

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

GILEAD SCIENCES, INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	C.A. No. 22-cv-00615 (MN)
	)	
LUPIN LTD., LAURUS LABS LIMITED, AND	)	
CIPLA LIMITED,	)	
Defendants.	)	
_____	)	

**DEFENDANTS LAURUS LABS LIMITED, CIPLA LIMITED, AND LUPIN LIMITED'S
AMENDED INITIAL INVALIDITY CONTENTIONS REGARDING U.S. PATENT NOS.
10,548,846, 10,385,067, 9,708,342 AND 11,744,802**

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Claims 2 and 6-8 are also obvious over WO '116 in view of the prior art and arguments discussed in Sections V.F.(1).a.ii-iv, V.F.(2).b-d, and V.F.(3).b-d. Indeed, the further limitations for these claims are obvious in view of the contentions made in those sections.

VI. NVALIDITY OF U.S. PATENT NO. 11,744,802

A. Background Information for the '802 Patent

The '802 patent issued on September 5, 2023 from U.S. Appl. No. 17/738,803 (“the '803 application”) filed on May 6, 2022, which is a continuation of U.S. Appl. 16/987,081 filed on August 6, 2020 (now abandoned), which is a continuation of U.S. Appl. No. 16/713,380 filed on December 13, 2019 (now abandoned), which is a continuation of U.S. Appl. No. 15/346,335 (“the '335 application”) filed on November 8, 2016 (now U.S. Patent No. 10,548,846). The '802 patent claims priority to U.S. Provisional Appl. Nos. 62/399,999 filed on September 26, 2016 and 62/253,042 filed on November 9, 2015. It names Benjamin Collman, Lei Hong, and Joanna Koziara as inventors and Gilead as the assignee. The '802 patent is also assigned to Gilead at reel/frame 063358/0446 in the U.S. Patent and Trademark Office assignment database.

The '802 patent will expire on November 8, 2036, which is 20 years from the filing date of the '335 application. It did not receive any extension to its term based on patent term adjustment (PTA) time, and Gilead filed a terminal disclaimer in view of the '846 patent, which also reportedly expires on November 8, 2036.

B. Specification of the '802 Patent

The '802 patent is titled “Therapeutic Compositions for Treatment of Human Immunodeficiency Virus,” and relates to “[a] solid oral dosage form ... comprising [BIC] or a pharmaceutically acceptable salt thereof, [TAF] or a pharmaceutically acceptable salt thereof, and [FTC] or a pharmaceutically acceptable salt thereof.” '802 patent, Abstract.

According to the Background of the Invention, “[a] goal of antiretroviral therapy is to achieve viral suppression in the HIV infected patient[, where] [t]reatment guidelines published by the United States Department of Health and Human Services provide that achievement of viral suppression requires the use of combination therapies, i.e., several drugs from at least two or more drug classes.” ’802 patent, 1:46-51. Accordingly, the inventors named on the ’802 patent are said to have “successfully formulated an oral dosage form containing [BIC (an HIV integrase inhibitor)], [TAF (a nucleotide reverse transcriptase inhibitor (NtRTI))] and [FTC (a nucleoside reverse transcriptase inhibitor (NRTI))] ... [for] treating viral infections such as HIV.” *Id.* at 2:36-40; *see also id.* at 8:50-60.

According to the ’802 patent, “the inventors have found that the use of a fixed dose combination may assist in achieving appropriate pharmacokinetic parameters and/or adequate tablet stability[, where] ... the use of a multilayer tablet as a particular type of fixed dose combination may also provide pharmacokinetic and/or stability benefits.” ’802 patent, 4:10-15. As such, the ’802 patent is further directed to a “multilayer tablet” comprising (a) BIC or a pharmaceutically acceptable salt thereof, (b) TAF or a pharmaceutically acceptable salt thereof, and (c) FTC or a pharmaceutically acceptable salt thereof. *Id.*

The ’802 patent states that “[i]n certain embodiments, the use of a fixed dose combinations [sic, combination], 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.” ’802 patent, 9:53-58. In particular, the patent states that “it has been observed that the dissolution of [BIC] varies depending on whether the tablet is in a fixed dose combination formulation with [TAF] and [FTC] and/or whether the tablet is a monolayer or multilayer tablet.” *Id.* at 9:58-63. The ’802 patent further notes that “the presence

of certain excipients in the multilayer tablet formulation (or absence of others) affects the dissolution profile of one or more of the active ingredients within the dosage form.” *Id.* at 9:63-66. As such, the provision of a tablet with particular pharmacokinetic parameters, e.g., pharmacokinetic parameters is said to be “a particular advantage afforded by the present disclosure.” *Id.* at 9:66-10:2.

Regarding the amount of BIC, TAF, and FTC contained in a tablet when present as pharmaceutically acceptable salts, the ’802 patent states the following:

As used herein, and in the absence of a specific reference to a particular pharmaceutically acceptable salt and/or solvate of [BIC], any dosages, whether expressed in e.g. milligrams or as a % by weight, should be taken as referring to the amount of the compound of Formula I free acid A reference to ‘50 mg of BIC or a pharmaceutically acceptable salt and/or solvate thereof’ means an amount of [BIC] or a pharmaceutically acceptable salt and/or solvate thereof which provides the same amount of [BIC] as 50 mg of [BIC] free acid.

’802 patent, 6:4-28.

[I]n the absence of a specific reference to a particular pharmaceutically acceptable salt and/or solvate of [TAF], any dosages, whether expressed in e.g. milligrams or as a % by weight, should be taken as referring to the amount of [TAF] For example, therefore, a reference to ‘25 mg [TAF] or a pharmaceutically acceptable salt and/or solvate thereof’ means an amount of [TAF] or a pharmaceutically acceptable salt and/or solvate thereof which provides the same amount of [TAF] as 25 mg of [TAF] free base.

Id. at 7:22-48.

Typically, [FTC] is present as a free base. As used herein, and in the absence of a specific reference to a particular pharmaceutically acceptable salt and/or solvate of [FTC], any dosages, whether expressed in e.g. milligrams or as a % by weight, should be taken as referring to the amount of [FTC]”

Id. at 8:22-36.³⁶

³⁶ In view of these disclosures, a 50 mg dose of BIC freebase translates into a 52.450 mg dose of BIC Na (50 mg/449.39 MW BIC X 471.38 MW BIC Na = 52.450 mg). A 25 mg dose of TAF freebase translates into a 28.045 mg dose of TAF hemifumarate (25mg/476.47 MW TAF X 534.51 MW TAF Hemi = 28.045 mg). Since EMT is used as a free base, there is no need for a similar calculation.

The '802 patent states that the tablets disclosed therein will typically include one or more excipients, such as “basifying agents, solubilisers, glidants, fillers, binders, lubricants, diluents, preservatives, surface active agents, dispersing agents and the like[, which] ... will generally be present in admixture within the tablet.” '802 patent, 13:10-17. Examples of lubricants, glidants and flow aids include, but are not limited to, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oil, glyceryl palmitostearate, glyceryl behenate, sodium stearyl fumarate, colloidal silicon dioxide, and talc. *Id.* at 13:30-51. Examples of disintegrants include, but are not limited to, starches, celluloses, cross-linked PVP (crospovidone), sodium starch glycolate, and croscarmellose sodium. *Id.* at 13:25-67. Examples of fillers (also known as bulking agents or diluents) include, but are not limited to, starches, maltodextrins, polyols (such as lactose), and celluloses. *Id.* at 14:1-25.

Certain embodiments of the '802 patent provide for tablets containing microcrystalline cellulose as a filler and do not contain lactose. '802 patent, 14:3-6. In one embodiment directed to multilayer tablets, the layer containing TAF does not contain lactose and/or starch. *Id.* at 10:56-61. In another embodiment directed to multilayer tablets, the layer containing BIC does not contain lactose, crospovidone and/or sodium stearyl fumarate. *Id.* In a further embodiment directed to multilayer tablets, about 5% to about 10% by weight of the second layer of the multilayer tablet is croscarmellose sodium, where the use of about 5 to 7% (e.g. about 6%) croscarmellose sodium by weight of the second layer may provide enhanced dissolution of BIC, relative to other disintegrants e.g. polyvinylpyrrolidone (crospovidone). *Id.* at 29:39-46. For example, the '802 patent states that “the use of about 5 to 10% croscarmellose sodium by weight of the second layer may provide enhanced dissolution of [BIC or BIC sodium], relative to other disintegrants e.g. polyvinylpyrrolidone (crospovidone).” *Id.* at 29:46-51.

Although uncoated tablets may be used according to the '802 patent, it is said that coated tablets are more typical, in which case a conventional non-enteric coating may be used. '802 patent, 14:28-33. This includes film coatings composed of hydrophilic polymer materials, such as hydroxypropylmethyl cellulose (HPMC), methylcellulose, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), poly(vinylalcohol-co-ethylene glycol) and other water soluble polymers. *Id.* at 14:33-39. The amount of coating is said to be generally between about 2-4% of the core's weight. *Id.* at 14:51-53.

The '802 patent concludes with a number of exemplary multilayer tablet formulations, including the following:

Example 2 – Bilayer Tablet Formulation F2

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

'802 patent, 58:33-58. The formulation of bilayer tablet F2 was manufactured using a dry granulation by roller compaction process, where the FTC/TAF final powder blend was manufactured by dry granulation of FTC and TAF with excipients (microcrystalline cellulose, croscarmellose sodium, intergranular magnesium stearate), followed by blending with extragranular lubricant (extragranular magnesium stearate), and where the final powder blend of

BIC Na 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), followed by compression of the FTC/TAF final powder blend into a layer 1 and compression of the BIC sodium final powder blend into a layer 2 to give a final bilayer tablet core, which was then film coated. *Id.* at 58:63-59:13.

Example 5 – Bilayer Tablet Formulations F4, F5, and F6

Ingredient	Emtricitabine/ tenofovir alafenamide hemifumarate Layer (mg/tablet)	Bilayer tablet F4	Bilayer tablet F5	Bilayer tablet F6
		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
Tablet Core Weight		730	730	730

Id. at 65:52-66:24.

Example 6 – Bilayer Tablet Formulation F7

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

Id. at 66:32-66.

The '802 patent also provides dissolution data for the aforementioned bilayer tablet formulations F2, F4, F5 and F6, as shown below in Figure 3.

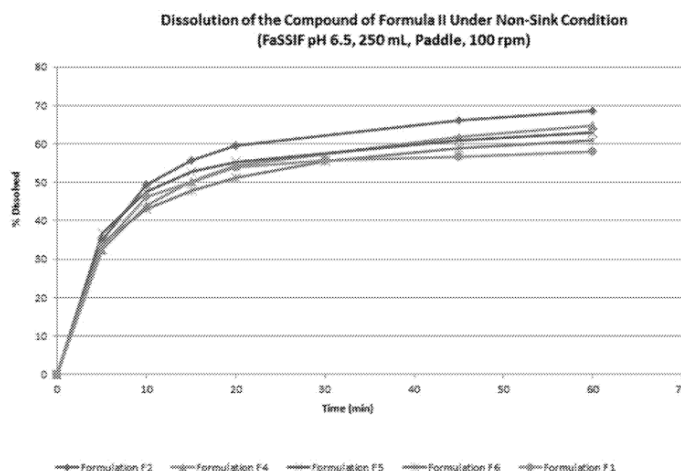


FIGURE 3

These dissolution studies were carried out to assess “the effect of specific excipients on dissolution of [BIC],” where formulation F4 is similar to formulation F2, with croscarmellose sodium being replaced with crospovidone, formulation F5 is similar to formulation F2, with magnesium stearate being replaced with sodium stearyl fumarate, and 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. '802 patent, 65:52-62. According to the specification, the data provided in Figure 3 “demonstrates that the substitution of each excipient enhances the dissolution of [BIC].” *Id.* at 66:26-30.

Further according to the '802 patent:

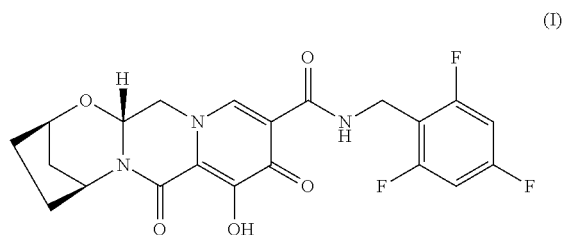
The total exposure of the compound of [BIC], under fasted conditions, was approximately 30% higher when dosed in the bilayer tablet formulation F2, containing two additional therapeutic agents (TAF and FTC), compared to single agent tablet formulation F1, co-dosed with a fixed dose combination tablet 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).

'802 patent, 61:24-36.

C. Asserted Claims of the '802 Patent

The claims of the '846 patent asserted against one or more defendants, *i.e.*, claims 1-13, are as follows:

1. 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.

2. The tablet of claim 1, wherein the tablet comprises 50 mg of the compound of Formula I as a pharmaceutically acceptable salt thereof.
3. The tablet of claim 1, wherein the tablet comprises 25 mg tenofovir alafenamide as a pharmaceutically acceptable salt thereof.
4. The tablet of claim 1, 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.
5. The tablet of claim 1, wherein the tablet comprises 52 mg of the sodium salt of the compound of Formula I.

In a December 6, 2022 Non-Final Office Action, the Examiner rejected claims 52-59 for anticipation by Carra. 12-6-22 Action, 2-4. The Examiner also rejected claims 52-64 for obviousness over Carra in view of Dahl. *Id.* at 4-8. Claims 52-64 were additionally rejected for obviousness-type double patenting over claims 1-10 of the '846 patent. *Id.* at 8-9.

In an April 5, 2023 Response, the applicant argued that the Carra references were published after the effective filing date of the '803 application, and are not available as prior art because the '803 application and Carra are commonly owned by Gilead. 4-5-23 Response, 4. The applicant therefore requested withdrawal of the anticipation and obviousness rejections over Carra. *Id.* at 4-5. In responding to the double patenting rejection, the applicant filed a terminal disclaimer over the '846 patent. *Id.* at 5; *see also* 4-5-23 Terminal Disclaimer.

On April 17, 2023, claims 52-64 were allowed. 4-17-23 Notice of Allowance, 1. The Examiner stated the following reasons for allowance:

The closest prior art of Carra et al. (WO2015/196116, U.S. Patent 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 1 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 bicitegravir in a fixed dose combination of bicitegravir, emtricitabine, and tenofovir alafenamide relative to its exposure when co-administered as a single agent of bicitegravir with a fixed dose combination of emtricitabine and tenofovir alafenamide.

Id. at 2.

On April 20, 2023, the Applicant submitted a Request for Continued Examination (RCE) with an Information Disclosure Statement (IDS). 4-20-23 RCE, 1. A second Notice of Allowance followed on June 1, 2023. 6-1-23 Notice of Allowance, 1. On June 8, 2023, the Applicant submitted a second RCE with an IDS. 6-8-23 IDS and RCE. 6-8-23 RCE, 1. A third Notice of Allowance followed on June 30, 2023. 6-30-23 Notice of Allowance, 1.

The issue fee was paid on July 10, 2023, and the '803 application issued as the '802 patent on September 5, 2023. See 8-16-23 Issue Notification.

E. The Person of Ordinary Skill in the Art for the '802 Patent

For the purposes of these invalidity contentions as to the '802 patent, a POSA (or “skilled artisan”) would include someone with a Ph.D. and at least three years of work experience in the field(s) of pharmaceuticals, pharmacology, and/or pharmaceutical formulations, or possibly a related discipline such as pharmacy, who had at least two years of practical experience working in pharmaceutical formulations. The skilled artisan could hold a lesser degree such as a bachelor’s or master’s in one of these disciplines but would need greater practical experience in drug discovery. The skilled artisan would possess certain skills and experience relevant to the formulation of fixed dose combinations containing multiple active pharmaceutical ingredients (API), including an understanding of when different APIs require separation from one another in a formulation and/or need to be separated from excipients in a formulation. Further, the POSA had access to and would consult with a collaborative team of skilled artisans comprising those skilled in other fields such as virology, pharmacokinetics, organic chemistry, medicinal chemistry, as well as those familiar with the regulatory context within which solid pharmaceutical products are developed, and approved, by the US FDA, or individuals working in comparable fields with an advanced degree (such as a Ph.D. or M.D.).

F. Invalidity Contentions for the '802 Patent

(1) The Asserted Claims of the '802 Patent Would Have Been Obvious

The obviousness analysis for the Asserted Claims of the '846 patent in Section V.F.3 is incorporated herein in its entirety. The Asserted Claims of the '802 patent contain many of the same limitations of the Asserted Claims of the '846 patent, albeit without the “multilayer” term in

the preamble of claim 1 of the '846 patent, and where the total tablet weight of “less than 1000 mg” in claim 1 of the '846 patent appears in dependent claim 9 of the '802 patent. Accordingly, Defendants' obviousness contentions for the Asserted Claims of the '846 patent apply equally to the Asserted Claims of the '802 patent, including Defendants' obviousness contentions when the “multilayer” preamble is limiting because such multilayer tablets constitute species of the Asserted Claims of the '802 patent.

As set forth in Appendix D, the Asserted Claims of the '802 patent are invalid as obvious under 35 U.S.C. § 103 over the prior art identified in Section II or Appendix D. Defendants identify the following example prior art combinations, each of which (i) a POSA would have been motivated to combine, and (ii) provide, at the very least, a reasonable expectation of success. In addition to the below sections VI.F.2.a-d, which outline exemplary combinations, Defendants identify the following example prior art combinations, each of which (i) a POSA would have been motivated to combine, and (ii) provide, at the very least, a reasonable expectation of success:

- The '385 patent + the knowledge of one of ordinary skill in the art;
- US '356 + the knowledge of one of ordinary skill in the art;
- WO '323 + the knowledge of one of ordinary skill in the art;
- The '385 patent + WO '846 + the knowledge of one of ordinary skill in the art;
- US '356 (or WO '323) + WO '351 (or US '332) + the knowledge of one of ordinary skill in the art;
- US '356 + WO '846 + the knowledge of one of ordinary skill in the art;
- The '356 patent + NCT '694 + BIC Safety Study + the knowledge of one of ordinary skill in the art;
- WO '323 patent + WO '846 + the knowledge of one of ordinary skill in the art;
- The '323 patent + NCT '694 + BIC Safety Study + the knowledge of one of ordinary skill in the art;

- The '385 patent + WO '351 + the knowledge of one of ordinary skill in the art;
- US '356 + WO '846 + WO '351 + the knowledge of one of ordinary skill in the art;
- US '356 + NCT '694 + BIC Safety Study + WO '351 + the knowledge of one of ordinary skill in the art; WO '323 patent + WO '846 + WO '351 + the knowledge of one of ordinary skill in the art;
- The '385 patent + Shende + the knowledge of one of ordinary skill in the art;
- US '356 + Shende + the knowledge of one of ordinary skill in the art;
- WO '323 + Shende + the knowledge of one of ordinary skill in the art;
- The '385 patent + WO '846 + Shende + the knowledge of one of ordinary skill in the art;
- US '356 + WO '846 + Shende + the knowledge of one of ordinary skill in the art;
- WO '323 patent + WO '846 + Shende + the knowledge of one of ordinary skill in the art;
- The '385 patent + WO '351 + Shende + the knowledge of one of ordinary skill in the art;
- The '385 patent + Abebe + the knowledge of one of ordinary skill in the art;
- US '356 + Abebe + the knowledge of one of ordinary skill in the art;
- WO '323 + Abebe + the knowledge of one of ordinary skill in the art;
- The '385 patent + WO '846 + Abebe + the knowledge of one of ordinary skill in the art;
- US '356 + WO '846 + Abebe + the knowledge of one of ordinary skill in the art;
- WO '323 patent + WO '846 + Abebe + the knowledge of one of ordinary skill in the art;
- The '385 patent + WO '351 + Abebe + the knowledge of one of ordinary skill in the art;
- The '385 patent + WO '466 + the knowledge of one of ordinary skill in the art;
- US '356 + WO '466 + the knowledge of one of ordinary skill in the art;
- WO '323 + WO '466 + the knowledge of one of ordinary skill in the art;

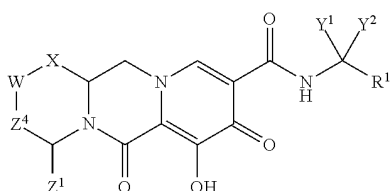
- The '385 patent + WO '846 + WO '466 + the knowledge of one of ordinary skill in the art;
- US '356 + WO '846 + WO '466 + the knowledge of one of ordinary skill in the art;
- WO '323 patent + WO '846 + WO '466 + the knowledge of one of ordinary skill in the art;
- The '385 patent + WO '351 + WO '466 + the knowledge of one of ordinary skill in the art;
- Any one of the above in view of one of ordinary skill in the art (as demonstrated by, and thus in further combination with, any of the other prior art references cited in Section II or Appendix D)

a. Claim 1

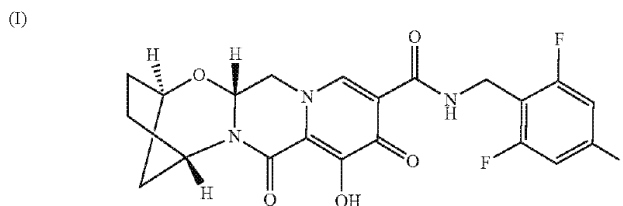
Claim 1 of the '802 patent is directed to a tablet comprising 50 mg of bicitgravir (BIC), i.e., the compound of Formula (I) appearing in the claim, or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide (TAF) or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine (FTC) or a pharmaceutically acceptable salt thereof.

As discussed in Section II.B, Gilead's US '356³⁷ discloses a class of oxepine compounds of Formula (I) and their use in the treatment of HIV. US '356, Abstract. These compounds are described as inhibitors of HIV integrase (HIV INSTIs), and are said to be useful for reducing HIV replication. *Id.* at [0010], [0089]. US '356 specifically discloses approximately 100 HIV INSTI compounds of Formula (I) and methods for their synthesis, including a Compound 42 corresponding to bicitgravir (BIC) (*see below*). *Id.* at [0312]-[0316] (Example 42).

³⁷ WO '323 is a PCT application having the essentially the same disclosure is US '356, and may be used as an alternative disclosure for US '356 for all purposes, including in this obviousness analysis and the forgoing analysis for obviousness-type double patenting. *See* Section II.PP.



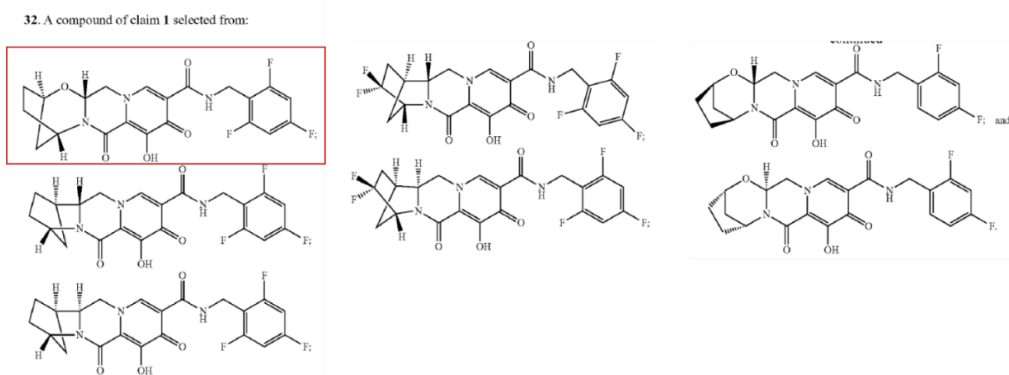
Formula I



Bictegravir (Compound 42)

Bictegravir (BIC) is also disclosed in a claim along with 6 other HIV INSTIs of Formula

I. *Id.* at claim 32 (below) (bictegravir emphasized in red).



US '356 discloses that BIC (compound 42) provided nanomolar activity ($EC_{50} = 2.5 \text{ nM}$) in an antiviral assay in MT4 cells infected with HIV, and was therefore deemed useful for treating the proliferation of the HIV virus. US '356, [0589]-[0592] (Example 104; *see* Table 1). It also discloses that BIC was orally bioavailable when administered to beagle dogs, and provided the second highest oral bioavailability (F (%)), C_{max} and AUC of the eleven Formula (I) compounds tested. *Id.* [0599]-[0603] (Example 107; *see* Table 4).

As such, a skilled artisan would have recognized that BIC was a known HIV INSTI having utility in the treatment of HIV, and would have specifically selected it from among the Formula (I) compounds disclosed and claimed in US '356 based on its high anti-HIV activity and beneficial pharmacological properties, including its ability to be administered orally.

US '356 also discloses pharmaceutical compositions containing a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof, including bicitgravir or a pharmaceutically acceptable salt thereof (*e.g.* a sodium salt), which can contain one or more pharmaceutically acceptable carriers, diluents, or excipients, and where the Formula (I) compound or salt thereof may be present in amounts from about 25 mg to 500 mg, including about 25 mg, 50 mg, and 100 mg. US '356, [0152]; *see also id.* at [0152]-[0153], [0075] (exemplifying sodium as a salt derived from an alkali metal), [0155] (compounds of the invention, or their pharmaceutically acceptable salts, are administered in a therapeutically effective amount), [0081] (therapeutically effective amount routinely determined). These pharmaceutical compositions are disclosed as being useful for the treatment of an HIV infection in a human having or at risk of having the infection, and are said to take the form of unit doses, where for example a tablet may be a single dosage unit. *Id.* at [0147]-[0149], [0153]-[0154] (pharmaceutical compositions are prepared by methodologies well known in the pharmaceutical art). Such pharmaceutical compositions and their use for the treatment of HIV are also claimed, including compositions where the Formula (I) compound is BIC or a pharmaceutically acceptable salt thereof. *See, e.g.*, pharmaceutical composition claim 33 (when depending from claim 32, which claims BIC as one of seven compounds), method of treatment claim 37 (when depending from claim 32, which claims BIC as one of seven compounds).

US '356 states that “a goal of antiretroviral therapy is to achieve viral suppression in the HIV infected patient[, where] treatment guidelines published by the United States Department of Health and Human Services provide that achievement of viral suppression requires the use of combination therapies, i.e., several drugs from at least two or more drug classes.” US '356, [0008]. In this regard, US '356 discloses therapies for the treatment of HIV comprising the administration

of a therapeutically effective amount of an HIV INSTIs of Formula (I) *in combination* with therapeutically effective amounts of one or more additional anti-HIV agents. *See generally id.* at [0156]-[0179]. Specifically disclosed is the combination of a Formula (I) compound with one or more anti-HIV agents “in a unitary dosage form for simultaneous administration, for example as a solid dosage form for oral administration” (*e.g.*, tablets as discussed above). *Id.* at [0177]; *see also* HIV Guidelines, D-1 (recommending the use of two nucleos(t)ide reverse transcriptase inhibitors in combination with a third active antiretroviral drug from one of three drug classes: an integrase strand transfer inhibitor, a nonnucleoside reverse transcriptase inhibitor, or a protease inhibitor with a pharmacokinetic enhancer); *id.* at 1, *i* (recommending the combination of the INSTIs elvitegravir and raltegravir with tenofovir and emtricitabine); British HIV Guidelines, 13 (describing tenofovir and emtricitabine as the *preferred NRTI backbone* for HIV therapy, to be combined with an additional agent such as an INSTI).

The additional anti-HIV agents disclosed in the US '356 include HIV nucleoside inhibitors of reverse transcriptase (NRTIs), *e.g.*, emtricitabine, and HIV nucleotide inhibitors of reverse transcriptase (NtRTIs), *e.g.*, GS-7340 (TAF) and tenofovir alafenamide (TAF) fumarate. *Id.* at [0156]-[0163]; *see also* British HIV Guidelines (tenofovir and emtricitabine is the preferred NRTI backbone to administer with an INSTI). US '356 also claims pharmaceutical compositions comprising an HIV INSTI of Formula (I) and one or more additional therapeutic agents selected from, *e.g.*, NRTIs and NtRTIs, and methods of treating HIV therewith. *See, e.g.*, claims 33-36 (when depending from claim 32, which claims bictegravir as one of seven compounds), claims 37-40 (when depending from claim 32, which claims bictegravir as one of seven compounds).

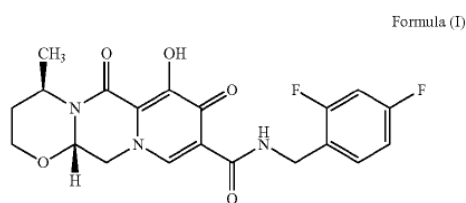
In view of these disclosures, a skilled artisan would have been motivated to select BIC (or a pharmaceutically acceptable salt thereof) based upon its beneficial oral bioavailability and

pharmacokinetic profile, and combine a therapeutically effective amount of it with additional anti-HIV agents, e.g., the preferred NRTI backbone of tenofovir and emtricitabine discussed above) into a solid pharmaceutical composition for oral administration, such as a tablet. And in view of BIC's high activity in cellular assays, the skilled artisan would have reasonably expected that such a combination would be useful in the treatment of HIV infection.

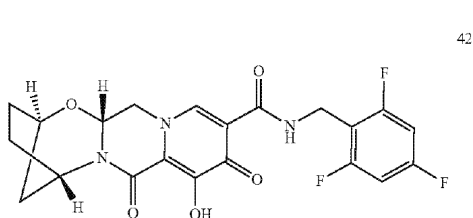
It was already known in the art that bicittegravir along with emtricitabine and tenofovir alafenamide could be used as an oral treatment for adults with HIV-1. NCT '694 discloses administering orally GS-9883, i.e. bicittegravir, along with 200 mg of emtricitabine and 25 mg of tenofovir alafenamide to treat adults with HIV-1. NCT '694, Study Description. Although NCT '694 does not disclose using 50 mg of bicittegravir, it discloses using as its active comparator, 50 mg of dolutegravir along with 200 mg of emtricitabine and 25 mg of tenofovir alafenamide. *Id.* Version 8 of NCT '694 further discloses a fixed combination containing 50 mg of bicittegravir, 200 mg of emtricitabine, and 25 mg of TAF to be administered orally once daily. As explained above in Section IV.H.1.a.iii, based on the structural similarities between dolutegravir and bicittegravir and their common utility as HIV INSTIs, the skilled artisan would have expected for the combination of bicittegravir with emtricitabine and tenofovir alafenamide to have similar properties for the treatment of HIV as the combination of dolutegravir, emtricitabine, and tenofovir alafenamide. And from the disclosure of using 50 mg of dolutegravir in the active comparator, the skilled artisan would have been motivated to prepare a tablet combination comprising 50 mg of bicittegravir for the treatment of HIV in a tablet combination. Moreover, Version 8 of NCT '694 does in fact disclose a fixed combination containing bicittegravir, FTC, and TAF (50 mg/200 mg/25 mg) to be administered to HIV patients orally once daily. And the BIC Safety Study had also disclosed a 50 mg dose of BIC for use in clinical trials.

Although US '356 does not specifically disclose the tablet composition of claim 1, i.e., that comprising 50 mg of the INSTI BIC, 200 mg of the NRTI FTC, and 25 mg of the NtRTI TAF (or their pharmaceutically acceptable salts), and Version 1 of NCT '694 does not disclose a single tablet comprising 50 mg of bictegravir with emtricitabine and tenofovir alafenamide, such a composition in a single tablet would have been obvious to a skilled artisan in view of additional prior art discussed in Section II. Moreover, Version 8 of NCT '694 specifically discloses a fixed combination containing bictegravir, FTC, and TAF (50 mg/200 mg/25 mg) to be administered to HIV patients orally once daily. And the BIC Safety Study had also disclosed a 50 mg dose of BIC for use in clinical trials.

As discussed in Section II.XX, WO '351 and US '332 each disclose the compound dolutegravir (DLT) as an INSTI that is useful for the treatment of HIV infections and AIDS. *See e.g.*, US '332, [0014]. The references identify dolutegravir sodium, and especially its mono-sodium salt, as a preferred form of DLT for such treatments. *Id.* at [0018], [0020]; *see also* Tivicay Assessment, 9 (disclosing the product Tivicay® as containing 50 mg of DLT sodium); 2013 Tivicay Label. As shown below, dolutegravir shares a common core structure with bictegravir, as it also shares a similar HIV INSTI activity and utility in the treatment of HIV, as evidenced by US '356.



Dolutegravir (HIV INSTI)



Bictegravir (HIV INSTI)

WO '351 and US '332 are specifically directed to pharmaceutical combinations comprising DLT, FTC, and tenofovir (TFV) or a prodrug thereof, in a specific weight ratio and/or specific

amounts for the treatment of HIV infection. *Id.* at Abstract, [0061]. These combinations are preferably in the form of a solid oral dosage form and particularly a tablet, and are preferably administered once daily. *Id.* at [0077], [0095], [0107]; *see also* 2013 Tivicay Label (identifying DLT sodium as an HIV INSTI indicated in combination with other antiretroviral agents, *e.g.*, emtricitabine/tenofovir (TRUVADA), for the treatment of HIV-1 infection). Tivicay Label, 1, 4, 24; *see also* Tivicay Assessment (identifying dolutegravir as “a new integrase inhibitor which has been studied in a full range of HIV treatment populations,” including in “patients who also had failed therapy with an integrase inhibitor with consequent integrase inhibitor class resistance”), 43, 50-51, 89 (disclosing combination therapies with DLT sodium, FTC and tenofovir disoproxil for treating HIV).

WO '351 and US '332 identify the prodrug tenofovir alafenamide (TAF), also known as GS 7340, as a preferred form or TFV for the pharmaceutical combination, where the TAF monofumarate and hemifumarate salts are particularly preferred, and the hemifumarate salt is especially preferred. *See e.g.*, US '332, [0053]. The references also disclose that emtricitabine (FTC) is preferred in its free base form, as opposed to its salt form. *Id.* at [0032].

WO '351 and US '332 describe specific embodiments where the pharmaceutical combination comprises 40 to 60 mg DLT, 150 to 250 mg FTC, and 5 to 42 mg TAF, along with pharmaceutical excipients. *Id.* at [0086]-[0090]. The references also describe combinations that preferably contain a total amount of DLT, FTC and TAF from 192 mg to 326 mg per day. *Id.* at [0075]. In a particularly preferred embodiment, the combination comprises about 50 mg DLT, about 200 mg FTC and about 25 mg TAF. *Id.* at [0091]-[0092].

In view of the structural similarities between DLT and BIC and their common utility as HIV INSTIs (*see* Section IV.H.1.a.iii), the skilled artisan would have recognized that DLT could

be replaced with BIC in the oral pharmaceutical combinations disclosed in WO '351 and US '332, to provide a new oral combination comprising BIC, FTC and TAF. That artisan would have expected for the new oral combination, e.g., the new tablet combination, to be useful in the treatment of HIV, given that it would contain a similar combination of an HIV INSTI (BIC), an NRTI (FTC) and an NtRTI (TAF) as the DLT combination disclosed in WO '351 and US '332. Indeed, the skilled artisan would have expected for this new combination of BIC/FTC/TAF to have similar properties for the treatment of HIV as the DLT/FTC/TAF combination already known in the prior art.

In making the above substitution, the skilled artisan would have been motivated to prepare a pharmaceutical combination comprising therapeutically effective amounts of BIC, FTC and TAF for the treatment of HIV. US '356 discloses compositions containing therapeutically effective amounts of, e.g., BIC or a pharmaceutically acceptable salt thereof, including amounts of about 25 mg, 50 mg, and 100 mg, and further notes that a therapeutically effective amount of INSTIs for treating HIV may be routinely determined. US '356, [0081], [0152]. These compositions may also contain therapeutically effective amounts of an NRTIs such as FTC, and an NtRTIs such as TAF or TAF fumarate. *Id.* at [0156]-[0157], [0162]-[0163], [0177]. The skilled artisan would have known from WO '351 and US '332 that 200 mg FTC and 25 mg TAF would be therapeutically effective when combined into an oral tablet with therapeutically effective amount of the HIV INSTI DLT. *See* US '332 [0091]-[0092] (combination of 50 mg DLT, 200 mg FTC and 25 mg TAF).

As such, the skilled artisan would have been motivated to prepare a tablet combination comprising a therapeutically effective amount of BIC (or a salt thereof), e.g., 50 mg as disclosed in US '356, and therapeutically effective amounts of FTC (or a salt thereof) TAF (or a salt thereof),

e.g., 200 mg FTC and 25 mg TAF as disclosed in WO '351 and US '332, and administer that combination to a patient having HIV infection with the expectation that it would be successful for that treatment. These dosages for BIC, FTC, and TAF in the tablet combination would have also been arrived at through routine optimization designed to identify the appropriate dose of BIC to co-administer with FTC and TAF, and the claimed dose of 50 mg BIC (or a salt thereof) would have not been surprising or unexpected to the skilled artisan. Moreover, in view of the structural similarity and identical utilities of dolutegravir and bictegravir, the skilled artisan would have expected that these compounds could be administered at a similar dose when used in combination with emtricitabine and tenofovir, *e.g.*, with Truvada (emtricitabine/tenofovir disoproxil). As such, the skilled artisan would have considered the 50 mg dose of bictegravir in the tablet of claim 1 (combined with the recited doses of TAF and FTC) to be a therapeutically effective amount of bictegravir for the treatment of HIV in combination with TAF and FTC. For this additional reason, a skilled artisan would have been motivated to use a 50 mg dose of bictegravir (or an equivalent dose of bictegravir sodium) as required by claim 1.

In further regard of the 200 mg dose of FTC recited in claim 1, the skilled artisan would have recognized it as the generally accepted dose for FTC in combination therapies for the treatment of HIV. Indeed, every approved combination tablet from Gilead discussed in Section II contains 200 mg of FTC. *See, e.g.*, Truvada Label (combination of 200 mg FTC and 300 mg TDF); Truvada Label (combination of 200 mg FTC, 300 mg TDF, 600 mg efavirenz); Complera Label (combination of 200 mg FTC, 300 mg TDF, 27.5 mg rilpivirine hydrochloride); Stribild Label (combination of 200 mg FTC, 300 mg TDF, 150 mg elvitegravir and 150 mg cobicistat); Genvoya Label (combination of 200 mg FTC, 10 mg TAF, 150 mg elvitegravir and 150 mg cobicistat); WO '351 19:3-12 (combination of 150 to 250 mg FTC, 5-42 mg TAF, 40 to 60

dolutegravir); US '332, [0091]-[0092] (pharmaceutical combination containing about 50 mg DLT, about 200 mg FTC, and about 25 mg TAF); WO '720, [0028] (combination of 200 mg FTC, 3-40 mg TAF, 50-500 mg cobicistat, 150 mg elvitegravir). A skilled artisan would therefore have been motivated to use a 200 mg dose of FTC for the treatment of HIV in the tablet combination, and reasonably expected that amount to be successful when combined with bictegravir and TAF (or their pharmaceutically acceptable salts).

In further regard of the 25 mg dose of TAF recited in claim 1, the skilled artisan would have also recognized it as an acceptable dose for TAF in combination therapies for the treatment of HIV. For one, it was known by at least 2014 that Gilead sought to replace TDF with TAF, because TAF had “demonstrated high antiviral efficacy at a dose 10 times lower than Viread, as well as an improved renal and bone safety profile.” Gilead/Janssen, 2. These advantages of TAF had long been appreciated in the art, including by Lee in 2005 and in the '791 patent in 2008. See Lee, 1900 (Table 1) (disclosing TAF as 10 times more potent than TDF toward HIV-1, with eight times improved selectivity index), 1905 (high concentrations of tenofovir observed in lymphatic tissues after oral administration of GS 7340 (TAF) are expected to result in increased clinical potency relative to TDF) (with TAF, it should be possible to reduce the total dose of tenofovir, thereby minimizing systemic exposure, while at the same time increasing antiviral activity); '791 patent, 27:29-28:37 (TAF shows a 10-fold increase in antiviral activity relative to TDF and a 200-fold increase in plasma stability; greater plasma stability is expected to result in higher circulating levels of TAF than TDF after oral administration), Tables 1-2; Ruane, 451-52 (“HIV-1 RNA responses for the 8-mg TAF treatment group were similar to that of the 300-mg TDF group. However, median DAVG₁₁ [(time-weighted average change from baseline to study day 11)] for plasma HIV-1 RNA . . . in the 25- and 40-mg TAF treatment groups showed significantly greater

decreases compared with the 300-mg TDF treatment group.”); Ruane, 454 (“Compared with 300 mg TDF, TAF, with doses as low as 25 mg, demonstrated greater antiviral effect at less than 1/10th the dose, with an almost 90% reduction in circulating TFV.”); Sax, 53 (“Relative to TDF, TAF is more stable in plasma.”); *see also* US ’856, [0010]-[0011], [0057] (disclosing pharmaceutical compositions comprising TAF hemifumarate, NRTIs and HIV integrase inhibitors); WO ’351 19:3-12 (disclosing a combination of 150 to 250 mg FTC, 5-42 mg TAF, 40 to 60 dolutegravir. *See also* Astuti, 10-11; Llibre, 172.

For at least these reasons, the skilled artisan would have been further motivated to utilize a ~10-fold lower dose of TAF vis-à-vis the approved 300 mg dose of TDF in combination tablets for the treatment of HIV, including in combinations also containing a therapeutically effective amount of an INSTI, and 200 mg of emtricitabine, *e.g.*, as in the Gilead’s Stribild product (combination of 200 mg FTC, 300 mg TDF, 150 mg elvitegravir and 150 mg cobicistat). Stribild Label, 1, 22-23. And given that TAF was known to be 10 times more potent than TDF toward HIV-1, with eight times improved selectivity index (*see* Lee, 1900), the skilled artisan would have reasonably expected such a 10-fold lower dose to be successful in the treatment of HIV. A 25 mg dose of TAF is approximately 10-fold lower than the 300 mg dose of TDF (equivalent to 245 mg tenofovir disoproxil). Thus, a skilled artisan would therefore have been motivated to use a 25 mg dose of TAF in a tablet), and reasonably expected that amount to be successful when combined with 50 mg of bictegravir (or its pharmaceutically acceptable sodium salt) and 200 mg of FTC. *See also* Astuti, 10-11; Llibre, 172. The skilled artisan would have also arrived at 25 mg TAF as a therapeutically effective dose of TAF for treating HIV through routine methods in the art of HIV combination therapies, *e.g.*, routine dose optimization.

In addition, the Genvoya Assessment describes film-coated tablet combinations containing the INSTI elvitegravir, along with FTC, cobicistat and TAF, *i.e.*, an updated version of Gilead's Stribild. Genvoya Assessment, 10. The Genvoya Assessment describes open-label crossover studies where the combination contained 25 mg of TAF, and where the exposures to TAF and tenofovir were substantially higher vs. TAF 25 mg administered alone, establishing that 25 mg TAF was an acceptable dose in an HIV combination. *Id.* at 74-75. That 25 mg was an acceptable dose for TAF in combination tablets was even recognized as early as 2004. WO '846, 3:13-18 (therapeutic combinations of TAF and FTC for treating HIV), 18:23-26 (combination can additionally include an INSTI), 37:13-20 (exemplary formulation containing 25 mg of TAF and 200 mg FTC); *see also* US '332 (disclosing combinations for treating HIV containing 40 to 60 mg dolutegravir, 150 to 250 mg FTC, and 5 to 42 mg tenofovir alafenamide). For these additional reasons, a skilled artisan would have been motivated to use a 25 mg dose of TAF for the treatment of HIV in a tablet combination, and reasonably expected that amount to be successful when combined with 50 mg of bictegravir (or its pharmaceutically acceptable sodium salt) and 200 mg of FTC. *See also* Astuti, 10-11; Llibre, 172.

In view of the above analysis, claim 1 of the '802 patent is obvious over US '356 in view of WO '351 or US '332, optionally in view of the additional prior art discussed in this section.

Additional prior art supports that the tablet combination of claim 1 would have been obvious. For example, the FDA approved Gilead's product Stribild® for the treatment of HIV in 2012. *See* Stribild Label, 1. Stribild® was known to be a tablet composition containing the 150 mg of the HIV INSTI elvitegravir (EVG) in combination with 200 mg of the NRTI FTC and 300 mg of the NtRTI tenofovir disoproxil fumarate (TDF), along with the pharmacokinetic enhancer cobicistat (COBI). *Id.* 22-23; *see also* US '122, Abstract, [0002]-[0005], [0007], [0022], [0063]-

[0065] (Examples 2-4) (describing similar EVG/FTC/TDF/COBI combination tablets). In 2015, Gilead had disclosed an improved version of Stribild® known as Genvoya®, where TDF had been replaced with TAF fumarate “at a much lower dose ... while maintaining the established doses and biopharmaceutical performance of the other active substances.” See Genvoya Assessment, 10, 13. The Genvoya® combination contained only 10 mg of TAF (as 11.2 mg of the fumarate) as opposed to 300 mg of TDF in Stribild®, and a combination containing 25 mg of TAF fumarate had also been successfully studied in the clinic. *Id.* Moreover, Gilead’s fixed dosage combination of FTC and TAF was known to be in Phase III clinical trials prior to November 9, 2015, where a fixed dose combination containing 25 mg of TAF and 200 mg of FTC was to be administered to HIV patients (and compared to a fixed dose combination containing 300 mg of TDF and 200 mg of FTC). FTC/TAF Study, 5 (further noting that an allowed third drug, e.g., the INSTI dolutegravir or raltegravir may also be administered).

A skilled artisan reading WO ’323 and US ’356 would have further looked to the teachings of WO ’846, which discloses combination pharmaceutical dosage forms that are chemically stable to acid degradation. The pharmaceutical compositions provided in WO ’846 comprise: (1) a first component, such as tenofovir alafenamide (GS7340); (2) a second component, such as emtricitabine; and (3) optionally, a third component having antiviral activity. WO ’846 at 18:19-23. The third therapeutic agent includes protease inhibitors, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and integrase inhibitors (INSTIs). *Id.* at 18:23-26. WO ’846 teaches that the pharmaceutical dosage forms disclosed therein can be formulated as an oral tablet, and further contain one or more pharmaceutically acceptable excipients, including diluents, such as croscarmellose sodium, binding agents, such as microcrystalline cellulose, and lubricating agents, such as magnesium stearate. *Id.* at 21:18-25.

The tablets may be uncoated or coated “by known techniques.” *Id.* at 21:26. The exemplary formulations taught in WO ’846 include 25 mg of tenofovir alafenamide and 200 mg of emtricitabine, in addition to microcrystalline cellulose, croscarmellose sodium, and magnesium stearate (among other excipients). *Id.* at 37:13-20 (Formulation D), 13:12-24 (Formulation G).

		<u>mg/tablet</u>			<u>mg/tablet</u>
Formulation D:			Formulation G		
GS-7340		25	GS-7340		300
emtricitabine		200	emtricitabine		200
Microcrystalline Cellulose		200	Hydroxypropyl Methylcellulose		112
Lactose Monohydrate		330	Lactose B.P.		53
Croscarmellose Sodium		60	Pregelatinized Starch B.P.		28
Pregelatinized Starch		50	Magnesium Stearate		7
Magnesium Stearate		10			
		875	total:		700

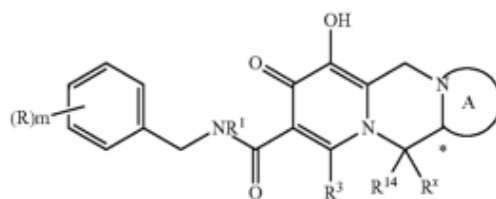
In view of these additional disclosures, the skilled artisan would have appreciated that therapeutically effective amounts of other HIV INSTIs, such as Gilead’s elvitegravir (EVG), had been combined into tablet compositions with therapeutically effective amounts of FTC and TAF for the treatment of HIV, including tablets containing 150 mg of EVG with 200 mg of FTC and 25 mg of TAF, and the pharmacoenhancer COBI. These disclosures would have further motivated the skilled artisan to combine a therapeutically effective amount of BIC (or a salt thereof) with 200 mg of FTC (or a salt thereof) and 25 mg of TAF (or a salt thereof) into a tablet composition for the treatment of HIV, where a 50 mg dose of BIC (or a salt thereof) would have been identified during routine dose optimization studies. *See also* US ’356, [0152] (disclosing a 50 mg dose for the HIV INSTI compounds such as bicitgravir or a salt thereof).

As such, a skilled artisan would have readily understood that the combination of US ’356 (or WO ’323) and WO ’846 teaches chemically stable pharmaceutical dosage forms, such as tablets, comprising 50 mg of an INSTI such as bicitgravir (or an equivalent amount of a bicitgravir salt, *e.g.*, a sodium salt), 25 mg of tenofovir alafenamide (or an equivalent amount of a salt thereof), and 200 mg of emtricitabine, in addition to pharmaceutically acceptable excipients such as

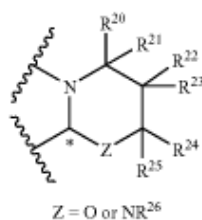
croscarmellose sodium, microcrystalline cellulose, and magnesium stearate. In view of these disclosures, the skilled artisan would be motivated to incorporate 50 mg of the INSTI bictegravir (or an equivalent amount of its sodium salt) into the tablet composition of WO '846, *e.g.*, Formulation D, to arrive at a tablet containing the amounts of bictegravir (bictegravir sodium), tenofovir alafenamide (or TAF fumarate) and emtricitabine recited in claim 1 of the '802 patent.

Accordingly, claim 1 of the '802 patent is obvious over US '356 in view of WO '351 or US '332, further in view of the Genvoya Assessment and/or WO '846.

Moreover, as discussed above, the '385 patent teaches example 17, which is comprised of Formula I-1-1 ('385 patent, 6:10-20) with the structure



and where group A is represented by A-1 ('385 patent, 7:35-45) with the structure



wherein “the stereochemistry of an asymmetric carbon represented by * shows R-or S-configuration or a mixture thereof; R14 and Rx are independently hydrogen,” “R3 is a hydrogen,” “R1 is hydrogen,” “R is independently selected from halogen,” “m is an integer of 0 to 3,” and “wherein R20 to R[25] are each independently a group selected from Substituent group S2.” '385 patent, 6:26-7:66. The '385 patent discloses that Substituent group S2 includes hydrogen and various types of alkyl groups. *Id.*, 8:9-34. The compound recited as Formula II in claim 1 of the

'342 patent as a compound disclosed by the Formula I-1-1 of the '385 patent where Z is Oxygen, each of R20, R21, R 22, R23, R24, and R25 are hydrogen or alkyl groups, the stereochemistry is an R-configuration or a mixture of R- and S- configurations, Rx is hydrogen, R14, is hydrogen, R1 is hydrogen, R is the halogen fluorine, and m is 3. The '385 patent also discusses that the compounds disclosed may be in the form of “pharmaceutically acceptable salts thereof” and specifically that it may be a “sodium salt” of the compound. *E.g.*, '385 patent, Abstract, 7:32-35, 38:6-9

Moreover, the '385 patent discloses that it “is useful as an integrase inhibiting agent for retrovirus (e.g., HIV-1, HIV-2, HTLV-1, SIV, FIV etc.) and useful as an anti-HIV drug etc.” '385 patent, 56:49-51. The '385 patent further discloses that it “may be used in joint use therapy by combining an anti-HIV drug having the different action mechanism such as a reverse transcriptase inhibitor and/or a protease inhibiting agent. Particularly, currently, an integrase inhibitor is not marketed, and it is useful to use in joint use therapy by combining the present compound with a reverse transcriptase inhibitor and/or a protease inhibitor. Further, the above use includes not only use as a medical mixture for anti-HIV, but also use as a joint use agent for increasing the anti-HIV activity of other anti-HIV drug such as cocktail therapy.” '385 patent, 56:52-62. A skilled artisan would have recognized that tenofovir alafenamide and emtricitabine are reverse transcriptase inhibitors (*supra*), and in fact were the preferred NRTI backbone to administer with an INSTI. The '385 patent further discloses that it can be administered orally, including in any dosage form including a tablet, and that it can be combined with a pharmaceutically acceptable carrier. '385 patent, 57:4-18. The '385 patent further discloses that “[a] dose of the present invention is different depending on administration method, an age, a weight and condition of a patient, and a kind of disease, and usually in the case of oral administration, above 0.05 mg to 3000 mg, preferable about

0.1 mg and 1000 mg may be administered per adult a day.” ’385 patent, 57:20-58:4. The ’385 patent also teaches that “[i]ngredients are mixed, and compressed to obtain tablets, each weighing 665 mg.” *Id.* at 177:38-39.

Claim 1 of the ’802 patent is also obvious over the ’385 patent and the knowledge of one of ordinary skill in the art.

Optionally, any of the above references would have been combined with WO ’351 with a reasonable likelihood of success because it is in the same field of invention as WO ’323, US ’356, WO ’846, and the ’385 patent and discloses a similar pharmaceutical composition containing an INSTI and reverse transcriptase inhibitors. WO ’351 teaches 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” for treatment of “a subject afflicted with a viral infection, preferably afflicted with an HIV infection.” WO ’351 at 3:18-24. In the composition, “[p]referably, dolutegravir is in the form of a pharmaceutically acceptable salt,” and “[p]articularly preferred, dolutegravir is used in the form of the sodium salt, especially the mono-sodium salt.” *Id.* at 5:22-27. WO ’351 also discloses embodiments where the pharmaceutical composition comprises (a) dolutegravir, (b) emtricitabine and (c) tenofovir alafenamide in which the weight ratio of (a) dolutegravir to (b) emtricitabine to (c) tenofovir alafenamide can be from 1:1:0.15 to 1:8:1.” *Id.* at 16:8-11. WO ’351 teaches, “[i]n a preferred embodiment of the pharmaceutical combination of the present invention the amount of dolutegravir administered is 20 to 75 mg per day, preferably 25 to 70 mg per day, more preferably 35 to 65 mg per day, in particular 40 to 60 mg per day.” *Id.* at 16:15-18. It also teaches, “[i]n case that the tenofovir is administered as tenofovir alafenamide, the amount of tenofovir alafenamide administered preferably is 0.5 to 50 mg per day, more preferably 1 to 45 mg per day, even more preferably 3 to

44 mg per day, in particular 5 to 42 mg per day.” *Id.* at 17:5-8. WO ’351 further teaches that “[i]n a preferred embodiment the pharmaceutical composition comprises (i) 20 to 75 mg, preferably 25 to 70 mg, more preferably 35 to 65 mg, in particular 40 to 60 mg dolutegravir (a); (ii) 50 to 300 mg, preferably 100 to 280 mg, more preferably 125 to 260 mg, in particular 150 to 250 mg emtricitabine (b); (iii) 0.5 to 50 mg, more preferably 1 to 45 mg, even more preferably 3 to 44mg, in particular 5 to 42 mg tenofovir (c), in particular tenofovir alafenamide; and (iv) pharmaceutical excipients.” *Id.* at 19:3-12. WO ’351 further discloses that “the combination of the present invention is administered once daily” and “can be preferably a solid oral dosage form” in “a capsule or tablet.” *Id.* at 17:27-28, 23:6-8.

As explained above, claim 1 of the ’802 patent reads on the species of “multilayer” tablets that include the claimed amounts of BIC, TAF, and FTC (or their salts). The skilled artisan would have readily appreciated that Gilead was employing bilayer technology in its HIV combination tablets for years before the effective filing date for the ’846 patent. Such combination tablets included Stribild (bilayer technology to physically separate of EVG and COBI from FTC and TDF to reduce potential physicochemical interaction between them), Atripla (bilayer tablet separating efavirenz from FTC and TDF), Genvoya (bilayer tablets separating EVG and COBI from FTC and TDF used in clinical trials), Eviplera (bilayer tablet containing rilpivirine, FTC and TDF used to study pharmacokinetics in dogs demonstrated comparable systemic exposure to all compounds to individual compounds administered individually). Stribild Assessment, 18, 33; Atripla Assessment, 5; Genvoya Assessment, 74-75; Eviplera Assessment, 18; *see also* US ’122, [0007] (tablets prepared in a bilayer manner have superior properties to alternatively structured tablets), FIG 1 and [0052] (disclosing a bilayer tablet having a first layer EVG and COBI, and a second layer that comprises FTC and TDF); US ’902, [0010], [0050]-[0052] (describing bilayer tablets

for keeping efavirenz separate from FTC and TDF); US '857, [0066]-[0071] (describing bilayer tablets for keeping rilpivirine separate from FTC and TDF).

In particular, Gilead's approved Stribild tablet contains the INSTI elvitegravir in a first layer, and FTC and TDF in second layer. Stribild Assessment, 18, 33. This bilayer tablet configuration was disclosed as having superior properties to alternatively structured tablets. US '122, [0007], *see also id* at [0061] (combining all of the compounds in a mixture to produce a monolayer tablet that compromises chemical stability).

For at least these additional reasons, a skilled artisan would have been motivated to formulate a bilayer tablet combination containing 50 mg bictegravir (or an equivalent amount of bictegravir sodium), 25 mg tenofovir alafenamide (or an equivalent amount of TAF fumarate), and 200 mg emtricitabine. And given that these APIs dosages were known (or expected to be useful) for the treatment of HIV, the skilled artisan would have reasonably expected these amounts amount to be successful for the treatment of HIV in a bilayer tablet.

For example, the skilled artisan would have been motivated to modify the bilayer tablet described in the Genvoya Assessment, *e.g.*, that contain 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 25 mg of tenofovir alafenamide, to replace the first generation INSTI elvitegravir with 50 mg of the second generation INSTI bictegravir (or an equivalent amount of bictegravir sodium), and to remove the PK booster COBI and its silicon dioxide absorbent to provide the multilayer tablet having the recited doses and total tablet weight of claim 1. Alternatively, the skilled artisan would have been motivated to modify the bilayer tablet described in the Stribild Assessment, *e.g.*, that contain 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 300 mg of TDF, to replace elvitegravir with 50 mg of bictegravir (or an equivalent amount of bictegravir sodium), to replace TDF with the improved

prodrug TAF (or an equivalent amount of TAF fumarate). This configuration would have been expected to reduce potential physicochemical interaction between bicitegravir sodium and the other APIs. And given that these API dosages were known (or expected to be useful) for the treatment of HIV, the skilled artisan would have reasonably expected these amounts to be successful for the treatment of HIV in a bilayer tablet.

In addition, US '079 discloses pharmaceutical compositions comprising at least one integrase inhibitor or its salt and at least one antiretroviral or anti-HIV agent or its salt, or prodrug. US '079, Abstract. It further discloses that “[e]xamples of suitable integrase inhibitors include but are not limited to dolutegravir, raltegravir, MK-2048, JTK-656,³⁸ elvitegravir,” that suitable nucleoside reverse transcriptase inhibitors (NRTIs) include emtricitabine, and that suitable nucleotide reverse transcriptase inhibitors (NtRTIs) tenofovir, where “[p]referably, the integrase inhibitor is dolutegravir, raltegravir or elvitegravir,” and “[p]referably, the NRTIs/NtRTIs are selected from tenofovir, emtricitabine, lamivudine or zidovudine, or any combination thereof.” *Id.* at [0042]-[0051].

Further according to US '079, such pharmaceutical compositions are presented in solid dosage forms where “[a] tablet formulation is the preferred solid dosage form due to its greater stability, less risk of chemical interaction between different medicaments, smaller bulk, accurate dosage, and ease of production.” US '079, [0070], [0078]. These tablets are said to be preferably in the form of single or bilayered or multilayered tablets. *Id.* at [0079]. Example 1 provides a bilayer tablet with the INSTI dolutegravir in a first layer that is separated from a second layer contained FTC and TDF. Similarly, Example 4 provides a bilayer tablet with the INSTI raltegravir in a first layer that is separated from a second layer contained FTC and TDF. *See* Section II.III.

³⁸ JTK-656 corresponds to bicitegravir, and is the code name originally assigned to it by the Japanese Tobacco Company.

'079 therefore provides additional motivation to separate an INSTI like BIC Na from FTC and TAF in a bi-layered tablet. Indeed, tenofovir prodrugs were known to be unstable toward alkaline conditions in both the solution and solid state, and a skilled artisan would have been specifically motivated to separate a basic INSTI such as dolutegravir Na or BIC Na from FTC and TAF in a bilayered tablet to reduce the degradation of TAF that would expectedly occur in the presence of these basic salts. *See, e.g.*, Havele, 3, 5 (TDF showed complete degradation occurred immediately after addition of at room temperature); Venkatasan, 4 (TDF undergoes 31% decomposition under basic stress conditions); Kurmi, 96121 (in a basic solution environment (0.5 N NaOH), TDF was completely converted into degradation product T1 in 3 h), 96121-25 (under basic solid state stress conditions, TDF degraded into several different products); *see also* Tivicay Information, 1 (noting that dolutegravir sodium has a pKa of 8.2, establishing its basicity).

For these additional reasons, the “multilayer” tablet species of claim 1 of the '802 patent would have been obvious, in view of the prior art discussed in this section. Any combination of the disclosures in Appendix C are also suitable combinations.

b. Claims 2-8

Defendant's obviousness analysis for claim 1 of the '802 patent is incorporated herein in its entirety, including the prior art disclosures and combinations discussed therein.

Claim 2 depends from claim 1 and requires the tablet to comprise 50 mg of bictegravir as a pharmaceutically acceptable salt thereof. Claim 3 depends from claim 1 and requires the tablet to comprise 25 mg tenofovir alafenamide as a pharmaceutically acceptable salt thereof. Claim 4 depends from claim 1 and requires the tablet to comprise 50 mg bictegravir as a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide as a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine.

Claim 5 depends from claim 1 and requires the tablet to comprise 52 mg of bictegravir sodium. Claim 6 depends from claim 1 and requires the tablet to comprise 25 mg of tenofovir alafenamide as tenofovir alafenamide fumarate. Claim 7 depends from claim 1 and requires the tablet to comprise 28 mg of tenofovir alafenamide hemifumarate. Claim 8 depends from claim 1 and requires the tablet to comprise 52 mg of bictegravir sodium, 28 mg of tenofovir alafenamide hemifumarate, and 200 mg emtricitabine.

Combinations of HIV INSTI compounds described as a genus including bictegravir and its salts, *e.g.*, bictegravir sodium, with emtricitabine, and TAF fumarate were known in the art. US '356, [0156]-[0157], [0162]-[0163]; [0177] (disclosing unitary dosage forms for simultaneous administration to a patient, for example as a solid dosage form for oral administration); *see also* '385 patent at 6:26-7:66. As discussed in Section II, TAF was well-known in the form of a monofumarate and hemifumarate salt, which could be dosed 10 times lower than the corresponding dose of TDF. Gilead/Janssen, 2; '791 patent, 24:38-48 (disclosing TAF monofumarate), US '856, [0010]-[0011], [0057] (disclosing TAF hemifumarate in combination with HIV nucleoside inhibitors of reverse transcriptase and HIV integrase inhibitors); Genvoya Label, 22 (tablet containing TAF fumarate in combination with EVG and FTC); Genvoya Assessment, 10 (disclosing the same), 13 (TAF fumarate can be administered at a much lower dose than tenofovir disoproxil fumarate (TDF) while maintaining the established doses and biopharmaceutical performance of the other active substances), 74-75 (bilayer tablet containing 25 mg of TAF (as fumarate) combined with EVG, FTC, and COBI).

As discussed above, it was well known in the art that FTC was employed as a free base. Truvada Label (combination of 200 mg FTC free base and 300 mg TD (as fumarate)); Truvada Label (combination of 200 mg FTC free base, 300 mg TD (as fumarate), 600 mg efavirenz);

Complera Label (combination of 200 mg FTC free base, 300 mg TD (as fumarate), 27.5 mg rilpivirine hydrochloride); Stribild Label (combination of 200 mg FTC free base, 300 mg TD (as fumarate), 150 mg elvitegravir and 150 mg cobicistat); Genvoya Label (combination of 200 mg FTC free base, 10 mg TAF (as fumarate), 150 mg elvitegravir and 150 mg cobicistat); WO '351 at 19:3-12 (teaching a preferred embodiment of the disclosed the pharmaceutical composition comprising “(i) 20 to 75 mg, preferably 25 to 70 mg, more preferably 35 to 65 mg, in particular 40 to 60 mg dolutegravir (a); (ii) 50 to 300 mg, preferably 100 to 280 mg, more preferably 125 to 260 mg, in particular 150 to 250 mg emtricitabine (b); (iii) 0.5 to 50 mg, more preferably 1 to 45 mg, even more preferably 3 to 44 mg, in particular 5 to 42 mg tenofovir (c), in particular tenofovir alafenamide; and (iv) pharmaceutical excipients).

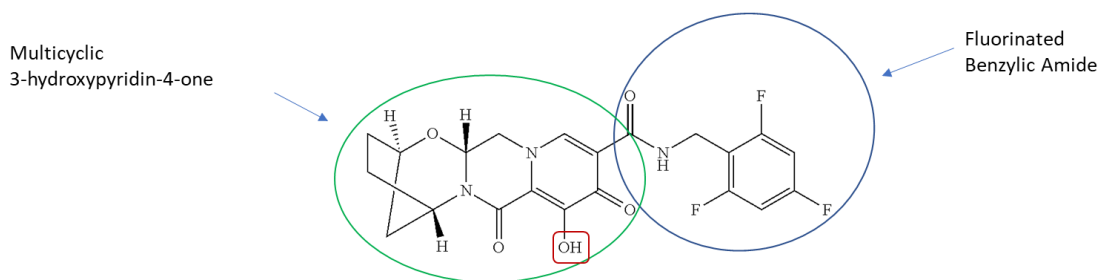
In view of the above disclosures and the analysis provided above for claim 1, the skilled artisan would have been motivated to provide a tablet composition, including a multilayer tablet composition, comprising bictegravir sodium (equivalent to 50 mg bictegravir), TAF monofumarate or hemifumarate (equivalent to 25 mg of TAF), and 200 mg emtricitabine, and expect such a tablet could successfully be made and be useful for the treatment of HIV.

For these reasons and those discussed above for claim 1, claims 2-8 of the '802 patent are obvious, when analyzed in view of the prior art discussed in this section and the section on claim 1. Any combination of the disclosures in Appendix D are also suitable combinations

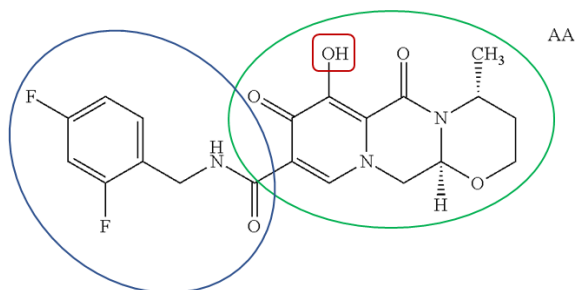
In particular, US '356 specifically discloses the INSTI BIC and identifies it as a highly active anti-HIV compound having good oral bioavailability. US '356 further discloses and claims pharmaceutical compositions comprising BIC or a pharmaceutically acceptable salt thereof, which optionally further comprise an NRTI such as FTC and an NtRTI such as TAF or a TAF fumarate salt. *See* US '356, [0156]-[0163], claims 32-36.

US '356 describes “pharmaceutically acceptable salts” of the disclosed INSTI compounds, e.g., bicitegravir, as including salts derived from an appropriate base, such as an alkali metal (for example, sodium). *See* US '356, [0075], [0077]. WO '351 and US '332 disclose the structurally related INSTI dolutegravir (DLT), which is preferably used as a sodium salt, and especially as a monosodium salt, when combined with FTC and TAF as second and third active pharmaceutical ingredients. *See e.g.*, US '332 [0018], [0020], [0025], [0037]; *see also* Tivicay Assessment, 9 (describing Tivicay[®] as a tablet containing 50 mg of DLT as a sodium salt).

The skilled artisan would recognize that BIC and DLT bear a close structural similarity, and would have similar physicochemical and biological properties because each compound contains a weakly acidic hydroxyl group (identified below in red), a fluorinated benzylic amide (identified below in blue), and a 3-hydroxypyridin-4-one multicyclic ring structure (identified below in green).



Bicitegravir



410

Dolutegravir

The skilled artisan would have further expected that BIC would form a pharmaceutically acceptable salt in the same manner as DLT, i.e., through reaction of its hydroxyl (-OH) with a strong base such as sodium hydroxide. As such, that artisan would have been specifically motivated to prepare BIC as a sodium salt and expected it to be stable, just as it had been done with DLT in the prior art. And because BIC sodium would expectedly have a higher aqueous solubility than BIC as a free acid, the skilled artisan would have preferred to use BIC sodium in a tablet composition also containing FTC (or a salt thereof) and TAF (or a salt thereof).

As further discussed for claim 1, WO '351 and US '332 describe preferable DLT combinations with FTC and TAF, where FTC is used as a free base (as opposed to a salt), and TAF is used as a monofumarate or hemifumarate salt, where the combination of FTC free base and TAF hemifumarate is especially preferred. *See e.g.*, US '332, [0032], [0053]; *see also* Genvoya Assessment, 10 (disclosing a tablet containing TAF fumarate and FTC free base in combination with the INSTI elvitegravir), 74 (describing PK studies with TAF monofumarate and hemifumarate, where the hemifumarate was selected for Phase 2/3 studies and the commercial presentation).

In view of these disclosures in combination with the above analysis for claim 1, the skilled artisan would have been motivated to provide a tablet composition, comprising 52 mg bictegravir sodium (equivalent to 50 mg bictegravir), TAF monofumarate or TAF hemifumarate (equivalent to 25 mg of TAF, e.g., 28 mg of TAF hemifumarate), and 200 mg emtricitabine free base, and expect such a tablet to be useful for the treatment of HIV.

Accordingly, claims 2-8 of the '802 patent are obvious for the same reasons as claim 1, further in view of the prior art disclosures discussed in this section. As an exemplary non-limiting

example, claims 2-8 are obvious over US '356 in view of WO '351 or US '332, optionally further in view of the Genvoya Assessment and/or WO '846.

c. Claims 9-11

Defendants' obviousness analysis for claims 1-8 of the '802 patent is incorporated herein in its entirety, including the prior art disclosures and combinations discussed therein.

Claim 9 depends from claim 1 and requires the tablet to have a total weight less than 1000 mg. Claim 10 depends from claim 9 and requires the tablet to have a total weight less than 800 mg. Claim 11 depends from claim 10 and requires the tablet to have a total weight less than 730 mg.

As discussed above for claim 1, it would have been obvious to provide a tablet composition, including a multilayer tablet composition, comprising 50 mg of BIC (or a salt thereof), 25 mg of TAF or a salt thereof, and 200 mg of FTC (or a salt thereof). Such an obvious tablet would have contained a total active ingredient amount of 275 mg.

A skilled artisan would have appreciated that tablet compositions, including a tablet composition containing 275 mg of the active ingredients BIC, TAF and FTC, would need to be formulated with pharmaceutical excipients to provide a composition suitable for oral administration. That artisan would have been motivated to combine the 275 total milligrams of BIC, TAF and FTC with the smallest amount of additional excipients as possible, in order to provide a total tablet size that would be easier for a patient to swallow. Indeed, it was common knowledge in the art that smaller tablets sizes were preferred for patient compliance.

WO '846 discloses tablet dosage forms containing TAF and FTC and a number of common pharmaceutical excipients. The following two formulations are exemplary.

Formulation D:	<u>mg/tablet</u>	Formulation G	<u>mg/tablet</u>
GS-7340	25	GS-7340	300
emtricitabine	200	emtricitabine	200
Microcrystalline Cellulose	200	Hydroxypropyl Methylcellulose	112
Lactose Monohydrate	330	Lactose B.P.	53
Croscarmellose Sodium	60	Pregelatinized Starch B.P.	28
Pregelatinized Starch	50	Magnesium Stearate	7
Magnesium Stearate	10		
	875	total:	700

WO '846, 37:13-20 (Formulation D), 13:12-24 (Formulation G). As shown above, Formulation D contains 225 mg of active ingredients (i.e., TAF and FTC) and 650 mg of additional excipients, for a total tablet weight of 875 mg. Similarly, Formulation G contains 500 mg of active ingredients (i.e., TAF and FTC) and 200 mg of additional excipients, for a total tablet weight of 700 mg. In view of these disclosures, a skilled artisan would have appreciated that tablets containing TAF and FTC had been prepared with a total weight in the range of 700-875 milligrams, and could be as low as 700 mg even when the total active ingredient content was 500 mg.

In view of these disclosures, the skilled artisan would have expected that a tablet containing 50 mg of BIC (or a salt thereof), 25 mg of TAF or a salt thereof, and 200 mg of FTC (or a salt thereof), i.e., 275 mg of active ingredients, could have easily been formulated with additional excipients to provide a total tablet weight of less than 1000 mg, and even less than 800 mg and less than 730 mg. And given that formulations could contain at least 450 milligrams of additional excipients and still fall below the total weight called for by the claims, a skilled artisan would have expected for such tablet compositions to be suitable for oral administration to patients having HIV infection.

Accordingly, claims 9-11 of the '802 patent are obvious for the same reasons as claim 1, further in view of the prior art disclosures discussed in this section. As an exemplary non-limiting

example, claims 9-11 are obvious over US '356 in view of WO '351 or US '332, further in view of WO '846.

Moreover, dolutegravir (DLT) was known as a “second-generation INSTI” that combines the advantages of its predecessor INSTIs raltegravir and elvitegravir (EVG), but can be administered once/day without the need for a pharmacokinetic booster such as cobicistat (COBI). Shah, 506 (also noting that COBI is a specific and potent inhibitor of CYP3A4 and associated with clinically significant drug–drug interactions), 517-518 (to be administered once/day, raltegravir must be coadministered with the COBI, which can lead to clinically significant drug–drug interactions). It was further known that DLT may be coformulated with other antiretrovirals in a single-tablet regimen for the treatment of HIV, without the need for COBI. *Id.* at 506; *see also* US '332, [0086]-[0090] (describing pharmaceutical combinations comprising 40 to 60 mg DLT, 150 to 250 mg FTC, and 5 to 42 mg TAF, along with pharmaceutical excipients), [0091]-[0092] (disclosing a specific combination comprising about 50 mg DLT, about 200 mg FTC and about 25 mg TAF).

Based on the structural similarity and common INSTI activity between DLT and BIC (*supra*), the skilled artisan would have identified BIC as a second-generation INSTI, and thus would have expected that BIC could also be administered once daily, *e.g.*, in combination with TAF and FTC as discussed above, without the need for the PK booster cobicistat (COBI), to provide a combination less susceptible to drug-drug interactions, that could be used in patients resistant to RAL or EVG. Indeed, based on structural similarity, the skilled artisan would have expected a similar mechanism of action, a similar resistance to CYP3A metabolism vis-à-vis EVG such that it would have be administered once-daily without a pharmacologic booster (*e.g.*, COBI), a similar ability to retain activity against many viral strains harboring major integrase resistance

mutations to the INSTIs RAL and EVG, and a similar relatively minimal drug-drug interactions and side effects, each of which are advantages of the second generation inhibitors. Shah and Dow (*supra*), Astuti, 10; Llibre, 175; *see also* Llibre, 172 (CYP3A is the main pathway by which EVG undergoes metabolism in the intestine and liver); Ostenholzer, 265 (DTG does not require boosting, and is primarily metabolized by UGT 1A1 with only a small contribution from CYP3A4), 269 (Given its relatively minimal drug interaction and side effect profile, DTG may prove useful for patients on other medications for tuberculosis, hepatitis C, seizure, or contraception as well as those intolerant to other ART. In addition, DTG appears to be a viable choice for salvage in some highly treatment experienced patients harboring resistance to the first-generation INSTIs (RAL and EVG)). As such, the skilled artisan would have been motivated to prepare a tablet composition comprising 50 mg BIC (or a salt thereof), 25 mg of TAF or a salt thereof, and 200 mg of FTC (or a salt thereof), i.e., 275 mg total active ingredients, without the need for COBI, leaving approximately 725 mg for tablet excipients to keep the total tablet weight below 1000 mg, 525 mg for tablet excipients to keep the total tablet weight below 800 mg, and 455 mg for tablet excipients to keep the total tablet weight below 730 mg.

US '122 is directed to solid oral dosage forms containing the APIs in Stribild[®], i.e., EVG, FTC, TDF, and COBI. US '122, Abstract, [0002]-[0005], [0007]. US '122 exemplifies a tablet embodiment containing 150 mg of EVG, 200 mg FTC, 300 mg of TDF, and 150 mg of COBI, i.e., the doses in the approved Stribild[®] tablet, along with a number of pharmaceutically acceptable tablet excipients. *Id.* at [0022] (*see table below*) (EVG = Formula I; COBI = Formula II; FTC = Formula III; TDF = Formula IV); *see also* [0063]-[0065] (Examples 2-4) (describing similar tablets); Stribild Label, 22-23.

Components	Compound of Formula II 150 mg Formulation	
	% w/w	mg/tablet
Compound of Formula III	13.9	200.0
Salt of Formula IV	20.9	300.0
Compound of Formula I	10.4	150.0
Compound of Formula II	10.4	150.0
Colloidal Silicon Dioxide	12.0	172.5
Lactose Monohydrate	0.8	10.9
Microcrystalline Cellulose	20.8	299.5
Hydroxypropyl Cellulose	0.5	7.5
Hydroxypropyl Cellulose	0.6	9.0
Sodium Lauryl Sulfate	0.8	11.3
Croscarmellose Sodium	7.3	104.3
Magnesium Stearate	1.6	22.4
Total	100	1437.

As shown in the above table, the Stribild[®] tablet had a total weight of 1437 mg, with 800 mg directed to the four APIs and the remaining 637 mg directed to the combined excipients, where the 172.5 mg of the excipient weight is attributed to colloidal silicon dioxide, *i.e.*, a required absorbent for COBI designed to enhance its stability. See Stribild Assessment, 12 (the active substance COBI is adsorbed on silicon dioxide), 13 (COBI is isolated by adsorption on silicon dioxide to provide a stable solid form, which is suitable for further finished product manufacture).

If identical tablet excipients and amounts were employed in the tablet combination containing 275 mg total milligrams of BIC, TAF and FTC (without the PK booster COBI), the total tablet weight would have been ~910 mg (or slightly more if the tablet employed bictegravir sodium and TAF fumarate). Thus, even if the tablet contained the large amount of silicon dioxide for absorption of COBI (which would not have been required with BIC), the total tablet weight would have been less than 1000 mg. And the total tablet weight would have been substantially lower than 1000 mg, e.g., ~740 mg, when silicon dioxide was significantly reduced or removed from the tablet altogether (which a skilled artisan would have been motivated to do for a tablet not containing COBI).

Further, the skilled artisan would have appreciated that the tablet excipients in the Stribild[®] formulation could have been reduced even further because significantly less BIC and TAF, i.e., 50 mg and 25 mg respectively, would have been needed compared to the 150 mg amount of EVG and 300 mg amount of TDF included in Stribild[®]. *See generally, e.g.,* Lee, 1900 (Table 1) (disclosing TAF as 10 times more potent than TDF toward HIV-1, with eight times improved selectivity index); Genvoya Assessment, 13 (TAF fumarate can be administered at a much lower dose than tenofovir disoproxil fumarate (TDF) while maintaining the established doses and biopharmaceutical performance of the other active substances); Stribild Label, 1 22; Stribild Assessment, 10-11, 18. As such, a skilled artisan would have appreciated that the total tablet weight could be reduced even further, e.g., to below 800 mg and below 730 mg, given that less excipients would be needed to properly formulate the lower amount of total active ingredients. And given that this lower total dose of BIC, TAF, and FTC vis-à-vis Stribild[®] was expected to be useful for the treatment of HIV, the skilled artisan would have reasonably expected tablets having total weight of less than 1000 mg, less than 800 mg, and less than 730 mg to be accessible and successful for the treatment of HIV.

Accordingly, as a further non-limiting example, claims 9-11 of the '802 patent are obvious over US '356 in view of WO '351 or US '332, further in view of WO '846, Shah, and/or US '122.

d. Claims 12-13

Defendants' obviousness analysis for claims 1-11 of the '802 patent is incorporated herein in its entirety.

Claim 12 depends from claim 1 and requires the tablet to contain less than 15% of bicitgravir or a pharmaceutically acceptable salt thereof. Claim 13 depends from claim 1 and requires the tablet to contain less than 11% of bicitgravir or a pharmaceutically acceptable salt thereof.

As explained above for claims 9-11, a tablet composition (including a multilayer tablet composition) containing 50 mg of BIC (or a salt thereof), 25 mg TAF (or a salt thereof), and 200 mg FTC (or a salt thereof) and having a total tablet weight significantly less than 1000 mg, e.g., less than 800 mg and less than 730 mg, would have been obvious. This is at least because the skilled artisan would have formulated such tablets to contain the least amount of excipients as possible, to provide a tablet that would be easier to swallow for increased patient compliance.

Given that the total active ingredient weight in those obvious tablets is 275 mg (or slightly more when including bictegravir sodium and a TAF fumarate salt), the skilled artisan would have significant room to provide a tablet composition containing less than about 15% BIC or BIC sodium (claim 12), and less than about 11% BIC or BIC sodium (claim 13). Indeed, the skilled artisan would have arrived at these percentages through routine optimization of common excipients and their amounts to provide a tablet composition having a total weight of less than about 1000 mg, such as less than 800 mg and less than 730 mg. And most reasonably achievable tablet weights, e.g., 275 mg of active ingredients and a total weight of 600-900 mg, would meet the 15% and 11% limitations of claims 12-13 when the BIC or BIC sodium dose is ~50 mg. Indeed, a 600 mg tablet would have contained ~8% BIC or BIC sodium, a 700 mg tablet would have contained ~7% BIC or BIC sodium, an 800 mg tablet would have contained ~6% BIC or BIC sodium, and a 900 mg tablet would have contained ~5.5% BIC or BIC sodium, each of which fall within the scope of claims 12-13.

Accordingly, claims 12-13 of the '802 patent are obvious for the same reasons as claim 1, further in view of the prior art disclosures discussed in this section. As an exemplary non-limiting example, claims 12-13 are obvious over US '356 in view of WO '351 or US '332, optionally further in view of the WO '846, Shah, and/or US '122.

(2) The Asserted Claims are Invalid for Obviousness-Type Double Patenting over Gilead's '067 Patent

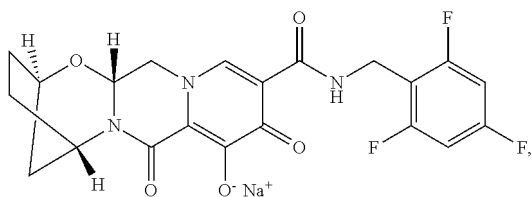
The obviousness analysis for claims 1-13 of the '802 patent from Section VI.F.1 are incorporated herein in its entirety, including the prior art disclosures and combinations discussed therein. The obviousness-type double patenting analysis from Section V.F.1 is incorporated herein in its entirety, including the prior art disclosures and combinations discussed therein.

As discussed in Section II.DDD, Gilead's '067 patent was filed on June 15, 2017, and issued on August 20, 2019. The '067 patent is listed in the Orange Book for BIKTARVY® as covering a method for treating HIV infection. According to the Orange Book, the '067 patent will expire on June 19, 2035, which is 17 months before the expiration of the '802 patent on November 8, 2036. The '067 patent is thus a commonly-owned patent that issued and will expire earlier than the '802 patent, and the '067 patent may therefore be considered in a double patenting analysis as to the '802 patent.

The '067 patent issued with nineteen (19) claims, including claims 10, 16, 17 and 19 (below) directed to methods for treating an HIV infection comprising administering a pharmaceutical composition comprising a therapeutically effective amount of bictegavir sodium Form I (claim 10), which may further comprise tenofovir alafenamide and emtricitabine (claim 16) or tenofovir alafenamide hemifumarate and emtricitabine (claim 17), where the composition is a unit dosage form in the form of a tablet (claims 18-19).

10. A method for treating an HIV infection in a human in need thereof, comprising administering to the human a pharmaceutical composition, the pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula II:

(II)



which is crystalline and is characterized by an x-ray powder diffraction (XRPD) pattern having peaks at about 5.5°, 16.1°, and 23.3° $2-\theta \pm 0.2^\circ \pm 2-\theta$, and a pharmaceutically acceptable carrier or excipient.

16. The method of claim 10, wherein the pharmaceutical composition further comprises tenofovir alafenamide and emtricitabine.

17. The method of claim 10, wherein the pharmaceutical composition further comprises tenofovir alafenamide hemifumarate and emtricitabine.

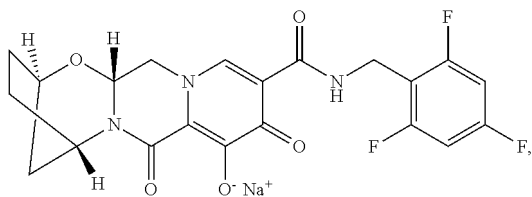
18. The method of any one of claims 10 to 17, wherein the pharmaceutical composition is in a unit dosage form.

19. The method of claim 18, wherein the unit dosage form is a tablet.

The following claim represents claim 19, incorporating the limitations from claims 10, 16, and 18-19 (as they depend from claim 16).

19. [A method for treating an HIV infection in a human in need thereof, comprising administering to the human a pharmaceutical composition, the pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula II:

(II)

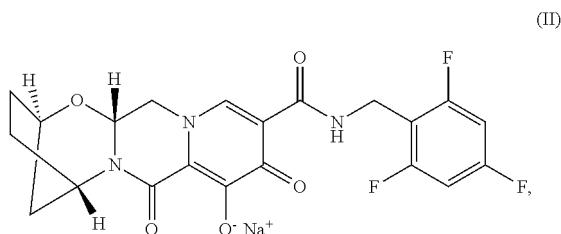


which is crystalline and is characterized by an x-ray powder diffraction (XRPD) pattern having peaks at about 5.5°, 16.1°, and 23.3° $2-\theta \pm 0.2^\circ \pm 2-\theta$, and a pharmaceutically acceptable carrier or excipient [(taken from claim 10)], wherein the pharmaceutical composition further comprises tenofovir alafenamide and emtricitabine [(taken from claim 16)], wherein the

pharmaceutical composition is in a unit dosage form [(taken from claim 18)], wherein the unit dosage form is a tablet.

Also provided is the following representation of claim 19, incorporating the limitations from claims 10, 16, and 18-19 (as they depend from claim 17).

19. [A method for treating an HIV infection in a human in need thereof, comprising administering to the human a pharmaceutical composition, the pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula II:



which is crystalline and is characterized by an x-ray powder diffraction (XRPD) pattern having peaks at about 5.5°, 16.1°, and 23.3° $2\theta \pm 0.2^\circ \pm 2\theta$, and a pharmaceutically acceptable carrier or excipient [(taken from claim 10)], wherein the pharmaceutical composition further comprises tenofovir alafenamide hemifumarate and emtricitabine [(taken from claim 17)], wherein the pharmaceutical composition is in a unit dosage form [(taken from claim 18)], wherein the unit dosage form is a tablet.

Claim 19 (depending from claim 16) and claim 19 (depending from claim 17) are each directed to a tablet comprising a therapeutically effective amount of crystalline bicitgravir (BIC) sodium Form I, along with tenofovir alafenamide (TAF), emtricitabine (FTC), and a pharmaceutically acceptable carrier or excipient. They differ only in that the former claim calls for TAF, while the latter calls for TAF as a hemifumarate salt.

Because the first step of a double patenting analysis involves the interpretation of the claims of the earlier and later expiring patents in question, the specifications of both patents may be consulted to ascertain the meaning of claim terms, including to determine whether the inventors accorded any special meaning to claim terms by definition.

The '067 patent provides specific definitions for the following terms appearing in the above claims:

The term “treatment” as used herein is intended to mean the administration of a compound or composition according to the present invention to alleviate or eliminate symptoms of HIV infection and/or to reduce viral load in a patient. The term “treatment” also encompasses the administration of a compound or composition according to the present invention post-exposure of the individual to the virus but before the appearance of symptoms of the disease, and/or prior to the detection of the virus in the blood, to prevent the appearance of symptoms of the disease and/or to prevent the virus from reaching detectable levels in the blood

'067 patent, 5:21-35

A “pharmaceutical composition” refers to a formulation of a compound of the invention and a medium generally accepted in the art for the delivery of the biologically active compound to mammals, e.g., humans. Such a medium includes all pharmaceutically acceptable carriers, diluents or excipients therefor.

Id. at 4:60-65.

“Pharmaceutically acceptable carrier, diluent or excipient” 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.

Id. at 4:52-59.

“Effective amount” or “therapeutically effective amount” refers to an amount of a compound according to the invention, which when administered to a patient in need thereof, is sufficient to effect treatment for disease-states, conditions, or disorders for which the compounds have utility. ... Such a therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to their own knowledge, the state of the art, and this disclosure.

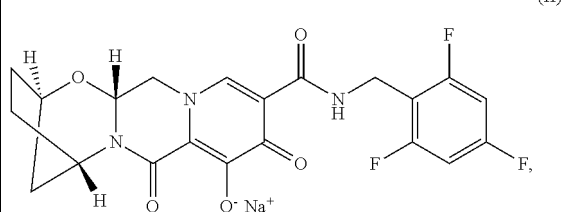
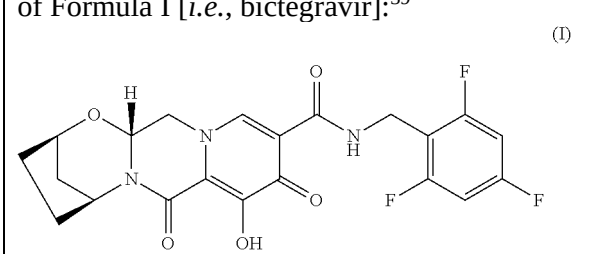
Id. at 4:66-5:20.

Each of the terms above are specifically defined by the inventors of the '067 patent, which takes precedence over any alternative ordinary and customary meaning that could be assigned by the skilled artisan.

a. Claim 1

Claim 1 of the '802 patent is directed to a tablet comprising 50 mg of BIC (*i.e.*, the compound of Formula (I) appearing the claim) 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.

A comparison of claim 19 (depending from claim 16) of Gilead's earlier expiring '067 patent with claim 1 of Gilead's later expiring '802 patent is provided in the table below:

Claim 19 (depending from Claim 16) of Gilead's '067 Patent	Claim 1 of Gilead's '802 Patent
19. [A method for treating an HIV infection in a human in need thereof, comprising administering to the human a pharmaceutical composition, the pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula II [<i>i.e.</i>, bictegrovir sodium]:  (II) which is crystalline and is characterized by an x-ray powder diffraction (XRPD) pattern having peaks at about 5.5°, 16.1°, and 23.3° 2-θ±0.2°±2-θ, and a pharmaceutically acceptable carrier or excipient [(taken from claim 10)], wherein the pharmaceutical composition further comprises tenofovir alafenamide and emtricitabine [(taken from claim 16)], wherein the pharmaceutical composition is in a unit dosage form [(taken	1. A tablet comprising 50 mg of the compound of Formula I [<i>i.e.</i>, bictegrovir]:³⁹  (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.

³⁹ The chemical structure of Formula (I) from claim 1 of the '802 patent represents bictegrovir in a different orientation from the chemical structure of Formula (II) from claim 10 of the '067 patent representing BIC sodium.

from claim 18)]]], wherein the unit dosage form is a tablet.	
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Claim 19 of the '067 patent (depending from claim 16) differs from claim 1 of the '802 patent in the following ways:

- Claim 19 is directed to a method of treating HIV in a human with a tablet composition comprising a therapeutically effective amount of crystalline BIC sodium Form I, whereas claim 1 is directed to a tablet comprising 50 mg of BIC or pharmaceutically acceptable salt thereof generally;⁴⁰
- Claim 19 calls for the tablet to comprise TAF and FTC, whereas claim 1 calls for a tablet comprising 25 mg TAF or a pharmaceutically acceptable salt thereof, and 200 mg FTC or a pharmaceutically acceptable salt thereof;
- Claim 19 calls for the tablet to comprise a pharmaceutically acceptable carrier or excipient, whereas claim 1 does not mention any carriers or excipients.

As explained above, the term “therapeutically effective amount” appearing in claim 19 (depending from claim 16) is defined in the '067 specification as an amount “which when administered to a patient in need thereof, is sufficient to effect treatment for disease-states, conditions, or disorders for which the compounds have utility[,]” which amount can be routinely determined by a skilled artisan. '067 patent, 4:66-5:20. As such, the pharmaceutical composition of claim 19 (depending from claim 16) contains an amount of BIC sodium Form I effective to treat HIV in a human when combined with TAF and FTC. Because claim 19 (depending from claim 16) is limited to a tablet, a skilled artisan would appreciate that the “pharmaceutically acceptable carrier or excipient” recited in the claim is any carrier or excipient suitable for tablet formulations approved by the United States Food and Drug Administration as being acceptable for use in humans. See above definition of “pharmaceutically acceptable carrier, diluent or excipient;” '067 patent, 4:52-59.

⁴⁰ Crystalline bicitgravir sodium Form I is a species of “bicitgravir or pharmaceutically acceptable salt thereof” recited in claim 1 of the '802 patent.

Upon the expiration of the '067 patent, the general public should be entitled to use the method of claim 19 (depending from claim 16) and any obvious variants thereof. In order to do so, Gilead cannot have any non-expired claims covering the tablet composition defined in claim 19 or its obvious variants, because the general public cannot practice the method of claim 19 without being able to use, *i.e.*, administer the claimed tablet composition (or obvious variants thereof) to an HIV patient in the United States without infringing upon the non-expired claim. As explained below, claim 1 of the '802 patent improperly covers an obvious variant of the claim 19 (depending from claim 16) tablet composition, and is therefore invalid for obviousness-type double patenting.

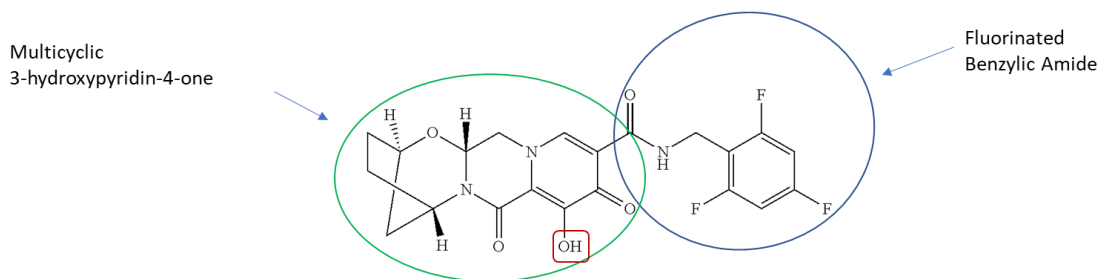
The '802 patent establishes that a particular utility of “an oral dosage form containing [bictegravir], tenofovir alafenamide and emtricitabine” is the “treat[ment] of viral infections such as HIV.” '802 patent, 2:36-40; *see also id.* at 54:47-53 (“[t]he solid oral dosage forms (in particular tablets) disclosed herein are used for treatment of HIV infection (e.g. HIV-1 infection).” It also establishes the utility of BIC as a “potent HIV integrase inhibitor with in vitro activity against wild type HIV-1” *Id.* at [0032]. Because the claimed tablet containing 50 mg of BIC or a pharmaceutically acceptable salt thereof (along with 25 mg of TAF and 200 mg of FTC or their pharmaceutically acceptable salts) is a solid oral dosage form of the alleged invention, a skilled artisan would conclude that the claimed 50 mg of BIC or a pharmaceutically acceptable salt thereof constitutes a therapeutically effective amount for the treatment of HIV. And because the definition of “therapeutically effective amount” in the '067 patent notes that such amount can be routinely determined by the skilled artisan, the 50 mg therapeutically effective dose of BIC is inherently disclosed by or obvious over claim 19 (depending from claim 16) of the '067 patent.

Additionally, the skilled artisan would note from claim 19 (depending from claim 16) of the '067 patent that the claimed tablet containing crystalline bicitgravir sodium Form I, TAF and FTC is to be used for treating “an HIV infection in a human in need thereof.” As such, the skilled artisan would have appreciated that the claimed tablet should also contain a therapeutically effective amount of TAF and FTC for the treatment of HIV infection in a human when co-administered with a therapeutically effective amount of crystalline bicitgravir sodium Form I. Though claim 19 (depending from claim 16) of the '067 patent does not specifically call for such therapeutically effective amounts of TAF and FTC for treating HIV, the skilled artisan would have been motivated to use such amounts in the claimed tablet, given the nature of the method claim. At the very least, such therapeutically effective amounts would have been routinely determined by the skilled artisan and incorporated into the tablet composition. *See* '802 patent, 4:66-5:20 (definition of “therapeutically effective amount”).

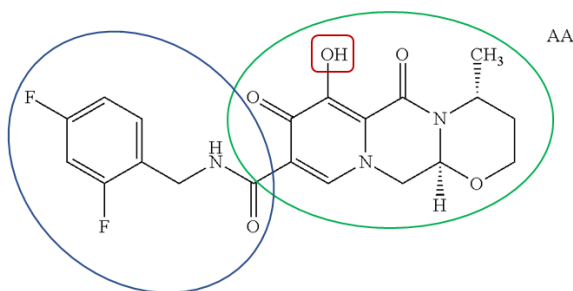
The 25 mg amount of tenofovir alafenamide (or a pharmaceutically acceptable salt thereof), and the 200 mg amount of emtricitabine (or a pharmaceutically acceptable salt thereof) recited in claim 1 of the '802 patent are nothing more than therapeutically effective amounts of these agents for the treatment of HIV in a human when used in combination with 50 mg of bicitgravir (or a pharmaceutically acceptable salt thereof). And because such amount would have been routinely determined by the skilled artisan, they do not confer a patentable distinction over claim 19 (depending from claim 16) of the '067 patent directed to a method for treating HIV in a human with a tablet composition containing crystalline bicitgravir sodium Form I, TAF and FTC and a pharmaceutically acceptable carrier or excipient.

In addition, as explained in Section VI.F.1 the skilled artisan would have recognized that BIC is an HIV integrase inhibitor (INSTI) that bears a close structural similarity to the FDA-

approved HIV INSTI dolutegravir (DLT). Based on this similarity, the skilled artisan would have also expected that BIC would have similar physicochemical and biological properties to DLT because each compound is weakly acidic and contains a fluorinated benzylic amide and a 3-hydroxypyridin-4-one multicyclic ring structure (see structural comparison below).



Bictegravir



Dolutegravir

The Tivicay Assessment identifies DLT sodium as an HIV INSTI indicated in combination with other antiretroviral agents, *e.g.*, emtricitabine/tenofovir (TRUVADA), for the treatment of HIV-1 infection. Tivicay Assessment, 43, 50-51 (identifying DLT as “a new integrase inhibitor which has been studied in a full range of HIV treatment populations”), 89 (disclosing combination therapies of DLT sodium with Truvada (FTC/FTC); *see also* US ’332 (disclosing pharmaceutical combinations of DLT, FTC and TAF). Tivicay is a film coated tablet composition containing DLT sodium at a dose of 52.6 mg, which is equivalent to 50 mg DLT free acid. Tivicay Assessment, 9

(Tivicay is an immediate release tablet formulation containing 50 mg of dolutegravir (as a sodium salt) as the active substance); *see also* US '332, [0091]-[0092] (disclosing particularly preferred embodiments of a pharmaceutical combination containing about 50 mg DLT, about 200 mg FTC, and about 25 mg tenofovir, in particular TAF), [0018] (stating a preference for DLT as a sodium salt), [0032] (stating a preference for FTC as a free base), [0032] (stating a preference for FTC as a free base), [0053] (stating a preference for TAF as a monofumarate or hemifumarate salt, and especially a hemifumarate salt); *see also* HIV Guidelines, D-1 (recommending the use of two nucleos(t)ide reverse transcriptase inhibitors in combination with a third active antiretroviral drug from one of three drug classes: an integrase strand transfer inhibitor, a nonnucleoside reverse transcriptase inhibitor, or a protease inhibitor with a pharmacokinetic enhancer); *id.* at 1, *i* (recommending the combination of the INSTIs elvitegravir and raltegravir with tenofovir and emtricitabine); British HIV Guidelines, 13 (describing tenofovir and emtricitabine as the *preferred NRTI backbone* for HIV therapy, to be combined with an additional agent such as an INSTI). Llibre, 175 (DLT is “the first integrase inhibitor dosed once daily without pharmacokinetic boosting[, which] has a higher barrier of resistance compared to RAL and EVG, retaining activity against many viral strains harboring major integrase resistance mutations selected for by both of them”), (“In a Phase IIb dose ranging study, DLT doses of 10 mg, 25 mg and 50 mg were well tolerated at all assessed doses with TDF/FTC, where no integrase mutations were selected in any of the patients studied, and the proportion of patients with viral load <50 copies/mL at 48 weeks was an impressive 88-91%”); Astuti, 10-11 (DLT is “an unboosted integrase inhibitor that has been effectively and safely used for the treatment of HIV-infected naïve patients (with 2 NRTIs) and experienced patients (with an optimized background regimen)”).

In view of the structural similarity and identical utilities of DLT and BIC, the skilled artisan would have expected that these compounds could be administered at similar doses in combination with FTC and tenofovir, *e.g.*, with Truvada (FTC/TDF) (as disclosed in the Tivicay Assessment) or FTC/TAF (as disclosed in US '332). As such, the skilled artisan would have considered the 50 mg dose of bicitgravir in the tablet of claim 1 (combined with the recited doses of TAF and FTC) to be at or near the “therapeutically effective amount” of BIC bicitgravir needed to treat HIV when administered in combination with TAF and FTC. For this additional reason, a skilled artisan would have been motivated to use a 50 mg dose of BIC (or an equivalent dose of bicitgravir sodium) for the treatment of HIV according to claim 19 (depending from claim 16) of the '067 patent, and reasonably expected that amount to be successful when combined with TAF and FTC. Such 50 mg dose of BIC would have also been achieved through routine methods of dose optimization in the art of HIV combination therapies. *See also* BIC Safety Study, 8-9 (a 50 mg dose of BIC had already been disclosed for the treatment of HIV by the FDA), NCT '694 (Version 8) (disclosing an FDC containing 50 mg BIC, 200 mg FTC, and 25 mg TAF).

Regarding the 200 mg dose FTC recited in claim 1, the skilled artisan would have also recognized it as the generally accepted dose for FTC in combination therapies for the treatment of HIV. Indeed, every approved combination tablet from Gilead discussed in Section II contains 200 mg of FTC. *See e.g.*, Truvada Label (combination of 200 mg FTC and 300 mg TDF); Truvada Label (combination of 200 mg FTC, 300 mg TDF, 600 mg efavirenz); Complera Label (combination of 200 mg FTC, 300 mg TDF, 27.5 mg rilpivirine hydrochloride); Stribild Label (combination of 200 mg FTC, 300 mg TDF, 150 mg EVG and 150 mg COBI); Genvoya Label (combination of 200 mg FTC, 10 mg TAF, 150 mg EVG and 150 mg COBI); *see also* US '122, [0022], [0063]-[0065] (bilayer tablets similar to Stribild® containing 200 mg FTC); US '902,

[0050]-[0052] (bilayer tablets similar to Atripla containing 200 mg FTC); US '857 [0066]-[0073] (bilayer tablets similar to Complera/Eviplera containing 200 mg FTC); WO '846, 37:13-20 (Formulation D) (combination of 25 mg TAF with 200 mg FTC); US '332, [0091]-[0092] (pharmaceutical combination containing about 50 mg DLT, about 200 mg FTC, and about 25 mg TAF). A skilled artisan would therefore have been motivated to use a 200 mg dose of FTC for the treatment of HIV using the tablet combination according to claim 19 (depending from claim 16) of the '067 patent, and reasonably expected that amount to be successful when combined with therapeutically effective amounts of bictegravir sodium Form I and TAF.

Regarding the 25 mg dose of TAF recited in claim 1, the skilled artisan would have also recognized it as an acceptable dose for TAF in combination therapies for the treatment of HIV. For one, it was known by at least 2014 that Gilead sought to replace TDF with TAF, because TAF had “demonstrated high antiviral efficacy at a dose 10 times lower than Viread, as well as an improved renal and bone safety profile.” Gilead/Janssen, 2. These advantages of TAF had long been appreciated in the art, including by Lee in 2005 and in the '791 patent in 2008. *See* Lee, 1900 (Table 1) (disclosing TAF as 10 times more potent than TDF toward HIV-1, with eight times improved selectivity index), 1905 (high concentrations of tenofovir observed in lymphatic tissues after oral administration of GS 7340 (TAF) are expected to result in increased clinical potency relative to TDF) (with TAF, it should be possible to reduce the total dose of tenofovir, thereby minimizing systemic exposure, while at the same time increasing antiviral activity); '791 patent, 27:29-28:37 (TAF shows a 10-fold increase in antiviral activity relative to TDF and a 200-fold increase in plasma stability; greater plasma stability is expected to result in higher circulating levels of TAF than TDF after oral administration), Tables 1-2; Ruane, 451-52 (“HIV-1 RNA responses for the 8-mg TAF treatment group were similar to that of the 300-mg TDF group.

However, median DAVG₁₁ [(time-weighted average change from baseline to study day 11)] for plasma HIV-1 RNA . . . in the 25- and 40-mg TAF treatment groups showed significantly greater decreases compared with the 300-mg TDF treatment group.”); Sax, 53 (“Relative to TDF, TAF is more stable in plasma.”); *See also, e.g.*, US ’332, [0091]-[0092] (pharmaceutical combination containing about 50 mg DLT, about 200 mg FTC, and about 25 mg TAF); WO ’846, 37:13-20 (Formulation D) (tablet composition containing 25 mg TAF and 200 mg FTC); US ’856, [0010]-[0011], [0057] (disclosing pharmaceutical compositions comprising TAF hemifumarate, NRTIs and HIV integrase inhibitors); Genvoya Assessment, 10 (describing Genvoya[®] as a tablet combination containing 150 mg EVG, 150 mg COBI, 200 mg of FTC, and 10 mg of TAF (as 11.2 mg of the fumarate)), 13 (describing monolayer and bilayer tablets of EVG/CCOBI/FTC/TAF containing 25 mg TAF as the monofumarate)). That artisan would have also known that TAF was 10-fold more active than its predecessor prodrug TDF with a 200-fold increase in plasma stability that would have provided higher circulating levels of TAF than TDF after oral administration. *See e.g.*, ’791 patent, 27:29-28:37 (Tables 1-2); *see also* Astuti, 10-11 (“a 25 mg dose of TAF has shown greater ARV activity than a standard 300 mg dose of TDF[, and that] [c]linically . . . TAF resulted in non-inferior efficacy to TDF both co-formulated with FTFC/EVG/COBI”); Llibre, 172 (TAF leads to significantly greater decreases in HIV-1 RNA compared with TDF 300 mg, with 86% lower plasma tenofovir exposures (AUC), and sevenfold higher intracellular tenofovir-diphosphate concentrations both in PBMC and lymphatic tissues, compared to TDF 300 mg in 10-day monotherapy studies).

For at a least these reasons, the skilled artisan would have been motivated to utilize a ~10-fold lower dose of TAF vis-à-vis the approved 300 mg dose of TDF in combination tablets for the treatment of HIV, including in combinations also containing a therapeutically effective amount of

an INSTI, and 200 mg of emtricitabine, *e.g.*, as in the Gilead's Stribild product ((combination of 200 mg FTC, 300 mg TDF, 150 mg elvitegravir and 150 mg cobicistat). *See, e.g.*, Stribild Label, 1, 22-23. And given that TAF was known to be 10 times more potent than TDF toward HIV-1, with an eight times improved selectivity index (*see* Lee, 1900), the skilled artisan would have reasonably expected such a 10-fold lower dose to be a therapeutically effective amount of TAF that would have been successful in the treatment of HIV. Indeed, such an ~10-fold lower dose (*i.e.*, 25 mg) had been specifically disclosed in WO '846 in combination with 200 mg of FTC.

A 25 mg dose of TAF is approximately 10-fold lower than the 300 mg dose of TDF (equivalent to 245 mg tenofovir disoproxil). Thus, a skilled artisan would therefore have been motivated to use a 25 mg dose of TAF (or an equivalent amount of pharmaceutically acceptable fumarate salt) for the treatment of HIV using the tablet combination according to claim 19 (depending from claim 16) of the '067 patent, and reasonably expected that amount to be successful when combined with 50 mg of BIC sodium Form I and 200 mg of FTC. The skilled artisan would have also arrived at 25 mg TAF as a therapeutically effective dose of TAF for treating HIV according to claim 19 (depending from claim 16) of the '067 patent through routine dose optimization methods in the art of HIV combination therapies. *See also* Astuti, 10-11; Llibre, 172; Sax, 53.

In addition, the Genvoya Assessment describes film-coated tablet combinations containing the INSTI elvitegravir, along with FTC, cobicistat and TAF, *i.e.*, an updated version of Gilead's Stribild. Genvoya Assessment, 10. Though the approved dose for TAF in the Genvoya product was 10 mg, the Genvoya Assessment also describes open-label crossover studies where the combination contained 25 mg of TAF, where the exposures to TAF and tenofovir were substantially higher vs. TAF 25 mg administered alone, establishing that 25 mg TAF was an

acceptable dose in an HIV combination. *Id.* at 74-75. Indeed, a 25 mg dose for TAF in combination tablets was even recognized as early as 2004. WO '846, 3:13-18 (therapeutic combinations of TAF and FTC for treating HIV), 18:23-26 (combination can additionally include an INSTI), 37:13-20 (exemplary formulation containing 25 mg of TAF and 200 mg FTC); *see also* US '332 (disclosing combinations for treating HIV containing 40 to 60 mg dolutegravir, 150 to 250 mg FTC, and 5 to 42 mg tenofovir alafenamide). For these additional reasons, a skilled artisan would have been motivated to use a 25 mg dose of TAF for the treatment of HIV in the tablet combination according to claim 19 (depending from claim 16) of the '067 patent, and reasonably expected that amount to be successful when combined with 50 mg of bictegravir (or its pharmaceutically acceptable sodium salt) and 200 mg of FTC. *See also* Astuti, 10-11; Llibre, 172.

For the reasons discussed above, it is our opinion that claim 1 of the '802 patent is an obvious variant of the claim 19 (depending from claim 16) of the '067 patent. Claim 1 is therefore invalid for obviousness-type double patenting over claim 19 (depending from claim 16) of the '067 patent, when claim 19 is analyzed in view of the prior art discussed in this section. The following non-limiting combinations of claim 19 (depending from claim 16) of the '067 patent with the prior art are exemplary.

- Claim 19 (depending from claim 16) of the '067 patent, in view of common knowledge in the art.
- Claim 19 (depending from claim 16) of the '067 patent, in view of common knowledge in the art and the Stribild product discussed in, *e.g.*, the Stribild Assessment.

- Claim 19 (depending from claim 16) of the '067 patent, in view of common knowledge in the art and the Atripla product discussed in, *e.g.*, the Atripla Assessment.
- Claim 19 (depending from claim 16) of the '067 patent, in view of common knowledge in the art and the Eviplera product discussed in, *e.g.*, the Eviplera Assessment.
- Claim 19 (depending from claim 16) of the '067 patent, in view of common knowledge in the art and the Genvoya product discussed in, *e.g.*, the Genvoya Assessment.
- Claim 19 (depending from claim 16) of the '067 patent, in view of common knowledge in the art and one or more of Stribild Label, Stribild Assessment, Genvoya Label, Genvoya Assessment, and US '122, optionally further in view of one or more of Tivicay Label, Tivicay Assessment, Shah, Dow and US '332.
- Claim 19 (depending from claim 16) of the '067 patent, in view of common knowledge in the art and one or more of Stribild Label, Stribild Assessment, Genvoya Label, Genvoya Assessment, and US '122, optionally further in view of one or more of Gilead/Janssen, Lee, the '791 patent, Ruane, Sax, Astuti, Llibre, WO '846, and US '856.
- Claim 19 (depending from claim 16) of the '067 patent, in view of common knowledge in the art and one or more of Truvada Label, Complera Label, Genvoya Label, Genvoya Assessment, and US '122, optionally further in view of one or more of Tivicay Label, Tivicay Assessment, Shah, Dow and US '332.

- Claim 19 (depending from claim 16) of the '067 patent, in view of common knowledge in the art and one or more of Truvada Label, Complera Label, Genvoya Label, Genvoya Assessment, and US '122, optionally further in view of one or more of Gilead/Janssen, Lee, the '791 patent, Ruane, Sax, Astuti, Llibre, WO '846, and US '856.
- Claim 19 (depending from claim 16) of the '067 patent, in view of common knowledge in the art and WO '846, optionally further in view of one or more of Gilead/Janssen, Lee, the '791 patent, Ruane, Sax, Astuti, and Llibre.
- Claim 19 (depending from claim 16) of the '067 patent, in view of common knowledge in the art and WO '846, optionally further in view of one or more of Tivicay Label, Tivicay Assessment, Shah, Dow and US '332.
- Claim 19 (depending from claim 16) of the '067 patent, in view of common knowledge in the art and one or more of US '122, US '902, and US '857, optionally further in view of one or more of Tivicay Label, Tivicay Assessment, Shah, Dow and US '332.
- Claim 19 (depending from claim 16) of the '067 patent, in view of common knowledge in the art and one or more of US '122, US '902, and US '857, optionally further in view of one or more of Gilead/Janssen, Lee, '791 patent, Ruane, Sax, Astuti, Llibre, WO '846, and US '856.
- Claim 19 (depending from claim 16) of the '067 patent in view of common knowledge in the art and any reference from Section II or Appendix C disclosing therapeutically effective amounts of INSTIs, FTC and TAF, and motivation to keep

the total tablet weight below 1000 mg, *e.g.*, by not requiring COBI or silicon dioxide in the tablet formulation.

Optionally, claim 19 (depending from claim 16) of the '067 patent would have been combined with WO '351 with a reasonable likelihood of success because it is in the same field of invention as WO '323, US '356, WO '846, and the '385 patent and discloses a similar pharmaceutical composition containing an INSTI and reverse transcriptase inhibitors. WO '351 teaches 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” for treatment of “a subject afflicted with a viral infection, preferably afflicted with an HIV infection.” WO '351 at 3:18-24. In the composition, “[p]referably, dolutegravir is in the form of a pharmaceutically acceptable salt,” and “[p]articularly preferred, dolutegravir is used in the form of the sodium salt, especially the mono-sodium salt.” *Id.* at 5:22-27. WO '351 also discloses embodiments where the pharmaceutical composition comprises (a) dolutegravir, (b) emtricitabine and (c) tenofovir alafenamide in which the weight ratio of (a) dolutegravir to (b) emtricitabine to (c) tenofovir alafenamide can be from 1:1:0.15 to 1:8:1.” *Id.* at 16:8-11. WO '351 teaches “In a preferred embodiment of the pharmaceutical combination of the present invention the amount of dolutegravir administered is 20 to 75 mg per day, preferably 25 to 70 mg per day, more preferably 35 to 65 mg per day, in particular 40 to 60 mg per day.” *Id.* at 16:15-18. It also teaches “In case that the tenofovir is administered as tenofovir alafenamide, the amount of tenofovir alafenamide administered preferably is 0.5 to 50 mg per day, more preferably 1 to 45 mg per day, even more preferably 3 to 44 mg per day, in particular 5 to 42 mg per day.” *Id.* at 17:5-8. WO '351 further teaches that “In a preferred embodiment the pharmaceutical composition comprises (i) 20 to 75 mg, preferably 25 to 70 mg, more preferably 35 to 65 mg, in particular 40 to 60 mg dolutegravir

(a); (ii) 50 to 300 mg, preferably 100 to 280 mg, more preferably 125 to 260 mg, in particular 150 to 250 mg emtricitabine (b); (iii) 0.5 to 50 mg, more preferably 1 to 45 mg, even more preferably 3 to 44mg, in particular 5 to 42 mg tenofovir (c), in particular tenofovir alafenamide; and (iv) pharmaceutical excipients.” *Id.* at 19:3-12. WO ’351 further discloses that “the combination of the present invention is administered once daily” and “can be preferably a solid oral dosage form” in “a capsule or tablet.” *Id.* at 17:27-28, 23:6-8.

As explained above, claim 1 of the ’802 patent reads on the species of “multilayer” tablets that include the claimed amounts of BIC, TAF, and FTC (or their salts). The skilled artisan would have readily appreciated that Gilead was employing bilayer technology in its HIV combination tablets for years before the effective filing date for the ’802 patent. Such combination tablets included Stribild (bilayer technology to physically separate of EVG and COBI from FTC and TDF to reduce potential physicochemical interaction between them), Atripla (bilayer tablet separating efavirenz from FTC and TDF), Genvoya (bilayer layer tablets separating EVG and COBI from FTC and TDF used in clinical trials), Eviplera (bilayer layer tablet containing rilpivirine, FTC and TDF used to study pharmacokinetics in dogs demonstrated comparable systemic exposure to all compounds to individual compounds administered individually). Stribild Assessment, 18, 33; Atripla Assessment, 5; Genvoya Assessment, 74-75; Eviplera Assessment, 18; *see also* US ’122, [0007] (tablets prepared in a bilayer manner have superior properties to alternatively structured tablets), FIG 1 and [0052] (disclosing a bilayer tablet having a first layer EVG and COBI, and a second layer that comprises FTC and TDF); US ’902, [0010], [0050]-[0052] (describing bilayer tablets for keeping efavirenz separate from FTC and TDF); US ’857, [0066]-[0071] (describing bilayer tablets for keeping rilpivirine separate from FTC and TDF).

In particular, Gilead's approved Stribild tablet contains the INSTI elvitegravir in a first layer, and FTC and TDF in second layer. Stribild Assessment, 18, 33. This bilayer tablet configuration was disclosed as having superior properties to alternatively structured tablets. US '122, [0007], *see also* [0061] (combining all of the compounds in a mixture to produce a monolayer tablet compromises chemical stability).

For at least these additional reasons, a skilled artisan would have been motivated to formulate a bilayer tablet combination containing 50 mg bicittegravir (or an equivalent amount of bicittegravir sodium), 25 mg tenofovir alafenamide (or an equivalent amount of TAF fumarate or TAF hemifumarate), and 200 mg emtricitabine. And given that these APIs dosages were known (or expected to be useful) for the treatment of HIV, the skilled artisan would have reasonably expected these amounts amount to be successful for the treatment of HIV in a bilayer tablet.

For example, the skilled artisan would have been motivated to modify the bilayer tablet described in the Genvoya Assessment, *e.g.*, that containing 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 25 mg of tenofovir alafenamide, to replace the first generation INSTI elvitegravir with 50 mg of the second generation INSTI bicittegravir (or an equivalent amount of bicittegravir sodium), and to remove the PK booster COBI and its silicon dioxide absorbent to provide the multilayer tablet having the recited doses and total tablet weight of claim 1. Alternatively, the skilled artisan would have been motivated to modify the bilayer tablet described in the Stribild Assessment, *e.g.*, that containing 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 300 mg of TDF, to replace elvitegravir with 50 mg of bicittegravir (or an equivalent amount of bicittegravir sodium), to replace TDF with the improved prodrug TAF (or an equivalent amount of TAF fumarate). This configuration would have been expected to reduce potential physicochemical interaction between bicittegravir sodium and the other

APIs. And given that these API dosages were known (or expected to be useful) for the treatment of HIV, the skilled artisan would have reasonably expected these amounts amount to be successful for the treatment of HIV in a bilayer tablet.

In addition, US '079 discloses pharmaceutical compositions comprising at least one integrase inhibitor or its salt and at least one antiretroviral or anti-HIV agent or its salt, or prodrug. US '079, Abstract. It further discloses that “[e]xamples of suitable integrase inhibitors include but are not limited to dolutegravir, raltegravir, MK-2048, JTK-656,⁴¹ elvitegravir,” that suitable nucleoside reverse transcriptase inhibitors (NRTIs) include emtricitabine, and that suitable nucleotide reverse transcriptase inhibitors (NtRTIs) tenofovir, where “[p]referably, the integrase inhibitor is dolutegravir, raltegravir or elvitegravir,” and “[p]referably, the NRTIs/NtRTIs are selected from tenofovir, emtricitabine, lamivudine or zidovudine, or any combination thereof.” *Id.* At [0042]-[0051].

Further according to US '079, such pharmaceutical compositions are presented in solid dosage forms where “[a] tablet formulation is the preferred solid dosage form due to its greater stability, less risk of chemical interaction between different medicaments, smaller bulk, accurate dosage, and ease of production.” US '079, [0070], [0078]. These tablets are said to be preferably in the form of single or bilayered or multilayered tablets. *Id.* at [0079]. Example 1 provides a bilayer tablet with the INSTI dolutegravir in a first layer that is separated from a second layer contained FTC and TDF. Similarly, Example 4 provides a bilayer tablet with the INSTI raltegravir in a first layer that is separated from a second layer contained FTC and TDF. *See* Section II.III. '079 therefore provides additional motivation to separate an INSTI like BIC Na from FTC and TAF in a bi-layered tablet. Indeed, tenofovir prodrugs were known to be unstable toward alkaline

⁴¹ JTK-656 corresponds to bictegravir, and is the code name originally assigned to it by the Japanese Tobacco Company.

conditions in both the solution and solid state, and a skilled artisan would have been specifically motivated to separate a basic INSTI such as dolutegravir Na or BIC Na from FTC and TAF in a bilayered tablet to reduce the degradation of TAF that would expectedly occur in the presence of these basic salts. *See e.g.*, Havele, 3, 5 (TDF showed complete degradation occurred immediately after addition of at room temperature); Venkatasen, 4 (TDF undergoes 31% decomposition under basic stress conditions); Kurmi, 96121 (in a basic solution environment (0.5 N NaOH), TDF was completely converted into degradation product T1 in 3 h), 96121-25 (under basic solid state stress conditions, TDF degraded into several different products); *see also* Tivicay Information, 1 (noting that dolutegravir sodium has a pKa of 8.2, establishing its basicity).

For these additional reasons, the “multilayer” tablet species of claim 1 of the ’802 patent would be an obvious variant of claim 19 (depending from claim 16) of the ’067 patent, in view of the prior art discussed in this section. Any combination of the disclosures in Appendix C are also suitable combinations.

b. Claims 2-8

Defendants’ obviousness-type double patenting analysis for claim 1 of the ’802 patent is incorporated herein in its entirety, including the prior art disclosures and combinations discussed therein.

Claim 2 depends from claim 1 and requires the tablet to comprise 50 mg of BIC as a pharmaceutically acceptable salt thereof. Claim 3 depends from claim 2 and requires the tablet to comprise 25 mg TAF as a pharmaceutically acceptable salt thereof. Claim 4 depends from claim 1 and requires the tablet to comprise 50 mg BIC as a pharmaceutically acceptable salt thereof, 25 mg TAF as a pharmaceutically acceptable salt thereof, and 200 mg FTC.

Claim 5 depends from claim 1 and requires the tablet to comprise 52 mg of BIC sodium. Claim 6 depends from claim 1 and requires the tablet to comprise 25 mg of TAF as TAF fumarate.

Claim 7 depends from claim 1 and requires the tablet to comprise 28 mg of TAF hemifumarate.

Claim 8 depends from claim 1 and requires the tablet to comprise 52 mg of BIC sodium, 28 mg of TAF hemifumarate, and 200 mg FTC.

Combinations of HIV INSTI compounds described as a genus including bictegravir and its salts, *e.g.*, bictegravir sodium, with emtricitabine, and TAF fumarate were known in the art. US '356, [0156]-[0157], [0162]-[0163]; [0177] (disclosing unitary dosage forms for simultaneous administration to a patient, for example as a solid dosage form for oral administration); *see also* '385 patent at 6:26-7:66. As discussed in Section II, TAF was well-known in the form of a monofumarate and hemifumarate salt, which could be dosed 10 times lower than the corresponding dose of TDF. Gilead/Janssen, 2; '791 patent, 24:38-48 (disclosing TAF monofumarate), US '856, [0010]-[0011], [0057] (disclosing TAF hemifumarate in combination with HIV nucleoside inhibitors of reverse transcriptase and HIV integrase inhibitors); Genvoya Label, 22 (tablet containing TAF fumarate in combination with EVG and FTC); Genvoya Assessment, 10 (disclosing the same), 13 (TAF fumarate can be administered at a much lower dose than tenofovir disoproxil fumarate (TDF) while maintaining the established doses and biopharmaceutical performance of the other active substances), 74-75 (bilayer tablet containing 25 mg of TAF (as fumarate) combined with EVG, FTC, and COBI).

As discussed above, it was well known in the art that FTC was employed as a free base. Truvada Label (combination of 200 mg FTC free base and 300 mg TD (as fumarate)); Truvada Label (combination of 200 mg FTC free base, 300 mg TD (as fumarate), 600 mg efavirenz); Complera Label (combination of 200 mg FTC free base, 300 mg TD (as fumarate), 27.5 mg rilpivirine hydrochloride); Stribild Label (combination of 200 mg FTC free base, 300 mg TD (as fumarate), 150 mg elvitegravir and 150 mg cobicistat); Genvoya Label (combination of 200 mg

FTC free base, 10 mg TAF (as fumarate), 150 mg elvitegravir and 150 mg cobicistat); WO '351 at 19:3-12 (teaching a preferred embodiment of the disclosed the pharmaceutical composition comprising “(i) 20 to 75 mg, preferably 25 to 70 mg, more preferably 35 to 65 mg, in particular 40 to 60 mg dolutegravir (a); (ii) 50 to 300 mg, preferably 100 to 280 mg, more preferably 125 to 260 mg, in particular 150 to 250 mg emtricitabine (b); (iii) 0.5 to 50 mg, more preferably 1 to 45 mg, even more preferably 3 to 44 mg, in particular 5 to 42 mg tenofovir (c), in particular tenofovir alafenamide; and (iv) pharmaceutical excipients).

As explained in Section V.F.1, Claim 19 of the '067 patent recites a tablet containing a therapeutically effective amount of crystalline BIC sodium Form I (*i.e.* a pharmaceutically acceptable salt of bictegravir), which a skilled artisan would routinely determine to be 50 mg based on bictegravir (52 mg as bictegravir sodium), *e.g.*, in view routine dose optimization studies as well as the dose of ~52 mg dose of DLT sodium (equivalent to 50 mg of DLT) in the previously approved Tivicay[®] product.

Claim 19 (depending from claim 16) of the '067 patent also calls for a tablet comprising TAF and FTC. WO '351 and US '332 describe preferable DLT combinations with FTC and TAF, where FTC is used as a free base (as opposed to a salt), and TAF is used as a monofumarate or hemifumarate salt, where the combination of FTC free base and TAF hemifumarate is especially preferred. *See, e.g.*, US '332, [0032], [0053]; *see also* Genvoya Assessment, 10 (disclosing a tablet containing TAF fumarate and FTC free base in combination with EVG and COBI); Stribild Label (combination of 200 mg FTC free base, 300 mg TD (as fumarate), 150 mg EVG and 150 mg COBI); US '856, [0010]-[0011], [0057] (disclosing TAF hemifumarate in combination with HIV nucleoside inhibitors of reverse transcriptase and HIV integrase inhibitors).

As further discussed for claim 1, WO '351 and US '332 describe preferable DLT combinations with FTC and TAF, where FTC is used as a free base (as opposed to a salt), and TAF is used as a monofumarate or hemifumarate salt, where the combination of FTC free base and TAF hemifumarate is especially preferred. *See, e.g.*, US '332, [0032], [0053]; *see also* Genvoya Assessment, 10 (disclosing a tablet containing TAF fumarate and FTC free base in combination with the INSTI elvitegravir), 74 (describing PK studies with TAF monofumarate and hemifumarate, where the hemifumarate was selected for Phase 2/3 studies and the commercial presentation).

In view of the above disclosures, the skilled artisan would have been motivated to provide a tablet composition comprising 52 mg BIC sodium (equivalent to 50 mg BIC), TAF monofumarate or TAF hemifumarate (equivalent to 25 mg of TAF, e.g., 28 mg of TAF hemifumarate), and 200 mg FTC free base, and expect such a tablet to be useful for the treatment of HIV.

For these reasons and those discussed above for claim 1, including the exemplary combinations discussed therein, each of claims 2-8 of the '802 patent are obvious variants of claim 19 (depending from claim 16) of the '067 patent. Claims 2-8 are therefore invalid for obviousness-type double patenting over claim 19 (depending from claim 16) of the '067 patent, when claim 19 is analyzed in view of the prior art discussed in this section and the preceding section on claim 1.

c. Claims 9-11

Defendants' obviousness-type double patenting analysis for claims 1-8 of the '802 patent is incorporated herein in its entirety, including the prior art disclosures and combinations discussed therein.

Claim 9 depends from claim 1 and requires the tablet to have a total weight less than 1000 mg. Claim 10 depends from claim 9 and requires the tablet to have a total weight less than 800

mg. Claim 11 depends from claim 10 and requires the tablet to have a total weight less than 730 mg.

As discussed above for claim 1, a tablet composition, including a multilayer tablet composition, comprising 50 mg of BIC (or a salt thereof), 25 mg of TAF (or a salt thereof), and 200 mg of FTC (or a salt thereof) is an obvious variant of claim 19 (depending from claim 16) of the '067 patent. This obvious variant tablet would have contained a total active ingredient amount of 275 mg.

Regarding the total tablet weights recited in claims 9-11, a skilled artisan would have appreciated that tablet compositions, including a tablet composition containing 275 mg of the active ingredients BIC, TAF and FTC, would need to be formulated with pharmaceutical excipients to provide a composition suitable for oral administration. That artisan would have been motivated to combine the 275 total milligrams of BIC, TAF and FTC with the smallest amount of additional excipients as possible, in order to provide a total tablet size that would be easier for a patient to swallow. Indeed, it was common knowledge in the art that smaller tablets sizes were preferred for patient compliance.

The skilled artisan would have also recognized each of those weights to be both desirable and achievable for a tablet combination comprising 50 mg BIC (or an equivalent amount of BIC sodium), 25 mg of TAF (or an equivalent amount TAF monofumarate or TAF hemifumarate), and 200 mg of FTC. Indeed, the skilled artisan would have been motivated to combine 275 total milligrams of BIC, TAF and FTC with the smallest amount of additional excipients possible, in order to provide a total tablet size that would be easier for a patient to swallow to improve patient compliance.

WO '846 discloses tablet dosage forms containing TAF and FTC and a number of common pharmaceutical excipients. The following two formulations are exemplary.

Formulation D:	<u>mg/tablet</u>	Formulation G	<u>mg/tablet</u>
GS-7340	25	GS-7340	300
emtricitabine	200	emtricitabine	200
Microcrystalline Cellulose	200	Hydroxypropyl Methylcellulose	112
Lactose Monohydrate	330	Lactose B.P.	53
Croscarmellose Sodium	60	Pregelatinized Starch B.P.	28
Pregelatinized Starch	50	Magnesium Stearate	7
Magnesium Stearate	10		
	875	total:	700

WO '846, 37:13-20 (Formulation D), 13:12-24 (Formulation G). As shown above, Formulation D contains 225 mg of active ingredients (i.e., TAF and FTC) and 650 mg of additional excipients, for a total tablet weight of 875 mg. Similarly, Formulation G contains 500 mg of active ingredients (i.e., TAF and FTC) and 200 mg of additional excipients, for a total tablet weight of 700 mg. In view of these disclosures, a skilled artisan would have appreciated that tablets containing TAF and FTC had been prepared with a total weight in the range of 700-875 milligrams, and could be as low as 700 mg even when the total active ingredient content was 500 mg.

In view of these disclosures, the skilled artisan would have expected that a tablet containing 50 mg of BIC (or a salt thereof), 25 mg of TAF (or a salt thereof), and 200 mg of FTC (or a salt thereof), i.e., 275 mg of active ingredients, could have easily been formulated with additional excipients to provide a total tablet weight of less than 1000 mg, and even less than 800 mg and less than 730 mg. And given that formulations could contain at least 450 milligrams of additional excipients and still fall below the total weight called for by the claims, a skilled artisan would have expected for such tablet compositions to be suitable for oral administration to patients having HIV infection.

For these reasons and those discussed above for claims 1-8, each of claims 9-11 of the '802 application is an obvious variant of claim 19 (depending from claim 16) of the '067 patent. Claims 2-8 are therefore invalid for obviousness-type double patenting over claim 19 (depending from claim 16) of the '067 patent, when claim 19 is analyzed in view of the prior art discussed in this section and the preceding section on claim 1.

Moreover, dolutegravir (DLT) was known as a “second-generation INSTI” that combines the advantages of its predecessor INSTIs raltegravir and elvitegravir (EVG), but can administered once/day without the need for a pharmacokinetic booster such as cobicistat (COBI). Shah, 506 (also noting that COBI is a specific and potent inhibitor of CYP3A4 and associated with clinically significant drug–drug interactions), 517-518 (to be administered once/day, raltegravir must be coadministered with the COBI, which can lead to clinically significant drug–drug interactions). It was further known that DLT may be coformulated with other antiretrovirals in a single-tablet regimen for the treatment of HIV, without the need for COBI. *Id.* at 506; *see also* US '332, [0086]-[0090] (describing pharmaceutical combinations comprising 40 to 60 mg DLT, 150 to 250 mg FTC, and 5 to 42 mg TAF, along with pharmaceutical excipients), [0091]-[0092] (disclosing a specific combination comprising about 50 mg DLT, about 200 mg FTC and about 25 mg TAF).

Based on the structural similarity and common INSTI activity between DLT and BIC (*supra*), the skilled artisan would have identified BIC as a second-generation INSTI, and thus would have expected that BIC could also be administered once daily, *e.g.*, in combination with TAF and FTC as discussed above, without the need for the PK booster cobicistat (COBI), to provide a combination less susceptible to drug-drug interactions, that could be used in patients resistant to RAL or EVG. Indeed, based on structural similarity, the skilled artisan would have expected a similar mechanism of action, a similar resistance to CYP3A metabolism vis-à-vis EVG

such that it would have be administered once-daily without a pharmacologic booster (e.g., COBI), a similar ability to retain activity against many viral strains harboring major integrase resistance mutations to the INSTIs RAL and EVG, and a similar relatively minimal drug-drug interactions and side effects, each of which are advantages of the second generation inhibitors. Shah and Dow (supra), Astuti, 10; Llibre, 175; *see also* Llibre, 172 (CYP3A is the main pathway by which EVG undergoes metabolism in the intestine and liver); Ostenholzer, 265 (DTG does not require boosting, and is primarily metabolized by UGT 1A1 with only a small contribution from CYP3A4), 269 (Given its relatively minimal drug interaction and side effect profile, DTG may prove useful for patients on other medications for tuberculosis, hepatitis C, seizure, or contraception as well as those intolerant to other ART. In addition, DTG appears to be a viable choice for salvage in some highly treatment experienced patients harboring resistance to the first-generation INSTIs (RAL and EVG)). As such, the skilled artisan would have been motivated to prepare a tablet composition comprising 50 mg BIC (or a salt thereof), 25 mg of TAF or a salt thereof, and 200 mg of FTC (or a salt thereof), i.e., 275 mg total active ingredients, without the need for COBI, leaving approximately 725 mg for tablet excipients to keep the total tablet weight below 1000 mg, 525 mg for tablet excipients to keep the total tablet weight below 800 mg, and 455 mg for tablet excipients to keep the total tablet weight below 730 mg.

US '122 is directed to solid oral dosage forms containing the APIs in Stribild[®], i.e., EVG, FTC, TDF, and COBI. US '122, Abstract, [0002]-[0005], [0007]. US '122 exemplifies a tablet embodiment containing 150 mg of EVG, 200 mg FTC, 300 mg of TDF, and 150 mg of COBI, i.e., the doses in the approved Stribild[®] tablet, along with a number of pharmaceutically acceptable tablet excipients. *Id.* at [0022] (*see* table below) (EVG = Formula I; COBI = Formula II; FTC =

Formula III; TDF = Formula IV); *see also* [0063]-[0065] (Examples 2-4) (describing similar tablets); Stribild Label, 22-23.

Components	Compound of Formula II 150 mg Formulation	
	% w/w	mg/tablet
Compound of Formula III	13.9	200.0
Salt of Formula IV	20.9	300.0
Compound of Formula I	10.4	150.0
Compound of Formula II	10.4	150.0
Colloidal Silicon Dioxide	12.0	172.5
Lactose Monohydrate	0.8	10.9
Microcrystalline Cellulose	20.8	299.5
Hydroxypropyl Cellulose	0.5	7.5
Hydroxypropyl Cellulose	0.6	9.0
Sodium Lauryl Sulfate	0.8	11.3
Croscarmellose Sodium	7.3	104.3
Magnesium Stearate	1.6	22.4
Total	100	1437.

As shown in the above table, the Stribild[®] tablet had a total weight of 1437 mg, with 800 mg directed to the four APIs and the remaining 637 mg directed to the combined excipients, where the 172.5 mg of the excipient weight is attributed to colloidal silicon dioxide, *i.e.*, a required absorbent for COBI designed to enhance its stability. *See* Stribild Assessment, 12 (the active substance COBI is adsorbed on silicon dioxide), 13 (COBI is isolated by adsorption on silicon dioxide to provide a stable solid form, which is suitable for further finished product manufacture).

If identical tablet excipients and amounts were employed in the tablet combination according to claim 19 (depending from claim 16) of the '067 patent, *i.e.*, that containing crystalline BIC sodium Form I, TAF, and FTC, without the need for COBI in the formulation, and including the obvious amount of BIC sodium (equivalent to 50 mg BIC), TAF (25 mg or an equivalent amount a mono- or hemifumarate salt), and FTC (200 mg) discussed above (~275 mg weight of combined APIs), the total tablet weight would have been ~910 mg (or slightly more if the tablet employed BIC sodium and TAF hemifumarate). Thus, even if the tablet contained the large

amount of silicon dioxide for absorption of COBI (which would not be required with BIC), the total tablet weight would have been less than 1000 mg. And the total tablet weight would have been substantially lower than 1000 mg, e.g., ~740 mg, when silicon dioxide was significantly reduced or removed from the tablet altogether (which a skilled artisan would have been motivated to do for a tablet not containing COBI).

Further, the skilled artisan would have appreciated that the tablet excipients in the Stribild[®] formulation could have been reduced even further because significantly less BIC and TAF, i.e., 50 mg and 25 mg respectively, would have been needed compared to the 150 mg amount of EVG and 300 mg amount of TDF included in Stribild[®]. As such, a skilled artisan would have appreciated that the total tablet weight could be reduced even further, e.g., to below 800 mg and below 730 mg, given that less excipients would be needed to properly formulate the lower amount of total active ingredients. And given that this lower total dose of BIC, TAF, and FTC vis-à-vis Stribild[®] was expected to be useful for the treatment of HIV, the skilled artisan would have reasonably expected tablets having total weight of less than 1000 mg, less than 800 mg, and less than 730 mg to be accessible and successful for the treatment of HIV.

For these reasons and those discussed above for claims 1-8, including the exemplary combinations discussed therein, claims 9-11 of the '802 patent are obvious variants of the claim 19 (depending from claim 16) of the '067 patent. Claims 9-11 are therefore invalid for obviousness-type double patenting over claim 19 (depending from claim 16) of the '067 patent, when claim 19 is analyzed in view of the prior art discussed in this section and the preceding sections on claim 1-8.

d. Claims 12-13

Defendants' obviousness-type double patenting analysis for claim 1 of the '802 patent is incorporated herein in its entirety, including the prior art disclosures and combinations discussed therein.

Claim 12 depends from claim 1 and requires the tablet to contain less than 15% of bicitgravir or a pharmaceutically acceptable salt thereof. Claim 13 depends from claim 1 and requires the tablet to contain less than 11% of bicitgravir or a pharmaceutically acceptable salt thereof.

As explained above for claims 9-11, a tablet composition containing 50 mg of BIC (or a salt thereof), 25 mg TAF (or a salt thereof), and 200 mg FTC (or a salt thereof) and having a total tablet weight significantly less than 1000 mg, e.g., less than 800 mg and less than 730 mg, would have been obvious an obvious variant of claim 19 (depending from claim 16) of the '067 patent. This is at least because the skilled artisan would have formulated such tablets to contain the least amount of excipients as possible, to provide a tablet that would be easier to swallow for increased patient compliance.

Given that the total active ingredient weight in those obvious variants is 275 mg (or slightly more when including bicitgravir sodium and a TAF fumarate salt), the skilled artisan would have significant room to provide a tablet composition containing less than about 15% BIC or BIC sodium (claim 12), and less than about 11% BIC or BIC sodium (claim 13). Indeed, the skilled artisan would have arrived at these percentages through routine optimization of common excipients and their amounts to provide a tablet composition having a total weight of less than about 1000 mg, such as less than 800 mg and less than 730 mg. And most reasonably achievable tablet weights, e.g., 275 mg of active ingredients and a total weight of 600-900 mg, would meet the 15% and 11% limitations of claims 12-13 when the BIC or BIC sodium dose is ~50 mg. Indeed,

a 600 mg tablet would have contained ~8% BIC or BIC sodium, a 700 mg tablet would have contained ~7% BIC or BIC sodium, an 800 mg tablet would have contained ~6% BIC or BIC sodium, and a 900 mg tablet would have contained ~5.5% BIC or BIC sodium, each of which fall within the scope of claims 12-13.

For these reasons and those discussed above for claims 1-11, including the exemplary combinations discussed therein, claims 12 and 13 of the '802 patent are obvious variants of the claim 19 (depending from claim 16) of the '067 patent. Claims 12-13 are therefore invalid for obviousness-type double patenting over claim 19 (depending from claim 16) of the '067 patent, when claim 19 is analyzed in view of the prior art discussed in this section and the preceding sections on claim 1-11.

- e. Claims 1-13 are also invalid for obviousness-type double patenting over claim 19 of the '067 patent (when depending from claim 17)

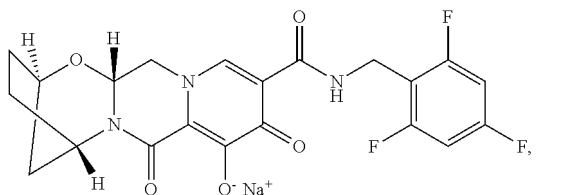
Defendants' obviousness-type double patenting analysis for claims 1-13 of the '802 patent in view of claim 19 (when depending from claim 16) of the '067 patent is incorporated herein in its entirety, including the prior art disclosures and combinations discussed therein.

A comparison of claim 19 (depending from claim 17) of Gilead's earlier expiring '067 patent with claim 1 of Gilead's later expiring '802 patent is provided in the table below:

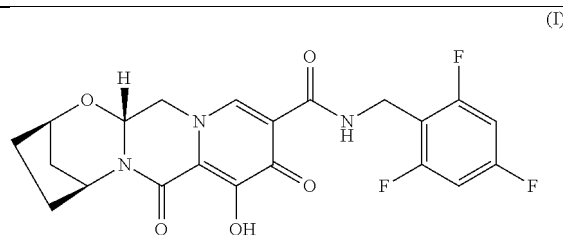
Claim 19 (depending from Claim 16) of Gilead's '067 Patent	Claim 1 of Gilead's '802 Patent
19. [A method for treating an HIV infection in a human in need thereof, comprising administering to the human a pharmaceutical composition, the pharmaceutical composition comprising a therapeutically	1. A multilayer tablet comprising 50 mg of the compound of Formula I [i.e., bicittegravir]: ⁴²

⁴² The chemical structure of Formula (I) from claim 52 of the '802 patent represents bicittegravir in a different orientation from the chemical structure of Formula (II) from claim 10 of the '067 patent representing bicittegravir sodium.

effective amount of a compound of Formula II [i.e., bictegrovir sodium]:



which is crystalline and is characterized by an x-ray powder diffraction (XRPD) pattern having peaks at about 5.5° , 16.1° , and 23.3° $2\theta \pm 0.2^\circ \pm 2\theta$, and a pharmaceutically acceptable carrier or excipient [(taken from claim 10)], wherein the pharmaceutical composition further comprises tenofovir alafenamide hemifumarate and emtricitabine [(taken from claim 17)], wherein the pharmaceutical composition is in a unit dosage form [(taken from claim 18)], wherein the unit dosage form is a tablet.



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.

Claim 19 of the '067 patent (depending from claim 17) differs from claim 1 of the '802 patent in the following ways:

- Claim 19 is directed to a method of treating HIV in a human with a tablet composition comprising a therapeutically effective amount of crystalline BIC sodium Form I, whereas claim 1 is directed to a tablet composition comprising 50 mg of BIC or pharmaceutically acceptable salt thereof generally;⁴³
- Claim 19 calls for the tablet to comprise TAF hemifumarate and FTC, whereas claim 1 calls for a tablet comprising 25 mg TAF or a pharmaceutically acceptable salt thereof, and 200 mg FTC or a pharmaceutically acceptable salt thereof;
- Claim 19 calls for the tablet to comprise a pharmaceutically acceptable carrier or excipient, whereas claim 1 does not mention any carriers or excipients.

The only difference between Claim 19 of the '067 patent (depending from claim 17), and Claim 19 of the '067 patent (depending from claim 16) discussed in the preceding sections, is that

⁴³ Crystalline bictegrovir sodium Form I is a species of "bictegrovir or pharmaceutically acceptable salt thereof" recited in claim 1.

the former claim calls specifically for TAF hemifumarate while the latter calls for tenofovir alafenamide generally. Thus, the analysis provided in the preceding section for claim 1 is equally applicable to a double patenting analysis over claim 19 of the '067 patent (depending from claim 17). Rather than repeat that analysis here, we provide the following summary.

As explained in Section VI.F.2.a, the skilled artisan would have been motivated to modify the method of claim 19 (depending from claim 16) of the '067 patent to arrive at the doses for BIC, TAF and FTC (or pharmaceutically acceptable salts thereof) called for by claim 1 of the '802 patent. Because that modified tablet would have contained a therapeutically effective amount of each of the active ingredient, the skilled artisan would have reasonably expected that it would successfully treat HIV.

As further explained in Sections VI.F.2.a, the skilled artisan would have been especially motivated to formulate the tablet of claim 19 (depending from claim 16) of the '067 patent with a therapeutically effective amount of BIC sodium, i.e., an amount containing 50 mg BIC, along with a therapeutically effective amount of TAF mono- or hemifumarate, i.e., an amount containing 25 mg of TAF, and a therapeutically effective amount of emtricitabine i.e., 200 mg, with a reasonable expectation that the resulting tablet would successfully treat HIV.

As shown in the above table, Claim 19 (depending from claim 17) of the '067 patent discloses a tablet that already contains BIC sodium (Form I), TAF hemifumarate, and FTC. Thus, it contains a pharmaceutically acceptable salt of BIC, a pharmaceutically acceptable salt of TAF, and emtricitabine as required by claims 2-8 of the '802 patent. And as explained in Sections VI.F.2.a-b, the skilled artisan would have been motivated to modify the tablet of claim 19 (depending from claim 17) of the '067 patent to provide a tablet composition, comprising BIC sodium (equivalent to 50 mg BIC, i.e., 52 mg), TAF hemifumarate (equivalent to 25 mg of TAF.

i.e., 28 mg of TAF hemifumarate), and 200 mg emtricitabine, and expect such a tablet to be useful for the treatment of HIV. Because claim 19 (depending from claim 17) of the '067 patent already requires BIC sodium, TAF hemifumarate, and FTC, there is no reason to select them from claim 19. The skilled artisan only needed to formulate them into a tablet in a therapeutically effective amount, i.e., the amounts recited in claims 2-8 of the '802 patent are therapeutically effective amounts known or expected from the prior art.

For these reasons and those discussed above for double patenting over claim 19 (depending from claim 16) of the '067 patent, claims 1-8 of the '802 patent are obvious variants of the claim 19 (depending from claim 17) of the '067 patent.

Claims 9-13 are obvious variants of claim 19 (depending from claim 17) of the '067 patent for the same reasons as discussed above in view of claim 19 (depending from claim 16) of the '067 patent. See Sections VI.F.2.c-d.

Claims 1-13 of the '802 patent are therefore invalid for obviousness-type double patenting over claim 19 (depending from claim 17) of the '067 patent, when claim 19 is analyzed in view of the prior art discussed in Sections VI.F.2.a-d.

(3) The Asserted Claims are Invalid for Obviousness-Type Double Patenting over Gilead's '342 Patent.

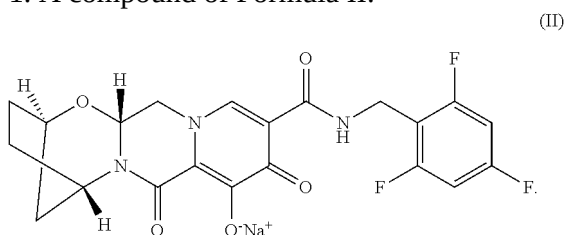
Defendants' obviousness-type double patenting analysis for claims 1-13 of the '802 patent in view of claim 19 of the '067 patent (when depending from claim 16 or 17) (see Section VI.F.2) is incorporated herein in its entirety, including the prior art disclosures and combinations discussed therein.

Gilead's '342 patent was filed on June 19, 2013 and issued on July 18, 2017. The '342 patent is listed in the Orange Book for BIKTARVY®. According to the Orange Book, the '342 patent will expire on June 19, 2035, which is 17 months before the expiration of the '802 patent

on November 8, 2036. The '342 patent is thus a commonly-owned patent that issued and will expire earlier than the '802 patent, and the '342 patent may therefore be considered in a double patenting analysis as to the '802 patent.

The '342 patent issued with twenty-six (26) claims, including claims 1, 12, and 18-19, directed to a bictegavir sodium compound (claim 1), and a pharmaceutical composition comprising a therapeutically effective amount of bictegavir sodium (claim 12 depending from claim 1), which may further comprise tenofovir alafenamide and emtricitabine (claim 18) or tenofovir alafenamide hemifumarate and emtricitabine (claim 19). The '342 patent also claims that a pharmaceutical composition comprising a therapeutically effective amount of bictegavir sodium is an oral unit dosage form in the form of a tablet (claims 20-21). Each of claims 1, 12, and 18-21 are shown below.

1. A compound of Formula II:



12. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of claims 1 to 9, and a pharmaceutically acceptable carrier or excipient.

18. The pharmaceutical composition of claim 12, further comprising tenofovir alafenamide and emtricitabine.

19. The pharmaceutical composition of claim 12, further comprising tenofovir alafenamide hemifumarate and emtricitabine.

20. The pharmaceutical composition of claim 12, wherein the pharmaceutical composition is in an oral unit dosage form.

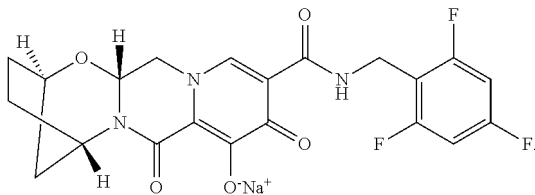
21. The pharmaceutical composition of claim 20, wherein the unit dosage form is a tablet.

The following claim represents claim 19, incorporating the limitations from claims 1 and

12.

19. [A pharmaceutical composition comprising a therapeutically effective amount of a compound [(taken from claim 12)] of Formula II:

(II)

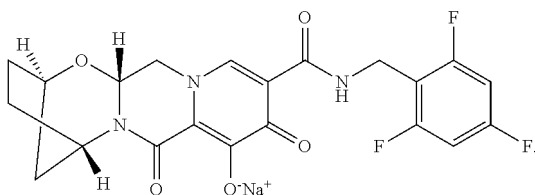


[(taken from claim 1)] and a pharmaceutically acceptable carrier or excipient,] further comprising tenofovir alafenamide hemifumarate and emtricitabine.

Also provided is the following representation of claim 21, incorporating the limitations from claims 1, 12, and 20.

21. [A pharmaceutical composition comprising a therapeutically effective amount of a compound [(taken from claim 12)] of Formula II:

(II)



[(taken from claim 1)] and a pharmaceutically acceptable carrier or excipient, wherein the pharmaceutical composition is in an oral unit dosage form [(taken from claim 20)], wherein the unit dosage form is a tablet.

Claim 18 (depending from claim 12) and claim 19 (depending from claim 12) are each directed to a pharmaceutical composition comprising a therapeutically effective amount of bictegravir (BIC) sodium, along with tenofovir alafenamide (TAF), emtricitabine (FTC), and a pharmaceutically acceptable carrier or excipient. They differ only in that the former claim calls for TAF, while the latter calls for TAF as a hemifumarate salt.

Claim 21 (depending from claim 20) is directed to a tablet comprising a pharmaceutical composition comprising a therapeutically effective amount of BIC sodium Form I, and a pharmaceutically acceptable carrier or excipient.

Because the first step of a double patenting analysis involves the interpretation of the claims of the earlier and later expiring patents in question, the specifications of both patents may be consulted to ascertain the meaning of claim terms, including to determine whether the inventors accorded any special meaning to claim terms by definition.

The '342 patent provides specific definitions for the following terms appearing in the above claims:

A “pharmaceutical composition” refers to a formulation of a compound of the invention and a medium generally accepted in the art for the delivery of the biologically active compound to mammals, e.g., humans. Such a medium includes all pharmaceutically acceptable carriers, diluents or excipients therefor.

'342 patent at 4:62-67.

“Pharmaceutically acceptable carrier, diluent or excipient” 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.

Id. at 4:54-61.

“Effective amount” or “therapeutically effective amount” refers to an amount of a compound according to the invention, which when administered to a patient in need thereof, is sufficient to effect treatment for disease-states, conditions, or disorders for which the compounds have utility. ... Such a therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to their own knowledge, the state of the art, and this disclosure.

Id. at 5:1-21.

“Pharmaceutically acceptable” or “physiologically acceptable” refer to compounds, salts, compositions, dosage forms and other materials which are useful in preparing a pharmaceutical composition that is suitable for veterinary or human pharmaceutical use.

Id. at 6:44-48.

Each of the terms above are specifically defined by the inventors of the '342 patent, which takes precedence over any alternative ordinary and customary meaning that could be assigned by the skilled artisan.

a. Claim 1

Claim 1 of the '802 patent is directed to a tablet comprising 50 mg of BIC (*i.e.*, the compound of Formula (I) appearing in the claim) 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.

A comparison of claim 19 (depending from claims 1 and 12) of Gilead's earlier expiring '342 patent with claim 1 of Gilead's later expiring '802 patent is provided in the table below:

Claim 19 (when depending from Claim 1) of Gilead's '342 Patent	Claim 1 of Gilead's '802 Patent
19. [A pharmaceutical composition comprising a therapeutically effective amount of a compound (<i>taken from claim 12</i>) of Formula II: (II) (<i>taken from claim 1</i>), and a	1. A tablet comprising 50 mg of the compound of Formula I [<i>i.e.</i>, bicitgravir]:⁴⁴ (I)

⁴⁴ The chemical structure of Formula (I) from claim 1 of the '802 patent represents bicitgravir in a different orientation from the chemical structure of Formula (II) from claim 1 of the '342 patent representing BIC sodium.

pharmaceutically acceptable carrier or excipient,] further comprising tenofovir alafenamide hemifumarate and emtricitabine.	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.
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Claim 19 (depending from claims 1 and 12) of the '342 patent differs from claim 1 of the '802 patent in the following ways:

- Claim 19 is directed to a pharmaceutical composition comprising a therapeutically effective amount of BIC sodium, whereas claim 1 is directed to a tablet comprising 50 mg of BIC or pharmaceutically acceptable salt thereof generally;⁴⁵
- Claim 19 calls for the pharmaceutical composition to comprise TAF hemifumarate and FTC, whereas claim 1 calls for a tablet comprising 25 mg TAF or a pharmaceutically acceptable salt thereof, and 200 mg FTC or a pharmaceutically acceptable salt thereof;
- Claim 19 calls for the pharmaceutical composition to comprise a pharmaceutically acceptable carrier or excipient, whereas claim 1 does not mention any carriers or excipients.

As explained above, the term “therapeutically effective amount” appearing in claim 19 (depending from claims 1 and 12) is defined in the '342 specification as an amount “which when administered to a patient in need thereof, is sufficient to effect treatment for disease-states, conditions, or disorders for which the compounds have utility[,]” which amount can be routinely determined by a skilled artisan. '342 patent, 5:1-21. As such, the pharmaceutical composition of claim 19 (depending from claims 1 and 12) contains an amount of BIC sodium Form I effective to treat HIV in a human when combined with TAF and FTC.

⁴⁵ Bictegravir sodium is a species of “bictegravir or pharmaceutically acceptable salt thereof” recited in claim 1 of the '802 patent, and defined in the '342 specification at 6:44-48.

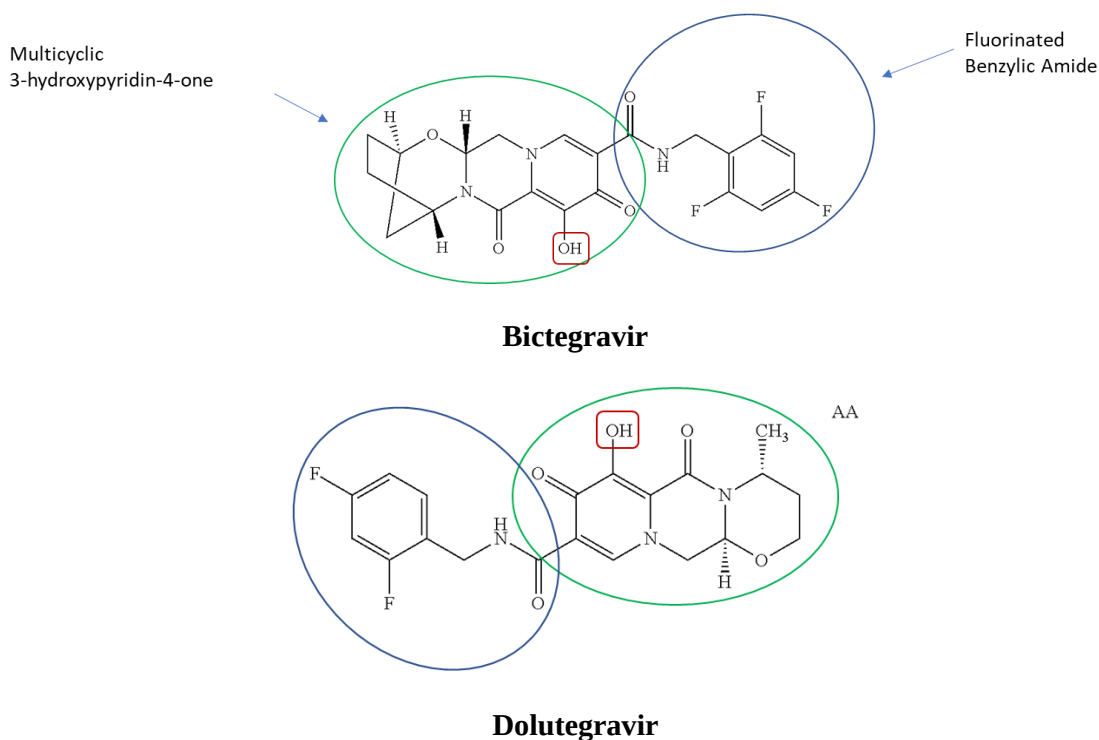
Because claim 19 (depending from claims 1 and 12) of the '342 patent includes a “pharmaceutically acceptable carrier or excipient,” a skilled artisan would appreciate that the “pharmaceutically acceptable carrier or excipient” recited in the claim is any carrier or excipient suitable for formulations approved by the United States Food and Drug Administration as being acceptable for use in humans. *See* above definition of “pharmaceutically acceptable carrier, diluent or excipient.” '342 patent, 4:54-61. In addition, a skilled artisan would appreciate that pharmaceutical formulations could be formulated for typical routes of administration, such as oral administration as a tablet. '342 patent, 12:31-37, *see also* claim 21.

Upon the expiration of the '342 patent, the general public should be entitled to use the pharmaceutical composition of claim 19 (depending from claims 1 and 12) and any obvious variants thereof. In order to do so, Gilead cannot have any non-expired claims covering the tablet composition defined in claim 19 or its obvious variants, because the general public cannot use the pharmaceutical composition of claim 19 without being able to use the claimed pharmaceutical composition (or obvious variants thereof) without infringing upon the non-expired claim. As explained below, claim 1 of the '802 patent improperly covers an obvious variant of claim 19 (depending from claims 1 and 12) of the '342 patent pharmaceutical composition, and is therefore invalid for obviousness-type double patenting.

The '802 patent establishes that a particular utility of “an oral dosage form containing [bictegravir], tenofovir alafenamide and emtricitabine” is the “treat[ment] of viral infections such as HIV.” '802 patent, 2:36-40; *see also id.* at 54:47-53 (“[t]he solid oral dosage forms (in particular tablets) disclosed herein are used for treatment of HIV infection (e.g. HIV-1 infection).” It also establishes the utility of BIC as a “potent HIV integrase inhibitor with in vitro activity against wild type HIV-1.” *Id.* at 5:11-15. Because the claimed tablet containing 50 mg of BIC or a

pharmaceutically acceptable salt thereof (along with 25 mg of TAF and 200 mg of FTC or their pharmaceutically acceptable salts) is a solid oral dosage form of the alleged invention, a skilled artisan would conclude that the claimed 50 mg of BIC or a pharmaceutically acceptable salt thereof constitutes a therapeutically effective amount for the treatment of HIV. And because the definition of “therapeutically effective amount” in the ’342 patent notes that such amount can be routinely determined by the skilled artisan, the 50 mg therapeutically effective dose of BIC is inherently disclosed by or obvious over claim 19 (depending from claims 1 and 12) of the ’342 patent.

As explained in Section VI.C, the skilled artisan would have recognized that BIC is an HIV integrase inhibitor (INSTI) that bears a close structural similarity to the FDA-approved HIV INSTI dolutegravir (DLT). Based on this similarity, the skilled artisan would have also expected that BIC would have similar physicochemical and biological properties to DLT because each compound is weakly acidic and contains a fluorinated benzylic amide and a 3-hydroxypyridin-4-one multicyclic ring structure (see structural comparison below).



The Tivicay Assessment identifies DLT sodium as an HIV INSTI indicated in combination with other antiretroviral agents, *e.g.*, emtricitabine/tenofovir (TRUVADA), for the treatment of HIV-1 infection. Tivicay Assessment, 43, 50-51 (identifying DLT as “a new integrase inhibitor which has been studied in a full range of HIV treatment populations”), 89 (disclosing combination therapies of DLT sodium with Truvada (FTC/FTC); *see also* US ’332 (disclosing pharmaceutical combinations of DLT, FTC and TAF). Tivicay is a film coated tablet composition containing DLT sodium at a dose of 52.6 mg, which is equivalent to 50 mg DLT free acid. Tivicay Assessment, 9 (Tivicay is an immediate release tablet formulation containing 50 mg of dolutegravir (as a sodium salt) as the active substance); *see also* US ’332, [0091]-[0092] (disclosing particularly preferred embodiments of a pharmaceutical combination containing about 50 mg DLT, about 200 mg FTC, and about 25 mg tenofovir, in particular TAF), [0018] (stating a preference for DLT as a sodium salt), [0032] (stating a preference for FTC as a free base), [0032] (stating a preference for FTC as a free base), [0053] (stating a preference for TAF as a monofumarate or hemifumarate salt, and especially a hemifumarate salt); *see also* See also HIV Guidelines, D-1 (recommending the use of two nucleos(t)ide reverse transcriptase inhibitors in combination with a third active antiretroviral drug from one of three drug classes: an integrase strand transfer inhibitor, a nonnucleoside reverse transcriptase inhibitor, or a protease inhibitor with a pharmacokinetic enhancer); *id.* at 1, *i* (recommending the combination of the INSTIs elvitegravir and raltegravir with tenofovir and emtricitabine); British HIV Guidelines, 13 (describing tenofovir and emtricitabine as the *preferred NRTI backbone* for HIV therapy, to be combined with an additional agent such as an INSTI). Llibre, 175 (DLT is “the first integrase inhibitor dosed once daily without pharmacokinetic boosting[, which] has a higher barrier of resistance compared to RAL and EVG, retaining activity against many viral strains harboring major integrase resistance mutations selected for by both of

them”), (“In a Phase IIb dose ranging study, DLT doses of 10 mg, 25 mg and 50 mg were well tolerated at all assessed doses with TDF/FTC, where no integrase mutations were selected in any of the patients studied, and the proportion of patients with viral load <50 copies/mL at 48 weeks was an impressive 88-91%.”); Astuti, 10-11 (DLT is “an unboosted integrase inhibitor that has been effectively and safely used for the treatment of HIV-infected naïve patients (with 2 NRTIs) and experienced patients (with an optimized background regimen)”).

In view of the structural similarity and identical utilities of DLT and BIC, the skilled artisan would have expected that these compounds could be administered at similar doses in combination with FTC and tenofovir, *e.g.*, with Truvada (FTC/TDF) (as disclosed in the Tivicay Assessment) or FTC/TAF (as disclosed in US ’332). As such, the skilled artisan would have considered the 50 mg dose of bictegravir in the tablet of claim 1 (combined with the recited doses of TAF and FTC) to be at or near the “therapeutically effective amount” of BIC bictegravir needed to treat HIV when administered in combination with TAF and FTC. *See also* BIC Safety Study, 8-9 (a 50 mg dose of BIC had already been disclosed for the treatment of HIV by the FDA); NCT ’694 (Version 8) (disclosing an FDC containing 50 mg BIC, 200 mg FTC, and 25 mg TAF).

For this additional reason, a skilled artisan would have been motivated to use a 50 mg dose of BIC (or an equivalent dose of bictegravir sodium) for the treatment of HIV according to claim 19 (depending from claims 1 and 12) of the ’342 patent, and reasonably expected that amount to be successful when combined with TAF and FTC. Such 50 mg dose of BIC would have also been achieved through routine methods of dose optimization in the art of HIV combination therapies.

Regarding the 200 mg dose FTC recited in claim 1, the skilled artisan would have also recognized it as the generally accepted dose for FTC in combination therapies for the treatment of HIV. Indeed, every approved combination tablet from Gilead discussed in Section II contains 200

mg of FTC. *See, e.g.*, Truvada Label (combination of 200 mg FTC and 300 mg TDF); Truvada Label (combination of 200 mg FTC, 300 mg TDF, 600 mg efavirenz); Complera Label (combination of 200 mg FTC, 300 mg TDF, 27.5 mg rilpivirine hydrochloride); Stribild Label (combination of 200 mg FTC, 300 mg TDF, 150 mg EVG and 150 mg COBI); Genvoya Label (combination of 200 mg FTC, 10 mg TAF, 150 mg EVG and 150 mg COBI); *see also* US '122, [0022], [0063]-[0065] (bilayer tablets similar to Stribild® containing 200 mg FTC); US '902, [0050]-[0052] (bilayer tablets similar to Atripla containing 200 mg FTC); US '857 [0066]-[0073] (bilayer tablets similar to Complera/Eviplera containing 200 mg FTC); WO '846, 37:13-20 (Formulation D) (combination of 25 mg TAF with 200 mg FTC); US '332, [0091]-[0092] (pharmaceutical combination containing about 50 mg DLT, about 200 mg FTC, and about 25 mg TAF). A skilled artisan would therefore have been motivated to use a 200 mg dose of FTC for the treatment of HIV using the tablet combination according to claim 19 (depending from claims 1 and 12) of the '342 patent, and reasonably expected that amount to be successful when combined with therapeutically effective amounts of bictegavir sodium Form I and TAF.

Regarding the 25 mg dose of TAF recited in claim 1, the skilled artisan would have also recognized it as an acceptable dose for TAF in combination therapies for the treatment of HIV. For one, it was known by at least 2014 that Gilead sought to replace TDF with TAF, because TAF had “demonstrated high antiviral efficacy at a dose 10 times lower than Viread, as well as an improved renal and bone safety profile.” Gilead/Janssen, 2. These advantages of TAF had long been appreciated in the art, including by Lee in 2005 and in the '791 patent in 2008. *See* Lee, 1900 (Table 1) (disclosing TAF as 10 times more potent than TDF toward HIV-1, with eight times improved selectivity index), 1905 (high concentrations of tenofovir observed in lymphatic tissues after oral administration of GS 7340 (TAF) are expected to result in increased clinical potency

relative to TDF) (with TAF, it should be possible to reduce the total dose of tenofovir, thereby minimizing systemic exposure, while at the same time increasing antiviral activity); '791 patent, 27:29-28:37 (TAF shows a 10-fold increase in antiviral activity relative to TDF and a 200-fold increase in plasma stability; greater plasma stability is expected to result in higher circulating levels of TAF than TDF after oral administration), Tables 1-2; Ruane, 451-52 ("HIV-1 RNA responses for the 8-mg TAF treatment group were similar to that of the 300-mg TDF group. However, median DAVG₁₁ [(time-weighted average change from baseline to study day 11)] for plasma HIV-1 RNA . . . in the 25- and 40-mg TAF treatment groups showed significantly greater decreases compared with the 300-mg TDF treatment group."); Ruane, 454 ("Compared with 300 mg TDF, TAF, with doses as low as 25 mg, demonstrated greater antiviral effect at less than 1/10th the dose, with an almost 90% reduction in circulating TFV."); Sax, 53 ("Relative to TDF, TAF is more stable in plasma."); *See also, e.g.*, US '332, [0091]-[0092] (pharmaceutical combination containing about 50 mg DLT, about 200 mg FTC, and about 25 mg TAF); WO '846, 37:13-20 (Formulation D) (tablet composition containing 25 mg TAF and 200 mg FTC); US '856, [0010]-[0011], [0057] (disclosing pharmaceutical compositions comprising TAF hemifumarate, NRTIs and HIV integrase inhibitors); Genvoya Assessment, 10 (describing Genvoya[®] as a tablet combination containing 150 mg EVG, 150 mg COBI, 200 mg of FTC, and 10 mg of TAF (as 11.2 mg of the fumarate)), 13 (describing monolayer and bilayer tablets of EVG/CCOBI/FTC/TAF containing 25 mg TAF as the monofumarate)); *see also* Astuti, 10-11 ("a 25 mg dose of TAF has shown greater ARV activity than a standard 300 mg dose of TDF[, and that] [c]linically ... TAF resulted in non-inferior efficacy to TDF both co-formulated with FTFC/EVG/COBI"); Llibre, 172 (TAF leads to significantly greater decreases in HIV-1 RNA compared with TDF 300 mg, with 86% lower plasma tenofovir exposures (AUC), and sevenfold higher intracellular tenofovir-

diphosphate concentrations both in PBMC and lymphatic tissues, compared to TDF 300 mg in 10-day monotherapy studies.). That artisan would have also known that TAF was 10-fold more active than its predecessor prodrug TDF with a 200-fold increase in plasma stability that would have provided higher circulating levels of TAF than TDF after oral administration. *See, e.g.*, '791 patent, 27:29-28:37 (Tables 1-2).

For at a least these reasons, the skilled artisan would have been motivated to utilize a ~10-fold lower dose of TAF vis-à-vis the approved 300 mg dose of TDF in combination tablets for the treatment of HIV, including in combinations also containing a therapeutically effective amount of an INSTI, and 200 mg of emtricitabine, *e.g.*, as in the Gilead's Stribild product ((combination of 200 mg FTC, 300 mg TDF, 150 mg elvitegravir and 150 mg cobicistat). *See, e.g.*, Stribild Label, 1, 22-23. And given that TAF was known to be 10 times more potent than TDF toward HIV-1, with an eight times improved selectivity index (*see* Lee, 1900), the skilled artisan would have reasonably expected such a 10-fold lower dose to be a therapeutically effective amount of TAF that would have been successful in the treatment of HIV. Indeed, such an ~10-fold lower dose (*i.e.*, 25 mg) had been specifically disclosed in WO '846 in combination with 200 mg of FTC.

A 25 mg dose of TAF is approximately 10-fold lower than the 300 mg dose of TDF (equivalent to 245 mg tenofovir disoproxil). Thus, a skilled artisan would therefore have been motivated to use a 25 mg dose of TAF (or an equivalent amount of pharmaceutically acceptable fumarate salt) for the treatment of HIV using the tablet combination according to claim 19 (depending from claim 16), and reasonably expected that amount to be successful when combined with 50 mg of BIC sodium Form I and 200 mg of FTC. *See also* Astuti, 10-11; Llibre, 172; Sax, 53. The skilled artisan would have also arrived at 25 mg TAF as a therapeutically effective dose

of TAF for treating HIV according to claim 19 (depending from claims 1 and 12) of the '342 patent through routine dose optimization methods in the art of HIV combination therapies.

In addition, the Genvoya Assessment describes film-coated tablet combinations containing the INSTI elvitegravir, along with FTC, cobicistat and TAF, *i.e.*, an updated version of Gilead's Stribild. Genvoya Assessment, 10. Though the approved dose for TAF in the Genvoya product was 10 mg, the Genvoya Assessment also describes open-label crossover studies where the combination contained 25 mg of TAF, where the exposures to TAF and tenofovir were substantially higher vs. TAF 25 mg administered alone, establishing that 25 mg TAF was an acceptable dose in an HIV combination. *Id.* at 74-75. Indeed, a 25 mg dose for TAF in combination tablets was even recognized as early as 2004. WO '846, 3:13-18 (therapeutic combinations of TAF and FTC for treating HIV), 18:23-26 (combination can additionally include an INSTI), 37:13-20 (exemplary formulation containing 25 mg of TAF and 200 mg FTC); *see also* US '332 (disclosing combinations for treating HIV containing 40 to 60 mg dolutegravir, 150 to 250 mg FTC, and 5 to 42 mg tenofovir alafenamide). For these additional reasons, a skilled artisan would have been motivated to use a 25 mg dose of TAF for the treatment of HIV in the tablet combination according to claim 19 (depending from claim 16), and reasonably expected that amount to be successful when combined with 50 mg of bictegravir (or its pharmaceutically acceptable sodium salt) and 200 mg of FTC. *See also* Astuti, 10-11; Llibre, 172; Sax, 53.

Moreover, claim 21 of the '342 patent is specifically directed to tablet compositions comprising BIC sodium, further establishing that it would have been obvious to formulate the pharmaceutical composition of claim 19 (depending on claims 1 and 12) of the '342 patent into a tablet composition, just as had been done in the prior art for other HIV combination formulations.

For the reasons discussed above, claim 1 of the '802 patent is an obvious variant of the claim 19 (depending from claims 1 and 12) of the '342 patent. Claim 1 is therefore invalid for obviousness-type double patenting over claim 19 (depending from claims 1 and 12) of the '342 patent, when claim 19 is analyzed in view of the prior art discussed in this section. The following non-limiting combinations of claim 19 (depending from claims 1 and 12) of the '342 patent with the prior art are exemplary.

- Claim 19 (depending from claims 1 and 12) of the '342 patent, in view of common knowledge in the art.
- Claim 19 (depending from claims 1 and 12) of the '342 patent, in view claim 21 of the '342 patent and common knowledge in the art.
- Claim 19 (depending from claims 1 and 12) of the '342 patent, in view of common knowledge in the art and the Stribild product discussed in, *e.g.*, the Stribild Assessment.
- Claim 19 (depending from claims 1 and 12) of the '342 patent, in view of common knowledge in the art and the Atripla product discussed in, *e.g.*, the Atripla Assessment.
- Claim 19 (depending from claims 1 and 12) of the '342 patent, in view of common knowledge in the art and the Eviplera product discussed in, *e.g.*, the Eviplera Assessment.
- Claim 19 (depending from claims 1 and 12) of the '342 patent, in view of common knowledge in the art and the Genvoya product discussed in, *e.g.*, the Genvoya Assessment.

- Claim 19 (depending from claims 1 and 12) of the '342 patent, in view of common knowledge in the art and one or more of Stribild Label, Stribild Assessment, Genvoya Label, Genvoya Assessment, and US '122, optionally further in view of one or more of Tivicay Label, Tivicay Assessment, Shah, Dow and US '332.
- Claim 19 (depending from claims 1 and 12) of the '342 patent, in view of common knowledge in the art and one or more of Stribild Label, Stribild Assessment, Genvoya Label, Genvoya Assessment, and US '122, optionally further in view of one or more of Gilead/Janssen, Lee, the '791 patent, Ruane, Sax, Astuti, and Llibre, WO '846, and US '856.
- Claim 19 (depending from claims 1 and 12) of the '342 patent, in view of common knowledge in the art and one or more of Truvada Label, Complera Label, Genvoya Label, Genvoya Assessment, and US '122, optionally further in view of one or more of Tivicay Label, Tivicay Assessment, Shah, Dow and US '332.
- Claim 19 (depending from claims 1 and 12) of the '342 patent, in view of common knowledge in the art and one or more of Truvada Label, Complera Label, Genvoya Label, Genvoya Assessment, and US '122, optionally further in view of one or more of Gilead/Janssen, Lee, the '791 patent, Ruane, Sax, Astuti, and Llibre, WO '846, and US '856.
- Claim 19 (depending from claims 1 and 12) of the '342 patent, in view of common knowledge in the art and WO '846, optionally further in view of one or more of Gilead/Janssen, Lee, the '791 patent, Ruane, Sax, Astuti, and Llibre.

- Claim 19 (depending from claims 1 and 12) of the '342 patent, in view of common knowledge in the art and WO '846, optionally further in view of one or more of Tivicay Label, Tivicay Assessment, Shah, Dow and US '332.
- Claim 19 (depending from claims 1 and 12) of the '342 patent, in view of common knowledge in the art and one or more of US '122, US '902, and US '857, optionally further in view of one or more of Tivicay Label, Tivicay Assessment, Shah, Dow and US '332.
- Claim 19 (depending from claims 1 and 12) of the '342 patent, in view of common knowledge in the art and one or more of US '122, US '902, and US '857, optionally further in view of one or more of Gilead/Janssen, Lee, '791 patent, Ruane, Sax, Astuti, and Llibre, WO '846, and US '856.
- Claim 19 (depending from claims 1 and 12) of the '342 patent in view of common knowledge in the art and any reference from Section II or Appendix D disclosing therapeutically effective amounts of INSTIs, FTC and TAF.
- Any of the above combinations taken further in view of claim 21 of the '342 patent.

Optionally, claim 19 (depending from claims 1 and 12) of the '342 patent would have been combined with WO '351 with a reasonable likelihood of success because it is in the same field of invention as WO '323, US '356, WO '846, and the '385 patent and discloses a similar pharmaceutical composition containing an INSTI and reverse transcriptase inhibitors. WO '351 teaches 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" for treatment of "a subject afflicted with a viral infection, preferably afflicted with an HIV infection." WO '351 at 3:18-24. In the composition, "[p]referably, dolutegravir is in the form of a

pharmaceutically acceptable salt,” and “[p]articularly preferred, dolutegravir is used in the form of the sodium salt, especially the mono-sodium salt.” *Id.* at 5:22-27. WO ’351 also discloses embodiments where the pharmaceutical composition comprises (a) dolutegravir, (b) emtricitabine and (c) tenofovir alafenamide in which the weight ratio of (a) dolutegravir to (b) emtricitabine to (c) tenofovir alafenamide can be from 1:1:0.15 to 1:8:1.” *Id.* at 16:8-11. WO ’351 teaches “In a preferred embodiment of the pharmaceutical combination of the present invention the amount of dolutegravir administered is 20 to 75 mg per day, preferably 25 to 70 mg per day, more preferably 35 to 65 mg per day, in particular 40 to 60 mg per day.” *Id.* at 16:15-18. It also teaches “In case that the tenofovir is administered as tenofovir alafenamide, the amount of tenofovir alafenamide administered preferably is 0.5 to 50 mg per day, more preferably 1 to 45 mg per day, even more preferably 3 to 44 mg per day, in particular 5 to 42 mg per day.” *Id.* at 17:5-8. WO ’351 further teaches that “In a preferred embodiment the pharmaceutical composition comprises (i) 20 to 75 mg, preferably 25 to 70 mg, more preferably 35 to 65 mg, in particular 40 to 60 mg dolutegravir (a); (ii) 50 to 300 mg, preferably 100 to 280 mg, more preferably 125 to 260 mg, in particular 150 to 250 mg emtricitabine (b); (iii) 0.5 to 50 mg, more preferably 1 to 45 mg, even more preferably 3 to 44mg, in particular 5 to 42 mg tenofovir (c), in particular tenofovir alafenamide; and (iv) pharmaceutical excipients.” *Id.* at 19:3-12. WO ’351 further discloses that “the combination of the present invention is administered once daily” and “can be preferably a solid oral dosage form” in “a capsule or tablet.” *Id.* at 17:27-28, 23:6-8.

As explained above, claim 1 of the ’802 patent reads on the species of “multilayer” tablets that include the claimed amounts of BIC, TAF, and FTC (or their salts). The skilled artisan would have readily appreciated that Gilead was employing bilayer technology in its HIV combination tablets for years before the effective filing date for the ’802 patent. Such combination tablets

included Stribild (bilayer technology to physically separate of EVG and COBI from FTC and TDF to reduce potential physicochemical interaction between them), Atripla (bilayer tablet separating efavirenz from FTC and TDF), Genvoya (bilayer layer tablets separating EVG and COBI from FTC and TDF used in clinical trials), Eviplera (bilayer layer tablet containing rilpivirine, FTC and TDF used to study pharmacokinetics in dogs demonstrated comparable systemic exposure to all compounds to individual compounds administered individually). Stribild Assessment, 18, 33; Atripla Assessment, 5; Genvoya Assessment, 74-75; Eviplera Assessment, 18; *see also* US '122, [0007] (tablets prepared in a bilayer manner have superior properties to alternatively structured tablets), FIG 1 and [0052] (disclosing a bilayer tablet having a first layer EVG and COBI, and a second layer that comprises FTC and TDF); US '902, [0010], [0050]-[0052] (describing bilayer tablets for keeping efavirenz separate from FTC and TDF); US '857, [0066]-[0071] (describing bilayer tablets for keeping rilpivirine separate from FTC and TDF).

In particular, Gilead's approved Stribild tablet contains the INSTI elvitegravir in a first layer, and FTC and TDF in second layer. Stribild Assessment, 18, 33. This bilayer tablet configuration was disclosed as having superior properties to alternatively structured tablets. US '122, [0007], *see also* [0061] (combining all of the compounds in a mixture to produce a monolayer tablet compromises chemical stability).

For at least these additional reasons, a skilled artisan would have been motivated to formulate a bilayer tablet combination containing 50 mg bictegravir (or an equivalent amount of bictegravir sodium), 25 mg tenofovir alafenamide (or an equivalent amount of TAF fumarate or TAF hemifumarate), and 200 mg emtricitabine. And given that these APIs dosages were known (or expected to be useful) for the treatment of HIV, the skilled artisan would have reasonably expected these amounts amount to be successful for the treatment of HIV in a bilayer tablet.

For example, the skilled artisan would have been motivated to modify the bilayer tablet described in the Genvoya Assessment, *e.g.*, that containing 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 25 mg of tenofovir alafenamide, to replace the first generation INSTI elvitegravir with 50 mg of the second generation INSTI bictegravir (or an equivalent amount of bictegravir sodium), and to remove the PK booster COBI and its silicon dioxide absorbent to provide the multilayer tablet having the recited doses and total tablet weight of claim 1. Alternatively, the skilled artisan would have been motivated to modify the bilayer tablet described in the Stribild Assessment, *e.g.*, that containing 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 300 mg of TDF, to replace elvitegravir with 50 mg of bictegravir (or an equivalent amount of bictegravir sodium), to replace TDF with the improved prodrug TAF (or an equivalent amount of TAF fumarate). This configuration would have been expected to reduce potential physicochemical interaction between bictegravir sodium and the other APIs. And given that these API dosages were known (or expected to be useful) for the treatment of HIV, the skilled artisan would have reasonably expected these amounts amount to be successful for the treatment of HIV in a bilayer tablet.

In addition, US '079 discloses pharmaceutical compositions comprising at least one integrase inhibitor or its salt and at least one antiretroviral or anti-HIV agent or its salt, or prodrug. US '079, Abstract. It further discloses that “[e]xamples of suitable integrase inhibitors include but are not limited to dolutegravir, raltegravir, MK-2048, JTK-656,⁴⁶ elvitegravir,” that suitable nucleoside reverse transcriptase inhibitors (NRTIs) include emtricitabine, and that suitable nucleotide reverse transcriptase inhibitors (NtRTIs) tenofovir, where “[p]referably, the integrase inhibitor is dolutegravir, raltegravir or elvitegravir,” and “[p]referably, the NRTIs/NtRTIs are

⁴⁶ JTK-656 corresponds to bictegravir, and is the code name originally assigned to it by the Japanese Tobacco Company.

selected from tenofovir, emtricitabine, lamivudine or zidovudine, or any combination thereof.” *Id.* at [0042]-[0051].

Further according to US '079, such pharmaceutical compositions are presented in solid dosage forms where “[a] tablet formulation is the preferred solid dosage form due to its greater stability, less risk of chemical interaction between different medicaments, smaller bulk, accurate dosage, and ease of production.” US '079, [0070], [0078]. These tablets are said to be preferably in the form of single or bilayered or multilayered tablets. *Id.* at [0079]. Example 1 provides a bilayer tablet with the INSTI dolutegravir in a first layer that is separated from a second layer contained FTC and TDF. Similarly, Example 4 provides a bilayer tablet with the INSTI raltegravir in a first layer that is separated from a second layer contained FTC and TDF. *See* Section II.III. '079 therefore provides additional motivation to separate an INSTI like BIC Na from FTC and TAF in a bi-layered tablet. Indeed, tenofovir prodrugs were known to be unstable toward alkaline conditions in both the solution and solid state, and a skilled artisan would have been specifically motivated to separate a basic INSTI such as dolutegravir Na or BIC Na from FTC and TAF in a bilayered tablet to reduce the degradation of TAF that would expectedly occur in the presence of these basic salts. *See, e.g.*, Havele, 3, 5 (TDF showed complete degradation occurred immediately after addition of at room temperature); Venkatasen, 4 (TDF undergoes 31% decomposition under basic stress conditions); Kurmi, 96121 (in a basic solution environment (0.5 N NaOH), TDF was completely converted into degradation product T1 in 3 h), 96121-25 (under basic solid state stress conditions, TDF degraded into several different products); *see also* Tivicay Information, 1 (noting that dolutegravir sodium has a pKa of 8.2, establishing its basicity).

For these additional reasons, the “multilayer” tablet species of claim 1 of the '802 patent would be an obvious variant of claim 19 (depending from claims 1 and 12) of the '342 patent, in

view of the prior art discussed in this section. Any combination of the disclosures in Appendix D are also suitable combinations.

b. Claims 2-8

Defendants' obviousness-type double patenting analysis for claim 1 of the '802 patent is incorporated herein in its entirety, including the prior art disclosures and combinations discussed therein.

Claim 2 depends from claim 1 and requires the tablet to comprise 50 mg of BIC as a pharmaceutically acceptable salt thereof. Claim 3 depends from claim 2 and requires the tablet to comprise 25 mg TAF as a pharmaceutically acceptable salt thereof. Claim 4 depends from claim 1 and requires the tablet to comprise 50 mg BIC as a pharmaceutically acceptable salt thereof, 25 mg TAF as a pharmaceutically acceptable salt thereof, and 200 mg FTC.

Claim 5 depends from claim 1 and requires the tablet to comprise 52 mg of BIC sodium. Claim 6 depends from claim 1 and requires the tablet to comprise 25 mg of TAF as TAF fumarate. Claim 7 depends from claim 1 and requires the tablet to comprise 28 mg of TAF hemifumarate. Claim 8 depends from claim 1 and requires the tablet to comprise 52 mg of BIC sodium, 28 mg of TAF hemifumarate, and 200 mg FTC.

Combinations of HIV INSTI compounds described as a genus including bicitgravir and its salts, *e.g.*, bicitgravir sodium, with emtricitabine, and TAF fumarate were known in the art. US '356, [0156]-[0157], [0162]-[0163]; [0177] (disclosing unitary dosage forms for simultaneous administration to a patient, for example as a solid dosage form for oral administration); *see also* '385 patent at 6:26-7:66. As discussed in Section II, TAF was well-known in the form of a monofumarate and hemifumarate salt, which could be dosed 10 times lower than the corresponding dose of TDF. Gilead/Janssen, 2; '791 patent, 24:38-48 (disclosing TAF monofumarate), US '856, [0010]-[0011], [0057] (disclosing TAF hemifumarate in combination with HIV nucleoside

inhibitors of reverse transcriptase and HIV integrase inhibitors); Genvoya Label, 22 (tablet containing TAF fumarate in combination with EVG and FTC); Genvoya Assessment, 10 (disclosing the same), 13 (TAF fumarate can be administered at a much lower dose than tenofovir disoproxil fumarate (TDF) while maintaining the established doses and biopharmaceutical performance of the other active substances), 74-75 (bilayer tablet containing 25 mg of TAF (as fumarate) combined with EVG, FTC, and COBI).

As discussed above, it was well known in the art that FTC was employed as a free base. Truvada Label (combination of 200 mg FTC free base and 300 mg TD (as fumarate)); Truvada Label (combination of 200 mg FTC free base, 300 mg TD (as fumarate), 600 mg efavirenz); Complera Label (combination of 200 mg FTC free base, 300 mg TD (as fumarate), 27.5 mg rilpivirine hydrochloride); Stribild Label (combination of 200 mg FTC free base, 300 mg TD (as fumarate), 150 mg elvitegravir and 150 mg cobicistat); Genvoya Label (combination of 200 mg FTC free base, 10 mg TAF (as fumarate), 150 mg elvitegravir and 150 mg cobicistat); WO '351 at 19:3-12 (teaching a preferred embodiment of the disclosed the pharmaceutical composition comprising “(i) 20 to 75 mg, preferably 25 to 70 mg, more preferably 35 to 65 mg, in particular 40 to 60 mg dolutegravir (a); (ii) 50 to 300 mg, preferably 100 to 280 mg, more preferably 125 to 260 mg, in particular 150 to 250 mg emtricitabine (b); (iii) 0.5 to 50 mg, more preferably 1 to 45 mg, even more preferably 3 to 44 mg, in particular 5 to 42 mg tenofovir (c), in particular tenofovir alafenamide; and (iv) pharmaceutical excipients).

As explained in Section VI.F.2, Claim 19 of the '067 patent recites a tablet containing a therapeutically effective amount of crystalline BIC sodium Form I (*i.e.* a pharmaceutically acceptable salt of bictegravir), which a skilled artisan would routinely determine to be 50 mg based on bictegravir (52 mg as bictegravir sodium), *e.g.*, in view routine dose optimization studies as

well as the dose of ~52 mg dose of DLT sodium (equivalent to 50 mg of DLT) in the previously approved Ticivay® product.

Claim 19 (depending from claims 1 and 12) of the '342 patent also calls for a tablet comprising TAF and FTC. WO '351 and US '332 describe preferable DLT combinations with FTC and TAF, where FTC is used as a free base (as opposed to a salt), and TAF is used as a monofumarate or hemifumarate salt, where the combination of FTC free base and TAF hemifumarate is especially preferred. *See, e.g.*, US '332, [0032], [0053]; *see also* Genvoya Assessment, 10 (disclosing a tablet containing TAF fumarate and FTC free base in combination with EVG and COBI); Stribild Label (combination of 200 mg FTC free base, 300 mg TD (as fumarate), 150 mg EVG and 150 mg COBI); US '856, [0010]-[0011], [0057] (disclosing TAF hemifumarate in combination with HIV nucleoside inhibitors of reverse transcriptase and HIV integrase inhibitors).

As further discussed for claim 1, WO '351 and US '332 describe preferable DLT combinations with FTC and TAF, where FTC is used as a free base (as opposed to a salt), and TAF is used as a monofumarate or hemifumarate salt, where the combination of FTC free base and TAF hemifumarate is especially preferred. *See, e.g.*, US '332, [0032], [0053]; *see also* Genvoya Assessment, 10 (disclosing a tablet containing TAF fumarate and FTC free base in combination with the INSTI elvitegravir), 74 (describing PK studies with TAF monofumarate and hemifumarate, where the hemifumarate was selected for Phase 2/3 studies and the commercial presentation).

In view of the above disclosures, the skilled artisan would have been motivated to provide a tablet composition comprising 52 mg BIC sodium (equivalent to 50 mg BIC), TAF monofumarate or TAF hemifumarate (equivalent to 25 mg of TAF, e.g., 28 mg of TAF

hemifumarate), and 200 mg FTC free base, and expect such a tablet to be useful for the treatment of HIV.

For these reasons and those discussed above for claim 1, including the exemplary combinations discussed therein, each of claims 2-8 of the '802 patent are obvious variants of claim 19 (depending from claims 1 and 12). Claims 2-8 are therefore invalid for obviousness-type double patenting over claim 19 (depending from claims 1 and 12) of the '342 patent, when claim 19 is analyzed in view of the prior art discussed in this section and the preceding section on claim 1.

c. Claims 9-11

Defendants' obviousness-type double patenting analysis for claims 1-8 of the '802 patent is incorporated herein in its entirety, including the prior art disclosures and combinations discussed therein.

Claim 9 depends from claim 1 and requires the tablet to have a total weight less than 1000 mg. Claim 10 depends from claim 9 and requires the tablet to have a total weight less than 800 mg. Claim 11 depends from claim 10 and requires the tablet to have a total weight less than 730 mg.

As discussed above for claim 1, a tablet composition, including a multilayer tablet composition, comprising 50 mg of BIC (or a salt thereof), 25 mg of TAF (or a salt thereof), and 200 mg of FTC (or a salt thereof) is an obvious variant of claim 19 (depending from claim 16). This obvious variant tablet would have contained a total active ingredient amount of 275 mg.

Regarding the total tablet weights recited in claims 9-11, a skilled artisan would have appreciated that tablet compositions, including a tablet composition containing 275 mg of the active ingredients BIC, TAF and FTC, would need to be formulated with pharmaceutical excipients to provide a composition suitable for oral administration. That artisan would have been motivated to combine the 275 total milligrams of BIC, TAF and FTC with the smallest amount of

additional excipients as possible, in order to provide a total tablet size that would be easier for a patient to swallow. Indeed, it was common knowledge in the art that smaller tablets sizes were preferred for patient compliance.

The skilled artisan would have also recognized each of those weights to be both desirable and achievable for a tablet combination comprising 50 mg BIC (or an equivalent amount of BIC sodium), 25 mg of TAF (or an equivalent amount TAF monofumarate or TAF hemifumarate), and 200 mg of FTC. Indeed, the skilled artisan would have been motivated to combine 275 total milligrams of BIC, TAF and FTC with the smallest amount of additional excipients possible, in order to provide a total tablet size that would be easier for a patient to swallow to improve patient compliance.

WO '846 discloses tablet dosage forms containing TAF and FTC and a number of common pharmaceutical excipients. The following two formulations are exemplary.

Formulation D:	<u>mg/tablet</u>	Formulation G	<u>mg/tablet</u>
GS-7340	25	GS-7340	300
emtricitabine	200	emtricitabine	200
Microcrystalline Cellulose	200	Hydroxypropyl Methylcellulose	112
Lactose Monohydrate	330	Lactose B.P.	53
Croscarmellose Sodium	60	Pregelatinized Starch B.P.	28
Pregelatinized Starch	50	Magnesium Stearate	7
Magnesium Stearate	10		
	875	total:	700

WO '846, 37:13-20 (Formulation D), 13:12-24 (Formulation G). As shown above, Formulation D contains 225 mg of active ingredients (i.e., TAF and FTC) and 650 mg of additional excipients, for a total tablet weight of 875 mg. Similarly, Formulation G contains 500 mg of active ingredients (i.e., TAF and FTC) and 200 mg of additional excipients, for a total tablet weight of 700 mg. In view of these disclosures, a skilled artisan would have appreciated that tablets

containing TAF and FTC had been prepared with a total weight in the range of 700-875 milligrams, and could be as low as 700 mg even when the total active ingredient content was 500 mg.

In view of these disclosures, the skilled artisan would have expected that a tablet containing 50 mg of BIC (or a salt thereof), 25 mg of TAF (or a salt thereof), and 200 mg of FTC (or a salt thereof), i.e., 275 mg of active ingredients, could have easily been formulated with additional excipients to provide a total tablet weight of less than 1000 mg, and even less than 800 mg and less than 730 mg. And given that formulations could contain at least 450 milligrams of additional excipients and still fall below the total weight called for by the claims, a skilled artisan would have expected for such tablet compositions to be suitable for oral administration to patients having HIV infection.

For these reasons and those discussed above for claims 1-8, each of claims 9-11 of the '802 application is an obvious variant of claim 19 (depending from claims 1 and 12) of the '342 patent. Claims 2-8 are therefore invalid for obviousness-type double patenting over claim 19 (depending from claims 1 and 12) of the '342 patent, when claim 19 is analyzed in view of the prior art discussed in this section and the preceding section on claim 1.

Moreover, dolutegravir (DLT) was known as a “second-generation INSTI” that combines the advantages of its predecessor INSTIs raltegravir and elvitegravir (EVG), but can administered once/day without the need for a pharmacokinetic booster such as cobicistat (COBI). Shah, 506 (also noting that COBI is a specific and potent inhibitor of CYP3A4 and associated with clinically significant drug–drug interactions), 517-518 (to be administered once/day, raltegravir must be coadministered with the COBI, which can lead to clinically significant drug–drug interactions). It was further known that DLT may be coformulated with other antiretrovirals in a single-tablet regimen for the treatment of HIV, without the need for COBI. *Id.* at 506; *see also* US '332, [0086]-

[0090] (describing pharmaceutical combinations comprising 40 to 60 mg DLT, 150 to 250 mg FTC, and 5 to 42 mg TAF, along with pharmaceutical excipients), [0091]-[0092] (disclosing a specific combination comprising about 50 mg DLT, about 200 mg FTC and about 25 mg TAF).

Based on the structural similarity and common INSTI activity between DLT and BIC (*supra*), the skilled artisan would have identified BIC as a second-generation INSTI, and thus would have expected that BIC could also be administered once daily, *e.g.*, in combination with TAF and FTC as discussed above, without the need for the PK booster cobicistat (COBI), to provide a combination less susceptible to drug-drug interactions, that could be used in patients resistant to RAL or EVG.. Indeed, based on structural similarity, the skilled artisan would have expected a similar mechanism of action, a similar resistance to CYP3A metabolism vis-à-vis EVG such that it would have be administered once-daily without a pharmacologic booster (*e.g.*, COBI), a similar ability to retain activity against many viral strains harboring major integrase resistance mutations to the INSTIs RAL and EVG, and a similar relatively minimal drug-drug interactions and side effects, each of which are advantages of the second generation inhibitors. Shah and Dow (*supra*), Astuti, 10; Llibre, 175; *see also* Llibre, 172 (CYP3A is the main pathway by which EVG undergoes metabolism in the intestine and liver); Ostenholzer, 265 (DTG does not require boosting, and is primarily metabolized by UGT 1A1 with only a small contribution from CYP3A4), 269 (Given its relatively minimal drug interaction and side effect profile, DTG may prove useful for patients on other medications for tuberculosis, hepatitis C, seizure, or contraception as well as those intolerant to other ART. In addition, DTG appears to be a viable choice for salvage in some highly treatment experienced patients harboring resistance to the first-generation INSTIs (RAL and EVG)). As such, the skilled artisan would have been motivated to prepare a tablet composition comprising 50 mg BIC (or a salt thereof), 25 mg of TAF or a salt

thereof, and 200 mg of FTC (or a salt thereof), i.e., 275 mg total active ingredients, without the need for COBI, leaving approximately 725 mg for tablet excipients to keep the total tablet weight below 1000 mg, 525 mg for tablet excipients to keep the total tablet weight below 800 mg, and 455 mg for tablet excipients to keep the total tablet weight below 730 mg.

US '122 is directed to solid oral dosage forms containing the APIs in Stribild®, i.e., EVG, FTC, TDF, and COBI. US '122, Abstract, [0002]-[0005], [0007]. US '122 exemplifies a tablet embodiment containing 150 mg of EVG, 200 mg FTC, 300 mg of TDF, and 150 mg of COBI, i.e., the doses in the approved Stribild® tablet, along with a number of pharmaceutically acceptable tablet excipients. *Id.* at [0022] (see table below) (EVG = Formula I; COBI = Formula II; FTC = Formula III; TDF = Formula IV); see also [0063]-[0065] (Examples 2-4) (describing similar tablets); Stribild Label, 22-23.

Components	Compound of Formula II 150 mg Formulation	
	% w/w	mg/tablet
Compound of Formula III	13.9	200.0
Salt of Formula IV	20.9	300.0
Compound of Formula I	10.4	150.0
Compound of Formula II	10.4	150.0
Colloidal Silicon Dioxide	12.0	172.5
Lactose Monohydrate	0.8	10.9
Microcrystalline Cellulose	20.8	299.5
Hydroxypropyl Cellulose	0.5	7.5
Hydroxypropyl Cellulose	0.6	9.0
Sodium Lauryl Sulfate	0.8	11.3
Croscarmellose Sodium	7.3	104.3
Magnesium Stearate	1.6	22.4
Total	100	1437.

As shown in the above table, the Stribild® tablet had a total weight of 1437 mg, with 800 mg directed to the four APIs and the remaining 637 mg directed to the combined excipients, where the 172.5 mg of the excipient weight is attributed to colloidal silicon dioxide, i.e., a required absorbent for COBI designed to enhance its stability. See Stribild Assessment, 12 (the active

substance COBI is adsorbed on silicon dioxide), 13 (COBI is isolated by adsorption on silicon dioxide to provide a stable solid form, which is suitable for further finished product manufacture).

If identical tablet excipients and amounts were employed in the tablet combination according to claim 19 (depending from claim 16), *i.e.*, that containing crystalline BIC sodium Form I, TAF, and FTC, without the need for COBI in the formulation, and including the obvious amount of BIC sodium (equivalent to 50 mg BIC), TAF (25 mg or an equivalent amount a mono- or hemifumarate salt), and FTC (200 mg) discussed above (~275 mg weight of combined APIs), the total tablet weight would have been ~910 mg (or slightly more if the tablet employed BIC sodium and TAF hemifumarate). Thus, even if the tablet contained the large amount of silicon dioxide for absorption of COBI (which would not be required with BIC), the total tablet weight would have been less than 1000 mg. And the total tablet weight would have been substantially lower than 1000 mg, e.g., ~740 mg, when silicon dioxide was significantly reduced or removed from the tablet altogether (which a skilled artisan would have been motivated to do for a tablet not containing COBI).

Further, the skilled artisan would have appreciated that the tablet excipients in the Stribild® formulation could have been reduced even further because significantly less BIC and TAF, *i.e.*, 50 mg and 25 mg respectively, would have been needed compared to the 150 mg amount of EVG and 300 mg amount of TDF included in Stribild®. As such, a skilled artisan would have appreciated that the total tablet weight could be reduced even further, e.g., to below 800 mg and below 730 mg, given that less excipients would be needed to properly formulate the lower amount of total active ingredients. And given that this lower total dose of BIC, TAF, and FTC vis-à-vis Stribild® was expected to be useful for the treatment of HIV, the skilled artisan would have reasonably

expected tablets having total weight of less than 1000 mg, less than 800 mg, and less than 730 mg to be accessible and successful for the treatment of HIV.

For these reasons and those discussed above for claims 1-8, including the exemplary combinations discussed therein, claims 9-11 of the '802 patent are obvious variants of the claim 19 (depending from claims 1 and 12) of the '342 patent. Claims 9-11 are therefore invalid for obviousness-type double patenting over claim 19 (depending from claims 1 and 12) of the '342 patent, when claim 19 is analyzed in view of the prior art discussed in this section and the preceding sections on claim 1-8.

d. Claims 12-13

Defendants' obviousness-type double patenting analysis for claim 1 of the '802 patent is incorporated herein in its entirety, including the prior art disclosures and combinations discussed therein.

Claim 12 depends from claim 1 and requires the tablet to contain less than 15% of bictegavir or a pharmaceutically acceptable salt thereof. Claim 13 depends from claim 1 and requires the tablet to contain less than 11% of bictegavir or a pharmaceutically acceptable salt thereof.

As explained above for claims 9-11, a tablet composition containing 50 mg of BIC (or a salt thereof), 25 mg TAF (or a salt thereof), and 200 mg FTC (or a salt thereof) and having a total tablet weight significantly less than 1000 mg, e.g., less than 800 mg and less than 730 mg, would have been an obvious variant of claim 19 of the '342 patent. This is at least because the skilled artisan would have formulated such tablets to contain the least amount of excipients as possible, to provide a tablet that would be easier to swallow for increased patient compliance.

Given that the total active ingredient weight in those obvious variants is 275 mg (or slightly more when including bictegavir sodium and a TAF fumarate salt), the skilled artisan would have

significant room to provide a tablet composition containing less than about 15% BIC or BIC sodium (claim 12), and less than about 11% BIC or BIC sodium (claim 13). Indeed, the skilled artisan would have arrived at these percentages through routine optimization of common excipients and their amounts to provide a tablet composition having a total weight of less than about 1000 mg, such as less than 800 mg and less than 730 mg. And most reasonably achievable tablet weights, e.g., 275 mg of active ingredients and a total weight of 600-900 mg, would meet the 15% and 11% limitations of claims 12-13 when the BIC or BIC sodium dose is ~50 mg. Indeed, a 600 mg tablet would have contained ~8% BIC or BIC sodium, a 700 mg tablet would have contained ~7% BIC or BIC sodium, an 800 mg tablet would have contained ~6% BIC or BIC sodium, and a 900 mg tablet would have contained ~5.5% BIC or BIC sodium, each of which fall within the scope of claims 12-13.

For these reasons and those discussed above for claims 1-11, including the exemplary combinations discussed therein, claims 12 and 13 of the '802 patent are obvious variants of the claim 19 ((depending from claims 1 and 12)). Claims 12-13 are therefore invalid for obviousness-type double patenting over claim 19 of the '342 patent, when claim 19 is analyzed in view of the prior art discussed in this section and the preceding sections on claim 1-11.

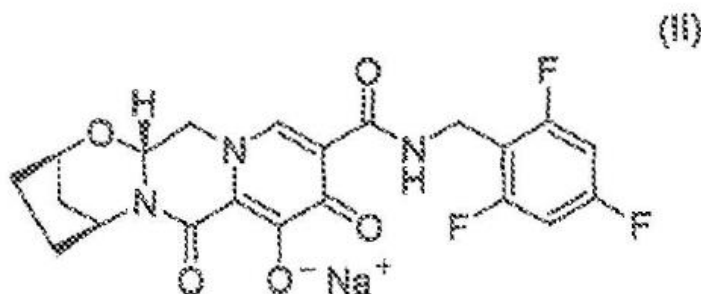
(4) Anticipation and Obviousness over WO '116

Defendants incorporate their contentions for double patenting and obviousness in Sections VI.F.(1)-(3) in their entirety, including all prior art and prior art combinations discussed above.

As explained in Section II.TTT, Gilead has acknowledged that the '802 patent is not entitled to its earliest priority date of November 9, 2015, then WO '116 is prior art under 35 U.S.C. § 102(a)(1) and cannot be disqualified under § 102(b)(1). If this is the case, then the '802 claims also are anticipated or would have been obvious over WO '116 in combination with any of the

prior art discussed in Sections VI.F.(1)-(3). Defendants provide an exemplary anticipation analysis below.

WO '116 is specifically directed to BIC sodium and a crystalline form thereof (Form I), along with pharmaceutical formulations and therapeutic uses therefore. WO '116, [0002]; *see also* Section IV.A (discussing the disclosure of the family member '342 and '067 patents). BIC sodium is identified by Formula II, and is the only compound disclosed in WO '116 outside of BIC free acid (Formula I) in the background. *Id.* at [0006]-[0008]; [0043]-[0057] (describing crystalline forms of Formula II). Thus, when WO '116 refers to “the compound described herein,” it is only referring to Formula II (BIC Na) and its crystalline Form I. *See e.g., id.* at [0058].



WO '116 describes tablet compositions containing BIC sodium (Formula II) with one or more compounds useful for treating HIV, such as NRTIs or NtRTIs, which are suitable for once-daily dosing. WO '116, [0081]; *see also id.* at [0099] (BIC sodium is combined with one or more additional therapeutic agents in a unitary dosage form for simultaneous administration to a patient, for example as a solid dosage form for oral administration). WO '116 specifically discloses embodiments where BIC sodium is combined with 25 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide and 200 mg emtricitabine, where BIC sodium can be present in any dosage amount. *Id.* at [0096]. Dosage amounts for BIC sodium include an amount of about 50 mg to about 100 mg, and also 50 mg, 75 mg and 100 mg specifically. *Id.* at [0058]. WO '116 also

points to a therapeutically effective amount of BIC sodium, which “can be determined routinely by one of ordinary skill in the art having regard to their own knowledge, the state of the art, and this disclosure.” *Id.* at [0033].

WO '116 also claims specific tablets compositions comprising a therapeutically effective amount of BIC sodium, and a pharmaceutically acceptable carrier or excipient (*see* claim 12 depending from claims 1 or 2), further comprising tenofovir alafenamide and emtricitabine (*see* claim 21 depending from claim 20 depending from claim 18 depending from claim 12), or tenofovir alafenamide hemifumarate and emtricitabine (*see* claim 21 depending from claim 20 depending from claim 19 depending from claim 12). WO '116, 49-51.

As such, WO '116 specifically discloses and claims a tablet composition comprising a therapeutically effective amount of BIC sodium combined with tenofovir alafenamide (or tenofovir alafenamide hemifumarate) and emtricitabine, where the dose of tenofovir alafenamide (or tenofovir alafenamide hemifumarate) is 25 mg, and the dose of emtricitabine is 200 mg. WO '116 also discloses a BIC sodium dose of about 50 mg to about 100 mg and specifically discloses a dose of 50 mg, as well as therapeutically effective doses that can be determined routinely by a skilled artisan.

There are no differences between the disclosure of WO '116 and claim 1 of the '802 patent. WO '116 discloses each and every limitation of claim 1, and claim 1 is therefore anticipated by WO '116.

There are also no differences between the disclosure of WO '116 and claims 2-8 of the '802 patent. WO '116 discloses each and every limitation these claims, and they are therefore anticipated by WO '116. Claims 1-8 are obvious over WO '116 in view of the prior art and arguments discussed in Sections VI.F.(1).a-b, VI.F.(2).a-b, and V.F.(3).a-b. Indeed, the doses and more specific compounds recited these claims would have been obvious to a skilled artisan over

WO '116 for the same reason discussed in Sections VI.F.(1).a-b, VI.F.(2).a-b, and V.F.(3).a-b above.

Claims 9-13 are also obvious over WO '116 in view of the prior art and arguments discussed in Sections V.F.(1).a.ii-iv, V.F.(2).b-d, and V.F.(3).b-d. Indeed, the further limitations for these claims are obvious in view of the contentions made in those sections.

Claims 2 and 6-8 are also obvious over WO '116 in view of the prior art and arguments discussed in Sections VI.F.(1).c-d, VI.F.(2).c-d, and V.F.(3).c-d. Indeed, the further limitations for these claims are obvious in view of the contentions made in those sections.

VII. RESERVATION OF RIGHTS

As discovery continues, Defendants reserve the right to supplement, amend or modify these Amended Initial Invalidity Contentions based on any supplements or amendments to Plaintiff's Infringement Contentions or Response to Defendants' Amended Initial Invalidity Contentions, or as Defendants obtain information through expert and fact discovery, or otherwise become aware of additional documents, data compilations or tangible things. Defendants do not, in making these contentions, concede their agreement with any claim constructions suggested by Plaintiff, and Defendants, therefore, reserve the right to supplement or amend these contentions if any claim constructions are issued or adopted by the Court or the United States Court of Appeals for the Federal Circuit in this case or in any related case. Defendants also provide these contentions without waiving any claim of privilege or work-product immunity.

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