-23_1147-KR-P2D_T.pdf		7	Non Patent Literature	732 KB

NPL_OA_2023-03-23_1147-KR-P2D2_T.pdf	6	Non Patent Literature	717 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
1147-US-P2C2DC_IDS.pdf	DEB44D6F3966A20404E32FA145A1BAD6E099071F1109338D74909DA3F832F9E14E5306C80A98ABBDBEAEEB8316F3CFC27836D5F365CCB4B769B799EA19FB4338
1147-US-P2C2DC_IDS-TRAN.LET.pdf	830CF8A57C1D311333A89BC6F88CF7CCB769AC6063A11DC8E7F8E1BA1CE417AC445CD17063AAD7A681CF5E30773368A94AD44F6A8382264D46DAAC5802F95404
1147-US-P2C2DC_IDS-IDS.pdf	D25160E17018D39681FE68A08459E30835263A590A774E9897F125810180776A30EB265DD0FC784B69EEE42CA6EF6068195A20A73A0EB686E216985B8ADA0C4A
1147-US-P2C2DC_RCE.pdf	12443D0E79727BFCDD95D012DA1D49FAD6817461C6B6A7A076EC3A32C290A293089C234E423F44C15A7A0EED6329D606BA51C2D385ABF8B4C3000DCA9A7B6B70
NPL_OA_2021-12-23_1147-KR-P2D_T.pdf	674C1F03071838828B2BDF6816B269F85B4B7CF85FACEC799A11D1124E41AC19EC25C8C1CEED816DFBB6B821524DD2317A3A8A82F9EB08707C9DDE0CCAAA7844
NPL_OA_2023-03-23_1147-KR-P2D2_T.pdf	5B81F27F9F7A792E7C07A0BBEF3BD4F6F8BA8CBA430E309845BDF5D3DE0EAE9EFD744D2D90362A5BC6EDA8C86AE1A4BE06EA8F60A75BAE22B522DE463D927610

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

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National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: April 20, 2023
Electronic Signature for Frances Tsai: /Frances Tsai/

Docket No.: 1147-US-P2C2DC
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Benjamin Micah Collman et al.

Application No.: 17/738,803

Confirmation No.: 2232

Filed: May 6, 2022

Art Unit: 1615

For: THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS

Examiner: J. N. Worsham

INFORMATION DISCLOSURE STATEMENT (IDS)

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

Pursuant to 37 C.F.R. §§ 1.56, 1.97, and 1.98, the attention of the United States Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of the above-identified application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Information Disclosure Statement, pursuant to 37 C.F.R. § 1.114(c), accompanies the Request for Continued Examination (37 C.F.R. § 1.114) submitted herewith.

A translation of the non-English language references is attached.

In accordance with 37 C.F.R. § 1.98(a)(2)(ii), copies of U.S. patents and U.S. patent application publications are not submitted. Submitted herewith are copies of foreign patents and non-patent literature in accordance with 37 C.F.R. § 1.98(a)(2).

In accordance with 37 C.F.R. § 1.97(g), the filing of this Information Disclosure Statement shall not be construed as a representation that a search has been made. In accordance with 37 C.F.R. § 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that the information cited in this Information Disclosure Statement is, or is considered to be, material to patentability as defined in 37 C.F.R. § 1.56(b).

It is submitted that the Information Disclosure Statement is in compliance with 37 C.F.R. § 1.98, and the Examiner is respectfully requested to consider the listed references.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 07-1250, under Order No. 1147-US-P2C2DC from which the undersigned is authorized to draw.

Dated: April 20, 2023

Respectfully submitted,

Electronic signature: /Donna Johnson Gressler/
Donna Johnson Gressler
Registration No.: 45,544
GILEAD SCIENCES, INC.
Correspondence Customer Number: 25000
(650) 574-3000
Agent For Applicant

PTO/SB/08a (07-09)
Approved for use through 05/31/2024. OMB 0651-0031
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	17/738,803
Filing Date	May 6, 2022
First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	J. N. Worsham
Attorney Docket Number	1147-US-P2C2DC

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

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Dated: April 20, 2023 Electronic Signature for Donna Johnson Gressler: /Donna Johnson Gressler/

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PTO/SB/08b (07-09)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	17/738,803
Filing Date	May 6, 2022
First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	J. N. Worsham
Attorney Docket Number	1147-US-P2C2DC

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CA	Notice of Preliminary Rejection dated 2021-12-23 for Korean Appl. No. 10-2020-7025458, 7 pages.	√
	CB	Notice of Preliminary Rejection dated 2023-03-23 for Korean Appl. No. 10-2023-7001933, 6 pages.	√

Examiner Signature		Date Considered	

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