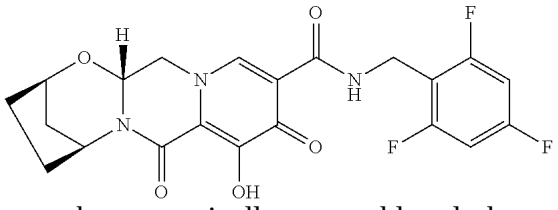
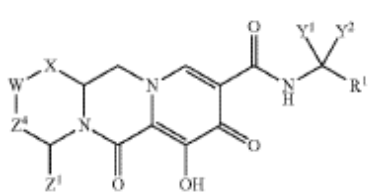
DEFENDANTS' 07/11/24 APPENDIX D – U.S. Patent No. 11,744,802

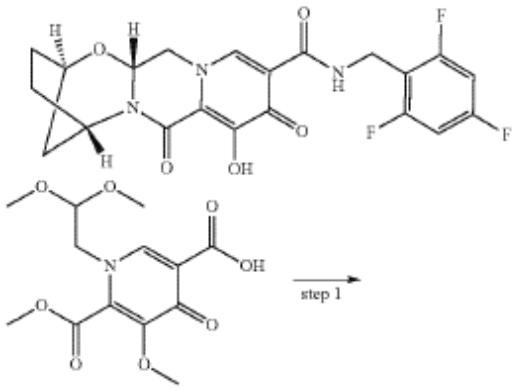
The claim chart below shows examples of how each and every element of the asserted claims of U.S. Patent No. 11,744,802 is taught by the prior art.[1,2,3]

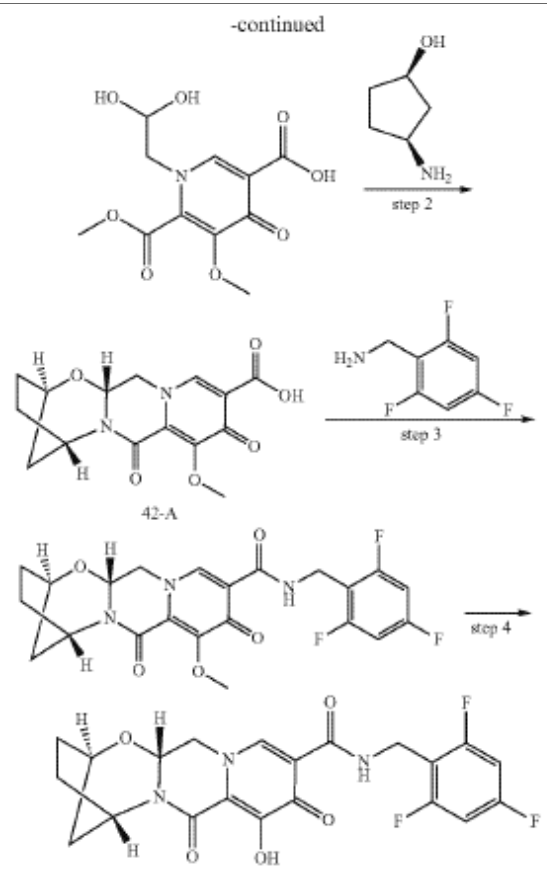
Claim 1	
Claim Elements	Prior Art Teachings of Claim Elements
A tablet comprising 50 mg of the compound of Formula I: (I)  or a pharmaceutically acceptable salt thereof	US '356 discloses "[c]ompounds for use in the treatment of human immunodeficiency virus (HIV) infection . . . hav[ing] the following Formula (I): (I)  including stereoisomers and pharmaceutically acceptable salts thereof, wherein R^1, X, W, Y^1, Y^2 , Z^1, and Z^4 are as defined herein. Methods associated with preparation and use of such compounds, as well as pharmaceutical compositions comprising such compounds, are also disclosed." US '356, Abstract, [0089]. US '356 further discloses "polycyclic carbamoylpyridone compounds, having antiviral activity, . . . and the use of such

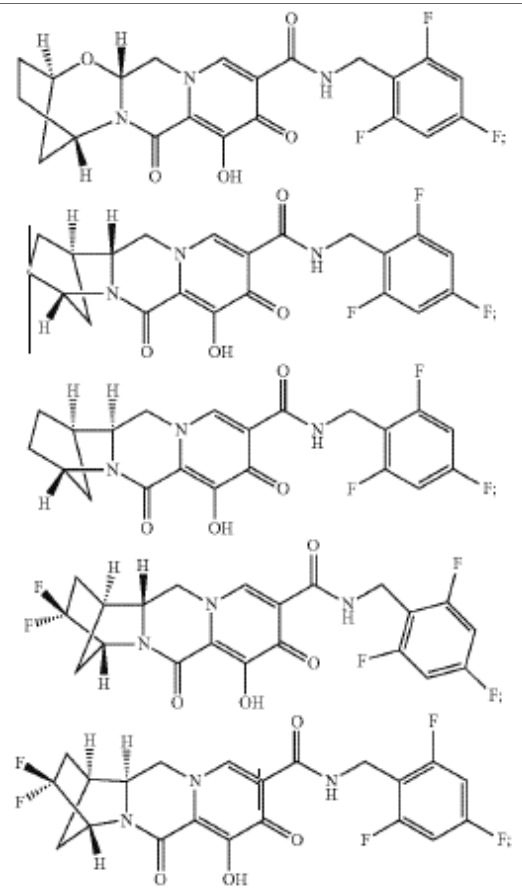
[1] Plaintiff has asserted the following claims, in whole or in part, against Defendants: claims 1-13 of the '802 patent.

[2] Nothing herein should be construed as an admission or concession by Defendants regarding the claim construction of the '802 patent. Defendants fully reserve the right to amend and supplement their contentions (including but not limited to this Appendix D), particularly if Plaintiff proffers constructions for the terms of the asserted claims.

[3] Defendants provide this invalidity analysis as representative only, and also rely on the disclosures of any reference discussed in Section II to support the disclosure of the limitations of the asserted claims. The cited disclosures of each reference are exemplary only. Defendants reserve the right to rely on additional citations within each reference cited herein, or otherwise in the version of the contentions served herewith, and do not waive that right by not expressly citing them here. Defendants reserve the right to rely on any disclosure in any of the cited references and reserve the right to amend or supplement this information as appropriate and/or necessary.

	compounds in the treatment of HIV infections. The compounds of the invention may be used to inhibit the activity of HIV integrase and may be used to reduce HIV replication." US '356, [0010]. US '356 further discloses approximately 100 HIV INSTI compounds of Formula (I) and methods for their synthesis, including a Compound 42 corresponding to bictegravir (BIC): 42 

	-continued  US ’356, [0312]-[0316] (Example 42). US ’356 further discloses 7 HIV INSTIs of Formula I, including bictegravir:

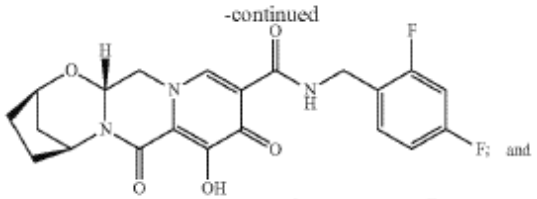
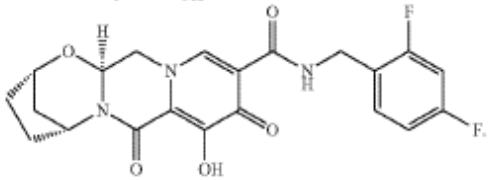
	-continued  ; and  US '356, claim 32. US '356 further discloses a tablet showing that BIC (compound 42) provided nanomolar activity (EC50 = 2.5 nm) in an antiviral assay in MT4 cells infected with HIV. "Compounds of the present invention demonstrate antiviral activity in this assay as depicted in Table 1 below. Accordingly, the compounds of the invention may be useful for treating the proliferation of the HIV virus, treating AIDS, or delaying the onset of AIDS or ARC symptoms." US '356, [0589]-[0592] (Example 104; see Table 1). US '356 further discloses Example 107, "Pharmacokinetic analysis Following Oral or Intravenous Administration to Beagle Dogs." US '356, [0599]-[0603]. US '356 provided the second highest oral bioavailability (F (%)), Cmax and AUC of the eleven Formula (I) compounds tested:

TABLE 4

Compound #	CL (L/h/kg)	V_{ss} (L/kg)	MRT (h)	F (%) aqueous suspension	C_{max} (μM) aqueous suspension	AUC (μM * h) aqueous suspension
98	0.047	0.16	3.3	n/a	n/a	n/a
83	0.161	0.38	2.4	n/a	n/a	n/a
55	0.058	0.24	4.2	n/a	n/a	n/a
77	0.300	0.64	2.2	n/a	n/a	n/a
41	0.015	0.11	7.5	10.7	2.4	16.3
42	0.020	0.15	7.1	28.0	4.5	28.6
47	0.014	0.10	7.4	12.6	2.8	20.4
8	0.498	0.87	1.8	n/a	n/a	n/a
7	0.510	1.20	2.3	n/a	n/a	n/a
3	0.047	0.23	4.9	18.7	1.2	9.2
2	0.030	0.20	6.5	40.7	7.8	66.1

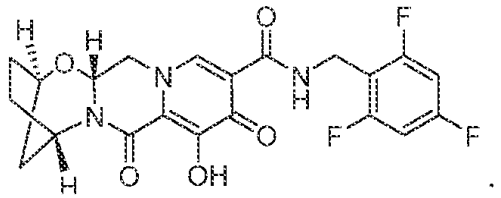
US ’356, Example 107; see Table 4.

US ’356 further discloses “[p]harmaceutical compositions . . . includ[ing] a compound of Formula (I) and one or more of: a pharmaceutically acceptable carrier, diluent or excipient. . . . In certain embodiments, a compound of Formula (I) is present in the pharmaceutical composition in an amount from about 25 mg to about 500 mg. In certain embodiments, a compound of Formula (I) is present in the pharmaceutical composition in an amount of about 100 mg to about 300 mg. In certain embodiments, a compound of Formula (I) is present in the pharmaceutical composition in an amount of about 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg or about 500 mg.” US ’356, [0152].

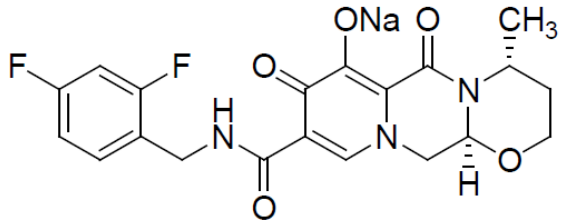
US ’356 refers “pharmaceutically acceptable salt” to “a salt of a compound that is pharmaceutically acceptable and that possesses (or can be converted to a form that possesses) the desired pharmacological activity of the parent compound. Examples of ‘pharmaceutically acceptable salts’ of the compounds disclosed herein include salts derived from an appropriate base, such as . . . an alkaline earth metal (for example, magnesium). . . .” US ’356, [0075].

	US ’356 states that “[t]he compounds of the invention, or their pharmaceutically acceptable salts, are administered in a therapeutically effective amount.” US ’356, [0155]. US ’356 further states that “a therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to their own know ledge, the state of the art, and this disclosure.” US ’356, [0081]. US ’356 discloses that these pharmaceutical compositions containing a therapeutically effective amount of a compound of Formula (I) are disclosed “for use in the therapeutic treatment of an HIV infection is provided.” US ’356, [0147]-[0149]. US ’356 states that “[a]dministration of the compounds of the invention, or their pharmaceutically acceptable salts, in pure form or in an appropriate pharmaceutical composition, is carried out via any of the accepted modes of administration of agents for serving similar utilities.” US ’356, [0153]-[0154] US ’356 also claims “[a] pharmaceutical composition comprising a compound of any one of claims 1-32, or a stereoisomer or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.” US ’356, claim 33. US ’356 further claims, “[a] method of treating an HIV infection in a human having or at risk of having the infection by administering to the human a therapeutically effective amount of a compound of any one of claims 1-32 or a pharmaceutical composition of claim 33.” US ’356, claim 37.

	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]. US ’356 also discloses combination therapy “for treating or preventing an HIV infection in a human having or at risk of having the infection.” US ’356, [0156]. US ’356 further discloses 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.US ’356, [0156]-[0163]. US ’356 also discloses an embodiment wherein pharmaceutical compositions comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with one or more additional therapeutic agents, and a pharmaceutically acceptable carrier, diluent or excipient are provided. US ’356, [0156]-[0179]. US ’356 further discloses that [i]n certain embodiments, a compound disclosed herein 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. US ’356, [0177]. US ’332 describes pharmaceutical combinations comprising 40 to 60 mg DLT, 150 to 250 mg FTC, and 5 to 42 mg TAF, along

	with pharmaceutical excipients. US '332, [0086]-[0090]. US '332 further discloses that "[i]n a preferred embodiment the pharmaceutical composition of the present invention comprises 50 mg dolutegravir, 50 mg dolutegravir, about 200 mg emtricitabine and about 25 mg tenofovir." *Id.* at [0091]-[0092]. HIV Guidelines states that "[a]n antiretroviral regimen for a treatment-naive patient generally consists of two nucleoside 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." HIV Guidelines, D-1. 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. US '356, 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). WO '323 claims, "A compound of claim 1 selected from: . .  WO '323, Claim 32. WO '323 further claims, "A pharmaceutical composition comprising a compound of any one of claims 1-32, or a

	stereoisomer or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient." WO '323, Claim 33. WO '323 discloses, "Compounds, compositions, and methods for the treatment of human immunodeficiency vims (HIV) infection are disclosed. In particular, novel poly cyclic carbamoylpyridone compounds and methods for their preparation and use as therapeutic or prophylactic agents are disclosed." WO '323, 1:12-15. WO '323 teaches, "In certain embodiments, a compound of Formula (I) is present in the pharmaceutical composition in an amount of about 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg or about 500 mg." WO '323, 35:19-23. WO '323 defines "Formula (I)" as including "the specific compounds disclosed herein[,]" which includes bictegravir. WO '323, 18-19. HIV Guidelines further recommends combination of the INSTIs elvitegravir and raltegravir with tenofovir and emtricitabine. HIV Guidelines, 1, i. British HIV Guidelines describes tenofovir and emtricitabine as the preferred NRTI backbone for HIV therapy, to be combined with an additional agent such as an INSTI. British HIV Guidelines, 13. NCT '694 discloses a study that "evaluate[s] the efficacy, safety and tolerability of GS-9883 + emtricitabine/tenofovir alafenamide (FTC/TAF) fixed dose combination (FDC) versus

	dolutegravir (DTG) + FTC/TAF in HIV-1 Infected, antiretroviral treatment-naive adults. This study will also evaluate the pharmacokinetic (PK) profile of GS-9883, FTC and TAF." NCT '694, Study Description. NCT '694 further discloses an "active comparator" with "Drug: FTC/TAF, Emtricitabine/Tenofovir Alafenamide (FTC/TAF) 200 mg/25 mg tablet administered orally; Drug: DTG, Dolutegravir (DTG) 50 mg tablet administered orally." NCT '694, Arms and Interventions. US '332 discloses dolutegravir, which it further states is "reported to have anti-viral activity, since it is considered to be an integrase inhibitor." US '332, [0014]. US '332 further discloses, "[p]referably, dolutegravir is in the form of a pharmaceutically acceptable salt. More preferred, dolutegravir is in the form of an alkali metal salt such as sodium or potassium salt or in the form of an earth-alkali metal salt such as calcium or magnesium salt. More preferred, dolutegravir is in the form of a sodium salt or a magnesium salt. Particularly preferred, dolutegravir is used in form of the sodium salt, especially the mono-sodium salt." US '332, [0018], [0020]. The Tivicay Assessment teaches the sodium salt form of dolutegravir with the following structure: 

	Tivicay Assessment, 9. The Tivicay Assessment also discloses that "Tivicay is presented as film-coated tablet containing 50 mg of dolutegravir (As dolutegravir sodium salt) as active substance." Tivicay Assessment, 9. Tivicay Assessment identifies 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." *Id.* at 43, 50-51, It further discloses combination therapies with DLT sodium, FTC and tenofovir disoproxil for treating HIV. *Id.* at 89. The 2013 Tivicay Label teaches, "TIVICAY is a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor (INSTI) indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and children aged 12 years and older and weighing at least 40 kg." Tivicay Label, 1. The 2013 Tivicay Label also discloses Tivicay containing 50 mg of dolutegravir sodium as an HIV INSTI indicated in combination with other antiretroviral agents (e.g., emtricitabine/tenfovoir (TRUVADA), for the treatment of HIV-1 infection. 2013 Tivicay Label, 1, 4, 24. US '332 further discloses "a pharmaceutical composition comprising (a) dolutegravir, (b) emtricitabine and (c) tenofovir, wherein (a) dolutegravir and (b) emtricitabine are present in a specific weight ratio, for use as a medicament. A further subject of the present invention is a method for treating a viral infection, comprising administering to a subject in need thereof the pharmaceutical combination or composition of the present

	invention, wherein the viral infection preferably comprises an HIV-infection." US '332, [0061]. US '332 discloses that the "[i]n another particularly preferred embodiment, the combination of the present invention is administered once daily." US '332, [0077]. US '332 further discloses that "[t]he pharmaceutical composition of the present invention can be preferably a solid oral dosage form. It is further preferred that the dosage form of the invention is a capsule or a tablet, in particular a tablet." *Id.* at [0107]. US '332 describe "preferred embodiment [of] the pharmaceutical composition compris[ing] … 40 to 60 mg dolutegravir, … 250 mg emtricitabine, … and 5 to 42 mg tenofovir; and pharmaceutical excipients." US '332, [0086]-[0090]. US '332 further discloses that "[i]n a preferred embodiment the pharmaceutical composition of the present invention comprises 50 mg dolutegravir, 50 mg dolutegravir, about 200 mg emtricitabine and about 25 mg tenofovir." US '332, [0092]. US '332 also discloses the total amount of dolutegravir, emtricitabine and tenofovir alafenamide comprised in the present pharmaceutical combination for use as a medicament is between 70.5 and425 mg per day, in particular 192 to 326 mg per day." US '332, [0075]. Genvoya Label discloses a tablet composition for oral administration that contains 150 mg of the INSTI elvitegravir (EVG), 150 mg of PK enhancer cobicistat (COBI), 200 mg of NRTI emtricitabine (FTC), and 11.2 mg of NRTI tenofovir alafenamide (TAF) fumarate (equivalent to 10 mg TAF)). Genvoya, 22.

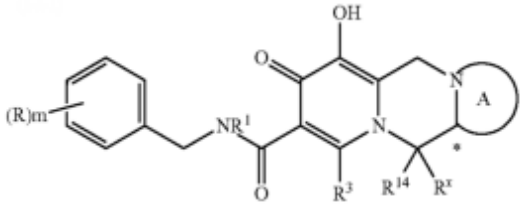
	Genvoya Assessment discloses film-coated tablets containing the following active substances: 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (as 11.2 mg of the fumarate)." Genvoya Assessment, 10. Genvoya Assessment further describes open-label 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. Genvoya Assessment, 74-75. WO '846 discloses therapeutic combinations of TAF and FTC for treating HIV. WO '846, 3:13-18. WO '846 further discloses that combination can additionally include an INSTI. WO '846, 18:23-26. WO '846 further discloses an exemplary formulation containing 25 mg of TAF and 200 mg FTC. WO '846, 37:13-20. WO '846 discloses a pharmaceutical composition comprising "(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. Stribild Label discloses a tablet composition for oral administration that contains a combination of 150 mg of the integrase strand transfer inhibitor elvitegravir, 200 mg and 300 mg respectively of the nucleos(t)ide analog HIV-1 reverse transcriptase inhibitors emtricitabine and tenofovir disoproxil

	fumarate, and 150 mg of the pharmacokinetic enhancer cobicistat. Stribild Label, 1. US '122 discloses a solid dose form (e.g. tablets) comprising a compound of Formula I (i.e. elvitegravir), Formula III (i.e. emtricitabine), Formula IV (i.e. tenofovir disoproxil fumarate), 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.

	Compound of Formula II 150 mg Formulation	
Components	% 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.

Id. at [0022].

US '122 further discloses examples of tablets similar to Stribild. *Id.* at [0063]-[0065] (Examples 2-4).

	The ’385 patent discloses 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  Z = O or NR^{26} 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. ’385 patent, 8:9-34. 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. ’385 patent, Abstract, 7:32-35, 38:6-9.

	The ’385 patent discloses, “[t]he present invention relates to novel compounds possessing an antiviral activity, in detail polycyclic carbamoylpyridone derivatives possessing an inhibitory activity against HIV integrase and a pharmaceutical composition containing the same, especially an anti-HIV agent.” ’385 patent, 1:15-20. 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. 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. 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. WO '351 further discloses that 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." WO '351, 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." WO '351, 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." WO '351, 16:15-18. WO '351 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." WO '351, 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." WO '351, 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." WO '351, 17:27-28, 23:6-8. The Stribild Assessment discloses, "Stribild is presented for use as a bilayer tablet – one layer contains EVG/COBI and one FTC/TDF." Stribild Assessment, 33. The Atripla Assessment teaches, "The granulations are blended separately with extra-granular magnesium stearate, compressed into bilayer tablets, and then film-coated. Process optimization studies were conducted in order to establish critical process parameters for the wet granulation of efavirenz, dry granulation of emtricitabine/tenofovir, bilayer tablet compression, and aqueous film-coating operations." Atripla Assessment, 5.

The Genvoya Assessment states, “GS-US-292-0101 was an open-label crossover study that compared two formulations (monolayer and bilayer) of E/C/F/TAF (each containing either 25 or 40 mg TAF as the monofumarate) with Stribild and with TAF 25 mg alone.” Genvoya Assessment, 75.

The Eviplera Assessment teaches, “The exposure of FTC/RPV/TDF after single oral administration of a bilayer formulation and the individual compounds was compared in fasted dogs and has demonstrated comparable systemic exposure to all compounds.” Eviplera Assessment, 18.

US ’857 discloses “a tablet of the invention wherein the first layer comprises:

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

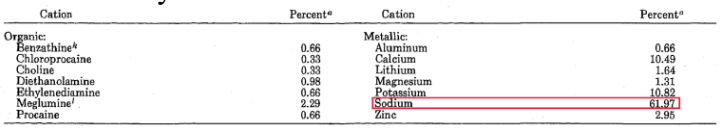
and the second layer comprises:

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

US ’857, [0066]. US ’857 further discloses bilayer tablets for keeping rilpivirine separate from FTC and TDF. *Id.* at [0067]-[0071].

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, 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]. US '079 also discloses that 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. 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. Havele discloses that TDF showed complete degradation occurred immediately after addition of at room temperature). Havele, 3, 5. Venkatasan discloses that TDF undergoes 31% decomposition under basic stress conditions. Venkatasan, 4. Kurmi discloses that in a basic solution environment (0.5 N NaOH), TDF was completely converted into degradation product

	T1 in 3 h. Kurmi, 96121. Kurmi further discloses that under basic solid state stress conditions, TDF degraded into several different products. *Id.* at 96121-25. Berge teaches "[t]he chemical, biological, physical and economic characteristics of medicinal agents can be manipulated and, hence, often optimized by conversion to a salt form," where "salt-forming agents are often chosen empirically … [and] the preferred form is selected by pharmaceutical chemists on a practical basis: cost of raw materials, ease of crystallization, and percent yield … [as well as] stability, hygroscopicity, and flowability of the resulting bulk drug." Berge at 1. Berge also teaches Table 1 as a list of "FDA-approved commercially marketed salts" that includes sodium:  Remington 21st teaches in Table 38-5 that sodium salts were an API-salt form known since at least 1983:

Cation	Percent[a]	Cation	Percent[a]
Organic:		Metallic:	
Benzathine[k]	0.66	Aluminum	0.66
Chloroprocaine	0.33	Calcium	10.49
Choline	0.33	Lithium	1.64
Diethanolamine	0.98	Magnesium	1.31
Ethylenediamine	0.66	Potassium	10.82
Meglumine[l]	2.29	Sodium	61.97
Procaine	0.66	Zinc	2.95

Table 38-5. Molecular Forms Marketed Worldwide Between 1983 and 1996

SALT FORM	FREQ.	GROUP[a]	PK_A	CLOGP	MW
No salt form	390	0			
Hydrobromide	1	1	−8	0.45	80.91
Hydrochloride	102	1	−6.1	0.24	36.46
Sulfate	5	1	−3	−1.58	98.08
Nitrate	6	1	−1.44	2.09	63.01
Phosphate	2	1	2.15	−1.95	96.99
Glucuronate	1	1	3.22[b]	−3.74	194.14
Acetate	8	1	4.76	−0.36	59.05
Maleate	3	2	1.92	−0.18	116.07
Fumarate	8	2	3.02	−0.18	116.07
Tartrate	1	2	3.03	−2.21	150.09
Citrate	1	2	3.13	−2.11	189.10
Succinate	2	2	4.21	−0.62	118.09
Mesylate	8	3	−1.20	−1.31	96.11
Acistrate	1	3	4.91[b]	7.98	284.49
Besylate	2	4	−2.80[b]	0.23	157.17
Tosylate	3	4	−1.34	0.88	171.20
Xinafoate	1	4	2.66[b]	3.00	188.18
Potassium	1	1	16		39.10
Sodium	37	1	14.77		23.00
Tromethamine	2	1	8.07[c]	−3.17	121.14
Bismuth	1	1	1.58		208.98
Bromide	6	5			79.90
Chloride	2	5			35.45

[a] Groups: 0 = No salt, 1 = Polar, 2 = Multifunctional, 3 = Flexible aliphatics, 4 = Planar aromatics, 5 = Quartenary.
[b] Calculated pK_a.
[c] Data from *CRC Handbook of Basic Tables for Chemical Analysis*, page 469.
From Serajuddin ATM, Sheen P, Augustine MA. To market, to market. In: Bristol J, ed. *Annu Rep Med Chem.* New York: Academic, 1983–1996.

Serajuddin teaches that "[s]alt formation is the most common and effective method of increasing solubility of acidic and basic drugs." Serajuddin at 603.

Serajuddin also teaches that "[s]alt formation is also the most common approach of increasing solubility, dissolution rate and ultimately bioavailability of poorly water-soluble ionizable drugs in solid dosage forms." Serajuddin at 614.

Serajuddin further informs that "Table 2 gives the distribution of 120 salts approved by the FDA during the 12-year period from 1995 to 2006, where the hydrochloride salt is the predominant salt form among the basic drugs and the sodium salt is the predominant form for acidic drugs." Serajuddin at 613. The portion of Table 2 that shows salts of acidic drugs shows:

Salts of acidic drugs	Total number
Sodium	12
Calcium	4
Potassium	2
Tromethamine	1
Total of all salts of acidic drugs	19

Paulekuhn teaches that "[s]alt formation is a well-known technique to modify and optimize the physical chemical properties of an ionizable research and development compound[, where] [p]roperties such as solubility, dissolution rate, hygroscopicity, stability, impurity profiles and crystal habit can be influenced by using a variety of pharmaceutically acceptable counterions." Paulekuhn, 6665 (also noting that "formation of salts is almost the only chemical technique available to change aqueous solubility and dissolution rate without changing the API molecule")

According to Paulekuhn, "[a]mong the cations used to form API salts of acidic molecules, the sodium ion strongly dominates with an incidence of 75.3% over the entire period. From 1982 to 1991, the fraction of sodium salts was more than 90%. This decreased to 62.5% during the 2002-2006 period." *Id.* at 6667.

Wells teaches, "A major improvement in solubility can be achieved by forming a salt." Wells at 116.

In discussing potential pharmaceutical salts to be used for the salt forms of drugs, Wells provides Table 8.4, which presents such salts, including sodium, , along with the pKa of each salt forming cation:

Table 8.4 Potential pharmaceutical salts

Basic drugs			Acidic drugs		
Anion	pK_a	% Usage	Cation	pK_a	% Usage
Hydrochloride	−6.10	43.0	Potassium	16.00	10.8
Sulphate	−3.00, +1.96	7.5	Sodium	14.77	62.0
Mesylate	−1.20	2.0	Lithium	13.82	1.6
Maleate	1.92, 6.23	3.0	Calcium	12.90	10.5
Phosphate	2.15, 7.20, 12.38	3.2	Magnesium	11.42	1.3
Salicylate	3.00	0.9	Diethanolamine	9.65	1.0
Tartrate	3.00	3.5	Zinc	8.96	3.0
Lactate	3.10	0.8	Choline	8.90	0.3
Citrate	3.13, 4.76, 6.40	3.0	Aluminium	5.00	0.7
Succinate	4.21, 5.64	0.4			
Acetate	4.76	1.3			
Others		31.4	Others		8.8

Bastin encourages the "[s]election of an appropriate salt form for a new chemical entity" because it "provides the pharmaceutical chemist and formulation scientist with the opportunity to modify the characteristics of the potential drug substance and to permit the development of dosage forms with good bioavailability, stability, manufacturability, and patient compliance." Bastin, 427.

Brittain teaches, "Prudent drug development programs will identify the preferred crystalline form early in development, with a polymorph/salt group working in close conjunction with process chemists to make the thermodynamically preferred polymorphic form the initial kilogram-scale batch." Brittain, 358.

The Triumeq Label discloses the ingredients of Triumeq as including the sodium salt form of dolutegravir, stating, "Each film-coated tablet contains abacavir sulfate equivalent to 600 mg of abacavir, dolutegravir sodium equivalent to 50 mg of dolutegravir, and 300 mg of lamivudine." Triumeq Label, 17.

	The Triumeq label teaches, "TRIUMEQ, a combination of dolutegravir (integrase strand transfer inhibitor [INSTI]), abacavir, and lamivudine (both nucleoside analogue reverse transcriptase inhibitors) is indicated for the treatment of HIV-1 infection." Triumeq Label, 1. The Triumeq Assessment discloses, "Triumeq is presented as film-coated tablets containing a fixed combination of dolutegravir sodium equivalent to 50 mg dolutegravir, 600 mg of abacavir (as sulfate) and 300 mg of lamivudine." Triumeq Assessment, 6. The Triumeq Assessment teaches, "A once-daily fixed-dose combination (FDC) single tablet regimen (STR) that combines the integrase inhibitor (INI) dolutegravir (DTG) with the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir sulfate (abacavir, ABC) and lamivudine (3TC) was developed for use in the treatment of human immunodeficiency virus (HIV) infection." Triumeq Assessment, 6. WO '116 is specifically directed to BIC sodium (Formula II) and a crystalline form thereof (Form I), along with pharmaceutical formulations and therapeutic uses therefore. WO '116, [0002], [0006]-[0008], [0043]-[0057] (describing crystalline forms of Formula II).; *see also* Section IV.A of the narrative (discussing the disclosure of the family member '342 and '067 patents). 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). 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]. *See also* Weller; Castagna; Juday; Lunzen; Walmsley; Johns; PR; Mathais; Min; Highleyman; Acosta; BICANDA01157927; NCT02607956-1; NCT02607856-2; Abebe; Shende; Poster #416; Poster # 414; Poster #413.
25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof,	US '332 discloses that "[i]n a preferred embodiment the pharmaceutical composition of the present invention comprises 50 mg dolutegravir, 50 mg dolutegravir, about 200 mg emtricitabine and about 25 mg tenofovir." US '332, [0092]. US '332 describes pharmaceutical combinations comprising 40 to 60 mg DLT, 150 to 250 mg FTC, and 5 to 42 mg TAF, along with pharmaceutical excipients. US '332, [0086]-[0090]. US '332 further discloses a specific combination comprising about 50 mg DLT, about 200 mg FTC and about 25 mg TAF. *Id.* at [0091]-[0092]. US '332 discloses, "Acids which are used to prepare pharmaceutically acceptable acid addition salts are preferably those which form non-toxic acid addition salts. In a particularly preferred embodiment tenofovir alafenamide is present in form of its hemifumarate or fumarate, especially its hemifumarate." US '332, [0053].

	US ’356 further discloses 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.US ’35, [0156]-[0163]. 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. US ’356, 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). US ’356 further discloses that [i]n certain embodiments, a compound disclosed herein 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. US ’356, [0177]. US ’356 refers “pharmaceutically acceptable salt” to “a salt of a compound that is pharmaceutically acceptable and that possesses (or can be converted to a form that possesses) the desired pharmacological activity of the parent compound. Examples of ‘pharmaceutically acceptable salts’ of the compounds disclosed herein include salts derived from an appropriate base, such as . . . an alkaline earth metal (for example, magnesium). . . .” US ’356, [0075]. US ’902 discloses, “a novel pharmaceutical product containing efavirenz, emitricitabine and tenofovir DF are provided as a multicomponent unitary oral dosage form.” US ’902, Abstract.

	US ’857 describes “multilayer tablets that contain rilpivirine hydrochloride, emtricitabine, and tenofivir disoproxil fumarate.” US ’857, Abstract. US ’856 discloses pharmaceutical compositions comprising TAF hemifumarate and one or more additional therapeutic agents selected from the group consisting of “HIV protease inhibiting compounds, HIV nonnucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, and CCR5 inhibitors.” *Id.* at [0010]-[0011], [0057]. WO ’846 teaches the following formulation: Formulation D: GS-7340 — 25 mg/tablet emtricitabine — 200 Microcrystalline Cellulose — 200 Lactose Monohydrate — 330 Croscarmellose Sodium — 60 Pregelatinized Starch — 50 Magnesium Stearate — 10 875 WO ’846, 13:12-24. WO ’846 discloses the following formulation:

	Formulation G — mg/tablet GS-7340 — 300 emtricitabine — 200 Hydroxypropyl Methylcellulose — 112 Lactose B.P. — 53 Pregelatinized Starch B.P. — 28 Magnesium Stearate — 7 total: — 700 WO ’846, 13:23-24. WO ’846 further discloses an exemplary formulation containing 25 mg of TAF and 200 mg FTC. WO ’846, 37:13-20. Gilead/Janssen discusses, “Phase III-ready HIV treatment that will combine Gilead’s tenofovir alafenamide (TAF) and emtricitabine, and Janssen’s rilpivirine.” Gilead/Janssen, 1. Gilead/Janssen states, “Gilead and Janssen agreed to develop and commercialize a once-daily single tablet regimen for HIV that combines darunavir with TAF, emtricitabine and a third Gilead compound, cobicistat (marketed as TYBOST®).” Gilead/Janssen, 2. Gilead/Janssen discloses that 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. WO ’323 discloses, “In further embodiments, the additional therapeutic agent is selected from one or more of: . . (3) HIV nucleoside inhibitors of reverse transcriptase selected from the group consisting of zidovudine, emtricitabine, didanosine, stavudine, zaicitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, ±-FTC, D-d4FC,

	emtricitabine, phosphazide, fozivudine tidoxil, apricitibine (AVX754), KP-1461, GS- 9131 (Gilead Sciences) and fosalvudine tidoxil (formerly HDP 99.0003); (4) HIV nucleotide inhibitors of reverse transcriptase selected from the group consisting of tenofovir, tenofovir disoproxil fumarate, tenofovir alafenarnide fumarate (Gilead Sciences), GS-7340 (Gilead Sciences), GS-9148 (Gilead Sciences), adefovir, adefovir dipivoxii, CMX-001 (Chimerix) or CMX-157 (Chimerix) . . . .” WO ’323, 38:1-2; 13-21. US ’426 states, “In further embodiments, Wnt signaling pathway inhibitor is administered in combination with one or more of the following agents: abacavir, acyclovir, acyclovir, adefovir, amantadine, amprenavir, ampligen, arbidol, atazanavir, atripla, boceprevir, cidofovir, combivir, complera, darunavir, delavirdine, didanosine, docosanol, dolutegravir, edoxudine, efavirenz, emtricitabine, enfuvirtide, entecavir, famciclovir, fomivirsen, fosamprenavir, foscarnet, fosfonet, ganciclovir, ibacitabine, imunovir, idoxuridine, imiquimod, indinavir, inosine, interferon type III, interferon type II, interferon type I, lamivudine, lopinavir, loviride, maraviroc, moroxydine, methisazone, nelfinavir, nevirapine, nexavir, oseltamivir, peginterferon alfa-2a, penciclovir, peramivir, pleconaril, podophyllotoxin, raltegravir, ribavirin, rimantadine, ritonavir, pyramidine, saquinavir, stavudine, stribild, tenofovir, tenofovir disoproxil, tenofovir alafenamide fumarate (TAF), tipranavir, trifluridine, trizivir, tromantadine, truvada, valaciclovir, valganciclovir, vicriviroc, vidarabine, viramidine, zalcitabine, zanamivir, or zidovudine, and combinations thereof.” US ’426, [0139]. US ’850 further claims, “The method of claim 1 wherein the compound that inhibits HIV replication are selected from the

	group consisting of nucleoside reverse transcriptase inhibitors (NRTIs) such as tenofovir, emtricitabine, zidovudine (AZT), lamivudine (3TC), abacavir, and tenofovir alafenamide fumarate; non-nucleotide reverse transcriptase inhibitors (NNRTIs) such as efavirenz, rilpivirine, and etravirine; integrase inhibitors such as raltegravir and elvitegravir; and protease inhibitors such as ritonavir, darunavir, atazanavir, lopinavir, and cobicistat." US '850, Claim 2. US '332 teaches, "[i]n a particularly preferred embodiment tenofovir alafenamide is present in form of its hemifumarate or fumarate, especially its hemifumarate." US '332, [0053]. US '332 claims, "Pharmaceutical combination comprising (a) dolutegravir, (b) emtricitabine and (c) tenofovir for use as a medicament, wherein the weight ratio of (a) dolutegravir and (b) emtricitabine is from 1:1 to 1:3." US '332, Claim 1. US '332 further claims, "Pharmaceutical combination for use according to any one of the preceding claims, wherein tenofovir is used in form of a prodrug of tenofovir." US '332, Claim 5. US '332 further claims, "Pharmaceutical combination for use according to claim 5, wherein the prodrug of tenofovir is tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide or hexadecyloxypropyl tenofovir." US '332, Claim 6. US '332 claims, "A kit for the treatment of a viral infection, in particular of an HIV-infection, comprising (i) 10 to 75 mg dolutegravir, (ii) 50 to 150 mg emtricitabine, (iii) 0.5 to 400 mg tenofovir or a prodrug thereof." US '332, Claim 15.

	WO ’466 claims, “[a] pharmaceutical composition comprising a self-emulsifying drug delivery system, wherein the self-emulsifying drug delivery system comprises efavirenz and one or more pharmaceutically acceptable excipient.” WO ’466, Claim 1. WO ’466 further claims, “[a] pharmaceutical composition according to any preceding claim, further comprising at least one additional active ingredient such as protease inhibitors, nucleoside reverse transcriptase inhibitors, non-nucleotide reverse transcriptase inhibitors, integrase inhibitors, or any combination thereof.” WO ’466, Claim 23. WO ’466 further claims, “[a] pharmaceutical composition according to claim 23, wherein the at least one additional active ingredient comprises emtricitabine, tenofovir disproxil fumarate, tenofovir alafanamide fumarate, lamivudine, stavudine, zidovudine, or any combination thereof.” WO ’466, Claim 24. WO ’720 discloses a combination of 200 mg FTC, 3-40 mg TAF, 50-500 mg cobicistat, 150 mg elvitegravir. WO ’720, [0028]. The ’791 patent discloses tenofovir alafenamide (TAF) as a compound of structure (6), having the chemical name 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino] phenoxyphosphinyl]methoxy]propyl]adenine, also designated as GS-7340.

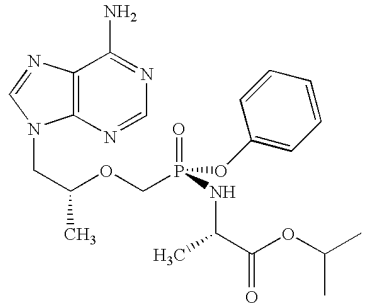
	(6)  ’791 patent, 4:13-32. Example 4 of the ’791 patent describes a method for the preparation of tenofovir alafenamide monofumarate (TAF monofumarate) from the compound GS-7340. The detailed procedure involves the crystallization of TAF monofumarate from acetonitrile. ’791 patent, 24:14-16, 24:38-48; *see also* 21:50-66 (preparation of TAF monofumarate (1:1) salts from a mixture of TAF (GS7340) and its diastereomer (GS-7339). Table 1 of the ’791 patent discloses that GS-7340 exhibits greater activity and stability compared to tenofovir disoproxil fumarate (TDF) and tenofovir. ’791 patent at 28:5-15. The ’791 patent also teaches that the TAF compounds disclosed therein may be “formulated into compositions containing pharmaceutically acceptable excipients, [which] are used in effective doses in the therapy or prophylaxis of viral (particularly HIV or hepadnaviral) infections.” ’791 patent, 4:54-59, 14:42-53. ’791 patent discloses TAF showing 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. ’791 patent, 27:29-28:37. ’791 patent further discloses the following tables:

TABLE 1

In Vitro Aetivity and Stability

	HIV-1		Stability T ½ (min)		
	Aetivity $IC_{50\,\mu M}$	Cytotoxicity $CC_{50\,\mu M}$	Human Plasma	MT-2 Cell Extract	(P/MT-2)
GS 7340	0,005	>40	90,0	28.3	3.2
TDF	0.05	70	0.41	70.7	0.006
Tenofovir	5	6000	—	—	—

TABLE 2

PMPA Metabolites in Plasma, PBMCs and RBCs After 1 h Incubation of PMPA Prodrugs or PMPA in Human Blood.

Compound	Matrix	Total C-14 Recovered, µg-eq	Metabolites (% of Total Peak Area)					
			PMPA %	PMPAp, %	PMPApp, %	Met. X, %	Met. Y, %	GS 7340, %
GS-7340	Plasma/FP	43.0	1	—	—	2	13	84
(60 µg-eq)	PBMC	1.25	45	16	21	18	—	—
	RBC/FP	12.6	8	—	—	24	11	57
			PMPA	PMPAp	PMPApp	Mono-POC	GS-4331	
GS-4331	Plasma/FP	48.1	11	—	—	89	—	
(TDF)	PBMC	0.133	50	25	18	7	—	
(60 µg-eq)	RBC/FP	10.5	93	7.0	—	—	—	
			PMPA	PMPAp	PMPApp			
PMPA	Plasma/FP	55.7	100	—	—			
(60 µg-eq)	PBMC	0.033	86	14	—			
	RBC/FP	3.72	74	10	16			

’791 patent, Tables 1-2.

Lee discloses that “[t]he amidate prodrug GS 7340 was designed to overcome the permeability limitations of tenofovir by masking the dianion with a neutral promoiety and increasing the plasma stability of the prodrug relative to its intracellular stability. The in vitro anti-HIV potency of GS 7340 (EC_{50}=0.005 µM) is comparable to the most potent protease inhibitors and reflects the greater cell permeation of GS 7340 compared to tenofovir. In addition to favorable potency and a long intracellular half-life, the *in vivo* administration of GS 7340 results in an enhanced

	distribution of lymphatic tissue compared to tenofovir DF." Lee at 1903. Lee further discloses that "[w]ith GS 7340, it should be possible to reduce the total dose of tenofovir, thereby minimizing systemic exposure, while at the same time increasing antiviral activity." *Id*. at 1905. Lee discloses TAF as 10 times more potent than TDF toward HIV-1, with eight times improved selectivity index. Lee, 1900 (Table 1). Lee further discloses, "the high concentrations of tenofovir observed in lymphatic tissues after oral administration of GS 7340 are expected to result in increased clinical potency relative to tenofovir DF." Lee, 1905 Lee further discloses that "[w]ith GS-7340, it should be possible to reduce the total dose of tenofovir, thereby minimizing systemic exposure, while at the same time increasing antiviral activity." Lee, 1905. US '856 discloses are pharmaceutical compositions comprising TAF hemifumarate and one or more additional therapeutic agents selected from the group consisting of "HIV protease inhibiting compounds, HIV nonnucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, and CCR5 inhibitors." *Id.* at [0010]-[0011], [0057]. HIV Guidelines states that "[a]n antiretroviral regimen for a treatment-naive patient generally consists of two nucleoside 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." HIV Guidelines, D-1. HIV Guidelines further recommends combination of the INSTIs elvitegravir and raltegravir with tenofovir and emtricitabine. HIV Guidelines, 1, i. British HIV Guidelines describes tenofovir and emtricitabine as the preferred NRTI backbone for HIV therapy, to be combined with an additional agent such as an INSTI. British HIV Guidelines, 13. NCT '694 discloses a study that "evaluate[s] the efficacy, safety and tolerability of GS-9883 + emtricitabine/tenofovir alafenamide (FTC/TAF) fixed dose combination (FDC) versus dolutegravir (DTG) + FTC/TAF in HIV-1 Infected, antiretroviral treatment-naive adults. This study will also evaluate the pharmacokinetic (PK) profile of GS-9883, FTC and TAF." NCT '694, Study Description. NCT '694 further discloses an "active comparator" with "Drug: FTC/TAF, Emtricitabine/Tenofovir Alafenamide (FTC/TAF) 200 mg/25 mg tablet administered orally; Drug: DTG, Dolutegravir (DTG) 50 mg tablet administered orally." NCT '694, Arms and Interventions. Tivicay Assessment discloses combination therapies with DLT sodium, FTC and tenofovir disoproxil for treating HIV. Tivicay Assessment, 43, 50-51, 89. 2013 Tivicay Label also discloses Tivicay containing 50 mg of dolutegravir sodium as an HIV INSTI indicated in combination with other antiretroviral agents (e.g., emtricitabine/tenfovoir

	(TRUVADA), for the treatment of HIV-1 infection. 2013 Tivicay Label, 1, 4, 24. Truvada Label discloses combining 200 mg emtricitabine, 300 mg tenofovir alafenamide, and 600 mg efavirenz. Truvada Label. Complera Label discloses a tablet composition for oral administration that contains 200 mg of NRTI emtricitabine, and 300 mg of NRTI tenofovir DF, and 27.5 mg of NNRTI rilpivirine hydrochloride. Complera Label, 1, 22 The Stribild Label states that a Stribild table consists of "150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 300 mg of tenofovir disoproxil fumarate." Stribild Label, 1; *see also id.* at 22-23. The Genvoya Label states, "Each GENVOYA tablet contains 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (TAF) (equivalent to 11.2 mg of tenofovir alafenamide fumarate)." Genvoya Label, 4. 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. Genvoya Assessment, 74-75. The Genvoya Assessment teaches, "The overall goal of Genvoya film coated tablet development was to create a tablet containing

	the same amounts of elvitegravir, cobicistat and emtricitabine active substances as currently combined in Stribild fixed dose combination film-coated tablet and to replace tenofovir disoproxil contained in Stribild with tenofovir alafenamide, a second-generation prodrug of tenofovir." Genvoya Assessment, 18. Genvoya Assessment discloses film-coated tablets containing the following active substances: 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (as 11.2 mg of the fumarate)." Genvoya Assessment, 10. WO '351 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." WO '351, 19:3-12. Ruane discloses that "HIV-1 RNA responses for the 8-mg TAF treatment group were similar to that of the 300-mg TDF group. However, median $DAVG_{11}$ [(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, 451-52

	Ruane further states that "[c]ompared 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." Ruane, 454. Sax teaches that "Relative to TDF, TAF is more stable in plasma." Sax, 53. Astuti refers to tenofovir alafenamide (TAF), where "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." Astuti, 11. Astuti further discloses that the "possibility to use small doses of TAF instead of TDF could further widen the STR options as bulky molecules such as PIs could be successfully coformulated." Astuti, 11. Llibre teaches that 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. Llibre, 172. WO '799 teaches, In addition, the compounds of the present invention may be used in combination with one or more other agents useful in the prevention or treatment of HIV. Examples of such agents include:

	Nucleotide reverse transcriptase inhibitors such as zidovudine, didanosine, lamivudine, zalcitabine, abacavir, stavudine, adefovir, adefovir dipivoxil, fozivudine, todoxil, emtricitabine, alovudine, amdoxovir, elvucitabine, tenofovir disoproxil fumarate, dexelvucitabine, festinavir, racivir, and similar agents; Non-nucleotide reverse transcriptase inhibitors (including an agent having anti- oxidation activity such as immunocal, oltipraz, etc.) such as nevirapine, delavirdine, efavirenz, loviride, immunocal, oltipraz, capravirine, lersivirine, doravirine, rilpivirine, etravirine, tenofovir alafenamide fumarate, and similar agents; Protease inhibitors such as saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, fosamprenavir, brecanavir, darunavir, atazanavir, tipranavir, palinavir, lasinavir, and similar agents; Entry, attachment and fusion inhibitors such as enfuvirtide (T -20), T - 1249, PRO -542, PRO - 140, ibalizumab, cenicriviroc, INCB -9471, monomeric DAPTA, AMD -070, ibalizumab, BMS- 806, fostemsavir, temsavir, and 5 -Helix and similar agents; Integrase strand transfer inhibitors such as raltegravir, elvitegravir, dolutegravir, cabotegravir, GS - 9883, and similar agents; Maturation inhibitors such as PA -344, PA - 457, BMS - 955176, as well as those disclosed in PCT Patent Application No. WO2011/100308, PCT Patent Application No. PCT/US2012/024288, Chinese PCT Application No. PCT/CN2011/001302, Chinese PCT Application No. PCT/CN2011/001303, Chinese PCT Application No. PCT/CN2011/002105, PCT/CN2011 /002159, WO2013/090664, WO2013/123019 , WO 2013/043778, WO 2014/123889, WO 2011/153315,

	WO2011/153319, WO2012/106188, WO 2012/106190, WO 2013/169578, and WO 2014/13081, and similar agents; CXCR4 and /or CCR5 inhibitors such as vicriviroc, TAK779, maraviroc, TAK449, as well as those disclosed in WO 02/74769, PCT/US03/39644, PCT/US03/39975, PCT/US03/39619, PCT/USO3/39618, PCT/US03/39740, and PCT/US03/39732, and similar agents. Neutralizing antibodies such as VRC01, VRC0710e8, pro140, PGT121, PGT128, PGT145, PG9, 3BNC117, ibalizumab, N6 and similar agents. WO '799, [0356]-[0365]. 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. WO '116 at [0096]. 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. 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. *See also* Weller; Castagna; Juday; Lunzen; Walmsley; Johns; PR; Mathais; Min; Highleyman; Acosta; BICANDA01157927; NCT02607956-1; NCT02607856-2; Abebe; Shende; Poster #416; Poster # 414; Poster #413.
and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof.	US '332 discloses that "[i]n a preferred embodiment the pharmaceutical composition of the present invention comprises 50 mg dolutegravir, 50 mg dolutegravir, about 200 mg emtricitabine and about 25 mg tenofovir." US '332, [0092]. US '332 describes pharmaceutical combinations comprising 40 to 60 mg DLT, 150 to 250 mg FTC, and 5 to 42 mg TAF, along with pharmaceutical excipients. US '332, [0086]-[0090]. US '332 further discloses a specific combination comprising about 50 mg DLT, about 200 mg FTC and about 25 mg TAF. *Id.* at [0091]-[0092]. US '332 claims, "Pharmaceutical combination comprising (a) dolutegravir, (b) emtricitabine and (c) tenofovir for use as a medicament, wherein the weight ratio of (a) dolutegravir and (b) emtricitabine is from 1:1 to 1:3." US '332, Claim 1. US'332 further discloses that "[i]n a preferred embodiment emtricitabine is present in the form of its free base, i.e. not in the form of an acid addition salt." US '332, [0032]. US '332 claims, "A kit for the treatment of a viral infection, in particular of an HIV-infection, comprising (i) 10 to 75 mg dolutegravir, (ii) 50 to 150 mg emtricitabine, (iii) 0.5 to 400 mg tenofovir or a prodrug thereof." US '332, Claim 15.

	US ’356 further discloses 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.US ’35, [0156]-[0163]. 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. US ’356, 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). US ’356 further discloses that [i]n certain embodiments, a compound disclosed herein 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. US ’356, [0177]. US ’902 discloses, “a novel pharmaceutical product containing efavirenz, emitricitabine and tenofovir DF are provided as a multicomponent unitary oral dosage form.” US ’902, Abstract. US ’857 describes “multilayer tablets that contain rilpivirine hydrochloride, emtricitabine, and tenofivir disoproxil fumarate.” US ’857, Abstract. WO ’846 discloses therapeutic combinations of TAF and FTC for treating HIV. WO ’846, 3:13-18. WO ’846 teaches the following formulation:

	Formulation D: mg/tablet GS-7340 25 emtricitabine 200 Microcrystalline Cellulose 200 Lactose Monohydrate 330 Croscarmellose Sodium 60 Pregelatinized Starch 50 Magnesium Stearate 10 875 WO '846, 13:12-24. WO '846 discloses the following formulation: Formulation G mg/tablet GS-7340 300 emtricitabine 200 Hydroxypropyl Methylcellulose 112 Lactose B.P. 53 Pregelatinized Starch B.P. 28 Magnesium Stearate 7 total: 700 WO '846, 13:23-24. WO '846 further discloses an exemplary formulation containing 25 mg of TAF and 200 mg FTC. WO '846, 37:13-20. Gilead/Janssen discusses, "Phase III-ready HIV treatment that will combine Gilead's tenofovir alafenamide (TAF) and emtricitabine, and Janssen's rilpivirine." Gilead/Janssen, 1. Gilead/Janssen states, "Gilead and Janssen agreed to develop and commercialize a once-daily single tablet regimen for HIV that

	combines darunavir with TAF, emtricitabine and a third Gilead compound, cobicistat (marketed as TYBOST®).” Gilead/Janssen, 2. WO ’323 discloses, “In further embodiments, the additional therapeutic agent is selected from one or more of: . . (3) HIV nucleoside inhibitors of reverse transcriptase selected from the group consisting of zidovudine, emtricitabine, didanosine, stavudine, zaicitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, ±-FTC, D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, apricitibine (AVX754), KP-1461, GS- 9131 (Gilead Sciences) and fosalvudine tidoxil (formerly HDP 99.0003); (4) HIV nucleotide inhibitors of reverse transcriptase selected from the group consisting of tenofovir, tenofovir disoproxil fumarate, tenofovir alafenarnide fumarate (Gilead Sciences), GS-7340 (Gilead Sciences), GS-9148 (Gilead Sciences), adefovir, adefovir dipivoxii, CMX-001 (Chimerix) or CMX-157 (Chimerix) . . . .” WO ’323, 38:1-2; 13-21. US ’332 claims, “Pharmaceutical combination comprising (a) dolutegravir, (b) emtricitabine and (c) tenofovir for use as a medicament, wherein the weight ratio of (a) dolutegravir and (b) emtricitabine is from 1:1 to 1:3.” US ’332, Claim 1. US ’332 claims, “A kit for the treatment of a viral infection, in particular of an HIV-infection, comprising (i) 10 to 75 mg dolutegravir, (ii) 50 to 150 mg emtricitabine, (iii) 0.5 to 400 mg tenofovir or a prodrug thereof.” US ’332, Claim 15. HIV Guidelines further recommends combination of the INSTIs elvitegravir and raltegravir with tenofovir and emtricitabine. HIV Guidelines, 1, i.

	HIV Guidelines states that "[a]n antiretroviral regimen for a treatment-naive patient generally consists of two nucleoside 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." HIV Guidelines, D-1. British HIV Guidelines describes tenofovir and emtricitabine as the preferred NRTI backbone for HIV therapy, to be combined with an additional agent such as an INSTI. British HIV Guidelines, 13. NCT '694 discloses a study that "evaluate[s] the efficacy, safety and tolerability of GS-9883 + emtricitabine/tenofovir alafenamide (FTC/TAF) fixed dose combination (FDC) versus dolutegravir (DTG) + FTC/TAF in HIV-1 Infected, antiretroviral treatment-naive adults. This study will also evaluate the pharmacokinetic (PK) profile of GS-9883, FTC and TAF." NCT '694, Study Description. NCT '694 further discloses an "active comparator" with "Drug: FTC/TAF, Emtricitabine/Tenofovir Alafenamide (FTC/TAF) 200 mg/25 mg tablet administered orally; Drug: DTG, Dolutegravir (DTG) 50 mg tablet administered orally." NCT '694, Arms and Interventions. Tivicay Assessment discloses the product Tivicay® as containing 50 mg of DLT sodium. Tivicay Assessment, 9. Tivicay Assessment identifies 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." *Id.* It further discloses combination therapies with DLT sodium, FTC and tenofovir disoproxil for treating HIV. *Id.* at 43, 50-51, 89. 2013 Tivicay Label also discloses Tivicay containing 50 mg of dolutegravir sodium as an HIV INSTI indicated in combination with other antiretroviral agents (e.g., emtricitabine/tenfovoir (TRUVADA), for the treatment of HIV-1 infection. 2013 Tivicay Label, 1, 4, 24. Truvada Label discloses combining 200 mg emtricitabine, 300 mg tenofovir alafenamide, and 600 mg efavirenz. Truvada Label. Complera Label discloses a tablet composition for oral administration that contains 200 mg of NRTI emtricitabine, and 300 mg of NRTI tenofovir DF, and 27.5 mg of NNRTI rilpivirine hydrochloride. Complera Label, 1, 22 The Stribild Label describes Stribild as "a combination of 1 integrase strand transfer inhibitor, 1 pharmacokinetic enhancer, and 2 nucleos(t)ide analog HIV-1 reverse transcriptase inhibitors, is indicated as a complete regimen for the treatment of HIV-1 infection in adults who are antiretroviral treatment-naïve." Stribild Label, 1. The Stribild Label states that a Stribild table consists of "150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 300 mg of tenofovir disoproxil fumarate." Stribild Label, 1; *see also id.* at 22-23.

	The Stribild Assessment describes Stribild as "a fixed drug combination tablet containing three ARVs (FTC/TDF and elvitegravir [EVG; an INSTI]) plus a new pharmacoenhancer cobicistat (COBI), which modifies the PK profile of EVG." Stribild Assessment, 10. The Genvoya Label states, "Each GENVOYA tablet contains 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (TAF) (equivalent to 11.2 mg of tenofovir alafenamide fumarate)." Genvoya Label, 4. Genvoya Assessment discloses film-coated tablets containing the following active substances: 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (as 11.2 mg of the fumarate)." Genvoya Assessment, 10. WO '351 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." WO '351, 19:3-12. WO '720 discloses a combination of 200 mg FTC, 3-40 mg TAF, 50-500 mg cobicistat, 150 mg elvitegravir. WO '720, [0028].

	WO ’466 claims, “[a] pharmaceutical composition comprising a self-emulsifying drug delivery system, wherein the self-emulsifying drug delivery system comprises efavirenz and one or more pharmaceutically acceptable excipient.” WO ’466, Claim 1. WO ’466 further claims, “[a] pharmaceutical composition according to any preceding claim, further comprising at least one additional active ingredient such as protease inhibitors, nucleoside reverse transcriptase inhibitors, non-nucleotide reverse transcriptase inhibitors, integrase inhibitors, or any combination thereof.” WO ’466, Claim 23. WO ’466 further claims, “[a] pharmaceutical composition according to claim 23, wherein the at least one additional active ingredient comprises emtricitabine, tenofovir disproxil fumarate, tenofovir alafanamide fumarate, lamivudine, stavudine, zidovudine, or any combination thereof.” WO ’466, Claim 24. The Atripla Label teaches, “Each tablet contains 600 mg of efavirenz, 200 mg of emtricitabine, and 300 mg of tenofovir DF (which is equivalent to 245 mg of tenofovir disoproxil) as active ingredients.” Atripla Label, 1. US ’902 discloses, “a novel pharmaceutical product containing efavirenz, emitricitabine and tenofovir DF are provided as a multicomponent unitary oral dosage form.” US ’902, Abstract. US ’902 further discloses bilayer tablets similar to Atripla containing 200 mg FTC. US ’902, [0050]-[0052]. The Complera Label describes the recommended dose as “[o]ne tablet (containing 200 mg of emtricitabine, 25 mg of rilpivirine,

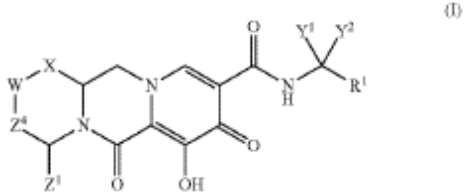
	and 300 mg of tenofovir disoproxil fumarate) taken once daily with a meal." Complera Label, 1. US '857 describes "multilayer tablets that contain rilpivirine hydrochloride, emtricitabine, and tenofivir disoproxil fumarate." US '857, Abstract. US '857 further discloses bilayer tablets similar to Complera/Eviplera containing 200 mg FTC. US '857 [0066]-[0073]. WO '799 teaches, In addition, the compounds of the present invention may be used in combination with one or more other agents useful in the prevention or treatment of HIV. Examples of such agents include: Nucleotide reverse transcriptase inhibitors such as zidovudine, didanosine , lamivudine , zalcitabine , abacavir, stavudine , adefovir, adefovir dipivoxil, fozivudine, todoxil, emtricitabine , alovudine, amdoxovir, elvucitabine , tenofovir disoproxil fumarate , dexelvucitabine , festinavir, racivir, and similar agents; Non-nucleotide reverse transcriptase inhibitors (including an agent having anti- oxidation activity such as immunocal, oltipraz, etc .) such as nevirapine, delavirdine, efavirenz, loviride , immunocal, oltipraz , capravirine , lersivirine, doravirine, rilpivirine , etravirine, tenofovir alafenamide fumarate , and similar agents; Protease inhibitors such as saquinavir, ritonavir, indinavir, nelfinavir , amprenavir , fosamprenavir, brecanavir, darunavir , atazanavir, tipranavir , palinavir , lasinavir, and similar agents ;

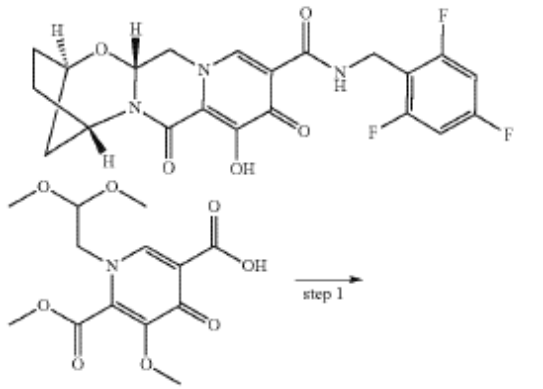
	Entry, attachment and fusion inhibitors such as enfuvirtide (T -20), T - 1249, PRO -542, PRO - 140, ibalizumab, cenicriviroc , INCB -9471, monomeric DAPTA, AMD -070, ibalizumab, BMS- 806, fostemsavir, temsavir, and 5 -Helix and similar agents; Integrase strand transfer inhibitors such as raltegravir, elvitegravir, dolutegravir, cabotegravir, GS - 9883, and similar agents; Maturation inhibitors such as PA -344, PA - 457, BMS - 955176, as well as those disclosed in PCT Patent Application No. WO2011/100308, PCT Patent Application No. PCT/US2012/024288, Chinese PCT Application No. PCT/CN2011/001302, Chinese PCT Application No. PCT/CN2011/001303, Chinese PCT Application No. PCT/CN2011/002105, PCT/CN2011 /002159, WO2013/090664, WO2013/123019 , WO 2013/043778, WO 2014/123889, WO 2011/153315, WO2011/153319, WO2012/106188, WO 2012/106190, WO 2013/169578, and WO 2014/13081, and similar agents; CXCR4 and /or CCR5 inhibitors such as vicriviroc, TAK779, maraviroc, TAK449, as well as those disclosed in WO 02/74769, PCT/US03/39644, PCT/US03/39975, PCT/US03/39619, PCT/USO3/39618, PCT/US03/39740, and PCT/US03/39732, and similar agents. Neutralizing antibodies such as VRC01, VRC0710e8, pro140, PGT121, PGT128, PGT145, PG9, 3BNC117, ibalizumab, N6 and similar agents. WO ’799, [0356]-[0365]. US ’426 states, “In further embodiments, Wnt signaling pathway inhibitor is administered in combination with one or more of the following agents: abacavir, acyclovir, acyclovir, adefovir,

	amantadine, amprenavir, ampligen, arbidol, atazanavir, atripla, boceprevir, cidofovir, combivir, complera, darunavir, delavirdine, didanosine, docosanol, dolutegravir, edoxudine, efavirenz, emtricitabine, enfuvirtide, entecavir, famciclovir, fomivirsen, fosamprenavir, foscarnet, fosfonet, ganciclovir, ibacitabine, imunovir, idoxuridine, imiquimod, indinavir, inosine, interferon type III, interferon type II, interferon type I, lamivudine, lopinavir, loviride, maraviroc, moroxydine, methisazone, nelfinavir, nevirapine, nexavir, oseltamivir, peginterferon alfa-2a, penciclovir, peramivir, pleconaril, podophyllotoxin, raltegravir, ribavirin, rimantadine, ritonavir, pyramidine, saquinavir, stavudine, stribild, tenofovir, tenofovir disoproxil, tenofovir alafenamide fumarate (TAF), tipranavir, trifluridine, trizivir, tromantadine, truvada, valaciclovir, valganciclovir, vicriviroc, vidarabine, viramidine, zalcitabine, zanamivir, or zidovudine, and combinations thereof." US '426, [0139]. US '850 claims, "A method of preventing or delaying a rise in viral load following cessation of treatment of human immunodeficiency virus (HIV) infection, the method comprising: administering to a subject infected with HIV at least three compounds collectively having the following activities: dampening of immune activation, wherein the dampening selectively affects the CD4 T cell response relative to the CD8 T cell response, inhibition of HIV replication, stimulation of reactivation of latent HIV, and inhibition of infection of CD4 T cells by HIV, wherein the compound that inhibits HIV infection of CD4 T cells is selected from the group consisting of C-C chemokine receptor type 5 (CCR5) inhibitors, C-X-X chemokine receptor type 4 (CXCR4) inhibitors, CD4 inhibitors, gp120 inhibitors, and gp41 inhibitors, wherein the compounds are provided in dosages reducing the number of cells infected with

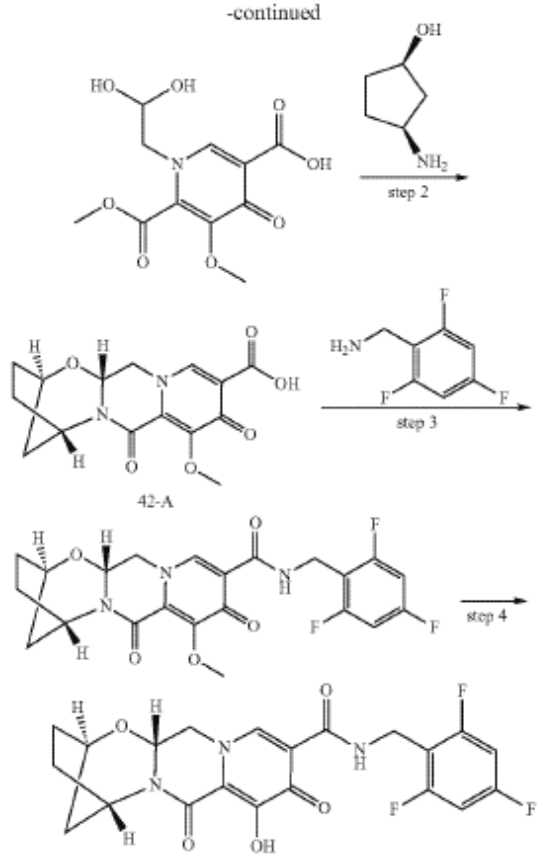
	HIV or the viral load of HIV, relative to which is achieved using just the combination of ART and compounds which activate latent HIV, wherein HIV infected cells or HIV viral load is not detectable at 12 months after the end of the course of treatment." US '850, Claim 1. US '850 further claims, "The method of claim 1 wherein the compound that inhibits HIV replication are selected from the group consisting of nucleoside reverse transcriptase inhibitors (NRTIs) such as tenofovir, emtricitabine, zidovudine (AZT), lamivudine (3TC), abacavir, and tenofovir alafenamide fumarate; non-nucleotide reverse transcriptase inhibitors (NNRTIs) such as efavirenz, rilpivirine, and etravirine; integrase inhibitors such as raltegravir and elvitegravir; and protease inhibitors such as ritonavir, darunavir, atazanavir, lopinavir, and cobicistat." US '850, Claim 2. 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. WO '116 at [0096]. 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. 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. *See also* Weller; Castagna; Juday; Lunzen; Walmsley; Johns; PR; Mathais; Min; Highleyman; Acosta; BICANDA01157927; NCT02607956-1; NCT02607856-2; Abebe; Shende; Poster #416; Poster # 414; Poster #413.

Claim 2	
Claim Elements	Prior Art Teachings of Claim Elements
The tablet of claim 1,	The prior art teachings disclosing the tablet of claim 1 are set forth above and incorporated herein by reference.
wherein the tablet comprises 50 mg of the compound of Formula I as a pharmaceutically acceptable salt thereof.	US '356 discloses "[c]ompounds for use in the treatment of human immunodeficiency virus (HIV) infection . . . hav[ing] the following Formula (I):  (I) including stereoisomers and pharmaceutically acceptable salts thereof, wherein R^1, X, W, Y^1, Y^2 , Z^1, and Z^4 are as defined herein. Methods associated with preparation and use of such compounds, as well as pharmaceutical compositions comprising such compounds, are also disclosed." US '356, Abstract, [0089]. US '356 further discloses "polycyclic carbamoylpyridone compounds, having antiviral activity, . . . and the use of such compounds in the treatment of HIV infections. The compounds

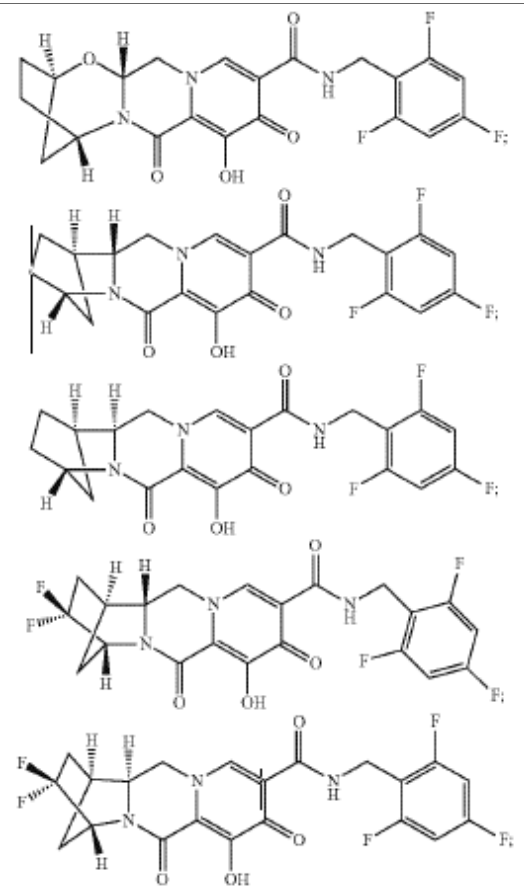
	of the invention may be used to inhibit the activity of HIV integrase and may be used to reduce HIV replication." US '356, [0010]. US '356 further discloses approximately 100 HIV INSTI compounds of Formula (I) and methods for their synthesis, including a Compound 42 corresponding to bictegravir (BIC): 42 

-continued



US ’356, [0312]-[0316] (Example 42).

US ’356 further discloses 7 HIV INSTIs of Formula I, including bictegravir:

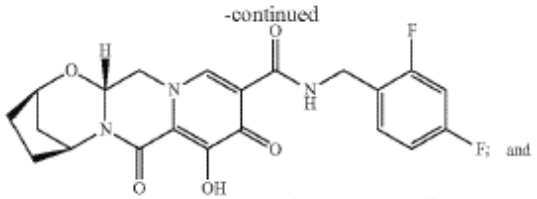
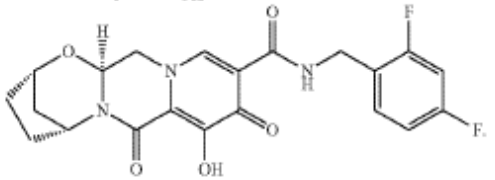
	-continued  F; and  US ’356, claim 32. US ’356 further discloses a tablet showing that BIC (compound 42) provided nanomolar activity (EC50 = 2.5 nm) in an antiviral assay in MT4 cells infected with HIV. “Compounds of the present invention demonstrate antiviral activity in this assay as depicted in Table 1 below. Accordingly, the compounds of the invention may be useful for treating the proliferation of the HIV virus, treating AIDS, or delaying the onset of AIDS or ARC symptoms.” US ’356, [0589]-[0592] (Example 104; see Table 1). US ’356 further discloses Example 107, “Pharmacokinetic analysis Following Oral or Intravenous Administration to Beagle Dogs.” US ’356, [0599]-[0603]. US ’356 provided the second highest oral bioavailability (F (%)), Cmax and AUC of the eleven Formula (I) compounds tested:

TABLE 4

Compound #	CL (L/h/kg)	V_{ss} (L/kg)	MRT (h)	F (%) aqueous suspension	C_{max} (μM) aqueous suspension	AUC (μM * h) aqueous suspension
98	0.047	0.16	3.3	n/a	n/a	n/a
83	0.161	0.38	2.4	n/a	n/a	n/a
55	0.058	0.24	4.2	n/a	n/a	n/a
77	0.300	0.64	2.2	n/a	n/a	n/a
41	0.015	0.11	7.5	10.7	2.4	16.3
42	0.020	0.15	7.1	28.0	4.5	28.6
47	0.014	0.10	7.4	12.6	2.8	20.4
8	0.498	0.87	1.8	n/a	n/a	n/a
7	0.510	1.20	2.3	n/a	n/a	n/a
3	0.047	0.23	4.9	18.7	1.2	9.2
2	0.030	0.20	6.5	40.7	7.8	66.1

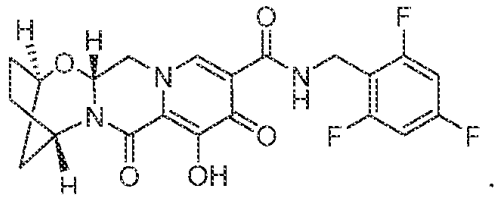
US '356, Example 107; see Table 4.

US '356 further discloses "[p]harmaceutical compositions . . . includ[ing] a compound of Formula (I) and one or more of: a pharmaceutically acceptable carrier, diluent or excipient. . . . In certain embodiments, a compound of Formula (I) is present in the pharmaceutical composition in an amount from about 25 mg to about 500 mg. In certain embodiments, a compound of Formula (I) is present in the pharmaceutical composition in an amount of about 100 mg to about 300 mg. In certain embodiments, a compound of Formula (I) is present in the pharmaceutical composition in an amount of about 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg or about 500 mg." US '356, [0152].

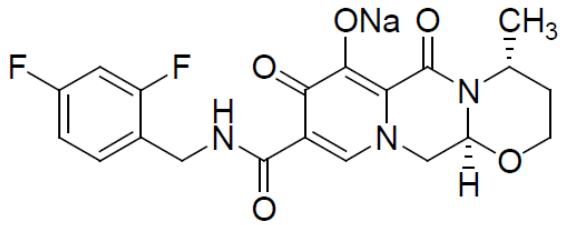
US '356 refers "pharmaceutically acceptable salt" to "a salt of a compound that is pharmaceutically acceptable and that possesses (or can be converted to a form that possesses) the desired pharmacological activity of the parent compound. Examples of 'pharmaceutically acceptable salts' of the compounds disclosed herein include salts derived from an appropriate base, such as . . . an alkaline earth metal (for example, magnesium). . . ." US '356, [0075].

	US ’356 states that “[t]he compounds of the invention, or their pharmaceutically acceptable salts, are administered in a therapeutically effective amount.” US ’356, [0155]. US ’356 further states that “a therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to their own know ledge, the state of the art, and this disclosure.” US ’356, [0081]. US ’356 discloses that these pharmaceutical compositions containing a therapeutically effective amount of a compound of Formula (I) are disclosed “for use in the therapeutic treatment of an HIV infection is provided.” US ’356, [0147]-[0149]. US ’356 states that “[a]dministration of the compounds of the invention, or their pharmaceutically acceptable salts, in pure form or in an appropriate pharmaceutical composition, is carried out via any of the accepted modes of administration of agents for serving similar utilities.” US ’356, [0153]-[0154] US ’356 also claims “[a] pharmaceutical composition comprising a compound of any one of claims 1-32, or a stereoisomer or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.” US ’356, claim 33. US ’356 further claims, “[a] method of treating an HIV infection in a human having or at risk of having the infection by administering to the human a therapeutically effective amount of a compound of any one of claims 1-32 or a pharmaceutical composition of claim 33.” US ’356, claim 37.

	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]. US ’356 also discloses combination therapy “for treating or preventing an HIV infection in a human having or at risk of having the infection.” US ’356, [0156]. US ’356 further discloses 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.US ’356, [0156]-[0163]. US ’356 also discloses an embodiment wherein pharmaceutical compositions comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with one or more additional therapeutic agents, and a pharmaceutically acceptable carrier, diluent or excipient are provided. US ’356, [0156]-[0179]. US ’356 further discloses that [i]n certain embodiments, a compound disclosed herein 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. US ’356, [0177]. US ’332 describes pharmaceutical combinations comprising 40 to 60 mg DLT, 150 to 250 mg FTC, and 5 to 42 mg TAF, along

	with pharmaceutical excipients. US '332, [0086]-[0090]. US '332 further discloses that "[i]n a preferred embodiment the pharmaceutical composition of the present invention comprises 50 mg dolutegravir, 50 mg dolutegravir, about 200 mg emtricitabine and about 25 mg tenofovir." *Id.* at [0091]-[0092]. HIV Guidelines states that "[a]n antiretroviral regimen for a treatment-naive patient generally consists of two nucleoside 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." HIV Guidelines, D-1. 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. US '356, 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). WO '323 claims, "A compound of claim 1 selected from: . .  WO '323, Claim 32. WO '323 further claims, "A pharmaceutical composition comprising a compound of any one of claims 1-32, or a

	stereoisomer or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient." WO '323, Claim 33. WO '323 discloses, "Compounds, compositions, and methods for the treatment of human immunodeficiency vims (HIV) infection are disclosed. In particular, novel poly cyclic carbamoylpyridone compounds and methods for their preparation and use as therapeutic or prophylactic agents are disclosed." WO '323, 1:12-15. WO '323 teaches, "In certain embodiments, a compound of Formula (I) is present in the pharmaceutical composition in an amount of about 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg or about 500 mg." WO '323, 35:19-23. WO '323 defines "Formula (I)" as including "the specific compounds disclosed herein[,]" which includes bictegravir. WO '323, 18-19. HIV Guidelines further recommends combination of the INSTIs elvitegravir and raltegravir with tenofovir and emtricitabine. HIV Guidelines, 1, i. British HIV Guidelines describes tenofovir and emtricitabine as the preferred NRTI backbone for HIV therapy, to be combined with an additional agent such as an INSTI. British HIV Guidelines, 13. NCT '694 discloses a study that "evaluate[s] the efficacy, safety and tolerability of GS-9883 + emtricitabine/tenofovir alafenamide (FTC/TAF) fixed dose combination (FDC) versus

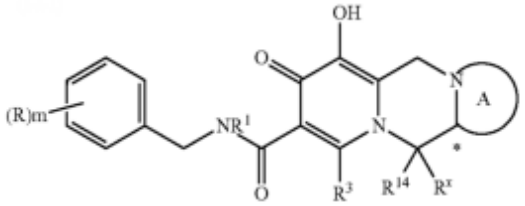
	dolutegravir (DTG) + FTC/TAF in HIV-1 Infected, antiretroviral treatment-naive adults. This study will also evaluate the pharmacokinetic (PK) profile of GS-9883, FTC and TAF." NCT '694, Study Description. NCT '694 further discloses an "active comparator" with "Drug: FTC/TAF, Emtricitabine/Tenofovir Alafenamide (FTC/TAF) 200 mg/25 mg tablet administered orally; Drug: DTG, Dolutegravir (DTG) 50 mg tablet administered orally." NCT '694, Arms and Interventions. US '332 discloses dolutegravir, which it further states is "reported to have anti-viral activity, since it is considered to be an integrase inhibitor." US '332, [0014]. US '332 further discloses, "[p]referably, dolutegravir is in the form of a pharmaceutically acceptable salt. More preferred, dolutegravir is in the form of an alkali metal salt such as sodium or potassium salt or in the form of an earth-alkali metal salt such as calcium or magnesium salt. More preferred, dolutegravir is in the form of a sodium salt or a magnesium salt. Particularly preferred, dolutegravir is used in form of the sodium salt, especially the mono-sodium salt." US '332, [0018], [0020]. The Tivicay Assessment teaches the sodium salt form of dolutegravir with the following structure: 

	Tivicay Assessment, 9. The Tivicay Assessment also discloses that "Tivicay is presented as film-coated tablet containing 50 mg of dolutegravir (As dolutegravir sodium salt) as active substance." Tivicay Assessment, 9. Tivicay Assessment identifies 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." *Id.* at 43, 50-51, It further discloses combination therapies with DLT sodium, FTC and tenofovir disoproxil for treating HIV. *Id.* at 89. The 2013 Tivicay Label teaches, "TIVICAY is a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor (INSTI) indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and children aged 12 years and older and weighing at least 40 kg." Tivicay Label, 1. The 2013 Tivicay Label also discloses Tivicay containing 50 mg of dolutegravir sodium as an HIV INSTI indicated in combination with other antiretroviral agents (e.g., emtricitabine/tenfovoir (TRUVADA), for the treatment of HIV-1 infection. 2013 Tivicay Label, 1, 4, 24. US '332 further discloses "a pharmaceutical composition comprising (a) dolutegravir, (b) emtricitabine and (c) tenofovir, wherein (a) dolutegravir and (b) emtricitabine are present in a specific weight ratio, for use as a medicament. A further subject of the present invention is a method for treating a viral infection, comprising administering to a subject in need thereof the pharmaceutical combination or composition of the present

	invention, wherein the viral infection preferably comprises an HIV-infection." US '332, [0061]. US '332 discloses that the "[i]n another particularly preferred embodiment, the combination of the present invention is administered once daily." US '332, [0077]. US '332 further discloses that "[t]he pharmaceutical composition of the present invention can be preferably a solid oral dosage form. It is further preferred that the dosage form of the invention is a capsule or a tablet, in particular a tablet." *Id.* at [0107]. US '332 describe "preferred embodiment [of] the pharmaceutical composition compris[ing] … 40 to 60 mg dolutegravir, … 250 mg emtricitabine, … and 5 to 42 mg tenofovir; and pharmaceutical excipients." US '332, [0086]-[0090]. US '332 further discloses that "[i]n a preferred embodiment the pharmaceutical composition of the present invention comprises 50 mg dolutegravir, 50 mg dolutegravir, about 200 mg emtricitabine and about 25 mg tenofovir." US '332, [0092]. US '332 also discloses the total amount of dolutegravir, emtricitabine and tenofovir alafenamide comprised in the present pharmaceutical combination for use as a medicament is between 70.5 and425 mg per day, in particular 192 to 326 mg per day." US '332, [0075]. Genvoya Label discloses a tablet composition for oral administration that contains 150 mg of the INSTI elvitegravir (EVG), 150 mg of PK enhancer cobicistat (COBI), 200 mg of NRTI emtricitabine (FTC), and 11.2 mg of NRTI tenofovir alafenamide (TAF) fumarate (equivalent to 10 mg TAF)). Genvoya, 22.

	Genvoya Assessment discloses film-coated tablets containing the following active substances: 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (as 11.2 mg of the fumarate)." Genvoya Assessment, 10. Genvoya Assessment further 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. Genvoya Assessment, 74-75. WO '846 discloses therapeutic combinations of TAF and FTC for treating HIV. WO '846, 3:13-18. WO '846 further discloses that combination can additionally include an INSTI. WO '846, 18:23-26. WO '846 further discloses an exemplary formulation containing 25 mg of TAF and 200 mg FTC. WO '846, 37:13-20. WO '846 discloses a pharmaceutical composition comprising "(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. Stribild Label discloses a tablet composition for oral administration that contains a combination of 150 mg of the integrase strand transfer inhibitor elvitegravir, 200 mg and 300 mg respectively of the nucleos(t)ide analog HIV-1 reverse transcriptase inhibitors emtricitabine and tenofovir disoproxil

	fumarate, and 150 mg of the pharmacokinetic enhancer cobicistat. Stribild Label, 1. US '122 discloses a solid dose form (e.g. tablets) comprising a compound of Formula I (i.e. elvitegravir), Formula III (i.e. emtricitabine), Formula IV (i.e. tenofovir disoproxil fumarate), 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. Compound of Formula II 150 mg Formulation Components / % 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. *Id.* at [0022]. US '122 further discloses examples of tablets similar to Stribild. *Id.* at [0063]-[0065] (Examples 2-4).

	The ’385 patent discloses 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. ’385 patent, 8:9-34. 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. ’385 patent, Abstract, 7:32-35, 38:6-9.

	The ’385 patent discloses, “[t]he present invention relates to novel compounds possessing an antiviral activity, in detail polycyclic carbamoylpyridone derivatives possessing an inhibitory activity against HIV integrase and a pharmaceutical composition containing the same, especially an anti-HIV agent.” ’385 patent, 1:15-20. 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. 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. 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. WO '351 further discloses that 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." WO '351, 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." WO '351, 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." WO '351, 16:15-18. WO '351 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." WO '351, 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." WO '351, 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." WO '351, 17:27-28, 23:6-8. The Stribild Assessment discloses, "Stribild is presented for use as a bilayer tablet – one layer contains EVG/COBI and one FTC/TDF." Stribild Assessment, 33. The Atripla Assessment teaches, "The granulations are blended separately with extra-granular magnesium stearate, compressed into bilayer tablets, and then film-coated. Process optimization studies were conducted in order to establish critical process parameters for the wet granulation of efavirenz, dry granulation of emtricitabine/tenofovir, bilayer tablet compression, and aqueous film-coating operations." Atripla Assessment, 5.

The Genvoya Assessment states, “GS-US-292-0101 was an open-label crossover study that compared two formulations (monolayer and bilayer) of E/C/F/TAF (each containing either 25 or 40 mg TAF as the monofumarate) with Stribild and with TAF 25 mg alone.” Genvoya Assessment, 75.

The Eviplera Assessment teaches, “The exposure of FTC/RPV/TDF after single oral administration of a bilayer formulation and the individual compounds was compared in fasted dogs and has demonstrated comparable systemic exposure to all compounds.” Eviplera Assessment, 18.

US ’857 discloses “a tablet of the invention wherein the first layer comprises:

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

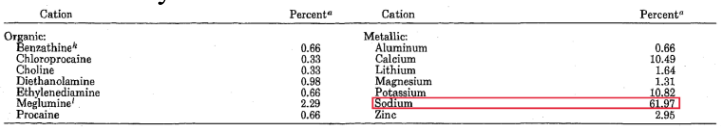
and the second layer comprises:

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

US ’857, [0066]. US ’857 further discloses bilayer tablets for keeping rilpivirine separate from FTC and TDF. *Id.* at [0067]-[0071].

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, 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]. US '079 also discloses that 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. 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. Havele discloses that TDF showed complete degradation occurred immediately after addition of at room temperature). Havele, 3, 5. Venkatasan discloses that TDF undergoes 31% decomposition under basic stress conditions. Venkatasan, 4. Kurmi discloses that in a basic solution environment (0.5 N NaOH), TDF was completely converted into degradation product

	T1 in 3 h. Kurmi, 96121. Kurmi further discloses that under basic solid state stress conditions, TDF degraded into several different products. *Id.* at 96121-25. Berge teaches "[t]he chemical, biological, physical and economic characteristics of medicinal agents can be manipulated and, hence, often optimized by conversion to a salt form," where "salt-forming agents are often chosen empirically … [and] the preferred form is selected by pharmaceutical chemists on a practical basis: cost of raw materials, ease of crystallization, and percent yield … [as well as] stability, hygroscopicity, and flowability of the resulting bulk drug." Berge at 1. Berge also teaches Table 1 as a list of "FDA-approved commercially marketed salts" that includes sodium:  Remington 21st teaches in Table 38-5 that sodium salts were an API-salt form known since at least 1983:

Cation	Percent[a]	Cation	Percent[a]
Organic:		Metallic:	
Benzathine[k]	0.66	Aluminum	0.66
Chloroprocaine	0.33	Calcium	10.49
Choline	0.33	Lithium	1.64
Diethanolamine	0.98	Magnesium	1.31
Ethylenediamine	0.66	Potassium	10.82
Meglumine[l]	2.29	Sodium	61.97
Procaine	0.66	Zinc	2.95

Table 38-5. Molecular Forms Marketed Worldwide Between 1983 and 1996

SALT FORM	FREQ.	GROUP[a]	pK_A	CLOGP	MW
No salt form	390	0			
Hydrobromide	1	1	−8	0.45	80.91
Hydrochloride	102	1	−6.1	0.24	36.46
Sulfate	5	1	−3	−1.58	98.08
Nitrate	6	1	−1.44	2.09	63.01
Phosphate	2	1	2.15	−1.95	96.99
Glucuronate	1	1	3.22[b]	−3.74	194.14
Acetate	8	1	4.76	−0.36	59.05
Maleate	3	2	1.92	−0.18	116.07
Fumarate	8	2	3.02	−0.18	116.07
Tartrate	1	2	3.03	−2.21	150.09
Citrate	1	2	3.13	−2.11	189.10
Succinate	2	2	4.21	−0.62	118.09
Mesylate	8	3	−1.20	−1.31	96.11
Acistrate	1	3	4.91[b]	7.98	284.49
Besylate	2	4	−2.80[b]	0.23	157.17
Tosylate	3	4	−1.34	0.88	171.20
Xinafoate	1	4	2.66[b]	3.00	188.18
Potassium	1	1	16		39.10
Sodium	37	1	14.77		23.00
Tromethamine	2	1	8.07[c]	−3.17	121.14
Bismuth	1	1	1.58		208.98
Bromide	6	5			79.90
Chloride	2	5			35.45

[a] Groups: 0 = No salt, 1 = Polar, 2 = Multifunctional, 3 = Flexible aliphatics, 4 = Planar aromatics, 5 = Quartenary.
[b] Calculated pK_a.
[c] Data from *CRC Handbook of Basic Tables for Chemical Analysis*, page 469.
From Serajuddin ATM, Sheen P, Augustine MA. To market, to market. In: Bristol J, ed. *Annu Rep Med Chem.* New York: Academic, 1983–1996.

Serajuddin teaches that "[s]alt formation is the most common and effective method of increasing solubility of acidic and basic drugs." Serajuddin at 603.

Serajuddin also teaches that "[s]alt formation is also the most common approach of increasing solubility, dissolution rate and ultimately bioavailability of poorly water-soluble ionizable drugs in solid dosage forms." Serajuddin at 614.

Serajuddin further informs that "Table 2 gives the distribution of 120 salts approved by the FDA during the 12-year period from 1995 to 2006, where the hydrochloride salt is the predominant salt form among the basic drugs and the sodium salt is the predominant form for acidic drugs." Serajuddin at 613. The portion of Table 2 that shows salts of acidic drugs shows:

Salts of acidic drugs	Total number
Sodium	12
Calcium	4
Potassium	2
Tromethamine	1
Total of all salts of acidic drugs	19

Paulekuhn teaches that "[s]alt formation is a well-known technique to modify and optimize the physical chemical properties of an ionizable research and development compound[, where] [p]roperties such as solubility, dissolution rate, hygroscopicity, stability, impurity profiles and crystal habit can be influenced by using a variety of pharmaceutically acceptable counterions." Paulekuhn, 6665 (also noting that "formation of salts is almost the only chemical technique available to change aqueous solubility and dissolution rate without changing the API molecule")

According to Paulekuhn, "[a]mong the cations used to form API salts of acidic molecules, the sodium ion strongly dominates with an incidence of 75.3% over the entire period. From 1982 to 1991, the fraction of sodium salts was more than 90%. This decreased to 62.5% during the 2002-2006 period." *Id.* at 6667.

Wells teaches, "A major improvement in solubility can be achieved by forming a salt." Wells at 116.

In discussing potential pharmaceutical salts to be used for the salt forms of drugs, Wells provides Table 8.4, which presents such salts, including sodium, , along with the pKa of each salt forming cation:

Table 8.4 Potential pharmaceutical salts

Basic drugs			Acidic drugs		
Anion	pK_a	% Usage	Cation	pK_a	% Usage
Hydrochloride	−6.10	43.0	Potassium	16.00	10.8
Sulphate	−3.00, +1.96	7.5	Sodium	14.77	62.0
Mesylate	−1.20	2.0	Lithium	13.82	1.6
Maleate	1.92, 6.23	3.0	Calcium	12.90	10.5
Phosphate	2.15, 7.20, 12.38	3.2	Magnesium	11.42	1.3
Salicylate	3.00	0.9	Diethanolamine	9.65	1.0
Tartrate	3.00	3.5	Zinc	8.96	3.0
Lactate	3.10	0.8	Choline	8.90	0.3
Citrate	3.13, 4.76, 6.40	3.0	Aluminium	5.00	0.7
Succinate	4.21, 5.64	0.4			
Acetate	4.76	1.3			
Others		31.4	Others		8.8

Bastin encourages the "[s]election of an appropriate salt form for a new chemical entity" because it "provides the pharmaceutical chemist and formulation scientist with the opportunity to modify the characteristics of the potential drug substance and to permit the development of dosage forms with good bioavailability, stability, manufacturability, and patient compliance." Bastin, 427.

Brittain teaches, "Prudent drug development programs will identify the preferred crystalline form early in development, with a polymorph/salt group working in close conjunction with process chemists to make the thermodynamically preferred polymorphic form the initial kilogram-scale batch." Brittain, 358.

The Triumeq Label discloses the ingredients of Triumeq as including the sodium salt form of dolutegravir, stating, "Each film-coated tablet contains abacavir sulfate equivalent to 600 mg of abacavir, dolutegravir sodium equivalent to 50 mg of dolutegravir, and 300 mg of lamivudine." Triumeq Label, 17.

	The Triumeq label teaches, "TRIUMEQ, a combination of dolutegravir (integrase strand transfer inhibitor [INSTI]), abacavir, and lamivudine (both nucleoside analogue reverse transcriptase inhibitors) is indicated for the treatment of HIV-1 infection." Triumeq Label, 1. The Triumeq Assessment discloses, "Triumeq is presented as film-coated tablets containing a fixed combination of dolutegravir sodium equivalent to 50 mg dolutegravir, 600 mg of abacavir (as sulfate) and 300 mg of lamivudine." Triumeq Assessment, 6. The Triumeq Assessment teaches, "A once-daily fixed-dose combination (FDC) single tablet regimen (STR) that combines the integrase inhibitor (INI) dolutegravir (DTG) with the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir sulfate (abacavir, ABC) and lamivudine (3TC) was developed for use in the treatment of human immunodeficiency virus (HIV) infection." Triumeq Assessment, 6. WO '116 is specifically directed to BIC sodium (Formula II) and a crystalline form thereof (Form I), along with pharmaceutical formulations and therapeutic uses therefore. WO '116, [0002], [0006]-[0008], [0043]-[0057] (describing crystalline forms of Formula II).; *see also* Section IV.A of the narrative (discussing the disclosure of the family member '342 and '067 patents). 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). 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]. *See also* Weller; Castagna; Juday; Lunzen; Walmsley; Johns; PR; Mathais; Min; Highleyman; Acosta; BICANDA01157927; NCT02607956-1; NCT02607856-2; Abebe; Shende; Poster #416; Poster # 414; Poster #413.

Claim 3	
Claim Elements	Prior Art Teachings of Claim Elements
The tablet of claim 1,	The prior art teachings disclosing the tablet of claim 1 are set forth above and incorporated herein by reference.
wherein the tablet comprises 25 mg tenofovir alafenamide as a pharmaceutically acceptable salt thereof.	US '332 discloses that "[i]n a preferred embodiment the pharmaceutical composition of the present invention comprises 50 mg dolutegravir, 50 mg dolutegravir, about 200 mg emtricitabine and about 25 mg tenofovir." US '332, [0092]. US '332 describes pharmaceutical combinations comprising 40 to 60 mg DLT, 150 to 250 mg FTC, and 5 to 42 mg TAF, along with pharmaceutical excipients. US '332, [0086]-[0090]. US '332 further discloses a specific combination comprising about 50 mg DLT, about 200 mg FTC and about 25 mg TAF. *Id.* at [0091]-[0092]. US '332 discloses, "Acids which are used to prepare pharmaceutically acceptable acid addition salts are preferably

	those which form non-toxic acid addition salts. In a particularly preferred embodiment tenofovir alafenamide is present in form of its hemifumarate or fumarate, especially its hemifumarate." US '332, [0053]. US '356 further discloses 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.US '35, [0156]-[0163]. 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. US '356, 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). US '356 further discloses that [i]n certain embodiments, a compound disclosed herein 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. US '356, [0177]. US '356 refers "pharmaceutically acceptable salt" to "a salt of a compound that is pharmaceutically acceptable and that possesses (or can be converted to a form that possesses) the desired pharmacological activity of the parent compound. Examples of 'pharmaceutically acceptable salts' of the compounds disclosed herein include salts derived from an appropriate base, such as . . . an alkaline earth metal (for example, magnesium). . . ." US '356, [0075].

US ’902 discloses, “a novel pharmaceutical product containing efavirenz, emitricitabine and tenofovir DF are provided as a multicomponent unitary oral dosage form.” US ’902, Abstract.

US ’857 describes “multilayer tablets that contain rilpivirine hydrochloride, emtricitabine, and tenofivir disoproxil fumarate.” US ’857, Abstract.

US ’856 discloses pharmaceutical compositions comprising TAF hemifumarate and one or more additional therapeutic agents selected from the group consisting of “HIV protease inhibiting compounds, HIV nonnucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, and CCR5 inhibitors.” *Id.* at [0010]-[0011], [0057].

WO ’846 teaches the following formulation:

Formulation D:		mg/tablet
	GS-7340	25
	emtricitabine	200
	Microcrystalline Cellulose	200
	Lactose Monohydrate	330
	Croscarmellose Sodium	60
	Pregelatinized Starch	50
	Magnesium Stearate	10
		875

WO ’846, 13:12-24.

WO ’846 discloses the following formulation:

	Formulation G — mg/tablet GS-7340 — 300 emtricitabine — 200 Hydroxypropyl Methylcellulose — 112 Lactose B.P. — 53 Pregelatinized Starch B.P. — 28 Magnesium Stearate — 7 total: — 700 WO ’846, 13:23-24. WO ’846 further discloses an exemplary formulation containing 25 mg of TAF and 200 mg FTC. WO ’846, 37:13-20. Gilead/Janssen discusses, “Phase III-ready HIV treatment that will combine Gilead’s tenofovir alafenamide (TAF) and emtricitabine, and Janssen’s rilpivirine.” Gilead/Janssen, 1. Gilead/Janssen states, “Gilead and Janssen agreed to develop and commercialize a once-daily single tablet regimen for HIV that combines darunavir with TAF, emtricitabine and a third Gilead compound, cobicistat (marketed as TYBOST®).” Gilead/Janssen, 2. Gilead/Janssen discloses that 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. WO ’323 discloses, “In further embodiments, the additional therapeutic agent is selected from one or more of: . . (3) HIV nucleoside inhibitors of reverse transcriptase selected from the group consisting of zidovudine, emtricitabine, didanosine, stavudine, zaicitabine, lamivudine, abacavir, amdoxovir,

	elvucitabine, alovudine, MIV-210, ±-FTC, D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, apricitibine (AVX754), KP-1461, GS- 9131 (Gilead Sciences) and fosalvudine tidoxil (formerly HDP 99.0003); (4) HIV nucleotide inhibitors of reverse transcriptase selected from the group consisting of tenofovir, tenofovir disoproxil fumarate, tenofovir alafenarnide fumarate (Gilead Sciences), GS-7340 (Gilead Sciences), GS-9148 (Gilead Sciences), adefovir, adefovir dipivoxii, CMX-001 (Chimerix) or CMX-157 (Chimerix) . . . .” WO ’323, 38:1-2; 13-21. US ’426 states, “In further embodiments, Wnt signaling pathway inhibitor is administered in combination with one or more of the following agents: abacavir, acyclovir, acyclovir, adefovir, amantadine, amprenavir, ampligen, arbidol, atazanavir, atripla, boceprevir, cidofovir, combivir, complera, darunavir, delavirdine, didanosine, docosanol, dolutegravir, edoxudine, efavirenz, emtricitabine, enfuvirtide, entecavir, famciclovir, fomivirsen, fosamprenavir, foscarnet, fosfonet, ganciclovir, ibacitabine, imunovir, idoxuridine, imiquimod, indinavir, inosine, interferon type III, interferon type II, interferon type I, lamivudine, lopinavir, loviride, maraviroc, moroxydine, methisazone, nelfinavir, nevirapine, nexavir, oseltamivir, peginterferon alfa-2a, penciclovir, peramivir, pleconaril, podophyllotoxin, raltegravir, ribavirin, rimantadine, ritonavir, pyramidine, saquinavir, stavudine, stribild, tenofovir, tenofovir disoproxil, tenofovir alafenamide fumarate (TAF), tipranavir, trifluridine, trizivir, tromantadine, truvada, valaciclovir, valganciclovir, vicriviroc, vidarabine, viramidine, zalcitabine, zanamivir, or zidovudine, and combinations thereof.” US ’426, [0139].

	US ’850 further claims, “The method of claim 1 wherein the compound that inhibits HIV replication are selected from the group consisting of nucleoside reverse transcriptase inhibitors (NRTIs) such as tenofovir, emtricitabine, zidovudine (AZT), lamivudine (3TC), abacavir, and tenofovir alafenamide fumarate; non-nucleotide reverse transcriptase inhibitors (NNRTIs) such as efavirenz, rilpivirine, and etravirine; integrase inhibitors such as raltegravir and elvitegravir; and protease inhibitors such as ritonavir, darunavir, atazanavir, lopinavir, and cobicistat.” US ’850, Claim 2. US ’332 teaches, “[i]n a particularly preferred embodiment tenofovir alafenamide is present in form of its hemifumarate or fumarate, especially its hemifumarate.” US ’332, [0053]. US ’332 claims, “Pharmaceutical combination comprising (a) dolutegravir, (b) emtricitabine and (c) tenofovir for use as a medicament, wherein the weight ratio of (a) dolutegravir and (b) emtricitabine is from 1:1 to 1:3.” US ’332, Claim 1. US ’332 further claims, “Pharmaceutical combination for use according to any one of the preceding claims, wherein tenofovir is used in form of a prodrug of tenofovir.” US ’332, Claim 5. US ’332 further claims, “Pharmaceutical combination for use according to claim 5, wherein the prodrug of tenofovir is tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide or hexadecyloxypropyl tenofovir.” US ’332, Claim 6. US ’332 claims, “A kit for the treatment of a viral infection, in particular of an HIV-infection, comprising (i) 10 to 75 mg

	dolutegravir, (ii) 50 to 150 mg emtricitabine, (iii) 0.5 to 400 mg tenofovir or a prodrug thereof." US '332, Claim 15. WO '466 claims, "[a] pharmaceutical composition comprising a self-emulsifying drug delivery system, wherein the self-emulsifying drug delivery system comprises efavirenz and one or more pharmaceutically acceptable excipient." WO '466, Claim 1. WO '466 further claims, "[a] pharmaceutical composition according to any preceding claim, further comprising at least one additional active ingredient such as protease inhibitors, nucleoside reverse transcriptase inhibitors, non-nucleotide reverse transcriptase inhibitors, integrase inhibitors, or any combination thereof." WO '466, Claim 23. WO '466 further claims, "[a] pharmaceutical composition according to claim 23, wherein the at least one additional active ingredient comprises emtricitabine, tenofovir disproxil fumarate, tenofovir alafanamide fumarate, lamivudine, stavudine, zidovudine, or any combination thereof." WO '466, Claim 24. WO '720 discloses a combination of 200 mg FTC, 3-40 mg TAF, 50-500 mg cobicistat, 150 mg elvitegravir. WO '720, [0028]. The '791 patent discloses tenofovir alafenamide (TAF) as a compound of structure (6), having the chemical name 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino] phenoxyphosphinyl]methoxy]propyl]adenine, also designated as GS-7340.

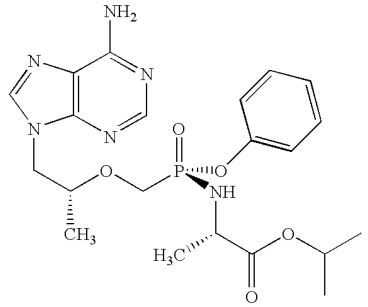
	(6)  ’791 patent, 4:13-32. Example 4 of the ’791 patent describes a method for the preparation of tenofovir alafenamide monofumarate (TAF monofumarate) from the compound GS-7340. The detailed procedure involves the crystallization of TAF monofumarate from acetonitrile. ’791 patent, 24:14-16, 24:38-48; *see also* 21:50-66 (preparation of TAF monofumarate (1:1) salts from a mixture of TAF (GS7340) and its diastereomer (GS-7339). Table 1 of the ’791 patent discloses that GS-7340 exhibits greater activity and stability compared to tenofovir disoproxil fumarate (TDF) and tenofovir. ’791 patent at 28:5-15. The ’791 patent also teaches that the TAF compounds disclosed therein may be “formulated into compositions containing pharmaceutically acceptable excipients, [which] are used in effective doses in the therapy or prophylaxis of viral (particularly HIV or hepadnaviral) infections.” ’791 patent, 4:54-59, 14:42-53. ’791 patent discloses TAF showing 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. ’791 patent, 27:29-28:37. ’791 patent further discloses the following tables:

TABLE 1

In Vitro Aetivity and Stability

	HIV-1		Stability T ½ (min)		
	Aetivity $IC_{50\,\mu M}$	Cytotoxicity $CC_{50\,\mu M}$	Human Plasma	MT-2 Cell Extract	(P/MT-2)
GS 7340	0,005	>40	90,0	28.3	3.2
TDF	0.05	70	0.41	70.7	0.006
Tenofovir	5	6000	—	—	—

TABLE 2

PMPA Metabolites in Plasma, PBMCs and RBCs After 1 h Incubation of PMPA Prodrugs or PMPA in Human Blood.

Compound	Matrix	Total C-14 Recovered, µg-eq	Metabolites (% of Total Peak Area)					
			PMPA %	PMPAp, %	PMPApp, %	Met. X, %	Met. Y, %	GS 7340, %
GS-7340	Plasma/FP	43.0	1	—	—	2	13	84
(60 µg-eq)	PBMC	1.25	45	16	21	18	—	—
	RBC/FP	12.6	8	—	—	24	11	57
			PMPA	PMPAp	PMPApp	Mono-POC	GS-4331	
GS-4331	Plasma/FP	48.1	11	—	—	89	—	
(TDF)	PBMC	0.133	50	25	18	7	—	
(60 µg-eq)	RBC/FP	10.5	93	7.0	—	—	—	
			PMPA	PMPAp	PMPApp			
PMPA	Plasma/FP	55.7	100	—	—			
(60 µg-eq)	PBMC	0.033	86	14	—			
	RBC/FP	3.72	74	10	16			

’791 patent, Tables 1-2.

Lee discloses that “[t]he amidate prodrug GS 7340 was designed to overcome the permeability limitations of tenofovir by masking the dianion with a neutral promoiety and increasing the plasma stability of the prodrug relative to its intracellular stability. The in vitro anti-HIV potency of GS 7340 (EC_{50}=0.005 µM) is comparable to the most potent protease inhibitors and reflects the greater cell permeation of GS 7340 compared to tenofovir. In addition to favorable potency and a long intracellular half-life, the *in vivo* administration of GS 7340 results in an enhanced

	distribution of lymphatic tissue compared to tenofovir DF." Lee at 1903. Lee further discloses that "[w]ith GS 7340, it should be possible to reduce the total dose of tenofovir, thereby minimizing systemic exposure, while at the same time increasing antiviral activity." *Id*. at 1905. Lee discloses TAF as 10 times more potent than TDF toward HIV-1, with eight times improved selectivity index. Lee, 1900 (Table 1). Lee further discloses, "the high concentrations of tenofovir observed in lymphatic tissues after oral administration of GS 7340 are expected to result in increased clinical potency relative to tenofovir DF." Lee, 1905 Lee further discloses that "[w]ith GS-7340, it should be possible to reduce the total dose of tenofovir, thereby minimizing systemic exposure, while at the same time increasing antiviral activity." Lee, 1905. US '856 discloses are pharmaceutical compositions comprising TAF hemifumarate and one or more additional therapeutic agents selected from the group consisting of "HIV protease inhibiting compounds, HIV nonnucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, and CCR5 inhibitors." *Id.* at [0010]-[0011], [0057]. HIV Guidelines states that "[a]n antiretroviral regimen for a treatment-naive patient generally consists of two nucleoside 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." HIV Guidelines, D-1. HIV Guidelines further recommends combination of the INSTIs elvitegravir and raltegravir with tenofovir and emtricitabine. HIV Guidelines, 1, i. British HIV Guidelines describes tenofovir and emtricitabine as the preferred NRTI backbone for HIV therapy, to be combined with an additional agent such as an INSTI. British HIV Guidelines, 13. NCT '694 discloses a study that "evaluate[s] the efficacy, safety and tolerability of GS-9883 + emtricitabine/tenofovir alafenamide (FTC/TAF) fixed dose combination (FDC) versus dolutegravir (DTG) + FTC/TAF in HIV-1 Infected, antiretroviral treatment-naive adults. This study will also evaluate the pharmacokinetic (PK) profile of GS-9883, FTC and TAF." NCT '694, Study Description. NCT '694 further discloses an "active comparator" with "Drug: FTC/TAF, Emtricitabine/Tenofovir Alafenamide (FTC/TAF) 200 mg/25 mg tablet administered orally; Drug: DTG, Dolutegravir (DTG) 50 mg tablet administered orally." NCT '694, Arms and Interventions. Tivicay Assessment discloses combination therapies with DLT sodium, FTC and tenofovir disoproxil for treating HIV. Tivicay Assessment, 43, 50-51, 89. 2013 Tivicay Label also discloses Tivicay containing 50 mg of dolutegravir sodium as an HIV INSTI indicated in combination with other antiretroviral agents (e.g., emtricitabine/tenfovoir

	(TRUVADA), for the treatment of HIV-1 infection. 2013 Tivicay Label, 1, 4, 24. Truvada Label discloses combining 200 mg emtricitabine, 300 mg tenofovir alafenamide, and 600 mg efavirenz. Truvada Label. Complera Label discloses a tablet composition for oral administration that contains 200 mg of NRTI emtricitabine, and 300 mg of NRTI tenofovir DF, and 27.5 mg of NNRTI rilpivirine hydrochloride. Complera Label, 1, 22 The Stribild Label states that a Stribild table consists of "150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 300 mg of tenofovir disoproxil fumarate." Stribild Label, 1; *see also id.* at 22-23. The Genvoya Label states, "Each GENVOYA tablet contains 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (TAF) (equivalent to 11.2 mg of tenofovir alafenamide fumarate)." Genvoya Label, 4. 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. Genvoya Assessment, 74-75. The Genvoya Assessment teaches, "The overall goal of Genvoya film coated tablet development was to create a tablet containing

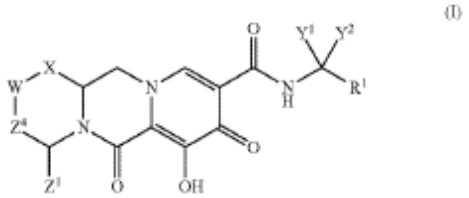
	the same amounts of elvitegravir, cobicistat and emtricitabine active substances as currently combined in Stribild fixed dose combination film-coated tablet and to replace tenofovir disoproxil contained in Stribild with tenofovir alafenamide, a second-generation prodrug of tenofovir." Genvoya Assessment, 18. Genvoya Assessment discloses film-coated tablets containing the following active substances: 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (as 11.2 mg of the fumarate)." Genvoya Assessment, 10. WO '351 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." WO '351, 19:3-12. Ruane discloses that "HIV-1 RNA responses for the 8-mg TAF treatment group were similar to that of the 300-mg TDF group. However, median $DAVG_{11}$ [(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, 451-52

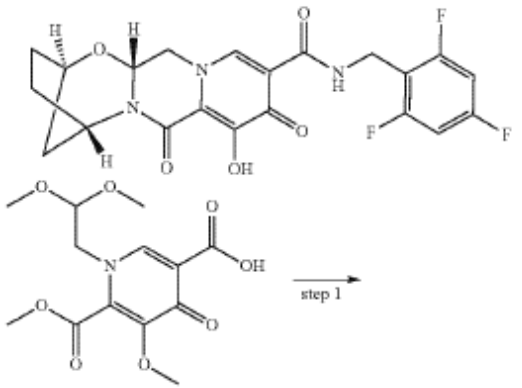
	Ruane further states that "[c]ompared with 300 mg TDF, TAF, with doses as low as 25 mg, demonstrated greater antiviral effect at less than 1/10th the dose, with an almost 90% reduction in circulating TFV." Ruane, 454. Sax teaches that "Relative to TDF, TAF is more stable in plasma." Sax, 53. Astuti refers to tenofovir alafenamide (TAF), where "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." Astuti, 11. Astuti further discloses that the "possibility to use small doses of TAF instead of TDF could further widen the STR options as bulky molecules such as PIs could be successfully coformulated." Astuti, 11. Llibre teaches that 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. Llibre, 172. WO '799 teaches, In addition, the compounds of the present invention may be used in combination with one or more other agents useful in the prevention or treatment of HIV. Examples of such agents include:

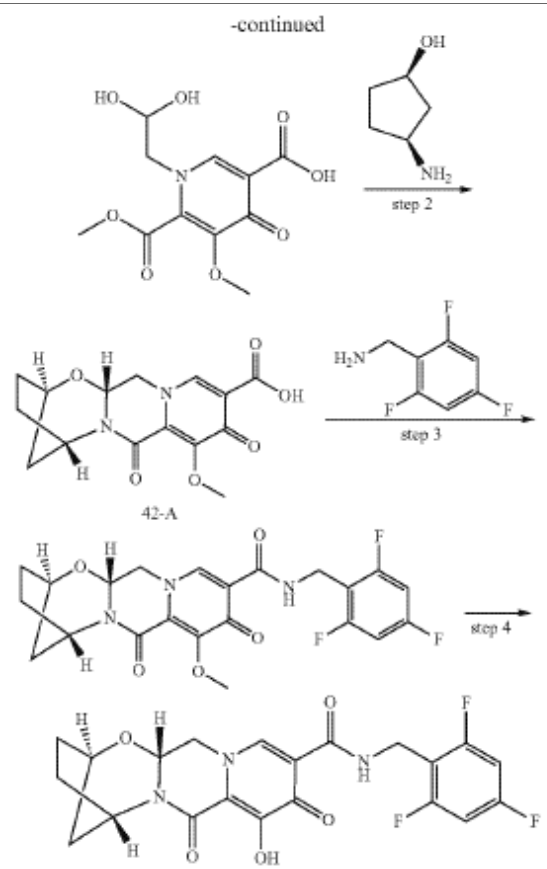
	Nucleotide reverse transcriptase inhibitors such as zidovudine, didanosine, lamivudine, zalcitabine, abacavir, stavudine, adefovir, adefovir dipivoxil, fozivudine, todoxil, emtricitabine, alovudine, amdoxovir, elvucitabine, tenofovir disoproxil fumarate, dexelvucitabine, festinavir, racivir, and similar agents; Non-nucleotide reverse transcriptase inhibitors (including an agent having anti- oxidation activity such as immunocal, oltipraz, etc.) such as nevirapine, delavirdine, efavirenz, loviride, immunocal, oltipraz, capravirine, lersivirine, doravirine, rilpivirine, etravirine, tenofovir alafenamide fumarate, and similar agents; Protease inhibitors such as saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, fosamprenavir, brecanavir, darunavir, atazanavir, tipranavir, palinavir, lasinavir, and similar agents; Entry, attachment and fusion inhibitors such as enfuvirtide (T -20), T - 1249, PRO -542, PRO - 140, ibalizumab, cenicriviroc, INCB -9471, monomeric DAPTA, AMD -070, ibalizumab, BMS- 806, fostemsavir, temsavir, and 5 -Helix and similar agents; Integrase strand transfer inhibitors such as raltegravir, elvitegravir, dolutegravir, cabotegravir, GS - 9883, and similar agents; Maturation inhibitors such as PA -344, PA - 457, BMS - 955176, as well as those disclosed in PCT Patent Application No. WO2011/100308, PCT Patent Application No. PCT/US2012/024288, Chinese PCT Application No. PCT/CN2011/001302, Chinese PCT Application No. PCT/CN2011/001303, Chinese PCT Application No. PCT/CN2011/002105, PCT/CN2011 /002159, WO2013/090664, WO2013/123019 , WO 2013/043778, WO 2014/123889, WO 2011/153315,

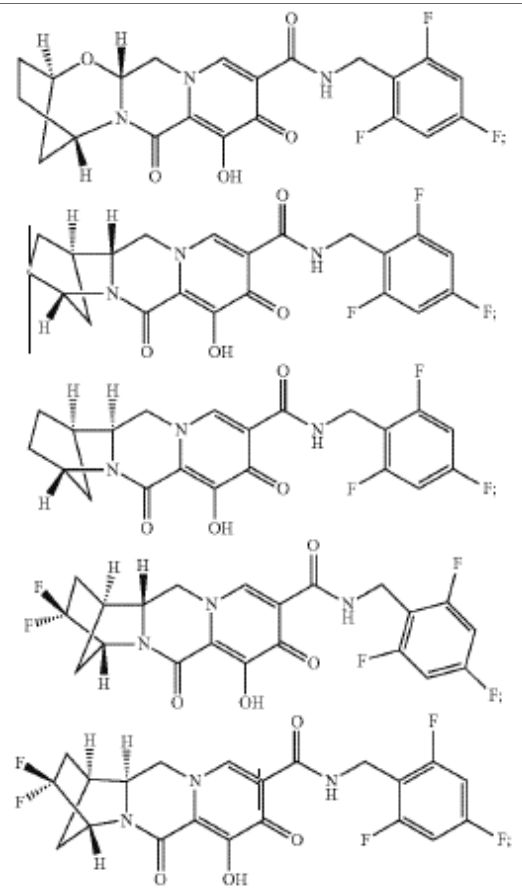
	WO2011/153319, WO2012/106188, WO 2012/106190, WO 2013/169578, and WO 2014/13081, and similar agents; CXCR4 and /or CCR5 inhibitors such as vicriviroc, TAK779, maraviroc, TAK449, as well as those disclosed in WO 02/74769, PCT/US03/39644, PCT/US03/39975, PCT/US03/39619, PCT/USO3/39618, PCT/US03/39740, and PCT/US03/39732, and similar agents. Neutralizing antibodies such as VRC01, VRC0710e8, pro140, PGT121, PGT128, PGT145, PG9, 3BNC117, ibalizumab, N6 and similar agents. WO '799, [0356]-[0365]. 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. WO '116 at [0096]. 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. 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. *See also* Weller; Castagna; Juday; Lunzen; Walmsley; Johns; PR; Mathais; Min; Highleyman; Acosta; BICANDA01157927; NCT02607956-1; NCT02607856-2; Abebe; Shende; Poster #416; Poster # 414; Poster #413.

Claim 4	
Claim Elements	Prior Art Teachings of Claim Elements
The tablet of claim 1,	The prior art teachings disclosing the tablets of any of claim 1 is set forth above and incorporated herein by reference.
wherein the tablet comprises 50 mg of the compound of Formula I as a pharmaceutically acceptable salt thereof,	US '356 discloses "[c]ompounds for use in the treatment of human immunodeficiency virus (HIV) infection . . . hav[ing] the following Formula (I):  including stereoisomers and pharmaceutically acceptable salts thereof, wherein R^1, X, W, Y^1, Y^2 , Z^1, and Z^4 are as defined herein. Methods associated with preparation and use of such compounds, as well as pharmaceutical compositions comprising such compounds, are also disclosed." US '356, Abstract, [0089]. US '356 further discloses "polycyclic carbamoylpyridone compounds, having antiviral activity, . . . and the use of such compounds in the treatment of HIV infections. The compounds of the invention may be used to inhibit the activity of HIV

	integrase and may be used to reduce HIV replication." US '356, [0010]. US '356 further discloses approximately 100 HIV INSTI compounds of Formula (I) and methods for their synthesis, including a Compound 42 corresponding to bictegravir (BIC): 42 

	-continued  US ’356, [0312]-[0316] (Example 42). US ’356 further discloses 7 HIV INSTIs of Formula I, including bictegravir:

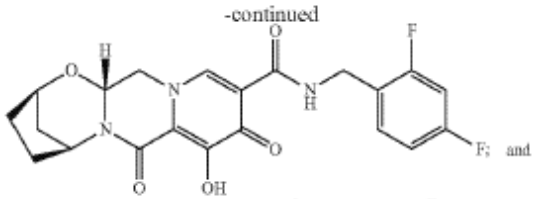
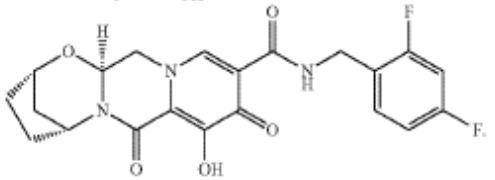
	-continued  ; and  US ’356, claim 32. US ’356 further discloses a tablet showing that BIC (compound 42) provided nanomolar activity (EC50 = 2.5 nm) in an antiviral assay in MT4 cells infected with HIV. “Compounds of the present invention demonstrate antiviral activity in this assay as depicted in Table 1 below. Accordingly, the compounds of the invention may be useful for treating the proliferation of the HIV virus, treating AIDS, or delaying the onset of AIDS or ARC symptoms.” US ’356, [0589]-[0592] (Example 104; see Table 1). US ’356 further discloses Example 107, “Pharmacokinetic analysis Following Oral or Intravenous Administration to Beagle Dogs.” US ’356, [0599]-[0603]. US ’356 provided the second highest oral bioavailability (F (%)), Cmax and AUC of the eleven Formula (I) compounds tested:

TABLE 4

Compound #	CL (L/h/kg)	V_{ss} (L/kg)	MRT (h)	F (%) aqueous suspension	C_{max} (μM) aqueous suspension	AUC (μM * h) aqueous suspension
98	0.047	0.16	3.3	n/a	n/a	n/a
83	0.161	0.38	2.4	n/a	n/a	n/a
55	0.058	0.24	4.2	n/a	n/a	n/a
77	0.300	0.64	2.2	n/a	n/a	n/a
41	0.015	0.11	7.5	10.7	2.4	16.3
42	0.020	0.15	7.1	28.0	4.5	28.6
47	0.014	0.10	7.4	12.6	2.8	20.4
8	0.498	0.87	1.8	n/a	n/a	n/a
7	0.510	1.20	2.3	n/a	n/a	n/a
3	0.047	0.23	4.9	18.7	1.2	9.2
2	0.030	0.20	6.5	40.7	7.8	66.1

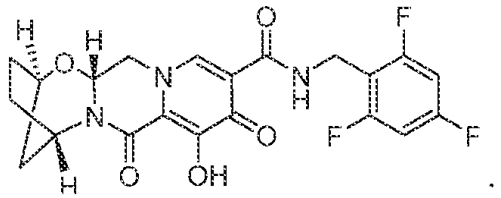
US ’356, Example 107; see Table 4.

US ’356 further discloses “[p]harmaceutical compositions . . . includ[ing] a compound of Formula (I) and one or more of: a pharmaceutically acceptable carrier, diluent or excipient. . . . In certain embodiments, a compound of Formula (I) is present in the pharmaceutical composition in an amount from about 25 mg to about 500 mg. In certain embodiments, a compound of Formula (I) is present in the pharmaceutical composition in an amount of about 100 mg to about 300 mg. In certain embodiments, a compound of Formula (I) is present in the pharmaceutical composition in an amount of about 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg or about 500 mg.” US ’356, [0152].

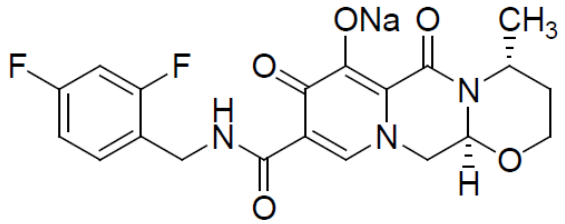
US ’356 refers “pharmaceutically acceptable salt” to “a salt of a compound that is pharmaceutically acceptable and that possesses (or can be converted to a form that possesses) the desired pharmacological activity of the parent compound. Examples of ‘pharmaceutically acceptable salts’ of the compounds disclosed herein include salts derived from an appropriate base, such as . . . an alkaline earth metal (for example, magnesium). . . .” US ’356, [0075].

	US ’356 states that “[t]he compounds of the invention, or their pharmaceutically acceptable salts, are administered in a therapeutically effective amount.” US ’356, [0155]. US ’356 further states that “a therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to their own know ledge, the state of the art, and this disclosure.” US ’356, [0081]. US ’356 discloses that these pharmaceutical compositions containing a therapeutically effective amount of a compound of Formula (I) are disclosed “for use in the therapeutic treatment of an HIV infection is provided.” US ’356, [0147]-[0149]. US ’356 states that “[a]dministration of the compounds of the invention, or their pharmaceutically acceptable salts, in pure form or in an appropriate pharmaceutical composition, is carried out via any of the accepted modes of administration of agents for serving similar utilities.” US ’356, [0153]-[0154] US ’356 also claims “[a] pharmaceutical composition comprising a compound of any one of claims 1-32, or a stereoisomer or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.” US ’356, claim 33. US ’356 further claims, “[a] method of treating an HIV infection in a human having or at risk of having the infection by administering to the human a therapeutically effective amount of a compound of any one of claims 1-32 or a pharmaceutical composition of claim 33.” US ’356, claim 37.

	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]. US ’356 also discloses combination therapy “for treating or preventing an HIV infection in a human having or at risk of having the infection.” US ’356, [0156]. US ’356 further discloses 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.US ’356, [0156]-[0163]. US ’356 also discloses an embodiment wherein pharmaceutical compositions comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with one or more additional therapeutic agents, and a pharmaceutically acceptable carrier, diluent or excipient are provided. US ’356, [0156]-[0179]. US ’356 further discloses that [i]n certain embodiments, a compound disclosed herein 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. US ’356, [0177]. US ’332 describes pharmaceutical combinations comprising 40 to 60 mg DLT, 150 to 250 mg FTC, and 5 to 42 mg TAF, along

	with pharmaceutical excipients. US '332, [0086]-[0090]. US '332 further discloses that "[i]n a preferred embodiment the pharmaceutical composition of the present invention comprises 50 mg dolutegravir, 50 mg dolutegravir, about 200 mg emtricitabine and about 25 mg tenofovir." *Id.* at [0091]-[0092]. HIV Guidelines states that "[a]n antiretroviral regimen for a treatment-naive patient generally consists of two nucleoside 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." HIV Guidelines, D-1. 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. US '356, 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). WO '323 claims, "A compound of claim 1 selected from: . .  WO '323, Claim 32. WO '323 further claims, "A pharmaceutical composition comprising a compound of any one of claims 1-32, or a

	stereoisomer or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient." WO '323, Claim 33. WO '323 discloses, "Compounds, compositions, and methods for the treatment of human immunodeficiency vims (HIV) infection are disclosed. In particular, novel poly cyclic carbamoylpyridone compounds and methods for their preparation and use as therapeutic or prophylactic agents are disclosed." WO '323, 1:12-15. WO '323 teaches, "In certain embodiments, a compound of Formula (I) is present in the pharmaceutical composition in an amount of about 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg or about 500 mg." WO '323, 35:19-23. WO '323 defines "Formula (I)" as including "the specific compounds disclosed herein[,]" which includes bictegravir. WO '323, 18-19. HIV Guidelines further recommends combination of the INSTIs elvitegravir and raltegravir with tenofovir and emtricitabine. HIV Guidelines, 1, i. British HIV Guidelines describes tenofovir and emtricitabine as the preferred NRTI backbone for HIV therapy, to be combined with an additional agent such as an INSTI. British HIV Guidelines, 13. NCT '694 discloses a study that "evaluate[s] the efficacy, safety and tolerability of GS-9883 + emtricitabine/tenofovir alafenamide (FTC/TAF) fixed dose combination (FDC) versus

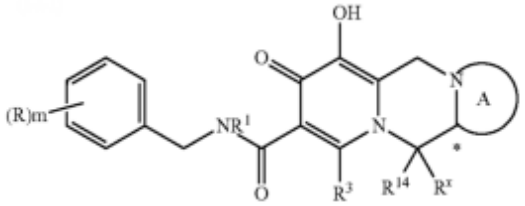
	dolutegravir (DTG) + FTC/TAF in HIV-1 Infected, antiretroviral treatment-naive adults. This study will also evaluate the pharmacokinetic (PK) profile of GS-9883, FTC and TAF." NCT '694, Study Description. NCT '694 further discloses an "active comparator" with "Drug: FTC/TAF, Emtricitabine/Tenofovir Alafenamide (FTC/TAF) 200 mg/25 mg tablet administered orally; Drug: DTG, Dolutegravir (DTG) 50 mg tablet administered orally." NCT '694, Arms and Interventions. US '332 discloses dolutegravir, which it further states is "reported to have anti-viral activity, since it is considered to be an integrase inhibitor." US '332, [0014]. US '332 further discloses, "[p]referably, dolutegravir is in the form of a pharmaceutically acceptable salt. More preferred, dolutegravir is in the form of an alkali metal salt such as sodium or potassium salt or in the form of an earth-alkali metal salt such as calcium or magnesium salt. More preferred, dolutegravir is in the form of a sodium salt or a magnesium salt. Particularly preferred, dolutegravir is used in form of the sodium salt, especially the mono-sodium salt." US '332, [0018], [0020]. The Tivicay Assessment teaches the sodium salt form of dolutegravir with the following structure: 

	Tivicay Assessment, 9. The Tivicay Assessment also discloses that "Tivicay is presented as film-coated tablet containing 50 mg of dolutegravir (As dolutegravir sodium salt) as active substance." Tivicay Assessment, 9. Tivicay Assessment identifies 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." *Id.* at 43, 50-51, It further discloses combination therapies with DLT sodium, FTC and tenofovir disoproxil for treating HIV. *Id.* at 89. The 2013 Tivicay Label teaches, "TIVICAY is a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor (INSTI) indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and children aged 12 years and older and weighing at least 40 kg." Tivicay Label, 1. The 2013 Tivicay Label also discloses Tivicay containing 50 mg of dolutegravir sodium as an HIV INSTI indicated in combination with other antiretroviral agents (e.g., emtricitabine/tenfovoir (TRUVADA), for the treatment of HIV-1 infection. 2013 Tivicay Label, 1, 4, 24. US '332 further discloses "a pharmaceutical composition comprising (a) dolutegravir, (b) emtricitabine and (c) tenofovir, wherein (a) dolutegravir and (b) emtricitabine are present in a specific weight ratio, for use as a medicament. A further subject of the present invention is a method for treating a viral infection, comprising administering to a subject in need thereof the pharmaceutical combination or composition of the present

	invention, wherein the viral infection preferably comprises an HIV-infection." US '332, [0061]. US '332 discloses that the "[i]n another particularly preferred embodiment, the combination of the present invention is administered once daily." US '332, [0077]. US '332 further discloses that "[t]he pharmaceutical composition of the present invention can be preferably a solid oral dosage form. It is further preferred that the dosage form of the invention is a capsule or a tablet, in particular a tablet." *Id.* at [0107]. US '332 describe "preferred embodiment [of] the pharmaceutical composition compris[ing] … 40 to 60 mg dolutegravir, … 250 mg emtricitabine, … and 5 to 42 mg tenofovir; and pharmaceutical excipients." US '332, [0086]-[0090]. US '332 further discloses that "[i]n a preferred embodiment the pharmaceutical composition of the present invention comprises 50 mg dolutegravir, 50 mg dolutegravir, about 200 mg emtricitabine and about 25 mg tenofovir." US '332, [0092]. US '332 also discloses the total amount of dolutegravir, emtricitabine and tenofovir alafenamide comprised in the present pharmaceutical combination for use as a medicament is between 70.5 and425 mg per day, in particular 192 to 326 mg per day." US '332, [0075]. Genvoya Label discloses a tablet composition for oral administration that contains 150 mg of the INSTI elvitegravir (EVG), 150 mg of PK enhancer cobicistat (COBI), 200 mg of NRTI emtricitabine (FTC), and 11.2 mg of NRTI tenofovir alafenamide (TAF) fumarate (equivalent to 10 mg TAF)). Genvoya, 22.

	Genvoya Assessment discloses film-coated tablets containing the following active substances: 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (as 11.2 mg of the fumarate)." Genvoya Assessment, 10. Genvoya Assessment further 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. Genvoya Assessment, 74-75. WO '846 discloses therapeutic combinations of TAF and FTC for treating HIV. WO '846, 3:13-18. WO '846 further discloses that combination can additionally include an INSTI. WO '846, 18:23-26. WO '846 further discloses an exemplary formulation containing 25 mg of TAF and 200 mg FTC. WO '846, 37:13-20. WO '846 discloses a pharmaceutical composition comprising "(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. Stribild Label discloses a tablet composition for oral administration that contains a combination of 150 mg of the integrase strand transfer inhibitor elvitegravir, 200 mg and 300 mg respectively of the nucleos(t)ide analog HIV-1 reverse transcriptase inhibitors emtricitabine and tenofovir disoproxil

	fumarate, and 150 mg of the pharmacokinetic enhancer cobicistat. Stribild Label, 1. US '122 discloses a solid dose form (e.g. tablets) comprising a compound of Formula I (i.e. elvitegravir), Formula III (i.e. emtricitabine), Formula IV (i.e. tenofovir disoproxil fumarate), 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. Compound of Formula II 150 mg Formulation Components / % 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. *Id.* at [0022]. US '122 further discloses examples of tablets similar to Stribild. *Id.* at [0063]-[0065] (Examples 2-4).

	The ’385 patent discloses 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. ’385 patent, 8:9-34. 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. ’385 patent, Abstract, 7:32-35, 38:6-9.

	The ’385 patent discloses, “[t]he present invention relates to novel compounds possessing an antiviral activity, in detail polycyclic carbamoylpyridone derivatives possessing an inhibitory activity against HIV integrase and a pharmaceutical composition containing the same, especially an anti-HIV agent.” ’385 patent, 1:15-20. 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. 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. 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. WO '351 further discloses that 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." WO '351, 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." WO '351, 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." WO '351, 16:15-18. WO '351 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." WO '351, 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." WO '351, 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." WO '351, 17:27-28, 23:6-8. The Stribild Assessment discloses, "Stribild is presented for use as a bilayer tablet – one layer contains EVG/COBI and one FTC/TDF." Stribild Assessment, 33. The Atripla Assessment teaches, "The granulations are blended separately with extra-granular magnesium stearate, compressed into bilayer tablets, and then film-coated. Process optimization studies were conducted in order to establish critical process parameters for the wet granulation of efavirenz, dry granulation of emtricitabine/tenofovir, bilayer tablet compression, and aqueous film-coating operations." Atripla Assessment, 5.

The Genvoya Assessment states, "GS-US-292-0101 was an open-label crossover study that compared two formulations (monolayer and bilayer) of E/C/F/TAF (each containing either 25 or 40 mg TAF as the monofumarate) with Stribild and with TAF 25 mg alone." Genvoya Assessment, 75.

The Eviplera Assessment teaches, "The exposure of FTC/RPV/TDF after single oral administration of a bilayer formulation and the individual compounds was compared in fasted dogs and has demonstrated comparable systemic exposure to all compounds." Eviplera Assessment, 18.

US '857 discloses "a tablet of the invention wherein the first layer comprises:

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

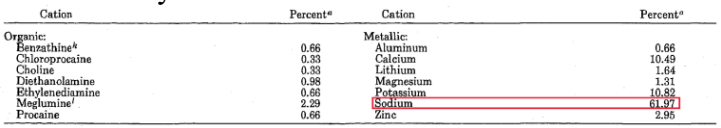
and the second layer comprises:

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

US '857, [0066]. US '857 further discloses bilayer tablets for keeping rilpivirine separate from FTC and TDF. *Id.* at [0067]-[0071].

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, 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]. US '079 also discloses that 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. 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. Havele discloses that TDF showed complete degradation occurred immediately after addition of at room temperature). Havele, 3, 5. Venkatasan discloses that TDF undergoes 31% decomposition under basic stress conditions. Venkatasan, 4. Kurmi discloses that in a basic solution environment (0.5 N NaOH), TDF was completely converted into degradation product

	T1 in 3 h. Kurmi, 96121. Kurmi further discloses that under basic solid state stress conditions, TDF degraded into several different products. *Id.* at 96121-25. Berge teaches "[t]he chemical, biological, physical and economic characteristics of medicinal agents can be manipulated and, hence, often optimized by conversion to a salt form," where "salt-forming agents are often chosen empirically … [and] the preferred form is selected by pharmaceutical chemists on a practical basis: cost of raw materials, ease of crystallization, and percent yield … [as well as] stability, hygroscopicity, and flowability of the resulting bulk drug." Berge at 1. Berge also teaches Table 1 as a list of "FDA-approved commercially marketed salts" that includes sodium:  Remington 21st teaches in Table 38-5 that sodium salts were an API-salt form known since at least 1983:

Cation	Percent[a]	Cation	Percent[a]
Organic:		Metallic:	
Benzathine[k]	0.66	Aluminum	0.66
Chloroprocaine	0.33	Calcium	10.49
Choline	0.33	Lithium	1.64
Diethanolamine	0.98	Magnesium	1.31
Ethylenediamine	0.66	Potassium	10.82
Meglumine[l]	2.29	Sodium	61.97
Procaine	0.66	Zinc	2.95

Table 38-5. Molecular Forms Marketed Worldwide Between 1983 and 1996

SALT FORM	FREQ.	GROUP[a]	PK_A	CLOGP	MW
No salt form	390	0			
Hydrobromide	1	1	−8	0.45	80.91
Hydrochloride	102	1	−6.1	0.24	36.46
Sulfate	5	1	−3	−1.58	98.08
Nitrate	6	1	−1.44	2.09	63.01
Phosphate	2	1	2.15	−1.95	96.99
Glucuronate	1	1	3.22[b]	−3.74	194.14
Acetate	8	1	4.76	−0.36	59.05
Maleate	3	2	1.92	−0.18	116.07
Fumarate	8	2	3.02	−0.18	116.07
Tartrate	1	2	3.03	−2.21	150.09
Citrate	1	2	3.13	−2.11	189.10
Succinate	2	2	4.21	−0.62	118.09
Mesylate	8	3	−1.20	−1.31	96.11
Acistrate	1	3	4.91[b]	7.98	284.49
Besylate	2	4	−2.80[b]	0.23	157.17
Tosylate	3	4	−1.34	0.88	171.20
Xinafoate	1	4	2.66[b]	3.00	188.18
Potassium	1	1	16		39.10
Sodium	37	1	14.77		23.00
Tromethamine	2	1	8.07[c]	−3.17	121.14
Bismuth	1	1	1.58		208.98
Bromide	6	5			79.90
Chloride	2	5			35.45

[a] Groups: 0 = No salt, 1 = Polar, 2 = Multifunctional, 3 = Flexible aliphatics, 4 = Planar aromatics, 5 = Quartenary.
[b] Calculated pK_a.
[c] Data from *CRC Handbook of Basic Tables for Chemical Analysis*, page 469.
From Serajuddin ATM, Sheen P, Augustine MA. To market, to market. In: Bristol J, ed. *Annu Rep Med Chem.* New York: Academic, 1983–1996.

Serajuddin teaches that "[s]alt formation is the most common and effective method of increasing solubility of acidic and basic drugs." Serajuddin at 603.

Serajuddin also teaches that "[s]alt formation is also the most common approach of increasing solubility, dissolution rate and ultimately bioavailability of poorly water-soluble ionizable drugs in solid dosage forms." Serajuddin at 614.

Serajuddin further informs that "Table 2 gives the distribution of 120 salts approved by the FDA during the 12-year period from 1995 to 2006, where the hydrochloride salt is the predominant salt form among the basic drugs and the sodium salt is the predominant form for acidic drugs." Serajuddin at 613. The portion of Table 2 that shows salts of acidic drugs shows:

Salts of acidic drugs	Total number
Sodium	12
Calcium	4
Potassium	2
Tromethamine	1
Total of all salts of acidic drugs	19

Paulekuhn teaches that "[s]alt formation is a well-known technique to modify and optimize the physical chemical properties of an ionizable research and development compound[, where] [p]roperties such as solubility, dissolution rate, hygroscopicity, stability, impurity profiles and crystal habit can be influenced by using a variety of pharmaceutically acceptable counterions." Paulekuhn, 6665 (also noting that "formation of salts is almost the only chemical technique available to change aqueous solubility and dissolution rate without changing the API molecule")

According to Paulekuhn, "[a]mong the cations used to form API salts of acidic molecules, the sodium ion strongly dominates with an incidence of 75.3% over the entire period. From 1982 to 1991, the fraction of sodium salts was more than 90%. This decreased to 62.5% during the 2002-2006 period." *Id.* at 6667.

Wells teaches, "A major improvement in solubility can be achieved by forming a salt." Wells at 116.

In discussing potential pharmaceutical salts to be used for the salt forms of drugs, Wells provides Table 8.4, which presents such salts, including sodium, , along with the pKa of each salt forming cation:

Table 8.4 Potential pharmaceutical salts

Basic drugs			Acidic drugs		
Anion	pK_a	% Usage	Cation	pK_a	% Usage
Hydrochloride	−6.10	43.0	Potassium	16.00	10.8
Sulphate	−3.00, +1.96	7.5	Sodium	14.77	62.0
Mesylate	−1.20	2.0	Lithium	13.82	1.6
Maleate	1.92, 6.23	3.0	Calcium	12.90	10.5
Phosphate	2.15, 7.20, 12.38	3.2	Magnesium	11.42	1.3
Salicylate	3.00	0.9	Diethanolamine	9.65	1.0
Tartrate	3.00	3.5	Zinc	8.96	3.0
Lactate	3.10	0.8	Choline	8.90	0.3
Citrate	3.13, 4.76, 6.40	3.0	Aluminium	5.00	0.7
Succinate	4.21, 5.64	0.4			
Acetate	4.76	1.3			
Others		31.4	Others		8.8

Bastin encourages the "[s]election of an appropriate salt form for a new chemical entity" because it "provides the pharmaceutical chemist and formulation scientist with the opportunity to modify the characteristics of the potential drug substance and to permit the development of dosage forms with good bioavailability, stability, manufacturability, and patient compliance." Bastin, 427.

Brittain teaches, "Prudent drug development programs will identify the preferred crystalline form early in development, with a polymorph/salt group working in close conjunction with process chemists to make the thermodynamically preferred polymorphic form the initial kilogram-scale batch." Brittain, 358.

The Triumeq Label discloses the ingredients of Triumeq as including the sodium salt form of dolutegravir, stating, "Each film-coated tablet contains abacavir sulfate equivalent to 600 mg of abacavir, dolutegravir sodium equivalent to 50 mg of dolutegravir, and 300 mg of lamivudine." Triumeq Label, 17.

	The Triumeq label teaches, "TRIUMEQ, a combination of dolutegravir (integrase strand transfer inhibitor [INSTI]), abacavir, and lamivudine (both nucleoside analogue reverse transcriptase inhibitors) is indicated for the treatment of HIV-1 infection." Triumeq Label, 1. The Triumeq Assessment discloses, "Triumeq is presented as film-coated tablets containing a fixed combination of dolutegravir sodium equivalent to 50 mg dolutegravir, 600 mg of abacavir (as sulfate) and 300 mg of lamivudine." Triumeq Assessment, 6. The Triumeq Assessment teaches, "A once-daily fixed-dose combination (FDC) single tablet regimen (STR) that combines the integrase inhibitor (INI) dolutegravir (DTG) with the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir sulfate (abacavir, ABC) and lamivudine (3TC) was developed for use in the treatment of human immunodeficiency virus (HIV) infection." Triumeq Assessment, 6. WO '116 is specifically directed to BIC sodium (Formula II) and a crystalline form thereof (Form I), along with pharmaceutical formulations and therapeutic uses therefore. WO '116, [0002], [0006]-[0008], [0043]-[0057] (describing crystalline forms of Formula II).; *see also* Section IV.A of the narrative (discussing the disclosure of the family member '342 and '067 patents). 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). 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]. *See also* Weller; Castagna; Juday; Lunzen; Walmsley; Johns; PR; Mathais; Min; Highleyman; Acosta; BICANDA01157927; NCT02607956-1; NCT02607856-2; Abebe; Shende; Poster #416; Poster # 414; Poster #413.
25 mg tenofovir alafenamide as a pharmaceutically acceptable salt thereof,	US '332 discloses that "[i]n a preferred embodiment the pharmaceutical composition of the present invention comprises 50 mg dolutegravir, 50 mg dolutegravir, about 200 mg emtricitabine and about 25 mg tenofovir." US '332, [0092]. US '332 describes pharmaceutical combinations comprising 40 to 60 mg DLT, 150 to 250 mg FTC, and 5 to 42 mg TAF, along with pharmaceutical excipients. US '332, [0086]-[0090]. US '332 further discloses a specific combination comprising about 50 mg DLT, about 200 mg FTC and about 25 mg TAF. *Id.* at [0091]-[0092]. US '332 discloses, "Acids which are used to prepare pharmaceutically acceptable acid addition salts are preferably those which form non-toxic acid addition salts. In a particularly preferred embodiment tenofovir alafenamide is present in form of its hemifumarate or fumarate, especially its hemifumarate." US '332, [0053].

	US ’356 further discloses 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.US ’35, [0156]-[0163]. 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. US ’356, 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). US ’356 further discloses that [i]n certain embodiments, a compound disclosed herein 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. US ’356, [0177]. US ’356 refers “pharmaceutically acceptable salt” to “a salt of a compound that is pharmaceutically acceptable and that possesses (or can be converted to a form that possesses) the desired pharmacological activity of the parent compound. Examples of ‘pharmaceutically acceptable salts’ of the compounds disclosed herein include salts derived from an appropriate base, such as . . . an alkaline earth metal (for example, magnesium). . . .” US ’356, [0075]. US ’902 discloses, “a novel pharmaceutical product containing efavirenz, emitricitabine and tenofovir DF are provided as a multicomponent unitary oral dosage form.” US ’902, Abstract.

	US ’857 describes “multilayer tablets that contain rilpivirine hydrochloride, emtricitabine, and tenofivir disoproxil fumarate.” US ’857, Abstract. US ’856 discloses pharmaceutical compositions comprising TAF hemifumarate and one or more additional therapeutic agents selected from the group consisting of “HIV protease inhibiting compounds, HIV nonnucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, and CCR5 inhibitors.” *Id.* at [0010]-[0011], [0057]. WO ’846 teaches the following formulation: Formulation D: GS-7340 — 25 mg/tablet emtricitabine — 200 Microcrystalline Cellulose — 200 Lactose Monohydrate — 330 Croscarmellose Sodium — 60 Pregelatinized Starch — 50 Magnesium Stearate — 10 875 WO ’846, 13:12-24. WO ’846 discloses the following formulation:

	Formulation G — mg/tablet GS-7340 — 300 emtricitabine — 200 Hydroxypropyl Methylcellulose — 112 Lactose B.P. — 53 Pregelatinized Starch B.P. — 28 Magnesium Stearate — 7 total: — 700 WO ’846, 13:23-24. WO ’846 further discloses an exemplary formulation containing 25 mg of TAF and 200 mg FTC. WO ’846, 37:13-20. Gilead/Janssen discusses, “Phase III-ready HIV treatment that will combine Gilead’s tenofovir alafenamide (TAF) and emtricitabine, and Janssen’s rilpivirine.” Gilead/Janssen, 1. Gilead/Janssen states, “Gilead and Janssen agreed to develop and commercialize a once-daily single tablet regimen for HIV that combines darunavir with TAF, emtricitabine and a third Gilead compound, cobicistat (marketed as TYBOST®).” Gilead/Janssen, 2. Gilead/Janssen discloses that 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. WO ’323 discloses, “In further embodiments, the additional therapeutic agent is selected from one or more of: . . (3) HIV nucleoside inhibitors of reverse transcriptase selected from the group consisting of zidovudine, emtricitabine, didanosine, stavudine, zaicitabine, lamivudine, abacavir, amdoxovir,

	elvucitabine, alovudine, MIV-210, ±-FTC, D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, apricitibine (AVX754), KP-1461, GS- 9131 (Gilead Sciences) and fosalvudine tidoxil (formerly HDP 99.0003); (4) HIV nucleotide inhibitors of reverse transcriptase selected from the group consisting of tenofovir, tenofovir disoproxil fumarate, tenofovir alafenarnide fumarate (Gilead Sciences), GS-7340 (Gilead Sciences), GS-9148 (Gilead Sciences), adefovir, adefovir dipivoxii, CMX-001 (Chimerix) or CMX-157 (Chimerix) . . . .” WO ’323, 38:1-2; 13-21. US ’426 states, “In further embodiments, Wnt signaling pathway inhibitor is administered in combination with one or more of the following agents: abacavir, acyclovir, acyclovir, adefovir, amantadine, amprenavir, ampligen, arbidol, atazanavir, atripla, boceprevir, cidofovir, combivir, complera, darunavir, delavirdine, didanosine, docosanol, dolutegravir, edoxudine, efavirenz, emtricitabine, enfuvirtide, entecavir, famciclovir, fomivirsen, fosamprenavir, foscarnet, fosfonet, ganciclovir, ibacitabine, imunovir, idoxuridine, imiquimod, indinavir, inosine, interferon type III, interferon type II, interferon type I, lamivudine, lopinavir, loviride, maraviroc, moroxydine, methisazone, nelfinavir, nevirapine, nexavir, oseltamivir, peginterferon alfa-2a, penciclovir, peramivir, pleconaril, podophyllotoxin, raltegravir, ribavirin, rimantadine, ritonavir, pyramidine, saquinavir, stavudine, stribild, tenofovir, tenofovir disoproxil, tenofovir alafenamide fumarate (TAF), tipranavir, trifluridine, trizivir, tromantadine, truvada, valaciclovir, valganciclovir, vicriviroc, vidarabine, viramidine, zalcitabine, zanamivir, or zidovudine, and combinations thereof.” US ’426, [0139].

	US ’850 further claims, “The method of claim 1 wherein the compound that inhibits HIV replication are selected from the group consisting of nucleoside reverse transcriptase inhibitors (NRTIs) such as tenofovir, emtricitabine, zidovudine (AZT), lamivudine (3TC), abacavir, and tenofovir alafenamide fumarate; non-nucleotide reverse transcriptase inhibitors (NNRTIs) such as efavirenz, rilpivirine, and etravirine; integrase inhibitors such as raltegravir and elvitegravir; and protease inhibitors such as ritonavir, darunavir, atazanavir, lopinavir, and cobicistat.” US ’850, Claim 2. US ’332 teaches, “[i]n a particularly preferred embodiment tenofovir alafenamide is present in form of its hemifumarate or fumarate, especially its hemifumarate.” US ’332, [0053]. US ’332 claims, “Pharmaceutical combination comprising (a) dolutegravir, (b) emtricitabine and (c) tenofovir for use as a medicament, wherein the weight ratio of (a) dolutegravir and (b) emtricitabine is from 1:1 to 1:3.” US ’332, Claim 1. US ’332 further claims, “Pharmaceutical combination for use according to any one of the preceding claims, wherein tenofovir is used in form of a prodrug of tenofovir.” US ’332, Claim 5. US ’332 further claims, “Pharmaceutical combination for use according to claim 5, wherein the prodrug of tenofovir is tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide or hexadecyloxypropyl tenofovir.” US ’332, Claim 6. US ’332 claims, “A kit for the treatment of a viral infection, in particular of an HIV-infection, comprising (i) 10 to 75 mg

	dolutegravir, (ii) 50 to 150 mg emtricitabine, (iii) 0.5 to 400 mg tenofovir or a prodrug thereof." US '332, Claim 15. WO '466 claims, "[a] pharmaceutical composition comprising a self-emulsifying drug delivery system, wherein the self-emulsifying drug delivery system comprises efavirenz and one or more pharmaceutically acceptable excipient." WO '466, Claim 1. WO '466 further claims, "[a] pharmaceutical composition according to any preceding claim, further comprising at least one additional active ingredient such as protease inhibitors, nucleoside reverse transcriptase inhibitors, non-nucleotide reverse transcriptase inhibitors, integrase inhibitors, or any combination thereof." WO '466, Claim 23. WO '466 further claims, "[a] pharmaceutical composition according to claim 23, wherein the at least one additional active ingredient comprises emtricitabine, tenofovir disproxil fumarate, tenofovir alafanamide fumarate, lamivudine, stavudine, zidovudine, or any combination thereof." WO '466, Claim 24. WO '720 discloses a combination of 200 mg FTC, 3-40 mg TAF, 50-500 mg cobicistat, 150 mg elvitegravir. WO '720, [0028]. The '791 patent discloses tenofovir alafenamide (TAF) as a compound of structure (6), having the chemical name 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino] phenoxyphosphinyl]methoxy]propyl]adenine, also designated as GS-7340.

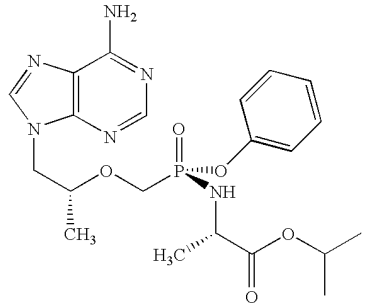
	(6)  ’791 patent, 4:13-32. Example 4 of the ’791 patent describes a method for the preparation of tenofovir alafenamide monofumarate (TAF monofumarate) from the compound GS-7340. The detailed procedure involves the crystallization of TAF monofumarate from acetonitrile. ’791 patent, 24:14-16, 24:38-48; *see also* 21:50-66 (preparation of TAF monofumarate (1:1) salts from a mixture of TAF (GS7340) and its diastereomer (GS-7339). Table 1 of the ’791 patent discloses that GS-7340 exhibits greater activity and stability compared to tenofovir disoproxil fumarate (TDF) and tenofovir. ’791 patent at 28:5-15. The ’791 patent also teaches that the TAF compounds disclosed therein may be “formulated into compositions containing pharmaceutically acceptable excipients, [which] are used in effective doses in the therapy or prophylaxis of viral (particularly HIV or hepadnaviral) infections.” ’791 patent, 4:54-59, 14:42-53. ’791 patent discloses TAF showing 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. ’791 patent, 27:29-28:37. ’791 patent further discloses the following tables:

TABLE 1

In Vitro Aetivity and Stability

	HIV-1		Stability T ½ (min)		
	Aetivity $IC_{50\,\mu M}$	Cytotoxicity $CC_{50\,\mu M}$	Human Plasma	MT-2 Cell Extract	(P/MT-2)
GS 7340	0,005	>40	90,0	28.3	3.2
TDF	0.05	70	0.41	70.7	0.006
Tenofovir	5	6000	—	—	—

TABLE 2

PMPA Metabolites in Plasma, PBMCs and RBCs After 1 h Incubation of PMPA Prodrugs or PMPA in Human Blood.

		Total C-14 Recovered,	Metabolites (% of Total Peak Area)					
Compound	Matrix	µg-eq	PMPA %	PMPAp, %	PMPApp, %	Met. X, %	Met. Y, %	GS 7340, %
GS-7340	Plasma/FP	43.0	1	—	—	2	13	84
(60 µg-eq)	PBMC	1.25	45	16	21	18	—	—
	RBC/FP	12.6	8	—	—	24	11	57
			PMPA	PMPAp	PMPApp	Mono-POC	GS-4331	
GS-4331	Plasma/FP	48.1	11	—	—	89	—	
(TDF)	PBMC	0.133	50	25	18	7	—	
(60 µg-eq)	RBC/FP	10.5	93	7.0	—	—	—	
			PMPA	PMPAp	PMPApp			
PMPA	Plasma/FP	55.7	100	—	—			
(60 µg-eq)	PBMC	0.033	86	14	—			
	RBC/FP	3.72	74	10	16			

’791 patent, Tables 1-2.

Lee discloses that “[t]he amidate prodrug GS 7340 was designed to overcome the permeability limitations of tenofovir by masking the dianion with a neutral promoiety and increasing the plasma stability of the prodrug relative to its intracellular stability. The in vitro anti-HIV potency of GS 7340 (EC_{50}=0.005 µM) is comparable to the most potent protease inhibitors and reflects the greater cell permeation of GS 7340 compared to tenofovir. In addition to favorable potency and a long intracellular half-life, the *in vivo* administration of GS 7340 results in an enhanced

	distribution of lymphatic tissue compared to tenofovir DF." Lee at 1903. Lee further discloses that "[w]ith GS 7340, it should be possible to reduce the total dose of tenofovir, thereby minimizing systemic exposure, while at the same time increasing antiviral activity." *Id*. at 1905. Lee discloses TAF as 10 times more potent than TDF toward HIV-1, with eight times improved selectivity index. Lee, 1900 (Table 1). Lee further discloses, "the high concentrations of tenofovir observed in lymphatic tissues after oral administration of GS 7340 are expected to result in increased clinical potency relative to tenofovir DF." Lee, 1905 Lee further discloses that "[w]ith GS-7340, it should be possible to reduce the total dose of tenofovir, thereby minimizing systemic exposure, while at the same time increasing antiviral activity." Lee, 1905. US '856 discloses are pharmaceutical compositions comprising TAF hemifumarate and one or more additional therapeutic agents selected from the group consisting of "HIV protease inhibiting compounds, HIV nonnucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, and CCR5 inhibitors." *Id.* at [0010]-[0011], [0057]. HIV Guidelines states that "[a]n antiretroviral regimen for a treatment-naive patient generally consists of two nucleoside 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." HIV Guidelines, D-1. HIV Guidelines further recommends combination of the INSTIs elvitegravir and raltegravir with tenofovir and emtricitabine. HIV Guidelines, 1, i. British HIV Guidelines describes tenofovir and emtricitabine as the preferred NRTI backbone for HIV therapy, to be combined with an additional agent such as an INSTI. British HIV Guidelines, 13. NCT '694 discloses a study that "evaluate[s] the efficacy, safety and tolerability of GS-9883 + emtricitabine/tenofovir alafenamide (FTC/TAF) fixed dose combination (FDC) versus dolutegravir (DTG) + FTC/TAF in HIV-1 Infected, antiretroviral treatment-naive adults. This study will also evaluate the pharmacokinetic (PK) profile of GS-9883, FTC and TAF." NCT '694, Study Description. NCT '694 further discloses an "active comparator" with "Drug: FTC/TAF, Emtricitabine/Tenofovir Alafenamide (FTC/TAF) 200 mg/25 mg tablet administered orally; Drug: DTG, Dolutegravir (DTG) 50 mg tablet administered orally." NCT '694, Arms and Interventions. Tivicay Assessment discloses combination therapies with DLT sodium, FTC and tenofovir disoproxil for treating HIV. Tivicay Assessment, 43, 50-51, 89. 2013 Tivicay Label also discloses Tivicay containing 50 mg of dolutegravir sodium as an HIV INSTI indicated in combination with other antiretroviral agents (e.g., emtricitabine/tenfovoir

	(TRUVADA), for the treatment of HIV-1 infection. 2013 Tivicay Label, 1, 4, 24. Truvada Label discloses combining 200 mg emtricitabine, 300 mg tenofovir alafenamide, and 600 mg efavirenz. Truvada Label. Complera Label discloses a tablet composition for oral administration that contains 200 mg of NRTI emtricitabine, and 300 mg of NRTI tenofovir DF, and 27.5 mg of NNRTI rilpivirine hydrochloride. Complera Label, 1, 22 The Stribild Label states that a Stribild table consists of "150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 300 mg of tenofovir disoproxil fumarate." Stribild Label, 1; *see also id.* at 22-23. The Genvoya Label states, "Each GENVOYA tablet contains 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (TAF) (equivalent to 11.2 mg of tenofovir alafenamide fumarate)." Genvoya Label, 4. 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. Genvoya Assessment, 74-75. The Genvoya Assessment teaches, "The overall goal of Genvoya film coated tablet development was to create a tablet containing

	the same amounts of elvitegravir, cobicistat and emtricitabine active substances as currently combined in Stribild fixed dose combination film-coated tablet and to replace tenofovir disoproxil contained in Stribild with tenofovir alafenamide, a second-generation prodrug of tenofovir." Genvoya Assessment, 18. Genvoya Assessment discloses film-coated tablets containing the following active substances: 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (as 11.2 mg of the fumarate)." Genvoya Assessment, 10. WO '351 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." WO '351, 19:3-12. Ruane discloses that "HIV-1 RNA responses for the 8-mg TAF treatment group were similar to that of the 300-mg TDF group. However, median $DAVG_{11}$ [(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, 451-52

	Ruane further states that "[c]ompared 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." Ruane, 454. Sax teaches that "Relative to TDF, TAF is more stable in plasma." Sax, 53. Astuti refers to tenofovir alafenamide (TAF), where "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." Astuti, 11. Astuti further discloses that the "possibility to use small doses of TAF instead of TDF could further widen the STR options as bulky molecules such as PIs could be successfully coformulated." Astuti, 11. Llibre teaches that 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. Llibre, 172. WO '799 teaches, In addition, the compounds of the present invention may be used in combination with one or more other agents useful in the prevention or treatment of HIV. Examples of such agents include:

	Nucleotide reverse transcriptase inhibitors such as zidovudine, didanosine, lamivudine, zalcitabine, abacavir, stavudine, adefovir, adefovir dipivoxil, fozivudine, todoxil, emtricitabine, alovudine, amdoxovir, elvucitabine, tenofovir disoproxil fumarate, dexelvucitabine, festinavir, racivir, and similar agents; Non-nucleotide reverse transcriptase inhibitors (including an agent having anti- oxidation activity such as immunocal, oltipraz, etc.) such as nevirapine, delavirdine, efavirenz, loviride, immunocal, oltipraz, capravirine, lersivirine, doravirine, rilpivirine, etravirine, tenofovir alafenamide fumarate, and similar agents; Protease inhibitors such as saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, fosamprenavir, brecanavir, darunavir, atazanavir, tipranavir, palinavir, lasinavir, and similar agents; Entry, attachment and fusion inhibitors such as enfuvirtide (T -20), T - 1249, PRO -542, PRO - 140, ibalizumab, cenicriviroc, INCB -9471, monomeric DAPTA, AMD -070, ibalizumab, BMS- 806, fostemsavir, temsavir, and 5 -Helix and similar agents; Integrase strand transfer inhibitors such as raltegravir, elvitegravir, dolutegravir, cabotegravir, GS - 9883, and similar agents; Maturation inhibitors such as PA -344, PA - 457, BMS - 955176, as well as those disclosed in PCT Patent Application No. WO2011/100308, PCT Patent Application No. PCT/US2012/024288, Chinese PCT Application No. PCT/CN2011/001302, Chinese PCT Application No. PCT/CN2011/001303, Chinese PCT Application No. PCT/CN2011/002105, PCT/CN2011 /002159, WO2013/090664, WO2013/123019 , WO 2013/043778, WO 2014/123889, WO 2011/153315,

	WO2011/153319, WO2012/106188, WO 2012/106190, WO 2013/169578, and WO 2014/13081, and similar agents; CXCR4 and /or CCR5 inhibitors such as vicriviroc, TAK779, maraviroc, TAK449, as well as those disclosed in WO 02/74769, PCT/US03/39644, PCT/US03/39975, PCT/US03/39619, PCT/USO3/39618, PCT/US03/39740, and PCT/US03/39732, and similar agents. Neutralizing antibodies such as VRC01, VRC0710e8, pro140, PGT121, PGT128, PGT145, PG9, 3BNC117, ibalizumab, N6 and similar agents. WO '799, [0356]-[0365]. 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. WO '116 at [0096]. 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. 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. *See also* Weller; Castagna; Juday; Lunzen; Walmsley; Johns; PR; Mathais; Min; Highleyman; Acosta; BICANDA01157927; NCT02607956-1; NCT02607856-2; Abebe; Shende; Poster #416; Poster # 414; Poster #413.
and 200 mg emtricitabine.	US '332 discloses that "[i]n a preferred embodiment the pharmaceutical composition of the present invention comprises 50 mg dolutegravir, 50 mg dolutegravir, about 200 mg emtricitabine and about 25 mg tenofovir." US '332, [0092]. US '332 describes pharmaceutical combinations comprising 40 to 60 mg DLT, 150 to 250 mg FTC, and 5 to 42 mg TAF, along with pharmaceutical excipients. US '332, [0086]-[0090]. US '332 further discloses a specific combination comprising about 50 mg DLT, about 200 mg FTC and about 25 mg TAF. *Id.* at [0091]-[0092]. US '332 claims, "Pharmaceutical combination comprising (a) dolutegravir, (b) emtricitabine and (c) tenofovir for use as a medicament, wherein the weight ratio of (a) dolutegravir and (b) emtricitabine is from 1:1 to 1:3." US '332, Claim 1. US'332 further discloses that "[i]n a preferred embodiment emtricitabine is present in the form of its free base, i.e. not in the form of an acid addition salt." US '332, [0032]. US '332 claims, "A kit for the treatment of a viral infection, in particular of an HIV-infection, comprising (i) 10 to 75 mg dolutegravir, (ii) 50 to 150 mg emtricitabine, (iii) 0.5 to 400 mg tenofovir or a prodrug thereof." US '332, Claim 15.

	US ’356 further discloses 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.US ’35, [0156]-[0163]. 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. US ’356, 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). US ’356 further discloses that [i]n certain embodiments, a compound disclosed herein 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. US ’356, [0177]. US ’902 discloses, “a novel pharmaceutical product containing efavirenz, emitricitabine and tenofovir DF are provided as a multicomponent unitary oral dosage form.” US ’902, Abstract. US ’857 describes “multilayer tablets that contain rilpivirine hydrochloride, emtricitabine, and tenofivir disoproxil fumarate.” US ’857, Abstract. WO ’846 discloses therapeutic combinations of TAF and FTC for treating HIV. WO ’846, 3:13-18.

WO ’846 teaches the following formulation:

Formulation D:	mg/tablet
GS-7340	25
emtricitabine	200
Microcrystalline Cellulose	200
Lactose Monohydrate	330
Croscarmellose Sodium	60
Pregelatinized Starch	50
Magnesium Stearate	10
	875

WO ’846, 13:12-24.

WO ’846 discloses the following formulation:

Formulation G	mg/tablet
GS-7340	300
emtricitabine	200
Hydroxypropyl Methylcellulose	112
Lactose B.P.	53
Pregelatinized Starch B.P.	28
Magnesium Stearate	7
total:	700

WO ’846, 13:23-24.

WO ’846 further discloses an exemplary formulation containing 25 mg of TAF and 200 mg FTC. WO ’846, 37:13-20.

Gilead/Janssen discusses, “Phase III-ready HIV treatment that will combine Gilead’s tenofovir alafenamide (TAF) and emtricitabine, and Janssen’s rilpivirine.” Gilead/Janssen, 1.

	Gilead/Janssen states, "Gilead and Janssen agreed to develop and commercialize a once-daily single tablet regimen for HIV that combines darunavir with TAF, emtricitabine and a third Gilead compound, cobicistat (marketed as TYBOST®)." Gilead/Janssen, 2. WO '323 discloses, "In further embodiments, the additional therapeutic agent is selected from one or more of: . . (3) HIV nucleoside inhibitors of reverse transcriptase selected from the group consisting of zidovudine, emtricitabine, didanosine, stavudine, zaicitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, ±-FTC, D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, apricitibine (AVX754), KP-1461, GS- 9131 (Gilead Sciences) and fosalvudine tidoxil (formerly HDP 99.0003); (4) HIV nucleotide inhibitors of reverse transcriptase selected from the group consisting of tenofovir, tenofovir disoproxil fumarate, tenofovir alafenarnide fumarate (Gilead Sciences), GS-7340 (Gilead Sciences), GS-9148 (Gilead Sciences), adefovir, adefovir dipivoxii, CMX-001 (Chimerix) or CMX-157 (Chimerix) . . . ." WO '323, 38:1-2; 13-21. US '332 claims, "Pharmaceutical combination comprising (a) dolutegravir, (b) emtricitabine and (c) tenofovir for use as a medicament, wherein the weight ratio of (a) dolutegravir and (b) emtricitabine is from 1:1 to 1:3." US '332, Claim 1. US '332 claims, "A kit for the treatment of a viral infection, in particular of an HIV-infection, comprising (i) 10 to 75 mg dolutegravir, (ii) 50 to 150 mg emtricitabine, (iii) 0.5 to 400 mg tenofovir or a prodrug thereof." US '332, Claim 15.

	HIV Guidelines further recommends combination of the INSTIs elvitegravir and raltegravir with tenofovir and emtricitabine. HIV Guidelines, 1, i. HIV Guidelines states that "[a]n antiretroviral regimen for a treatment-naive patient generally consists of two nucleoside 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." HIV Guidelines, D-1. British HIV Guidelines describes tenofovir and emtricitabine as the preferred NRTI backbone for HIV therapy, to be combined with an additional agent such as an INSTI. British HIV Guidelines, 13. NCT '694 discloses a study that "evaluate[s] the efficacy, safety and tolerability of GS-9883 + emtricitabine/tenofovir alafenamide (FTC/TAF) fixed dose combination (FDC) versus dolutegravir (DTG) + FTC/TAF in HIV-1 Infected, antiretroviral treatment-naive adults. This study will also evaluate the pharmacokinetic (PK) profile of GS-9883, FTC and TAF." NCT '694, Study Description. NCT '694 further discloses an "active comparator" with "Drug: FTC/TAF, Emtricitabine/Tenofovir Alafenamide (FTC/TAF) 200 mg/25 mg tablet administered orally; Drug: DTG, Dolutegravir (DTG) 50 mg tablet administered orally." NCT '694, Arms and Interventions. Tivicay Assessment discloses the product Tivicay® as containing 50 mg of DLT sodium. Tivicay Assessment, 9. Tivicay

	Assessment identifies 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." *Id.* It further discloses combination therapies with DLT sodium, FTC and tenofovir disoproxil for treating HIV. *Id.* at 43, 50-51, 89. 2013 Tivicay Label also discloses Tivicay containing 50 mg of dolutegravir sodium as an HIV INSTI indicated in combination with other antiretroviral agents (e.g., emtricitabine/tenfovoir (TRUVADA), for the treatment of HIV-1 infection. 2013 Tivicay Label, 1, 4, 24. Truvada Label discloses combining 200 mg emtricitabine, 300 mg tenofovir alafenamide, and 600 mg efavirenz. Truvada Label. Complera Label discloses a tablet composition for oral administration that contains 200 mg of NRTI emtricitabine, and 300 mg of NRTI tenofovir DF, and 27.5 mg of NNRTI rilpivirine hydrochloride. Complera Label, 1, 22 The Stribild Label describes Stribild as "a combination of 1 integrase strand transfer inhibitor, 1 pharmacokinetic enhancer, and 2 nucleos(t)ide analog HIV-1 reverse transcriptase inhibitors, is indicated as a complete regimen for the treatment of HIV-1 infection in adults who are antiretroviral treatment-naïve." Stribild Label, 1. The Stribild Label states that a Stribild table consists of "150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine,

	and 300 mg of tenofovir disoproxil fumarate." Stribild Label, 1; *see also id.* at 22-23. The Stribild Assessment describes Stribild as "a fixed drug combination tablet containing three ARVs (FTC/TDF and elvitegravir [EVG; an INSTI]) plus a new pharmacoenhancer cobicistat (COBI), which modifies the PK profile of EVG." Stribild Assessment, 10. The Genvoya Label states, "Each GENVOYA tablet contains 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (TAF) (equivalent to 11.2 mg of tenofovir alafenamide fumarate)." Genvoya Label, 4. Genvoya Assessment discloses film-coated tablets containing the following active substances: 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (as 11.2 mg of the fumarate)." Genvoya Assessment, 10. WO '351 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." WO '351, 19:3-12.

	WO ’720 discloses a combination of 200 mg FTC, 3-40 mg TAF, 50-500 mg cobicistat, 150 mg elvitegravir. WO ’720, [0028]. WO ’466 claims, “[a] pharmaceutical composition comprising a self-emulsifying drug delivery system, wherein the self-emulsifying drug delivery system comprises efavirenz and one or more pharmaceutically acceptable excipient.” WO ’466, Claim 1. WO ’466 further claims, “[a] pharmaceutical composition according to any preceding claim, further comprising at least one additional active ingredient such as protease inhibitors, nucleoside reverse transcriptase inhibitors, non-nucleotide reverse transcriptase inhibitors, integrase inhibitors, or any combination thereof.” WO ’466, Claim 23. WO ’466 further claims, “[a] pharmaceutical composition according to claim 23, wherein the at least one additional active ingredient comprises emtricitabine, tenofovir disproxil fumarate, tenofovir alafanamide fumarate, lamivudine, stavudine, zidovudine, or any combination thereof.” WO ’466, Claim 24. The Atripla Label teaches, “Each tablet contains 600 mg of efavirenz, 200 mg of emtricitabine, and 300 mg of tenofovir DF (which is equivalent to 245 mg of tenofovir disoproxil) as active ingredients.” Atripla Label, 1. US ’902 discloses, “a novel pharmaceutical product containing efavirenz, emitricitabine and tenofovir DF are provided as a multicomponent unitary oral dosage form.” US ’902, Abstract. US ’902 further discloses bilayer tablets similar to Atripla containing 200 mg FTC. US ’902, [0050]-[0052].

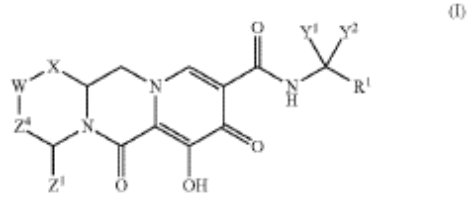
	The Complera Label describes the recommended dose as "[o]ne tablet (containing 200 mg of emtricitabine, 25 mg of rilpivirine, and 300 mg of tenofovir disoproxil fumarate) taken once daily with a meal." Complera Label, 1. US '857 describes "multilayer tablets that contain rilpivirine hydrochloride, emtricitabine, and tenofivir disoproxil fumarate." US '857, Abstract. US '857 further discloses bilayer tablets similar to Complera/Eviplera containing 200 mg FTC. US '857 [0066]-[0073]. WO '799 teaches, In addition, the compounds of the present invention may be used in combination with one or more other agents useful in the prevention or treatment of HIV. Examples of such agents include: Nucleotide reverse transcriptase inhibitors such as zidovudine, didanosine , lamivudine , zalcitabine , abacavir, stavudine , adefovir, adefovir dipivoxil, fozivudine, todoxil, emtricitabine , alovudine, amdoxovir, elvucitabine , tenofovir disoproxil fumarate , dexelvucitabine , festinavir, racivir, and similar agents; Non-nucleotide reverse transcriptase inhibitors (including an agent having anti- oxidation activity such as immunocal, oltipraz, etc .) such as nevirapine, delavirdine, efavirenz, loviride , immunocal, oltipraz , capravirine , lersivirine, doravirine, rilpivirine , etravirine, tenofovir alafenamide fumarate , and similar agents; Protease inhibitors such as saquinavir, ritonavir, indinavir, nelfinavir , amprenavir , fosamprenavir,

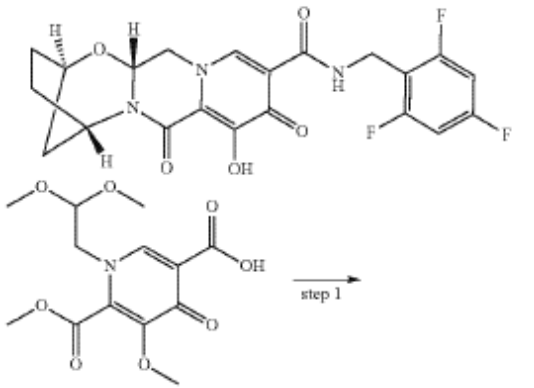
	brecanavir, darunavir , atazanavir, tipranavir , palinavir , lasinavir, and similar agents ; Entry, attachment and fusion inhibitors such as enfuvirtide (T -20), T - 1249, PRO -542, PRO - 140, ibalizumab, cenicriviroc , INCB -9471, monomeric DAPTA, AMD -070, ibalizumab, BMS- 806, fostemsavir, temsavir, and 5 -Helix and similar agents; Integrase strand transfer inhibitors such as raltegravir, elvitegravir, dolutegravir, cabotegravir, GS - 9883, and similar agents; Maturation inhibitors such as PA -344, PA - 457, BMS - 955176, as well as those disclosed in PCT Patent Application No. WO2011/100308, PCT Patent Application No. PCT/US2012/024288, Chinese PCT Application No. PCT/CN2011/001302, Chinese PCT Application No. PCT/CN2011/001303, Chinese PCT Application No. PCT/CN2011/002105, PCT/CN2011 /002159, WO2013/090664, WO2013/123019 , WO 2013/043778, WO 2014/123889, WO 2011/153315, WO2011/153319, WO2012/106188, WO 2012/106190, WO 2013/169578, and WO 2014/13081, and similar agents; CXCR4 and /or CCR5 inhibitors such as vicriviroc, TAK779, maraviroc, TAK449, as well as those disclosed in WO 02/74769, PCT/US03/39644, PCT/US03/39975, PCT/US03/39619, PCT/USO3/39618, PCT/US03/39740, and PCT/US03/39732, and similar agents. Neutralizing antibodies such as VRC01, VRC0710e8, pro140, PGT121, PGT128, PGT145, PG9, 3BNC117, ibalizumab, N6 and similar agents. WO ’799, [0356]-[0365].

	US ’426 states, “In further embodiments, Wnt signaling pathway inhibitor is administered in combination with one or more of the following agents: abacavir, acyclovir, acyclovir, adefovir, amantadine, amprenavir, ampligen, arbidol, atazanavir, atripla, boceprevir, cidofovir, combivir, complera, darunavir, delavirdine, didanosine, docosanol, dolutegravir, edoxudine, efavirenz, emtricitabine, enfuvirtide, entecavir, famciclovir, fomivirsen, fosamprenavir, foscarnet, fosfonet, ganciclovir, ibacitabine, imunovir, idoxuridine, imiquimod, indinavir, inosine, interferon type III, interferon type II, interferon type I, lamivudine, lopinavir, loviride, maraviroc, moroxydine, methisazone, nelfinavir, nevirapine, nexavir, oseltamivir, peginterferon alfa-2a, penciclovir, peramivir, pleconaril, podophyllotoxin, raltegravir, ribavirin, rimantadine, ritonavir, pyramidine, saquinavir, stavudine, stribild, tenofovir, tenofovir disoproxil, tenofovir alafenamide fumarate (TAF), tipranavir, trifluridine, trizivir, tromantadine, truvada, valaciclovir, valganciclovir, vicriviroc, vidarabine, viramidine, zalcitabine, zanamivir, or zidovudine, and combinations thereof.” US ’426, [0139]. US ’850 claims, “A method of preventing or delaying a rise in viral load following cessation of treatment of human immunodeficiency virus (HIV) infection, the method comprising: administering to a subject infected with HIV at least three compounds collectively having the following activities: dampening of immune activation, wherein the dampening selectively affects the CD4 T cell response relative to the CD8 T cell response, inhibition of HIV replication, stimulation of reactivation of latent HIV, and inhibition of infection of CD4 T cells by HIV, wherein the compound that inhibits HIV infection of CD4 T cells is selected from the group consisting of C-C chemokine receptor type 5 (CCR5) inhibitors, C-X-X chemokine

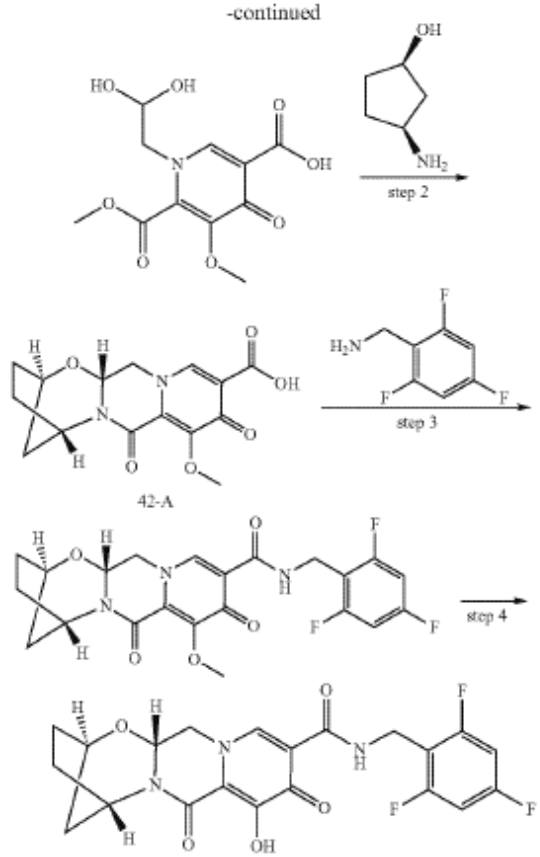
	receptor type 4 (CXCR4) inhibitors, CD4 inhibitors, gp120 inhibitors, and gp41 inhibitors, wherein the compounds are provided in dosages reducing the number of cells infected with HIV or the viral load of HIV, relative to which is achieved using just the combination of ART and compounds which activate latent HIV, wherein HIV infected cells or HIV viral load is not detectable at 12 months after the end of the course of treatment." US '850, Claim 1. US '850 further claims, "The method of claim 1 wherein the compound that inhibits HIV replication are selected from the group consisting of nucleoside reverse transcriptase inhibitors (NRTIs) such as tenofovir, emtricitabine, zidovudine (AZT), lamivudine (3TC), abacavir, and tenofovir alafenamide fumarate; non-nucleotide reverse transcriptase inhibitors (NNRTIs) such as efavirenz, rilpivirine, and etravirine; integrase inhibitors such as raltegravir and elvitegravir; and protease inhibitors such as ritonavir, darunavir, atazanavir, lopinavir, and cobicistat." US '850, Claim 2. 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. WO '116 at [0096]. 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. 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. *See also* Weller; Castagna; Juday; Lunzen; Walmsley; Johns; PR; Mathais; Min; Highleyman; Acosta; BICANDA01157927; NCT02607956-1; NCT02607856-2; Abebe; Shende; Poster #416; Poster # 414; Poster #413.

Claim 5	
Claim Elements	Prior Art Teachings of Claim Elements
The tablet of claim 1,	The prior art teachings disclosing the tablets of any of claim 1 is set forth above and incorporated herein by reference.
wherein the tablet comprises 52 mg of the sodium salt of the compound of Formula I.	US '356 discloses "[c]ompounds for use in the treatment of human immunodeficiency virus (HIV) infection . . . hav[ing] the following Formula (I):  (I) including stereoisomers and pharmaceutically acceptable salts thereof, wherein R^1, X, W, Y^1, Y^2, Z^1, and Z^4 are as defined herein. Methods associated with preparation and use of such compounds, as well as pharmaceutical compositions comprising such compounds, are also disclosed." US '356, Abstract, [0089].

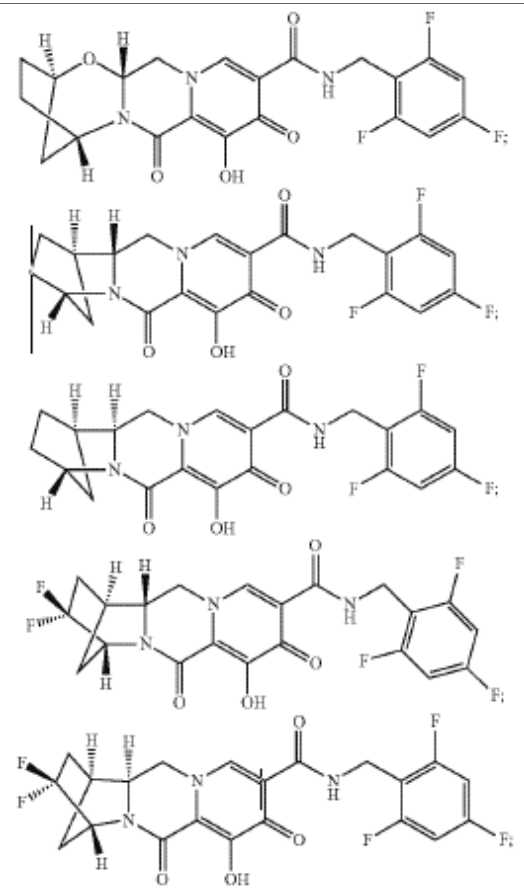
	US ’356 further discloses “polycyclic carbamoylpyridone compounds, having antiviral activity, . . . and the use of such compounds in the treatment of HIV infections. The compounds of the invention may be used to inhibit the activity of HIV integrase and may be used to reduce HIV replication.” US ’356, [0010]. US ’356 further discloses approximately 100 HIV INSTI compounds of Formula (I) and methods for their synthesis, including a Compound 42 corresponding to bictegravir (BIC): 42 

-continued



US ’356, [0312]-[0316] (Example 42).

US ’356 further discloses 7 HIV INSTIs of Formula I, including bictegravir:

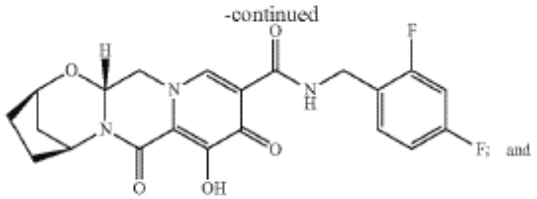
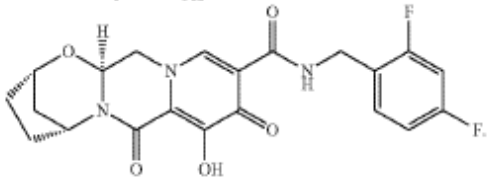
	-continued  F; and  F. US ’356, claim 32. US ’356 further discloses a tablet showing that BIC (compound 42) provided nanomolar activity (EC50 = 2.5 nm) in an antiviral assay in MT4 cells infected with HIV. “Compounds of the present invention demonstrate antiviral activity in this assay as depicted in Table 1 below. Accordingly, the compounds of the invention may be useful for treating the proliferation of the HIV virus, treating AIDS, or delaying the onset of AIDS or ARC symptoms.” US ’356, [0589]-[0592] (Example 104; see Table 1). US ’356 further discloses Example 107, “Pharmacokinetic analysis Following Oral or Intravenous Administration to Beagle Dogs.” US ’356, [0599]-[0603]. US ’356 provided the second highest oral bioavailability (F (%)), Cmax and AUC of the eleven Formula (I) compounds tested:

TABLE 4

Compound #	CL (L/h/kg)	V_{ss} (L/kg)	MRT (h)	F (%) aqueous suspension	C_{max} (μM) aqueous suspension	AUC (μM * h) aqueous suspension
98	0.047	0.16	3.3	n/a	n/a	n/a
83	0.161	0.38	2.4	n/a	n/a	n/a
55	0.058	0.24	4.2	n/a	n/a	n/a
77	0.300	0.64	2.2	n/a	n/a	n/a
41	0.015	0.11	7.5	10.7	2.4	16.3
42	0.020	0.15	7.1	28.0	4.5	28.6
47	0.014	0.10	7.4	12.6	2.8	20.4
8	0.498	0.87	1.8	n/a	n/a	n/a
7	0.510	1.20	2.3	n/a	n/a	n/a
3	0.047	0.23	4.9	18.7	1.2	9.2
2	0.030	0.20	6.5	40.7	7.8	66.1

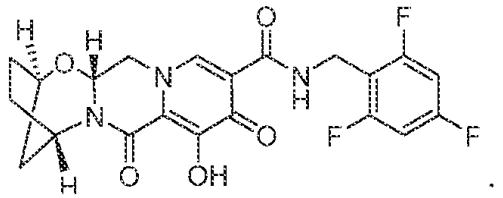
US ’356, Example 107; see Table 4.

US ’356 further discloses “[p]harmaceutical compositions . . . includ[ing] a compound of Formula (I) and one or more of: a pharmaceutically acceptable carrier, diluent or excipient. . . . In certain embodiments, a compound of Formula (I) is present in the pharmaceutical composition in an amount from about 25 mg to about 500 mg. In certain embodiments, a compound of Formula (I) is present in the pharmaceutical composition in an amount of about 100 mg to about 300 mg. In certain embodiments, a compound of Formula (I) is present in the pharmaceutical composition in an amount of about 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg or about 500 mg.” US ’356, [0152].

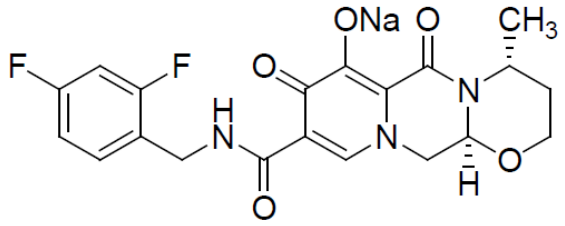
US ’356 refers “pharmaceutically acceptable salt” to “a salt of a compound that is pharmaceutically acceptable and that possesses (or can be converted to a form that possesses) the desired pharmacological activity of the parent compound. Examples of ‘pharmaceutically acceptable salts’ of the compounds disclosed herein include salts derived from an appropriate base, such as . . . an alkaline earth metal (for example, magnesium). . . .” US ’356, [0075].

	US ’356 states that “[t]he compounds of the invention, or their pharmaceutically acceptable salts, are administered in a therapeutically effective amount.” US ’356, [0155]. US ’356 further states that “a therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to their own know ledge, the state of the art, and this disclosure.” US ’356, [0081]. US ’356 discloses that these pharmaceutical compositions containing a therapeutically effective amount of a compound of Formula (I) are disclosed “for use in the therapeutic treatment of an HIV infection is provided.” US ’356, [0147]-[0149]. US ’356 states that “[a]dministration of the compounds of the invention, or their pharmaceutically acceptable salts, in pure form or in an appropriate pharmaceutical composition, is carried out via any of the accepted modes of administration of agents for serving similar utilities.” US ’356, [0153]-[0154] US ’356 also claims “[a] pharmaceutical composition comprising a compound of any one of claims 1-32, or a stereoisomer or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.” US ’356, claim 33. US ’356 further claims, “[a] method of treating an HIV infection in a human having or at risk of having the infection by administering to the human a therapeutically effective amount of a compound of any one of claims 1-32 or a pharmaceutical composition of claim 33.” US ’356, claim 37.

	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]. US ’356 also discloses combination therapy “for treating or preventing an HIV infection in a human having or at risk of having the infection.” US ’356, [0156]. US ’356 further discloses 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.US ’356, [0156]-[0163]. US ’356 also discloses an embodiment wherein pharmaceutical compositions comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with one or more additional therapeutic agents, and a pharmaceutically acceptable carrier, diluent or excipient are provided. US ’356, [0156]-[0179]. US ’356 further discloses that [i]n certain embodiments, a compound disclosed herein 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. US ’356, [0177]. US ’332 describes pharmaceutical combinations comprising 40 to 60 mg DLT, 150 to 250 mg FTC, and 5 to 42 mg TAF, along

	with pharmaceutical excipients. US '332, [0086]-[0090]. US '332 further discloses that "[i]n a preferred embodiment the pharmaceutical composition of the present invention comprises 50 mg dolutegravir, 50 mg dolutegravir, about 200 mg emtricitabine and about 25 mg tenofovir." *Id.* at [0091]-[0092]. HIV Guidelines states that "[a]n antiretroviral regimen for a treatment-naive patient generally consists of two nucleoside 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." HIV Guidelines, D-1. 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. US '356, 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). WO '323 claims, "A compound of claim 1 selected from: . .  WO '323, Claim 32. WO '323 further claims, "A pharmaceutical composition comprising a compound of any one of claims 1-32, or a

	stereoisomer or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient." WO '323, Claim 33. WO '323 discloses, "Compounds, compositions, and methods for the treatment of human immunodeficiency vims (HIV) infection are disclosed. In particular, novel poly cyclic carbamoylpyridone compounds and methods for their preparation and use as therapeutic or prophylactic agents are disclosed." WO '323, 1:12-15. WO '323 teaches, "In certain embodiments, a compound of Formula (I) is present in the pharmaceutical composition in an amount of about 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg or about 500 mg." WO '323, 35:19-23. WO '323 defines "Formula (I)" as including "the specific compounds disclosed herein[,]" which includes bictegravir. WO '323, 18-19. HIV Guidelines further recommends combination of the INSTIs elvitegravir and raltegravir with tenofovir and emtricitabine. HIV Guidelines, 1, i. British HIV Guidelines describes tenofovir and emtricitabine as the preferred NRTI backbone for HIV therapy, to be combined with an additional agent such as an INSTI. British HIV Guidelines, 13. NCT '694 discloses a study that "evaluate[s] the efficacy, safety and tolerability of GS-9883 + emtricitabine/tenofovir alafenamide (FTC/TAF) fixed dose combination (FDC) versus

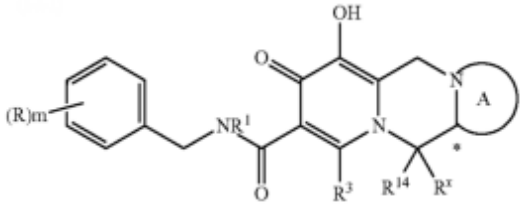
	dolutegravir (DTG) + FTC/TAF in HIV-1 Infected, antiretroviral treatment-naive adults. This study will also evaluate the pharmacokinetic (PK) profile of GS-9883, FTC and TAF." NCT '694, Study Description. NCT '694 further discloses an "active comparator" with "Drug: FTC/TAF, Emtricitabine/Tenofovir Alafenamide (FTC/TAF) 200 mg/25 mg tablet administered orally; Drug: DTG, Dolutegravir (DTG) 50 mg tablet administered orally." NCT '694, Arms and Interventions. US '332 discloses dolutegravir, which it further states is "reported to have anti-viral activity, since it is considered to be an integrase inhibitor." US '332, [0014]. US '332 further discloses, "[p]referably, dolutegravir is in the form of a pharmaceutically acceptable salt. More preferred, dolutegravir is in the form of an alkali metal salt such as sodium or potassium salt or in the form of an earth-alkali metal salt such as calcium or magnesium salt. More preferred, dolutegravir is in the form of a sodium salt or a magnesium salt. Particularly preferred, dolutegravir is used in form of the sodium salt, especially the mono-sodium salt." US '332, [0018], [0020]. The Tivicay Assessment teaches the sodium salt form of dolutegravir with the following structure: 

	Tivicay Assessment, 9. The Tivicay Assessment also discloses that "Tivicay is presented as film-coated tablet containing 50 mg of dolutegravir (As dolutegravir sodium salt) as active substance." Tivicay Assessment, 9. Tivicay Assessment identifies 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." *Id.* at 43, 50-51, It further discloses combination therapies with DLT sodium, FTC and tenofovir disoproxil for treating HIV. *Id.* at 89. The 2013 Tivicay Label teaches, "TIVICAY is a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor (INSTI) indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and children aged 12 years and older and weighing at least 40 kg." Tivicay Label, 1. The 2013 Tivicay Label also discloses Tivicay containing 50 mg of dolutegravir sodium as an HIV INSTI indicated in combination with other antiretroviral agents (e.g., emtricitabine/tenfovoir (TRUVADA), for the treatment of HIV-1 infection. 2013 Tivicay Label, 1, 4, 24. US '332 further discloses "a pharmaceutical composition comprising (a) dolutegravir, (b) emtricitabine and (c) tenofovir, wherein (a) dolutegravir and (b) emtricitabine are present in a specific weight ratio, for use as a medicament. A further subject of the present invention is a method for treating a viral infection, comprising administering to a subject in need thereof the pharmaceutical combination or composition of the present

	invention, wherein the viral infection preferably comprises an HIV-infection." US '332, [0061]. US '332 discloses that the "[i]n another particularly preferred embodiment, the combination of the present invention is administered once daily." US '332, [0077]. US '332 further discloses that "[t]he pharmaceutical composition of the present invention can be preferably a solid oral dosage form. It is further preferred that the dosage form of the invention is a capsule or a tablet, in particular a tablet." *Id.* at [0107]. US '332 describe "preferred embodiment [of] the pharmaceutical composition compris[ing] … 40 to 60 mg dolutegravir, … 250 mg emtricitabine, … and 5 to 42 mg tenofovir; and pharmaceutical excipients." US '332, [0086]-[0090]. US '332 further discloses that "[i]n a preferred embodiment the pharmaceutical composition of the present invention comprises 50 mg dolutegravir, 50 mg dolutegravir, about 200 mg emtricitabine and about 25 mg tenofovir." US '332, [0092]. US '332 also discloses the total amount of dolutegravir, emtricitabine and tenofovir alafenamide comprised in the present pharmaceutical combination for use as a medicament is between 70.5 and425 mg per day, in particular 192 to 326 mg per day." US '332, [0075]. Genvoya Label discloses a tablet composition for oral administration that contains 150 mg of the INSTI elvitegravir (EVG), 150 mg of PK enhancer cobicistat (COBI), 200 mg of NRTI emtricitabine (FTC), and 11.2 mg of NRTI tenofovir alafenamide (TAF) fumarate (equivalent to 10 mg TAF)). Genvoya, 22.

	Genvoya Assessment discloses film-coated tablets containing the following active substances: 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (as 11.2 mg of the fumarate)." Genvoya Assessment, 10. Genvoya Assessment further 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. Genvoya Assessment, 74-75. WO '846 discloses therapeutic combinations of TAF and FTC for treating HIV. WO '846, 3:13-18. WO '846 further discloses that combination can additionally include an INSTI. WO '846, 18:23-26. WO '846 further discloses an exemplary formulation containing 25 mg of TAF and 200 mg FTC. WO '846, 37:13-20. WO '846 discloses a pharmaceutical composition comprising "(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. Stribild Label discloses a tablet composition for oral administration that contains a combination of 150 mg of the integrase strand transfer inhibitor elvitegravir, 200 mg and 300 mg respectively of the nucleos(t)ide analog HIV-1 reverse transcriptase inhibitors emtricitabine and tenofovir disoproxil

	fumarate, and 150 mg of the pharmacokinetic enhancer cobicistat. Stribild Label, 1. US '122 discloses a solid dose form (e.g. tablets) comprising a compound of Formula I (i.e. elvitegravir), Formula III (i.e. emtricitabine), Formula IV (i.e. tenofovir disoproxil fumarate), 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. Compound of Formula II 150 mg Formulation Components / % 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. *Id.* at [0022]. US '122 further discloses examples of tablets similar to Stribild. *Id.* at [0063]-[0065] (Examples 2-4).

	The ’385 patent discloses 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. ’385 patent, 8:9-34. 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. ’385 patent, Abstract, 7:32-35, 38:6-9.

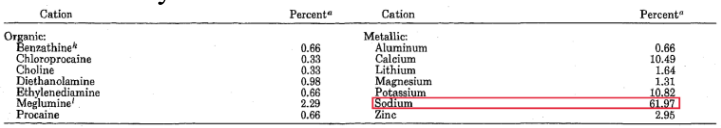
	The ’385 patent discloses, “[t]he present invention relates to novel compounds possessing an antiviral activity, in detail polycyclic carbamoylpyridone derivatives possessing an inhibitory activity against HIV integrase and a pharmaceutical composition containing the same, especially an anti-HIV agent.” ’385 patent, 1:15-20. 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. 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. 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. WO '351 further discloses that 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." WO '351, 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." WO '351, 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." WO '351, 16:15-18. WO '351 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." WO '351, 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." WO '351, 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." WO '351, 17:27-28, 23:6-8. The Stribild Assessment discloses, "Stribild is presented for use as a bilayer tablet – one layer contains EVG/COBI and one FTC/TDF." Stribild Assessment, 33. The Atripla Assessment teaches, "The granulations are blended separately with extra-granular magnesium stearate, compressed into bilayer tablets, and then film-coated. Process optimization studies were conducted in order to establish critical process parameters for the wet granulation of efavirenz, dry granulation of emtricitabine/tenofovir, bilayer tablet compression, and aqueous film-coating operations." Atripla Assessment, 5.

	The Genvoya Assessment states, "GS-US-292-0101 was an open-label crossover study that compared two formulations (monolayer and bilayer) of E/C/F/TAF (each containing either 25 or 40 mg TAF as the monofumarate) with Stribild and with TAF 25 mg alone." Genvoya Assessment, 75. The Eviplera Assessment teaches, "The exposure of FTC/RPV/TDF after single oral administration of a bilayer formulation and the individual compounds was compared in fasted dogs and has demonstrated comparable systemic exposure to all compounds." Eviplera Assessment, 18. US '857 discloses "a tablet of the invention wherein the first layer comprises: Ingredient / Unit Formula for Tablets (mg/tablet) Rilpivirine HCl — 27.5 ± 1.4 Microcrystalline Cellulose — 60.0 ± 3 Polysorbate 20 — 0.4 ± 0.02 Croscarmellose Sodium — 16.1 ± 0.8 and the second layer comprises: Ingredient / Unit Formula for Tablets (mg/tablet) Emtricitabine — 200 ± 10 Tenofovir DF — 300 ± 15 Microcrystalline Cellulose — 150 ± 7.5 Croscarmellose Sodium — 60 ± 3 US '857, [0066]. US '857 further discloses bilayer tablets for keeping rilpivirine separate from FTC and TDF. *Id.* at [0067]-[0071]. 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, 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]. US '079 also discloses that 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. 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. Havele discloses that TDF showed complete degradation occurred immediately after addition of at room temperature). Havele, 3, 5. Venkatasan discloses that TDF undergoes 31% decomposition under basic stress conditions. Venkatasan, 4. Kurmi discloses that in a basic solution environment (0.5 N NaOH), TDF was completely converted into degradation product

	T1 in 3 h. Kurmi, 96121. Kurmi further discloses that under basic solid state stress conditions, TDF degraded into several different products. *Id.* at 96121-25. Berge teaches "[t]he chemical, biological, physical and economic characteristics of medicinal agents can be manipulated and, hence, often optimized by conversion to a salt form," where "salt-forming agents are often chosen empirically … [and] the preferred form is selected by pharmaceutical chemists on a practical basis: cost of raw materials, ease of crystallization, and percent yield … [as well as] stability, hygroscopicity, and flowability of the resulting bulk drug." Berge at 1. Berge also teaches Table 1 as a list of "FDA-approved commercially marketed salts" that includes sodium:  Remington 21st teaches in Table 38-5 that sodium salts were an API-salt form known since at least 1983:

Cation	Percent[a]	Cation	Percent[a]
Organic:		Metallic:	
Benzathine[k]	0.66	Aluminum	0.66
Chloroprocaine	0.33	Calcium	10.49
Choline	0.33	Lithium	1.64
Diethanolamine	0.98	Magnesium	1.31
Ethylenediamine	0.66	Potassium	10.82
Meglumine[l]	2.29	Sodium	61.97
Procaine	0.66	Zinc	2.95

Table 38-5. Molecular Forms Marketed Worldwide Between 1983 and 1996

SALT FORM	FREQ.	GROUP[a]	PK_A	CLOGP	MW
No salt form	390	0			
Hydrobromide	1	1	−8	0.45	80.91
Hydrochloride	102	1	−6.1	0.24	36.46
Sulfate	5	1	−3	−1.58	98.08
Nitrate	6	1	−1.44	2.09	63.01
Phosphate	2	1	2.15	−1.95	96.99
Glucuronate	1	1	3.22[b]	−3.74	194.14
Acetate	8	1	4.76	−0.36	59.05
Maleate	3	2	1.92	−0.18	116.07
Fumarate	8	2	3.02	−0.18	116.07
Tartrate	1	2	3.03	−2.21	150.09
Citrate	1	2	3.13	−2.11	189.10
Succinate	2	2	4.21	−0.62	118.09
Mesylate	8	3	−1.20	−1.31	96.11
Acistrate	1	3	4.91[b]	7.98	284.49
Besylate	2	4	−2.80[b]	0.23	157.17
Tosylate	3	4	−1.34	0.88	171.20
Xinafoate	1	4	2.66[b]	3.00	188.18
Potassium	1	1	16		39.10
Sodium	37	1	14.77		23.00
Tromethamine	2	1	8.07[c]	−3.17	121.14
Bismuth	1	1	1.58		208.98
Bromide	6	5			79.90
Chloride	2	5			35.45

[a] Groups: 0 = No salt, 1 = Polar, 2 = Multifunctional, 3 = Flexible aliphatics, 4 = Planar aromatics, 5 = Quartenary.
[b] Calculated pK_a.
[c] Data from *CRC Handbook of Basic Tables for Chemical Analysis*, page 469.
From Serajuddin ATM, Sheen P, Augustine MA. To market, to market. In: Bristol J, ed. *Annu Rep Med Chem.* New York: Academic, 1983–1996.

Serajuddin teaches that "[s]alt formation is the most common and effective method of increasing solubility of acidic and basic drugs." Serajuddin at 603.

Serajuddin also teaches that "[s]alt formation is also the most common approach of increasing solubility, dissolution rate and ultimately bioavailability of poorly water-soluble ionizable drugs in solid dosage forms." Serajuddin at 614.

Serajuddin further informs that "Table 2 gives the distribution of 120 salts approved by the FDA during the 12-year period from 1995 to 2006, where the hydrochloride salt is the predominant salt form among the basic drugs and the sodium salt is the predominant form for acidic drugs." Serajuddin at 613. The portion of Table 2 that shows salts of acidic drugs shows:

Salts of acidic drugs	Total number
Sodium	12
Calcium	4
Potassium	2
Tromethamine	1
Total of all salts of acidic drugs	19

Paulekuhn teaches that "[s]alt formation is a well-known technique to modify and optimize the physical chemical properties of an ionizable research and development compound[, where] [p]roperties such as solubility, dissolution rate, hygroscopicity, stability, impurity profiles and crystal habit can be influenced by using a variety of pharmaceutically acceptable counterions." Paulekuhn, 6665 (also noting that "formation of salts is almost the only chemical technique available to change aqueous solubility and dissolution rate without changing the API molecule")

According to Paulekuhn, "[a]mong the cations used to form API salts of acidic molecules, the sodium ion strongly dominates with an incidence of 75.3% over the entire period. From 1982 to 1991, the fraction of sodium salts was more than 90%. This decreased to 62.5% during the 2002-2006 period." *Id.* at 6667.

Wells teaches, "A major improvement in solubility can be achieved by forming a salt." Wells at 116.

In discussing potential pharmaceutical salts to be used for the salt forms of drugs, Wells provides Table 8.4, which presents such salts, including sodium, , along with the pKa of each salt forming cation:

Table 8.4 Potential pharmaceutical salts

Basic drugs			Acidic drugs		
Anion	pK_a	% Usage	Cation	pK_a	% Usage
Hydrochloride	−6.10	43.0	Potassium	16.00	10.8
Sulphate	−3.00, +1.96	7.5	Sodium	14.77	62.0
Mesylate	−1.20	2.0	Lithium	13.82	1.6
Maleate	1.92, 6.23	3.0	Calcium	12.90	10.5
Phosphate	2.15, 7.20, 12.38	3.2	Magnesium	11.42	1.3
Salicylate	3.00	0.9	Diethanolamine	9.65	1.0
Tartrate	3.00	3.5	Zinc	8.96	3.0
Lactate	3.10	0.8	Choline	8.90	0.3
Citrate	3.13, 4.76, 6.40	3.0	Aluminium	5.00	0.7
Succinate	4.21, 5.64	0.4			
Acetate	4.76	1.3			
Others		31.4	Others		8.8

Bastin encourages the "[s]election of an appropriate salt form for a new chemical entity" because it "provides the pharmaceutical chemist and formulation scientist with the opportunity to modify the characteristics of the potential drug substance and to permit the development of dosage forms with good bioavailability, stability, manufacturability, and patient compliance." Bastin, 427.

Brittain teaches, "Prudent drug development programs will identify the preferred crystalline form early in development, with a polymorph/salt group working in close conjunction with process chemists to make the thermodynamically preferred polymorphic form the initial kilogram-scale batch." Brittain, 358.

The Triumeq Label discloses the ingredients of Triumeq as including the sodium salt form of dolutegravir, stating, "Each film-coated tablet contains abacavir sulfate equivalent to 600 mg of abacavir, dolutegravir sodium equivalent to 50 mg of dolutegravir, and 300 mg of lamivudine." Triumeq Label, 17.

	The Triumeq label teaches, "TRIUMEQ, a combination of dolutegravir (integrase strand transfer inhibitor [INSTI]), abacavir, and lamivudine (both nucleoside analogue reverse transcriptase inhibitors) is indicated for the treatment of HIV-1 infection." Triumeq Label, 1. The Triumeq Assessment discloses, "Triumeq is presented as film-coated tablets containing a fixed combination of dolutegravir sodium equivalent to 50 mg dolutegravir, 600 mg of abacavir (as sulfate) and 300 mg of lamivudine." Triumeq Assessment, 6. The Triumeq Assessment teaches, "A once-daily fixed-dose combination (FDC) single tablet regimen (STR) that combines the integrase inhibitor (INI) dolutegravir (DTG) with the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir sulfate (abacavir, ABC) and lamivudine (3TC) was developed for use in the treatment of human immunodeficiency virus (HIV) infection." Triumeq Assessment, 6. WO '116 is specifically directed to BIC sodium (Formula II) and a crystalline form thereof (Form I), along with pharmaceutical formulations and therapeutic uses therefore. WO '116, [0002], [0006]-[0008], [0043]-[0057] (describing crystalline forms of Formula II).; *see also* Section IV.A of the narrative (discussing the disclosure of the family member '342 and '067 patents). 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). 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]. *See also* Weller; Castagna; Juday; Lunzen; Walmsley; Johns; PR; Mathais; Min; Highleyman; Acosta; BICANDA01157927; NCT02607956-1; NCT02607856-2; Abebe; Shende; Poster #416; Poster # 414; Poster #413.

Claim 6	
Claim Elements	Prior Art Teachings of Claim Elements
The tablet of claim 1,	The prior art teachings disclosing the tablets of any of claim 1 is set forth above and incorporated herein by reference.
wherein the tablet comprises 25 mg tenofovir alafenamide as tenofovir alafenamide fumarate.	US '332 discloses that "[i]n a preferred embodiment the pharmaceutical composition of the present invention comprises 50 mg dolutegravir, 50 mg dolutegravir, about 200 mg emtricitabine and about 25 mg tenofovir." US '332, [0092]. US '332 describes pharmaceutical combinations comprising 40 to 60 mg DLT, 150 to 250 mg FTC, and 5 to 42 mg TAF, along with pharmaceutical excipients. US '332, [0086]-[0090]. US '332 further discloses a specific combination comprising about 50 mg DLT, about 200 mg FTC and about 25 mg TAF. *Id.* at [0091]-[0092]. US '332 discloses, "Acids which are used to prepare pharmaceutically acceptable acid addition salts are preferably

	those which form non-toxic acid addition salts. In a particularly preferred embodiment tenofovir alafenamide is present in form of its hemifumarate or fumarate, especially its hemifumarate." US '332, [0053]. US '356 further discloses 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.US '35, [0156]-[0163]. 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. US '356, 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). US '356 further discloses that [i]n certain embodiments, a compound disclosed herein 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. US '356, [0177]. US '356 refers "pharmaceutically acceptable salt" to "a salt of a compound that is pharmaceutically acceptable and that possesses (or can be converted to a form that possesses) the desired pharmacological activity of the parent compound. Examples of 'pharmaceutically acceptable salts' of the compounds disclosed herein include salts derived from an appropriate base, such as . . . an alkaline earth metal (for example, magnesium). . . ." US '356, [0075].

	US ’902 discloses, “a novel pharmaceutical product containing efavirenz, emitricitabine and tenofovir DF are provided as a multicomponent unitary oral dosage form.” US ’902, Abstract. US ’857 describes “multilayer tablets that contain rilpivirine hydrochloride, emtricitabine, and tenofivir disoproxil fumarate.” US ’857, Abstract. US ’856 discloses pharmaceutical compositions comprising TAF hemifumarate and one or more additional therapeutic agents selected from the group consisting of “HIV protease inhibiting compounds, HIV nonnucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, and CCR5 inhibitors.” *Id.* at [0010]-[0011], [0057]. WO ’846 teaches the following formulation: Formulation D: |	mg/tablet
GS-7340	25
emtricitabine	200
Microcrystalline Cellulose	200
Lactose Monohydrate	330
Croscarmellose Sodium	60
Pregelatinized Starch	50
Magnesium Stearate	10
	875 | WO ’846, 13:12-24. WO ’846 discloses the following formulation:

	Formulation G — mg/tablet GS-7340 — 300 emtricitabine — 200 Hydroxypropyl Methylcellulose — 112 Lactose B.P. — 53 Pregelatinized Starch B.P. — 28 Magnesium Stearate — 7 total: — 700 WO ’846, 13:23-24. WO ’846 further discloses an exemplary formulation containing 25 mg of TAF and 200 mg FTC. WO ’846, 37:13-20. Gilead/Janssen discusses, “Phase III-ready HIV treatment that will combine Gilead’s tenofovir alafenamide (TAF) and emtricitabine, and Janssen’s rilpivirine.” Gilead/Janssen, 1. Gilead/Janssen states, “Gilead and Janssen agreed to develop and commercialize a once-daily single tablet regimen for HIV that combines darunavir with TAF, emtricitabine and a third Gilead compound, cobicistat (marketed as TYBOST®).” Gilead/Janssen, 2. Gilead/Janssen discloses that 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. WO ’323 discloses, “In further embodiments, the additional therapeutic agent is selected from one or more of: . . (3) HIV nucleoside inhibitors of reverse transcriptase selected from the group consisting of zidovudine, emtricitabine, didanosine, stavudine, zaicitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, ±-FTC, D-d4FC,

	emtricitabine, phosphazide, fozivudine tidoxil, apricitibine (AVX754), KP-1461, GS- 9131 (Gilead Sciences) and fosalvudine tidoxil (formerly HDP 99.0003); (4) HIV nucleotide inhibitors of reverse transcriptase selected from the group consisting of tenofovir, tenofovir disoproxil fumarate, tenofovir alafenarnide fumarate (Gilead Sciences), GS-7340 (Gilead Sciences), GS-9148 (Gilead Sciences), adefovir, adefovir dipivoxii, CMX-001 (Chimerix) or CMX-157 (Chimerix) . . . .” WO ’323, 38:1-2; 13-21. US ’426 states, “In further embodiments, Wnt signaling pathway inhibitor is administered in combination with one or more of the following agents: abacavir, acyclovir, acyclovir, adefovir, amantadine, amprenavir, ampligen, arbidol, atazanavir, atripla, boceprevir, cidofovir, combivir, complera, darunavir, delavirdine, didanosine, docosanol, dolutegravir, edoxudine, efavirenz, emtricitabine, enfuvirtide, entecavir, famciclovir, fomivirsen, fosamprenavir, foscarnet, fosfonet, ganciclovir, ibacitabine, imunovir, idoxuridine, imiquimod, indinavir, inosine, interferon type III, interferon type II, interferon type I, lamivudine, lopinavir, loviride, maraviroc, moroxydine, methisazone, nelfinavir, nevirapine, nexavir, oseltamivir, peginterferon alfa-2a, penciclovir, peramivir, pleconaril, podophyllotoxin, raltegravir, ribavirin, rimantadine, ritonavir, pyramidine, saquinavir, stavudine, stribild, tenofovir, tenofovir disoproxil, tenofovir alafenamide fumarate (TAF), tipranavir, trifluridine, trizivir, tromantadine, truvada, valaciclovir, valganciclovir, vicriviroc, vidarabine, viramidine, zalcitabine, zanamivir, or zidovudine, and combinations thereof.” US ’426, [0139]. US ’850 further claims, “The method of claim 1 wherein the compound that inhibits HIV replication are selected from the

	group consisting of nucleoside reverse transcriptase inhibitors (NRTIs) such as tenofovir, emtricitabine, zidovudine (AZT), lamivudine (3TC), abacavir, and tenofovir alafenamide fumarate; non-nucleotide reverse transcriptase inhibitors (NNRTIs) such as efavirenz, rilpivirine, and etravirine; integrase inhibitors such as raltegravir and elvitegravir; and protease inhibitors such as ritonavir, darunavir, atazanavir, lopinavir, and cobicistat." US '850, Claim 2. US '332 teaches, "[i]n a particularly preferred embodiment tenofovir alafenamide is present in form of its hemifumarate or fumarate, especially its hemifumarate." US '332, [0053]. US '332 claims, "Pharmaceutical combination comprising (a) dolutegravir, (b) emtricitabine and (c) tenofovir for use as a medicament, wherein the weight ratio of (a) dolutegravir and (b) emtricitabine is from 1:1 to 1:3." US '332, Claim 1. US '332 further claims, "Pharmaceutical combination for use according to any one of the preceding claims, wherein tenofovir is used in form of a prodrug of tenofovir." US '332, Claim 5. US '332 further claims, "Pharmaceutical combination for use according to claim 5, wherein the prodrug of tenofovir is tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide or hexadecyloxypropyl tenofovir." US '332, Claim 6. US '332 claims, "A kit for the treatment of a viral infection, in particular of an HIV-infection, comprising (i) 10 to 75 mg dolutegravir, (ii) 50 to 150 mg emtricitabine, (iii) 0.5 to 400 mg tenofovir or a prodrug thereof." US '332, Claim 15.

	WO ’466 claims, “[a] pharmaceutical composition comprising a self-emulsifying drug delivery system, wherein the self-emulsifying drug delivery system comprises efavirenz and one or more pharmaceutically acceptable excipient.” WO ’466, Claim 1. WO ’466 further claims, “[a] pharmaceutical composition according to any preceding claim, further comprising at least one additional active ingredient such as protease inhibitors, nucleoside reverse transcriptase inhibitors, non-nucleotide reverse transcriptase inhibitors, integrase inhibitors, or any combination thereof.” WO ’466, Claim 23. WO ’466 further claims, “[a] pharmaceutical composition according to claim 23, wherein the at least one additional active ingredient comprises emtricitabine, tenofovir disproxil fumarate, tenofovir alafanamide fumarate, lamivudine, stavudine, zidovudine, or any combination thereof.” WO ’466, Claim 24. WO ’720 discloses a combination of 200 mg FTC, 3-40 mg TAF, 50-500 mg cobicistat, 150 mg elvitegravir. WO ’720, [0028]. The ’791 patent discloses tenofovir alafenamide (TAF) as a compound of structure (6), having the chemical name 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino] phenoxyphosphinyl]methoxy]propyl]adenine, also designated as GS-7340.

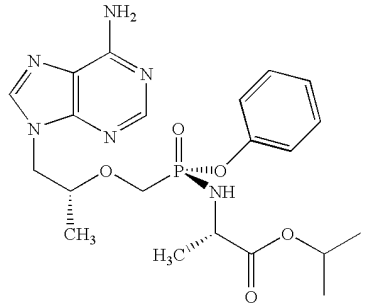
	(6)  ’791 patent, 4:13-32. Example 4 of the ’791 patent describes a method for the preparation of tenofovir alafenamide monofumarate (TAF monofumarate) from the compound GS-7340. The detailed procedure involves the crystallization of TAF monofumarate from acetonitrile. ’791 patent, 24:14-16, 24:38-48; *see also* 21:50-66 (preparation of TAF monofumarate (1:1) salts from a mixture of TAF (GS7340) and its diastereomer (GS-7339). Table 1 of the ’791 patent discloses that GS-7340 exhibits greater activity and stability compared to tenofovir disoproxil fumarate (TDF) and tenofovir. ’791 patent at 28:5-15. The ’791 patent also teaches that the TAF compounds disclosed therein may be “formulated into compositions containing pharmaceutically acceptable excipients, [which] are used in effective doses in the therapy or prophylaxis of viral (particularly HIV or hepadnaviral) infections.” ’791 patent, 4:54-59, 14:42-53. ’791 patent discloses TAF showing 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. ’791 patent, 27:29-28:37. ’791 patent further discloses the following tables:

TABLE 1

In Vitro Activity and Stability

	HIV-1		Stability T ½ (min)		
	Activity $IC_{50\ \mu M}$	Cytotoxicity $CC_{50\ \mu M}$	Human Plasma	MT-2 Cell Extract	(P/MT-2)
GS 7340	0.005	>40	90.0	28.3	3.2
TDF	0.05	70	0.41	70.7	0.006
Tenofovir	5	6000	—	—	—

TABLE 2

PMPA Metabolites in Plasma, PBMCs and RBCs After 1 h Incubation of PMPA Prodrugs or PMPA in Human Blood.

		Total C-14 Recovered,	Metabolites (% of Total Peak Area)					
Compound	Matrix	μg-eq	PMPA %	PMPAp, %	PMPApp, %	Met. X, %	Met. Y, %	GS 7340, %
GS-7340	Plasma/FP	43.0	1	—	—	2	13	84
(60 μg-eq)	PBMC	1.25	45	16	21	18	—	—
	RBC/FP	12.6	8	—	—	24	11	57
			PMPA	PMPAp	PMPApp	Mono-POC	GS-4331	
GS-4331	Plasma/FP	48.1	11	—	—	89	—	
(TDF)	PBMC	0.133	50	25	18	7	—	
(60 μg-eq)	RBC/FP	10.5	93	7.0	—	—	—	
			PMPA	PMPAp	PMPApp			
PMPA	Plasma/FP	55.7	100	—	—			
(60 μg-eq)	PBMC	0.033	86	14	—			
	RBC/FP	3.72	74	10	16			

’791 patent, Tables 1-2.

Lee discloses that “[t]he amidate prodrug GS 7340 was designed to overcome the permeability limitations of tenofovir by masking the dianion with a neutral promoiety and increasing the plasma stability of the prodrug relative to its intracellular stability. The in vitro anti-HIV potency of GS 7340 (EC_{50}=0.005 μM) is comparable to the most potent protease inhibitors and reflects the greater cell permeation of GS 7340 compared to tenofovir. In addition to favorable potency and a long intracellular half-life, the *in vivo* administration of GS 7340 results in an enhanced

	distribution of lymphatic tissue compared to tenofovir DF." Lee at 1903. Lee further discloses that "[w]ith GS 7340, it should be possible to reduce the total dose of tenofovir, thereby minimizing systemic exposure, while at the same time increasing antiviral activity." *Id*. at 1905. Lee discloses TAF as 10 times more potent than TDF toward HIV-1, with eight times improved selectivity index. Lee, 1900 (Table 1). Lee further discloses, "the high concentrations of tenofovir observed in lymphatic tissues after oral administration of GS 7340 are expected to result in increased clinical potency relative to tenofovir DF." Lee, 1905 Lee further discloses that "[w]ith GS-7340, it should be possible to reduce the total dose of tenofovir, thereby minimizing systemic exposure, while at the same time increasing antiviral activity." Lee, 1905. US '856 discloses are pharmaceutical compositions comprising TAF hemifumarate and one or more additional therapeutic agents selected from the group consisting of "HIV protease inhibiting compounds, HIV nonnucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, and CCR5 inhibitors." *Id.* at [0010]-[0011], [0057]. HIV Guidelines states that "[a]n antiretroviral regimen for a treatment-naive patient generally consists of two nucleoside 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." HIV Guidelines, D-1. HIV Guidelines further recommends combination of the INSTIs elvitegravir and raltegravir with tenofovir and emtricitabine. HIV Guidelines, 1, i. British HIV Guidelines describes tenofovir and emtricitabine as the preferred NRTI backbone for HIV therapy, to be combined with an additional agent such as an INSTI. British HIV Guidelines, 13. NCT '694 discloses a study that "evaluate[s] the efficacy, safety and tolerability of GS-9883 + emtricitabine/tenofovir alafenamide (FTC/TAF) fixed dose combination (FDC) versus dolutegravir (DTG) + FTC/TAF in HIV-1 Infected, antiretroviral treatment-naive adults. This study will also evaluate the pharmacokinetic (PK) profile of GS-9883, FTC and TAF." NCT '694, Study Description. NCT '694 further discloses an "active comparator" with "Drug: FTC/TAF, Emtricitabine/Tenofovir Alafenamide (FTC/TAF) 200 mg/25 mg tablet administered orally; Drug: DTG, Dolutegravir (DTG) 50 mg tablet administered orally." NCT '694, Arms and Interventions. Tivicay Assessment discloses combination therapies with DLT sodium, FTC and tenofovir disoproxil for treating HIV. Tivicay Assessment, 43, 50-51, 89. 2013 Tivicay Label also discloses Tivicay containing 50 mg of dolutegravir sodium as an HIV INSTI indicated in combination with other antiretroviral agents (e.g., emtricitabine/tenfovoir

	(TRUVADA), for the treatment of HIV-1 infection. 2013 Tivicay Label, 1, 4, 24. Truvada Label discloses combining 200 mg emtricitabine, 300 mg tenofovir alafenamide, and 600 mg efavirenz. Truvada Label. Complera Label discloses a tablet composition for oral administration that contains 200 mg of NRTI emtricitabine, and 300 mg of NRTI tenofovir DF, and 27.5 mg of NNRTI rilpivirine hydrochloride. Complera Label, 1, 22 The Stribild Label states that a Stribild table consists of "150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 300 mg of tenofovir disoproxil fumarate." Stribild Label, 1; *see also id.* at 22-23. The Genvoya Label states, "Each GENVOYA tablet contains 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (TAF) (equivalent to 11.2 mg of tenofovir alafenamide fumarate)." Genvoya Label, 4. 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. Genvoya Assessment, 74-75. The Genvoya Assessment teaches, "The overall goal of Genvoya film coated tablet development was to create a tablet containing the same amounts of elvitegravir, cobicistat and emtricitabine

	active substances as currently combined in Stribild fixed dose combination film-coated tablet and to replace tenofovir disoproxil contained in Stribild with tenofovir alafenamide, a second-generation prodrug of tenofovir." Genvoya Assessment, 18. Genvoya Assessment discloses film-coated tablets containing the following active substances: 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (as 11.2 mg of the fumarate)." Genvoya Assessment, 10. WO '351 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." WO '351, 19:3-12. Ruane discloses that "HIV-1 RNA responses for the 8-mg TAF treatment group were similar to that of the 300-mg TDF group. However, median $DAVG_{11}$ [(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, 451-52 Ruane further states that "[c]ompared 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." Ruane, 454. Sax teaches that "Relative to TDF, TAF is more stable in plasma." Sax, 53. Astuti refers to tenofovir alafenamide (TAF), where "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." Astuti, 11. Astuti further discloses that the "possibility to use small doses of TAF instead of TDF could further widen the STR options as bulky molecules such as PIs could be successfully coformulated." Astuti, 11. Llibre teaches that 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. Llibre, 172. WO '799 teaches, In addition, the compounds of the present invention may be used in combination with one or more other agents useful in the prevention or treatment of HIV. Examples of such agents include: Nucleotide reverse transcriptase inhibitors such as zidovudine, didanosine, lamivudine, zalcitabine, abacavir, stavudine, adefovir, adefovir dipivoxil,

	fozivudine, todoxil, emtricitabine, alovudine, amdoxovir, elvucitabine, tenofovir disoproxil fumarate, dexelvucitabine, festinavir, racivir, and similar agents; Non-nucleotide reverse transcriptase inhibitors (including an agent having anti- oxidation activity such as immunocal, oltipraz, etc.) such as nevirapine, delavirdine, efavirenz, loviride, immunocal, oltipraz, capravirine, lersivirine, doravirine, rilpivirine, etravirine, tenofovir alafenamide fumarate, and similar agents; Protease inhibitors such as saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, fosamprenavir, brecanavir, darunavir, atazanavir, tipranavir, palinavir, lasinavir, and similar agents; Entry, attachment and fusion inhibitors such as enfuvirtide (T -20), T - 1249, PRO -542, PRO - 140, ibalizumab, cenicriviroc, INCB -9471, monomeric DAPTA, AMD -070, ibalizumab, BMS- 806, fostemsavir, temsavir, and 5 -Helix and similar agents; Integrase strand transfer inhibitors such as raltegravir, elvitegravir, dolutegravir, cabotegravir, GS - 9883, and similar agents; Maturation inhibitors such as PA -344, PA - 457, BMS - 955176, as well as those disclosed in PCT Patent Application No. WO2011/100308, PCT Patent Application No. PCT/US2012/024288, Chinese PCT Application No. PCT/CN2011/001302, Chinese PCT Application No. PCT/CN2011/001303, Chinese PCT Application No. PCT/CN2011/002105, PCT/CN2011 /002159, WO2013/090664, WO2013/123019 , WO 2013/043778, WO 2014/123889, WO 2011/153315, WO2011/153319, WO2012/106188, WO 2012/106190, WO 2013/169578, and WO 2014/13081, and similar agents;

	CXCR4 and /or CCR5 inhibitors such as vicriviroc, TAK779, maraviroc, TAK449, as well as those disclosed in WO 02/74769, PCT/US03/39644, PCT/US03/39975, PCT/US03/39619, PCT/USO3/39618, PCT/US03/39740, and PCT/US03/39732, and similar agents. Neutralizing antibodies such as VRC01, VRC0710e8, pro140, PGT121, PGT128, PGT145, PG9, 3BNC117, ibalizumab, N6 and similar agents. WO '799, [0356]-[0365]. 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. WO '116 at [0096]. 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. 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.

	See also Weller; Castagna; Juday; Lunzen; Walmsley; Johns; PR; Mathais; Min; Highleyman; Acosta; BICANDA01157927; NCT02607956-1; NCT02607856-2; Abebe; Shende; Poster #416; Poster # 414; Poster #413.

Claim 7	
Claim Elements	Prior Art Teachings of Claim Elements
The tablet of claim 1,	The prior art teachings disclosing the tablets of any of claim 1 is set forth above and incorporated herein by reference.
wherein the tablet comprises 28 mg tenofovir alafenamide hemifumarate.	US '332 discloses that "[i]n a preferred embodiment the pharmaceutical composition of the present invention comprises 50 mg dolutegravir, 50 mg dolutegravir, about 200 mg emtricitabine and about 25 mg tenofovir." US '332, [0092]. US '332 describes pharmaceutical combinations comprising 40 to 60 mg DLT, 150 to 250 mg FTC, and 5 to 42 mg TAF, along with pharmaceutical excipients. US '332, [0086]-[0090]. US '332 further discloses a specific combination comprising about 50 mg DLT, about 200 mg FTC and about 25 mg TAF. *Id.* at [0091]-[0092]. US '332 discloses, "Acids which are used to prepare pharmaceutically acceptable acid addition salts are preferably those which form non-toxic acid addition salts. In a particularly preferred embodiment tenofovir alafenamide is present in form of its hemifumarate or fumarate, especially its hemifumarate." US '332, [0053]. US '356 further discloses HIV nucleoside inhibitors of reverse transcriptase (NRTIs), e.g., emtricitabine, and HIV nucleotide inhibitors of reverse transcriptase (NtRTIs), e.g., GS-7340

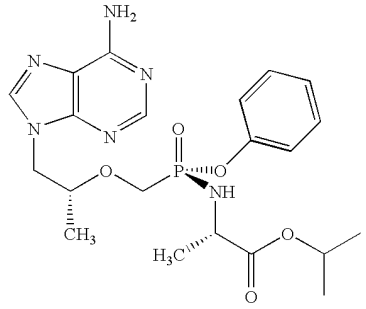
	(TAF) and tenofovir alafenamide (TAF) fumarate.US '35, [0156]-[0163]. US '356 also claims pharmaceutical compositions comprising an HIV INSTI of Formula (I) and one or more additional therapeutic agents selected from, e.g., NRTIs and NtRTIs, and methods of treating HIV therewith. US '356, claims 33-36 (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). US '356 further discloses that [i]n certain embodiments, a compound disclosed herein 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. US '356, [0177]. US '356 refers "pharmaceutically acceptable salt" to "a salt of a compound that is pharmaceutically acceptable and that possesses (or can be converted to a form that possesses) the desired pharmacological activity of the parent compound. Examples of 'pharmaceutically acceptable salts' of the compounds disclosed herein include salts derived from an appropriate base, such as . . . an alkaline earth metal (for example, magnesium). . . ." US '356, [0075]. US '902 discloses, "a novel pharmaceutical product containing efavirenz, emitricitabine and tenofovir DF are provided as a multicomponent unitary oral dosage form." US '902, Abstract. US '857 describes "multilayer tablets that contain rilpivirine hydrochloride, emtricitabine, and tenofivir disoproxil fumarate." US '857, Abstract.

	US ’856 discloses pharmaceutical compositions comprising TAF hemifumarate and one or more additional therapeutic agents selected from the group consisting of “HIV protease inhibiting compounds, HIV nonnucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, and CCR5 inhibitors.” *Id.* at [0010]-[0011], [0057]. WO ’846 teaches the following formulation: Formulation D: GS-7340 — 25 mg/tablet emtricitabine — 200 Microcrystalline Cellulose — 200 Lactose Monohydrate — 330 Croscarmellose Sodium — 60 Pregelatinized Starch — 50 Magnesium Stearate — 10 875 WO ’846, 13:12-24. WO ’846 discloses the following formulation: Formulation G — mg/tablet GS-7340 — 300 emtricitabine — 200 Hydroxypropyl Methylcellulose — 112 Lactose B.P. — 53 Pregelatinized Starch B.P. — 28 Magnesium Stearate — 7 total: 700 WO ’846, 13:23-24.

	WO ’846 further discloses an exemplary formulation containing 25 mg of TAF and 200 mg FTC. WO ’846, 37:13-20. Gilead/Janssen discusses, “Phase III-ready HIV treatment that will combine Gilead’s tenofovir alafenamide (TAF) and emtricitabine, and Janssen’s rilpivirine.” Gilead/Janssen, 1. Gilead/Janssen states, “Gilead and Janssen agreed to develop and commercialize a once-daily single tablet regimen for HIV that combines darunavir with TAF, emtricitabine and a third Gilead compound, cobicistat (marketed as TYBOST®).” Gilead/Janssen, 2. Gilead/Janssen discloses that 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. WO ’323 discloses, “In further embodiments, the additional therapeutic agent is selected from one or more of: . . (3) HIV nucleoside inhibitors of reverse transcriptase selected from the group consisting of zidovudine, emtricitabine, didanosine, stavudine, zaicitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, ±-FTC, D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, apricitibine (AVX754), KP-1461, GS- 9131 (Gilead Sciences) and fosalvudine tidoxil (formerly HDP 99.0003); (4) HIV nucleotide inhibitors of reverse transcriptase selected from the group consisting of tenofovir, tenofovir disoproxil fumarate, tenofovir alafenarnide fumarate (Gilead Sciences), GS-7340 (Gilead Sciences), GS-9148 (Gilead Sciences), adefovir, adefovir dipivoxii, CMX-001 (Chimerix) or CMX-157 (Chimerix) . . . .” WO ’323, 38:1-2; 13-21.

	US ’426 states, “In further embodiments, Wnt signaling pathway inhibitor is administered in combination with one or more of the following agents: abacavir, acyclovir, acyclovir, adefovir, amantadine, amprenavir, ampligen, arbidol, atazanavir, atripla, boceprevir, cidofovir, combivir, complera, darunavir, delavirdine, didanosine, docosanol, dolutegravir, edoxudine, efavirenz, emtricitabine, enfuvirtide, entecavir, famciclovir, fomivirsen, fosamprenavir, foscarnet, fosfonet, ganciclovir, ibacitabine, imunovir, idoxuridine, imiquimod, indinavir, inosine, interferon type III, interferon type II, interferon type I, lamivudine, lopinavir, loviride, maraviroc, moroxydine, methisazone, nelfinavir, nevirapine, nexavir, oseltamivir, peginterferon alfa-2a, penciclovir, peramivir, pleconaril, podophyllotoxin, raltegravir, ribavirin, rimantadine, ritonavir, pyramidine, saquinavir, stavudine, stribild, tenofovir, tenofovir disoproxil, tenofovir alafenamide fumarate (TAF), tipranavir, trifluridine, trizivir, tromantadine, truvada, valaciclovir, valganciclovir, vicriviroc, vidarabine, viramidine, zalcitabine, zanamivir, or zidovudine, and combinations thereof.” US ’426, [0139]. US ’850 further claims, “The method of claim 1 wherein the compound that inhibits HIV replication are selected from the group consisting of nucleoside reverse transcriptase inhibitors (NRTIs) such as tenofovir, emtricitabine, zidovudine (AZT), lamivudine (3TC), abacavir, and tenofovir alafenamide fumarate; non-nucleotide reverse transcriptase inhibitors (NNRTIs) such as efavirenz, rilpivirine, and etravirine; integrase inhibitors such as raltegravir and elvitegravir; and protease inhibitors such as ritonavir, darunavir, atazanavir, lopinavir, and cobicistat.” US ’850, Claim 2.

	US ’332 teaches, “[i]n a particularly preferred embodiment tenofovir alafenamide is present in form of its hemifumarate or fumarate, especially its hemifumarate.” US ’332, [0053]. US ’332 claims, “Pharmaceutical combination comprising (a) dolutegravir, (b) emtricitabine and (c) tenofovir for use as a medicament, wherein the weight ratio of (a) dolutegravir and (b) emtricitabine is from 1:1 to 1:3.” US ’332, Claim 1. US ’332 further claims, “Pharmaceutical combination for use according to any one of the preceding claims, wherein tenofovir is used in form of a prodrug of tenofovir.” US ’332, Claim 5. US ’332 further claims, “Pharmaceutical combination for use according to claim 5, wherein the prodrug of tenofovir is tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide or hexadecyloxypropyl tenofovir.” US ’332, Claim 6. US ’332 claims, “A kit for the treatment of a viral infection, in particular of an HIV-infection, comprising (i) 10 to 75 mg dolutegravir, (ii) 50 to 150 mg emtricitabine, (iii) 0.5 to 400 mg tenofovir or a prodrug thereof.” US ’332, Claim 15. WO ’466 claims, “[a] pharmaceutical composition comprising a self-emulsifying drug delivery system, wherein the self-emulsifying drug delivery system comprises efavirenz and one or more pharmaceutically acceptable excipient.” WO ’466, Claim 1. WO ’466 further claims, “[a] pharmaceutical composition according to any preceding claim, further comprising at least one

	additional active ingredient such as protease inhibitors, nucleoside reverse transcriptase inhibitors, non-nucleotide reverse transcriptase inhibitors, integrase inhibitors, or any combination thereof." WO '466, Claim 23. WO '466 further claims, "[a] pharmaceutical composition according to claim 23, wherein the at least one additional active ingredient comprises emtricitabine, tenofovir disproxil fumarate, tenofovir alafanamide fumarate, lamivudine, stavudine, zidovudine, or any combination thereof." WO '466, Claim 24. WO '720 discloses a combination of 200 mg FTC, 3-40 mg TAF, 50-500 mg cobicistat, 150 mg elvitegravir. WO '720, [0028]. The '791 patent discloses tenofovir alafenamide (TAF) as a compound of structure (6), having the chemical name 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino] phenoxyphosphinyl]methoxy]propyl]adenine, also designated as GS-7340. (6)  '791 patent, 4:13-32. Example 4 of the '791 patent describes a method for the preparation of tenofovir alafenamide monofumarate (TAF monofumarate) from the compound GS-7340. The detailed procedure involves the crystallization of TAF

	monofumarate from acetonitrile. '791 patent, 24:14-16, 24:38-48; *see also* 21:50-66 (preparation of TAF monofumarate (1:1) salts from a mixture of TAF (GS7340) and its diastereomer (GS-7339). Table 1 of the '791 patent discloses that GS-7340 exhibits greater activity and stability compared to tenofovir disoproxil fumarate (TDF) and tenofovir. '791 patent at 28:5-15. The '791 patent also teaches that the TAF compounds disclosed therein may be "formulated into compositions containing pharmaceutically acceptable excipients, [which] are used in effective doses in the therapy or prophylaxis of viral (particularly HIV or hepadnaviral) infections." '791 patent, 4:54-59, 14:42-53. '791 patent discloses TAF showing 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. '791 patent, 27:29-28:37. '791 patent further discloses the following tables: TABLE 1 In Vitro Activity and Stability HIV-1 / Stability T ½ (min) Activity $IC_{50\,\mu M}$ / Cytotoxicity $CC_{50\,\mu M}$ / Human Plasma / MT-2 Cell Extract / (P/MT-2) GS 7340: 0.005 / >40 / 90.0 / 28.3 / 3.2 TDF: 0.05 / 70 / 0.41 / 70.7 / 0.006 Tenofovir: 5 / 6000 / — / — / —

TABLE 2

PMPA Metabolites in Plasma, PBMCs and RBCs After 1 h Incubation of PMPA Prodrugs or PMPA in Human Blood.

Compound	Matrix	Total C-14 Recovered, µg-eq	Metabolites (% of Total Peak Area)					
			PMPA %	PMPAp, %	PMPApp, %	Met. X, %	Met. Y, %	GS 7340, %
GS-7340	Plasma/FP	43.0	1	—	—	2	13	84
(60 µg-eq)	PBMC	1.25	45	16	21	18	—	—
	RBC/FP	12.6	8	—	—	24	11	57
			PMPA	PMPAp	PMPApp	Mono-POC	GS-4331	
GS-4331	Plasma/FP	48.1	11	—	—	89	—	
(TDF)	PBMC	0.133	50	25	18	7	—	
(60 µg-eq)	RBC/FP	10.5	93	7.0	—	—	—	
			PMPA	PMPAp	PMPApp			
PMPA	Plasma/FP	55.7	100	—	—			
(60 µg-eq)	PBMC	0.033	86	14	—			
	RBC/FP	3.72	74	10	16			

'791 patent, Tables 1-2.

Lee discloses that "[t]he amidate prodrug GS 7340 was designed to overcome the permeability limitations of tenofovir by masking the dianion with a neutral promoiety and increasing the plasma stability of the prodrug relative to its intracellular stability. The in vitro anti-HIV potency of GS 7340 (EC_{50}=0.005 µM) is comparable to the most potent protease inhibitors and reflects the greater cell permeation of GS 7340 compared to tenofovir. In addition to favorable potency and a long intracellular half-life, the *in vivo* administration of GS 7340 results in an enhanced distribution of lymphatic tissue compared to tenofovir DF." Lee at 1903. Lee further discloses that "[w]ith GS 7340, it should be possible to reduce the total dose of tenofovir, thereby minimizing systemic exposure, while at the same time increasing antiviral activity." *Id*. at 1905.

Lee discloses TAF as 10 times more potent than TDF toward HIV-1, with eight times improved selectivity index. Lee, 1900 (Table 1).

	Lee further discloses, "the high concentrations of tenofovir observed in lymphatic tissues after oral administration of GS 7340 are expected to result in increased clinical potency relative to tenofovir DF." Lee, 1905 Lee further discloses that "[w]ith GS-7340, it should be possible to reduce the total dose of tenofovir, thereby minimizing systemic exposure, while at the same time increasing antiviral activity." Lee, 1905. US '856 discloses are pharmaceutical compositions comprising TAF hemifumarate and one or more additional therapeutic agents selected from the group consisting of "HIV protease inhibiting compounds, HIV nonnucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, and CCR5 inhibitors." *Id.* at [0010]-[0011], [0057]. HIV Guidelines states that "[a]n antiretroviral regimen for a treatment-naive patient generally consists of two nucleoside 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." HIV Guidelines, D-1. HIV Guidelines further recommends combination of the INSTIs elvitegravir and raltegravir with tenofovir and emtricitabine. HIV Guidelines, 1, i. British HIV Guidelines describes tenofovir and emtricitabine as the preferred NRTI backbone for HIV therapy, to be combined

	with an additional agent such as an INSTI. British HIV Guidelines, 13. NCT '694 discloses a study that "evaluate[s] the efficacy, safety and tolerability of GS-9883 + emtricitabine/tenofovir alafenamide (FTC/TAF) fixed dose combination (FDC) versus dolutegravir (DTG) + FTC/TAF in HIV-1 Infected, antiretroviral treatment-naive adults. This study will also evaluate the pharmacokinetic (PK) profile of GS-9883, FTC and TAF." NCT '694, Study Description. NCT '694 further discloses an "active comparator" with "Drug: FTC/TAF, Emtricitabine/Tenofovir Alafenamide (FTC/TAF) 200 mg/25 mg tablet administered orally; Drug: DTG, Dolutegravir (DTG) 50 mg tablet administered orally." NCT '694, Arms and Interventions. Tivicay Assessment discloses combination therapies with DLT sodium, FTC and tenofovir disoproxil for treating HIV. Tivicay Assessment, 43, 50-51, 89. 2013 Tivicay Label also discloses Tivicay containing 50 mg of dolutegravir sodium as an HIV INSTI indicated in combination with other antiretroviral agents (e.g., emtricitabine/tenfovoir (TRUVADA), for the treatment of HIV-1 infection. 2013 Tivicay Label, 1, 4, 24. Truvada Label discloses combining 200 mg emtricitabine, 300 mg tenofovir alafenamide, and 600 mg efavirenz. Truvada Label. Complera Label discloses a tablet composition for oral administration that contains 200 mg of NRTI emtricitabine, and

	300 mg of NRTI tenofovir DF, and 27.5 mg of NNRTI rilpivirine hydrochloride. Complera Label, 1, 22 The Stribild Label states that a Stribild table consists of "150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 300 mg of tenofovir disoproxil fumarate." Stribild Label, 1; *see also id.* at 22-23. The Genvoya Label states, "Each GENVOYA tablet contains 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (TAF) (equivalent to 11.2 mg of tenofovir alafenamide fumarate)." Genvoya Label, 4. 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. Genvoya Assessment, 74-75. The Genvoya Assessment teaches, "The overall goal of Genvoya film coated tablet development was to create a tablet containing the same amounts of elvitegravir, cobicistat and emtricitabine active substances as currently combined in Stribild fixed dose combination film-coated tablet and to replace tenofovir disoproxil contained in Stribild with tenofovir alafenamide, a second-generation prodrug of tenofovir." Genvoya Assessment, 18. Genvoya Assessment discloses film-coated tablets containing the following active substances: 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir

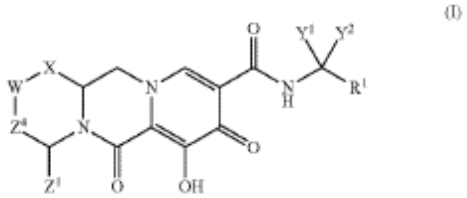
	alafenamide (as 11.2 mg of the fumarate)." Genvoya Assessment, 10. WO '351 teaches that "[i]n a preferred embodiment the pharmaceutical composition comprises (i) 20 to 75 mg, preferably 25 to 70 mg, more preferably 35 to 65 mg, in particular 40 to 60 mg dolutegravir (a); (ii) 50 to 300 mg, preferably 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." WO '351, 19:3-12. Ruane discloses that "HIV-1 RNA responses for the 8-mg TAF treatment group were similar to that of the 300-mg TDF group. However, median $DAVG_{11}$ [(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, 451-52 Ruane further states that "[c]ompared 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." Ruane, 454. Sax teaches that "Relative to TDF, TAF is more stable in plasma." Sax, 53. Astuti refers to tenofovir alafenamide (TAF), where "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

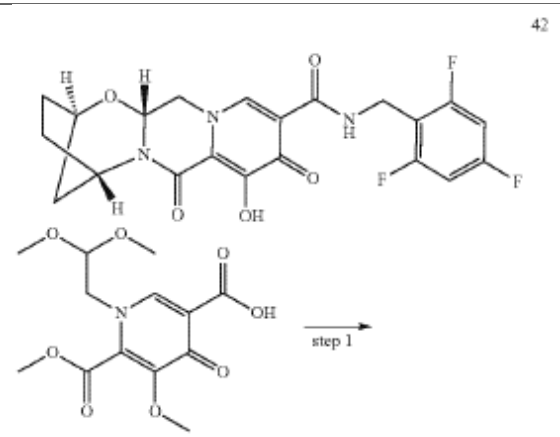
	non-inferior efficacy to TDF both co-formulated with FTFC/EVG/COBI." Astuti, 11. Astuti further discloses that the "possibility to use small doses of TAF instead of TDF could further widen the STR options as bulky molecules such as PIs could be successfully coformulated." Astuti, 11. Llibre teaches that 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. Llibre, 172. WO '799 teaches, In addition, the compounds of the present invention may be used in combination with one or more other agents useful in the prevention or treatment of HIV. Examples of such agents include: Nucleotide reverse transcriptase inhibitors such as zidovudine, didanosine, lamivudine, zalcitabine, abacavir, stavudine, adefovir, adefovir dipivoxil, fozivudine, todoxil, emtricitabine, alovudine, amdoxovir, elvucitabine, tenofovir disoproxil fumarate, dexelvucitabine, festinavir, racivir, and similar agents; Non-nucleotide reverse transcriptase inhibitors (including an agent having anti- oxidation activity such as immunocal, oltipraz, etc.) such as nevirapine, delavirdine, efavirenz, loviride, immunocal, oltipraz, capravirine, lersivirine, doravirine, rilpivirine, etravirine, tenofovir alafenamide fumarate, and similar agents;

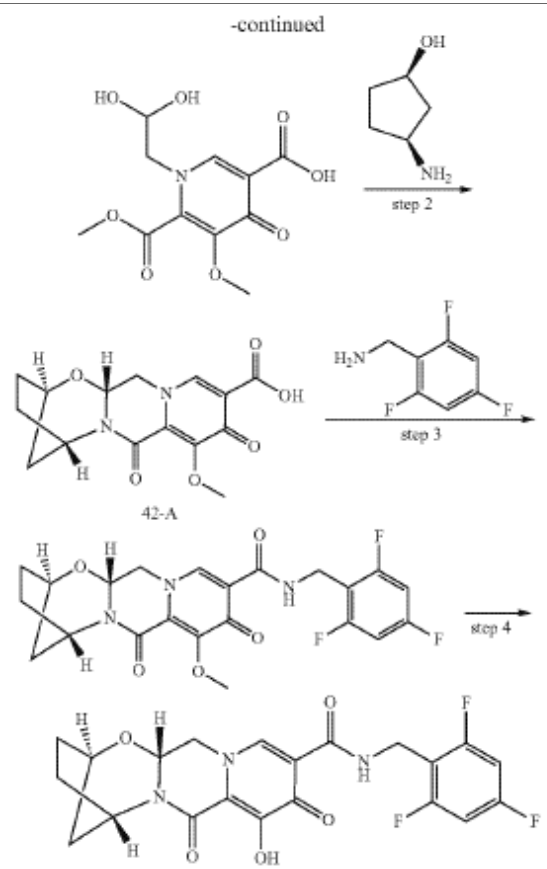
	Protease inhibitors such as saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, fosamprenavir, brecanavir, darunavir, atazanavir, tipranavir, palinavir, lasinavir, and similar agents; Entry, attachment and fusion inhibitors such as enfuvirtide (T -20), T - 1249, PRO -542, PRO - 140, ibalizumab, cenicriviroc, INCB -9471, monomeric DAPTA, AMD -070, ibalizumab, BMS- 806, fostemsavir, temsavir, and 5 -Helix and similar agents; Integrase strand transfer inhibitors such as raltegravir, elvitegravir, dolutegravir, cabotegravir, GS - 9883, and similar agents; Maturation inhibitors such as PA -344, PA - 457, BMS - 955176, as well as those disclosed in PCT Patent Application No. WO2011/100308, PCT Patent Application No. PCT/US2012/024288, Chinese PCT Application No. PCT/CN2011/001302, Chinese PCT Application No. PCT/CN2011/001303, Chinese PCT Application No. PCT/CN2011/002105, PCT/CN2011 /002159, WO2013/090664, WO2013/123019 , WO 2013/043778, WO 2014/123889, WO 2011/153315, WO2011/153319, WO2012/106188, WO 2012/106190, WO 2013/169578, and WO 2014/13081, and similar agents; CXCR4 and /or CCR5 inhibitors such as vicriviroc, TAK779, maraviroc, TAK449, as well as those disclosed in WO 02/74769, PCT/US03/39644, PCT/US03/39975, PCT/US03/39619, PCT/USO3/39618, PCT/US03/39740, and PCT/US03/39732, and similar agents. Neutralizing antibodies such as VRC01, VRC0710e8, pro140, PGT121, PGT128, PGT145, PG9, 3BNC117, ibalizumab, N6 and similar agents. WO ’799, [0356]-[0365].

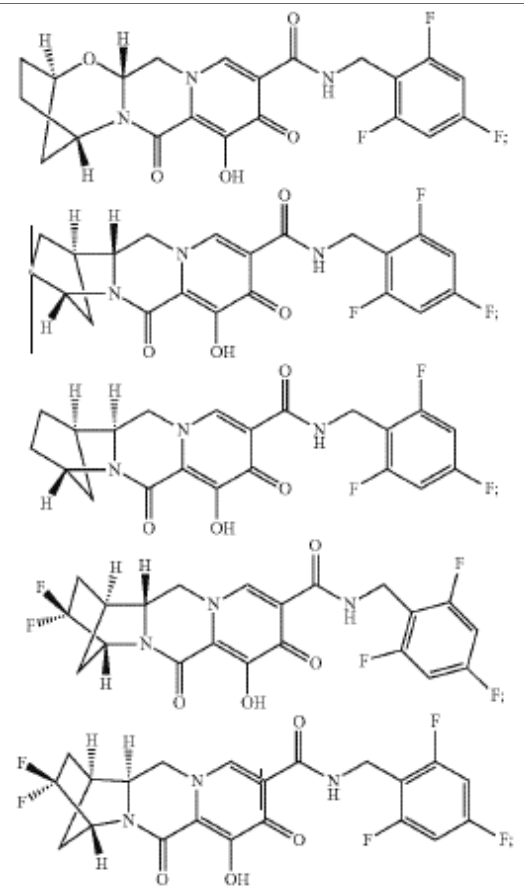
	WO ’116 specifically discloses embodiments where BIC sodium is combined with 25 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide and 200 mg emtricitabine. WO ’116 at [0096]. WO ’116 also claims specific tablets compositions comprising a therapeutically effective 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. 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. *See also* Weller; Castagna; Juday; Lunzen; Walmsley; Johns; PR; Mathais; Min; Highleyman; Acosta; BICANDA01157927; NCT02607956-1; NCT02607856-2; Abebe; Shende; Poster #416; Poster # 414; Poster #413.

Claim 8	
Claim Elements	Prior Art Teachings of Claim Elements
The tablet of claim 1,	The prior art teachings disclosing the tablets of any of claim 1 is set forth above and incorporated herein by reference.

wherein the tablet comprises 52 mg of the sodium salt of the compound of Formula I,	US ’356 discloses “[c]ompounds for use in the treatment of human immunodeficiency virus (HIV) infection . . . hav[ing] the following Formula (I):  (I) including stereoisomers and pharmaceutically acceptable salts thereof, wherein R^1, X, W, Y^1, Y^2, Z^1, and Z^4 are as defined herein. Methods associated with preparation and use of such compounds, as well as pharmaceutical compositions comprising such compounds, are also disclosed.” US ’356, Abstract, [0089]. US ’356 further discloses “polycyclic carbamoylpyridone compounds, having antiviral activity, . . . and the use of such compounds in the treatment of HIV infections. The compounds of the invention may be used to inhibit the activity of HIV integrase and may be used to reduce HIV replication.” US ’356, [0010]. US ’356 further discloses approximately 100 HIV INSTI compounds of Formula (I) and methods for their synthesis, including a Compound 42 corresponding to bictegravir (BIC):

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	-continued  US ’356, [0312]-[0316] (Example 42). US ’356 further discloses 7 HIV INSTIs of Formula I, including bictegravir:

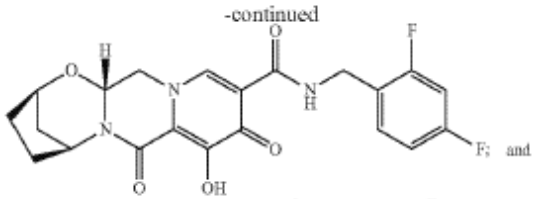
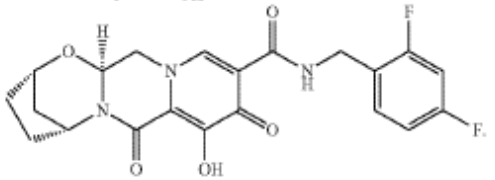
	-continued  F; and  F. US ’356, claim 32. US ’356 further discloses a tablet showing that BIC (compound 42) provided nanomolar activity (EC50 = 2.5 nm) in an antiviral assay in MT4 cells infected with HIV. “Compounds of the present invention demonstrate antiviral activity in this assay as depicted in Table 1 below. Accordingly, the compounds of the invention may be useful for treating the proliferation of the HIV virus, treating AIDS, or delaying the onset of AIDS or ARC symptoms.” US ’356, [0589]-[0592] (Example 104; see Table 1). US ’356 further discloses Example 107, “Pharmacokinetic analysis Following Oral or Intravenous Administration to Beagle Dogs.” US ’356, [0599]-[0603]. US ’356 provided the second highest oral bioavailability (F (%)), Cmax and AUC of the eleven Formula (I) compounds tested:

TABLE 4

Compound #	CL (L/h/kg)	V_{ss} (L/kg)	MRT (h)	F (%) aqueous suspension	C_{max} (μM) aqueous suspension	AUC (μM * h) aqueous suspension
98	0.047	0.16	3.3	n/a	n/a	n/a
83	0.161	0.38	2.4	n/a	n/a	n/a
55	0.058	0.24	4.2	n/a	n/a	n/a
77	0.300	0.64	2.2	n/a	n/a	n/a
41	0.015	0.11	7.5	10.7	2.4	16.3
42	0.020	0.15	7.1	28.0	4.5	28.6
47	0.014	0.10	7.4	12.6	2.8	20.4
8	0.498	0.87	1.8	n/a	n/a	n/a
7	0.510	1.20	2.3	n/a	n/a	n/a
3	0.047	0.23	4.9	18.7	1.2	9.2
2	0.030	0.20	6.5	40.7	7.8	66.1

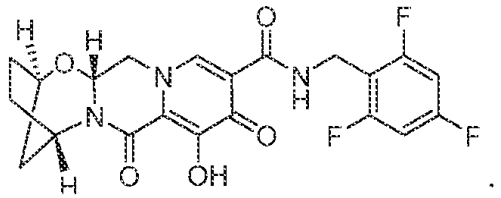
US ’356, Example 107; see Table 4.

US ’356 further discloses “[p]harmaceutical compositions . . . includ[ing] a compound of Formula (I) and one or more of: a pharmaceutically acceptable carrier, diluent or excipient. . . . In certain embodiments, a compound of Formula (I) is present in the pharmaceutical composition in an amount from about 25 mg to about 500 mg. In certain embodiments, a compound of Formula (I) is present in the pharmaceutical composition in an amount of about 100 mg to about 300 mg. In certain embodiments, a compound of Formula (I) is present in the pharmaceutical composition in an amount of about 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg or about 500 mg.” US ’356, [0152].

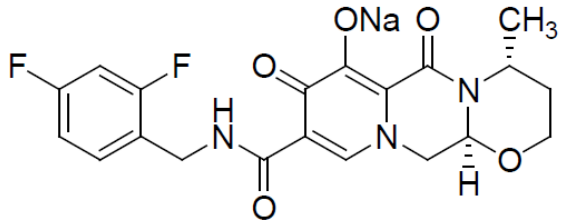
US ’356 refers “pharmaceutically acceptable salt” to “a salt of a compound that is pharmaceutically acceptable and that possesses (or can be converted to a form that possesses) the desired pharmacological activity of the parent compound. Examples of ‘pharmaceutically acceptable salts’ of the compounds disclosed herein include salts derived from an appropriate base, such as . . . an alkaline earth metal (for example, magnesium). . . .” US ’356, [0075].

	US ’356 states that “[t]he compounds of the invention, or their pharmaceutically acceptable salts, are administered in a therapeutically effective amount.” US ’356, [0155]. US ’356 further states that “a therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to their own know ledge, the state of the art, and this disclosure.” US ’356, [0081]. US ’356 discloses that these pharmaceutical compositions containing a therapeutically effective amount of a compound of Formula (I) are disclosed “for use in the therapeutic treatment of an HIV infection is provided.” US ’356, [0147]-[0149]. US ’356 states that “[a]dministration of the compounds of the invention, or their pharmaceutically acceptable salts, in pure form or in an appropriate pharmaceutical composition, is carried out via any of the accepted modes of administration of agents for serving similar utilities.” US ’356, [0153]-[0154] US ’356 also claims “[a] pharmaceutical composition comprising a compound of any one of claims 1-32, or a stereoisomer or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.” US ’356, claim 33. US ’356 further claims, “[a] method of treating an HIV infection in a human having or at risk of having the infection by administering to the human a therapeutically effective amount of a compound of any one of claims 1-32 or a pharmaceutical composition of claim 33.” US ’356, claim 37.

	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]. US ’356 also discloses combination therapy “for treating or preventing an HIV infection in a human having or at risk of having the infection.” US ’356, [0156]. US ’356 further discloses 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.US ’356, [0156]-[0163]. US ’356 also discloses an embodiment wherein pharmaceutical compositions comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with one or more additional therapeutic agents, and a pharmaceutically acceptable carrier, diluent or excipient are provided. US ’356, [0156]-[0179]. US ’356 further discloses that [i]n certain embodiments, a compound disclosed herein 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. US ’356, [0177]. US ’332 describes pharmaceutical combinations comprising 40 to 60 mg DLT, 150 to 250 mg FTC, and 5 to 42 mg TAF, along

	with pharmaceutical excipients. US '332, [0086]-[0090]. US '332 further discloses that "[i]n a preferred embodiment the pharmaceutical composition of the present invention comprises 50 mg dolutegravir, 50 mg dolutegravir, about 200 mg emtricitabine and about 25 mg tenofovir." *Id.* at [0091]-[0092]. HIV Guidelines states that "[a]n antiretroviral regimen for a treatment-naive patient generally consists of two nucleoside 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." HIV Guidelines, D-1. 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. US '356, 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). WO '323 claims, "A compound of claim 1 selected from: . .  WO '323, Claim 32. WO '323 further claims, "A pharmaceutical composition comprising a compound of any one of claims 1-32, or a

	stereoisomer or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient." WO '323, Claim 33. WO '323 discloses, "Compounds, compositions, and methods for the treatment of human immunodeficiency vims (HIV) infection are disclosed. In particular, novel poly cyclic carbamoylpyridone compounds and methods for their preparation and use as therapeutic or prophylactic agents are disclosed." WO '323, 1:12-15. WO '323 teaches, "In certain embodiments, a compound of Formula (I) is present in the pharmaceutical composition in an amount of about 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg or about 500 mg." WO '323, 35:19-23. WO '323 defines "Formula (I)" as including "the specific compounds disclosed herein[,]" which includes bictegravir. WO '323, 18-19. HIV Guidelines further recommends combination of the INSTIs elvitegravir and raltegravir with tenofovir and emtricitabine. HIV Guidelines, 1, i. British HIV Guidelines describes tenofovir and emtricitabine as the preferred NRTI backbone for HIV therapy, to be combined with an additional agent such as an INSTI. British HIV Guidelines, 13. NCT '694 discloses a study that "evaluate[s] the efficacy, safety and tolerability of GS-9883 + emtricitabine/tenofovir alafenamide (FTC/TAF) fixed dose combination (FDC) versus

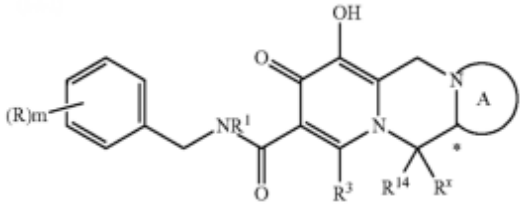
	dolutegravir (DTG) + FTC/TAF in HIV-1 Infected, antiretroviral treatment-naive adults. This study will also evaluate the pharmacokinetic (PK) profile of GS-9883, FTC and TAF." NCT '694, Study Description. NCT '694 further discloses an "active comparator" with "Drug: FTC/TAF, Emtricitabine/Tenofovir Alafenamide (FTC/TAF) 200 mg/25 mg tablet administered orally; Drug: DTG, Dolutegravir (DTG) 50 mg tablet administered orally." NCT '694, Arms and Interventions. US '332 discloses dolutegravir, which it further states is "reported to have anti-viral activity, since it is considered to be an integrase inhibitor." US '332, [0014]. US '332 further discloses, "[p]referably, dolutegravir is in the form of a pharmaceutically acceptable salt. More preferred, dolutegravir is in the form of an alkali metal salt such as sodium or potassium salt or in the form of an earth-alkali metal salt such as calcium or magnesium salt. More preferred, dolutegravir is in the form of a sodium salt or a magnesium salt. Particularly preferred, dolutegravir is used in form of the sodium salt, especially the mono-sodium salt." US '332, [0018], [0020]. The Tivicay Assessment teaches the sodium salt form of dolutegravir with the following structure: 

	Tivicay Assessment, 9. The Tivicay Assessment also discloses that "Tivicay is presented as film-coated tablet containing 50 mg of dolutegravir (As dolutegravir sodium salt) as active substance." Tivicay Assessment, 9. Tivicay Assessment identifies 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." *Id.* at 43, 50-51, It further discloses combination therapies with DLT sodium, FTC and tenofovir disoproxil for treating HIV. *Id.* at 89. The 2013 Tivicay Label teaches, "TIVICAY is a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor (INSTI) indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and children aged 12 years and older and weighing at least 40 kg." Tivicay Label, 1. The 2013 Tivicay Label also discloses Tivicay containing 50 mg of dolutegravir sodium as an HIV INSTI indicated in combination with other antiretroviral agents (e.g., emtricitabine/tenfovoir (TRUVADA), for the treatment of HIV-1 infection. 2013 Tivicay Label, 1, 4, 24. US '332 further discloses "a pharmaceutical composition comprising (a) dolutegravir, (b) emtricitabine and (c) tenofovir, wherein (a) dolutegravir and (b) emtricitabine are present in a specific weight ratio, for use as a medicament. A further subject of the present invention is a method for treating a viral infection, comprising administering to a subject in need thereof the pharmaceutical combination or composition of the present

	invention, wherein the viral infection preferably comprises an HIV-infection." US '332, [0061]. US '332 discloses that the "[i]n another particularly preferred embodiment, the combination of the present invention is administered once daily." US '332, [0077]. US '332 further discloses that "[t]he pharmaceutical composition of the present invention can be preferably a solid oral dosage form. It is further preferred that the dosage form of the invention is a capsule or a tablet, in particular a tablet." *Id.* at [0107]. US '332 describe "preferred embodiment [of] the pharmaceutical composition compris[ing] … 40 to 60 mg dolutegravir, … 250 mg emtricitabine, … and 5 to 42 mg tenofovir; and pharmaceutical excipients." US '332, [0086]-[0090]. US '332 further discloses that "[i]n a preferred embodiment the pharmaceutical composition of the present invention comprises 50 mg dolutegravir, 50 mg dolutegravir, about 200 mg emtricitabine and about 25 mg tenofovir." US '332, [0092]. US '332 also discloses the total amount of dolutegravir, emtricitabine and tenofovir alafenamide comprised in the present pharmaceutical combination for use as a medicament is between 70.5 and425 mg per day, in particular 192 to 326 mg per day." US '332, [0075]. Genvoya Label discloses a tablet composition for oral administration that contains 150 mg of the INSTI elvitegravir (EVG), 150 mg of PK enhancer cobicistat (COBI), 200 mg of NRTI emtricitabine (FTC), and 11.2 mg of NRTI tenofovir alafenamide (TAF) fumarate (equivalent to 10 mg TAF)). Genvoya, 22.

	Genvoya Assessment discloses film-coated tablets containing the following active substances: 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (as 11.2 mg of the fumarate)." Genvoya Assessment, 10. Genvoya Assessment further 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. Genvoya Assessment, 74-75. WO '846 discloses therapeutic combinations of TAF and FTC for treating HIV. WO '846, 3:13-18. WO '846 further discloses that combination can additionally include an INSTI. WO '846, 18:23-26. WO '846 further discloses an exemplary formulation containing 25 mg of TAF and 200 mg FTC. WO '846, 37:13-20. WO '846 discloses a pharmaceutical composition comprising "(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. Stribild Label discloses a tablet composition for oral administration that contains a combination of 150 mg of the integrase strand transfer inhibitor elvitegravir, 200 mg and 300 mg respectively of the nucleos(t)ide analog HIV-1 reverse transcriptase inhibitors emtricitabine and tenofovir disoproxil

	fumarate, and 150 mg of the pharmacokinetic enhancer cobicistat. Stribild Label, 1. US '122 discloses a solid dose form (e.g. tablets) comprising a compound of Formula I (i.e. elvitegravir), Formula III (i.e. emtricitabine), Formula IV (i.e. tenofovir disoproxil fumarate), 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. Compound of Formula II 150 mg Formulation Components / % 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. *Id.* at [0022]. US '122 further discloses examples of tablets similar to Stribild. *Id.* at [0063]-[0065] (Examples 2-4).

	The ’385 patent discloses 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. ’385 patent, 8:9-34. 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. ’385 patent, Abstract, 7:32-35, 38:6-9.

	The ’385 patent discloses, “[t]he present invention relates to novel compounds possessing an antiviral activity, in detail polycyclic carbamoylpyridone derivatives possessing an inhibitory activity against HIV integrase and a pharmaceutical composition containing the same, especially an anti-HIV agent.” ’385 patent, 1:15-20. 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. 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. 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. WO '351 further discloses that 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." WO '351, 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." WO '351, 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." WO '351, 16:15-18. WO '351 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." WO '351, 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." WO '351, 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." WO '351, 17:27-28, 23:6-8. The Stribild Assessment discloses, "Stribild is presented for use as a bilayer tablet – one layer contains EVG/COBI and one FTC/TDF." Stribild Assessment, 33. The Atripla Assessment teaches, "The granulations are blended separately with extra-granular magnesium stearate, compressed into bilayer tablets, and then film-coated. Process optimization studies were conducted in order to establish critical process parameters for the wet granulation of efavirenz, dry granulation of emtricitabine/tenofovir, bilayer tablet compression, and aqueous film-coating operations." Atripla Assessment, 5.

The Genvoya Assessment states, "GS-US-292-0101 was an open-label crossover study that compared two formulations (monolayer and bilayer) of E/C/F/TAF (each containing either 25 or 40 mg TAF as the monofumarate) with Stribild and with TAF 25 mg alone." Genvoya Assessment, 75.

The Eviplera Assessment teaches, "The exposure of FTC/RPV/TDF after single oral administration of a bilayer formulation and the individual compounds was compared in fasted dogs and has demonstrated comparable systemic exposure to all compounds." Eviplera Assessment, 18.

US '857 discloses "a tablet of the invention wherein the first layer comprises:

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

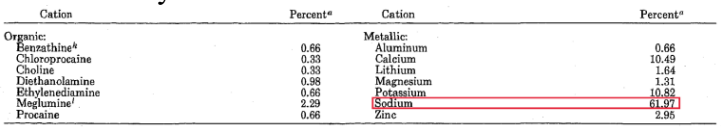
and the second layer comprises:

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

US '857, [0066]. US '857 further discloses bilayer tablets for keeping rilpivirine separate from FTC and TDF. *Id.* at [0067]-[0071].

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, 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]. US '079 also discloses that 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. 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. Havele discloses that TDF showed complete degradation occurred immediately after addition of at room temperature). Havele, 3, 5. Venkatasan discloses that TDF undergoes 31% decomposition under basic stress conditions. Venkatasan, 4. Kurmi discloses that in a basic solution environment (0.5 N NaOH), TDF was completely converted into degradation product

	T1 in 3 h. Kurmi, 96121. Kurmi further discloses that under basic solid state stress conditions, TDF degraded into several different products. *Id.* at 96121-25. Berge teaches "[t]he chemical, biological, physical and economic characteristics of medicinal agents can be manipulated and, hence, often optimized by conversion to a salt form," where "salt-forming agents are often chosen empirically … [and] the preferred form is selected by pharmaceutical chemists on a practical basis: cost of raw materials, ease of crystallization, and percent yield … [as well as] stability, hygroscopicity, and flowability of the resulting bulk drug." Berge at 1. Berge also teaches Table 1 as a list of "FDA-approved commercially marketed salts" that includes sodium:  Remington 21st teaches in Table 38-5 that sodium salts were an API-salt form known since at least 1983:

Cation	Percent[a]	Cation	Percent[a]
Organic:		Metallic:	
Benzathine[k]	0.66	Aluminum	0.66
Chloroprocaine	0.33	Calcium	10.49
Choline	0.33	Lithium	1.64
Diethanolamine	0.98	Magnesium	1.31
Ethylenediamine	0.66	Potassium	10.82
Meglumine[l]	2.29	Sodium	61.97
Procaine	0.66	Zinc	2.95

Table 38-5. Molecular Forms Marketed Worldwide Between 1983 and 1996

SALT FORM	FREQ.	GROUP[a]	PK_A	CLOGP	MW
No salt form	390	0			
Hydrobromide	1	1	−8	0.45	80.91
Hydrochloride	102	1	−6.1	0.24	36.46
Sulfate	5	1	−3	−1.58	98.08
Nitrate	6	1	−1.44	2.09	63.01
Phosphate	2	1	2.15	−1.95	96.99
Glucuronate	1	1	3.22[b]	−3.74	194.14
Acetate	8	1	4.76	−0.36	59.05
Maleate	3	2	1.92	−0.18	116.07
Fumarate	8	2	3.02	−0.18	116.07
Tartrate	1	2	3.03	−2.21	150.09
Citrate	1	2	3.13	−2.11	189.10
Succinate	2	2	4.21	−0.62	118.09
Mesylate	8	3	−1.20	−1.31	96.11
Acistrate	1	3	4.91[b]	7.98	284.49
Besylate	2	4	−2.80[b]	0.23	157.17
Tosylate	3	4	−1.34	0.88	171.20
Xinafoate	1	4	2.66[b]	3.00	188.18
Potassium	1	1	16		39.10
Sodium	37	1	14.77		23.00
Tromethamine	2	1	8.07[c]	−3.17	121.14
Bismuth	1	1	1.58		208.98
Bromide	6	5			79.90
Chloride	2	5			35.45

[a] Groups: 0 = No salt, 1 = Polar, 2 = Multifunctional, 3 = Flexible aliphatics, 4 = Planar aromatics, 5 = Quartenary.
[b] Calculated pK_a.
[c] Data from *CRC Handbook of Basic Tables for Chemical Analysis*, page 469.
From Serajuddin ATM, Sheen P, Augustine MA. To market, to market. In: Bristol J, ed. *Annu Rep Med Chem.* New York: Academic, 1983–1996.

Serajuddin teaches that "[s]alt formation is the most common and effective method of increasing solubility of acidic and basic drugs." Serajuddin at 603.

Serajuddin also teaches that "[s]alt formation is also the most common approach of increasing solubility, dissolution rate and ultimately bioavailability of poorly water-soluble ionizable drugs in solid dosage forms." Serajuddin at 614.

Serajuddin further informs that "Table 2 gives the distribution of 120 salts approved by the FDA during the 12-year period from 1995 to 2006, where the hydrochloride salt is the predominant salt form among the basic drugs and the sodium salt is the predominant form for acidic drugs." Serajuddin at 613. The portion of Table 2 that shows salts of acidic drugs shows:

Salts of acidic drugs	Total number
Sodium	12
Calcium	4
Potassium	2
Tromethamine	1
Total of all salts of acidic drugs	19

Paulekuhn teaches that "[s]alt formation is a well-known technique to modify and optimize the physical chemical properties of an ionizable research and development compound[, where] [p]roperties such as solubility, dissolution rate, hygroscopicity, stability, impurity profiles and crystal habit can be influenced by using a variety of pharmaceutically acceptable counterions." Paulekuhn, 6665 (also noting that "formation of salts is almost the only chemical technique available to change aqueous solubility and dissolution rate without changing the API molecule")

According to Paulekuhn, "[a]mong the cations used to form API salts of acidic molecules, the sodium ion strongly dominates with an incidence of 75.3% over the entire period. From 1982 to 1991, the fraction of sodium salts was more than 90%. This decreased to 62.5% during the 2002-2006 period." *Id.* at 6667.

Wells teaches, "A major improvement in solubility can be achieved by forming a salt." Wells at 116.

In discussing potential pharmaceutical salts to be used for the salt forms of drugs, Wells provides Table 8.4, which presents such salts, including sodium, , along with the pKa of each salt forming cation:

Table 8.4 Potential pharmaceutical salts

Basic drugs			Acidic drugs		
Anion	pK_a	% Usage	Cation	pK_a	% Usage
Hydrochloride	−6.10	43.0	Potassium	16.00	10.8
Sulphate	−3.00, +1.96	7.5	Sodium	14.77	62.0
Mesylate	−1.20	2.0	Lithium	13.82	1.6
Maleate	1.92, 6.23	3.0	Calcium	12.90	10.5
Phosphate	2.15, 7.20, 12.38	3.2	Magnesium	11.42	1.3
Salicylate	3.00	0.9	Diethanolamine	9.65	1.0
Tartrate	3.00	3.5	Zinc	8.96	3.0
Lactate	3.10	0.8	Choline	8.90	0.3
Citrate	3.13, 4.76, 6.40	3.0	Aluminium	5.00	0.7
Succinate	4.21, 5.64	0.4			
Acetate	4.76	1.3			
Others		31.4	Others		8.8

Bastin encourages the "[s]election of an appropriate salt form for a new chemical entity" because it "provides the pharmaceutical chemist and formulation scientist with the opportunity to modify the characteristics of the potential drug substance and to permit the development of dosage forms with good bioavailability, stability, manufacturability, and patient compliance." Bastin, 427.

Brittain teaches, "Prudent drug development programs will identify the preferred crystalline form early in development, with a polymorph/salt group working in close conjunction with process chemists to make the thermodynamically preferred polymorphic form the initial kilogram-scale batch." Brittain, 358.

The Triumeq Label discloses the ingredients of Triumeq as including the sodium salt form of dolutegravir, stating, "Each film-coated tablet contains abacavir sulfate equivalent to 600 mg of abacavir, dolutegravir sodium equivalent to 50 mg of dolutegravir, and 300 mg of lamivudine." Triumeq Label, 17.

	The Triumeq label teaches, "TRIUMEQ, a combination of dolutegravir (integrase strand transfer inhibitor [INSTI]), abacavir, and lamivudine (both nucleoside analogue reverse transcriptase inhibitors) is indicated for the treatment of HIV-1 infection." Triumeq Label, 1. The Triumeq Assessment discloses, "Triumeq is presented as film-coated tablets containing a fixed combination of dolutegravir sodium equivalent to 50 mg dolutegravir, 600 mg of abacavir (as sulfate) and 300 mg of lamivudine." Triumeq Assessment, 6. The Triumeq Assessment teaches, "A once-daily fixed-dose combination (FDC) single tablet regimen (STR) that combines the integrase inhibitor (INI) dolutegravir (DTG) with the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir sulfate (abacavir, ABC) and lamivudine (3TC) was developed for use in the treatment of human immunodeficiency virus (HIV) infection." Triumeq Assessment, 6. WO '116 is specifically directed to BIC sodium (Formula II) and a crystalline form thereof (Form I), along with pharmaceutical formulations and therapeutic uses therefore. WO '116, [0002], [0006]-[0008], [0043]-[0057] (describing crystalline forms of Formula II).; *see also* Section IV.A of the narrative (discussing the disclosure of the family member '342 and '067 patents). 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). 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]. *See also* Weller; Castagna; Juday; Lunzen; Walmsley; Johns; PR; Mathais; Min; Highleyman; Acosta; BICANDA01157927; NCT02607956-1; NCT02607856-2; Abebe; Shende; Poster #416; Poster # 414; Poster #413.
28 mg tenofovir alafenamide hemifumarate,	US '332 discloses that "[i]n a preferred embodiment the pharmaceutical composition of the present invention comprises 50 mg dolutegravir, 50 mg dolutegravir, about 200 mg emtricitabine and about 25 mg tenofovir." US '332, [0092]. US '332 describes pharmaceutical combinations comprising 40 to 60 mg DLT, 150 to 250 mg FTC, and 5 to 42 mg TAF, along with pharmaceutical excipients. US '332, [0086]-[0090]. US '332 further discloses a specific combination comprising about 50 mg DLT, about 200 mg FTC and about 25 mg TAF. *Id.* at [0091]-[0092]. US '332 discloses, "Acids which are used to prepare pharmaceutically acceptable acid addition salts are preferably those which form non-toxic acid addition salts. In a particularly preferred embodiment tenofovir alafenamide is present in form of its hemifumarate or fumarate, especially its hemifumarate." US '332, [0053].

	US ’356 further discloses 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.US ’35, [0156]-[0163]. 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. US ’356, 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). US ’356 further discloses that [i]n certain embodiments, a compound disclosed herein 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. US ’356, [0177]. US ’356 refers “pharmaceutically acceptable salt” to “a salt of a compound that is pharmaceutically acceptable and that possesses (or can be converted to a form that possesses) the desired pharmacological activity of the parent compound. Examples of ‘pharmaceutically acceptable salts’ of the compounds disclosed herein include salts derived from an appropriate base, such as . . . an alkaline earth metal (for example, magnesium). . . .” US ’356, [0075]. US ’902 discloses, “a novel pharmaceutical product containing efavirenz, emitricitabine and tenofovir DF are provided as a multicomponent unitary oral dosage form.” US ’902, Abstract.

	US ’857 describes “multilayer tablets that contain rilpivirine hydrochloride, emtricitabine, and tenofivir disoproxil fumarate.” US ’857, Abstract. US ’856 discloses pharmaceutical compositions comprising TAF hemifumarate and one or more additional therapeutic agents selected from the group consisting of “HIV protease inhibiting compounds, HIV nonnucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, and CCR5 inhibitors.” *Id.* at [0010]-[0011], [0057]. WO ’846 teaches the following formulation: Formulation D: GS-7340 — 25 mg/tablet emtricitabine — 200 Microcrystalline Cellulose — 200 Lactose Monohydrate — 330 Croscarmellose Sodium — 60 Pregelatinized Starch — 50 Magnesium Stearate — 10 875 WO ’846, 13:12-24. WO ’846 discloses the following formulation:

	Formulation G — mg/tablet GS-7340 — 300 emtricitabine — 200 Hydroxypropyl Methylcellulose — 112 Lactose B.P. — 53 Pregelatinized Starch B.P. — 28 Magnesium Stearate — 7 total: — 700 WO ’846, 13:23-24. WO ’846 further discloses an exemplary formulation containing 25 mg of TAF and 200 mg FTC. WO ’846, 37:13-20. Gilead/Janssen discusses, “Phase III-ready HIV treatment that will combine Gilead’s tenofovir alafenamide (TAF) and emtricitabine, and Janssen’s rilpivirine.” Gilead/Janssen, 1. Gilead/Janssen states, “Gilead and Janssen agreed to develop and commercialize a once-daily single tablet regimen for HIV that combines darunavir with TAF, emtricitabine and a third Gilead compound, cobicistat (marketed as TYBOST®).” Gilead/Janssen, 2. Gilead/Janssen discloses that 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. WO ’323 discloses, “In further embodiments, the additional therapeutic agent is selected from one or more of: . . (3) HIV nucleoside inhibitors of reverse transcriptase selected from the group consisting of zidovudine, emtricitabine, didanosine, stavudine, zaicitabine, lamivudine, abacavir, amdoxovir,

	elvucitabine, alovudine, MIV-210, ±-FTC, D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, apricitibine (AVX754), KP-1461, GS- 9131 (Gilead Sciences) and fosalvudine tidoxil (formerly HDP 99.0003); (4) HIV nucleotide inhibitors of reverse transcriptase selected from the group consisting of tenofovir, tenofovir disoproxil fumarate, tenofovir alafenarnide fumarate (Gilead Sciences), GS-7340 (Gilead Sciences), GS-9148 (Gilead Sciences), adefovir, adefovir dipivoxii, CMX-001 (Chimerix) or CMX-157 (Chimerix) . . . .” WO ’323, 38:1-2; 13-21. US ’426 states, “In further embodiments, Wnt signaling pathway inhibitor is administered in combination with one or more of the following agents: abacavir, acyclovir, acyclovir, adefovir, amantadine, amprenavir, ampligen, arbidol, atazanavir, atripla, boceprevir, cidofovir, combivir, complera, darunavir, delavirdine, didanosine, docosanol, dolutegravir, edoxudine, efavirenz, emtricitabine, enfuvirtide, entecavir, famciclovir, fomivirsen, fosamprenavir, foscarnet, fosfonet, ganciclovir, ibacitabine, imunovir, idoxuridine, imiquimod, indinavir, inosine, interferon type III, interferon type II, interferon type I, lamivudine, lopinavir, loviride, maraviroc, moroxydine, methisazone, nelfinavir, nevirapine, nexavir, oseltamivir, peginterferon alfa-2a, penciclovir, peramivir, pleconaril, podophyllotoxin, raltegravir, ribavirin, rimantadine, ritonavir, pyramidine, saquinavir, stavudine, stribild, tenofovir, tenofovir disoproxil, tenofovir alafenamide fumarate (TAF), tipranavir, trifluridine, trizivir, tromantadine, truvada, valaciclovir, valganciclovir, vicriviroc, vidarabine, viramidine, zalcitabine, zanamivir, or zidovudine, and combinations thereof.” US ’426, [0139].

	US ’850 further claims, “The method of claim 1 wherein the compound that inhibits HIV replication are selected from the group consisting of nucleoside reverse transcriptase inhibitors (NRTIs) such as tenofovir, emtricitabine, zidovudine (AZT), lamivudine (3TC), abacavir, and tenofovir alafenamide fumarate; non-nucleotide reverse transcriptase inhibitors (NNRTIs) such as efavirenz, rilpivirine, and etravirine; integrase inhibitors such as raltegravir and elvitegravir; and protease inhibitors such as ritonavir, darunavir, atazanavir, lopinavir, and cobicistat.” US ’850, Claim 2. US ’332 teaches, “[i]n a particularly preferred embodiment tenofovir alafenamide is present in form of its hemifumarate or fumarate, especially its hemifumarate.” US ’332, [0053]. US ’332 claims, “Pharmaceutical combination comprising (a) dolutegravir, (b) emtricitabine and (c) tenofovir for use as a medicament, wherein the weight ratio of (a) dolutegravir and (b) emtricitabine is from 1:1 to 1:3.” US ’332, Claim 1. US ’332 further claims, “Pharmaceutical combination for use according to any one of the preceding claims, wherein tenofovir is used in form of a prodrug of tenofovir.” US ’332, Claim 5. US ’332 further claims, “Pharmaceutical combination for use according to claim 5, wherein the prodrug of tenofovir is tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide or hexadecyloxypropyl tenofovir.” US ’332, Claim 6. US ’332 claims, “A kit for the treatment of a viral infection, in particular of an HIV-infection, comprising (i) 10 to 75 mg

	dolutegravir, (ii) 50 to 150 mg emtricitabine, (iii) 0.5 to 400 mg tenofovir or a prodrug thereof." US '332, Claim 15. WO '466 claims, "[a] pharmaceutical composition comprising a self-emulsifying drug delivery system, wherein the self-emulsifying drug delivery system comprises efavirenz and one or more pharmaceutically acceptable excipient." WO '466, Claim 1. WO '466 further claims, "[a] pharmaceutical composition according to any preceding claim, further comprising at least one additional active ingredient such as protease inhibitors, nucleoside reverse transcriptase inhibitors, non-nucleotide reverse transcriptase inhibitors, integrase inhibitors, or any combination thereof." WO '466, Claim 23. WO '466 further claims, "[a] pharmaceutical composition according to claim 23, wherein the at least one additional active ingredient comprises emtricitabine, tenofovir disproxil fumarate, tenofovir alafanamide fumarate, lamivudine, stavudine, zidovudine, or any combination thereof." WO '466, Claim 24. WO '720 discloses a combination of 200 mg FTC, 3-40 mg TAF, 50-500 mg cobicistat, 150 mg elvitegravir. WO '720, [0028]. The '791 patent discloses tenofovir alafenamide (TAF) as a compound of structure (6), having the chemical name 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino] phenoxyphosphinyl]methoxy]propyl]adenine, also designated as GS-7340.

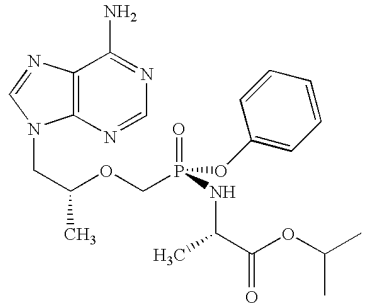
	(6)  ’791 patent, 4:13-32. Example 4 of the ’791 patent describes a method for the preparation of tenofovir alafenamide monofumarate (TAF monofumarate) from the compound GS-7340. The detailed procedure involves the crystallization of TAF monofumarate from acetonitrile. ’791 patent, 24:14-16, 24:38-48; *see also* 21:50-66 (preparation of TAF monofumarate (1:1) salts from a mixture of TAF (GS7340) and its diastereomer (GS-7339). Table 1 of the ’791 patent discloses that GS-7340 exhibits greater activity and stability compared to tenofovir disoproxil fumarate (TDF) and tenofovir. ’791 patent at 28:5-15. The ’791 patent also teaches that the TAF compounds disclosed therein may be “formulated into compositions containing pharmaceutically acceptable excipients, [which] are used in effective doses in the therapy or prophylaxis of viral (particularly HIV or hepadnaviral) infections.” ’791 patent, 4:54-59, 14:42-53. ’791 patent discloses TAF showing 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. ’791 patent, 27:29-28:37. ’791 patent further discloses the following tables:

TABLE 1

In Vitro Aetivity and Stability

	HIV-1		Stability T ½ (min)		
	Aetivity $IC_{50\,\mu M}$	Cytotoxicity $CC_{50\,\mu M}$	Human Plasma	MT-2 Cell Extract	(P/MT-2)
GS 7340	0,005	>40	90,0	28.3	3.2
TDF	0.05	70	0.41	70.7	0.006
Tenofovir	5	6000	—	—	—

TABLE 2

PMPA Metabolites in Plasma, PBMCs and RBCs After 1 h Incubation of PMPA Prodrugs or PMPA in Human Blood.

Compound	Matrix	Total C-14 Recovered, µg-eq	Metabolites (% of Total Peak Area)					
			PMPA %	PMPAp, %	PMPApp, %	Met. X, %	Met. Y, %	GS 7340, %
GS-7340	Plasma/FP	43.0	1	—	—	2	13	84
(60 µg-eq)	PBMC	1.25	45	16	21	18	—	—
	RBC/FP	12.6	8	—	—	24	11	57
			PMPA	PMPAp	PMPApp	Mono-POC	GS-4331	
GS-4331	Plasma/FP	48.1	11	—	—	89	—	
(TDF)	PBMC	0.133	50	25	18	7	—	
(60 µg-eq)	RBC/FP	10.5	93	7.0	—	—	—	
			PMPA	PMPAp	PMPApp			
PMPA	Plasma/FP	55.7	100	—	—			
(60 µg-eq)	PBMC	0.033	86	14	—			
	RBC/FP	3.72	74	10	16			

’791 patent, Tables 1-2.

Lee discloses that “[t]he amidate prodrug GS 7340 was designed to overcome the permeability limitations of tenofovir by masking the dianion with a neutral promoiety and increasing the plasma stability of the prodrug relative to its intracellular stability. The in vitro anti-HIV potency of GS 7340 (EC_{50}=0.005 µM) is comparable to the most potent protease inhibitors and reflects the greater cell permeation of GS 7340 compared to tenofovir. In addition to favorable potency and a long intracellular half-life, the *in vivo* administration of GS 7340 results in an enhanced

	distribution of lymphatic tissue compared to tenofovir DF." Lee at 1903. Lee further discloses that "[w]ith GS 7340, it should be possible to reduce the total dose of tenofovir, thereby minimizing systemic exposure, while at the same time increasing antiviral activity." *Id*. at 1905. Lee discloses TAF as 10 times more potent than TDF toward HIV-1, with eight times improved selectivity index. Lee, 1900 (Table 1). Lee further discloses, "the high concentrations of tenofovir observed in lymphatic tissues after oral administration of GS 7340 are expected to result in increased clinical potency relative to tenofovir DF." Lee, 1905 Lee further discloses that "[w]ith GS-7340, it should be possible to reduce the total dose of tenofovir, thereby minimizing systemic exposure, while at the same time increasing antiviral activity." Lee, 1905. US '856 discloses are pharmaceutical compositions comprising TAF hemifumarate and one or more additional therapeutic agents selected from the group consisting of "HIV protease inhibiting compounds, HIV nonnucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, and CCR5 inhibitors." *Id.* at [0010]-[0011], [0057]. HIV Guidelines states that "[a]n antiretroviral regimen for a treatment-naive patient generally consists of two nucleoside 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." HIV Guidelines, D-1. HIV Guidelines further recommends combination of the INSTIs elvitegravir and raltegravir with tenofovir and emtricitabine. HIV Guidelines, 1, i. British HIV Guidelines describes tenofovir and emtricitabine as the preferred NRTI backbone for HIV therapy, to be combined with an additional agent such as an INSTI. British HIV Guidelines, 13. NCT '694 discloses a study that "evaluate[s] the efficacy, safety and tolerability of GS-9883 + emtricitabine/tenofovir alafenamide (FTC/TAF) fixed dose combination (FDC) versus dolutegravir (DTG) + FTC/TAF in HIV-1 Infected, antiretroviral treatment-naive adults. This study will also evaluate the pharmacokinetic (PK) profile of GS-9883, FTC and TAF." NCT '694, Study Description. NCT '694 further discloses an "active comparator" with "Drug: FTC/TAF, Emtricitabine/Tenofovir Alafenamide (FTC/TAF) 200 mg/25 mg tablet administered orally; Drug: DTG, Dolutegravir (DTG) 50 mg tablet administered orally." NCT '694, Arms and Interventions. Tivicay Assessment discloses combination therapies with DLT sodium, FTC and tenofovir disoproxil for treating HIV. Tivicay Assessment, 43, 50-51, 89. 2013 Tivicay Label also discloses Tivicay containing 50 mg of dolutegravir sodium as an HIV INSTI indicated in combination with other antiretroviral agents (e.g., emtricitabine/tenfovoir

	(TRUVADA), for the treatment of HIV-1 infection. 2013 Tivicay Label, 1, 4, 24. Truvada Label discloses combining 200 mg emtricitabine, 300 mg tenofovir alafenamide, and 600 mg efavirenz. Truvada Label. Complera Label discloses a tablet composition for oral administration that contains 200 mg of NRTI emtricitabine, and 300 mg of NRTI tenofovir DF, and 27.5 mg of NNRTI rilpivirine hydrochloride. Complera Label, 1, 22 The Stribild Label states that a Stribild table consists of "150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 300 mg of tenofovir disoproxil fumarate." Stribild Label, 1; *see also id.* at 22-23. The Genvoya Label states, "Each GENVOYA tablet contains 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (TAF) (equivalent to 11.2 mg of tenofovir alafenamide fumarate)." Genvoya Label, 4. 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. Genvoya Assessment, 74-75. The Genvoya Assessment teaches, "The overall goal of Genvoya film coated tablet development was to create a tablet containing

	the same amounts of elvitegravir, cobicistat and emtricitabine active substances as currently combined in Stribild fixed dose combination film-coated tablet and to replace tenofovir disoproxil contained in Stribild with tenofovir alafenamide, a second-generation prodrug of tenofovir." Genvoya Assessment, 18. Genvoya Assessment discloses film-coated tablets containing the following active substances: 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (as 11.2 mg of the fumarate)." Genvoya Assessment, 10. WO '351 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." WO '351, 19:3-12. Ruane discloses that "HIV-1 RNA responses for the 8-mg TAF treatment group were similar to that of the 300-mg TDF group. However, median $DAVG_{11}$ [(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, 451-52

	Ruane further states that "[c]ompared 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." Ruane, 454. Sax teaches that "Relative to TDF, TAF is more stable in plasma." Sax, 53. Astuti refers to tenofovir alafenamide (TAF), where "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." Astuti, 11. Astuti further discloses that the "possibility to use small doses of TAF instead of TDF could further widen the STR options as bulky molecules such as PIs could be successfully coformulated." Astuti, 11. Llibre teaches that 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. Llibre, 172. WO '799 teaches, In addition, the compounds of the present invention may be used in combination with one or more other agents useful in the prevention or treatment of HIV. Examples of such agents include:

	Nucleotide reverse transcriptase inhibitors such as zidovudine, didanosine, lamivudine, zalcitabine, abacavir, stavudine, adefovir, adefovir dipivoxil, fozivudine, todoxil, emtricitabine, alovudine, amdoxovir, elvucitabine, tenofovir disoproxil fumarate, dexelvucitabine, festinavir, racivir, and similar agents; Non-nucleotide reverse transcriptase inhibitors (including an agent having anti- oxidation activity such as immunocal, oltipraz, etc.) such as nevirapine, delavirdine, efavirenz, loviride, immunocal, oltipraz, capravirine, lersivirine, doravirine, rilpivirine, etravirine, tenofovir alafenamide fumarate, and similar agents; Protease inhibitors such as saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, fosamprenavir, brecanavir, darunavir, atazanavir, tipranavir, palinavir, lasinavir, and similar agents; Entry, attachment and fusion inhibitors such as enfuvirtide (T -20), T - 1249, PRO -542, PRO - 140, ibalizumab, cenicriviroc, INCB -9471, monomeric DAPTA, AMD -070, ibalizumab, BMS- 806, fostemsavir, temsavir, and 5 -Helix and similar agents; Integrase strand transfer inhibitors such as raltegravir, elvitegravir, dolutegravir, cabotegravir, GS - 9883, and similar agents; Maturation inhibitors such as PA -344, PA - 457, BMS - 955176, as well as those disclosed in PCT Patent Application No. WO2011/100308, PCT Patent Application No. PCT/US2012/024288, Chinese PCT Application No. PCT/CN2011/001302, Chinese PCT Application No. PCT/CN2011/001303, Chinese PCT Application No. PCT/CN2011/002105, PCT/CN2011 /002159, WO2013/090664, WO2013/123019 , WO 2013/043778, WO 2014/123889, WO 2011/153315,

	WO2011/153319, WO2012/106188, WO 2012/106190, WO 2013/169578, and WO 2014/13081, and similar agents; CXCR4 and /or CCR5 inhibitors such as vicriviroc, TAK779, maraviroc, TAK449, as well as those disclosed in WO 02/74769, PCT/US03/39644, PCT/US03/39975, PCT/US03/39619, PCT/USO3/39618, PCT/US03/39740, and PCT/US03/39732, and similar agents. Neutralizing antibodies such as VRC01, VRC0710e8, pro140, PGT121, PGT128, PGT145, PG9, 3BNC117, ibalizumab, N6 and similar agents. WO '799, [0356]-[0365]. 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. WO '116 at [0096]. 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. 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. *See also* Weller; Castagna; Juday; Lunzen; Walmsley; Johns; PR; Mathais; Min; Highleyman; Acosta; BICANDA01157927; NCT02607956-1; NCT02607856-2; Abebe; Shende; Poster #416; Poster # 414; Poster #413.
and 200 mg emtricitabine.	US '332 discloses that "[i]n a preferred embodiment the pharmaceutical composition of the present invention comprises 50 mg dolutegravir, 50 mg dolutegravir, about 200 mg emtricitabine and about 25 mg tenofovir." US '332, [0092]. US '332 describes pharmaceutical combinations comprising 40 to 60 mg DLT, 150 to 250 mg FTC, and 5 to 42 mg TAF, along with pharmaceutical excipients. US '332, [0086]-[0090]. US '332 further discloses a specific combination comprising about 50 mg DLT, about 200 mg FTC and about 25 mg TAF. *Id.* at [0091]-[0092]. US '332 claims, "Pharmaceutical combination comprising (a) dolutegravir, (b) emtricitabine and (c) tenofovir for use as a medicament, wherein the weight ratio of (a) dolutegravir and (b) emtricitabine is from 1:1 to 1:3." US '332, Claim 1. US'332 further discloses that "[i]n a preferred embodiment emtricitabine is present in the form of its free base, i.e. not in the form of an acid addition salt." US '332, [0032]. US '332 claims, "A kit for the treatment of a viral infection, in particular of an HIV-infection, comprising (i) 10 to 75 mg dolutegravir, (ii) 50 to 150 mg emtricitabine, (iii) 0.5 to 400 mg tenofovir or a prodrug thereof." US '332, Claim 15.

	US ’356 further discloses 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.US ’35, [0156]-[0163]. 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. US ’356, 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). US ’356 further discloses that [i]n certain embodiments, a compound disclosed herein 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. US ’356, [0177]. US ’902 discloses, “a novel pharmaceutical product containing efavirenz, emitricitabine and tenofovir DF are provided as a multicomponent unitary oral dosage form.” US ’902, Abstract. US ’857 describes “multilayer tablets that contain rilpivirine hydrochloride, emtricitabine, and tenofivir disoproxil fumarate.” US ’857, Abstract. WO ’846 discloses therapeutic combinations of TAF and FTC for treating HIV. WO ’846, 3:13-18.

WO ’846 teaches the following formulation:

Formulation D:	mg/tablet
GS-7340	25
emtricitabine	200
Microcrystalline Cellulose	200
Lactose Monohydrate	330
Croscarmellose Sodium	60
Pregelatinized Starch	50
Magnesium Stearate	10
	875

WO ’846, 13:12-24.

WO ’846 discloses the following formulation:

Formulation G	mg/tablet
GS-7340	300
emtricitabine	200
Hydroxypropyl Methylcellulose	112
Lactose B.P.	53
Pregelatinized Starch B.P.	28
Magnesium Stearate	7
total:	700

WO ’846, 13:23-24.

WO ’846 further discloses an exemplary formulation containing 25 mg of TAF and 200 mg FTC. WO ’846, 37:13-20.

Gilead/Janssen discusses, “Phase III-ready HIV treatment that will combine Gilead’s tenofovir alafenamide (TAF) and emtricitabine, and Janssen’s rilpivirine.” Gilead/Janssen, 1.

	Gilead/Janssen states, "Gilead and Janssen agreed to develop and commercialize a once-daily single tablet regimen for HIV that combines darunavir with TAF, emtricitabine and a third Gilead compound, cobicistat (marketed as TYBOST®)." Gilead/Janssen, 2. WO '323 discloses, "In further embodiments, the additional therapeutic agent is selected from one or more of: . . (3) HIV nucleoside inhibitors of reverse transcriptase selected from the group consisting of zidovudine, emtricitabine, didanosine, stavudine, zaicitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, ±-FTC, D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, apricitibine (AVX754), KP-1461, GS- 9131 (Gilead Sciences) and fosalvudine tidoxil (formerly HDP 99.0003); (4) HIV nucleotide inhibitors of reverse transcriptase selected from the group consisting of tenofovir, tenofovir disoproxil fumarate, tenofovir alafenarnide fumarate (Gilead Sciences), GS-7340 (Gilead Sciences), GS-9148 (Gilead Sciences), adefovir, adefovir dipivoxii, CMX-001 (Chimerix) or CMX-157 (Chimerix) . . . ." WO '323, 38:1-2; 13-21. US '332 claims, "Pharmaceutical combination comprising (a) dolutegravir, (b) emtricitabine and (c) tenofovir for use as a medicament, wherein the weight ratio of (a) dolutegravir and (b) emtricitabine is from 1:1 to 1:3." US '332, Claim 1. US '332 claims, "A kit for the treatment of a viral infection, in particular of an HIV-infection, comprising (i) 10 to 75 mg dolutegravir, (ii) 50 to 150 mg emtricitabine, (iii) 0.5 to 400 mg tenofovir or a prodrug thereof." US '332, Claim 15.

	HIV Guidelines further recommends combination of the INSTIs elvitegravir and raltegravir with tenofovir and emtricitabine. HIV Guidelines, 1, i. HIV Guidelines states that "[a]n antiretroviral regimen for a treatment-naive patient generally consists of two nucleoside 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." HIV Guidelines, D-1. British HIV Guidelines describes tenofovir and emtricitabine as the preferred NRTI backbone for HIV therapy, to be combined with an additional agent such as an INSTI. British HIV Guidelines, 13. NCT '694 discloses a study that "evaluate[s] the efficacy, safety and tolerability of GS-9883 + emtricitabine/tenofovir alafenamide (FTC/TAF) fixed dose combination (FDC) versus dolutegravir (DTG) + FTC/TAF in HIV-1 Infected, antiretroviral treatment-naive adults. This study will also evaluate the pharmacokinetic (PK) profile of GS-9883, FTC and TAF." NCT '694, Study Description. NCT '694 further discloses an "active comparator" with "Drug: FTC/TAF, Emtricitabine/Tenofovir Alafenamide (FTC/TAF) 200 mg/25 mg tablet administered orally; Drug: DTG, Dolutegravir (DTG) 50 mg tablet administered orally." NCT '694, Arms and Interventions. Tivicay Assessment discloses the product Tivicay® as containing 50 mg of DLT sodium. Tivicay Assessment, 9. Tivicay

	Assessment identifies 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." *Id.* It further discloses combination therapies with DLT sodium, FTC and tenofovir disoproxil for treating HIV. *Id.* at 43, 50-51, 89. 2013 Tivicay Label also discloses Tivicay containing 50 mg of dolutegravir sodium as an HIV INSTI indicated in combination with other antiretroviral agents (e.g., emtricitabine/tenfovoir (TRUVADA), for the treatment of HIV-1 infection. 2013 Tivicay Label, 1, 4, 24. Truvada Label discloses combining 200 mg emtricitabine, 300 mg tenofovir alafenamide, and 600 mg efavirenz. Truvada Label. Complera Label discloses a tablet composition for oral administration that contains 200 mg of NRTI emtricitabine, and 300 mg of NRTI tenofovir DF, and 27.5 mg of NNRTI rilpivirine hydrochloride. Complera Label, 1, 22 The Stribild Label describes Stribild as "a combination of 1 integrase strand transfer inhibitor, 1 pharmacokinetic enhancer, and 2 nucleos(t)ide analog HIV-1 reverse transcriptase inhibitors, is indicated as a complete regimen for the treatment of HIV-1 infection in adults who are antiretroviral treatment-naïve." Stribild Label, 1. The Stribild Label states that a Stribild table consists of "150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine,

	and 300 mg of tenofovir disoproxil fumarate." Stribild Label, 1; *see also id.* at 22-23. The Stribild Assessment describes Stribild as "a fixed drug combination tablet containing three ARVs (FTC/TDF and elvitegravir [EVG; an INSTI]) plus a new pharmacoenhancer cobicistat (COBI), which modifies the PK profile of EVG." Stribild Assessment, 10. The Genvoya Label states, "Each GENVOYA tablet contains 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (TAF) (equivalent to 11.2 mg of tenofovir alafenamide fumarate)." Genvoya Label, 4. Genvoya Assessment discloses film-coated tablets containing the following active substances: 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (as 11.2 mg of the fumarate)." Genvoya Assessment, 10. WO '351 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." WO '351, 19:3-12.

	WO ’720 discloses a combination of 200 mg FTC, 3-40 mg TAF, 50-500 mg cobicistat, 150 mg elvitegravir. WO ’720, [0028]. WO ’466 claims, “[a] pharmaceutical composition comprising a self-emulsifying drug delivery system, wherein the self-emulsifying drug delivery system comprises efavirenz and one or more pharmaceutically acceptable excipient.” WO ’466, Claim 1. WO ’466 further claims, “[a] pharmaceutical composition according to any preceding claim, further comprising at least one additional active ingredient such as protease inhibitors, nucleoside reverse transcriptase inhibitors, non-nucleotide reverse transcriptase inhibitors, integrase inhibitors, or any combination thereof.” WO ’466, Claim 23. WO ’466 further claims, “[a] pharmaceutical composition according to claim 23, wherein the at least one additional active ingredient comprises emtricitabine, tenofovir disproxil fumarate, tenofovir alafanamide fumarate, lamivudine, stavudine, zidovudine, or any combination thereof.” WO ’466, Claim 24. The Atripla Label teaches, “Each tablet contains 600 mg of efavirenz, 200 mg of emtricitabine, and 300 mg of tenofovir DF (which is equivalent to 245 mg of tenofovir disoproxil) as active ingredients.” Atripla Label, 1. US ’902 discloses, “a novel pharmaceutical product containing efavirenz, emitricitabine and tenofovir DF are provided as a multicomponent unitary oral dosage form.” US ’902, Abstract. US ’902 further discloses bilayer tablets similar to Atripla containing 200 mg FTC. US ’902, [0050]-[0052].

	The Complera Label describes the recommended dose as "[o]ne tablet (containing 200 mg of emtricitabine, 25 mg of rilpivirine, and 300 mg of tenofovir disoproxil fumarate) taken once daily with a meal." Complera Label, 1. US '857 describes "multilayer tablets that contain rilpivirine hydrochloride, emtricitabine, and tenofivir disoproxil fumarate." US '857, Abstract. US '857 further discloses bilayer tablets similar to Complera/Eviplera containing 200 mg FTC. US '857 [0066]-[0073]. WO '799 teaches, In addition, the compounds of the present invention may be used in combination with one or more other agents useful in the prevention or treatment of HIV. Examples of such agents include: Nucleotide reverse transcriptase inhibitors such as zidovudine, didanosine , lamivudine , zalcitabine , abacavir, stavudine , adefovir, adefovir dipivoxil, fozivudine, todoxil, emtricitabine , alovudine, amdoxovir, elvucitabine , tenofovir disoproxil fumarate , dexelvucitabine , festinavir, racivir, and similar agents; Non-nucleotide reverse transcriptase inhibitors (including an agent having anti- oxidation activity such as immunocal, oltipraz, etc .) such as nevirapine, delavirdine, efavirenz, loviride , immunocal, oltipraz , capravirine , lersivirine, doravirine, rilpivirine , etravirine, tenofovir alafenamide fumarate , and similar agents; Protease inhibitors such as saquinavir, ritonavir, indinavir, nelfinavir , amprenavir , fosamprenavir,

	brecanavir, darunavir , atazanavir, tipranavir , palinavir , lasinavir, and similar agents ; Entry, attachment and fusion inhibitors such as enfuvirtide (T -20), T - 1249, PRO -542, PRO - 140, ibalizumab, cenicriviroc , INCB -9471, monomeric DAPTA, AMD -070, ibalizumab, BMS- 806, fostemsavir, temsavir, and 5 -Helix and similar agents; Integrase strand transfer inhibitors such as raltegravir, elvitegravir, dolutegravir, cabotegravir, GS - 9883, and similar agents; Maturation inhibitors such as PA -344, PA - 457, BMS - 955176, as well as those disclosed in PCT Patent Application No. WO2011/100308, PCT Patent Application No. PCT/US2012/024288, Chinese PCT Application No. PCT/CN2011/001302, Chinese PCT Application No. PCT/CN2011/001303, Chinese PCT Application No. PCT/CN2011/002105, PCT/CN2011 /002159, WO2013/090664, WO2013/123019 , WO 2013/043778, WO 2014/123889, WO 2011/153315, WO2011/153319, WO2012/106188, WO 2012/106190, WO 2013/169578, and WO 2014/13081, and similar agents; CXCR4 and /or CCR5 inhibitors such as vicriviroc, TAK779, maraviroc, TAK449, as well as those disclosed in WO 02/74769, PCT/US03/39644, PCT/US03/39975, PCT/US03/39619, PCT/USO3/39618, PCT/US03/39740, and PCT/US03/39732, and similar agents. Neutralizing antibodies such as VRC01, VRC0710e8, pro140, PGT121, PGT128, PGT145, PG9, 3BNC117, ibalizumab, N6 and similar agents. WO ’799, [0356]-[0365].

	US ’426 states, “In further embodiments, Wnt signaling pathway inhibitor is administered in combination with one or more of the following agents: abacavir, acyclovir, acyclovir, adefovir, amantadine, amprenavir, ampligen, arbidol, atazanavir, atripla, boceprevir, cidofovir, combivir, complera, darunavir, delavirdine, didanosine, docosanol, dolutegravir, edoxudine, efavirenz, emtricitabine, enfuvirtide, entecavir, famciclovir, fomivirsen, fosamprenavir, foscarnet, fosfonet, ganciclovir, ibacitabine, imunovir, idoxuridine, imiquimod, indinavir, inosine, interferon type III, interferon type II, interferon type I, lamivudine, lopinavir, loviride, maraviroc, moroxydine, methisazone, nelfinavir, nevirapine, nexavir, oseltamivir, peginterferon alfa-2a, penciclovir, peramivir, pleconaril, podophyllotoxin, raltegravir, ribavirin, rimantadine, ritonavir, pyramidine, saquinavir, stavudine, stribild, tenofovir, tenofovir disoproxil, tenofovir alafenamide fumarate (TAF), tipranavir, trifluridine, trizivir, tromantadine, truvada, valaciclovir, valganciclovir, vicriviroc, vidarabine, viramidine, zalcitabine, zanamivir, or zidovudine, and combinations thereof.” US ’426, [0139]. US ’850 claims, “A method of preventing or delaying a rise in viral load following cessation of treatment of human immunodeficiency virus (HIV) infection, the method comprising: administering to a subject infected with HIV at least three compounds collectively having the following activities: dampening of immune activation, wherein the dampening selectively affects the CD4 T cell response relative to the CD8 T cell response, inhibition of HIV replication, stimulation of reactivation of latent HIV, and inhibition of infection of CD4 T cells by HIV, wherein the compound that inhibits HIV infection of CD4 T cells is selected from the group consisting of C-C chemokine receptor type 5 (CCR5) inhibitors, C-X-X chemokine

	receptor type 4 (CXCR4) inhibitors, CD4 inhibitors, gp120 inhibitors, and gp41 inhibitors, wherein the compounds are provided in dosages reducing the number of cells infected with HIV or the viral load of HIV, relative to which is achieved using just the combination of ART and compounds which activate latent HIV, wherein HIV infected cells or HIV viral load is not detectable at 12 months after the end of the course of treatment." US '850, Claim 1. US '850 further claims, "The method of claim 1 wherein the compound that inhibits HIV replication are selected from the group consisting of nucleoside reverse transcriptase inhibitors (NRTIs) such as tenofovir, emtricitabine, zidovudine (AZT), lamivudine (3TC), abacavir, and tenofovir alafenamide fumarate; non-nucleotide reverse transcriptase inhibitors (NNRTIs) such as efavirenz, rilpivirine, and etravirine; integrase inhibitors such as raltegravir and elvitegravir; and protease inhibitors such as ritonavir, darunavir, atazanavir, lopinavir, and cobicistat." US '850, Claim 2. 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. WO '116 at [0096]. 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. 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. *See also* Weller; Castagna; Juday; Lunzen; Walmsley; Johns; PR; Mathais; Min; Highleyman; Acosta; BICANDA01157927; NCT02607956-1; NCT02607856-2; Abebe; Shende; Poster #416; Poster # 414; Poster #413.

Claim 9	
Claim Elements	Prior Art Teachings of Claim Elements
The tablet of claim 1,	The prior art teachings disclosing the tablets of any of claim 1 is set forth above and incorporated herein by reference.
wherein the tablet has a total weight of less than 1000 mg.	WO '846 teaches the following formulation: Formulation D: GS-7340 — 25 mg/tablet emtricitabine — 200 Microcrystalline Cellulose — 200 Lactose Monohydrate — 330 Croscarmellose Sodium — 60 Pregelatinized Starch — 50 Magnesium Stearate — 10 875 WO '846, 13:12-24. WO '846 discloses the following formulation:

	Formulation G — mg/tablet GS-7340 — 300 emtricitabine — 200 Hydroxypropyl Methylcellulose — 112 Lactose B.P. — 53 Pregelatinized Starch B.P. — 28 Magnesium Stearate — 7 total: — 700 WO '846, 13:23-24. Shah teaches, "The second-generation INSTI dolutegravir (S/GSK 1349572) combines the advantages of its predecessors, but it is administered once/day without the need for a pharmacokinetic booster and may be coformulated with other antiretrovirals in a single-tablet regimen[, and] [d]olutegravir has been investigated as part of an antiretroviral therapy (ART) regimen for treatment-naive and treatment experienced patients" Shah, 506. Shah further teaches that "Cobicistat is a specific and potent inhibitor of CYP3A4 and associated with clinically significant drug–drug interactions." Shah, 506. Shah further teaches that DLT may be coformulated with other antiretrovirals in a single-tablet regimen for the treatment of HIV, without the need for COBI. *Id.* Shah further teaches that "to be administered once/day, raltegravir must be coadministered with the potent CYP3A4 inhibitor cobicistat, which can lead to clinically significant drug-drug interactions." Shah, 517-518. US '332 claims, "Pharmaceutical combination comprising (a) dolutegravir, (b) emtricitabine and (c) tenofovir for use as a

	medicament, wherein the weight ratio of (a) dolutegravir and (b) emtricitabine is from 1:1 to 1:3." US '332, Claim 1. US '332 further claims, "Pharmaceutical combination for use according to any one of the preceding claims, wherein tenofovir is used in form of a prodrug of tenofovir." US '332, Claim 5. US '332 further claims, "Pharmaceutical combination for use according to claim 5, wherein the prodrug of tenofovir is tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide or hexadecyloxypropyl tenofovir." US '332, Claim 6. US '332 claims, "A kit for the treatment of a viral infection, in particular of an HIV-infection, comprising (i) 10 to 75 mg dolutegravir, (ii) 50 to 150 mg emtricitabine, (iii) 0.5 to 400 mg tenofovir or a prodrug thereof." US '332, Claim 15. US '332 describes pharmaceutical combinations comprising 40 to 60 mg DLT, 150 to 250 mg FTC, and 5 to 42 mg TAF, along with pharmaceutical excipients. US '332, [0086]-[0090]. US '332 further discloses a specific combination comprising about 50 mg DLT, about 200 mg FTC and about 25 mg TAF. *Id.* at [0091]-[0092]. Dow discloses that elvitegravir must be pharmacokinetically boosted with the CYP3A4 inhibitor cobicistat. Dow, 84. Llibre discloses that 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%." Llibre, 175. Llibre further discloses that CYP3A is the main pathway by which EVG undergoes metabolism in the intestine and liver. *Id.* at 172. Llibre teaches that 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. Llibre, 172. Astuti discloses that 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)". Astuti, 10-11. Astuti refers to tenofovir alafenamide (TAF), where "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." Astuti, 11. Astuti further discloses that the "possibility to use small doses of TAF instead of TDF could further widen the STR options as bulky molecules such as PIs could be successfully coformulated." Astuti, 11.

	Ostenholzer discloses that DTG does not require boosting, and is primarily metabolized by UGT 1A1 with only a small contribution from CYP3A4. Ostenholzer, 265. Ostenholzer further discloses that 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. *Id.* at 269. US '122 discloses a solid dose form (e.g. tablets) comprising a compound of Formula I (i.e. elvitegravir), Formula III (i.e. emtricitabine), Formula IV (i.e. tenofovir disoproxil fumarate), 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.

	<table><tr><th></th><th colspan="2">Compound of Formula II 150 mg Formulation</th></tr><tr><th>Components</th><th>% w/w</th><th>mg/tablet</th></tr><tr><td>Compound of Formula III</td><td>13.9</td><td>200.0</td></tr><tr><td>Salt of Formula IV</td><td>20.9</td><td>300.0</td></tr><tr><td>Compound of Formula I</td><td>10.4</td><td>150.0</td></tr><tr><td>Compound of Formula II</td><td>10.4</td><td>150.0</td></tr><tr><td>Colloidal Silicon Dioxide</td><td>12.0</td><td>172.5</td></tr><tr><td>Lactose Monohydrate</td><td>0.8</td><td>10.9</td></tr><tr><td>Microcrystalline Cellulose</td><td>20.8</td><td>299.5</td></tr><tr><td>Hydroxypropyl Cellulose</td><td>0.5</td><td>7.5</td></tr><tr><td>Hydroxypropyl Cellulose</td><td>0.6</td><td>9.0</td></tr><tr><td>Sodium Lauryl Sulfate</td><td>0.8</td><td>11.3</td></tr><tr><td>Croscarmellose Sodium</td><td>7.3</td><td>104.3</td></tr><tr><td>Magnesium Stearate</td><td>1.6</td><td>22.4</td></tr><tr><td>Total</td><td>100</td><td>1437.</td></tr></table> *Id.* at [0022]. US ’122 further discloses examples of tablets similar to Stribild. *Id.* at [0063]-[0065] (Examples 2-4). The Stribild Label states that a Stribild table consists of “150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 300 mg of tenofovir disoproxil fumarate.” Stribild Label, 1; *see also id.* at 22-23. Lee discloses TAF as 10 times more potent than TDF toward HIV-1, with eight times improved selectivity index. Lee, 1900 (Table 1). Lee further discloses, “the high concentrations of tenofovir observed in lymphatic tissues after oral administration of GS

	7340 are expected to result in increased clinical potency relative to tenofovir DF." Lee, 1905 Lee further discloses that "[w]ith GS-7340, it should be possible to reduce the total dose of tenofovir, thereby minimizing systemic exposure, while at the same time increasing antiviral activity." Lee, 1905. Gilead/Janssen discloses that 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. '791 patent discloses TAF showing 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. '791 patent, 27:29-28:37. '791 patent further discloses the following tables: TABLE 1 In Vitro Activity and Stability HIV-1 / Stability T ½ (min) Activity $IC_{50\,\mu M}$ / Cytotoxicity $CC_{50\,\mu M}$ / Human Plasma / MT-2 Cell Extract / (P/MT-2) GS 7340 0.005 >40 90.0 28.3 3.2 TDF 0.05 70 0.41 70.7 0.006 Tenofovir 5 6000 — — —

TABLE 2

PMPA Metabolites in Plasma, PBMCs and RBCs After 1 h Incubation of PMPA Prodrugs or PMPA in Human Blood.

Compound	Matrix	Total C-14 Recovered, µg-eq	Metabolites (% of Total Peak Area)					
			PMPA %	PMPAp, %	PMPApp, %	Met. X, %	Met. Y, %	GS 7340, %
GS-7340	Plasma/FP	43.0	1	—	—	2	13	84
(60 µg-eq)	PBMC	1.25	45	16	21	18	—	—
	RBC/FP	12.6	8	—	—	24	11	57
			PMPA	PMPAp	PMPApp	Mono-POC	GS-4331	
GS-4331	Plasma/FP	48.1	11	—	—	89	—	
(TDF)	PBMC	0.133	50	25	18	7	—	
(60 µg-eq)	RBC/FP	10.5	93	7.0	—	—	—	
			PMPA	PMPAp	PMPApp			
PMPA	Plasma/FP	55.7	100	—	—			
(60 µg-eq)	PBMC	0.033	86	14	—			
	RBC/FP	3.72	74	10	16			

’791 patent, Tables 1-2.

’791 patent discloses TAF showing 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. ’791 patent, 27:29-28:37.

’791 patent further discloses the following tables:

TABLE 1

In Vitro Activity and Stability

	HIV-1		Stability T ½ (min)		
	Activity $IC_{50\,\mu M}$	Cytotoxicity $CC_{50\,\mu M}$	Human Plasma	MT-2 Cell Extract	(P/MT-2)
GS 7340	0.005	>40	90.0	28.3	3.2
TDF	0.05	70	0.41	70.7	0.006
Tenofovir	5	6000	—	—	—

TABLE 2

PMPA Metabolites in Plasma, PBMCs and RBCs After 1 h Incubation of PMPA Prodrugs or PMPA in Human Blood.

Compound	Matrix	Total C-14 Recovered, µg-eq	Metabolites (% of Total Peak Area)					
			PMPA %	PMPAp, %	PMPApp, %	Met. X, %	Met. Y, %	GS 7340, %
GS-7340	Plasma/FP	43.0	1	—	—	2	13	84
(60 µg-eq)	PBMC	1.25	45	16	21	18	—	—
	RBC/FP	12.6	8	—	—	24	11	57
			PMPA	PMPAp	PMPApp	Mono-POC	GS-4331	
GS-4331	Plasma/FP	48.1	11	—	—	89	—	
(TDF)	PBMC	0.133	50	25	18	7	—	
(60 µg-eq)	RBC/FP	10.5	93	7.0	—	—	—	
			PMPA	PMPAp	PMPApp			
PMPA	Plasma/FP	55.7	100	—	—			
(60 µg-eq)	PBMC	0.033	86	14	—			
	RBC/FP	3.72	74	10	16			

'791 patent, Tables 1-2.

The Genvoya Assessment discloses, "The finished product is presented as film-coated tablets containing the following active substances: 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (as 11.2 mg of the fumarate)." Genvoya Assessment, 10.

The Genvoya Assessment further discloses that 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. Genvoya Assessment, 13.

The Genvoya Label states, "Each GENVOYA tablet contains 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (TAF) (equivalent to 11.2 mg of tenofovir alafenamide fumarate)." Genvoya Label, 4.

	Stribild Assessment describes Stribild as a fixed drug combination tablet containing three antiretroviral agents, *i.e.* the INSTI elvitegravir (EVG), and the NRTIs FTC and TDF, plus the pharmacoenhancer cobicistat (COBI), which is indicated as a complete regimen for the treatment of HIV-1 infection in adults aged 18 years and over who are antiretroviral treatment-naïve or who have no known mutations associated with resistance to the individual components of Stribild. Stribild Assessment, 10. Stribild Assessment further discloses that Stribild is a fixed dose combination containing two new active substances not previously authorized in the EU -elvitegravir and cobicistat – and two known active substances – emtricitabine and tenofovir. *Id.* at 11. The fixed-dose combination product in a solid oral dosage form was "designed in order to provide patient dosing convenience of a single tablet." *Id.* at 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 teaches that "[i]ngredients are mixed, and compressed to obtain tablets, each weighing 665 mg." *Id*. at 177:38-39. US '902 discloses, "a novel pharmaceutical product containing efavirenz, emitricitabine and tenofovir DF are provided as a multicomponent unitary oral dosage form." US '902, Abstract. The Complera Label teaches, "[A] combination of 2 nucleoside analog HIV-1 reverse transcriptase inhibitors (emtricitabine and

	tenofovir disoproxil fumarate) and 1 non-nucleoside reverse transcriptase inhibitor (rilpivirine).” Complera Label, 1. The Complera Label describes the recommended dose as “[o]ne tablet (containing 200 mg of emtricitabine, 25 mg of rilpivirine, and 300 mg of tenofovir disoproxil fumarate) taken once daily with a meal.” Complera Label, 1. US ’857 describes “multilayer tablets that contain rilpivirine hydrochloride, emtricitabine, and tenofivir disoproxil fumarate.” US ’857, Abstract. *See also* Weller; Castagna; Juday; Lunzen; Walmsley; Johns; PR; Mathais; Min; Highleyman; Acosta; BICANDA01157927; NCT02607956-1; NCT02607856-2; Abebe; Shende; Poster #416; Poster # 414; Poster #413.

Claim 10	
Claim Elements	Prior Art Teachings of Claim Elements
The tablet of claim 1,	The prior art teachings disclosing the tablets of any of claim 1 is set forth above and incorporated herein by reference.
wherein the tablet has a total weight of less than 800 mg.	WO ’846 teaches the following formulation: Formulation D: mg/tablet GS-7340 25 emtricitabine 200 Microcrystalline Cellulose 200 Lactose Monohydrate 330 Croscarmellose Sodium 60 Pregelatinized Starch 50 Magnesium Stearate 10 875

	WO ’846, 13:12-24. WO ’846 discloses the following formulation: Formulation G — mg/tablet GS-7340 — 300 emtricitabine — 200 Hydroxypropyl Methylcellulose — 112 Lactose B.P. — 53 Pregelatinized Starch B.P. — 28 Magnesium Stearate — 7 total: — 700 WO ’846, 13:23-24. Shah teaches, “The second-generation INSTI dolutegravir (S/GSK 1349572) combines the advantages of its predecessors, but it is administered once/day without the need for a pharmacokinetic booster and may be coformulated with other antiretrovirals in a single-tablet regimen[, and] [d]olutegravir has been investigated as part of an antiretroviral therapy (ART) regimen for treatment-naive and treatment experienced patients” Shah, 506. Shah further teaches that “Cobicistat is a specific and potent inhibitor of CYP3A4 and associated with clinically significant drug–drug interactions.” Shah, 506. Shah further teaches that DLT may be coformulated with other antiretrovirals in a single-tablet regimen for the treatment of HIV, without the need for COBI. *Id.* Shah further teaches that “to be administered once/day, raltegravir must be coadministered with the potent CYP3A4

	inhibitor cobicistat, which can lead to clinically significant drug-drug interactions." Shah, 517-518. US '332 claims, "Pharmaceutical combination comprising (a) dolutegravir, (b) emtricitabine and (c) tenofovir for use as a medicament, wherein the weight ratio of (a) dolutegravir and (b) emtricitabine is from 1:1 to 1:3." US '332, Claim 1. US '332 further claims, "Pharmaceutical combination for use according to any one of the preceding claims, wherein tenofovir is used in form of a prodrug of tenofovir." US '332, Claim 5. US '332 further claims, "Pharmaceutical combination for use according to claim 5, wherein the prodrug of tenofovir is tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide or hexadecyloxypropyl tenofovir." US '332, Claim 6. US '332 claims, "A kit for the treatment of a viral infection, in particular of an HIV-infection, comprising (i) 10 to 75 mg dolutegravir, (ii) 50 to 150 mg emtricitabine, (iii) 0.5 to 400 mg tenofovir or a prodrug thereof." US '332, Claim 15. US '332 describes pharmaceutical combinations comprising 40 to 60 mg DLT, 150 to 250 mg FTC, and 5 to 42 mg TAF, along with pharmaceutical excipients. US '332, [0086]-[0090]. US '332 further discloses a specific combination comprising about 50 mg DLT, about 200 mg FTC and about 25 mg TAF. *Id.* at [0091]-[0092]. Dow discloses that elvitegravir must be pharmacokinetically boosted with the CYP3A4 inhibitor cobicistat. Dow, 84.

	Llibre discloses that 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%." Llibre, 175. Llibre further discloses that CYP3A is the main pathway by which EVG undergoes metabolism in the intestine and liver. *Id.* at 172. Llibre teaches that 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. Llibre, 172. Astuti discloses that 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)". Astuti, 10-11. Astuti refers to tenofovir alafenamide (TAF), where "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." Astuti, 11.

	Astuti further discloses that the "possibility to use small doses of TAF instead of TDF could further widen the STR options as bulky molecules such as PIs could be successfully coformulated." Astuti, 11. Ostenholzer discloses that DTG does not require boosting, and is primarily metabolized by UGT 1A1 with only a small contribution from CYP3A4. Ostenholzer, 265. Ostenholzer further discloses that 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. *Id.* at 269. US '122 discloses a solid dose form (e.g. tablets) comprising a compound of Formula I (i.e. elvitegravir), Formula III (i.e. emtricitabine), Formula IV (i.e. tenofovir disoproxil fumarate), 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.

	Compound of Formula II 150 mg Formulation Components / % 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. *Id.* at [0022]. US '122 further discloses examples of tablets similar to Stribild. *Id.* at [0063]-[0065] (Examples 2-4). The Stribild Label states that a Stribild table consists of "150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 300 mg of tenofovir disoproxil fumarate." Stribild Label, 1; *see also id.* at 22-23. Lee discloses TAF as 10 times more potent than TDF toward HIV-1, with eight times improved selectivity index. Lee, 1900 (Table 1). Lee further discloses, "the high concentrations of tenofovir observed in lymphatic tissues after oral administration of GS

	7340 are expected to result in increased clinical potency relative to tenofovir DF." Lee, 1905 Lee further discloses that "[w]ith GS-7340, it should be possible to reduce the total dose of tenofovir, thereby minimizing systemic exposure, while at the same time increasing antiviral activity." Lee, 1905. Gilead/Janssen discloses that 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. '791 patent discloses TAF showing 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. '791 patent, 27:29-28:37. '791 patent further discloses the following tables: TABLE 1 In Vitro Activity and Stability HIV-1 / Stability T ½ (min) Activity $IC_{50\,\mu M}$ / Cytotoxicity $CC_{50\,\mu M}$ / Human Plasma / MT-2 Cell Extract / (P/MT-2) GS 7340: 0.005 / >40 / 90.0 / 28.3 / 3.2 TDF: 0.05 / 70 / 0.41 / 70.7 / 0.006 Tenofovir: 5 / 6000 / — / — / —

TABLE 2

PMPA Metabolites in Plasma, PBMCs and RBCs After 1 h Incubation of PMPA Prodrugs or PMPA in Human Blood.

Compound	Matrix	Total C-14 Recovered, µg-eq	Metabolites (% of Total Peak Area)					
			PMPA %	PMPAp, %	PMPApp, %	Met. X, %	Met. Y, %	GS 7340, %
GS-7340	Plasma/FP	43.0	1	—	—	2	13	84
(60 µg-eq)	PBMC	1.25	45	16	21	18	—	—
	RBC/FP	12.6	8	—	—	24	11	57
			PMPA	PMPAp	PMPApp	Mono-POC	GS-4331	
GS-4331	Plasma/FP	48.1	11	—	—	89	—	
(TDF)	PBMC	0.133	50	25	18	7	—	
(60 µg-eq)	RBC/FP	10.5	93	7.0	—	—	—	
			PMPA	PMPAp	PMPApp			
PMPA	Plasma/FP	55.7	100	—	—			
(60 µg-eq)	PBMC	0.033	86	14	—			
	RBC/FP	3.72	74	10	16			

’791 patent, Tables 1-2.

’791 patent discloses TAF showing 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. ’791 patent, 27:29-28:37.

’791 patent further discloses the following tables:

TABLE 1

In Vitro Activity and Stability

	HIV-1		Stability T ½ (min)		
	Activity $IC_{50\,\mu M}$	Cytotoxicity $CC_{50\,\mu M}$	Human Plasma	MT-2 Cell Extract	(P/MT-2)
GS 7340	0.005	>40	90.0	28.3	3.2
TDF	0.05	70	0.41	70.7	0.006
Tenofovir	5	6000	—	—	—

TABLE 2

PMPA Metabolites in Plasma, PBMCs and RBCs After 1 h Incubation of PMPA Prodrugs or PMPA in Human Blood.

Compound	Matrix	Total C-14 Recovered, µg-eq	Metabolites (% of Total Peak Area)					
			PMPA %	PMPAp, %	PMPApp, %	Met. X, %	Met. Y, %	GS 7340, %
GS-7340	Plasma/FP	43.0	1	—	—	2	13	84
(60 µg-eq)	PBMC	1.25	45	16	21	18	—	—
	RBC/FP	12.6	8	—	—	24	11	57
			PMPA	PMPAp	PMPApp	Mono-POC	GS-4331	
GS-4331	Plasma/FP	48.1	11	—	—	89	—	
(TDF)	PBMC	0.133	50	25	18	7	—	
(60 µg-eq)	RBC/FP	10.5	93	7.0	—	—	—	
			PMPA	PMPAp	PMPApp			
PMPA	Plasma/FP	55.7	100	—	—			
(60 µg-eq)	PBMC	0.033	86	14	—			
	RBC/FP	3.72	74	10	16			

'791 patent, Tables 1-2.

The Genvoya Assessment discloses, "The finished product is presented as film-coated tablets containing the following active substances: 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (as 11.2 mg of the fumarate)." Genvoya Assessment, 10.

The Genvoya Assessment further discloses that 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. Genvoya Assessment, 13.

The Genvoya Label states, "Each GENVOYA tablet contains 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (TAF) (equivalent to 11.2 mg of tenofovir alafenamide fumarate)." Genvoya Label, 4.

	Stribild Assessment describes Stribild as a fixed drug combination tablet containing three antiretroviral agents, *i.e.* the INSTI elvitegravir (EVG), and the NRTIs FTC and TDF, plus the pharmacoenhancer cobicistat (COBI), which is indicated as a complete regimen for the treatment of HIV-1 infection in adults aged 18 years and over who are antiretroviral treatment-naïve or who have no known mutations associated with resistance to the individual components of Stribild. Stribild Assessment, 10. Stribild Assessment further discloses that Stribild is a fixed dose combination containing two new active substances not previously authorized in the EU -elvitegravir and cobicistat – and two known active substances – emtricitabine and tenofovir. *Id.* at 11. The fixed-dose combination product in a solid oral dosage form was "designed in order to provide patient dosing convenience of a single tablet." *Id.* at 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 teaches that "[i]ngredients are mixed, and compressed to obtain tablets, each weighing 665 mg." *Id*. at 177:38-39. US '902 discloses, "a novel pharmaceutical product containing efavirenz, emitricitabine and tenofovir DF are provided as a multicomponent unitary oral dosage form." US '902, Abstract.

	The Complera Label teaches, "[A] combination of 2 nucleoside analog HIV-1 reverse transcriptase inhibitors (emtricitabine and tenofovir disoproxil fumarate) and 1 non-nucleoside reverse transcriptase inhibitor (rilpivirine)." Complera Label, 1. The Complera Label describes the recommended dose as "[o]ne tablet (containing 200 mg of emtricitabine, 25 mg of rilpivirine, and 300 mg of tenofovir disoproxil fumarate) taken once daily with a meal." Complera Label, 1. US '857 describes "multilayer tablets that contain rilpivirine hydrochloride, emtricitabine, and tenofivir disoproxil fumarate." US '857, Abstract. *See also* Weller; Castagna; Juday; Lunzen; Walmsley; Johns; PR; Mathais; Min; Highleyman; Acosta; BICANDA01157927; NCT02607956-1; NCT02607856-2; Abebe; Shende; Poster #416; Poster # 414; Poster #413.

Claim 11	
Claim Elements	Prior Art Teachings of Claim Elements
The tablet of claim 1,	The prior art teachings disclosing the tablets of any of claim 1 is set forth above and incorporated herein by reference.
wherein the tablet has a total weight of less than 730 mg.	WO '846 teaches the following formulation:

	Formulation D: mg/tablet GS-7340 25 emtricitabine 200 Microcrystalline Cellulose 200 Lactose Monohydrate 330 Croscarmellose Sodium 60 Pregelatinized Starch 50 Magnesium Stearate 10 875 WO '846, 13:12-24. WO '846 discloses the following formulation: Formulation G mg/tablet GS-7340 300 emtricitabine 200 Hydroxypropyl Methylcellulose 112 Lactose B.P. 53 Pregelatinized Starch B.P. 28 Magnesium Stearate 7 total: 700 WO '846, 13:23-24. Shah teaches, "The second-generation INSTI dolutegravir (S/GSK 1349572) combines the advantages of its predecessors, but it is administered once/day without the need for a pharmacokinetic booster and may be coformulated with other antiretrovirals in a single-tablet regimen[, and] [d]olutegravir has been investigated as part of an antiretroviral therapy (ART) regimen for treatment-naive and treatment experienced patients" Shah, 506.

	Shah further teaches that "Cobicistat is a specific and potent inhibitor of CYP3A4 and associated with clinically significant drug–drug interactions." Shah, 506. Shah further teaches that DLT may be coformulated with other antiretrovirals in a single-tablet regimen for the treatment of HIV, without the need for COBI. *Id.* Shah further teaches that "to be administered once/day, raltegravir must be coadministered with the potent CYP3A4 inhibitor cobicistat, which can lead to clinically significant drug-drug interactions." Shah, 517-518. US '332 claims, "Pharmaceutical combination comprising (a) dolutegravir, (b) emtricitabine and (c) tenofovir for use as a medicament, wherein the weight ratio of (a) dolutegravir and (b) emtricitabine is from 1:1 to 1:3." US '332, Claim 1. US '332 further claims, "Pharmaceutical combination for use according to any one of the preceding claims, wherein tenofovir is used in form of a prodrug of tenofovir." US '332, Claim 5. US '332 further claims, "Pharmaceutical combination for use according to claim 5, wherein the prodrug of tenofovir is tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide or hexadecyloxypropyl tenofovir." US '332, Claim 6. US '332 claims, "A kit for the treatment of a viral infection, in particular of an HIV-infection, comprising (i) 10 to 75 mg dolutegravir, (ii) 50 to 150 mg emtricitabine, (iii) 0.5 to 400 mg tenofovir or a prodrug thereof." US '332, Claim 15. US '332 describes pharmaceutical combinations comprising 40 to 60 mg DLT, 150 to 250 mg FTC, and 5 to 42 mg TAF, along

	with pharmaceutical excipients. US '332, [0086]-[0090]. US '332 further discloses a specific combination comprising about 50 mg DLT, about 200 mg FTC and about 25 mg TAF. *Id.* at [0091]-[0092]. Dow discloses that elvitegravir must be pharmacokinetically boosted with the CYP3A4 inhibitor cobicistat. Dow, 84. Llibre discloses that 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%." Llibre, 175. Llibre further discloses that CYP3A is the main pathway by which EVG undergoes metabolism in the intestine and liver. *Id.* at 172. Llibre teaches that 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. Llibre, 172. Astuti discloses that 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)". Astuti, 10-11. Astuti refers to tenofovir alafenamide (TAF), where "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." Astuti, 11. Astuti further discloses that the "possibility to use small doses of TAF instead of TDF could further widen the STR options as bulky molecules such as PIs could be successfully coformulated." Astuti, 11. Ostenholzer discloses that DTG does not require boosting, and is primarily metabolized by UGT 1A1 with only a small contribution from CYP3A4. Ostenholzer, 265. Ostenholzer further discloses that 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. *Id.* at 269. US '122 discloses a solid dose form (e.g. tablets) comprising a compound of Formula I (i.e. elvitegravir), Formula III (i.e. emtricitabine), Formula IV (i.e. tenofovir disoproxil fumarate), 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. Compound of Formula II 150 mg Formulation Components / % 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. *Id.* at [0022]. US '122 further discloses examples of tablets similar to Stribild. *Id.* at [0063]-[0065] (Examples 2-4). The Stribild Label states that a Stribild table consists of "150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 300 mg of tenofovir disoproxil fumarate." Stribild Label, 1; *see also id.* at 22-23. Lee discloses TAF as 10 times more potent than TDF toward HIV-1, with eight times improved selectivity index. Lee, 1900 (Table 1).

	Lee further discloses, "the high concentrations of tenofovir observed in lymphatic tissues after oral administration of GS 7340 are expected to result in increased clinical potency relative to tenofovir DF." Lee, 1905 Lee further discloses that "[w]ith GS-7340, it should be possible to reduce the total dose of tenofovir, thereby minimizing systemic exposure, while at the same time increasing antiviral activity." Lee, 1905. Gilead/Janssen discloses that 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. '791 patent discloses TAF showing 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. '791 patent, 27:29-28:37. '791 patent further discloses the following tables: TABLE 1 In Vitro Activity and Stability HIV-1 / Stability T ½ (min) Activity $IC_{50\,\mu M}$ / Cytotoxicity $CC_{50\,\mu M}$ / Human Plasma / MT-2 Cell Extract / (P/MT-2) GS 7340 0.005 >40 90.0 28.3 3.2 TDF 0.05 70 0.41 70.7 0.006 Tenofovir 5 6000 — — —

TABLE 2

PMPA Metabolites in Plasma, PBMCs and RBCs After 1 h Incubation of PMPA Prodrugs or PMPA in Human Blood.

Compound	Matrix	Total C-14 Recovered, µg-eq	Metabolites (% of Total Peak Area) PMPA %	PMPAp, %	PMPApp, %	Met. X, %	Met. Y, %	GS 7340, %
GS-7340	Plasma/FP	43.0	1	—	—	2	13	84
(60 µg-eq)	PBMC	1.25	45	16	21	18	—	—
	RBC/FP	12.6	8	—	—	24	11	57
			PMPA	PMPAp	PMPApp	Mono-POC	GS-4331	
GS-4331	Plasma/FP	48.1	11	—	—	89	—	
(TDF)	PBMC	0.133	50	25	18	7	—	
(60 µg-eq)	RBC/FP	10.5	93	7.0	—	—	—	
			PMPA	PMPAp	PMPApp			
PMPA	Plasma/FP	55.7	100	—	—			
(60 µg-eq)	PBMC	0.033	86	14	—			
	RBC/FP	3.72	74	10	16			

’791 patent, Tables 1-2.

’791 patent discloses TAF showing 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. ’791 patent, 27:29-28:37.

’791 patent further discloses the following tables:

TABLE 1

In Vitro Activity and Stability

	HIV-1 Activity $IC_{50\ \mu M}$	Cytotoxicity $CC_{50\ \mu M}$	Stability T ½ (min) Human Plasma	MT-2 Cell Extract	(P/MT-2)
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'791 patent, Tables 1-2.

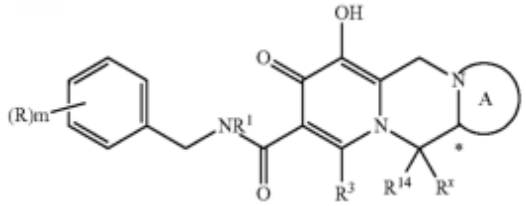
The Genvoya Assessment discloses, "The finished product is presented as film-coated tablets containing the following active substances: 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (as 11.2 mg of the fumarate)." Genvoya Assessment, 10.

The Genvoya Assessment further discloses that 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. Genvoya Assessment, 13.

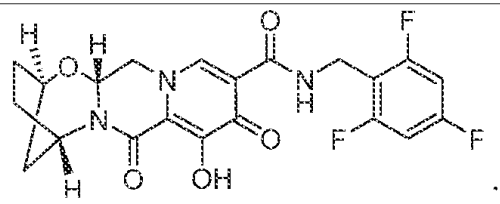
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	Stribild Assessment describes Stribild as a fixed drug combination tablet containing three antiretroviral agents, *i.e.* the INSTI elvitegravir (EVG), and the NRTIs FTC and TDF, plus the pharmacoenhancer cobicistat (COBI), which is indicated as a complete regimen for the treatment of HIV-1 infection in adults aged 18 years and over who are antiretroviral treatment-naïve or who have no known mutations associated with resistance to the individual components of Stribild. Stribild Assessment, 10. Stribild Assessment further discloses that Stribild is a fixed dose combination containing two new active substances not previously authorized in the EU -elvitegravir and cobicistat – and two known active substances – emtricitabine and tenofovir. *Id.* at 11. The fixed-dose combination product in a solid oral dosage form was "designed in order to provide patient dosing convenience of a single tablet." *Id.* at 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 teaches that "[i]ngredients are mixed, and compressed to obtain tablets, each weighing 665 mg." *Id*. at 177:38-39. US '902 discloses, "a novel pharmaceutical product containing efavirenz, emitricitabine and tenofovir DF are provided as a multicomponent unitary oral dosage form." US '902, Abstract. The Complera Label teaches, "[A] combination of 2 nucleoside analog HIV-1 reverse transcriptase inhibitors (emtricitabine and

	tenofovir disoproxil fumarate) and 1 non-nucleoside reverse transcriptase inhibitor (rilpivirine).” Complera Label, 1. The Complera Label describes the recommended dose as “[o]ne tablet (containing 200 mg of emtricitabine, 25 mg of rilpivirine, and 300 mg of tenofovir disoproxil fumarate) taken once daily with a meal.” Complera Label, 1. US ’857 describes “multilayer tablets that contain rilpivirine hydrochloride, emtricitabine, and tenofivir disoproxil fumarate.” US ’857, Abstract. *See also* Weller; Castagna; Juday; Lunzen; Walmsley; Johns; PR; Mathais; Min; Highleyman; Acosta; BICANDA01157927; NCT02607956-1; NCT02607856-2; Abebe; Shende; Poster #416; Poster # 414; Poster #413.

Claim 12	
Claim Elements	Prior Art Teachings of Claim Elements
The tablet of claim 1,	The prior art teachings disclosing the tablets of any of claim 1 is set forth above and incorporated herein by reference.
wherein the tablet contains less than about 15% of the compound of Formula I or a pharmaceutically acceptable salt thereof.	*See* claims 9-11 above. The ’385 patent discloses 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 ’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. The ’385 patent discloses, “The present invention relates to novel compounds possessing an antiviral activity, in detail polycyclic carbamoylpyridone derivatives possessing an inhibitory activity against HIV integrase and a pharmaceutical composition containing the same, especially an anti-HIV agent.” ’385 patent, 1:15-20. WO ’323 claims, “A compound of claim 1 selected from: . .

	 WO ’323, Claim 32. WO ’323 further claims, “A pharmaceutical composition comprising a compound of any one of claims 1-32, or a stereoisomer or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.” WO ’323, Claim 33. WO ’323 discloses, “Compounds, compositions, and methods for the treatment of human immunodeficiency vims (HIV) infection are disclosed. In particular, novel poly cyclic carbamoylpyridone compounds and methods for their preparation and use as therapeutic or prophylactic agents are disclosed.” WO ’323, 1:12-15. Berge teaches “[t]he chemical, biological, physical and economic characteristics of medicinal agents can be manipulated and, hence, often optimized by conversion to a salt form,” where “salt-forming agents are often chosen empirically … [and] the preferred form is selected by pharmaceutical chemists on a practical basis: cost of raw materials, ease of crystallization, and percent yield … [as well as] stability, hygroscopicity, and flowability of the resulting bulk drug.” Berge at 1. Berge also teaches Table 1 as a list of “FDA-approved commercially marketed salts” that includes sodium:

Cation	Percent[a]	Cation	Percent[a]
Organic:		Metallic:	
Benzathine[k]	0.66	Aluminum	0.66
Chloroprocaine	0.33	Calcium	10.49
Choline	0.33	Lithium	1.64
Diethanolamine	0.98	Magnesium	1.31
Ethylenediamine	0.66	Potassium	10.82
Meglumine[l]	2.29	Sodium	61.97
Procaine	0.66	Zinc	2.95

Remington 21st teaches in Table 38-5 that sodium salts were an API-salt form known since 1983:

Table 38-5. Molecular Forms Marketed Worldwide Between 1983 and 1996

SALT FORM	FREQ.	GROUP[A]	pK_a	CLOGP	MW
No salt form	390	0			
Hydrobromide	1	1	−8	0.45	80.91
Hydrochloride	102	1	−6.1	0.24	36.46
Sulfate	5	1	−3	−1.58	98.08
Nitrate	6	1	−1.44	2.09	63.01
Phosphate	2	1	2.15	−1.95	96.99
Glucuronate	1	1	3.22[b]	−3.74	194.14
Acetate	8	1	4.76	−0.36	59.05
Maleate	3	2	1.92	−0.18	116.07
Fumarate	8	2	3.02	−0.18	116.07
Tartrate	1	2	3.03	−2.21	150.09
Citrate	1	2	3.13	−2.11	189.10
Succinate	2	2	4.21	−0.62	118.09
Mesylate	8	3	−1.20	−1.31	96.11
Acistrate	1	3	4.91[b]	7.98	284.49
Besylate	2	4	−2.80[b]	0.23	157.17
Tosylate	3	4	−1.34	0.88	171.20
Xinafoate	1	4	2.66[b]	3.00	188.18
Potassium	1	1	16		39.10
Sodium	37	1	14.77		23.00
Tromethamine	2	1	8.07[c]	−3.17	121.14
Bismuth	1	1	1.58		208.98
Bromide	6	5			79.90
Chloride	2	5			35.45

[a] Groups: 0 = No salt, 1 = Polar, 2 = Multifunctional, 3 = Flexible aliphatics, 4 = Planar aromatics, 5 = Quartenary.
[b] Calculated pK_a.
[c] Data from *CRC Handbook of Basic Tables for Chemical Analysis*, page 469. From Serajuddin ATM, Sheen P, Augustine MA. To market, to market. In: Bristol J, ed. *Annu Rep Med Chem*. New York: Academic, 1983–1996.

Serajuddin teaches that "[s]alt formation is the most common and effective method of increasing solubility of acidic and basic drugs." Serajuddin at 603.

Serajuddin also teaches that "[s]alt formation is also the most common approach of increasing solubility, dissolution rate and ultimately bioavailability of poorly water-soluble ionizable drugs in solid dosage forms." Serajuddin at 614.

Serajuddin further informs that "Table 2 gives the distribution of 120 salts approved by the FDA during the 12-year period from 1995 to 2006, where the hydrochloride salt is the predominant salt form among the basic drugs and the sodium salt is the predominant form for acidic drugs." Serajuddin at 613. The portion of Table 2 that shows salts of acidic drugs shows:

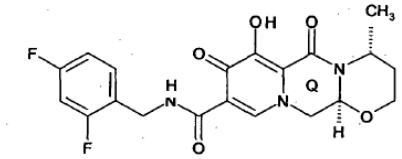
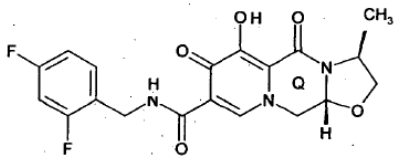
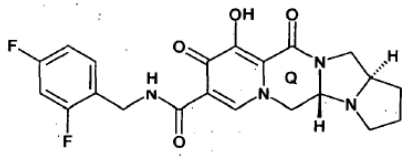
Salts of acidic drugs	Total number
Sodium	12
Calcium	4
Potassium	2
Tromethamine	1
Total of all salts of acidic drugs	19

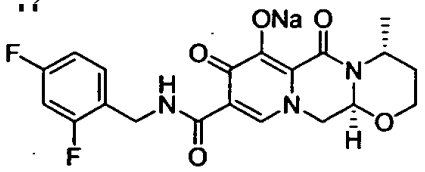
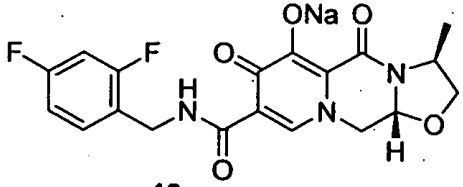
Wells teaches, "A major improvement in solubility can be achieved by forming a salt." Wells at 116.

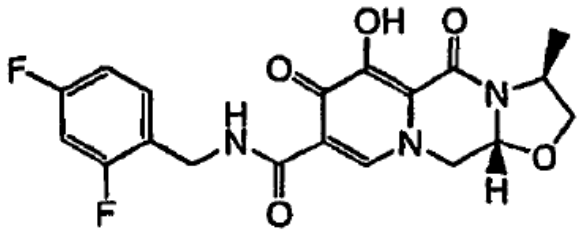
In discussing potential pharmaceutical salts to be used for the salt forms of drugs, Wells provides Table 8.4, which presents such salts, including sodium:

Table 8.4 Potential pharmaceutical salts

Basic drugs			Acidic drugs		
Anion	pK_a	% Usage	Cation	pK_a	% Usage
Hydrochloride	−6.10	43.0	Potassium	16.00	10.8
Sulphate	−3.00, +1.96	7.5	Sodium	14.77	62.0
Mesylate	−1.20	2.0	Lithium	13.82	1.6
Maleate	1.92, 6.23	3.0	Calcium	12.90	10.5
Phosphate	2.15, 7.20, 12.38	3.2	Magnesium	11.42	1.3
Salicylate	3.00	0.9	Diethanolamine	9.65	1.0
Tartrate	3.00	3.5	Zinc	8.96	3.0
Lactate	3.10	0.8	Choline	8.90	0.3
Citrate	3.13, 4.76, 6.40	3.0	Aluminium	5.00	0.7
Succinate	4.21, 5.64	0.4			
Acetate	4.76	1.3			
Others		31.4	Others		8.8

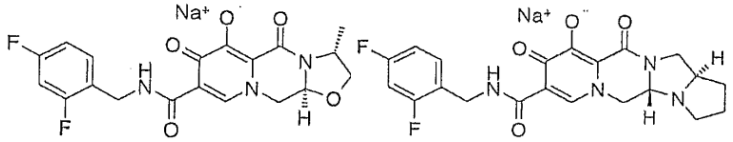
	Bastin encourages the "[s]election of an appropriate salt form for a new chemical entity" because it "provides the pharmaceutical chemist and formulation scientist with the opportunity to modify the characteristics of the potential drug substance and to permit the development of dosage forms with good bioavailability, stability, manufacturability, and patient compliance." Bastin, 427. Brittain teaches, "Prudent drug development programs will identify the preferred crystalline form early in development, with a polymorph/salt group working in close conjunction with process chemists to make the thermodynamically preferred polymorphic form the initial kilogram-scale batch." Brittain, 358. WO '253 teaches a compound of formula AA, known today as dolutegravir, and compound BB known today as cabotegravir with the following formulas:  AA  BB  CC

	WO ’253 further teaches that in a final synthetic step, dolutegravir and cabotegravir are converted into their corresponding sodium salts (dolutegravir sodium identified in compound 13 and cabotegravir sodium identified in compound 18):  13  18 WO ’253 discloses, “The present invention comprises modifications of known processes for synthesizing compounds having HIV integrase inhibitory activity.” WO ’253, 1:8-9. EP ’580 also teaches novel compounds possessing an antiviral activity, in detail polycyclic carbamoylpyridone derivatives possessing an inhibitory activity against HIV integrase and a pharmaceutical composition containing the same, especially an anti-HIV agent.” EP ’580, [0001]. EP ’580 further teaches the following compound, known today as cabotegravir, and its pharmaceutically acceptable salts and solvates.



Id. at [0009]; *see also* claim 1.

WO ’764 teaches the sodium salt forms of dolutegravir and cabotegravir.

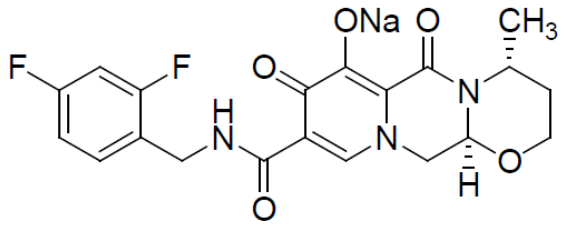


WO ’764 at 128-130.

The 2013 Tivicay Label teaches the sodium salt form of dolutegravir. 2013 Tivicay Label, 1.

The Tivicay Label teaches, “TIVICAY is a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor (INSTI) indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and children aged 12 years and older and weighing at least 40 kg.” Tivicay Label, 1.

The Tivicay Assessment teaches the sodium salt form of dolutegravir with the following structure:

	 Tivicay Assessment, 9. The Tivicay Assessment discloses, "Dolutegravir is a new integrase inhibitor which has been studied in a full range of HIV treatment populations; in those without prior HIV therapy, in patients with prior failing therapies and resistance to drug classes other than integrase inhibitors, and in patients who also had failed therapy with an integrase inhibitor with consequent integrase inhibitor class resistance." Tivicay Assessment, 9. The Triumeq Label discloses the ingredients of Triumeq as including the sodium salt form of dolutegravir, stating, "Each film-coated tablet contains abacavir sulfate equivalent to 600 mg of abacavir, dolutegravir sodium equivalent to 50 mg of dolutegravir, and 300 mg of lamivudine." Triumeq Label, 17. The Triumeq label teaches, "TRIUMEQ, a combination of dolutegravir (integrase strand transfer inhibitor [INSTI]), abacavir, and lamivudine (both nucleoside analogue reverse transcriptase inhibitors) is indicated for the treatment of HIV-1 infection." Triumeq Label, 1. The Triumeq Assessment discloses, "Triumeq is presented as film-coated tablets containing a fixed combination of dolutegravir sodium equivalent to 50 mg dolutegravir, 600 mg of

	abacavir (as sulfate) and 300 mg of lamivudine." Triumeq Assessment, 6. The Triumeq Assessment teaches, "A once-daily fixed-dose combination (FDC) single tablet regimen (STR) that combines the integrase inhibitor (INI) dolutegravir (DTG) with the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir sulfate (abacavir, ABC) and lamivudine (3TC) was developed for use in the treatment of human immunodeficiency virus (HIV) infection." Triumeq Assessment, 6. US '353 discloses, "Dolutegravir may be present in the solid pharmaceutical dosage form in its non-salt form or any pharmaceutically acceptable salt or solvate thereof. Suitable pharmaceutically acceptable salts are known to the skilled person. For example, dolutegravir may be present as alkali metal salt, such as dolutegravir sodium or dolutegravir potassium. The potassium salt being preferred." US '353, [0011]. US '353 teaches, "The present invention relates to a solid pharmaceutical dosage form comprising dolutegravir, a method of its preparation and its use in the treatment of an HIV infection." US '353, [0002]. US '332 teaches, "The sodium salt of dolutegravir and a specific crystalline form of this sodium salt or a hydrate thereof are disclosed in WO 2010/068253." US '332, [0020]. US '332 claims, "Pharmaceutical combination for use according to claim 1 or 2, wherein dolutegravir is used in the form of the sodium salt." US '332, Claim 3.

US ’332 further claims, “Pharmaceutical combination for use according to any one of the preceding claims, wherein tenofovir is used in form of a prodrug of tenofovir.” US ’332, Claim 5.

US ’332 further claims, “Pharmaceutical combination for use according to claim 5, wherein the prodrug of tenofovir is tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide or hexadecyloxypropyl tenofovir.” US ’332, Claim 6.

US ’332 claims, “A kit for the treatment of a viral infection, in particular of an HIV-infection, comprising (i) 10 to 75 mg dolutegravir, (ii) 50 to 150 mg emtricitabine, (iii) 0.5 to 400 mg tenofovir or a prodrug thereof.” US ’332, Claim 15.

US ’332 describes pharmaceutical combinations comprising 40 to 60 mg DLT, 150 to 250 mg FTC, and 5 to 42 mg TAF, along with pharmaceutical excipients. US ’332, [0086]-[0090]. US ’332 further discloses a specific combination comprising about 50 mg DLT, about 200 mg FTC and about 25 mg TAF. *Id.* at [0091]-[0092].

WO ’846 teaches the following formulation:

		mg/tablet
Formulation D:		
	GS-7340	25
	emtricitabine	200
	Microcrystalline Cellulose	200
	Lactose Monohydrate	330
	Croscarmellose Sodium	60
	Pregelatinized Starch	50
	Magnesium Stearate	10
		875

WO ’846, 13:12-24.

	WO ’846 discloses the following formulation: Formulation G — mg/tablet GS-7340 — 300 emtricitabine — 200 Hydroxypropyl Methylcellulose — 112 Lactose B.P. — 53 Pregelatinized Starch B.P. — 28 Magnesium Stearate — 7 total: — 700 WO ’846, 13:23-24. Shah teaches, “The second-generation INSTI dolutegravir (S/GSK 1349572) combines the advantages of its predecessors, but it is administered once/day without the need for a pharmacokinetic booster and may be coformulated with other antiretrovirals in a single-tablet regimen[, and] [d]olutegravir has been investigated as part of an antiretroviral therapy (ART) regimen for treatment-naive and treatment experienced patients” Shah, 506. Shah further teaches that “Cobicistat is a specific and potent inhibitor of CYP3A4 and associated with clinically significant drug–drug interactions.” Shah, 506. Shah further teaches that DLT may be coformulated with other antiretrovirals in a single-tablet regimen for the treatment of HIV, without the need for COBI. *Id.* Shah further teaches that “to be administered once/day, raltegravir must be coadministered with the potent CYP3A4 inhibitor cobicistat, which can lead to clinically significant drug-drug interactions.” Shah, 517-518.

US ’332 claims, “Pharmaceutical combination comprising (a) dolutegravir, (b) emtricitabine and (c) tenofovir for use as a medicament, wherein the weight ratio of (a) dolutegravir and (b) emtricitabine is from 1:1 to 1:3.” US ’332, Claim 1.

US ’122 discloses a solid dose form (e.g. tablets) comprising a compound of Formula I (i.e. elvitegravir), Formula III (i.e. emtricitabine), Formula IV (i.e. tenofovir disoproxil fumarate), 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.

	Compound of Formula II 150 mg Formulation	
Components	% 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.

Id. at [0022].

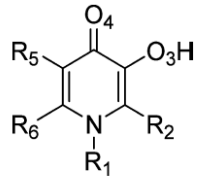
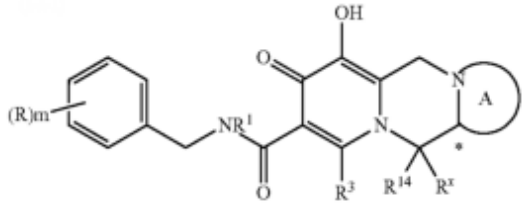
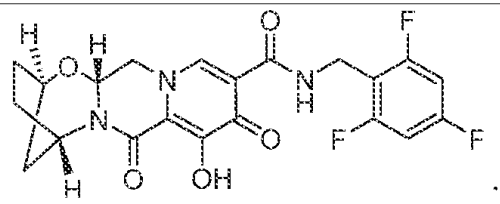
	US '122 further discloses examples of tablets similar to Stribild. *Id.* at [0063]-[0065] (Examples 2-4). The Stribild Label states that a Stribild table consists of "150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 300 mg of tenofovir disoproxil fumarate." Stribild Label, 1; *see also id.* at 22-23. Chen teaches a number of of 3-hydroxypyridin-4-ones (HPOs) in Figure 1 (below):  **Figure 1.** 3-Hydroxypyridin-4-one. Deferiprone (CP20), $R_1 = R_2 = CH_3$ and $R_5 = R_6 = H$ CP60, $R_1 = CH_3$ and $R_2 = R_5 = R_6 = H$ CP751, $R_1 = R_2 = R_5 = CH_3$ and $R_6 = H$ CP90, $R_1 = R_2 = R_5 = R_6 = H$. Chen, 2980. Chen also teaches the measured and calculated pKa values for the hydroxyl group of the above compounds CP20, CP60, and CP751, where the measured values are in the range of ~8.8-10.3. *Id.* at Table 1 (below).

	Table 1. pK_a Prediction Results Using Different Methods | | CP60 | CP20 | CP751 | average absolute error | | measured value | 8.79[31] | 9.76[31] | 10.31[42] | | | CPMD | 9.00 | 9.36 | 10.73 | 0.34 | | ACD/pK_a DB 12.0 | 9.59 | 9.90 | 10.03 | 0.41 | | Marvin 5.4.0.1 | 10.79 | 10.72 | 10.71 | 1.12 | | simple scheme using B3LYP/6-31+G(d)/CPCM | 14.32 | 15.90 | 17.36 | 6.25 | | proton exchange scheme using B3LYP/6-31+G(d)/CPCM | 9.07 | 10.65 | 12.11 | 0.99 | *See also* Weller; Castagna; Juday; Lunzen; Walmsley; Johns; PR; Mathais; Min; Highleyman; Acosta; BICANDA01157927; NCT02607956-1; NCT02607856-2; Abebe; Shende; Poster #416; Poster # 414; Poster #413.

Claim 13	
Claim Elements	Prior Art Teachings of Claim Elements
The tablet of claim 1 or 2,	The prior art teachings disclosing the tablets of any of claims 1 and 2 are set forth above and incorporated herein by reference.
wherein the tablet contains less than about 11% of the compound of Formula I or a pharmaceutically acceptable salt thereof.	*See* claims 9-11 above. The ’385 patent discloses 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

	 Z = O or NR^{26} 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 '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. The '385 patent discloses, "The present invention relates to novel compounds possessing an antiviral activity, in detail polycyclic carbamoylpyridone derivatives possessing an inhibitory activity against HIV integrase and a pharmaceutical composition containing the same, especially an anti-HIV agent." '385 patent, 1:15-20. WO '323 claims, "A compound of claim 1 selected from: . .

	 WO ’323, Claim 32. WO ’323 further claims, “A pharmaceutical composition comprising a compound of any one of claims 1-32, or a stereoisomer or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.” WO ’323, Claim 33. WO ’323 discloses, “Compounds, compositions, and methods for the treatment of human immunodeficiency vims (HIV) infection are disclosed. In particular, novel poly cyclic carbamoylpyridone compounds and methods for their preparation and use as therapeutic or prophylactic agents are disclosed.” WO ’323, 1:12-15. Berge teaches “[t]he chemical, biological, physical and economic characteristics of medicinal agents can be manipulated and, hence, often optimized by conversion to a salt form,” where “salt-forming agents are often chosen empirically … [and] the preferred form is selected by pharmaceutical chemists on a practical basis: cost of raw materials, ease of crystallization, and percent yield … [as well as] stability, hygroscopicity, and flowability of the resulting bulk drug.” Berge at 1. Berge also teaches Table 1 as a list of “FDA-approved commercially marketed salts” that includes sodium:

Cation	Percent[a]	Cation	Percent[a]
Organic:		Metallic:	
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Chloroprocaine	0.33	Calcium	10.49
Choline	0.33	Lithium	1.64
Diethanolamine	0.98	Magnesium	1.31
Ethylenediamine	0.66	Potassium	10.82
Meglumine[l]	2.29	Sodium	61.97
Procaine	0.66	Zinc	2.95

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Nitrate	6	1	−1.44	2.09	63.01
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Glucuronate	1	1	3.22[b]	−3.74	194.14
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Mesylate	8	3	−1.20	−1.31	96.11
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Tosylate	3	4	−1.34	0.88	171.20
Xinafoate	1	4	2.66[b]	3.00	188.18
Potassium	1	1	16		39.10
Sodium	37	1	14.77		23.00
Tromethamine	2	1	8.07[c]	−3.17	121.14
Bismuth	1	1	1.58		208.98
Bromide	6	5			79.90
Chloride	2	5			35.45

[a] Groups: 0 = No salt, 1 = Polar, 2 = Multifunctional, 3 = Flexible aliphatics, 4 = Planar aromatics, 5 = Quartenary.
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Serajuddin also teaches that "[s]alt formation is also the most common approach of increasing solubility, dissolution rate and ultimately bioavailability of poorly water-soluble ionizable drugs in solid dosage forms." Serajuddin at 614.

Serajuddin further informs that "Table 2 gives the distribution of 120 salts approved by the FDA during the 12-year period from 1995 to 2006, where the hydrochloride salt is the predominant salt form among the basic drugs and the sodium salt is the predominant form for acidic drugs." Serajuddin at 613. The portion of Table 2 that shows salts of acidic drugs shows:

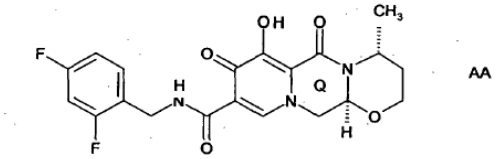
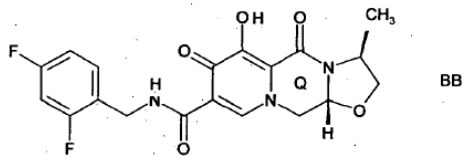
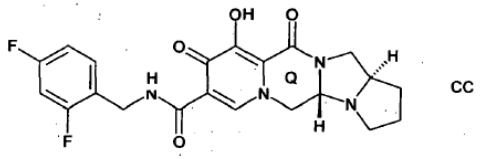
Salts of acidic drugs	Total number
Sodium	12
Calcium	4
Potassium	2
Tromethamine	1
Total of all salts of acidic drugs	19

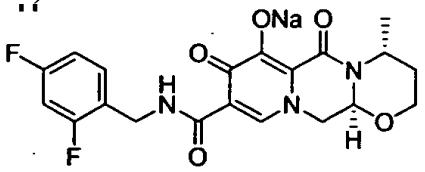
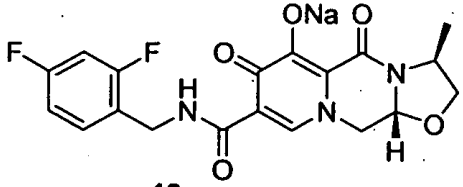
Wells teaches, "A major improvement in solubility can be achieved by forming a salt." Wells at 116.

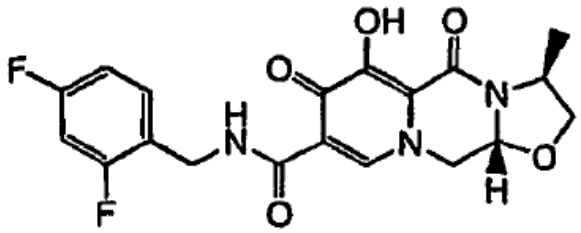
In discussing potential pharmaceutical salts to be used for the salt forms of drugs, Wells provides Table 8.4, which presents such salts, including sodium:

Table 8.4 Potential pharmaceutical salts

Basic drugs			Acidic drugs		
Anion	pK_a	% Usage	Cation	pK_a	% Usage
Hydrochloride	−6.10	43.0	Potassium	16.00	10.8
Sulphate	−3.00, +1.96	7.5	Sodium	14.77	62.0
Mesylate	−1.20	2.0	Lithium	13.82	1.6
Maleate	1.92, 6.23	3.0	Calcium	12.90	10.5
Phosphate	2.15, 7.20, 12.38	3.2	Magnesium	11.42	1.3
Salicylate	3.00	0.9	Diethanolamine	9.65	1.0
Tartrate	3.00	3.5	Zinc	8.96	3.0
Lactate	3.10	0.8	Choline	8.90	0.3
Citrate	3.13, 4.76, 6.40	3.0	Aluminium	5.00	0.7
Succinate	4.21, 5.64	0.4			
Acetate	4.76	1.3			
Others		31.4	Others		8.8

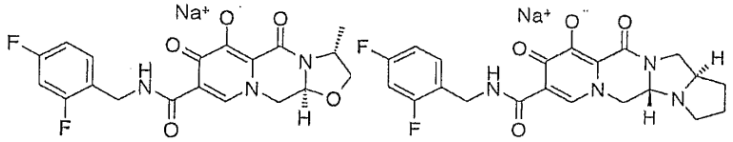
	Bastin encourages the "[s]election of an appropriate salt form for a new chemical entity" because it "provides the pharmaceutical chemist and formulation scientist with the opportunity to modify the characteristics of the potential drug substance and to permit the development of dosage forms with good bioavailability, stability, manufacturability, and patient compliance." Bastin, 427. Brittain teaches, "Prudent drug development programs will identify the preferred crystalline form early in development, with a polymorph/salt group working in close conjunction with process chemists to make the thermodynamically preferred polymorphic form the initial kilogram-scale batch." Brittain, 358. WO '253 teaches a compound of formula AA, known today as dolutegravir, and compound BB known today as cabotegravir with the following formulas:  AA  BB  CC

	WO ’253 further teaches that in a final synthetic step, dolutegravir and cabotegravir are converted into their corresponding sodium salts (dolutegravir sodium identified in compound 13 and cabotegravir sodium identified in compound 18):  13  18 WO ’253 discloses, “The present invention comprises modifications of known processes for synthesizing compounds having HIV integrase inhibitory activity.” WO ’253, 1:8-9. EP ’580 also teaches novel compounds possessing an antiviral activity, in detail polycyclic carbamoylpyridone derivatives possessing an inhibitory activity against HIV integrase and a pharmaceutical composition containing the same, especially an anti-HIV agent.” EP ’580, [0001]. EP ’580 further teaches the following compound, known today as cabotegravir, and its pharmaceutically acceptable salts and solvates.



Id. at [0009]; *see also* claim 1.

WO ’764 teaches the sodium salt forms of dolutegravir and cabotegravir.

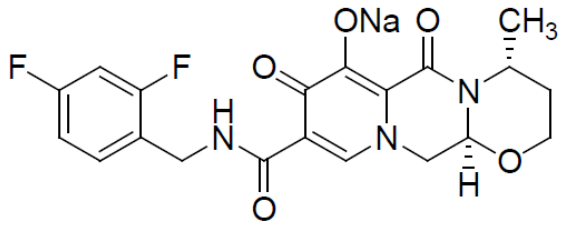


WO ’764 at 128-130.

The 2013 Tivicay Label teaches the sodium salt form of dolutegravir. 2013 Tivicay Label, 1.

The Tivicay Label teaches, “TIVICAY is a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor (INSTI) indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and children aged 12 years and older and weighing at least 40 kg.” Tivicay Label, 1.

The Tivicay Assessment teaches the sodium salt form of dolutegravir with the following structure:



Tivicay Assessment, 9.

The Tivicay Assessment discloses, “Dolutegravir is a new integrase inhibitor which has been studied in a full range of HIV treatment populations; in those without prior HIV therapy, in patients with prior failing therapies and resistance to drug classes other than integrase inhibitors, and in patients who also had failed therapy with an integrase inhibitor with consequent integrase inhibitor class resistance.” Tivicay Assessment, 9.

The Triumeq Label discloses the ingredients of Triumeq as including the sodium salt form of dolutegravir, stating, “Each film-coated tablet contains abacavir sulfate equivalent to 600 mg of abacavir, dolutegravir sodium equivalent to 50 mg of dolutegravir, and 300 mg of lamivudine.” Triumeq Label, 17.

The Triumeq label teaches, “TRIUMEQ, a combination of dolutegravir (integrase strand transfer inhibitor [INSTI]), abacavir, and lamivudine (both nucleoside analogue reverse transcriptase inhibitors) is indicated for the treatment of HIV-1 infection.” Triumeq Label, 1.

The Triumeq Assessment discloses, “Triumeq is presented as film-coated tablets containing a fixed combination of dolutegravir sodium equivalent to 50 mg dolutegravir, 600 mg of

	abacavir (as sulfate) and 300 mg of lamivudine." Triumeq Assessment, 6. The Triumeq Assessment teaches, "A once-daily fixed-dose combination (FDC) single tablet regimen (STR) that combines the integrase inhibitor (INI) dolutegravir (DTG) with the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir sulfate (abacavir, ABC) and lamivudine (3TC) was developed for use in the treatment of human immunodeficiency virus (HIV) infection." Triumeq Assessment, 6. US '353 discloses, "Dolutegravir may be present in the solid pharmaceutical dosage form in its non-salt form or any pharmaceutically acceptable salt or solvate thereof. Suitable pharmaceutically acceptable salts are known to the skilled person. For example, dolutegravir may be present as alkali metal salt, such as dolutegravir sodium or dolutegravir potassium. The potassium salt being preferred." US '353, [0011]. US '353 teaches, "The present invention relates to a solid pharmaceutical dosage form comprising dolutegravir, a method of its preparation and its use in the treatment of an HIV infection." US '353, [0002]. US '332 teaches, "The sodium salt of dolutegravir and a specific crystalline form of this sodium salt or a hydrate thereof are disclosed in WO 2010/068253." US '332, [0020]. US '332 claims, "Pharmaceutical combination for use according to claim 1 or 2, wherein dolutegravir is used in the form of the sodium salt." US '332, Claim 3.

	US ’332 further claims, “Pharmaceutical combination for use according to any one of the preceding claims, wherein tenofovir is used in form of a prodrug of tenofovir.” US ’332, Claim 5. US ’332 further claims, “Pharmaceutical combination for use according to claim 5, wherein the prodrug of tenofovir is tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide or hexadecyloxypropyl tenofovir.” US ’332, Claim 6. US ’332 claims, “A kit for the treatment of a viral infection, in particular of an HIV-infection, comprising (i) 10 to 75 mg dolutegravir, (ii) 50 to 150 mg emtricitabine, (iii) 0.5 to 400 mg tenofovir or a prodrug thereof.” US ’332, Claim 15. US ’332 describes pharmaceutical combinations comprising 40 to 60 mg DLT, 150 to 250 mg FTC, and 5 to 42 mg TAF, along with pharmaceutical excipients. US ’332, [0086]-[0090]. US ’332 further discloses a specific combination comprising about 50 mg DLT, about 200 mg FTC and about 25 mg TAF. *Id.* at [0091]-[0092]. WO ’846 teaches the following formulation: Formulation D: mg/tablet GS-7340 25 emtricitabine 200 Microcrystalline Cellulose 200 Lactose Monohydrate 330 Croscarmellose Sodium 60 Pregelatinized Starch 50 Magnesium Stearate 10 875 WO ’846, 13:12-24.

	WO ’846 discloses the following formulation: Formulation G — mg/tablet GS-7340 — 300 emtricitabine — 200 Hydroxypropyl Methylcellulose — 112 Lactose B.P. — 53 Pregelatinized Starch B.P. — 28 Magnesium Stearate — 7 total: — 700 WO ’846, 13:23-24. Shah teaches, “The second-generation INSTI dolutegravir (S/GSK 1349572) combines the advantages of its predecessors, but it is administered once/day without the need for a pharmacokinetic booster and may be coformulated with other antiretrovirals in a single-tablet regimen[, and] [d]olutegravir has been investigated as part of an antiretroviral therapy (ART) regimen for treatment-naive and treatment experienced patients” Shah, 506. Shah further teaches that “Cobicistat is a specific and potent inhibitor of CYP3A4 and associated with clinically significant drug–drug interactions.” Shah, 506. Shah further teaches that DLT may be coformulated with other antiretrovirals in a single-tablet regimen for the treatment of HIV, without the need for COBI. *Id.* Shah further teaches that “to be administered once/day, raltegravir must be coadministered with the potent CYP3A4 inhibitor cobicistat, which can lead to clinically significant drug-drug interactions.” Shah, 517-518.

US ’332 claims, “Pharmaceutical combination comprising (a) dolutegravir, (b) emtricitabine and (c) tenofovir for use as a medicament, wherein the weight ratio of (a) dolutegravir and (b) emtricitabine is from 1:1 to 1:3.” US ’332, Claim 1.

US ’122 discloses a solid dose form (e.g. tablets) comprising a compound of Formula I (i.e. elvitegravir), Formula III (i.e. emtricitabine), Formula IV (i.e. tenofovir disoproxil fumarate), 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.

	Compound of Formula II 150 mg Formulation	
Components	% 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.

Id. at [0022].

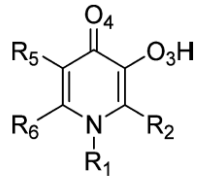
	US '122 further discloses examples of tablets similar to Stribild. *Id.* at [0063]-[0065] (Examples 2-4). The Stribild Label states that a Stribild table consists of "150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 300 mg of tenofovir disoproxil fumarate." Stribild Label, 1; *see also id.* at 22-23. Chen teaches a number of of 3-hydroxypyridin-4-ones (HPOs) in Figure 1 (below):  **Figure 1.** 3-Hydroxypyridin-4-one. Deferiprone (CP20), $R_1 = R_2 = CH_3$ and $R_5 = R_6 = H$ CP60, $R_1 = CH_3$ and $R_2 = R_5 = R_6 = H$ CP751, $R_1 = R_2 = R_5 = CH_3$ and $R_6 = H$ CP90, $R_1 = R_2 = R_5 = R_6 = H$. Chen, 2980. Chen also teaches the measured and calculated pKa values for the hydroxyl group of the above compounds CP20, CP60, and CP751, where the measured values are in the range of ~8.8-10.3. *Id.* at Table 1 (below).

Table 1. pK_a Prediction Results Using Different Methods

	CP60	CP20	CP751	average absolute error
measured value	8.79[31]	9.76[31]	10.31[42]	
CPMD	9.00	9.36	10.73	0.34
ACD/pK_a DB 12.0	9.59	9.90	10.03	0.41
Marvin 5.4.0.1	10.79	10.72	10.71	1.12
simple scheme using B3LYP/6-31+G(d)/CPCM	14.32	15.90	17.36	6.25
proton exchange scheme using B3LYP/6-31+G(d)/CPCM	9.07	10.65	12.11	0.99

See also Weller; Castagna; Juday; Lunzen; Walmsley; Johns; PR; Mathais; Min; Highleyman; Acosta; BICANDA01157927; NCT02607956-1; NCT02607856-2; Abebe; Shende; Poster #416; Poster # 414; Poster #413.