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10. I further understand that Dr. Muzzio, an expert in the area of formulation science has offered his opinions, concluding that the “multilayer,” coating, and tablet weight limitations of the claims of the ’846 and ’802 patents that I analyze in this report would have been obvious to the POSA as well. I assume this conclusion to be accurate for the purposes of my analysis as well.

11. Based on my analysis and investigation, I have developed and reached certain conclusions and opinions on these issues, which I discuss in this report. If called to testify, I expect to offer the opinions and the basis for those opinions set forth in this report.

II. QUALIFICATIONS

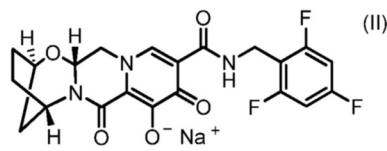
12. I am an Internal Medicine and Infectious Diseases Board-Certified physician and an Associate Professor of Medicine (Infectious Diseases) and of Microbiology and Immunology at Stanford University School of Medicine. A copy of my Curriculum Vitae is attached to this report as **Appendix B**, and it includes a list of all of my publications in the previous 10 years.

13. I have testified as an expert at trial or by deposition in one matter in the previous 4 years: *Shareholder Representative Services LLC v. Alexion Pharmaceuticals, Inc.*, Civil Action No. 2020-1069-MTZ, Court of Chancery for the State of Delaware on behalf of Defendant Alexion Pharmaceuticals, Inc.

14. I am being compensated at the rate of \$950 per hour plus expenses for the work I do in this case, and \$1150 per hour when testifying. My compensation is not based in any way on the outcome of the case.

15. I received my B.A. in Religious Studies from the University of California, Berkeley in 1998 and my M.D. from Harvard Medical School in 2005. As a medical student at Harvard, I trained in outpatient HIV medicine through a longitudinal 2-year clerkship with Dr. Laura Kogelman at Tufts New England Medical Center Infectious Diseases Clinic and spent 2

25. (Currently Amended) A method for treating an HIV infection in a human in need thereof, comprising administering to the human a therapeutically effective amount of a compound of Formula II:



which is crystalline and is characterized by an x-ray powder diffraction (XRPD) pattern having peaks at about 5.5°, 16.1°, and 23.3° 2-θ ± 0.2° 2-θ.

²²² No explanation for the above amendment was provided.

179. The Examiner allowed all pending claims on August 23, 2018. No Reasons for Allowance were provided. After several requests for continued examination were filed, each disclosing further prior art for the examination²²³ the Examiner issued a final Notice of Allowance on June 12, 2019, again without providing any reasons for allowance.

180. Thereafter, the '166 application issued into the '067 patent on July 31, 2019.

B. The Tablet Patents

1. The '846 and '802 Patents

a) The Common Specification of the Tablet Patents

181. I understand that the '846 and '802 patents belong to the same patent family, and so they share a common specification (the “common specification”). This summary of that common specification will cite to the '802 patent alone, but the same text also appears in the '846 patent in slightly different locations. Citations to the '802 specification in this report should be read to include the corresponding location in the '846 specification.

²²² *Id.* at BICANDA00004336.

²²³ *See id.* at BICANDA00004400-16 (November 19, 2018 RCE and IDS), BICANDA00004446-51 (February 27, 2019 RCE and IDS), and BICANDA00004585-95 (June 5, 2019 RCE and IDS).

182. The '846 patent issued on February 4, 2020, from U.S. Patent Application No. 15/346,335 (“the '335 application”) filed on November 8, 2016, which claims priority to U.S. Provisional Applications No. 62/399,999 (“the '999 provisional”) filed September 26, 2016, and 62/253,042 (“the '042 provisional”) filed November 9, 2015. The '846 patent reportedly will expire on November 8, 2036.

183. The '802 patent issued on September 5, 2023, from U.S. Appl. No. 17/738,803 (“the '803 application”), which was filed on May 6, 2022. The '803 application claims priority to a string of continuation patents that date back to the same provisional applications to which the '846 patent claims priority. The '802 patent will expire on November 8, 2036, on the same day as the '846 patent, as Gilead filed a terminal disclaimer, limiting the term of the '802 patent to that of the '846 patent.

184. The abstract of the common specification summarizes its content as providing “a solid oral dosage form,” with three anti-viral compounds, or pharmaceutically acceptable salts of each compound.²²⁴

185. The “Background” section of the patent recognizes that the standard of care for the treatment of patients with AIDS was to administer a combination of multiple types of antiretroviral agents to “suppress viral replication to below detectable limits, increase CD4 cell counts, and halt disease progression.”²²⁵ The same section identifies the DHHS treatment guidelines, which provide that “achievement of viral suppression requires the use of combination therapies, i.e., several drugs from at least two or more drug classes.”²²⁶

²²⁴ '802 Patent (BICANDA01160880-928) at BICANDA01160880 (Abstract).

²²⁵ *Id.* at 1:31-35.

²²⁶ *Id.* at 1:46-51.

186. The “Summary” part of the common specification begins by identifying the disclosed oral dosage form as containing “a compound of Formula I,” combined with both tenofovir alafenamide and emtricitabine.²²⁷ This section lists several different aspects of the dosage forms, which (basically) includes various tablet configurations with 50 mg of “Formula I,” and others with 75 mg of the same compound, both combined with emtricitabine and tenofovir alafenamide.²²⁸

187. The “Detailed Description” section of the common specification begins with an explanation that the first compound, “Formula I,” is a “potent HIV integrase inhibitor” (INSTI) (hereafter, referred to as “BIC”).²²⁹ The second and third compounds are described as both nucleotide (tenofovir alafenamide) (“TAF”) and nucleoside (emtricitabine) (“FTC”) reverse transcriptase inhibitors (N(t)RTIs).²³⁰ The patent explains that each of the active ingredients had been independently established as effective in suppressing HIV infection in patients.²³¹ It also reports that FTC was (at the time) “a part of” several FDA approved single regimen dosage forms.²³² Each of the approved single regimen dosage forms included 200 mg of FTC and 300 mg of tenofovir disoproxil fumarate, in addition to other active ingredients, all in the same tablet.²³³

188. After identifying three active ingredients, the common specification states that the applicants “have successfully formulated [BIC], [FTC] and [TAF] in a single, stable dosage form that is pharmacologically efficacious and physically acceptable.”²³⁴ The patent also states that

²²⁷ *Id.* at 2:36-40.

²²⁸ *Id.* at 2:41-4:31.

²²⁹ *Id.* at 5:14-16.

²³⁰ *Id.* at 6:37-7:17.

²³¹ *Id.* at 4:66-8:49.

²³² *Id.* at 8:4-13 (referring to TRUVADA®, ATRIPLA®, STRIBILD® and COMPLERA®).

²³³ *Id.*

²³⁴ *Id.* at 8:41-54.

the oral dosage forms that are the subject of the patent are intended for use in humans, and so “they must be of an appropriate size and weight for oral human administration,” which is defined as weighing less than 1.5 grams, in addition to being efficacious.²³⁵

189. The common specification also identifies the FDA-approved single regimen dosage form TRIUMEQ[®] as a tablet containing 50 mg of dolutegravir (DTG) and two N(t)RTIs (abacavir (ABC) (600 mg) and lamivudine (3TC) (300 mg)).²³⁶ TRIUMEQ[®] is said to contain 950 mg of combined active ingredients and a total weight more than 1000 mg “due to excipient amounts required to make a pharmaceutically acceptable tablet.”²³⁷

190. The common specification states that its inventors “found that the use of fixed dose combinations *may assist* in optimizing pharmacokinetic properties, particularly the total exposure of the compound of Formula (I) [(BIC)] or a pharmaceutically acceptable salt thereof” in patients taking the different types of dosage forms disclosed.²³⁸ The patent also states the following:

In certain embodiments, the use of a fixed dose combinations, e.g., multilayer tablets, may affect the dissolution profile of one or more of the active ingredients within the dosage form, and is therefore likely to have an impact on the in vivo pharmacokinetics of the dosage form. In particular, it has been observed that the dissolution of the compound of Formula I (e.g., as Formula II) varies depending on whether the tablet is in a fixed dose combination formulation with tenofovir alafenamide and emtricitabine and/or whether the tablet is a monolayer or multilayer tablet. It has also been observed that the presence of certain excipients in the multilayer tablet formulation (or absence of others) affects the dissolution profile of one or more of the active ingredients within the dosage form.²³⁹

²³⁵ *Id.* at 8:54-60.

²³⁶ *Id.* at 8:65-9:4.

²³⁷ *Id.*

²³⁸ *Id.* at 9:44-53 (emphasis added).

²³⁹ *Id.* at 9:53-66 (emphasis added)

191. The common specification then catalogs multiple configurations of various “embodiments” of tablets in several subsequent columns and pages of the specification.²⁴⁰ Beginning at column 57, the patent provides specific examples of the tablets that were used in various experiments that are also disclosed. The first, “F1”, is a “single agent tablet,” containing only one active ingredient – 75 mg BIC (78.7 mg as sodium salt) – along with the excipients microcrystalline cellulose, lactose monohydrate crospovidone and sodium stearyl fumarate in specific amounts.²⁴¹ The “F1” tablet is disclosed at column 58, line 1 of the common specification as follows:

Component	Tablet Formulation F1	
	Mass (mg/tablet)	% w/w/tablet
Compound of Formula II	78.7*	26.2
Microcrystalline cellulose	120	40
Lactose monohydrate	75.8	25.3
Crospovidone	21	7
Sodium Stearyl Fumarate**	4.5	1.5
Total Weight	300	

*Equivalent to 75 mg of the Compound of Formula I
 **Intergranular: 2.25 mg (0.75%); Extragranular: 2.25 mg (0.75%)

192. Another type of tablet, “F3”, named a “fixed dose combination” tablet, contains a mixture of 200 mg FTC and 25 mg TAF (28 mg as hemifumarate salt) in a single non-layered tablet with the excipients microcrystalline cellulose, croscarmellose sodium and magnesium stearate in specific amounts.²⁴² The “F3” tablet is as follows:

²⁴⁰ *Id.* at 8:61-55:25.

²⁴¹ *Id.* at 57:60-58:27.

²⁴² *Id.* at 59:14-45.

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

193. A third type of tablet is identified as a “Bilayer Tablet,” which contains BIC in either 75 mg (78.7 mg as sodium salt) (“F2”) or 50 mg (52.5 mg as sodium salt) (“F7”), where the BIC is segregated into one layer, and 200 mg FTC and 25 mg TAF (28 mg as hemifumarate salt) are segregated into another layer, each containing microcrystalline cellulose, croscarmellose sodium and magnesium stearate in specific amounts.²⁴³ The 75 mg and 50 mg BIC bilayer tablets, identified as “F2” and “F7” are as follows:

²⁴³ *Id.* at 57:54-59:37 (“F2”); 66:33-67:5 (“F7”).

Ingredient	Bilayer tablet F2 (mg/tablet)	
	Compound of Formula II Layer	Emtricitabine/ tenofovir alafenamide hemifumarate Layer
Compound of Formula II	78.7*	
Emtricitabine		200
Tenofovir alafenamide hemifumarate		28.1**
Microcrystalline cellulose	247.8***	113.1
Croscarmellose sodium	21.2	30.2
Magnesium Stearate	5.3 [†]	5.7 ^{††}
Layer Weight	353	377
Tablet Core Weight		730

*Equivalent to 75 mg of the Compound of Formula I

**Equivalent to 25 mg tenofovir alafenamide

***Intergranular: 212.5 mg (29.1%); Extragranular: 2.65 mg (0.4%)

[†]Intergranular: 2.65 mg (0.4%); Extragranular: 2.65 mg (0.4%)

^{††}Intergranular: 2.83 mg (0.4%); Extragranular: 2.83 mg (0.4%)

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

*Equivalent to 50 mg of the Compound of Formula I

**Equivalent to 25 mg tenofovir alafenamide

194. The common specification describes multiple different theoretical types of solid oral dosage forms, and those containing all three active ingredients (BIC, TAF, and FTC) use layering as the means for segregating the active ingredients.²⁴⁴ The common specification also teaches that segregation of the active ingredients by layering allows for one layer to be “substantially free of [TAF], and/or the second layer is substantially free of [BIC].”²⁴⁵ The common specification also generally defines “segregation” to be the way in which to keep components “physically discrete” from each other, “such that the presence of one component...does not substantially affect the stability in storage of the other component[s].”²⁴⁶

195. The common specification also provides dissolution data comparing the dissolution of each of the three active ingredients when constructed in differing bilayer configurations to the dissolution characteristics of the F1 tablet.²⁴⁷ All four bilayer tablet configurations resulted in a greater amount of Bic Na dissolution as compared to the F1 tablet under the conditions of the experiment conducted.²⁴⁸ According to the specification, the data provided in Figure 3 demonstrates that the substitution of each excipient enhances the dissolution of BIC.²⁴⁹

196. Only the Bilayer Tablet F2 is reported by the common specification as providing a total exposure of BIC in the blood of patients enrolled in a PK study that “was approximately 30% higher when dosed in the bilayer tablet formulation F2,” as compared to the dosing the same amount of BIC, administered in its own single agent tablet (F1) co-dosed with the tablet containing TAF and FTC (F3).²⁵⁰

²⁴⁴ *Id.* at 1:65-53:52.

²⁴⁵ *Id.* at 10:15-19; 10:19-27; 10:62-11:22.

²⁴⁶ *Id.* at 56:4-17.

²⁴⁷ *Id.* at 65:52-66:30 (Figure 3).

²⁴⁸ *Id.*

²⁴⁹ *Id.*

²⁵⁰ *Id.* at 60:43-61:29 (Example 3).

198. There is no disclosure in the common specification of a Bilayer tablet with 50 mg of BIC combined with FTC and TAF that resulted in a 30% higher exposure of BIC as compared to dosing the same amount of BIC in a single tablet, co-dosed with a second tablet containing TAF and FTC. The only tablet that demonstrated a 30% increase in exposure of BIC in the studies disclosed is Table F2, which contains 75mg of BIC sodium.

pharmaceutically acceptable salt thereof wherein the tablet has a total weight of less than about 1000 mg.

2. The tablet of claim 1, wherein the tablet comprises 50 mg of the compound of Formula I as a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide as a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine.

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

4. The tablet of claim 3, wherein the tablet has a total weight of less than 800 mg.

5. The tablet of claim 3, wherein the tablet has a total weight of less than 730 mg.

6. The tablet of claim 1 or 2, wherein the tablet contains less than about 15% of the compound of Formula I or a pharmaceutically acceptable salt thereof.

7. The tablet of claim 1 or 2, wherein the tablet contains less than about 11% of the compound of Formula I or a pharmaceutically acceptable salt thereof.

8. The tablet of claim 1 or 2, wherein the tablet is a coated tablet.

c) The Prosecution History of the '846 Patent

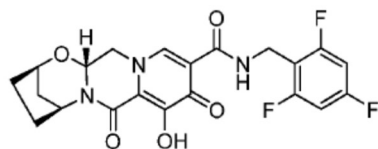
200. The '846 patent was filed as the '335 application on November 8, 2016 with fifty-one (51) claims directed to solid oral dosage forms containing bicitgravir (BIC), tenofovir alafenamide (TAF) and emtricitabine (FTC) or their pharmaceutically acceptable salts.²⁵³ The original 51 claims also included claims for tablets that segregate bicitgravir and tenofovir alafenamide within separated layers (claims 1-30 and 40-51), methods for producing such dosage forms and kits containing them (claims 31-37), and methods of treating HIV infection with such dosage forms (claims 38-39).²⁵⁴ The following originally presented claims are exemplary.

²⁵³ '846 File History (BICANDA00004902-6816) at BICANADA00004913-5027.

²⁵⁴ See *id.* at BICANDA00005015-20 (November 18, 2016 claims as originally filed); see also *id.* at BICANDA00005040-48 (January 18, 2017 Preliminary Amendment (removing multiple dependencies and canceling claims 36-38)).

1. A solid oral dosage form comprising the compound of Formula I:

(I)

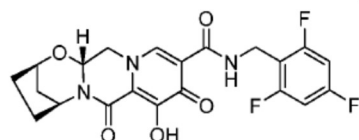


or a pharmaceutically acceptable salt thereof, tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and emtricitabine or a pharmaceutically acceptable salt thereof.

6. The solid oral dosage form of any preceding claim, wherein the dosage form is a tablet.

9. A tablet comprising (a) 50 mg of the compound of Formula I:

(I)

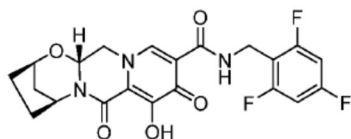


or a pharmaceutically acceptable salt thereof, (b) 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, wherein (a) and (b) are segregated, and wherein the tablet has a total weight of less than about 1 g.

10. The tablet of claim 9, wherein (a) and (b) are within separate layers in a multilayer tablet.

16. A multilayer tablet comprising (a) a compound of Formula I:

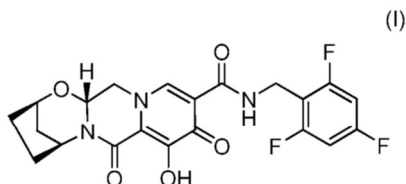
(I)



or a pharmaceutically acceptable salt thereof, (b) tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) emtricitabine or a pharmaceutically acceptable salt thereof.

201. When responding to a requirement from the examiner that the applicant restrict to the claims to one category, the applicant amended then pending claim 1 to limit the claimed solid oral dosage forms to tablets having specific amounts of bictegravir, tenofovir alafenamide and emtricitabine, or their pharmaceutically acceptable salts, as follows:

1. (Currently Amended) A ~~solid oral dosage form~~ tablet comprising 50 mg of the compound of Formula I:



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

²⁵⁵ New claims 52-54, directed to coated tablets (claim 52), tablets having a first BIC layer and a second TAF/FTC layer (claim 53), and tablets having a total weight less than about 1000 mg were also added.²⁵⁶

202. In a May 11, 2018 Non-Final Action²⁵⁷, the Examiner rejected tablet claims 1-3 for anticipation over Carra et al.²⁵⁸ For each Carra reference, the Examiner pointed to its disclosure of tablets containing bictegavir, in combination with tenofovir alafenamide and emtricitabine in ranges of amounts that read on the amounts in the claims.²⁵⁹ The remaining claims were objected to for being dependent on a rejected base claim.

203. In a September 10, 2018, Response, the applicant amended claim 1 to call for a multilayer tablet having a total weight limit as follows:

²⁵⁵ *Id.* at BICANDA00006381 (April 24, 2018 Response, 2).

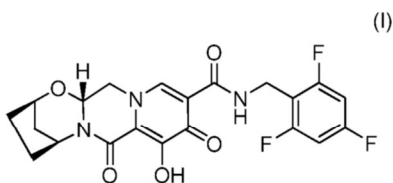
²⁵⁶ *Id.* at BICANDA00006382-83 (April 24, 2018 Response, 3-4).

²⁵⁷ *Id.* at BICANDA00006394-99 (May 11, 2018 Office Action).

²⁵⁸ WO 2015/196116 and US 2016/0016973 (collectively called “Carra”).

²⁵⁹ ‘846 File History at BICANDA00006397-99 (May 11, 2018 Office Action, 3-4).

1. (Currently Amended) A multilayer tablet comprising 50 mg of the compound of Formula I:



or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof wherein the tablet has a total weight of less than about 1000 mg.

²⁶⁰ Claims 6-25 were also canceled in the Response.²⁶¹

204. In addressing the Examiner’s rejection over Carra, the applicant explained that the claimed formulations, *i.e.*, multilayer tablets having a total weight less than 1000 mg, have “surprising pharmacokinetic benefits ... [f]or example a bilayer tablet formulation of [BIC], [TAF], and [FTC] results in approximately 30% higher total exposure of [BIC] compared to the corresponding total exposure achieved with a single agent formulation of [BIC] co-administered with a fixed dose combination of [TAF] and [FTC] ... [where] the exposure to [TAF] and [FTC] is similar for both treatments.”²⁶²

205. In a December 21, 2018 Final Action, the Examiner rejected all pending claims for obviousness over Carra in view of Dahl et al. (US 2007/0099902).²⁶³ The Examiner rejected the applicant's alleged unexpected results argument as not commensurate in scope with the claims, since only the "F2" tablet with 78.7 mg of BIC had shown an increased exposure of that compound.²⁶⁴ The examiner also contended that, although Carra did not teach a multilayer tablet, such tablets were disclosed in Dahl for the combination of tenofovir and emtricitabine

²⁶⁰ *Id.* at BICANDA00006420 (September 10, 2018 Response, 2).

261 *Id.*

²⁶² *Id.* at BICANDA00006424-25.

²⁶³ *Id.* at BICANDA00006436-40 (December 21, 2018 Action, 4-8).

²⁶⁴ *Id.* at BICANDA00006440-41.

with efavirenz, where tenofovir is placed into a separate layer from efavirenz to avoid destabilizing contact with a surfactant in the efavirenz layer.²⁶⁵

206. In a March 20, 2019 Response, the applicant argued that the rejections for obviousness due to the Carra references were in error because those reference were not prior art, based on the earlier filing date of the '335 application.²⁶⁶ Gilead also disputed the examiner's characterization, asserting "the unexpected results are associated with the *combination* of [BIC, TAF, and FTC], *not the specific amounts*."²⁶⁷ Gilead also urged disqualification of the Carra applications as prior art.²⁶⁸

207. In a Notice of Allowance dated May 2, 2019, the examiner agreed that the Carra applicants were not prior art.²⁶⁹ The examiner also identified WO '323 as the "next closest prior art," but stated (in error) that it only disclosed "administering [BIC] at a different time than additional drugs such as tenofovir and emtricitabine."²⁷⁰ The examiner accepted Gilead's allegation of a 30% higher exposure of BIC when administered in a bilayer tablet, as opposed to giving the same dosage amounts in a separate tablet.²⁷¹

208. Gilead thereafter filed several requests for continuing examination,²⁷² disclosing additional prior art, and the examiner eventually finally allowed the claims, on the same basis as stated in the May 2, 2019 Notice of Allowance.²⁷³

²⁶⁵ *Id.* at BICANDA00006437.

²⁶⁶ *Id.* at BICANDA00006456 (March 20, 2019 Response, 6).

²⁶⁷ *Id.* at BICANDA00006457 (citing 96 (paragraph [0317]; Tablet F2)) (emphasis added).

²⁶⁸ *Id.* at BICANDA00006456.

²⁶⁹ *Id.* at BICANDA00006507 (May 2, 2019 Notice of Allowance, 2).

²⁷⁰ *Id.*

²⁷¹ *Id.*

²⁷² Gilead did not, in any of its requests for continued examination, advise the examiner that it had listed U.S. Patent No. 9,216,996 (the U.S. patent issuing from the application related to WO '323) as a patent covering its Biktarvy[®] tablet – a single tablet with all three active ingredients—in the Orange Book. See February 23, 2018 FDA Form 3542 re '996 patent (BICANDA00079337-42) at BICANDA00079337.

²⁷³ '846 File History at BICANDA00006791-92 (November 27, 2019 Notice of Allowance, 2-3).

209. I provide my detailed analysis and review of WO 2014/100323 later in this report, but it is my opinion that the examiner was mistaken in her conclusion that this reference only discloses administering the compound of Formula I at a different time than additional drugs such as tenofovir or emtricitabine. That reference does in fact disclose embodiments where Formula (I), e.g., compound 42 (BIC), is combined with additional therapeutic agents in the same dosage form, as follows (red underlying added):²⁷⁴

In certain emboiments, a compound disclosed herein is combined with one or more additional therapeutic agents in a unitary dosage form for simultaneous
20 administration to a patient, for example as a solid dosage form for oral administration.

210. In other parts of this reference, combination dosage forms containing two additional therapeutic agents, e.g., anti-HIV agents including the N(t)RTIs FTC and TAF are disclosed.²⁷⁵ Such combinations containing compound **42** (BIC) and N(t)RTIs are then claimed in a single “pharmaceutical composition,” including for treating HIV infection in a human.²⁷⁶ As detailed below, this clear disclosure of combination dosage forms, e.g., tablet, forms the basis for my analyses and opinions as to obviousness below.

d) The claims of the '802 Patent

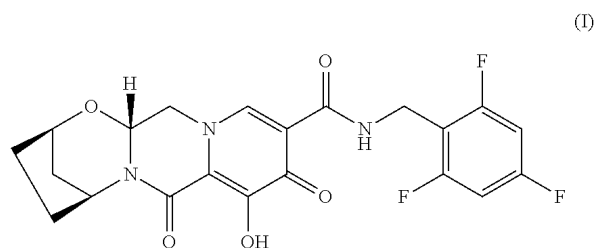
211. The '802 patent has 13 claims and I understand that all 13 are asserted against one or more defendants. The claims are as follows:

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

²⁷⁴ WO '323 (DEFS_BIC_00002214-474) at 40:18-20 (emphasis added); *see also id.* at 37:13-21.

²⁷⁵ *Id.* at 37:20-38:2, 39:25-27.

²⁷⁶ *Id.* at 241 (claims 33 (depending from claim 32) and claims 35-36); *see also id.* at 241-42 (claim 37 (treating HIV infection by administering pharmaceutical composition of claim 33) and claims 39-40).



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

2. The tablet of claim 1, wherein the tablet comprises 50 mg of the compound of Formula I as a pharmaceutically acceptable salt thereof.
3. The tablet of claim 1, wherein the tablet comprises 25 mg tenofovir alafenamide as a pharmaceutically acceptable salt thereof.
4. The tablet of claim 1, wherein the tablet comprises 50 mg of the compound of Formula I as a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide as a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine.
5. The tablet of claim 1, wherein the tablet comprises 52 mg of the sodium salt of the compound of Formula I.
6. The tablet of claim 1, wherein the tablet comprises 25 mg tenofovir alafenamide as tenofovir alafenamide fumarate.
7. The tablet of claim 1, wherein the tablet comprises 28 mg tenofovir alafenamide hemifumarate.
8. The tablet of claim 1, wherein the tablet comprises 52 mg of the sodium salt of the compound of Formula I, 28 mg tenofovir alafenamide hemifumarate, and 200 mg emtricitabine.
9. The tablet of claim 1, wherein the tablet has a total weight of less than 1000 mg.
10. The tablet of claim 9, wherein the tablet has a total weight of less than 800 mg.
11. The tablet of claim 10, wherein the tablet has a total weight of less than 730 mg.
12. The tablet of claim 1, wherein the tablet contains less than 15% of the compound of Formula I or a pharmaceutically acceptable salt thereof.

13. The tablet of claim 1, wherein the tablet contains less than 11 % of the compound of Formula I or a pharmaceutically acceptable salt thereof.

e) The Prosecution History of the '802 Patent

212. I have reviewed what I understand to be the record of correspondence between the applicants for the '802 Patent and the USPTO, a collection of documents I understand is referred to as a “prosecution history.” I understand that the application that led to the '802 Patent was filed on May 6, 2022, and that it claims priority to a provisional application that was filed several years earlier, on November 9, 2015. For the purposes of my analysis, I have been asked to assume that the '802 is entitled to this priority date.

213. The application filed on May 6, 2022 listed a total of 51 claims, and I have reviewed those claims.²⁷⁷ Initially, the applicants claimed its tablets by describing a variety of different kinds of solid oral dosage forms. For example, the applicants claimed a “solid oral dosage form” (claim 1) a “coated tablet” (claim 7), a “tablet” (claim 8), a “multilayer tablet” (claim 16), and methods for making the same kinds of tablets.²⁷⁸

214. The applicant however filed an amendment to the original 51 claims on August 19, 2022, cancelling all of them.²⁷⁹ In their place, the applicant presented a new set of claims for examination, narrowed to only “a tablet,” and claim 52 is an example, as follows:²⁸⁰

²⁷⁷ '802 Patent File History (BICANDA01159806-60879) at BICANDA01159912-17.

²⁷⁸ *Id.*

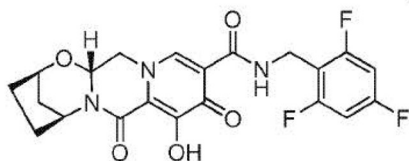
²⁷⁹ *Id.* at BICANDA01159944 (August 19, 2022 Amendment, 3).

²⁸⁰ *Id.*

1-51. (Canceled)

52. (New) A tablet comprising 50 mg of the compound of Formula I:

(I)



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

215. The examiner rejected these claims on December 6, 2022 in similar manner as she had when examining the claims of the '846 patent, explaining (again) that two of Gilead's patent publications ("the Carra references;") rendered the claims under examination anticipated, and that the combination with another Gilead publication rendered the claims obvious.²⁸¹

216. The examiner also rejected the same claims as not patentably distinct from the claims 1-10 of U.S. Patent No. 10,548,846.²⁸² As I understand this rejection, it was based on obviousness-type double patenting, which prohibits the extension of the term of an issued patent by claiming, in a later filed application, essentially the same invention.

217. In response to the examiner's rejections, in a filing submitted on April 5, 2023, Gilead explained first that the Carra references were not prior art.²⁸³ Gilead also filed a terminal disclaimer to the '846 patent.²⁸⁴ My understanding of a terminal disclaimer is that Gilead agreed that any new patent claims issuing from the pending prosecution would expire on the same day as the '846 patent.

²⁸¹ *Id.* at BICANDA01159968-76 (December 6, 2022 Office Action, 2-4).

²⁸² *Id.* at BICANDA01159975 (December 6, 2022 Office Action, 9).

²⁸³ *Id.* at BICANDA01160049-54 (April 5, 2023 Response to December 6, 2022 Office Action, 1-6).

²⁸⁴ *Id.* at BICANDA01160053 (April 5, 2023 Response to December 6, 2022 Office Action, 5).

218. On April 17, 2023, the USPTO examiner allowed the claims of the '802 Patent.²⁸⁵ In the Notice of Allowance, the examiner first explains that publications from “Carra et al.” were published after “the effective filing date of the instant application and have a common assignee.”²⁸⁶ I understand this means those reference are not prior art to the '802 Patent.

219. The examiner then appears to have copied her reasons for allowance of the prior '846 patent claims, stating that “[t]he next closest prior art of WO2014/100323 comprises administering the compound of Formula 1 at a different time than additional drugs such as tenofovir or emtricitabine.”²⁸⁷ The examiner then repeated again that the prior art “does not teach all three drugs within the same tablet.”²⁸⁸ The examiner also notes in her “reasons for allowance” that “[a]pplicants have shown a 30% higher exposure of [BIC] in a fixed dose combination of [the three active ingredients] relative to its exposure when co-administered as a single agent of [BIC] with a fixed dose combination of [FTC and TAF].”²⁸⁹ The '802 specification ascribes a 30% higher exposure of BIC only to Tablet F2, which is a bilayer tablet containing 75 mg of BIC (78.7 mg sodium salt) contained in one layer with specific amounts of excipients, with both TAF and FTC in another layer with different amount of excipients.²⁹⁰

²⁸⁵ *Id.* at BICANDA01160579-80 (April 17, 2023 Notice of Allowance, 2-3).

²⁸⁶ *Id.* at BICANDA01160579.

²⁸⁷ *Id.*

²⁸⁸ *Id.*

²⁸⁹ *Id.* at BICANDA01160579-80.

²⁹⁰ '802 patent (BICANDA01160880-928) at 59:47-64:16 (F2 PK Study).

220. Gilead thereafter filed two requests for continuing examination,²⁹¹ disclosing additional prior art, and the examiner eventually finally allowed the claims on June 30, 2023, on the same basis as stated in the April 17, 2023 Notice of Allowance.²⁹²

221. I provide my detailed analysis and review of WO 2014/100323 later in this report, but it is my opinion that the examiner was mistaken in her conclusion that this reference only discloses administering the compound of Formula I at a different time than additional drugs such as tenofovir or emtricitabine. That reference does in fact disclose embodiments where Formula (I), e.g., compound 42 (BIC), is combined with additional therapeutic agents in the same dosage form, as follows (red underlying added):²⁹³

In certain emboiments, a compound disclosed herein is combined with one or more additional therapeutic agents in a unitary dosage form for simultaneous
20 administration to a patient, for example as a solid dosage form for oral administration.

222. In other parts of this reference, combination dosage forms containing two additional therapeutic agents, e.g., anti-HIV agents including the N(t)RTIs FTC and TAF are disclosed.²⁹⁴ Such combinations containing compound **42** (BIC) and N(t)RTIs are then claimed in a single “pharmaceutical composition,” including for treating HIV infection in a human.²⁹⁵ As detailed below, this clear disclosure of combination dosage forms, e.g., tablet, forms the basis for my analyses and opinions as to obviousness below.

²⁹¹ Gilead did not, in any of its requests for continued examination, advise the examiner that it had listed U.S. Patent No. 9,216,996 (the U.S. patent issuing from the application related to WO '323) as a patent covering its Biktarvy[®] tablet – a single tablet with all three active ingredients—in the Orange Book. See February 23, 2018 FDA Form 3542 re '996 patent (BICANDA00079337-42) at BICANDA00079337.

²⁹² '802 Patent File History (BICANDA01159806-60879) at BICANDA01160856-57 (June 30, 2023 Notice of Allowance, 2-3).

²⁹³ WO '323 (DEFS_BIC_00002214-474) at 40:18-20 (emphasis added); see also *id.* at 37:13-21.

²⁹⁴ *Id.* at 37:20-38:2, 39:25-27.

²⁹⁵ *Id.* at 241 (claims 33 (depending from claim 32) and claims 35-36); see also *id.* at 241-242 (claim 37 (treating HIV infection by administering pharmaceutical composition of claim 33) and claims 39-40).

VIII. THE SCOPE AND CONTENT OF THE STATUTORY PRIOR ART

223. I have reviewed in detail the prior art publications that I discuss in this section. I understand each of these publications qualify as prior art to the BIC Sodium Patents as well as the Tablet Patents, except that the Triumeq Assessment (published in June of 2014) is prior art only to the Tablet Patents.

224. As I explain in more detail below, it is my opinion that all recited elements of the asserted claims from BIC Sodium and the Tablet Patents are disclosed (or at least suggested) to a POSA in these references. This is especially true when considered in the context of the POSA's general understanding of available treatments for HIV infection as of the priority date of each of the respective patents, which I have explained in Section V of this report, which provides a background tutorial to explain the accumulated common knowledge of the POSA.

A. Lunzen Disclosed the Therapeutically Effective Use of a Second Generation INSTI Anchoring The N(t)RTI Backbone of TDF and FTC to Treat HIV-1 Infection.

225. On October 21, 2011, the interim 48 week results from an ongoing phase 2b dose-ranging clinical study were published, reporting that DTG (when administered in combination with an N(t)RTI backbone) was shown to be “effective when given once daily without a pharmacokinetic booster and was well tolerated at all assessed doses.”²⁹⁶ I understand this publication qualifies as prior art to both the BIC Sodium and Tablet Patents.

226. The Lunzen article discloses a clinical study design that randomly divided treatment naïve patients into four groups, three of which received varying doses of once daily DTG (10 mg, 35 mg, or 50 mg), and one received the NNRTI efavirenz (EFV) once daily.²⁹⁷ All

²⁹⁶ Lunzen et al., “Once daily dolutegravir (S/GSK1349572) in combination therapy in antiretroviral-naïve adults with HIV: planned interim 48-week results from SPRING-1, a dose-ranging, randomised, phase 2b trial,” 12(2) LANCET INFECTIOUS DISEASE 111-18 (2011) (“Lunzen”) (DEFS_BIC_00005086-93) at DEFS_BIC_00005086.

²⁹⁷ *Id.*

patients across the four treatment groups were also given an N(t)RTI backbone regimen of either ABC/3TC or TDF/FTC “at the investigator’s discretion as fixed dose combination tablets,” also given once daily.²⁹⁸ The N(t)RTI backbones were administered “in accordance with the product labels.”²⁹⁹

227. After 48 weeks of treatment, 87% of the patients receiving DTG achieved viral suppression, and the response rates between patients receiving either ABC/3TC or TDF/FTC were reported to be similar.³⁰⁰ The Lunzen article also reported that among the 205 individuals in the study at week 48, “[m]ore participants were started on [TDF/FTC] than [ABC/3TC] as the dual-N[t]RTI backbone.”³⁰¹ A table in the study reporting the baseline characteristics of the patients across all study groups reflects a 2 to 1 preference for the TDF/FTC backbone.³⁰² Further, Lunzen reported that “all doses of dolutegravir in combination with dual N[t]RTI were well tolerated.”³⁰³

228. The Lunzen article also provides a summary of the published research “in context,” which reported that “[a]ntiretroviral combination therapy against HIV has been extended by a new drug class that inhibits the integration of proviral DNA into the host genome.”³⁰⁴ The summary notes that “[a]ll integrase inhibitors have a unique antiviral profile with a very rapid decay of viral load in previously untreated patients when combined with other antiretroviral drugs.”³⁰⁵ Importantly, the authors recognize that a potential advantage of DTG included “once daily application as a single tablet, no need for pharmacological boosting,

²⁹⁸ *Id.* at DEFS_BIC_00005087.

²⁹⁹ *Id.*

³⁰⁰ *Id.* at DEFS_BIC_00005086.

³⁰¹ *Id.* at DEFS_BIC_00005089.

³⁰² *Id.*

³⁰³ *Id.* at DEFS_BIC_00005091.

³⁰⁴ *Id.* at DEFS_BIC_00005092.

³⁰⁵ *Id.*

established dose-response characteristics, higher genetic barrier to resistance, and good tolerability.”³⁰⁶

B. The Tivicay Assessment Taught the Therapeutically Effective Use of a Second Generation INSTI Anchored by the N(t)RTI Backbone of TDF and FTC to Treat HIV-1 Infection.

229. The Tivicay Assessment published in November of 2013, and it provides a detailed report concerning the assessment by the European Medicines Agency (“EMA”) that authorized the marketing of tablets containing 50 mg of the sodium salt of DTG to treat patients infected with HIV that are older than 12 years, in combination with other anti-retroviral products also approved to treat HIV infection.³⁰⁷ The tablets were disclosed in the assessment as immediate release tablets for oral administration, that are film-coated “containing 50 mg of dolutegravir (as dolutegravir sodium salt) as active substance.”³⁰⁸

230. DTG is identified as a compound that “inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step or retroviral DNA integration, which is essential for the HIV replication cycle.”³⁰⁹ The sodium salt of DTG used in the approved tablets is reported to be “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.”³¹⁰

231. Several clinical trials using the approved tablets were also summarized in the Tivicay Assessment, including studies to select “a once daily oral dose of DTG administered”

³⁰⁶ *Id.*

³⁰⁷ Assessment Report for Tivicay/Dolutegravir from the European Medicine Agency (November 21, 2013) (the “Tivicay Assessment”) (DEFS_BIC_00000696-797) at DEFS_BIC_00000704.

³⁰⁸ *Id.*

³⁰⁹ *Id.* at DEFS_BIC_00000719.

³¹⁰ *Id.*

with one of the two accepted N(t)RTI backbones of ABC/3TC or TDF/FTC.³¹¹ Studies were also conducted to compare DTG to regimens using the INSTI raltegravir (RAL) and the NNRTI known as efavirenz (EFV) in combination with both N(t)RTI backbones as well.³¹² The Tivica Assessment concludes that the efficacy of DTG was confirmed, when used “in combination with the two main NRTI backbones used in first line treatment [ABC/3TC and TDF/FTC].”³¹³

C. US 2015/0231079 (“US ’079”) Disclosed Single Pharmaceutical Compositions with a Second Generation INSTI Anchoring the N(t)RTI Backbone of TDF and FTC.

232. US ’079 is a patent application filed by Cipla on October 23, 2013, that was published on August 20, 2015. It claims priority to an application filed in India on October 23, 2012, and is drawn generally to pharmaceutical compositions that combine an INSTI with at least one other anti-HIV drug compound in a single oral dosage form.³¹⁴

233. US ’079 confirms that scientists in this time frame knew that for the successful treatment of HIV infection, it was necessary to administer “a combination of antiretroviral drugs (ARV) taken together.”³¹⁵ US ’079 also observes that the available drug regimens at the time were “far from ideal,” due to HIV strains in patients developing “resistance to one or more of antiretroviral medications.”³¹⁶ US ’079 emphasizes that successful therapy depends upon adherence by patients to the prescribed regimen, and that “the combination of antiretroviral drugs administered in a single unit dosage form may result in increased patient compliance as the pill burden is reduced and dosing schedules are simplified.”³¹⁷

³¹¹ *Id.* at DEFS_BIC_00000724 (describing ING112276); *id.* at DEFS_BIC_00000737 (providing summary table 13 summarizing several clinical studies).

³¹² *Id.* at DEFS_BIC_00000768 (summarizing studies).

³¹³ *Id.* at DEFS_BIC_00000793-94.

³¹⁴ US ’079 at ¶ [0029] (DEFS_BIC_00002975-86) at DEFS_BIC_00002977.

³¹⁵ *Id.* at ¶ [0005] (DEFS_BIC_00002976).

³¹⁶ *Id.* at ¶ [0012] (DEFS_BIC_00002976).

³¹⁷ *Id.* at ¶ [0022] (DEFS_BIC_00002977).

234. US '079 prefers that the pharmaceutical composition comprises dolutegravir (DTG), tenofovir (TFV) and emtricitabine (FTC) or lamivudine (3TC) with one or more pharmaceutically acceptable excipients, where DTG is preferably present in the range of 25 to 50 mg.³¹⁸

235. According to US '079, such pharmaceutical compositions are presented in solid dosage forms where “[a] tablet formulation is the preferred solid dosage form due to its greater stability, less risk of chemical interaction between different medicaments, smaller bulk, accurate dosage, and ease of production.”³¹⁹ These tablets are said to be preferably in the form of single or bilayered or multilayered tablets.³²⁰

236. 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.³²¹ Similarly, Example 4 provides a bilayer tablet with the INSTI raltegravir in a first layer that is separated from a second layer contained FTC and TDF.³²²

237. It then discloses an example of this embodiment (Example 7)³²³ which (in a single tablet) combines the INSTI DTG with tenofovir and emtricitabine, as follows:

³¹⁸ *Id.* at ¶¶ [0044], [0055] (DEFS_BIC_00002978-79).

³¹⁹ *Id.* at ¶¶ [0070], [0078] (DEFS_BIC_00002979-80).

³²⁰ *Id.* at ¶ [0079] (DEFS_BIC_00002980).

³²¹ *Id.* at ¶ [0117] (DEFS_BIC_00002982).

³²² *Id.* at ¶ [0123] (DEFS_BIC_00002983).

³²³ *Id.* at ¶ [0129] (DEFS_BIC_00002984-85).

EXAMPLE 7					
[0129] Manufacturing Formula:			-continued		
Sr. No.	Ingredients	Qty (mg)/ Tablet	Sr. No.	Ingredients	Qty (mg)/ Tablet
Dry Mix			Film Coating		
1	Dolutegravir	50.00	12	Opadry™	25.00
2	Entricitabine	200.00	13	Purified Water	q.s.
3	Tenofovir Disoproxil Fumarate	300.00			
4	Microcrystalline Cellulose PH 102	350.00			
5	Croscarmellose Sodium	25.00		Final Coated Tablet weight	1055.00
Binder					
6	Hypromellose E15 cps	20.00			
7	Purified Water	q.s.			
Blending & Lubrication					
8	Colloidal Silicon Dioxide	2.50			
9	Microcrystalline Cellulose PH 102	50.00			
10	Croscarmellose Sodium	25.00			
11	Magnesium Stearate	7.50			
Total weight uncoated tablet		1030.00			

238. A POSA would have appreciated that this single tablet includes DTG (50 mg) as an anchor to the DHHS preferred N(t)RTI backbone of FTC (200 mg) + TDF (300 mg), each in an amount approved by the FDA in different drug products, e.g., 50 mg DTG in Tivicay[®] and Triumeq[®], 300 mg TDF and 200 mg FTC in Truvada[®] and Stribild[®], and therefore considered preferred by the POSA.³²⁴ The total uncoated weight of this particular tablet is 1030 mg, and roughly half (550 mg) of the tablet weight is attributable to the three active ingredients.

239. Here, the INSTI DTG is present in an amount or ~5% of the total tablet weight, which is less than 15% and less than 11% of the total weight of the tablet. This tablet also combines all three active ingredients together in a dry mix of excipients before a binder is added, followed by blending and lubrication before being compressed into a tablet and then coated.³²⁵ The final coated tablet weighs 1055 mg.³²⁶

³²⁴ See Section V.A-B.

³²⁵ US '079 at ¶ [0130] (DEFS_BIC_00002985).

³²⁶ *Id.* at ¶ [0129] (DEFS_BIC_00002984).

D. The Stribild Assessment Taught a Single Pharmaceutical Composition Containing a First Generation INSTI Anchoring the N(t)RTI Backbone of TDF and FTC to Treat HIV-1 Infection.

240. The Stribild Assessment published on March 21, 2013.³²⁷ The Stribild Assessment reports that the applicant (Gilead) developed Stribild® as “a fixed drug combination tablet containing three [antiretroviral]s (FTC/TDF and elvitegravir [EVG; an INSTI]) plus a new pharmacoenhancer (COBI), which modifies the PK profile of EVG.”³²⁸ The fixed dose combination tablet was reported to be “a useful alternative to existing [single tablet regimens]” for several reasons. One reason was that the tablet did not include an NNRTI, which the assessment reports “may have treatment-limiting tolerability issues.”³²⁹ Another was that the tablet avoided the use of EFV, which Gilead described as not appropriate for use by “women of childbearing potential.”³³⁰ It was also said to be the first single tablet regimen that combined an INSTI as the anchor to an “N[t]RTI backbone,” which was TDF + FTC.³³¹ Finally, the tablet was said to provide an alternative for patients who could not tolerate a boosted PI, and it “provides a simplified treatment regimen.”³³²

241. The Stribild Assessment reports that the approved tablet was a fixed-dose combination product made using “bilayer technology,” which provided a physical separation of the EVG and COBI ingredients from the FTC and TDF ingredients.³³³ This separation by use of “bilayer technology was chosen to reduce physicochemical interaction between them,” according to the Stribild Assessment.³³⁴ And, it was also reported that tablet was “designed in order to provide

³²⁷ Stribild Assessment (DEFS_BIC_00001336-482).

³²⁸ *Id.* at DEFS_BIC_00001345.

³²⁹ *Id.*

³³⁰ *Id.*

³³¹ *Id.*

³³² *Id.*

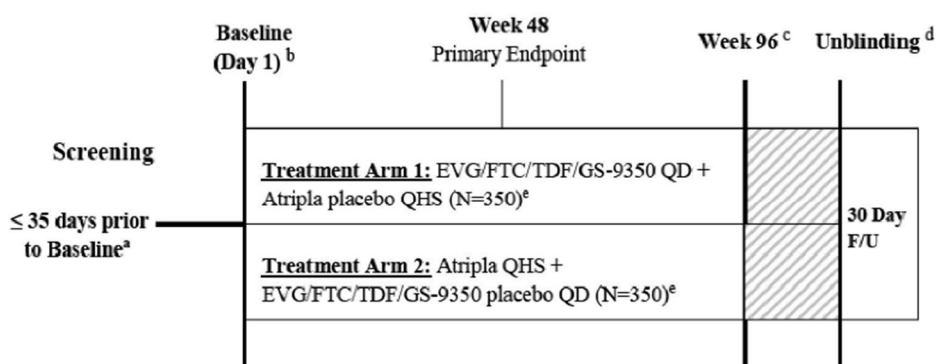
³³³ *Id.* at DEFS_BIC_00001353.

³³⁴ *Id.*

patient dosing convenience of a single tablet.”³³⁵ The Stribild tablet is said to contain a film coating.³³⁶

242. The Stribild Assessment also included a summary of several clinical studies that were conducted to support the beneficial effects of the tablet under review, most of which involve the administration of multiple antiretroviral compounds from different classes at the same time to patients with HIV-1 infections.³³⁷ The following table provides a summary of the clinical studies that ultimately supported the approval of Stribild®:

Figure 7. GS-US-236-0102: Study Schema



GS-9350, cobicistat; QD, once daily; QHS, once daily prior to bedtime; F/U, follow-up

As can be seen, one study compared Stribild (EVG/FTC/TDF/GS-9350) to “Atripla” which is, a single tablet with the same amount of the N(t)RTI backbone of FTC/TDF combined with an NNRTI anchor efavirenz.³³⁸ A second study chose a different regimen as the comparator to Stribild (identified as QUAD in the figure), using the PI atazanavir (ATV) boosted with ritonavir (/r) as an anchor to the same FTC/TDF backbone N(t)RTI pair (TVD in the figure), as follows:³³⁹

³³⁵ *Id.*

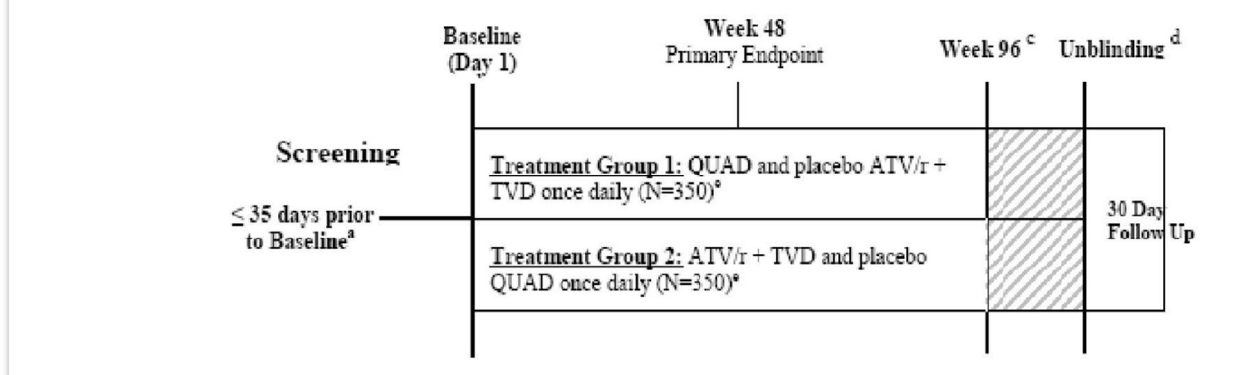
³³⁶ *Id.* at DEFS_BIC_00001354.

³³⁷ *Id.* at DEFS_BIC_00001414-15 (Tables 52-54 summarizing the pivotal, supportive, and ongoing studies).

³³⁸ *Id.* at DEFS_BIC_00001416.

³³⁹ *Id.* at DEFS_BIC_00001417.

Figure 8. GS-US-236-0103: Study Schema



The Stribild Assessment concluded that both studies “demonstrated non-inferiority of Stribild compared to the other regimens,” and further found that Stribild “compare[s] very well with many other studies” in patients who have not previously had any antiretroviral treatment.³⁴⁰ The assessment further notes that “Stribild is the first [fixed dose combination] including a INSTI to be taken once a day for use in adults,” which “provides a simplified regimen.”³⁴¹

E. The Triumeq Assessment Taught the Therapeutically Effective Use of a Second Generation INSTI Anchoring an N(t)RTI Backbone Regimen to Treat HIV-1 Infection Disclosures in a Single Tablet.

243. The EMA issued its assessment of the Triumeq[®] tablet on June 26, 2014, and so I understand that it is prior art to the Tablet Patents.

244. As I have explained in this report, the Triumeq[®] product was a single tablet that provided a complete antiretroviral regimen, with the anchor drug being the sodium salt of the second generation INSTI DTG (equivalent to 50 mg dolutegravir) combined with the N(t)RTI backbone of abacavir (ABC) and lamivudine (3TC).³⁴² The Triumeq Assessment confirms that DTG was recognized in June of 2014 to be a “potent, low nanomolar inhibitor of HIV integrase that provides the excellent antiviral activity and tolerability demonstrated for the [INSTI] class,

³⁴⁰ *Id.* at DEFS_BIC_00001478.

³⁴¹ *Id.*

³⁴² Triumeq Assessment (DEFS_BIC_00002048-161).

while also offering once-daily dosing without the need for pharmacokinetic (PK) boosting.”³⁴³

According to the Triumeq Assessment, the Triumeq[®] product contains a film-coating.³⁴⁴

245. The Triumeq Assessment reports that the primary clinical studies supporting the approval of Triumeq[®] compared it to Atripla[®] (a single tablet with the NNRTI efavirenz anchoring the N(t)RTI pair of TDF/FTC) and found Triumeq[®] to be superior to Atripla[®].³⁴⁵ The assessment also reports, however, that a comparison between Triumeq[®] and a regimen with DTG combined with TDF/FTC was “not formally studied” in patients with a high baseline viral load.³⁴⁶

246. In the “beneficial effects” section of the assessment, however, the EMA observed that similar response rates were “seen with the ‘Triumeq-combination’ and the other preferred NRTI-backbone, tenofovir/emtricitabine, given with an integrase inhibitor (dolutegravir or raltegravir), or darunavir/ritonavir.”³⁴⁷ The EMA assessment noted that the “choice of NRTI backbone in those studies were according to the discretion of the investigator.”³⁴⁸ Importantly, the assessment also notes that in previous studies, “the abacavir/lamivudine components showed a signal for suboptimal efficacy” in high viral load patients “which was not seen with tenofovir/emtricitabine.”³⁴⁹ Even in the absence of such a study, however, the EMA reported that “the outcomes versus various preferred regimens in the studies presented are considered reassuring, in particular as no resistance development (to the integrase class or to the NRTIs) was seen any patients who were treated with dolutegravir.”³⁵⁰

³⁴³ *Id.* at DEFS_BIC_00002053.

³⁴⁴ *Id.* at DEFS_BIC_00002061

³⁴⁵ *Id.* at DEFS_BIC_00002125 (discussion on clinical efficacy).

³⁴⁶ *Id.*

³⁴⁷ *Id.* at DEFS_BIC_00002155.

³⁴⁸ *Id.*

³⁴⁹ *Id.* at DEFS_BIC_00002156.

³⁵⁰ *Id.*

247. The assessment also notes, and I agree, that “Triumeq provides a regimen as 1 tablet taken once daily, and without regards to food intake,” which “increases the quality of life for patients, the compliance to the treatment, and also minimizes the risk for erroneous intake/dosing.”³⁵¹

F. WO ’351 Taught Single Pharmaceutical Compositions with a Second Generation INSTI Anchoring an N(t)RTI Backbone Regimen with the Hemifumarate Form of TAF.

248. WO ’351 is a patent application filed by Ratiopharm GMBH, a pharmaceutical company in Denmark, that claims priority back to a provisional application filed on December 19, 2013, and it published on February 19, 2015.³⁵² The abstract provides a concise summary of the content of the application,³⁵³ as follows:

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

249. As can be seen, applicant Ratiopharm disclosed the combination of the “second generation” INSTI DTG with emtricitabine and tenofovir (or a prodrug of tenofovir) for use as a medication for the treatment of HIV.³⁵⁴ The application also discusses the results from a phase 3 clinical study (published in 2013), where DTG (50 mg) was compared to “first generation” INSTI raltegravir (RAL) (400 mg), both in further combination with one of two known N(t)RTI-backbones.³⁵⁵ WO ’351 reports that the study found DTG to be a “suitable alternative to” RAL,

³⁵¹ *Id.* at DEFS_BIC_00002155.

³⁵² WO ’351 (BICANDA01155483-513).

³⁵³ *Id.* at BICANDA01155484 (Abstract).

³⁵⁴ *Id.*

³⁵⁵ *Id.* at 2:14-21.

but that the combinations in the clinical study “seem to be improvable in view of their effic[a]cy and/or safety.”³⁵⁶

250. WO ’351 then specifically discloses pharmaceutical combinations employing DTG as the anchor drug, with the N(t)RTI backbone of FTC and “tenofovir or a prodrug thereof,” e.g., TAF, including combinations with specific amounts of each compound for the treatment of HIV infection.³⁵⁷ When identifying DTG, the publication includes pharmaceutically acceptable salts, and particularly prefers the sodium salt.³⁵⁸ The salt form of TAF is preferably a “hemifumarate or fumarate” salt, and “especially the hemifumarate[,]” and FTC is preferably used in its free base form.³⁵⁹

251. The pharmaceutical combinations of WO ’351 are administered once daily “preferably [as] a solid oral dosage form ... in particular a tablet.”³⁶⁰ Specific pharmaceutical combinations include those containing about 50 mg DTG, about 200 mg of FTC, and about 25 mg of the prodrug tenofovir alafenamide (TAF).³⁶¹

252. The total amount of active ingredients of the compositions disclosed in WO ’351 that use TAF as the tenofovir prodrug are reported as preferably in the range of 192-326 mg per day,³⁶² which covers particular embodiments with 50 mg DTG, 25 mg TAF, and 200 mg FTC, i.e., 275 mg of total active ingredients.³⁶³

³⁵⁶ *Id.* at 2:21-26.

³⁵⁷ *Id.* at 3:22-26 (amounts of compounds taken together are effective to treat HIV infection in a human); *see also id.* at 4:1-9 (DTG is an INSTI) 6:24-32 (FTC is an NRTI), 9:4-25 (TFV and its prodrugs are NtRTIs).

³⁵⁸ *Id.* at 4:22-25 (the term “dolutegravir” comprises all the pharmaceutically acceptable salts thereof; dolutegravir can be obtained according to procedures outlined in WO 2006/116764 or WO 2010/068253), 5:21-27 (dolutegravir sodium salt particularly preferred).

³⁵⁹ *Id.* at 5:22-27 (DTG sodium), 13:16-18 (TAF fumarate or hemifumarate), 8:10-11 (emtricitabine free form).

³⁶⁰ *Id.* at 17:27-28, 23:6-8 (emphasis added).

³⁶¹ *Id.* at 19:30-20:2.

³⁶² *Id.* at 17:17-18, 19:5-12.

³⁶³ *Id.* at 19:30-20:2.

253. WO '351, consistent with similar teachings in WO '323, generally discloses the preparation of pharmaceutical compositions,³⁶⁴ which includes the use of excipients “with which the person skilled in the art is familiar, such as those which are described . . . in the US Pharmacopeia (USP).”³⁶⁵ WO '351 also lists six categories of excipients commonly used to prepare such compositions, which are taught to be present in certain ranges of amounts, each based on the total weight of the oral dosage form.³⁶⁶ As explained further below, pharmaceutical tablets containing 275 mg of total active ingredients and excipient amounts in the preferred ranges disclosed in WO '351 provide total tablet weights less than 730 mg, where the INSTI DTG is present in an amount less than 15% and less than 11% of the total weight of the tablet.

254. WO '351 also reports on the results of a pre-clinical study testing the anti-viral activity of three compositions, comparing the “second generation” INSTI DTG (50 mg) coupled with two different N(t)RTI pairs.³⁶⁷ In one part of the study, two compositions using DTG (50 mg) as an anchor for the N(t)RTI pair of FTC (200 and 100 mg) and TDF (300 and 150 mg) are used.³⁶⁸ The study also used a comparator composition (named “Tri-572”) that uses DTG (50 mg) to anchor the N(t)RTI pair of lamivudine (300 mg) and abacavir (600 mg).³⁶⁹

255. All three compositions were tested in CEM-M7 cells infected with HIV-1 NL4-3 (wild type) and dolutegravir resistant HIV-1 R263K.³⁷⁰ The combinations using DTG to anchor the N(t)RTI pair of FTC + TDF are reported to “show[] unexpected and significantly better anti-

³⁶⁴ WO '323 (DEFS_BIC_00002214-474) at DEFS_BIC_00002249-50 (35-36).

³⁶⁵ WO '351 at 20:24-27 (BICANDA01155503).

³⁶⁶ *Id.* at 20:29-23:17.

³⁶⁷ *Id.* at 25:1-13.

³⁶⁸ *Id.* at 25:7-13.

³⁶⁹ *Id.* at 25:4-5.

³⁷⁰ *Id.* at 23:19-24:13.

viral activity than the combination of the product Tri-572,” the latter of which is said to be “promising in clinical trials and expected to be launched in the future.”³⁷¹

G. Gilead’s U.S. Published Patent Application No. 2013/0065856 (“US ’856”).

256. US ’856 is the publication of Gilead’s U.S. Appl. No. 13/586,358, that published on March 14, 2013. The publication discloses “tenofovir alafenamide hemifumarate,” and discloses the use of that specific form of TAF in antiviral therapy regimens.³⁷² It also specifically discloses pharmaceutical compositions that combine TAF hemifumarate with one or more additional therapeutic agents among the following: “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.”³⁷³ These pharmaceutical compositions include those for therapeutic oral administration, such as ingestible tablets, and US ’856 discloses that tablets may be coated with gelatin, polymers, wax, shellac, or sugar.³⁷⁴

H. WO ’323 Disclosed the Second Generation INSTI BIC and Taught Its Administration With N(t)RTI Backbones Including TAF and FTC.

257. WO ’323 is an international patent application filed on behalf of Gilead on December 19, 2013, that published on June 26, 2014.³⁷⁵ Its abstract summarizes the application as one that discloses compounds “for use in the treatment of human immunodeficiency virus (HIV) infection,” as well as methods for preparing those compounds, “as well as pharmaceutical compositions comprising such compounds.”³⁷⁶

³⁷¹ *Id.* at 25:15-26:15.

³⁷² US ’856 (DEFS_BIC_00002202-13) at DEFS_BIC_00002202 (Abstract).

³⁷³ *Id.* at DEFS_BIC_00002207, DEFS_BIC_00002210, ¶¶ [0010]-[0011], [0057].

³⁷⁴ *Id.* at DEFS_BIC_00002209

³⁷⁵ WO ’323 (DEFS_BIC_00002214-474) at DEFS_BIC_00002214. WO ’323 contains basically the same disclosure as the ’996 patent, which I summarized earlier in this report, but has a larger set of claims at the end of its disclosure, as explained herein.

³⁷⁶ *Id.* at Abstract.

258. WO '323 discloses a family of compounds, named as compounds “of Formula (I),” which may have antiviral activity, and which “may be used to inhibit the activity of HIV integrase and may be used to reduce HIV replication.”³⁷⁷ WO '323 then discloses ~100 particular examples of Formula (I) compounds, which include detailed methods for preparing them.³⁷⁸ Following the examples, a table (Table 1) reports results of an antiviral assay performed on each exemplary compound.³⁷⁹

259. This assay details the impact of these different compounds on infectivity of HIV in a cell line known to be permissive for HIV replication. The table reports half maximal effective concentrations (EC₅₀; drug concentration that inhibits 50% of the virus) for the compounds in the range of 1.5 to 422 nM. Compounds with lower EC₅₀ would be understood by a POSA to have more potent anti-HIV activity.³⁸⁰ A POSA would have appreciated that a majority of the exemplary compounds exhibited good to excellent anti-HIV activity, with ~50% having an EC₅₀ of ≤ 5 nM, and ~30% having an EC₅₀ ≤ 2.5 nM. And given the INSTI function of these compounds, a POSA would have recognized that their anti-HIV activity was the result of HIV integrase inhibition. Moreover, WO '323 states that these compounds “may be useful for treating the proliferation of the HIV virus, treating AIDS, or delaying the onset of AIDS or ARC symptoms.”³⁸¹

260. A second table (Table 2) reports results from another assay, designed to assess pregnane X receptor (PXR) activation as a tool to evaluate induction of cytochrome P450 3A (CYP3A).³⁸² CYP3A is a critical enzyme, known to the POSA to be implicated in drug

³⁷⁷ *Id.* at 3:8-12.

³⁷⁸ *Id.* at 43:15-212:3

³⁷⁹ *Id.* at 212:5-216.

³⁸⁰ *See also* Winkler Report at Section IX.A. ¶ 75.

³⁸¹ WO '323 at DEFS_BIC_00002426.

³⁸² *Id.* at 217-19.

metabolism. The table reports the %E_{max}, or percent effective concentration in relation to PXR activation with a positive control. PXR activation within a subset (75) of the ~100 examples tested for anti-HIV activity is reported.³⁸³ Most of the tested compounds provided an EC₅₀ in the activity assay < 10 nM, while most compounds providing an EC₅₀ > 10 nM were excluded. The ~75 compounds tested provided an %E_{max} within the range from 0% to 123%, with lower values in this table representing more desirable compounds.

261. Next, WO '323 reports a third table (Table 3) disclosing a compound's ability to inhibit the organic cation transporter OCT2. OCT2 is thought to be important in the renal excretion of cationic drugs; inhibitors of OCT2 may decrease OCT2-dependent renal clearance of other drugs, thus resulting in important drug-drug interactions.³⁸⁴ Table 3 reports results from a smaller subset of compounds (23 of the ~100 examples).³⁸⁵ The table reveals a range of inhibitory concentrations (IC₅₀) from 42 to 10000 nM, with lower values in this table representing more desirable compounds.

262. Following the above *in vitro* assays, a series of *in vivo* experiments were performed on an even smaller subset of selected compounds (11 of the ~100 examples) to assess the pharmacokinetic properties of the subset.³⁸⁶ Each of the 11 compounds were administered to beagle dogs intravenously, and then a subset of 5 of those compounds were also administered orally.³⁸⁷

263. A POSA would have understood that the 5 compounds selected for oral administration, compounds 2, 3, 41, 42, and 47, provided more ideal pharmacokinetics in the IV

³⁸³ *Id.* at 216:1-219.

³⁸⁴ *Id.* at 220-21.

³⁸⁵ *Id.*

³⁸⁶ *Id.* at DEFS_BIC_00002436.

³⁸⁷ *Id.* at 222:1-224 (including Table 4).

study. Specifically, as shown in the leftmost columns in Table 4 (annotated below), these compounds provided lower clearance (CL) values and a longer mean residence times (MRT) as compared with the 6 other compounds tested.³⁸⁸

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

264. Dr. Winkler calculated the expected half-life ($t_{1/2}$) of the 11 compounds tested in the IV study using the clearance (CL) and volume of distribution (V_{ss}) values reported above, where the five compounds tested in the oral study provided longer half-lives compared to the remaining 6 compounds when administered intravenously (*see* expected $t_{1/2}$ below).³⁸⁹

Compound	Half-Life ($t_{1/2}$) (h)
98	~2.4
83	~1.6
55	~2.9
77	~1.5
41	~5.1
42	~5.2
47	~5.0

³⁸⁸ *Id.* at 223-24 (Table 4 (annotated in green to emphasize the 5 compounds selected for oral administration)).

³⁸⁹ Winkler Report at Section X.C. ¶¶ 154-55.

8	~1.2
7	~1.6
3	~3.4
2	~4.6

265. Notably, compounds **41**, **42**, and **47** provided longer expected half-lives than compounds **2** and **3** (~5.0-5.2 h versus ~3.4-4.6 respectively), though the Gilead inventors selected each of these compounds for the oral study.³⁹⁰

266. Table 4 reports results from the oral study including **F%**, or the fractional percentage of the drug dosage that reaches the therapeutic site of action (i.e., oral bioavailability), as well as the maximum plasma concentration (**C_{max}**) and area under curve (**AUC**) for compounds **2**, **3**, **41**, **42**, and **47**.³⁹¹ Among the tested compounds administered orally, compounds **42** and **2** had the highest oral bioavailability (**F%**), **C_{max}**, and **AUC** values.³⁹²

267. In my opinion, a POSA would have understood from WO '323 that the Gilead inventors progressively narrowed the ~100 exemplary compound tested in the HIV activity assay (Example 104) based on their activity, data from PXR assay (Example 105; 75 of ~100 compounds tested) and OCT assay (Example 106; 23 of ~100 compounds tested), followed by an *in vivo* IV study (11 of ~100 compounds tested), and finally an *in vivo* oral study (5 of ~100 compounds tested) (Example 107). That POSA would have appreciated that Gilead used these assays to hone in on the most desirable INSTI compounds for treating the proliferation of the HIV virus, treating AIDS, or delaying the onset of AIDS or ARC symptoms upon oral administration. In my opinion, this was not surprising given that oral administration e.g., single tablet regimens for ART, had long been favored for HIV treatment.³⁹³ And based on the half-

³⁹⁰ See also Winkler Report at ¶ 154.

³⁹¹ WO '323 (DEFS_BIC_00002214-474) at DEFS_BIC_00002437-38 (Table 4, right three columns).

³⁹² See also Winkler Report at ¶ 157.

³⁹³ See e.g., Sections V.A.-B.

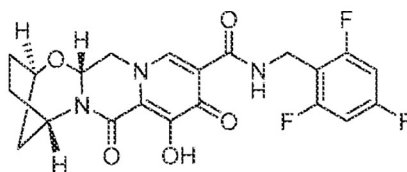
lives ($t_{1/2}$), **F%**, **C_{max}**, and **AUC** values reported in Table 4 (above), the POSA would have specifically selected compounds **42** and **2** for further study, e.g., in the clinic.³⁹⁴

268. The chemical structure of compound **42** is disclosed in WO '323 as follows:

Example 42

Preparation of Compound 42

(2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



42

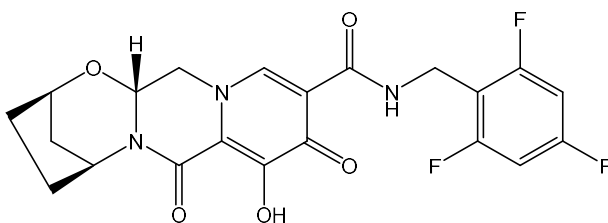
I understand that this “Compound 42”³⁹⁵ corresponds to Gilead’s compound with code name “GS-9883” and is now known as bicitegravir (BIC).³⁹⁶ Dr. Winkler provides different structural orientations for compound **42**, including the following structure that corresponds to Formula (I) in the Asserted Tablet Claims.³⁹⁷

³⁹⁴ See also Winkler Report at Section X.C., ¶¶ 156-60.

³⁹⁵ WO '323 at 99:8-101:25.

³⁹⁶ See Tsiang et al., “Antiviral Activity of Bicitegravir (GS-9883), a Novel Potent HIV-1 Integrase Strand Transfer Inhibitor with an Improved Resistance Profile,” 60(12) ANTIMICROBIAL AGENTS AND CHEMOTHERAPY 7086-97, 7086 (2016) (“Tsiang”) (BICANDA00230560-71). This later correlation between compound **42**, GS-9883, and BIC does not factor into the analysis and opinions set forth herein.

³⁹⁷ Winkler Report at ¶ 159.



Compound 42 (BIC)

Dr. Winkler also identifies the chemical structure of compound **2** and notes its close structural similarity to compound **42**.³⁹⁸

269. WO '323 confirms that “[a] goal of antiretroviral therapy is to achieve viral suppression of in the HIV infected patient,” and it refers to the 2013 version of DHHS treatment guidelines.³⁹⁹ WO '323 also notes that “achievement of viral suppression requires the use of combination therapies, i.e., several drugs from at least two or more drug classes,” and that drug regimen choices are complicated where patients are receiving treatment for other medical conditions, as “the potential for drug interaction is a criterion for selection of a drug regimen.”⁴⁰⁰ On this basis, WO '323 reported that a need existed (at the time) “for antiretroviral therapies having a decreased potential for drug interactions,” and “for new agents that inhibit the replication of HIV” while also reducing drug interactions “when co-administered with other drugs.”⁴⁰¹

270. WO '323 also discusses “combination therapy,” and states that one embodiment of the inventions disclosed in the publication involves administering a therapeutically effective amount of “a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more additional therapeutic

³⁹⁸ Winkler Report at Sections X.C.-D. (Table 4 analysis and structural comparison of compounds **42** and **2** showing identical structures except for an additional fluorine atom on the phenyl ring of compound **42**).

³⁹⁹ WO '323 at 2:22-3:6 (DEFS_BIC_00002216-17).

⁴⁰⁰ *Id.* at 2:22-3:2.

⁴⁰¹ *Id.* at 3:2-6.

agents.”⁴⁰² The publication then details what it means by such “additional therapeutic agents” by listing multiple classes of antiretroviral compounds, including the NRTI emtricitabine (FTC) and the NtRTI tenofovir alafenamide fumarate (TAF), among the list.⁴⁰³

271. WO '323 further notes that when “a compound disclosed herein is combined with one or more additional therapeutic agents,” the administration can be “as a simultaneous or sequential regimen.”⁴⁰⁴ The same combinations are, in certain embodiments, “*in a unitary dosage form* for simultaneous administration to a patient, for example as a solid dosage form for oral administration[.]”⁴⁰⁵ and WO '323 identifies a tablet as a single dosage unit.⁴⁰⁶ In my opinion, a POSA would have understood from WO '323 that an INSTI compound, especially one with good oral bioavailability, e.g., compound **42**, would be an optimal choice for combination with additional anti-HIV compounds such as FTC and TAF fumarate into a single oral dosage, including in a tablet, allowing for simultaneous administration. Such dosage forms contained therapeutically effective amounts of each anti-HIV agent.⁴⁰⁷

272. Importantly, WO '323 also confirms that a skilled artisan, “[f]or purposes of administration,” may prepare pharmaceutical compositions where compounds are mixed with acceptable carriers, diluents, or excipients “in an amount which is effective to treat a particular disease or condition of interest.”⁴⁰⁸ WO '323 reports that “the activity of compounds of Formula (I) can be determined by one skilled in the art,” and it notes in particular that the *in vitro* and *in vivo* examples (discussed above) can be used to assess activity.⁴⁰⁹

⁴⁰² *Id.* at 37:7-12.

⁴⁰³ *Id.* at 37:20-39:23 (emtricitabine at 38:14; tenofovir alafenamide fumarate at 38:19-20; dolutegravir at 38:28).

⁴⁰⁴ *Id.* at 40:13-15.

⁴⁰⁵ *Id.* at 40:18-20 (emphasis added).

⁴⁰⁶ *Id.* at 36:9-15.

⁴⁰⁷ *Id.* at 37:7-21.

⁴⁰⁸ *Id.* at 35:9-23.

⁴⁰⁹ *Id.* at 35:14-16.

273. Upon determining activity, WO '323 states with regards to pharmaceutical compositions that “[a]ppropriate concentrations and dosages can be readily determined by one skilled in the art.”⁴¹⁰ It also states that a “therapeutically effective amount can be determined routinely by [a POSA] having regard to their own knowledge, the state of the art, and this disclosure.”⁴¹¹ A POSA would have appreciated that “a tablet [which] may be a single dosage unit”⁴¹² would have been suitable, and in fact preferred for oral administration.

274. In my experience, these are accurate observations, and the POSA would agree. Once the anti-HIV activity of a compound is established, an appropriate (or therapeutically effective) amount of that compound for treating HIV⁴¹³ (e.g., by oral administration) can be readily determined by the POSA using routine pre-clinical and clinical experimentation, e.g., the beagle dog studies from Example 107 in the WO '323 patent. *See Infra* Section V.E. (discussing routine dose ranging studies for the INSTIs DTG and EVG, where doses that reduced HIV viral load were identified and considered efficacious). This would have included, of course, the preparation of a tablet containing an appropriate (or therapeutically effective) amount of a disclosed INSTI compound for “treatment” as defined in WO '323⁴¹⁴, which “may be a single dosage unit.”⁴¹⁵ According to WO '323, such a composition would have also been readily “prepared by methodologies well known in the pharmaceutical art.”⁴¹⁶

⁴¹⁰ *Id.* at 35:16-17.

⁴¹¹ *Id.* at 16:19-21; *see also id.* at 36:31-37:5 (noting that a therapeutically effective amount considers factors such as the activity of the specific compound employed; the metabolic stability and length of action of the compound; the age, weight, general health, sex, and diet of the patient of the patients; the mode and time of administration; the rate of excretion; the drug combination; the severity of the particular disorder or condition; and the subject undergoing therapy).

⁴¹² *Id.* at 36:13.

⁴¹³ As noted in Section V.E. ¶ 119, treatment in WO '323 includes preventing the appearance of symptoms and/or preventing viral load from reaching detectable levels post-exposure to the HIV virus. *See* WO '323 at 16:22-32 (DEFS_BIC_00002230).

⁴¹⁴ *Id.* at 36:31-37:5.

⁴¹⁵ *Id.*

⁴¹⁶ *Id.* at 36:22-23.

275. WO '323 also discloses combination therapy for the treatment of HIV infection where a “therapeutically effective amount of a compound disclosed herein[, e.g., INSTI compound **42** that a POSA would have preferred for oral administration], or a pharmaceutically acceptable salt thereof” is administered in combination with a “therapeutically effective amount of one or more additional therapeutic agents[.]” including in a single composition containing each agent and a pharmaceutically acceptable carrier, diluent or excipient.^{417,418,419} Thus, a POSA would have understood WO '323 to disclose single tablets containing a therapeutically effective amount of an INSTI, e.g., preferred compound **42**, and therapeutically effective amounts of anti-HIV agents such as FTC and TAF fumarate.

276. WO '323 discloses therapeutically effective amounts in the range of “about 25 mg to about 500 mg,” including specific doses of 25 mg, 50 mg, and 100 mg.⁴²⁰ A POSA would have known and expected from WO '323 that: (1) more active compounds of Formula (I) (smaller **EC**₅₀ values) would be orally administrable at lower doses within this range, (2) compounds having lower clearance rates (**CL**) and longer residence times (**MRT**) (and longer half-lives (**t**_{1/2})) would be orally administrable at lower doses within this range, and (3) that compounds with higher oral bioavailability (**F%**) would be orally administrable at lower doses within this range. That person also would have agreed with Gilead’s statement in WO '323 that factors such as the age and weight of the patient and the severity of the disease to be treated would have an impact on dose, e.g., lower doses within the “about 25 mg to about 500 mg” range would be appropriate and therapeutically effective in children and lower weight individuals, and

⁴¹⁷ *Id.* at 37:7-16.

⁴¹⁸ *Id.* at 16:8-21 (defining “therapeutically effective amount” as “an amount . . . sufficient to effect treatment of disease-states conditions or disorders for which the compounds have utility,” which can be “determined routinely by one of skill in the art having regard to their own knowledge, the state of the art, and this disclosure.”).

⁴¹⁹ *Id.* at 16:22-25 (defining “treatment” to mean “the administration of a compound or composition according to the present invention to alleviate or eliminate symptoms of HIV infection and/or to reduce viral load in a patient.”).

⁴²⁰ *Id.* at 35:16-23.

also patients with less severe conditions, e.g., those exposed to HIV-1 but without symptoms and/or without detectable levels of HIV in the blood.

277. As already explained, a POSA would have selected compound **42** based on the combination of its lower nanomolar **EC₅₀**, lower **CL**, longer **MRT**, longer expected **t_{1/2}**, higher **F%** and higher **C_{max}** and **AUC**, as compared to other compounds of Formula (I), such as the ~100 exemplary compounds evaluated *in vitro*. For the above reasons, that person would have expected that compound **42** itself would be “therapeutically effective” at lower doses in the range of about 25 mg to about 500 mg disclosed in WO ’323, e.g., doses in the range of 25-100 mg such as 50 mg and 100 mg.

278. In the claims set forth at the end of WO ’323, claim 32 lists compound **42** as the first among a group of 7 structurally related compounds of Formula (I).⁴²¹ Notably, four of the seven compounds are those tested in the oral administration assay in Example 107.⁴²² Claim 33 then refers to the compounds of claim 32, as part of “[a] pharmaceutical composition comprising a compound” of claims 1-32, “or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.”⁴²³ Claims 34 and then 35 (in sequence) then recite the further addition of “one or more additional therapeutic agents” and “anti-HIV agents” respectively to the pharmaceutical compositions of claim 33, which includes compositions containing a compound of claim 32.⁴²⁴ Finally, claim 36, incorporates claim 35, and recites several classes of HIV agents from which additional agents are selected, including the

⁴²¹ *Id.* at DEFS_BIC_00002454-55.

⁴²² See Winkler Report at ¶ 151 (correlating to compounds of claim 32 with compound numbers, which include orally tested compounds **2**, **3**, **41**, and **42**).

⁴²³ WO ’323 (DEFS_BIC_00002214-474) at DEFS_BIC_00002455.

⁴²⁴ *Id.* at DEFS_BIC_00002454-55.

classes of NRTIs and NtRTIs that contain emtricitabine (FTC) and TAF fumarate according to the specification (*supra*).⁴²⁵

I. The Genvoya Assessment Taught a Single Pharmaceutical Composition Containing a First Generation INSTI Anchoring the N(t)RTI Backbone of the Hemifumarate Salt of TAF and FTC to Treat HIV-1 Infection.

279. The Genvoya Assessment published on September 24, 2015, and it reports on the EMA’s 2015 approval of Genvoya®, Gilead’s updated Stribild® tablet, which substituted 10 mg of TAF (as a hemifumarate salt) in place of the 300 mg of TDF that had been approved in the previously approved Stribild® product.⁴²⁶

280. The Genvoya Assessment confirms in its introduction that, when the assessment was prepared, HIV-1 infection remained “a life threatening and serious disease of major public health significance, with approximately 35 million people infected worldwide.”⁴²⁷ It also reports (accurately) that the standard of care for treating the infection was to use a combination of therapeutic agents (antiretroviral agents) to suppress the virus.⁴²⁸ The Genvoya Assessment confirms that guidelines (at the time) suggested that initial therapy should include a pair of “two nucleos(t)ide reverse transcriptase inhibitors (N[t]RTIs)” along with a NNRTI, a boosted PI, or an INSTI.⁴²⁹ It also reports that “[a]ll patient populations may benefit from once daily fixed dose combination (FDC) regimens as these have been shown to provide increased adherence and improved clinical and virologic outcomes.”⁴³⁰

281. The Genvoya Assessment also reported (and I agree) that antiretroviral treatments were so successful by 2015 that “morbidity and mortality in the HIV infected population is

⁴²⁵ *Id.* at DEFS_BIC_00002455.

⁴²⁶ Assessment Report for Genvoya® from the European Medicine Agency (September 24, 2015) (“Genvoya Assessment”) (DEFS_BIC_00001811-969); *see id.* at DEFS_BIC_00001826 (for the hemifumarate salt).

⁴²⁷ *Id.* at DEFS_BIC_00001818.

⁴²⁸ *Id.* at DEFS_BIC_00001819.

⁴²⁹ *Id.*

⁴³⁰ *Id.*

increasingly driven by non-AIDS-associated comorbidities.”⁴³¹ In the clinic, this meant that treatment had “become more focused on the optimization of tolerability, long term safety, and adherence to potent [antiretroviral] regimens.”⁴³² The Genvoya Assessment reported that there was “a significant medical need for new, effective therapies that take into consideration the non-HIV comorbidities, demographics of the aging HIV infected population, antiretroviral (ARV) resistance and regimen simplification.”⁴³³ Importantly, the Genvoya Assessment also discloses that Gilead had investigated the use of the monofumarate salt form of TAF during clinical development, and that the hemifumarate form “was selected for Phase 2/3 studies in the commercial presentation.”⁴³⁴

282. Further, the Genvoya Assessment explains that the presence of the pharmacokinetic booster COBI produces a “2 to 3-fold increase” in TAF exposure in the blood, and that administration of 10mg of TAF in the fixed dose combination tablet “were comparable to those observed following administration of TAF 25 mg co-administered with FTC,” without the booster compound.⁴³⁵ From a pharmacokinetic perspective, however, administration of 25mg of TAF without a booster is an acceptable dose in an HIV combination regimen.⁴³⁶ In fact, the Genvoya Assessment discloses that, in some preliminary small scale clinical studies, both monolayer and bilayer dosage forms with all four active ingredients were prepared, including some with 25 mg of TAF.⁴³⁷

⁴³¹ *Id.*

⁴³² *Id.*

⁴³³ *Id.*

⁴³⁴ *Id.* at DEFS_BIC_00001884.

⁴³⁵ *Id.* at DEFS_BIC_00001888.

⁴³⁶ *Id.*; *see also id.* at DEFS_BIC_00001921 (“Based on the TAF monotherapy study . . . it was calculated that the final FDC formulation should contain ~10 mg TAF in order to provide steady state plasma TAF and [tenofovir] exposures and antiviral effects similar to those achieved with ~25 mg TAF given alone.”).

⁴³⁷ *Id.* at DEFS_BIC_00001885.

283. The Genvoya Assessment describes the Genvoya[®] product as including a tablet core and a film-coating containing the polymers polyvinyl alcohol and polyethylene glycol.⁴³⁸

IX. LEVEL OF SKILL IN THE ART

284. Given my review of the patents involved in this case, including the prior art to each that I have analyzed and explained herein, it is my opinion that the POSA for both the Tablet Patents and the BIC Sodium patents would share a common understanding of the HIV pharmaceutical market and HIV treatment market in the United States. In particular, it is my opinion that the POSA would be aware of the substantial financial implications of developing a single tablet containing a complete regimen for the treatment of HIV, including tablets containing a second generation INSTI that anchors a pair of N(t)RTIs such as the well-known pairing of emtricitabine (FTC) and tenofovir (TFV).

285. Further, I believe that the definition of the POSA is otherwise slightly different as between the Tablet Patents, and the Bic Sodium Patents. I provide my opinions on each in this section.

A. The Tablet Patents POSA

286. Upon review of documents described herein relevant to the BIC Sodium Patent (including those patents themselves), I agree with Dr. Chyall's definition, except that the POSA of the BIC Sodium Patents would also necessarily be aware of the regulatory context within which solid pharmaceutical products are approved.

287. In my opinion, the POSA as it pertains to those aspects of the claims of the Tablet Patents that address methods of treating patients, or compositions for use in treating patients, would have an M.D. or a Ph.D. with at least three years of work experience with HIV therapy

⁴³⁸ *Id.* at DEFS_BIC_00001820, DEFS_BIC_00001828-29.

and clinical investigations, drug development, medicinal chemistry, pharmaceuticals, pharmacokinetics, and/or pharmaceutical formulations. The POSA could also hold a B.S. or master's degree, so long as that person had at least five years of work experience in one or more of the above fields.

288. A POSA for the Tablet Patents would also consult with a collaborative team of skilled artisans in the same or related fields (e.g., MDs and PhDs), including other POSAs (as defined above) with different skill sets, such as skilled artisans in virology, organic chemistry, pharmacokinetics, pharmacodynamics, and/or conducting clinical trials, as well as artisans skilled in regulatory frameworks under which solid oral dosage forms are developed and approved by the FDA or other regulatory body.

B. The BIC Sodium Patents POSA

289. I understand that in this litigation, Leonard J. Chyall, Ph.D has submitted a declaration in which he applied a definition of a POSA in the field of the BIC Sodium Patents proffered by Gilead. *See* Decl. of Leonard J. Chyall, Ph.D. in Support of Plaintiff's Opening Claim Construction Brief at ¶¶ 24-26 ("Chyall Decl."). The definition that Dr. Chyall applied defines the POSA as follows:

. . . a person or team of persons working as part of a multidisciplinary drug development team with an advanced degree or degrees (such as a Ph.D. and/or M.D.) in the relevant fields, which could include chemistry (for example, organic, synthetic, computational, pharmaceutical, or medicinal chemistry), biochemistry, biology, medicine, pharmacology, pharmaceuticals, and/or pharmaceutical sciences. This person or team of persons would have at least two years of practical experience in one or more of these relevant fields. This person(s) could also be someone with a lower degree level (e.g., a masters (M.S.) degree) in one of these disciplines, but with greater practical experience (e.g., at least four years in the case of a person with a M.S. degree). As needed in the course of the drug development process, this team would include persons of skill possessing combinations of these relevant qualifications as well as other people with whom the persons of ordinary skill in the art may consult. The particular field of education and experience of the person or team of persons of ordinary skill in the art will vary between the various Asserted Patents. For example, a person or team of persons of ordinary skill in the art of the

'342 patent would have training and experience in chemistry, biochemistry, pharmacology, pharmaceuticals, and/or pharmaceutical sciences, including training and experience in identifying and characterizing crystalline forms of compounds.

See Chyall Decl. at ¶¶ 24-25.

290. Upon review of documents described herein relevant to the BIC Sodium Patent (including those patents themselves), I agree with Dr. Chyall's definition, except that the POSA of the BIC Sodium Patents would also be aware of the regulatory context within which solid pharmaceutical products are approved.

291. As I explain herein, and as is set forth in my curriculum vitae in more detail, prior to June 20, 2014, and continuing through November 9, 2015, I was actively engaged in the care of HIV-infected persons and sought to identify optimal treatments for HIV as well as other infectious diseases.

292. On the basis of my personal knowledge and experience, I am very familiar with the knowledge and practice available to the POSA of the BIC Sodium Patents as well as the Tablet Patents.

X. CONSTRUCTION OF CLAIM TERMS

A. Claim Constructions Pertaining to the BIC Sodium Patents

293. I understand that the words used in patent claims are to be given their plain and ordinary meaning, as would be understood by the POSA at the time of the claimed invention, unless an applicant provides a particular definition of the words used in the specification of the patent.

294. I also understand that the parties have agreed that the term "therapeutically effective amount" as used in claims 11 and 12 of the '342 patent mean "an amount of the claimed compound which when administered to a patient in need thereof, is sufficient to effect treatment for disease-states, conditions, or disorders for which the compounds have utility."

295. I further understand that the parties have also agreed that the phrase “[a] method for treating an HIV infection in a human in need thereof” as claimed in the claims 1 and 10 of the ’067 patent to mean “a method for alleviating or eliminating symptoms of an HIV infection and/or reducing HIV viral load in a human in need thereof, which may yield a variety of clinical outcomes, depending on the patient.”

B. Claim Constructions Pertaining to the Tablet Patents

296. I understand that the words used in patent claims are to be given their plain and ordinary meaning, as would be understood by the POSA at the time of the claimed invention, unless an applicant provides a particular definition of the words used in the specification of the patent.

297. I understand that the plain and ordinary meaning should be apparent from the content of the common specification of the Tablet Patents and (if necessary) the record of correspondence between the applicant and the USPTO for each patent, which I understand to be the intrinsic record. I have followed these principles in my analysis to the extent necessary throughout this report.

298. Claims 1-4, and 12-13 of the ’802 patent, and claims 1-2 and 6-7 of the ’846 patent refer to “a pharmaceutically acceptable salt” of the active ingredients that are identified. The common specification of the Tablet Patents explains that the amount of “pharmaceutically acceptable salt” is the amount of the salt that provides for the same amount of the recited compound in its free acid, or base, form.⁴³⁹ In my analysis, I have applied this definition to all claims in the Tablet Patents that recite an amount of “a pharmaceutically acceptable salt thereof.”

⁴³⁹ ’802 patent (BICANDA01160880-928) at 6:4-28; 7:22-48; 8:22-36.

299. As for the term “multilayer” recited in the ’846 patent, I understand the Court has construed this term to mean: “a tablet with two or more layers, in which at least one of the claimed components is in a separate layer, wherein a layer is a section or compartment of components.” I have also applied this definition in my analysis, to the extent it involves claims of the ’846 patent.

300. Otherwise, all of my opinions are based on the plain and ordinary meaning of the words used in each of the claims of the Tablet Patents to a POSA.

XI. THE TABLET PATENTS ARE OBVIOUS

301. As I explain below, it is my professional opinion from the viewpoint of a POSA, prior to November 9, 2015, that claims 1-13 of the ’802 Patent and claims 1-8 of the ’846 patent (hereafter “the Asserted Tablet Claims”) are not patentable under the law of obviousness, when considered in the context of the analysis I present in this report.

A. By November 9, 2015, a POSA had Several Reasons to Prepare Tablets containing Compound 42 (BIC), TAF, and FTC.

302. On November 9, 2015, the POSA would have understood that an HIV-1 infection remained a serious disease, and that its treatment required the use of a combination of therapeutic agents, which should include a backbone regimen of a pair of N(t)RTIs anchored by an NNRTI, a boosted PI, or an INSTI.⁴⁴⁰ It was also clear by then that an HIV-1 infection would require a lifetime of antiretroviral therapy, and that a simplified regimen was an ideal way to encourage long term adherence to an antiretroviral regimen.⁴⁴¹

303. At that time, physicians (including myself) were prescribing the “second generation” INSTI DTG in a single tablet (Tivicay®), and combining that tablet with another

⁴⁴⁰ Genvoya Assessment (DEFS_BIC_00001811-969) at DEFS_BIC_00001819.

⁴⁴¹ *Id.*

prescription for the N(t)RTI pair of emtricitabine (FTC) and tenofovir disoproxil (TDF) in a second tablet (Truvada®).⁴⁴² The N(t)RTI pair of FTC and TDF was a backbone recommended by DHHS, and was preferred over the N(t)RTI pair of ABC/3TC at the time for the reasons I have already explained above (Section V.B).

304. This preference for the TDF/FTC backbone when treating HIV-1 infection was first demonstrated even before the approval of Tivicay®. As shown in the Lunzen article, the interim results of a pending clinical study on the efficacy of DTG reported that investigators were given the discretion to administer, as the N(t)RTI backbone, either TDF/FTC or ABC/3TC tablets.⁴⁴³ The investigators chose the TDF/FTC N(t)RTI pair to anchor a 50 mg DTG dose, given once daily, in 67% of the patients.⁴⁴⁴

305. In addition, by November of 2015, DTG was preferred over the approved “first generation” INSTIs RAL and EVG, since it offered the combination of once-a-day dosing without the need for a pharmacokinetic booster such as COBI. DTG also proved to have a higher genetic barrier to resistance to mutation than RAL and EVG and maintained activity toward mutated strains of HIV integrase including those with known resistance to RAL and EVG.⁴⁴⁵ The use of TAF in a further improved N(t)RTI backbone pair over TDF that would be administered at ~10 times lower dose was also well known at the time.⁴⁴⁶

306. The only single tablet regimen containing the preferred INSTI DTG available prior to November 9, 2015, was Triumeq®, a product that combined DTG with the N(t)RTI backbone ABC/3TC. Triumeq® required screening patients for the HLA-B5701 allele, as

⁴⁴² This particular regimen was also specifically recommended by the DHHS Guidelines. *See* DHHS Guidelines (DEFS_BIC_00001000-287) at DEFS_BIC_00001082 (“On the basis of clinical trial data, the Panel categorizes DTG in combination with either ABC/3TC or TDF/FTC as a Recommended regimen in ART-naïve patients.”).

⁴⁴³ Lunzen (DEFS_BIC_00005086-93) at DEFS_BIC_00005091.

⁴⁴⁴ *Id.* at DEFS_BIC_00005089 (Table 1 providing baseline characteristics of all patients).

⁴⁴⁵ *See e.g.*, Section V.B (DTG was the preferred INSTI).

⁴⁴⁶ *See e.g.*, Section V.C (benefits of TAF over TDF were known).

patients with this allele could experience severe hypersensitivity reactions due to ABC.⁴⁴⁷ As Triumeq[®] was not active against HBV, treatment could also result in severe acute exacerbation of hepatitis B (HBV) in patients co-infected with HIV and HBV.⁴⁴⁸ As explained above, the DHHS Guidelines included the combination of DTG with TDF/FTC (administered as two separate tablets) as an option, as this combination was known to provide fewer treatment complications than the Triumeq[®] combination, and had become the preferred combination by physicians.⁴⁴⁹

307. Further, prior to November 9, 2015, a single tablet regimen that also employed TAF paired with FTC as the N(t)RTI backbone would have been recognized by the POSA as an improvement over TDF.⁴⁵⁰ TAF had (by then) been recognized as a safer prodrug of tenofovir, which would be dosed in a much lower daily amount than TDF (25 mg vs. 300 mg). TAF was also reported to have a reduced effect on serum creatinine and is associated with reduced tubular proteinuria, both important clinical markers of chronic kidney disease, as well as significantly smaller changes in bone mineral density.^{451,452} Indeed, the POSA would have known that a fixed dose co-formulated tablet using TAF and FTC was in Phase 3 clinical trials prior to November 9, 2015,⁴⁵³ and that TDF had already been replaced with TAF to provide an improved single tablet regimen over Stribild[®] known as Genvoya[®].⁴⁵⁴

⁴⁴⁷ See Section V.B.

⁴⁴⁸ *Id.*

⁴⁴⁹ See Sections V.A.-V.B.

⁴⁵⁰ See Section V.C.

⁴⁵¹ Astuti (DEFS_BIC_00003137-53) at DEFS_BIC_00003147 (noting that “a 25 mg dose of TAF has shown greater [antiretroviral activity] than a standard 300 mg dose of TDF,” and recognizing “[t]he possibility to use small doses of TAF instead of TDF could further widen the [single tablet regimen] options” and confirming that studies substituting in TAF with other single table regimens were under way).

⁴⁵² Sax (DEFS_BIC_00003013-19) at DEFS_BIC_00003016 and DEFS_BIC_00003018.

⁴⁵³ Press Release, Gilead Sciences, Inc., Gilead’s Investigational Fixed-Dose Combination of Emtricitabine/Tenofovir Alafenamide (F/TAF) Meets Primary 48-Week Objective in Phase 3 Study (September 2, 2015), <https://www.businesswire.com/news/home/20150902005495/en/Gilead%E2%80%99s-Investigational-Fixed-Dose-Combination-of-EmtricitabineTenofovir-Alafenamide-FTAF-Meets-Primary-48-Week-Objective-in-Pha> (“Gilead September 2015 Press Release”) (DEFS_BIC_00006198-201) (announcing that a pending Phase 3 clinical study evaluating its fixed-dose combination of FTC and TAF had met its 48 week objective).

⁴⁵⁴ Gilead November 2015 Press Release (DEFS_BIC_00006174-80) at DEFS_BIC_00006174-80.

308. Gilead had also announced in September of 2015 that it had filed two additional drug applications seeking approval to use TAF in place of TDF in other single tablet regimens, along with a third investigation using TAF in yet another single regimen tablet.⁴⁵⁵ The POSA also would have also understood that the N(t)RTI pair of TAF/FTC anchored by an INSTI in a single tablet that could be given once-a-day without the need for a pharmacokinetic booster, would have provided a simpler, more convenient and safer dosage regimens than the ART regimens employing TDF/FTC combinations recommended by DHHS at the time, including the RAL + TDF/FTC (in 2 separate tablets) and EVG + TDF/FTC + COBI in the single tablet Stribild®.^{456,457}

309. In my opinion, prior to November 9, 2015, a POSA would have recognized the need for a single tablet regimen containing a “second generation” INSTI like DTG or a structurally related analogue, in combination with the N(t)RTI pair of FTC and tenofovir (as TAF), which would have allowed for a more convenient, simplified, and safer regimen for treating HIV-1 infection, and that would have improved patient adherence over the two tablet regimen recommended by the DHHS at the time.⁴⁵⁸ That person would have been particularly motivated, in view of design needs and market forces, to identify a “second generation” INSTI similar to DTG that was combinable with FTC and tenofovir (as TAF) in a single tablet to achieve the aforementioned benefits of convenience, increased safety, and improved patient adherence. A POSA would have appreciated that such a tablet would have been provided more

⁴⁵⁵ Gilead September 2015 Press Release at DEFS_BIC_00006199 (describing the filing of NDAs with the FDA “for two other TAF-based HIV medicines,” and another “TAF-based regimen” with darunavir that was under investigation).

⁴⁵⁶ See Section V.A.-B.

⁴⁵⁷ See Gilead 2014 10-K (DEFS_BIC_00005568-6007) at DEFS_BIC_00005571 (Gilead itself acknowledging that “single tablet regimens allow patients to adhere to a fully suppressive course of therapy more easily and consistently, which is critical for the successful management of the disease.”).

⁴⁵⁸ See Section V.B; Section VIII.C.

efficiently and expeditiously if a single entity owned the rights, e.g., patent and marketing rights, to all three active ingredients.⁴⁵⁹

310. In my opinion, the need for a single tablet regimen with an N(t)RTI backbone of TAF/FTC, combined with a “second generation” INSTI having a higher genetic barrier to resistance than RAL and EVG given once daily without the need for a pharmacokinetic booster, would have motivated the POSA to prepare a single tablet with appropriate amounts, i.e., therapeutically effective amounts, of TAF, FTC, and a “second generation” INSTI similar to DTG for the treatment of HIV-1 infection.⁴⁶⁰ Moreover, as explained above, a POSA additionally would have been motivated to prepare single tablet combining TAF and FTC with a commonly owned INSTI, i.e., one owned by Gilead, such that a single tablet regimen would have been provided to the public more efficiently and expeditiously than a single tablet containing, e.g., DTG (owned by ViiV) and TAF/FTC (owned by Gilead).⁴⁶¹

311. As I also explain in Section V.D., my review of the patent literature confirms that at least two other pharmaceutical companies (Ratiopharm and Cipla) had already recognized the need for combining the “second generation” INSTI DTG with FTC and tenofovir (as TDF and TAF) in a single tablet, and had filed patent applications on the same.⁴⁶² These applications, however, utilized DTG in combination with TDF (or TAF) and FTC, i.e., a combination that would have required the approval of competing pharmaceutical companies for any potential clinical evaluation or marketing to occur. Otherwise, such a combination would have to be

⁴⁵⁹ See Section V.D.

⁴⁶⁰ See Sections V.E (dose ranging studies) and VIII.H (Gilead’s definitions of appropriate and therapeutically effective amounts in WO ’323).

⁴⁶¹ See Section V.D.

⁴⁶² See Section V.D.

delayed until the expiration of patents covering DTG (owned by ViiV), and TDF (or TAF) and FTC (owned by Gilead).

312. In this sense, it is important to reiterate that Gilead, in 2014, publicly acknowledged that Triumeq[®], a single tablet with DTG paired with N(t)RTI backbone of ABC/3TC drugs, “could adversely impact sales of our HIV products[,]”⁴⁶³ confirming a recognized need for POSAs working in the field to identify a similar single tablet containing a structurally similar “second generation” INSTI with the DHHS and physician preferred backbone of tenofovir and emtricitabine, and specifically the known improved backbone of TAF/FTC.

313. Prior to November 9, 2015, it had also been recognized that long term patient compliance and adherence to an ART drug combination would have been enhanced by the availability of a single tablet taken once-a-day.⁴⁶⁴ In my opinion, the POSA would have also understood that a single tablet with a “second generation” DTG analog combined with TAF/FTC would benefit patients if it could be made smaller in size than other available single tablet regimens employing an INSTI combined with an N(t)RTI pair of ingredients, such as Stribild[®] and Triumeq[®] containing total active ingredient amounts of 800 mg (when considering COBI) and 950 mg respectively. The DHHS Guidelines also included oral dosage form size as a factor that is important to consider when individualizing a treatment plan to which a patient can commit.⁴⁶⁵ A POSA would have appreciated that smaller tablet sizes would be achievable

⁴⁶³ Gilead 2014 10-K (DEFS_BIC_00005568-6007) at DEFS_BIC_00005602.

⁴⁶⁴ See e.g., *id.* at DEFS_BIC_00005571; see also Shah (BICANDA01156298-312) at BICANDA01156298 (“Patients with HIV infection prefer once/day regimens, especially single-tablet regimens.”); Sax (DEFS_BIC_00003013-019) at DEFS_BIC_00003013 (“Single-tablet regimens (STRs) represent a simple and convenient way for patients to maximize adherence and to control their HIV for many years.”); Genvoya Assessment (DEFS_BIC_00001811-969) at DEFS_BIC_00001819.

⁴⁶⁵ DHHS Guidelines (DEFS_BIC_00001000-287) at DEFS_BIC_00001188 (stating that it is important to consider the patient’s daily schedule and “patient tolerance of pill number, size and frequency,” when devising a successful treatment design to which a patient can commit) (emphasis added).

simply by substituting the approved 300 mg dose of TDF with a significantly lower dose of TAF (i.e., 25 mg), because this change alone would reduce total API content by 275 mg.

314. In my opinion, there existed a need in the art and the pharmaceutical market for a single tablet with a once-a-day INSTI not requiring a booster that also had a high genetic barrier to resistance anchoring an N(t)RTI backbone of TAF/FTC. This would have also allowed for smaller and lighter tablets (vis-à-vis Stribild[®] and Triumeq[®]) given the significantly lower total dose required from this combination. For this additional reason, a POSA would have been motivated to develop a single tablet combining the NRTI backbone of TAF/FTC with a “second generation” INSTI similar to DTG.

315. In sum, based on my personal experience as well as my consideration of the material cited herein, the POSA prior to November 9, 2015, would have recognized a need for a simplified, single tablet regimen that provided a “second generation” INSTI (i.e., a once-a-day unboosted INSTI with a high genetic barrier to resistance), anchoring the N(t)RTI backbone of TAF/FTC. Moreover, in my opinion, the remarkable commercial success of other single tablet regimens marketed by that time would have provided the POSA (and Gilead itself) with a substantial underlying financial motivation to direct significant resources to offer such a tablet. Indeed, Gilead understood (at the time) that its HIV products “primarily compete with the fixed-dose combination products in the nucleotide/nucleoside reverse transcriptase inhibitors (NTRI) class,” and so a POSA would have been acutely aware of the need to develop an INSTI similar to DTG that could be used with Gilead’s leading N(t)RTI combination of TAF and FTC.⁴⁶⁶

⁴⁶⁶ Gilead 2014 10-K (DEFS_BIC_00005568-6007) at DEFS_BIC_00005577.

1. The Combination of WO '323 and WO '351

316. By June of 2014, clinicians had recognized the need for a simplified, single tablet regimen that coupled a “second generation” INSTI with the established N(t)RTI backbone of TAF/FTC. Confirmation of this fact comes from the fact that a single tablet regimen containing a “second generation” INSTI combined with TAF and FTC had been disclosed WO '323 and WO '351.⁴⁶⁷ Indeed, these published patent applications were directed to pharmaceutical compositions and methods for treating HIV infections with an INSTI compound combined with other anti-HIV compounds, including in a single dosage form.⁴⁶⁸ One (WO '351) disclosed a single composition with 50 mg of DTG (preferably as DTG sodium), 25 mg of TAF (preferably as TAF fumarate or TAF hemifumarate), and 200 mg of FTC (preferably as a free base), and the other (Gilead's WO '323) disclosed a family of INSTI compounds which included compound **42** (BIC), along with compositions (including unit dosage forms such as tablets) containing a therapeutically effective amount of the INSTI compound, e.g., compound **42**, combined with therapeutically effective amounts of one or more anti-HIV agents including the NRTI FTC and the N(t)RTI TAF fumarate. These therapeutically effective amounts for the INSTIs disclosed in WO '323, e.g., compound **42**, include doses in the range of 25 mg to 500 mg, including specific doses 25 mg, 50 mg, and 100 mg.⁴⁶⁹

317. Gilead's WO '323 disclosed ~100 INSTI compounds sharing structural attributes to DTG, all of which were progressively narrowed through *in vitro* and *in vivo* screening to only five compounds given orally to beagle dogs.⁴⁷⁰ Two of those five compounds, i.e., compounds

⁴⁶⁷ See Section VIII.H (providing summary of WO '323 (DEFS_BIC_00002214-474)) and Section VIII.F (providing summary of WO '351 (BICANDA01155483-513)).

⁴⁶⁸ *Id.*

⁴⁶⁹ See Section VIII.H.

⁴⁷⁰ WO '323 (DEFS_BIC_00002214-474) at DEFS_BIC_00002436-38.

42 and **2**, were shown to be markedly more orally bioavailable, and provided significantly higher $C_{\max}$ and AUC compared the other three.⁴⁷¹ Compound **42** also provided longest half-life ($t_{1/2}$) and mean residence time (**MRT**) of the compounds tested, and compound **2** provided the largest oral bioavailability (**F%**), $C_{\max}$ and AUC.⁴⁷² Based on these more optimal pharmacokinetic properties, a POSA would have specifically selected compound **42** (along with compound **2**) from among the INSTI compounds disclosed in WO '323 as prime candidates for once-a-day administration.⁴⁷³ After selection of compound **42**, in my professional opinion, its appropriate concentrations and dosages in a pharmaceutical composition, including therapeutically effective amounts for treating HIV, would have been routinely determined by a POSA, who would have considered and tested dosages in WO '323 such as 25 mg, 50 mg, and 100 mg.⁴⁷⁴

318. In my opinion, a POSA would have known and expected from WO '323 itself that more active compounds of Formula (I) for WO '323 (smaller EC_{50} values), compounds having lower clearance rates (**CL**) and longer residence times (**MRT**) (and longer half-lives), and compounds with higher oral bioavailability (**F%**) would be orally administrable at lower doses within the “about 25 mg to about 500 mg” range disclosed in WO '323. Compound **42** offered the combination of lower nanomolar activity, lower **CL**, longer **MRT**, and longer expected $t_{1/2}$ compared to many other INSTI compounds disclosed in WO '323, and so a POSA would have known that its therapeutically dose would be significantly lower than other compounds.

319. That POSA also would have known that factors such as the age and weight of the patient and the severity HIV to be treated would also have an impact on the dose, e.g., children and lower weight individuals would be orally administered lower doses within this range, as

⁴⁷¹ *Id.* (Table 4); *see also* Section VIII.H, ¶¶ 264-67; Winkler Report at Section X.C., ¶ 157.

⁴⁷² *Id.* (Table 4); *see also* Section VIII.H, ¶¶ 264-67; Winkler Report at Section X.C., ¶ 158.

⁴⁷³ *See also* Winkler Report at Section X.C., ¶¶ 158-60.

⁴⁷⁴ WO '323 (DEFS_BIC_00002214-474) at 19:21, 35:15-17.

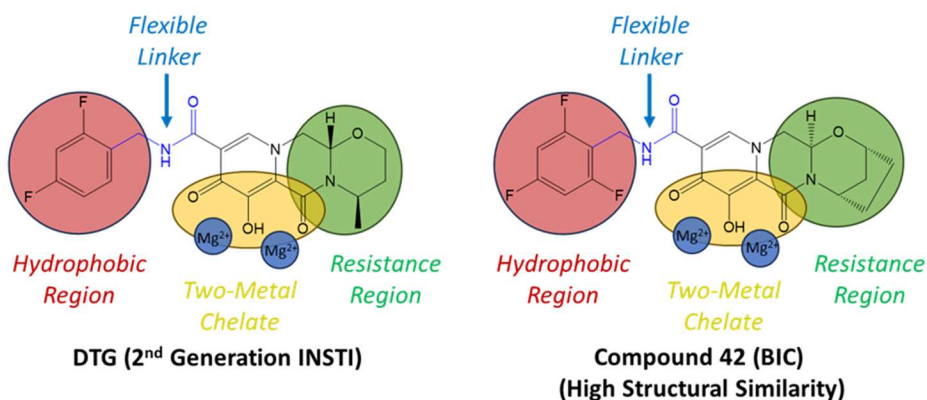
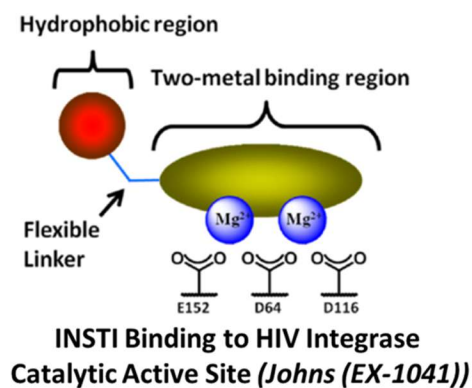
would patients with less severe disease states, e.g., those with exposure to the virus but without symptoms and/or without detectable levels of HIV in the blood.

320. WO '351 discloses similar pharmaceutical compositions, including tablets, where the “second generation” INSTI DTG (50 mg) is combined with TAF (25 mg) and FTC (200 mg).⁴⁷⁵ I have considered Dr. Winkler’s analyses and opinions regarding the large degree of structural similarity between compound **42** and DTG, including his opinion that an ordinarily skilled medicinal chemist would have expected that compound **42** (BIC) would have similar physicochemical and biological properties to DTG, an established, FDA-approved, INSTI compound.⁴⁷⁶

321. In particular, I have considered Dr. Winkler’s specific analysis on the function of specific structural features present in both compound **42** (BIC) and DTG, that form the basis of his opinion that compound **42** would provide a similar binding mode to the active site HIV integrase through a two-metal chelate, and an expected high genetic barrier to resistance and ability to maintain activity against HIV integrase in view of its structurally similar “resistance region.” For clarity, I reproduce an illustration from the Winkler Report (at ¶ 124) that I found useful to summarize his opinions.

⁴⁷⁵ See Section VIII.F, ¶ 251.

⁴⁷⁶ Winkler Report, Sections X.C.-D. at ¶¶ 160, 162-67.



322. In my opinion, as shown in this diagram, the structural similarity between compound **42** and DTG, as emphasized by Dr. Winkler, would have further motivated the POSA to select compound **42** (BIC) in view of its expectedly similar physicochemical and biological properties to DTG (i.e., a “second generation” INSTI with an activity and PK profile allowing for once-a-day oral administration without a booster, and an expected higher genetic barrier to resistance to mutations compared to the approved “first generation” INSTIs RAL and EVG).

323. Each of WO '323 and WO '351 include disclosures teaching the use of two (or more) and preferably three active ingredients in a single dosage form (including tablets) all designed to reduce replication of the HIV-1 virus and thus reduce viral load in HIV-1 infected patients. In my professional opinion, the POSA therefore would have had good reason to combine WO '323 and WO '351 when exploring options for a smaller, single tablet regimen compared to Triumeq[®] and Stribild[®], that would treat HIV-1 infection with a “second

generation” INSTI similar to DTG anchoring the DHHS preferred N(t)RTI backbone of emtricitabine and tenofovir, and especially a backbone of TAF/FTC.

2. The Combination of WO ’323 and WO ’351 with US ’079.

324. I incorporate my discussion of WO ’323 and WO ’351 herein.

325. US ’079 is an application filed by Defendant Cipla that, like WO ’323 and WO ’351, seeks to solve the need in the art for a single tablet that could be given once a day with a “second generation” INSTI anchoring the DHHS preferred N(t)RTI pair of emtricitabine and tenofovir.⁴⁷⁷ The additional disclosure of US ’079 also informs the POSA of available options for the precise amounts of additional ingredients to use when preparing such a tablet. It also discloses a preference for tablets due to their greater stability, smaller bulk, and ease of production.⁴⁷⁸ As discussed above in Section VIII.C, US ’079 also exemplifies a tablet containing 50 mg of “second generation” INSTI DTG as an anchor for the N(t)RTIs pair of TDF (300 mg) and FTC (200 mg) having a total API weight of 550 mg, a total uncoated weight of 1030 mg, and a coated weight of 1055 mg.⁴⁷⁹

326. In my opinion, the POSA would have been further motivated to combine US ’079 with both WO ’323 and WO ’351. This is because US ’079 also addresses the need in the art for a single tablet containing a “second generation” INSTI combined with the N(t)RTI pair of emtricitabine and tenofovir, and because it provides the POSA with additional guidance on the construction of single tablets, including the amounts of excipients contained those tablets.⁴⁸⁰ In essence, US ’079 independently confirms what Gilead stated in WO ’323: “[a]ctual methods of preparing such dosage forms [e.g., tablets] are known, or will be apparent, to those skilled in this

⁴⁷⁷ US ’079 at ¶ [0029] (DEFS_BIC_00002975 at 2977).

⁴⁷⁸ *Id.* at ¶¶ [0078]-[0079] (DEFS_BIC_00002980) (disclosing single, bilayered or multilayered tablets).

⁴⁷⁹ *Id.* at ¶ [0129] (DEFS_BIC_00002984-85) (Example 7).

⁴⁸⁰ *See* Section VIII.C, ¶¶ 233-39.

art,” “[a]ppropriate concentrations and dosages [of INSTIs] can be readily determined by one skilled in the art[,]” and a “therapeutically effective amount” of compounds for treating HIV infection “can be determined routinely by one of ordinary skill in the art.”⁴⁸¹

327. In my opinion, consistent with intent of the publications, a POSA would have been motivated to combine WO ’323, WO ’351, and US ’079 to address the need in the art for a single tablet regimen containing a “second generation” INSTI similar to DTG anchoring the N(t)RTI backbone of emtricitabine and tenofovir, and especially the TAF/FTC backbone.

3. Combining WO ’323 and WO ’351 Leaves Only Obvious Differences Between the Asserted Tablet Claims and the Prior Art

328. In my opinion, the combination of WO ’323 and WO ’351 places on the POSA’s work bench two publications that contain nearly all limitations of The Asserted Tablet Claims (as arranged in those claims).

329. With reference to my summaries of WO ’323 and WO ’351 in Sections VIII.F and VIII.H above, the combination of WO ’323 and WO ’351 discloses the claimed tablet containing a “second generation” INSTI compound (e.g., DTG or compound **42** (BIC)) in an amount of 50 mg including as a pharmaceutically acceptable salt thereof (e.g., DTG or BIC sodium), TAF in an amount of 25 mg including as a pharmaceutically acceptable salt thereof (e.g., TAF fumarate and hemifumarate), and FTC in an amount of 200 mg or a pharmaceutically acceptable salt thereof (FTC preferred in free base (non-salt) form).

330. WO ’323 also teaches therapeutically effective amounts of it INSTI compounds, including compound **42** (BIC), in a unitary dosage form in combination with therapeutically effective amounts of other HIV agents, which include TAF fumarate and FTC, and discloses pharmaceutically acceptable salts such as sodium salt. WO ’351 specifically discloses a

⁴⁸¹ WO ’323 (DEFS_BIC_00002214-474) at 16:8-14, 16:19-25, 35:16-17.

preference for the sodium salt of DTG, combined with a preference for TAF fumarate or hemifumarate and especially TAF hemifumarate, and FTC as free base and prefers tablets.

331. WO '323 and WO '351, considered together, therefore leave only obvious differences between the prior art and the claimed tablets. First, while the combination generally discloses the limitations of the Asserted Tablet Claims, it does not expressly recite a single tablet specifically containing 50 mg of compound **42** (BIC) (or 52 mg of its sodium salt) also containing 25 mg TAF (or its fumarate or hemifumarate salt, including 28 mg of TAF hemifumarate) and 200 mg of FTC (as free base). Second, though a POSA would have been drawn to lower doses in the range of “about 25 mg to 500 mg” based on compound **42**’s beneficial combination of properties (*supra*), the WO '323/WO '351 combination does not specifically disclose a 50 mg dose for compound **42** (BIC) (or 52 mg its sodium salt). Third, for some of the dependent claims, the combination does not specifically disclose a compound **42** (BIC) as a sodium salt (claims 5, 8), a tablet with a total weight or less than 1000 mg, less than 800 mg, or less than 730 mg (claims 9-11), or a tablet having the required amounts of active ingredients where compound **42** (BIC) is present in less than 15% or less than 11% by weight of the total tablet (claims 12-13).

332. As for the '846 Asserted Claims specifically, the WO '323/WO '351 combination also does not specifically disclose “multilayer tablets” (claim 1) or coated tablets (claim 8).

333. My claim-by-claim analysis of each of the Tablet Patents is provided below.

4. The '802 Patent

a) *'802 Patent, Claim 1*

334. Claim 1 of the '802 patent is drawn to a tablet comprising 50 mg BIC, 25 mg TAF, and 200 mg FTC, each of which may be present as a pharmaceutically acceptable salt.⁴⁸²

335. As explained in Sections VIII.F and VIII.H, each of these limitations is rendered obvious by the combination of WO '323 and WO '351, except that the combination does not specifically disclose a tablet with the claimed doses of each ingredient, or the specific selection of a pharmaceutically acceptable salt of BIC (e.g., its sodium salt).

336. WO '323 teaches pharmaceutical compositions containing a therapeutically effective amount “a compound of Formula (I)” which includes embodiments containing seven discrete amounts that include 50 mg.⁴⁸³ It also teaches compositions containing a therapeutically effective amount of a Formula (I) compound along with therapeutically effective amounts of one or more additional anti-HIV agents.⁴⁸⁴ Further, and perhaps most important to my analysis, WO '323 explicitly advises (and I agree) that “appropriate concentrations and dosages” of the compounds it discloses “can be readily determined by one skilled in the art[,]”⁴⁸⁵ and that a “therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to the own knowledge, the state of the art, and this disclosure.”⁴⁸⁶

337. WO '323 also provides results from a relatively detailed and progressive series of *in vitro* and *in vivo* experiments that the POSA would have understood to be pre-clinical experimentation that was well-known for determining the activity of the INSTI compounds under investigation. WO '323 confirms “[t]he activity of compounds of Formula (I) can be

⁴⁸² '802 patent (BICANDA01160880-928) at 77:23-78:4.

⁴⁸³ WO '323 (DEFS_BIC_00002214-474) at 35:22-23.

⁴⁸⁴ *Id.* at 37:7-13; 38:13-21.

⁴⁸⁵ *Id.* at 35:16-17.

⁴⁸⁶ *Id.* at 16:19-21.

determined by one skilled in the art, for example, as described in the Examples below,” and the POSA would have understood those examples to include the *in vitro* antiviral assay of Example 104.⁴⁸⁷

338. As explained above, WO '323 further discloses *in vivo* animal experiments that narrowed the disclosed INSTIs to only 5 compounds that progressed into oral dosing experiments.⁴⁸⁸ In my opinion (and in Dr. Winkler's opinion), a POSA would have selected compound **42** (BIC) from among these compounds as a prime candidate based on its expected longer half-life ($t_{1/2}$) and mean residence time (MRT) combined with its good oral bioavailability (F%) and promising C_{max} and AUC.⁴⁸⁹ That POSA would have also been motivated by the combination of WO '323 and WO '351 to select compound **42** (BIC) and include it into a single tablet in a therapeutically effective amount (that the POSA could routinely determine) combined with therapeutically effective amounts of TAF (25 mg in WO '351), and FTC (200 mg in WO '351).

339. A POSA would have appreciated that one important goal of INSTI development was to maintain once-a-day administration, and so would have preferred compounds to be both sufficiently bioavailable, and with a long enough half-life to support dosing once a day. Applying this criteria, the PK analysis from WO '323 also establishes to a POSA, in my opinion, that compound **42** would have been prime candidates for once-a-day administration in a tablet also containing TAF and FTC. Indeed, among those five compounds tested, compounds **2** and **42** provided the best PK properties for once daily dosing.

⁴⁸⁷ *Id.* at 35:14-16, 212:7-216:1.

⁴⁸⁸ *Id.* at 222-24 (including Table 4).

⁴⁸⁹ See Section VIII.H, ¶¶ 266-67; Winkler Report at Section X.C., ¶¶ 158-60.

340. Dr. Winkler also concludes that compound **42** bears a close structural similarity to the “second generation” INSTI DTG (disclosed in a composition comprising 50 mg, 25 mg TAF, and 200 mg FTC in WO ’351) such that a POSA would have expected compound **42** (BIC) to share similar physicochemical and biological properties with DTG, including an ability for once-a-day dosing without a pharmacokinetic booster, and a higher genetic barrier to resistance to provide the ability to maintain activity toward HIV integrase mutants resistant to RAL and EVG.⁴⁹⁰ As such, a POSA would have been motivated to use a therapeutically effective amount of compound **42** (BIC) in the WO ’351 composition containing 25 mg TAF and 200 mg FTC in the place of DTG.

341. Moreover, as I have explained in detail in Sections V.B and VIII.F, it is my opinion that the POSA would have recognized that the N(t)RTI pair of tenofovir and emtricitabine (as disclosed in WO ’351) was a preferred backbone for ART therapy in treating HIV infections. As such, a POSA would have been motivated to prepare a unit dose regimen similar to the DTG (50 mg)/TAF (25 mg)/FTC (200 mg) composition disclosed in WO ’351, where DTG is replaced by a therapeutically effective amount of compound **42** (BIC). WO ’351 also states a preference for single tablet compositions, and so a POSA would have been motivated to prepare this modified composition as a tablet.⁴⁹¹ Moreover, the POSA would have also known that TAF (as disclosed in both WO ’351 and WO ’323) was a clear improvement over TDF in terms of safety profile and that TAF had proven to be therapeutically effective at a significantly lower dose (e.g., 25 mg TAF vs 300 mg TDF), and would have therefore opted for TAF over TDF.

⁴⁹⁰ Winkler Report, Sections X.C.-D. at ¶¶ 163-67.

⁴⁹¹ WO ’351 at 19:30-20:2, 23:6-8 (BICANDA01155483 at 5502, 5503, 5506); *see also id.* at 5:22-27 (preference for DTG sodium), 13:16-18 (preference for TAF fumarate or hemifumarate), 8:10-11 (preference for FTC free base).

342. In sum, the combination of WO '323 and WO '351 would have motivated a POSA to prepare single tablets containing a therapeutically effective amount of INSTI compound **42** (BIC) and therapeutically effective amounts of TAF and FTC, i.e., 25 mg of TAF and 200 mg FTC as disclosed in WO '351. From there, as WO '323 advises (and I agree), a “therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to their own knowledge, the state of the art, and this disclosure,” meaning that therapeutically effective amounts of compound **42** (BIC) would have been determined by a POSA as a matter of routine experimentation, in view of the dose options disclosed in WO '323.⁴⁹²

343. As explained above, a POSA would have been drawn to lower doses in the range of “about 25 mg to 500 mg” disclosed in WO '323 based on compound **42**'s beneficial combination of properties compared to many other disclosed INSTI compounds. The low end of this range includes doses in the range of 25 mg to 100 mg, and WO '323 also specifically discloses doses of 25 mg, 50 mg and 100 mg. A POSA would have been drawn to even lower amounts in the “about 25 mg to 500 mg” range in children and low weight individuals (who require less drug to achieve similar drug concentrations in the blood), and in patients with a lower severity of HIV-1 infection (or no detectable infection at all) who would be treatable with lower drug concentrations as well.

344. Considering the advanced state of the art by November 9, 2015, the POSA, in my opinion, would have identified specific doses and therapeutically effective amounts for compound **42** (BIC) falling in the lower end of the “about 25 mg to 500 mg,” by employing routine dose ranging studies like those discussed in Section V.E. These effective doses would

⁴⁹² WO '323 at 16:19-21.

have been readily incorporated into a tablet in combination with the N(t)RTI pair of TAF (25 mg)/FTC (200 mg) as disclosed by WO '351 (as a preferred alternative to 50 mg of DTG). Because the POSA would have routinely determined appropriate doses from clinical dose ranging studies, it is my opinion that the claimed 50 mg is not significant, because a POSA would have arrived at that dose routinely when assessing dose levels that, e.g., provided suitable reductions in HIV RNA viral load. And again, lower doses also would expectedly be sufficient in children and low weight adults. Indeed, as explained above in Section V.E, multiple doses of the INSTI DTG were considered efficacious, including a dose five times smaller (10 mg) than the FDA approved dose of 50 mg, which (like the 50 mg dose) provided an HIV RNA count of <50 copies/mL in a large majority of patients at 96 weeks.

345. The same was true for Gilead's INSTI EVG, which was approved at a dose of 150 mg (when combined with COBI, TDF, and FTC) but was shown to effectively reduce viral load at lower doses, i.e., 50 mg and 125 mg.⁴⁹³ And Gilead had also entered clinical evaluation of its compound GS-9983 (75 mg) combined with TAF (25 mg) and FTC (200 mg) after conducting a routine dose ranging study in a Phase 1b trial where GS-9883 was administered at doses including 50 mg and 100 mg. Though a 75 mg dose of GS-9883 was apparently selected as the recommended Phase 2 dose, a POSA would have expected that the 50 mg dose would have also provided significant reductions in HIV RNA counts, just as had been shown for DTG and EVG. Indeed, there would be no basis to choose a 75 mg dose for Phase 2 studies if a 50 mg dose failed to reduce viral load in the Phase 1b study.

346. Moreover, compound 42 (BIC) provided similar anti-HIV activity, half-life ($t_{1/2}$), and oral bioavailability (F%) to DTG, as follows⁴⁹⁴:

⁴⁹³ See Section V.E. (citing Zolopa (DEFS_BIC_00006189-197) at DEFS_BIC_00006193).

⁴⁹⁴ See Winkler Report at Sections IX.D., X.C. ¶¶ 121-25 (properties of DTG), 154-59 (properties of compound 42).

	Compound 42 (BIC)	DTG
Anti-HIV activity	2.5 nM (IC ₅₀)	1.7 nM (EC ₅₀)
Half-Life (t _{1/2})	5.2 h	5.2-6.2 h
Oral Bioavailability (F%)	28%	25-35%

347. Given their substantial structural similarity and expectation of shared biological functions as discussed by Dr. Winkler,⁴⁹⁵ a POSA would have expected to learn from routine dose determination studies that an effective amount of compound **42** would be similar to that of DTG.

348. Finally, as had been repeatedly shown by multiple teams of ordinarily skilled artisans prior to November 9, 2015, the development of FDA-approved single tablets containing therapeutically effective amounts of three (and sometimes four) active ingredients to treat HIV-1 infection had been accomplished several times.⁴⁹⁶ This included the Genvoya[®] tablet, approved in September of 2015, employing a first generation INSTI (EVG) to anchor the improved N(t)RTI pair of TAF and FTC.⁴⁹⁷

349. On these bases, it is my opinion that the POSA would have been motivated to prepare the tablet ultimately recited in claim 1 and would have had a reasonable expectation of success in preparing it. Though not required, as explained in this section and above,⁴⁹⁸ that person would have also reasonably expected that such a tablet contained amounts of BIC, TAF, and FTC effective to reduce HIV-1 viral load in a patient. At the very least, the tablet of claim 1

⁴⁹⁵ *Id.*

⁴⁹⁶ See Sections V.B-V.D., *supra* (summarizing multiple FDA approved single regimen tablets with multiple APIs to treat HIV infection).

⁴⁹⁷ Genvoya Assessment (DEFS_BIC_00001811-969) at DEFS_BIC_00001826.

⁴⁹⁸ See *supra* Section VIII.H (summarizing routine dose determination and dose determination from WO '323) and V.E, ¶¶ 121-22 (appropriate dosages and therapeutically effective amounts can be routinely determined by a POSA).

would have expectedly been effective to alleviate or eliminate symptoms of an HIV infection, including reduction of HIV viral load in an infected patient, as contemplated by the term “treatment” in both WO ’323 and the Tablet Patents.⁴⁹⁹

350. In my professional opinion, from the standpoint of a POSA and in view of the legal principles of obviousness above, claim 1 would have been obvious over the combination of WO ’323 and WO ’351 as informed by common knowledge and well-known accumulated knowledge of the use of single tablet regimens to treat HIV-1 infection, as discussed in Section V of my report, all well-known and widely available prior to November 9, 2015.

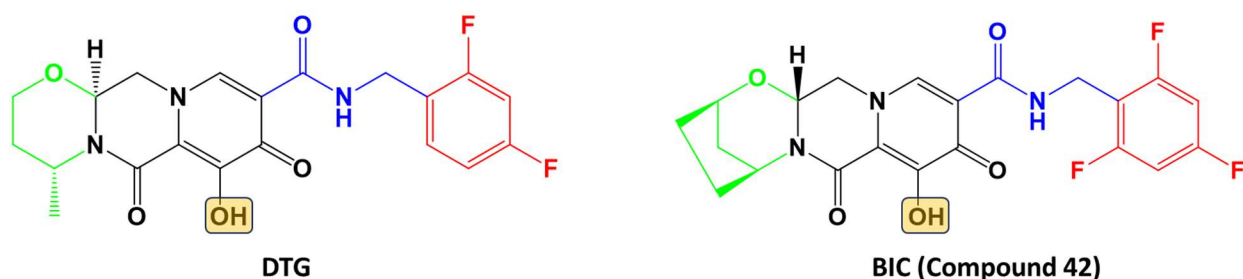
b) Claims 2-8 of the ’802 patent

351. Claims 2-4 are similar in scope to claim 1, except that they call for pharmaceutically acceptable salts BIC and/or TAF, and FTC in its free base form. This is done by narrowing the Formula (I) compound (BIC) in **1[a]** to a pharmaceutically acceptable salt thereof (claims 2, 4); narrowing TAF in **1[b]** to a pharmaceutically acceptable salt thereof (claims 3, 4), and FTC in **1[c]** to its free base (claim 4). Claim 5 also depends from claim 1 and requires 52 mg of the Formula (I) compound (BIC) as BIC sodium (equivalent to 50 mg BIC), whereas claims 6-8 require TAF as TAF fumarate (claim 6) or TAF hemifumarate (claim 7). Claim 8 then calls for 52 mg of BIC sodium (equivalent to 50 mg BIC), 28 mg of TAF hemifumarate (equivalent to 52 mg BIC), and 200 mg FTC (as free base).

352. Dr. Winkler has conducted an analysis that focuses, from the perspective of an ordinarily skilled medicinal chemist, on what that person would have understood concerning the selection of a pharmaceutically acceptable salt of the INSTI compounds disclosed in WO

⁴⁹⁹ See WO ’323 (DEFS_BIC_00002214-474) at 16:22-32; ’802 Patent (BICANDA01160880-928) at 57:32-52; ’846 Patent (BICANDA00000031-77) at 57:15-25.

'323.⁵⁰⁰ In particular, Dr. Winkler points to pharmaceutically acceptable salts in WO '323, including “salts derived from an appropriate base, such as an alkali metal (for example, sodium)[,]” and notes that the structurally similar INSTI DTG was preferred as a sodium salt in WO '351, that was being used in both Tivicay[®] and Triumeq[®].⁵⁰¹ Dr. Winkler notes that compound **42** and DTG share an identical metal chelation binding group (black below) that contains the same acidic hydroxy group (yellow below), which was the only reasonable functionality for salt formation.⁵⁰² I have reproduced below an illustration from Dr. Winkler's report to summarize his analysis and opinion in this regard.⁵⁰³



353. Dr. Winkler further opines that an ordinarily skilled medicinal chemist would have expected that compound **42** (BIC) would form a sodium salt (using NaOH as base) in the same way as DTG, based on their expectedly similar low acidity (both are weak acids) and similar pKa.⁵⁰⁴ He then concludes that a “POSA would have been specifically motivated to prepare a pharmaceutically acceptable salt of compound **42** (BIC) with sodium hydroxide (NaOH) to provide BIC sodium, and would have expected that it would be stable for the same reasons as the DTG sodium salt used in Tivicay[®].” Dr. Winkler further opines that, “[b]ased on the high degree of structural similarity with DTG, and the improved solubility property of DTG

⁵⁰⁰ See generally Winkler Report, Sections X.B., D.

⁵⁰¹ *Id.* at Section X.D., ¶¶ 161-62.

⁵⁰² *Id.* at ¶ 163.

⁵⁰³ *Id.*

⁵⁰⁴ *Id.* at ¶ 165.

sodium relative to the corresponding free acid, a POSA would have also expected for BIC sodium to be more soluble in an aqueous environment than BIC free acid, and thus a more suitable choice for oral administration.”⁵⁰⁵

354. After consideration of Dr. Winkler’s analysis and opinions on the specific selection of sodium for preparing a salt of compound **42** (BIC) I accept his expertise and adopt his conclusions, just as a POSA would have done. I have also considered Dr. Winkler’s analysis and opinion that “a POSA would have selected FTC free base and TAF fumarate and hemifumarate first and foremost over salts of FTC and TAF free base and other salt forms of TAF.” I adopt his conclusions on these points for the same reasons.

355. Additionally, from the perspective of clinical practice in the relevant time frame, (as I explain in Section V), among the FDA approved compounds, the “second generation” INST DTG was (in my experience) a preferred INSTI, as it was available for dosing once-a-day, without needing a booster.⁵⁰⁶ DTG was frequently used as a single 50 mg tablet, in combination with the N(t)RTI pair of tenofovir and emtricitabine.⁵⁰⁷ The single tablet containing a 50 mg dose of DTG was recognized to be effective as established during a dose-ranging clinical study, and was marketed as a sodium salt.⁵⁰⁸

356. Regarding pharmaceutically acceptable salts of TAF in claims 3-4 and the specific salts TAF fumarate and TAF hemifumarate in claims 6-8, these were also disclosed in WO ’351 as particularly preferred options to combine with the structurally similar INSTI DTG in a single tablet regimen.⁵⁰⁹ WO ’323 also identifies TAF fumarate as a salt of TAF that is

⁵⁰⁵ *Id.* at ¶ 167.

⁵⁰⁶ Tivicay Label (DEFS_BIC_00000659-95).

⁵⁰⁷ *See* Section V.E, ¶¶ 125-30.

⁵⁰⁸ Tivicay Label (DEFS_BIC_00000659-95) at DEFS_BIC_00000672.

⁵⁰⁹ WO ’351 at 13:16-18, 19:30-20:6 (BICANDA01155496, BICANDA01155502, BICANDA01155503) (Single Tablet with 50 mg DTG, 25 mg TAF, 200 mg FTC).

suitable for use in the combinations disclosed and claimed in the reference.⁵¹⁰ Moreover, Gilead's combination product Genvoya[®] was approved on November 5, 2015, employing the hemifumarate salt of TAF.⁵¹¹

357. Accepting Dr. Winkler's conclusions, it is my opinion based on the above analysis that a POSA would have specifically selected BIC sodium (as covered by claims 2, 4, 5 and 8), TAF fumarate or hemifumarate, and especially TAF hemifumarate (as covered by claims 6, 7, 8) and FTC free base (as covered by claims 5 and 8), and prepared a tablet comprising therapeutically effective amounts of these compounds, e.g., 52 mg BIC sodium (equivalent to 50 mg BIC), 28 mg of TAF hemifumarate (equivalent to 25 mg TAF as disclosed in WO '351), and 200 mg FTC (as also disclosed in WO '351).

358. A POSA therefore, in my opinion, would have been motivated to arrive at the tablets of claims 2-8 with a reasonable expectation that such tablets could be made. Though not required, as explained above, that person would have also expected that such tablets would contain amounts of BIC sodium, TAF fumarate or hemifumarate, and FTC free base that were effective to reduce HIV-1 viral load in a patient, or at the very least expectedly been effective to prevent or reduce the risk of developing HIV-1 infection in patients exposed to the HIV virus.

359. In my professional opinion, from the standpoint of a POSA and in view of the legal principles of obviousness discussed herein, claims 2-8 would have been obvious over the combination of WO '323 and WO '351 as informed by common knowledge and well-known technical principles discussed in Section V available prior to November 9, 2015.

⁵¹⁰ WO '323 (DEFS_BIC_00002214-474) at 38:19-20.

⁵¹¹ Gilead November 2015 Press Release (DEFS_BIC_00006174-80) at DEFS_BIC_00006174.

c) Claims 9-11 of the '802 Patent

360. Claims 9-11 depend from claim 1 and respectively call for a total tablet weight of less than 1000 mg, less than 800 mg, and less than 730 mg. All three APIs must be present in the amounts recited in claim 1, and the tablet must be (depending on the claim) less than a specified total weight.

361. WO '351 describes single tablet compositions where the total amount of DTG, TAF, and FTC are preferably in the range of 192-326 mg per day.⁵¹² The same publication discloses a preferred design with 50 mg DTG, 25 mg TAF, and 200 mg FTC, which would have a total active ingredient weight of 275 mg. WO '351 also includes a description⁵¹³ of “suitable pharmaceutical excipients,” organized into six categories, as follows:

Examples of suitable pharmaceutical excipients are glidants (d), fillers (e),
30 disintegrants (f), binders (g), lubricants (h) and surfactants (j).

362. The total weight of each of these excipient categories, as described by WO '351, will vary within stated “preferable,” “more preferable,” and “in particular” ranges for each category.⁵¹⁴ Each of the ranges disclosed were provided as a percentage of the total weight of the composition.⁵¹⁵

363. I have prepared the following chart that summarizes the amounts of the most preferred (i.e., “in particular”) ranges for each excipient category, along with the expected total weight for a composition containing 275 mg of total active ingredients (i.e., 50 mg DTG, 25 mg TAF, and 200 mg FTC) at each end point of these ranges as well as a midpoint for each range:

⁵¹² WO '351 at 17:17-18, 19:5-12 (BICANDA01155500, BICANDA01155502).

⁵¹³ *Id.* at 20:29-30.

⁵¹⁴ *Id.* at 20:29-22:25.

⁵¹⁵ *Id.*

	Range (wt %)	High (wt %)	Mid (wt %)	Low (wt %)
Glidants	0.2 - 1.5	1.5	0.9	0.2
Fillers	10 - 15	15	12.5	10
Disintegrants	3-6	6	4.5	3
Binders	2.5 - 4.5	4.5	3.5	2.5
Lubricants	0.2 - 2	2.0	1.1	0.2
Surfactants	1-3	3.0	2.0	1.0
Total Excipients	~17 – ~32	~32	~25	~17
Total Actives (based on 275 mg)	~68 - ~83	~68	~75	~83
Total Tablet Weight (with 275 mg total active pharmaceutical ingredient)	~330 mg – ~410 mg	~410 mg	~370 mg	~330 mg

364. As shown above, the low end of the preferred “in particular” set of ranges produces a total weight percent of excipients of ~17% and the high end of this set of ranges produces a total weight percent of excipients of ~32%, based on the total weight of the composition.⁵¹⁶ The 275 mg total weight of active ingredients makes up the rest of the total weight of these compositions: ~83 weight percent of total actives for the lower end of the excipient ranges and ~68% weight percent of total actives for the high end of the excipient ranges, based on the total weight of the composition. Accordingly, based on 275 mg of actives (i.e., 50 mg DTG, 25 mg TAF, and 200 mg FTC), the high end of the “in particular” excipient ranges disclosed by WO ’351 produces a composition with a total weight of ~410 mg and the low end of these ranges produces a composition with a total weight of ~330 mg.

⁵¹⁶ *Id.*

365. Choosing excipient weight percents falling in the middle of these excipient ranges produces a composition with a total weight of ~370 mg. In my experience, the smaller a tablet is, the easier it is for a patient to swallow. And, in my opinion, the POSA would understand that in the art of HIV therapy, smaller tablets could greatly improve patient adherence to therapy.⁵¹⁷ Further, as Gilead admits in WO '323, “[a]ctual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art,” and such tablets would be “prepared by methodologies well known in the pharmaceutical art.”⁵¹⁸

366. In my opinion, a POSA working from a tablet of WO '351 containing 50 mg of INSTI DTG, 25 mg of TAF, and 200 mg FTC as a starting point, would understand that they would be able to include up to ~725 mg (total weight) of excipients and still have a tablet with a total weight less than 1000 mg (claim 9).

367. Given the large amounts of available excipients relative to the 275 mg total API weight, a POSA (in my opinion) would have been motivated to make the tablets as small as possible - for improved convenience, safety, and patient adherence. As I have explained, in that time frame, the DHHS Guidelines cautioned that successful treatment of HIV infection requires consideration of many factors, including “patient tolerance of pill number, size and frequency.”⁵¹⁹ Accordingly, it is my opinion that the POSA would have arrived at tablets containing 50 mg of compound **42** (BIC), 25 mg TAF, and 200 mg FTC (as already discussed

⁵¹⁷ DHHS Guidelines (DEFS_BIC_00001000-287) at DEFS_BIC_00001188 (discussing interventions to improve adherence to ARV treatments, including assessing tablet size); *see also* Center for Drug Evaluation and Research (CDER) Guidance for Industry, Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules (June 2015) (“June 2015 CDER Guidance”) (BICANDA00537522-31) at BICANDA00537527 (“Studies in adults evaluating the effect of tablet and capsule size on ease of swallowing suggest that increases in size are associated with increases in patient complaints related to swallowing difficulties and tablet sizes greater than approximately 8 mm in diameter.”)

⁵¹⁸ WO '323 (DEFS_BIC_00002214-474) at 36:15-21.

⁵¹⁹ DHHS Guidelines (DEFS_BIC_00001000-287) at DEFS_BIC_00001187-88 (discussing interventions to improve adherence to ARV treatments).

above for claim 1), with a sufficient amount of excipients (up to ~465 mg as for the similar tablet in WO '351 containing 50 mg DTG, 25 mg TAF, and 200 mg FTC) to provide a tablet weighing less than 730 mg (claim 11), which is less than 800 mg (claim 10).

368. That POSA would have reasonably expected success in preparing such tablets using common excipients and routine techniques in the art. Again, though not required, that person would have also expected that such tablets contained amounts of compound **42** (BIC) or a sodium salt thereof, TAF (or a fumarate or hemifumarate salt thereof), and FTC (as a free base) would be effective to reduce viral load in a patient, or at the very least expectedly been effective to prevent or reduce the risk of developing HIV-1 infection in patients exposed to the HIV virus.

369. In my professional opinion, on the basis I have explained herein, from the standpoint of a POSA and in view of the legal principles of obviousness discussed herein, claim 9 would have been obvious over the combination of WO '323 and WO '351 as informed by common knowledge and well-known technical principles discussed in Section V all available prior to November 9, 2015.

d) Claims 12-13 of the '802 Patent

370. Claims 12-13 depend from claim 1, and limit the claimed tablet to one containing less than 15% and less than 11% respectively of Formula (I) (BIC) or a pharmaceutically acceptable salt thereof.

371. As discussed for claim 9, a POSA would have expected success in making a tablet containing 50 mg compound **42** (BIC), 25 mg TAF, and 200 mg of FTC having a total weight of less than 730 mg (e.g., 725 mg, 650 mg, 600 mg). Each of these tablets would have contained less than 15% and less than 11% of compound **42** (BIC) or a pharmaceutically salt thereof, so long as the total weight of the tablet was greater than 375 mg and 450 mg, respectively. Indeed,

even tablets with a total weight of 1000 mg or greater would have met these limitations, i.e., 50 mg BIC is 5% of a tablet weighing 1000 mg and 2.5% by weight of a tablet weighing 2000 mg.

372. On these bases and those provided above for claim 1, is it my opinion that the POSA would have been motivated to arrive at the tablet of claims 12-13 with reasonable expectation of success in preparing such a tablet. Though not required, as explained above, that person would have also expected that such a tablet contained amounts of compound **42** (BIC), TAF, and FTC effective to reduce HIV-1 viral load in a patient, or at the very least expectedly been effective to prevent or reduce the risk of developing HIV-1 infection in patients exposed to the HIV virus.

373. In my professional opinion, from the standpoint of a POSA and in view of the legal principles of obviousness discussed herein, claims 12-13 would have been obvious over the combination of WO '323 and WO '351 as informed by common knowledge and well-known technical principles discussed in Section V available prior to November 9, 2015.

e) Adding '079 to the Combination of WO '323 and WO '351 renders Tablet Size as the Only Difference

374. My obviousness analysis based on the combination of WO '323 and WO '351 above is incorporated into this section.

375. As explained above, in my opinion, the POSA would also alternatively be motivated to combine US '079 with WO '323 and WO '351, as this publication similarly discloses single tablet containing a “second generation” INSTI anchoring the preferred N(t)RTI backbone of tenofovir and emtricitabine and adds a specific tablet formulation containing these ingredients (complete with excipients) to the workbench of the POSA prior to November 9, 2015.

376. As discussed in Section VIII.C., US '079 is an application filed by Cipla that, like WO '323 and WO '351, relates to single dosage units with multiple antiretroviral compounds, used to treat HIV infection with a “second generation” INSTI anchoring at least one other antiretroviral or anti-HIV agent.⁵²⁰ US '079 discloses a preference for tablets due to their greater stability, smaller bulk, and ease of production.⁵²¹ It also exemplifies a tablet containing 50 mg DTG as an anchor for the N(t)RTIs TDF (300 mg) and FTC (200 mg) having a total API weight of 550 mg, a total uncoated weight of 1030 mg, and a coated weight of 1055 mg.⁵²²

377. As discussed in Sections XI.A.4.a-d., it is my opinion (adopting the opinions of Dr. Winkler) that the combination of WO '323 and 'WO 351 alone would have provided the POSA with sufficient information to arrive at the tablets of claims 1-13 of the '802 patent with a reasonable expectation of success – a tablet having 50 mg BIC, 25 mg TAF, and 200 mg FTC, including the tablets further limited by each of claims 2-13.

378. For each of the obvious tablet claims from the '802 patent, the three APIs would have a combined weight on 275 mg, which is 275 mg less than the APIs are included in the “Dry Mix” of excipients provided in Example 7 of US '079

379. The total weight of these uncoated tablets modified to replace 300 mg TDF with 25 mg TAF (without modifying any remaining excipients) would be 780 mg (Example 7). In my opinion, the POSA would have understood that excipient amounts could also be reduced to correspond with the 50% decrease in weight of the APIs. As I mentioned above, it is my opinion that the POSA would want to make the smallest tablet possible, in order to maximize patient compliance. In my opinion, this would have produced, with a reasonable likelihood of success, a

⁵²⁰ US '079 at ¶ [0129] (DEFS_BIC_00002984-85).

⁵²¹ *Id.* at DEFS_BIC_00002980, ¶¶ [0078]-[0079] (disclosing single, bilayered or multilayered tablets).

⁵²² *Id.* at DEFS_BIC_00002984-85, ¶ [0129] (Example 7).

tablet with all three APIs, that weighed less than 730 mg (modified tablet of Example 7 = 556 mg).

380. If an acceptable tablet with a total coated weight of 1055 mg had been successfully made when containing twice as much API (as in tablet Example 7), a POSA would have reasonably expected to succeed in making a tablet with 275 mg of total active ingredients that (even when coated) would have weighed less than 730 mg as well.

381. As such, a POSA motivated to arrive at a tablet containing 50 mg compound **42** (BIC), 25 mg TAF, and 200 mg FTC (275 mg active ingredients) with a reasonable expectation of success (as addressed in claim 1 of the '802 patent) would have been further motivated to prepare that tablet in the smallest size (and weight possible) possible, in order to maximize patient compliance.

382. For the same reasons, a POSA preparing a tablet, like those exemplified in US '079 (modified to replace 50 mg DTG with a therapeutically effective amount of compound **42** (BIC) and 300 mg TDF with 25 mg of TAF) would have reasonably expected to succeed in making the tablet of claim 1 of the '802 patent (whether coated or uncoated) that would weigh less than 730 mg. And as explained above, that tablet would have contained less than 15% and less than 11% of compound **42** (BIC) based on total tablet weight, as required by claims 12-13 of the '802 patent, and claims 6-7 of the '846 patent.

383. In my professional opinion, from the standpoint of a POSA and in view of the legal principles of obviousness discussed herein, each of Claims 1-13 of the '802 patent, would have been obvious in view of the combination of WO '323, WO '351, and US '079 as informed by common knowledge and well-known technical principles discussed in Section V available prior to November 9, 2015.

f) The Combination of WO '323 and WO '351 with Bowker and Paulekuhn Bolsters a POSA's Motivation to Select BIC Sodium with a Reasonable Expectation of Success.

384. Again, I have reviewed and considered Dr. Winkler's analysis and opinions on the specific selection of compound **42** as a sodium salt (BIC sodium).⁵²³ Part of Dr Winkler's analysis and opinion in this regard relies on additional disclosures from Bowker⁵²⁴ and Paulekuhn.^{525, 526} I understand that Dr. Winkler includes these disclosures to provide additional bases for concluding that compound **42** (BIC) as a sodium salt was a clearly preferred selection over compound **42** (BIC) free acid and other pharmaceutically acceptable salts disclosed in WO '323.⁵²⁷ This is because, according to Dr. Winkler, an ordinarily skilled medicinal chemist would have known from Paulekuhn that "sodium was far and above the most common cation to use with acidic drugs, including weakly acidic drugs like DTG and BIC," and that POSA would have known from Bowker that the preparation of compound **42** (BIC) sodium salt (from NaOH) would provide a pKa difference (i.e., ≥ 3 units) necessary to form a stable (i.e., irreversible) salt.⁵²⁸

385. As stated by Dr. Winkler, "[a POSA] would have expected success making BIC sodium given the structural similarities between BIC and DTG, the preference for DTG sodium in WO '351, and the expected >3 pKa difference between BIC and sodium hydroxide that would have expectedly provided the formation of an irreversible (and stable) salt."⁵²⁹

⁵²³ Winkler Report, Section X.D.

⁵²⁴ Michael J. Bowker, "A Procedure for Salt Selection and Optimization" in HANDBOOK OF PHARMACEUTICAL SALTS: PROPERTIES, SELECTION, AND USE 161-89 (P. Heinrich Stahl & Camille G. Wermuth eds., 2002) ("Bowker") (DEFS_BIC_00000807-37).

⁵²⁵ Paulekuhn et al., "Trends in Active Pharmaceutical Ingredient Salt Selection Based on Analysis of the Orange Book Database," 50 J. MED. CHEM. 6665-72 (2007) ("Paulekuhn") (DEFS_BIC_00000266-73).

⁵²⁶ Winkler Report, Section X.D. at ¶¶ 168-69.

⁵²⁷ *Id.* at ¶¶ 168-73.

⁵²⁸ *Id.* at ¶ 168.

⁵²⁹ *Id.* at ¶ 172.

386. After consideration of Dr. Winkler’s analysis and opinions in view of Bowker and Paulekuhn, I accept his expertise and adopt his conclusions, just as a POSA would have done. Adopting Dr. Winkler’s conclusions, in my professional opinion, from the standpoint of a POSA and in view of the legal principles of obviousness discussed herein, each of Claims 1-13 of the ’802 patent would have been obvious in view of the combination of WO ’323, WO ’351, Bowker, and Paulekuhn, as informed by common knowledge and well-known technical principles discussed in Section V available prior to November 9, 2015.

5. The ’846 Patent

387. As for the construction of the “multilayer” term, I understand the Court has construed this term to mean: “a tablet with two or more layers, in which at least one of the claimed components is in a separate layer, wherein a layer is a section or compartment of components.” I have also applied this definition in my analysis herein.

a) *The Combination of WO ’323, WO ’351, and US ’079*

388. My obviousness analysis based on the combination of WO ’323, WO ’351, and US ’079 above (pertaining to the ’802 patent) is incorporated into this section.

389. As explained above, in my opinion, the POSA would be motivated to combine US ’079 with WO ’323 and WO ’351, because US ’079 discloses single tablets containing a “second generation” INSTI anchoring the preferred N(t)RTI backbone of tenofovir and emtricitabine and adds a specific tablet formulation examples containing these ingredients (complete with excipients) to the workbench of the POSA prior to November 9, 2015. Importantly, as it pertains to the ’846 patent, US ’079 also exemplifies a multilayer tablet with 50 mg DTG as an anchor for

the N(t)RTIs TDF (300 mg) and FTC (200 mg) prepared as a bilayer tablet, where DTG is provided in one layer and TDF/FTC are provided in another layer.⁵³⁰

390. It is therefore also my opinion that the combination of WO '323, 'WO 351, and US '079, would have provided the POSA with sufficient information to arrive at the tablets of claim 1 of the '846 patents with a reasonable expectation of success – a multilayer tablet having 50 mg BIC, 25 mg TAF, and 200 mg FTC, including the multilayer tablets further limited by each of claims 2-8.

391. For each of the obvious multilayer tablet claims from the '846 patent, the three APIs would have a combined weight on 275 mg, which is 275 mg less than the APIs are included in the “Dry Mix” of excipients provided in the bilayer tablet provided in Example 1 of US '079. The total weight of this uncoated tablet, modified to replace 300 mg TDF with 25 mg TAF (without modifying any remaining excipients) would be 838 mg (Example 1). In my opinion, the POSA, especially in consultation with a formulation scientist on the team, would have understood that excipient amounts could also be reduced to correspond with the 50% decrease in weight of the APIs.

392. As I mentioned above (in my analysis of the '802 patent), it is my opinion that the POSA would want to make the smallest tablet possible, in order to maximize patient compliance. In my opinion, this would have produced, with a reasonable likelihood of success, a bilayer tablet with all three APIs, that weighed less than 730 mg (modified multilayer tablet of Example 1 = 556 mg). After all, if an acceptable bilayer tablet with a total coated weight of 1140 mg had been successfully made when containing twice as much API (as in US '079 bilayer tablet

⁵³⁰ US '079 at DEFS_BIC_00002982, ¶ [0117] (Example 1).

Example 1), a POSA would have reasonably expected to succeed in making a tablet with 275 mg of total active ingredients that (even when coated) would have weighed less than 730 mg as well.

393. As such, a POSA motivated to arrive at a bilayer tablet containing 50 mg BIC, 25 mg TAF, and 200 mg FTC (275 mg active ingredients), would have been further motivated to prepare that tablet in the smallest size (and weight possible) possible, in order to maximize patient compliance.⁵³¹ For the same reasons, a POSA preparing a bilayer tablet, like those exemplified in US '079 (modified to replace 50 mg DTG with a therapeutically effective amount of compound **42** (BIC) and 300 mg TDF with 25 mg of TAF) would have reasonably expected to succeed in making the tablet of claim 1 of the '846 patent (whether coated or uncoated) that would weigh less than 730 mg. And as explained above, that tablet would have contained less than 15% and less than 11% of compound **42** (BIC) based on total tablet weight, as required by claims 6-7 of the '846 patent.

394. In my professional opinion, from the standpoint of a POSA and in view of the legal principles of obviousness discussed herein, each of Claims 1-8 of the '846 patent would have been obvious in view of the combination of WO '323, WO '351, and US '079 as informed by common knowledge and well-known technical principles discussed in Section V available prior to November 9, 2015.

b) Claim 1 of the '846 Patent

395. Claim 1 of the '846 patent is drawn to a “multilayer tablet” comprising 50 mg BIC, 25 mg TAF, and 200 mg FTC, each of which may be present as a pharmaceutically acceptable salt.⁵³² I understand that the Court has construed “multilayer” to mean “a tablet with

⁵³¹ See DHHS Guidelines at DEFS_BIC_00001187-88 (discussing interventions to improve adherence to ARV treatments that include choosing smaller pill sizes).

⁵³² '846 patent (BICANDA00000031-77) at 76:33-53.

two or more layers, in which at least one of the claimed components is in a separate layer, wherein a layer is a section or compartment of components.” I have applied this definition in my analysis of this patent.

396. Claim 1 is further limited by the total weight of the tablet, which is “less than about 1000 mg.”

397. For the limitations of claim 1 that are identical to those appearing in the ’802 patent claims, I incorporate my analysis and opinions on those limitations as discussed in Section XI, including Section XI.A.4 specifically.

(1) The API Amounts

398. As explained in Section XI, each of the limitations of Claim 1 are disclosed by the combination of WO ’323, WO ’351, and US ’079, except that the combination does not specifically disclose a tablet with the quantity of each of the different active ingredients (dose amounts) of each ingredient, and does not disclose the specific selection of a pharmaceutically acceptable salt of BIC (e.g., its sodium salt). I have already addressed why the 50 mg BIC, 25 mg TAF, and 200 mg FTC amounts would have been obvious in my analysis of claim 1 of the ’802 patent, and my basis for concluding that the POSA would have selected the sodium salt of BIC. *See* Section XI.A.4. For the sake of brevity, my analysis and opinions from Section XI.A.4. is incorporated herein.

399. In view of the analysis presented in that section, it is my opinion for the perspective of a POSA that the same active ingredients and amounts of those ingredients, as recited by claim 1 of the ’846 are obvious for the same reasons.

(2) Tablet Size claimed in ’846 Patent, Claim 1

400. As mentioned, claim 1 of the ’846 patent is also claimed as a tablet that “has a total weight of less than about 1000 mg.”

401. For the limitations of claim 1, I incorporate my analysis and opinions on the same limitation as discussed for claim 9 of the '802 patent. *See* Section XI.A.4.c. In view of the analysis presented in Section XI.A.4.c., it is my opinion for the perspective of a POSA that the same a total tablet weight of less than about 1000 mg provided by claim 1 of the '846 is obvious for the same reasons.

(3) Multilayer Tablet claimed in '846 Patent, Claim 1

402. It is also my opinion that the POSA would have been motivated to prepare a multilayer tablet containing the same amounts BIC, TAF, and FTC as were the subject of my opinions concerning the '802 patent, in a multilayer configuration, and could have done so with a reasonable expectation of success.

403. Indeed, as I have explained in this report, prior to November 9, 2015, several multilayer tablets with two, three, and even more active ingredients had been approved by regulatory authorities around the globe for the effective treatment of HIV.⁵³³ As I have stated in this report, Atripla[®], Eviplera[®], and Stribild[®] are all multilayer (and film coated) coated tablets.⁵³⁴ In each of these approved tablets, the FTC and the tenofovir component are contained in one layer, which were the components of the well-established backbone of the regimen for treatment of HIV-1 infection. Further, the anchor drug in each of the single tablet regimens was also placed into a separate layer from that backbone, and it would have been obvious for the POSA to separate BIC sodium (the anchor drug in the regimen) from the FTC/TAF backbone as well. As such, it is my opinion that a POSA would have been motivated to prepare multilayer tablets as they are defined by claim 1 '846 patent with a reasonable expectation of success,

⁵³³ *See* Section V.A.

⁵³⁴ Atripla Assessment (DEFS_BIC_00001547-94) at 1-2 DEFS_BIC_00001547-48; Eviplera Assessment at 18 ((DEFS_BIC_00001666); Stribild Assessment (DEFS_BIC_00001336-482) at 33 (DEFS_BIC_00001368).

where at least one of the active ingredients is segregated in its own layer – just as it had been done repeatedly before November 15, 2015 in these approved tablets.

404. In my professional opinion, for the further reasons I explain herein, accepting the opinions of Dr. Winkler as discussed above for the '802 patent, that claim 1 of the '846 patent would have been obvious over the combination of WO '323, WO '351 and US '079, as informed by the accumulated common knowledge of the POSA as explained in Section V of this report by November 9, 2015.

405. I further understand that Dr. Muzzio, an expert in the area of formulation science has offered his opinions, concluding that the “multilayer,” coating, and tablet weight limitations of the claims of the '846 and '802 patents that I analyze in this report would have been obvious to the POSA as well. I assume this conclusion to be accurate for the purposes of my analysis as well.

406. In my professional opinion, for the reasons stated herein, that claim 1 of the '846 patent would have been obvious over the combination of WO '323, WO '351 and US '079, as informed by the accumulated common knowledge of the POSA as explained in Section V of this report by November 9, 2015.

c) Claims 2-3 of the '846 patent

407. Claims 2-3 are similar in scope to claim 1, except that they call for pharmaceutically acceptable salts BIC and/or TAF, and FTC in its free base form. Claim 2 narrows the Formula (I) compound (BIC) in **1[a]** to a pharmaceutically acceptable salt thereof and narrowing TAF in **1[b]** to a pharmaceutically acceptable salt thereof. Claim 3 then further narrows the salts of Formula (I) (BIC) to 52 mg of the sodium salt (equivalent to 50 mg BIC), and the salt of TAF to 28 mg of the hemifumarate salt (equivalent to 25 mg of TAF).

408. For claims 2-3 of the '846 patent, I incorporate my analysis and opinions on the same limitations as discussed for claims 2-8 of the '802 patent. *See* Section XI.A.4.b. In view of the analysis presented in Section XI.A.4.b., it is my opinion for the perspective of a POSA that the pharmaceutically acceptable salts BIC (including 52 mg of BIC sodium) and TAF (including 28 mg of TAF hemifumarate), and FTC in its free base form provided in claims 2-3 of the '846 patent are obvious for the same reasons.

409. A POSA, in my opinion, would have been motivated to arrive at the tablets of claims 2-3 with a reasonable expectation that such tablets could be made. Though not required, as explained above, that person would have also expected that such tablets would contain amounts of BIC sodium, TAF fumarate or hemifumarate, and FTC free base that were effective to reduce HIV-1 viral load in a patient, or at the very least expectedly been effective to prevent or reduce the risk of developing HIV-1 infection in patients exposed to the HIV virus.

410. In my professional opinion (adopting the opinions of Dr. Winkler discussed above for the '802 patent and with the assumption that Dr. Muzzio's conclusions concerning the multilayer aspect of the claim to be accurate and accepted), from the standpoint of a POSA and in view of the legal principles of obviousness discussed herein, claims 2-3 would have been obvious over the combination of WO '323, WO '351, and US '079, as informed by common knowledge and well-known technical principles discussed in Section V available prior to November 9, 2015.

d) Claims 4-5 of the '846 Patent

411. Claims 4-5 depend from claim 1 and respectively call for a total tablet weight of less than less than 800 mg, and less than 730 mg. All three APIs must be present in the multilayer tablet in the amounts recited in claim 1.

412. For claims 4-5 of the '846 patent, I incorporate my analysis and opinions on the same limitations as discussed for claims 10-11 of the '802 patent. *See* Section XI.A.4.c. In view of the analysis presented in Section XI.A.4.c., it is my opinion for the perspective of a POSA that the total tablet weights provided in claims 4-5 of the '846 patent are obvious for the same reasons.

413. In my professional opinion (adopting the opinions of Dr. Winkler discussed above for the '802 patent and with the assumption that Dr. Muzzio's conclusions concerning the multilayer aspect of the claim to be accurate and accepted) from the standpoint of a POSA and in view of the legal principles of obviousness discussed herein, claims 4-5 would have been obvious over the combination of WO '323, WO '351 and US '079 as informed by common knowledge and well-known technical principles discussed in Section V available prior to November 9, 2015.

e) Claims 6-7 of the '846 Patent

414. Claims 6-7 depend from claims 1 or 2, and respectively limit the claimed tablet to one containing less than 15% (claim 6) and less than 11% (claim 7) of Formula (I) (BIC) or a pharmaceutically acceptable salt thereof (claims 6 and 7).

415. For claims 6-7 of the '846 patent, I incorporate my analysis and opinions on the same limitations as discussed for claims 12-13 of the '802 patent. *See* Section XI.A.4.d. In view of the analysis presented in Section XI.A.4.d., it is my opinion for the perspective of a POSA that the total tablet weights provided in claims 6-5 of the '846 patent are obvious for the same reasons.

416. A POSA, in my opinion, would have been motivated to arrive at the tablets of claims 6-7 with a reasonable expectation that such tablets could be made. Though not required, as explained above, that person would have also expected that such tablets would contain

amounts of BIC sodium, TAF fumarate or hemifumarate, and FTC free base that were effective to reduce HIV-1 viral load in a patient, or at the very least expectedly been effective to prevent or reduce the risk of developing HIV-1 infection in patients exposed to the HIV virus.

417. In my professional opinion (adopting the opinions of Dr. Winkler discussed above for the '802 patent and with the assumption that Dr. Muzzio's conclusions concerning the multilayer aspect of the claim to be accurate and accepted), from the standpoint of a POSA and in view of the legal principles of obviousness discussed herein, claims 6–7 would have been obvious over the combination of WO '323, WO '351 and US '079, as informed by common knowledge and well-known technical principles discussed in Section V available prior to November 9, 2015.

f) Claim 8 of the '846 Patent

418. Claim 8 depends from claims 1 or 2 and limits the tablet to a coated tablet.

419. Each of Tivicay[®], Stribild[®], Triumeq[®] and Genvoya[®] are all film coated tablets.⁵³⁵ A POSA would have certainly known to film coat the claimed tablets, as multiple teams of scientists had successfully applied film coatings to approved anti-HIV tablets for years. As such A POSA would have been motivated to apply a coating to the tablets defined by claims 1 and 2 with a reasonable expectation of success.

420. On these bases and those provided above for claim 1, is it my opinion that the POSA would have been motivated to arrive at the tablet of claims 8 with reasonable expectation of success in preparing such a tablet. Though not required, as explained above, that person would have also expected that such a tablet contained amounts of compound 42 (BIC), TAF, and

⁵³⁵ Stribild Assessment (DEFS_BIC_00001336-482) at DEFS_BIC_00001346; Tivicay Assessment (DEFS_BIC_00000696-797) at DEFS_BIC_00000704; Triumeq Assessment (DEFS_BIC_00002048-161) at DEFS_BIC_00002053; Genvoya Assessment (DEFS_BIC_00001811-969) at DEFS_BIC00001828.

FTC effective to reduce HIV-1 viral load in a patient, or at the very least expectedly been effective to prevent or reduce the risk of developing HIV-1 infection in patients exposed to the HIV virus.

g) The Combination of WO '323 and WO '351 with Bowker and Paulekuhn Bolsters a POSA's Motivation to Select BIC Sodium with a Reasonable Expectation of Success.

421. Again, I have reviewed and considered Dr. Winkler's analysis and opinions on the specific selection of compound 42 as a sodium salt (BIC sodium).⁵³⁶ Part of Dr Winkler's analysis and opinion in this regard relies on additional disclosures from Bowker⁵³⁷ and Paulekuhn.^{538, 539} I understand that Dr. Winkler includes these disclosures to provide additional bases for concluding that compound 42 (BIC) as a sodium salt was a clearly preferred selection over compound 42 (BIC) free acid and other pharmaceutically acceptable salts disclosed in WO '323.⁵⁴⁰ This is because, according to Dr. Winkler, an ordinarily skilled medicinal chemist would have known from Paulekuhn that "sodium was far and above the most common cation to use with acidic drugs, including weakly acidic drugs like DTG and BIC," and that POSA would have known from Bowker that the preparation of compound 42 (BIC) sodium salt (from NaOH) would provide a pKa difference (i.e., > 3 units) necessary to form a stable (i.e., irreversible) salt.⁵⁴¹

422. As stated by Dr. Winkler, "[a POSA] would have expected success making BIC sodium given the structural similarities between BIC and DTG, the preference for DTG sodium in WO '351, and the expected >3 pKa difference between BIC and sodium hydroxide that would

⁵³⁶ Winkler Report, Section X.D.

⁵³⁷ Bowker (DEFS_BIC_00000807-837) at DEFS_BIC_00000807-37.

⁵³⁸ Paulekuhn (DEFS_BIC_00000266-273) at DEFS_BIC_00000266-73.

⁵³⁹ Winkler Report, Section X.D. at ¶¶ 168-69.

⁵⁴⁰ *Id.* at ¶¶ 168-73.

⁵⁴¹ *Id.* at ¶ 168.

have expectedly provided the formation of an irreversible (and stable) salt.”⁵⁴² After consideration of Dr. Winkler’s analysis and opinions in view of Bowker and Paulekuhn, I accept his expertise and adopt his conclusions, just as a POSA would have done.

423. Further, as it pertains to the “multilayer” aspect of the claims of the ’846 patent, I understand that Dr. Muzzio, a formulation scientist, has also analyzed whether the POSA would consider such a tablet configuration to have been obvious, and has concluded such a tablet to be obvious. I also accept his expertise and have assumed his conclusion to be accurate as well.

424. On the further grounds that I have explained in this report, it is my opinion that, from the standpoint of a POSA and in view of the legal principles of obviousness discussed herein, each of Claims 1-8 of the ’846 patent would have been obvious in view of the combination of WO ’323, WO ’351, Bowker, and Paulekuhn, as informed by common knowledge and well-known technical principles discussed in Section V. available prior to November 9, 2015.

XII. THE ’802 TABLET PATENT CLAIMS ARE OBVIOUS VARIANTS OF THE BIC SODIUM PATENTS.

425. For the sake of simplicity my opinions on obviousness-type double patenting closely follow my obviousness opinions on obvious. This is because many of the same obviousness principles and my analyses supporting obviousness apply equally here. As such, where there is overlap in my opinions on a particular claim limitation, I incorporate my analysis and opinions for obviousness of the ’802 patent claims as needed.

426. Moreover, as I understand the law, my analysis under the framework of obviousness-type double patenting does not require a POSA to select bictegravir (BIC) from among any group of compounds or select BIC sodium from any class of pharmaceutically

⁵⁴² *Id.* at ¶ 172.

acceptable salts. This is because my obviousness-type double patenting analyses begin with claims that specifically require BIC sodium ('342 patent claims) or more specifically BIC sodium Form I ('067 patent claims).

427. I explain in Section IV.D. of this report my understanding of the law of obviousness-type double patenting. As I understand the legal principles involved, the law allows a common inventor or a common owner to obtain only one patent for an invention. Obviousness-type double patenting prevents a common inventor or owner from securing an effective extension of the time period that precludes others from practicing the claimed invention of the first patent after it expires. In other words, when a common inventor or owner claims subject matter in a second later-expiring patent that is not “patentably distinct” from the claims of a first earlier-expiring patent, they effectively prevent the public, including their competitors, from practicing the earlier claimed inventions after the public is entitled to practice them.

428. I understand that a later-expiring claim is not patentably distinct from an earlier-expiring claim if that earlier claim renders the later claim anticipated or obvious, each of which leads to “obvious variants” of the earlier claim. And, as I understand it, an obviousness analysis under the OTDP framework essentially follows that of traditional obviousness analysis, except that it starts from an earlier-expiring claim where the earlier patent specification is not necessarily considered prior art. The earlier specification, however, may be used to determine the utility of the earlier claimed invention, interpret the meaning of a claim term or the scope of coverage of an earlier-expiring claim, determine whether the later-expiring claims merely define an obvious variation of what was disclosed and claimed in the earlier patent, and to establish any inherent characteristics of the earlier claimed product or process. I employ these principles provided to me by counsel in the following analysis.

429. As I explain herein, it is my opinion that a POSA, prior to November 9, 2015, would not consider any claim of the '802 Tablet Patent to be “patentably distinct” over claim 19 of the '067 BIC Sodium Patent, when it is depending from either claim 16 and claim 17 of that patent. The '067 patent expires on June 19, 2035, and my understanding of the law is that the general public (e.g., competitors) should be free to practice claim 19 in addition to all obvious variants of that claim beginning on June 20, 2035.

430. I also explain in this section that no claim of the '802 Patent is “patentably distinct” over claim 19 of the '342 BIC Sodium Patent, when depending from claims 1 and 12 of that patent (especially in view of claim 21 of the '342 patent directed to a tablet). Since the '342 patent also expires on June 19, 2035, and my understanding of the law that the general public (e.g., competitors) should be free to practice claim 19 in addition to all obvious variants of that claim beginning on June 20, 2035.

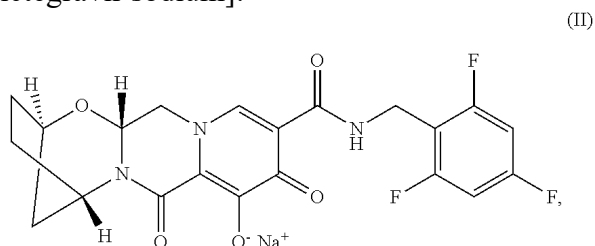
431. In Section XI.A, I provide a number of motivations that I believe the POSA would have followed to arrive at the '802 Asserted Claims with a reasonable expectation of success. I incorporate those motivations herein, while also appreciating that some are not required in the double patenting analysis that follows, i.e., the selection of BIC and BIC sodium already recited in the '067 and '342 patent. Moreover, my analyses in this section are provided also in the context of the background information provided in Section V of this report, as the POSA in this field, in my opinion, would have had an advanced level of accumulated knowledge of HIV-treatment in general by November 9, 2015.

A. Claims 1-13 of the '802 Patent are Obvious Variants of Claim 19 of the '067 BIC Sodium Patent (when Depending from Both Claims 16 and 17).

432. The application that led to the issuance of the '067 patent was filed on June 15, 2017, and the '067 patent issued on August 20, 2019.⁵⁴³ I understand that on August 28, 2019, Gilead listed the '067 patent on the Orange Book as well, representing to the FDA that specific claims of the '067 patent cover approved methods of using the Biktarvy® drug product.⁵⁴⁴ Gilead in particular identified claims 10 and claims 16-19 of the '067 patents as covering an approved method of treating HIV infection.⁵⁴⁵

433. The '067 claims are directed to methods for treating an HIV infection by administering a pharmaceutical composition comprising a therapeutically effective amount of BIC sodium Form I (claim 10), with tenofovir alafenamide and emtricitabine (claim 16) or tenofovir alafenamide hemifumarate and emtricitabine (claim 17), where the composition is a unit dosage form (claim 18) in the form of a tablet (claim 19). The following analysis begins with claim 19 (as it depends from either claim 16 or 17, which depend from independent claim 10). That claim is represented below after incorporating all the limitations of its preceding claims 16 (or 17) and 10.

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



⁵⁴³ '067 patent (BICANDA00000001-30) at BICANDA00000001 (cover page).

⁵⁴⁴ See August 19, 2019 FDA Form 3542 re '067 patent (BICANDA00209585-92) at BICANDA00209589.

⁵⁴⁵ *Id.* at § 4.2 (BICANDA00209589).

which is crystalline and is characterized by an x-ray powder diffraction (XRPD) pattern having peaks at about 5.5°, 16.1°, and 23.3° $2-\theta \pm 0.2^\circ \pm 2-\theta$, and a pharmaceutically acceptable carrier or excipient (*taken from claim 10*), wherein the pharmaceutical composition further comprises tenofovir alafenamide and emtricitabine [*taken from claim 16*] (**or** tenofovir alafenamide hemifumarate and emtricitabine [*taken from claim 17*]) wherein the pharmaceutical composition is in a unit dosage form [(*taken from claim 18*)], and wherein the unit dosage form is a tablet.

434. I understand that the first step in a double patenting analysis requires that scope of the earlier- and later-expiring claims be determined from the viewpoint of a POSA using principles of claim constructions.

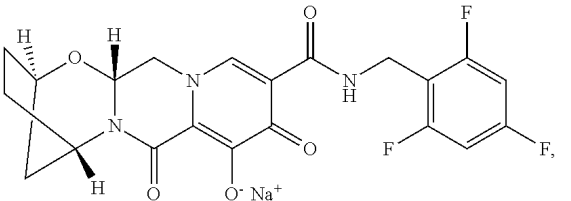
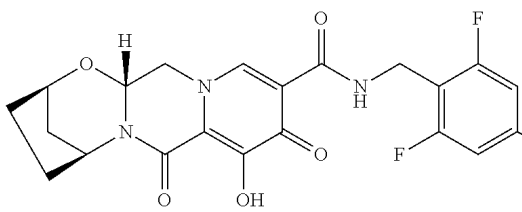
435. To begin, however, I understand that the parties have agreed that the term “therapeutically effective amount” as used in claim 10 of the ’067 patent means “an amount of the claimed compound which when administered to a patient in need thereof, is sufficient to effect treatment for disease-states, conditions, or disorders for which the compounds have utility.”

436. I further understand that the parties have agreed that the phrase “[a] method for treating an HIV infection in a human in need thereof” appearing in claim and 10 of the ’067 patent means “a method for alleviating or eliminating symptoms of an HIV infection and/or reducing HIV viral load in a human in need thereof, which may yield a variety of clinical outcomes, depending on the patient.”

437. For any additional terms appearing in claim 19 (depending from either claim 16 or 17) of the ’067 BIC Sodium patent, I may rely upon inventor definitions provided in ’067 specification, as set forth in Section VII.A.1.a, or their plain and ordinary meaning if not clearly defined.

1. Claim 19 of the '067 Patent when Depending from Claim 16.

438. As I just explained, claim 19 of the '067 patent depends from other claims. I have reproduced below a table provided by counsel that compares claim 19 of the '067 patent (when depending specifically from claim 16) and claim 1 of the '802 patent. This comports with the scope of claim 19 that I provide in the preceding section.

Claim 19 (depending from Claim 16) of Gilead's '067 Patent	Claim 1 of Gilead's '802 Patent
19. [A method for treating an HIV infection in a human in need thereof, comprising administering to the human a pharmaceutical composition, the pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula II [<i>i.e.</i>, bictegavir sodium]: (II)  which is crystalline and is characterized by an x-ray powder diffraction (XRPD) pattern having peaks at about 5.5°, 16.1°, and 23.3° 2-θ±0.2°±2-θ, and a pharmaceutically acceptable carrier or excipient (<i>taken from claim 10</i>), wherein the pharmaceutical composition further comprises tenofovir alafenamide and emtricitabine [<i>taken from claim 16</i>], wherein the pharmaceutical composition is in a unit dosage form [<i>taken from claim 18</i>]], wherein the unit dosage form is a tablet.	1. A tablet comprising 50 mg of the compound of Formula I [<i>i.e.</i>, bictegavir]:  or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof.

439. As can be seen in this table, the pharmaceutical composition in claim 19 of the '067 patent (when it depends from claim 16 and then claim 10) is substantially the same as claim 1 of the '802 patent. In fact, some limitations of claim 19 are more specific than claim 1, e.g., claim 19 (depending from claim 16) begins with BIC sodium Form I, while other limitations

are more specific in claim 1 than in claim 19 (depending from 16), e.g., the specific amounts of BIC, TAF, and FTC (or a pharmaceutically acceptable salt of each). The similarity between the claims is particularly apparent when considering that: (1) the agreed upon construction for “therapeutically effective amount” (*supra*) comports with the inventors’ definition of the term, which further states that such an amount “can be routinely determined by a skilled artisan[,]”⁵⁴⁶ and (2) the agreed upon construction for the “method of treatment” term only requires “alleviating symptoms of an HIV infection and/or reducing HIV viral load, to provide some form of clinical outcome depending on the patient.”

440. The “pharmaceutical composition” of claim 19 (depending from claim 16) therefore includes an amount of BIC sodium Form I effective to treat HIV in a human, i.e., for alleviating HIV symptoms and/or reducing viral load in a patient, when combined in a tablet with TAF and FTC. Because claim 19 (depending from claim 16) is limited to a tablet, a skilled artisan would appreciate that the “pharmaceutically acceptable carrier or excipient” recited in the claim is any carrier or excipient suitable for tablet formulations approved by the United States Food and Drug Administration as being acceptable for use in humans.⁵⁴⁷ The pharmaceutical composition of claim 19 (depending from claim 16) is, therefore, more specific in these respects. They are covered in claim 1 by virtue of its broader terminology “[BIC] or a pharmaceutically acceptable salt thereof” and claim 1’s description of a pharmaceutical composition as “comprising” BIC, TAF, and FTC (or salts thereof) allowing for additional pharmaceutically acceptable carriers or excipients. According to my understanding of legal standards (*see* Section IV), these features of claim 19 (depending from claim 16) constitute species of broader limitations in claim 1, and therefore anticipate those limitations.

⁵⁴⁶ ’067 patent (BICANDA00000001-30) at 4:66-5:20.

⁵⁴⁷ *Id.* at 4:52-59 (defining “[p]harmaceutically acceptable carrier, diluent or excipient”).

441. In addition, claim 19 (depending from claim 16) requires TAF and FTC, where claim 1 allows for these same agents or their pharmaceutically acceptable salts. The use of the pharmaceutical composition of claim 19 (depending from claim 16) is clear from the claim itself: it should treat HIV infection in a patient in need thereof, i.e., it should “alleviat[e] symptoms of an HIV infection and/or reduc[e] HIV viral load, to provide some form of clinical outcome depending on the patient,” the agreed meaning of the claim term “[a] method for treating an HIV infection in a human in need thereof.”

442. Thus, the differences between earlier-expiring claim 19 (depending from claim 16) most relevant to my analysis reside in limitations of later-expiring claim 1 that are more specific than earlier claim 19 (depending from claim 16). These differences reside in the specific amounts *50 mg* BIC, *25 mg* TAF, and *200 mg* FTC (or a pharmaceutically acceptable salt of any of them), where the earlier-expiring claim 19 claim requires a tablet containing a “therapeutically effective amount” of BIC sodium Form I combined with TAF and FTC.

443. These differences, in my opinion, would have been obvious to the POSA prior to November of 2015.

444. According to the '802 patent, the utility of the pharmaceutical combinations it discloses, e.g., combination tablets with BIC, TAF, and FTC, is for “treating viral infections such as HIV.”⁵⁴⁸ In addition, TAF is described as a previously known compound having utility as a “nucleotide reverse transcriptase inhibitor” (NtRTI), and FTC is described as a compound having utility as a “nucleoside reverse transcriptase inhibitor” (NRTI).⁵⁴⁹ The '802 patent also states a utility that the “combination of [BIC], [FTC], and [TAF] in a single stable dosage form is

⁵⁴⁸ '802 Patent (BICANDA01160880-928) at 1:20-23.

⁵⁴⁹ '802 Patent (BICANDA01160880-928) at 6:37-39; 7:56-57.

pharmaceutically efficacious and physically acceptable.”⁵⁵⁰ In this sense, a POSA would have considered 50 mg BIC, 25 mg TAF, and 200 mg FTC (or their salts) to be pharmaceutically efficacious in combination, i.e., therapeutically efficacious amounts of therapeutically effective amounts when combined.⁵⁵¹

445. Regarding the “therapeutically effective amount” limitation in claim 19 (depending from claim 16) of the ’067 patent, its definition from the specification states that “such a therapeutically effective amount can be routinely determined by one of ordinary skill in the art having regard to their own knowledge, the state of the art, and this disclosure.”⁵⁵² This is identical to the statement made in the definition of “therapeutically effective amount” in WO ’323 discussed above in my obviousness analysis.⁵⁵³ As such, I apply the routine determination of a “therapeutically effective amount” here starting from claim 19 (depending from claim 16), similar to how I applied it above starting from WO ’323.⁵⁵⁴

446. As I explained above in my obviousness analysis for the ’802 patent (*see* Section XI.A.4), a “therapeutically effective amount” of BIC would have been determined using routine clinical dose ranging studies such as those discussed in Section V.E. In the same way, the POSA would have routinely determined “therapeutically effective amounts” for BIC sodium Form I in claim 19 using these same well-known clinical studies on anti-HIV drugs applied to BIC.

⁵⁵⁰ ’802 Patent (BICANDA01160880-928) at 8:50-60.

⁵⁵¹ *See also e.g.*, ’802 patent at 57:45-52 (defining the term “effective amount” as “an amount that may be effective to elicit the desired biological or medical response, including the amount of a compound that, when administered to a subject for treating a disease, is sufficient to effect such treatment for the disease. The effective amount will vary depending on the compound, the disease and its severity and the age, weight, etc. of the subject to be treated.”); 57:33-44 (defining “treating” or “treatment” to broadly include “relieving the disease,” inhibiting the disease,” and even “preventing or reducing the risk of developing the disease.”)

⁵⁵² ’067 patent (BICANDA00000001-30) at 5:16-20.

⁵⁵³ *See e.g.*, Sections VIII.H and XI.A.1

⁵⁵⁴ *Id.*

447. As I explained above in Section V.E, multiple doses of the INSTI DTG were considered efficacious, including a dose five times smaller (10 mg) than the FDA approved dose of 50 mg, which like the 50 mg dose provided an HIV RNA count of <50 copies/mL in a large majority of patients at 96 weeks.⁵⁵⁵ The same was true for Gilead's INSTI EVG, which was approved at a dose of 150 mg (when combined with COBI, TDF, and FTC) but was shown to effectively reduce viral load at lower doses, i.e., 50 mg and 125 mg.⁵⁵⁶ And Gilead had also entered clinical evaluation of its compound GS-9983 (75 mg) combined with TAF (25 mg) and FTC (200 mg) after conducting a routine dose ranging study in a Phase 1b trial where GS-9883 was administered at doses including 50 mg and 100 mg.⁵⁵⁷ Though a 75 mg dose of GS-9883 was apparently selected as the recommended phase 2 dose, a POSA would have expected that the 50 mg dose would have also provided significant reductions in HIV RNA counts, just as had been shown for DTG and EVG. Indeed, there would likely be no basis to choose a 75 mg dose for phase 2 studies if a 50 mg dose failed to reduce viral load in the phase 1b study.

448. As discussed in Section XI.A.1, WO '351 also includes disclosures teaching the use of two (or more) and preferably three active ingredients in a single dosage form (including tablets) all designed to reduce replication of the HIV-1 virus and thus reduce viral load in HIV-1 infected patients. Specifically disclosed are compositions containing about 50 mg DTG, about 200 mg of FTC, and about 25 mg of TAF.⁵⁵⁸

449. Moreover, as had repeatedly been shown by multiple teams of ordinarily skilled artisans prior to November 9, 2015, the development of FDA-approved single tablets containing therapeutically effective amounts of three (and sometimes four) active ingredients to treat HIV-1

⁵⁵⁵ See Section V.E.

⁵⁵⁶ *Id.*

⁵⁵⁷ *Id.*

⁵⁵⁸ WO '351 at 19:30-20:2 (BICANDA01155483 at 5502-03).

infection had been accomplished several times.⁵⁵⁹ This included the Genvoya[®] tablet, approved in Europe in September of 2015, that employed a COBI-boosted first generation INSTI (EVG) to anchor the improved N(t)RTI pair of TAF and FTC.⁵⁶⁰

450. In my opinion, the 50 mg of BIC (or a pharmaceutically acceptable salt thereof) in claim 1 of the '802 patent is not patentably distinct over claim 19 (depending from claim 16), because a POSA would have arrived at that dose routinely when assessing dose levels that, e.g., provided a reduction in HIV RNA viral load. Moreover, given the structural similarities and expectedly biological function properties of DTG and BIC noted by Dr. Winkler, a POSA would not have been surprised to learn from routine dose determination studies that an effective amount of BIC (or BIC sodium Form I) would be similar to DTG (or DTG sodium in Tivicay[®]). At the very least, a POSA would have expected that a 50 mg dose of BIC sodium Form I would be “therapeutically effective” according to claim 19 (depending from claim 16) of the '067 patent to reduce viral load and provide a clinical outcome in some patients, because patients receiving even a 10 mg dose of DTG in dose determination studies maintained viral suppression (a benchmark of HIV-1 RNA less than 50 copies/mL), throughout a 96 week period.⁵⁶¹

451. As such, a POSA would have considered 50 mg BIC (or a salt thereof) in claim 1 (when combined with TAF and FTC) to be a “therapeutically effective amount” as called for by claim 19 (depending from claim 16) of the '067 patent when used in combination with TAF and FTC. This amount would not only have been routinely determined, but a POSA also would have also expected it to be therapeutically effective to treat HIV infection according to claim 19 (depending from claim 16), i.e., an amount that reduce HIV viral load to provide a clinical

⁵⁵⁹ See Section V.A., supra (summarizing multiple FDA approved single regimen tablets with multiple APIs to treat HIV infection).

⁵⁶⁰ Genvoya Assessment (DEFS_BIC_00001811-969) at DEFS_BIC_00001826.

⁵⁶¹ *Id.* at DEFS_BIC_00006186.

outcome depending on the patient. Nothing in claim 19 (depending from claim 16) requires that the claimed “therapeutically effective amount” be an optimal amount, and nothing in claim 1 of the ’802 defines 50 mg in terms of being optimal either.

452. In fact, when the ’802 patent specification refers to “treating” or “treatment,” it includes “preventing or reducing the risk of developing the disease, i.e., causing the clinical symptoms of the disease not to develop in a subject that may be exposed to or predisposed to develop.”⁵⁶² In this sense, it is my opinion that the 50 mg BIC dose in claim 1 need not even provide a reduction of viral load to provide a clinical outcome, because it can be enough to just prevent HIV symptoms from a patient who does not yet have HIV infection.

453. Next, a POSA would appreciate from claim 19 (depending from claim 16) itself, that TAF and FTC are used in a method for treating “HIV infection in a human in need thereof,” and therefore should have been administered in therapeutically effective amounts themselves. Indeed, according to the specification, each of TAF and FTC are described as useful “additional *therapeutic agents*” and also useful as “HIV [N(t)RTIs].”⁵⁶³

454. Though not expressly included in the claim, a POSA would have known (or at least desired) that the tablet of claim 19 (depending from claim 16) contained “therapeutically effective amounts” of TAF and FTC for treating HIV infection in a patient in need thereof when co-administered with a BIC sodium Form I. At the very least, the POSA would have been motivated to identify therapeutically effective amounts of TAF and FTC in a tablet designed for treating HIV-1 infection when combined with a next-generation INSTI like BIC.

⁵⁶² ’802 Patent (BICANDA01160880) at 57:33-39.

⁵⁶³ ’067 patent at 16:22-23, 16:38-51.

455. WO '351 discloses those amounts as “about 25 mg TAF” and “about 200 mg of FTC” when used in a composition also containing the “second generation” INSTI DTG.⁵⁶⁴ These amounts of FTC and TAF were also known to be effective according to the Genvoya Assessment’s disclosure that a 10 mg dose of TAF in tablet containing the 150 mg EVG, 150 mg of the booster COBI, and 200 mg FTC “were comparable to those observed following administration of TAF 25 mg co-administered with [200 mg] FTC,” without the booster compound.⁵⁶⁵ Further, US '079 discloses pharmaceutical compositions comprising at least one INSTI or its salt and at least one antiretroviral or anti-HIV agent or its salt or prodrug, and their use in the treatment of HIV infection.⁵⁶⁶ It further discloses suitable N(t)RTIs including TAF and FTC, and prefers the N(t)RTIs selected from tenofovir, emtricitabine, lamivudine or zidovudine, or any combination thereof.⁵⁶⁷ Because a POSA would have known (prior to November 9, 2015) that TAF was a prodrug of tenofovir that provided efficacy at a dose of 25 mg, that person would have considered TAF to be a suitable prodrug to combine with an INSTI (e.g., 50 mg DTG as disclosed in Examples 1 and 7), and FTC (e.g., 50 mg DTG as disclosed in Examples 1 and 7).

456. The recited amounts of 25 mg tenofovir alafenamide (or its salt), and the 200 mg FTC (or its salt) recited in claim 1 of the '802 patent are nothing more than “therapeutically effective amounts” of these additional therapeutic agents for the “treatment of HIV infection patient in need thereof” when used in combination the “therapeutically effective amount” of BIC sodium Form I as called for in claim 19 (depending from claim 16). And because such amounts would have been routinely identified in the prior art, they would have been obvious over claim

⁵⁶⁴ WO '351 at 20:2-3 (BICANDA01155503).

⁵⁶⁵ Genvoya Assessment at 78 (DEFS_BIC_00001888).

⁵⁶⁶ US '079 at Abstract, [0055]-[0070] (DEFS_BIC_00002975, DEFS_BIC_0000979).

⁵⁶⁷ *Id.* at [0042]-[0051] (DEFS_BIC_00002978).

19 (depending from claim 16) in view of WO '351 and the Genvoya Assessment. They also would have been obvious over claim 19 (depending from claim 16) in view of WO '351, the Genvoya Assessment, and US '079.

457. In sum, it is my opinion from the viewpoint of a POSA that later-expiring claim 1 of the '802 presents an obvious variant of earlier-expiring claim 19 (depending from claim 16) when considered as a whole in further view of WO '351 and the Genvoya Assessment, and WO '351, the Genvoya Assessment, and US '079.

458. As for Claims 2-8 of the '802 patent, the use of INSTI compounds including bicitgravir and its salts to anchor the N(t)RTI pair of FTC and TAF salts were known to the POSA prior to November of 2015.⁵⁶⁸ For one, in addition to disclosing compositions containing 50 mg of structurally related DTG, 25 mg TAF, and 200 mg FTC, WO '351 discloses that DTG monosodium salt is preferred, TAF fumarate and especially TAF hemifumarate are preferred, and FTC free base as preferred.⁵⁶⁹ As such, a POSA would have been motivated to specifically use TAF fumarate or hemifumarate, and FTC free base in a tablet also containing BIC sodium Form I as in claim 19 (depending from claim 16). Moreover, the use of even 1/10th the amount of the hemifumarate salt of TAF (25 mg) as compared to TDF (300 mg) had been established before November of 2015.⁵⁷⁰ It was also well established in the art that 200 mg FTC free base, when paired with tenofovir, was effective at reducing HIV-1 viral load.⁵⁷¹

459. On these bases, in addition to those explained for Claim 1, it is my opinion that the POSA would have been motivated to prepare a tablet composition comprising 52 mg BIC

⁵⁶⁸ See Section XI.A.4.b above.

⁵⁶⁹ WO '351 at 5:22-27 (DTG sodium), 13:16-18 (TAF fumarate or hemifumarate), 8:10-11 (emtricitabine free form) (BICANDA01155488, BICANDA01155496, BICANDA01155491).

⁵⁷⁰ Ruane at 454-455 (DEFS BIC_00003011-12).

⁵⁷¹ Genvoya Assessment at 10 (DEFS BIC_00001820); see also the Stribild®, Triumeq®, Atripla®, and Genvoya® products summarized in Section V.A, all of which contain 200 mg of FTC.

sodium (equivalent to 50 mg BIC), TAF monofumarate or TAF hemifumarate (equivalent to 25 mg of TAF, e.g., 28 mg of TAF hemifumarate), and 200 mg FTC free base, and would expect such a tablet to be useful for the treatment of HIV. Accordingly, it is my opinion that each of claims 2-8 of the '802 patent are obvious variants of claim 19 (depending from claim 16) of the '067 patent.

460. Claims 9-11 of the '802 patent limit the claimed tablets to total weights of 1000, 800, and 730 mg respectfully. As I have explained in Section XI.A.4.a. as to obviousness of claim 1 of the '802 patent, the tablet compositions disclosed in WO '351 would have motivated the POSA routinely determine a therapeutically effective amount of BIC, i.e., 50 mg as explained above (or an equivalent amount of BIC sodium Form I) to combine with 25 mg TAF (or an equivalent amount of TAF fumarate or hemifumarate) and 200 mg of FTC free base (or a salt thereof). This would have provided a tablet having a total active ingredient weight of 275 mg (or no more than 280 mg when using BIC sodium Form I and TAF mono- or hemifumarate). Indeed, the total amount of active ingredients of the compositions disclosed in WO '351 that use TAF as the tenofovir prodrug are reported as preferably in the range of 192-326 mg per day,⁵⁷² which covers particular embodiments with 50 mg DTG, 25 mg TAF, and 200 mg FTC, i.e., 275 mg of total active ingredients.⁵⁷³ And as explained in Section XI.A.4.a., it would have been obvious to a POSA replace 50 mg of DTG with a therapeutically effective amount (a 50 mg amount) of BIC.

461. In my opinion, a POSA working from the tablet of WO '351 containing 50 mg of DTG, 25 mg of TAF, and 200 mg FTC as a starting point, would understand that they would be able to include up to ~725 mg (total weight) of excipients and still have a tablet with a total

⁵⁷² WO '351 at 17:17-18, 19:5-12 (BICANDA01155500, BICANDA01155502).

⁵⁷³ *Id.* at 19:30-20:2.

weight less than 1000 mg (claim 9). The same is true for an obvious tablet containing 50 mg BIC, 25 mg TAF, and 200 mg FTC.

462. Given the large amounts of available excipients relative to the 275 mg total active ingredient weight required by claim 9 (1000 mg total weight), claim 10 (800 mg total weight), and claim 11 (730 mg totally weight), a POSA (in my opinion) motivated to provide smaller tablets for improved convenience, safety, and patient adherence, and would have arrived at tablets containing 50 mg of BIC (or 52 mg BIC sodium Form I), 25 mg TAF (or 28 mg of TAF mono- or hemifumarate), and 200 mg FTC free base with a sufficient amount of excipients (~465 mg or ~460 mg with BIC sodium Form I and TAF mono-or hemifumarate) for a total weight less than 730 mg (from claim 11) to provide a tablet weighing less than 730 mg.

463. As discussed in Section VIII.C., US '079 discloses a preference for tablets due to their greater stability, smaller bulk, and ease of production.⁵⁷⁴ It also exemplifies a tablet containing 50 mg DTG as an anchor for the N(t)RTIs TDF (300 mg) and FTC (200 mg) having a total API weight of 550 mg, a total uncoated weight of 1030 mg, and a coated weight of 1055 mg.⁵⁷⁵ It also discloses a bilayer tablet that contains the same amount of total APIs, a total uncoated weight of 1113 mg, and a coated weight of 1140 mg.⁵⁷⁶ This would have motivated the POSA to prepare a tablet containing BIC (or 52 mg BIC sodium Form I), 25 mg TAF (or 28 mg of TAF mono- or hemifumarate), and 200 mg FTC free base, i.e., ~275 mg total API. With these dosage amounts, the POSA would have understood that the total excipient amounts from WO '351 could also be reduced to correspond with the 50% decrease in weight of the APIs. In my opinion, this would have produced, with a reasonable likelihood of success, an uncoated tablet

⁵⁷⁴ US '079 at ¶¶ [0078]-[0079] (DEFS_BIC_00002980) (disclosing single, bilayered or multilayered tablets).

⁵⁷⁵ *Id.* at ¶ [0129] (DEFS_BIC_00002984-85) (Example 7).

⁵⁷⁶ *Id.* at ¶ [0117] (DEFS_BIC_00002982).

with all three APIs from Claim 19 (depending from claim 16), that weighed less than 730 mg (with 50% excipient reduction modified bilayer tablet of Example 1, the uncoated tablet weighs 556 mg; and the uncoated modified tablet of Example 7 = 515 mg).

464. If an acceptable tablet with a total coated weight of 1055 mg had been successfully made when containing twice as much API (as in WO '351 Example 7), a POSA would have reasonably expected to succeed in making a tablet with ~ 275 mg of total active ingredients that (even when coated) would have weighed less than 730 mg as well.

465. As such, a POSA motivated to arrive at a tablet containing an amount of BIC Sodium Form I equivalent to 50 mg BIC, 25 mg TAF (or an equivalent amount of TAF mono-or hemifumarate, and 200 mg FTC free base from claim 19 (depending on claim 16), i.e., ~275 mg active ingredients, with a reasonable expectation of success would have reasonably expected to also arrive at a tablet having a total weight less than 730 mg, whether that tablet was coated or uncoated.

466. Accordingly, in addition to the reasons explained above for claim 1, it is my opinion that the Claims 9-11 are also obvious variants of claim 19 (depending from Claim 16) of the '067 patent. That POSA would also have reasonably expected success in preparing such tablets from the tablet of claim 19 (depending on 16) using common excipients and routine techniques in the art. Again, though not required, that person would have also expected that such tablets contained amounts of BIC (or a sodium salt thereof), TAF (or a fumarate or hemifumarate salt thereof), and FTC (as a free base) would be effective to reduce viral load in a patient, or at the very least expectedly been effective to prevent or reduce the risk of developing HIV-1 infection in patients exposed to the HIV virus.

467. Claims 12 and 13, which limit the claimed tablets by the percentage of Formula (I) (BIC) in the tablets (less than 15% and 11%) respectively. As discussed for claim 9, a POSA motivated to prepare a tablet having an amount BIC Sodium Form I equivalent to 50 mg BIC, 25 mg TAF (or an equivalent amount of TAF mono- or hemifumarate), and 200 mg FTC free base from claim 19 (depending on claim 16) (e.g., 725 mg, 650 mg, 600 mg) would have arrived at a tablet having less than 15% and less than 11% of BIC Sodium Form I from claim 19 (depending on claim 16). Indeed, even tablets with a total weight of 1000 mg or greater would have met these limitations, i.e., 50 mg BIC is 5% of a tablet weighing 1000 mg and 2.5% by weight of a tablet weighing 2000 mg.

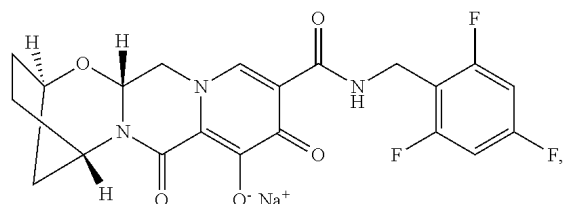
468. On these bases and those provided above for claim 1, is it my opinion that the POSA would have been motivated to arrive at the tablet of claims 12-13 of the '802 from claim 19 (depending on claim 16) of the '067 with reasonable expectation of success in preparing such a tablet. Again, though not required, that person would have also expected that such tablets contained amounts of BIC (or a sodium salt thereof), TAF (or a fumarate or hemifumarate salt thereof), and FTC (as a free base) would be effective to reduce viral load in a patient, or at the very least expectedly been effective to prevent or reduce the risk of developing HIV-1 infection in patients exposed to the HIV virus. Accordingly, it is my opinion that both claims are obvious variants of claim 19 (when dependent from claim 16) of the '067 patent on the same grounds.

2. Claim 19 of the '067 When Depending from Claim 17.

469. When claim 19 depends from claim 17 of the '067 patent, it is also virtually identical to claim 1 of the '802 patent, as follows:

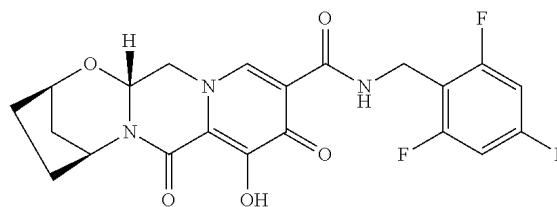
Claim 19 (depending from Claim 17) of Gilead's '067 Patent	Claim 1 of Gilead's '802 Patent
19. [A method for treating an HIV infection in a human in need thereof,	1. A multilayer tablet comprising 50 mg of the compound of Formula I [<i>i.e.</i> , bictegravir]:

comprising administering to the human a pharmaceutical composition, the pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula II [*i.e.*, bictegravir sodium]:



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

(II)



(I)

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

470. In brief, claim 19 of the '067 patent is directed to a method of treating HIV with a tablet composition comprising BIC sodium Form I, TAF hemifumarate, FTC free base, and a pharmaceutically acceptable carrier or excipient. As explain in the preceding section, Claim 1 of the '802 patent is more generally directed to a tablet comprising 50 mg of BIC or pharmaceutically acceptable BIC salt (e.g., BIC Sodium Form I), 25 mg TAF or a pharmaceutically acceptable TAF salt (e.g., TAF hemifumarate), and 200 mg FTC or a pharmaceutically acceptable FTC salt. As shown in the above table, Claim 19 (when depending from claim 17) claims the same tablet as Claim 19 (depending on claim 16), except that the hemifumarate form of TAF is used specifically. The result is that claim 19 (depending from

claim 17) renders claim 1 of the '802 patent an obvious variant for the same reasons as the claim 19 (depending on claim 16) above.

471. As for claims 2-8, claim 19 (depending from claim 17) specifically includes TAF hemifumarate and FTC free base. It therefore provides a more specific disclosure to the salts BIC sodium and TAF hemifumarate, and FTC free base covered by claims 2-8, and no additional prior art is required to address those claims. As to the 52 mg of BIC sodium and 28 mg TAF hemifumarate required in claims 5, 7, and 8, they are simply equivalent to the obvious 50 mg amounts of BIC and 25 TAF already discussed in the preceding section.

472. Regarding the dependent claims, claims 9-13 of the '802 patent are obvious variants of claim 19 (depending from claim 17) of the '067 patent for the same reason discussed in Section XII.A.2. for those claims, and those discussed above for the “tablet” limitation in this section.

473. As such, for the same reasons discussed above pertaining to Claim 19 (depending from claim 16), it is my opinion that claims 1-13 of the '802 patent are obvious variants of claim 19 (depending from claim 17) of the '067 patent, but that claims 2-8 require no additional prior art to meet the BIC sodium, TAF hemifumarate, and FTC free bases limitations in those claims.

B. Claims 1-13 of the '802 Patent are Obvious Variants of Claim 19 of the '342 BIC Sodium Patent.

474. The application that led to the issuance of the '342 patent was filed on June 20, 2014, and the '342 patent issued on July 18, 2017.⁵⁷⁷ I understand that on February 23, 2018, Gilead listed the '342 patent on the Orange Book as well, representing to the FDA that specific

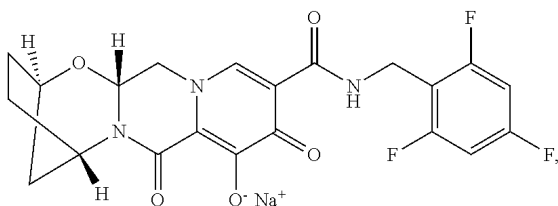
⁵⁷⁷ '342 Patent at 1 (BICANDA0000078).

claims of the '342 patent cover an approved drug substance that is an the active ingredient in Biktarvy[®], and also the entire drug product that is Biktarvy[®].⁵⁷⁸

475. The '342 patent includes claims 1, 12, and 19, which are directed to a bictegavir sodium compound (claim 1), and a pharmaceutical composition comprising a therapeutically effective amount of bictegavir sodium (claim 12 depending from claim 1 and its dependent claims 2-9), which may further comprise tenofovir alafenamide hemifumarate and emtricitabine (claim 19).

476. The following analysis begins with claim 19 (as it depends from claim 12 when it depends from independent claim 1). That claim is represented below after incorporating all the limitations of preceding claims.

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



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

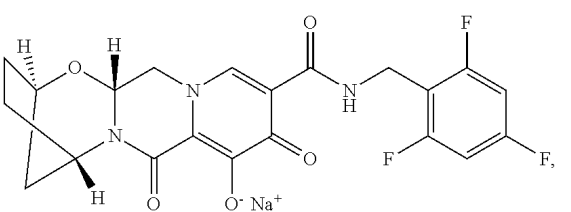
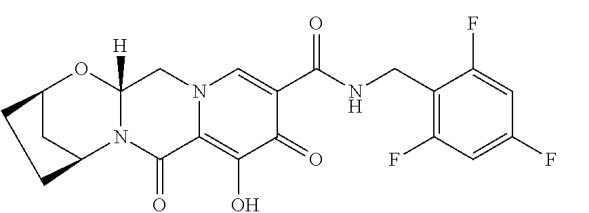
477. Again, I understand that the first step in a double patenting analysis requires that scope of the earlier- and later-expiring claims be determined from the viewpoint of a POSA using principles of claim constructions. In my opinion, no additional terms in claim 19 (when depending from claims 12 and independent claim 1) as shown directly above require me to interpret any terms now already address above for the '067 patent double patenting analysis. As such, the only term recited here that needs construction is “therapeutically effective amount”

⁵⁷⁸ See February 23, 2018 FDA Form 3542 re '342 patent (BICANDA00079349-54) at BICANDA00079350-51.

which the parties have agreed to mean “an amount of the claimed compound which when administered to a patient in need thereof, is sufficient to effect treatment for disease-states, conditions, or disorders for which the compounds have utility.”

478. For any additional terms appearing in claim 19 (depending from claim 12 and independent claim 1) of the '342 BIC Sodium patent, I rely on their plain and ordinary meaning to a POSA.

479. Below is a chart that compares earlier expiring claim 19 (depending from claims 1 and 12) of the '342 patent with later-expiring claim 1 of the '802 patent:

Claim 19 (when depending from Claim 1) of Gilead's '342 Patent	Claim 1 of Gilead's '802 Patent
19. [A pharmaceutical composition comprising a therapeutically effective amount of a compound (<i>taken from claim 12</i>) of Formula II:  (<i>taken from claim 1</i>), and a pharmaceutically acceptable carrier or excipient,] further comprising tenofovir alafenamide hemifumarate and emtricitabine.	1. A tablet comprising 50 mg of the compound of Formula I [<i>i.e.</i>, bictegravir]:  (I) or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof.

480. The only differences between claim 19 of the '342 (when depending from claims 12 and 1) and claim 19 (depending from claim 17) of the '067 patent are that '342 patent claim is a pharmaceutical composition claim instead of a method claim, it broadly claims pharmaceutical compositions and not just a tablet, and it broadly claims BIC sodium and not its specific Form I. As such, all aspects of claim 1 of the '802 patent that are anticipated by or obvious over claim 19

(depending from claim 17) of the '067 patent are incorporated herein, such that my analysis herein only considers whether the “tablet” of claim 1 of the '802 patent is an obvious variant of the general “pharmaceutical composition” of claim 19 (depending from claims 12 and 1). To cover any elements of claim 1 of the '802 patent that cross reference Section XII.A.1 on claim 19 (depending from claim 16) of the '067 patent, I incorporate the entirety of Sections XIII.A-B herein and refers to them only to the extent needed.

481. I incorporate herein my discussion on the utility of the '802 patent in Section XII.A.1. Because claim 19 (depending from claims 12 and 1) of the '342 patent are not method claims, I assess the utility of the claimed pharmaceutical compositions in view of the '342 patent specification.

482. According to the '342 specification, the “present invention relates to [BIC sodium], the crystalline forms, the pharmaceutical formulations, the therapeutic uses thereof.”⁵⁷⁹

483. Regarding the “therapeutically effective amount” limitation in claim 19 (depending from claims 12 and 1) of the '342 patent, it is defined in the specification as an amount “. . . [that] can be routinely determined by one of ordinary skill in the art having regard to their own knowledge, the state of the art, and this disclosure.”⁵⁸⁰ As such, all aspects on why a POSA would have been motivated to arrive at an amount of BIC sodium Form I equivalent to 50 mg BIC with a reasonable expectation of success, through routine experimentation optionally in further view of WO '351 and any additional references used in Section XII.1.A are the same here. My discussion on the structural similarity, and expectedly similar physicochemical and biological properties of DTG and BIC as described in the same section (XII.1.A) apply equally here as well. This leaves the only difference between claim 19 (depending from claims 12 and 1)

⁵⁷⁹ '342 patent at BICANDA0000078 (Abstract).

⁵⁸⁰ '067 patent (BICANDA00000001-30) at 5:16-20.

of the '342 patent and claim 1 of the '802 that needs to be considered in this section is that claim 1 of the '802 patent specifically recites a tablet.

484. In my opinion, the POSA would be motivated to prepare the tablet of claim 1 of the '802 patent because claim 21 of the '342 patent recites a tablet, and the preparation of a tablet is routine in the art. Indeed, the pharmaceutical combinations disclosed in WO '351, including the specific examples containing 50 DTG (preferably as BIC sodium), 25 mg TAF (preferably as TAF mono- or hemifumarate), and 200 FTC (preferably FTC free bas) were to be administered once daily “preferably [as] a solid oral dosage form ... in particular a tablet.”⁵⁸¹ And, all of the FDA approved tablets with multiple active ingredients for the treatment of HIV infections prior to November 9, 2015 were coated tablets, as I explain in Section V.A (referring to the Stribild[®], Triumeq[®], Atripla[®], and Complera[®] tablets).

485. In my opinion, any of these disclosures would have motivated a POSA to formulate the general pharmaceutical formulation of claim 19 (depending from claims 12 and 1) into a tablet. It was such a preference in the art prior to November 9, 2015 that (in my opinion) a POSA would have immediately initiated investigations into tablet formulations, and consider alternative oral dosage forms if there was an issue with the tablets themselves. In my opinion from the viewpoint of a POSA, claim 1 of the '802 patent is therefore an obvious variant of claim 19 (depending from claims 12 and 1) of the '342 patent for the reasons incorporated herein from Sections XII.A.1-2 and those discussed here.

486. As for claims 2-8 of the '802 patent, claim 19 (depending from claims 12 and 1) of the '342 patent specifically includes TAF hemifumarate and FTC free base. It therefore provides a more specific disclosure to the salts BIC sodium and TAF hemifumarate, and FTC

⁵⁸¹ WO '351 at 17:27-28, and 23:6-8 (BICANDA01155500, BICANDA01155506).

free base covered by claims 2-8, and no additional prior art is required to address those claims. As to the 52 mg of BIC sodium and 28 mg TAF hemifumarate required in claims 5-8, they are simply equivalent to the obvious 50 mg amounts of BIC and 25 TAF already discussed in the preceding section.

487. Regarding the dependent claims, claims 9-13 of the '802 patent are obvious variants of claim 19 (depending from claims 12 and 1) of the '342 patent for the same reason discussed in Section XII.A.1 for those claims, and those discussed above for the “tablet” limitation in this section.

488. As such, for the same reasons discussed above pertaining to Claim 19 (depending from claim 16 or claim 17) of the '067, it is my opinion that claims 1-13 of the '802 patent are obvious variants of claim 19 (depending from claims 12 and 1) of the '342 patent, but that claims 2-8 require no additional prior art to meet the BIC sodium, TAF hemifumarate, and FTC free bases limitations in those claims.

XIII. THE '846 TABLET PATENT CLAIMS ARE OBVIOUS VARIANTS OF THE BIC SODIUM PATENTS.

489. Claims 1-8 of the '846 patent differ from claims 1-13 of the '802 patent in the two ways. First, the '846 claims require a “multilayer” tablet where the '802 claims require only a tablet. Second, claim 8 of the '846 patent requires the “multilayer” tablet to contain a coating. In all other respects, the '846 and '802 patents include the same limitations (to the extent present in the '846 patent claims), albeit with some appearing in different claims, e.g., claim 1 of the '846 patent requires a total tablet weight less than 1000 mg where that limitation appears in claim 9 of the '802 patent. As such, the common limitations in claims 1-8 of the '846 patent claims have already been addressed in Sections XII.A-B on obviousness-type double patenting in view