

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

GILEAD SCIENCES, INC.

Plaintiff

v.

LUPIN LTD., LAURUS LABS LIMITED, AND
CIPLA LIMITED,

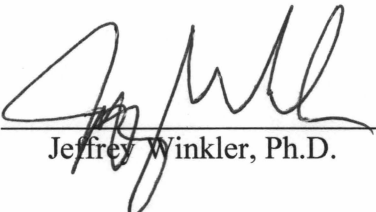
Defendants.

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C.A. No. 22-cv-00615 (MN)

OPENING EXPERT REPORT OF JEFFREY WINKLER, PH.D.

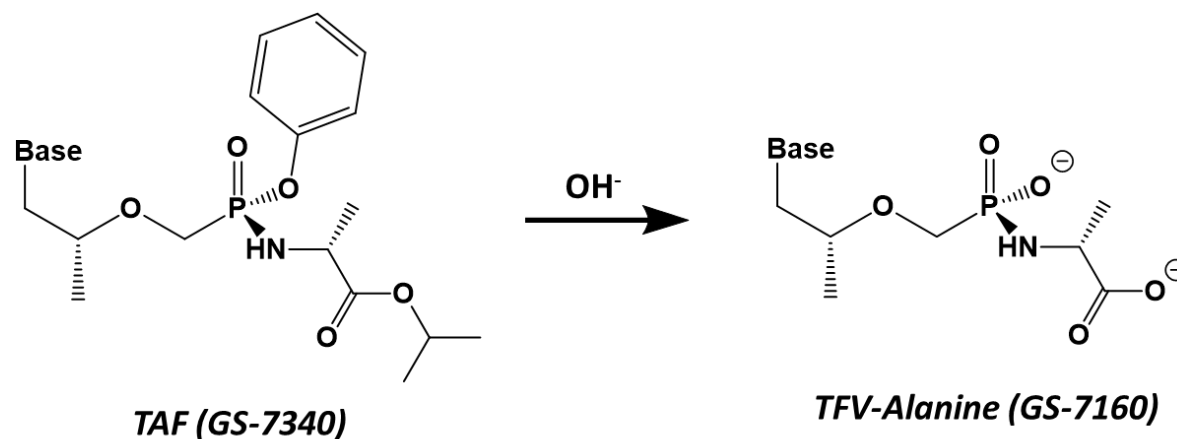
Dated: January 29, 2025



Jeffrey Winkler, Ph.D.

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provide TFV-Alanine (GS-7160). That highly expected transformation is illustrated in the scheme below.

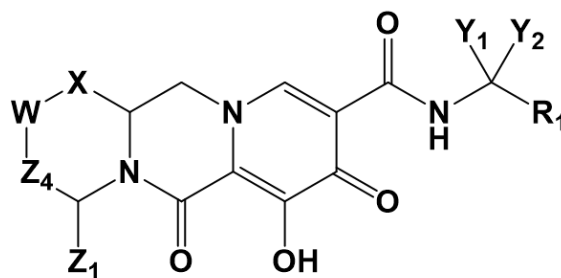


138. In my opinion, a POSA certainly would have expected the above transformation to occur in a basic solution, i.e., a solution having excess hydroxide ion (OH⁻), at some appreciable rate. In addition, that person would have also expected that transformation to occur in a basic solid-state environment, especially in the presence of moisture (to allow formation of hydroxide ion). Although ester hydrolysis would have occurred at a slower rate in the solid state (with or without moisture), a POSA would have expected TAF to degrade through hydrolysis under storage, and especially under storage in a high humidity environment.

X. Opinions Relevant to Obviousness of the Asserted Claims of the '802 and '846 Patents

A. The Emergence of Gilead's Next Generation INSTIs

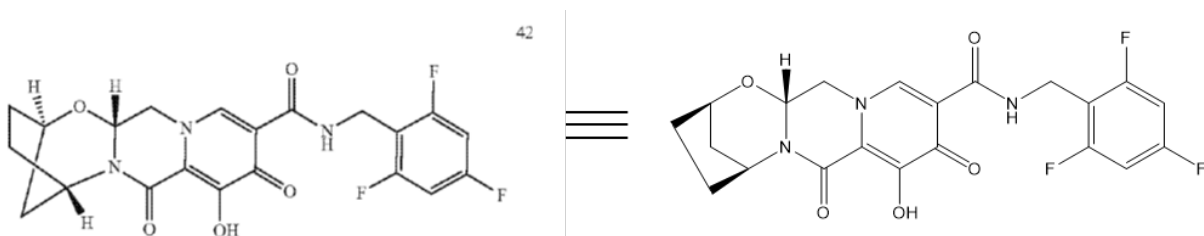
139. Around the same time as the approval of ViiV's DTG product Tivicay[®] in 2013, Gilead filed an international (PCT) application directed to "Polycyclic-Carbamoylpyridone Compounds and Their Pharmaceutical Use," which later published as WO 2014/100323 ("WO '323") (DEFS_BIC_00002214-474) on June 26, 2014. WO '323 disclosed a class of compounds defined by Formula (I) (below) and their use in the treatment of HIV infection. WO '323 (DEFS_BIC_00002214-474) at DEFS_BIC_00002214 (Abstract).



Formula (I)

Id. The compounds of Formula (I) contain a tricyclic ring system with a two-metal chelate binding site (left-hand side of structure) and a methylene amide linker (i.e., C(=O)-NH-C(Y₁)(Y₂)-; right-hand side of structure) connected to a halogen substituted phenyl ring (R₁). *Id.* at 3:13–4:4 (defining R₁ as a “phenyl substituted with one or more halogens”).

140. According to WO '323, these compounds “may be used to inhibit the activity of HIV integrase [(INST)] and may be used to reduce HIV replication.” *Id.* at 3:8–4:4. WO '323 discloses INSTI compounds of Formula (I), including compound **42** which I understand became known as the INSTI bicitgravir (“BIC”) (*see below* (left structure = compound **42** (BIC) as appearing in WO '323; right structure = compound **42** (BIC) in the orientation of '802 patent, claim 1, and '846 patent, claim 1)). *Id.* at 99:8–101:25 (Example 42).



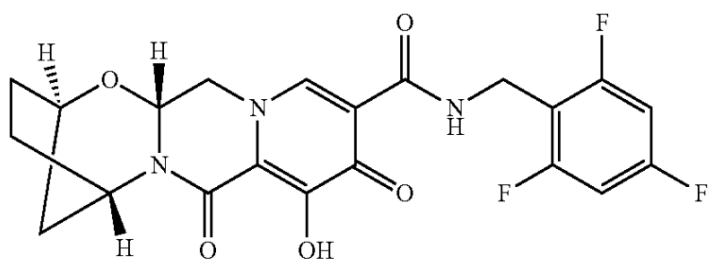
Compound 42 (BIC)

141. The same application as WO '323 was filed in the United States as US Appl. No. 14/133,828 (published as 2014/0221356), which later issued as Gilead's U.S. Patent No. 9,216,996 (“the '996 patent”) (DEFS_BIC_00000001-100). Though the '996 patent issued in December of 2015, it specifically claimed the chemical structure for BIC or pharmaceutically

acceptable salt thereof, as depicted in claim 1, below. '996 patent at 188:55-67

(DEFS_BIC_00000099). Nonetheless, the '996 patent is used in my analyses related to obviousness-type double patenting in Section XI below.

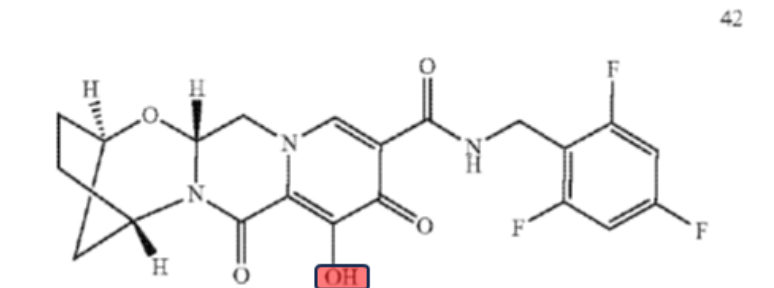
1. A compound which is:



or a pharmaceutically acceptable salt thereof.

B. WO '323 Expressly Disclosed Bictegravir and Sodium Salts, along with TAF and FTC, and Pharmaceutical Combinations

142. I note that WO '323 expressly disclosed bictegravir as compound **42** (shown below), which is one of five compounds orally administered to beagle dogs in a PK study and claimed the same within a class of seven INSTI compounds (i.e., claim 32). *See* WO '323 at 99-101 (Example 42) (DEFS_BIC_00002313-15), 223-24 (Table 4) (DEFS_BIC_00002437-38), 240-41 Claim 32 (DEFS_BIC_00002454-55). It also exemplified sodium as a specific salt derived from the compounds disclosed therein and an appropriate base. *Id.* at 14:16-17:9 (further disclosing “salts formed when an acidic proton present in the parent compound is replaced by ... an alkali metal ion . . . ” where sodium is the example of the alkali metal ion provided).



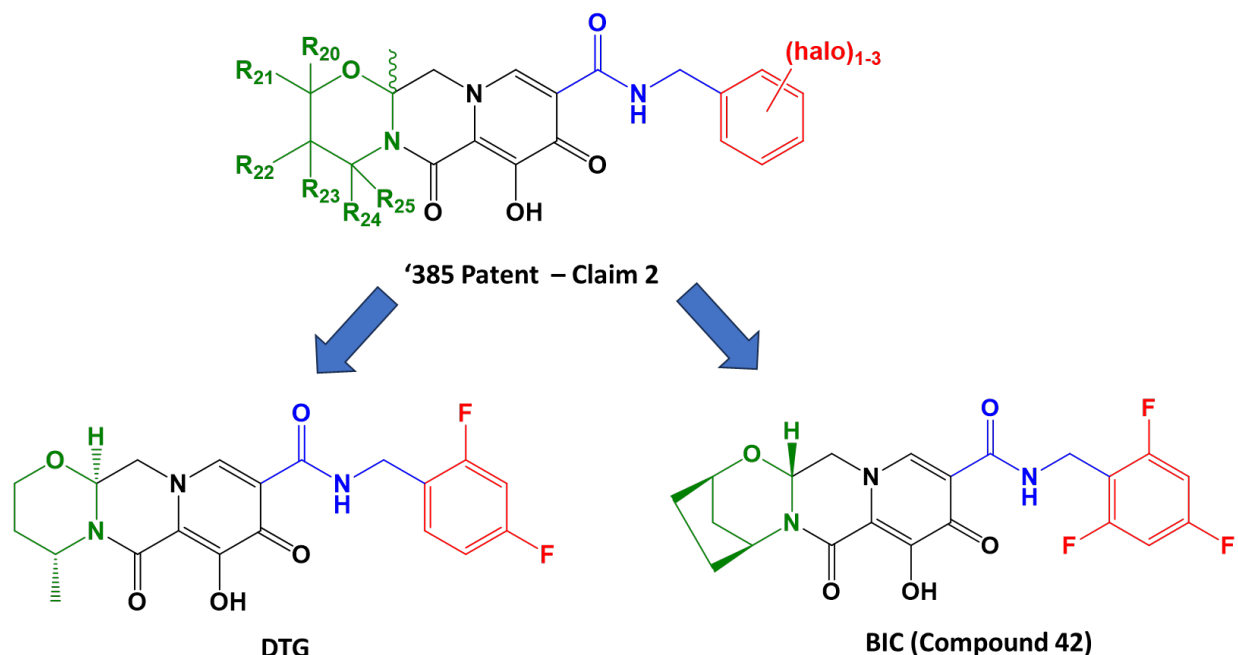
Compound 42 (BIC) and its Acidic Hydroxy Group

143. Based on my understanding of anticipation in Section VII.C, the specific disclosure of bictegavir and exemplification of sodium salts in WO '323 are directly related to one another, as sodium salts are salts of compounds such as bictegavir disclosed in the reference. This is especially the case because bictegavir contains an acidic proton (its hydroxyl group emphasized above in red) and WO '323 speaks directly to making salts from an acidic proton and an alkali metal cation, where sodium is the exemplified alkali metal cation. WO '323 at 14:20-22, 14:32-15:4. Accordingly, WO '323 discloses bictegavir and bictegavir sodium with the specificity required for anticipation of BIC or a pharmaceutically acceptable salt thereof, including BIC sodium as claimed in the '802 and '846 patents (*see* Sections VI.B-C).

144. WO '323 further describes pharmaceutical compositions containing an INSTI, e.g., compound 42 (BIC) and BIC sodium as discussed above, along with an NRTI such as FTC and an NtRTI such as TAF fumarate. WO '323 (DEFS_BIC_00002214-474) at 37:7-11, 38:13-17 (NRTIs), 38:18-21 (NtRTIs), 39:25-27 (disclosing an embodiment where the INSTI, e.g., compound 42 (BIC), is combined with two additional therapeutic agents).

1. A POSA Would Have Immediately Appreciated Bictegavir's Similarity to the FDA-Approved INSTI Dolutegravir

145. The illustration below shows the general structure claimed in the '385 patent (i.e., claim 2) along with the structures for DTG and compound **42** (BIC) from WO '323, each color-coded to emphasize their hydrophobic region (red), metal chelate region (black), expanded ring system (green), and linker (blue).



146. In addition to the specific disclosure of BIC in WO '323, in my opinion, a POSA would have also immediately appreciated that compound **42** (BIC) bore a close structural similarity to the “second generation” INSTIs studied by Johns and generally disclosed and claimed in the '385 patent, including the resistance optimized INSTI DTG.

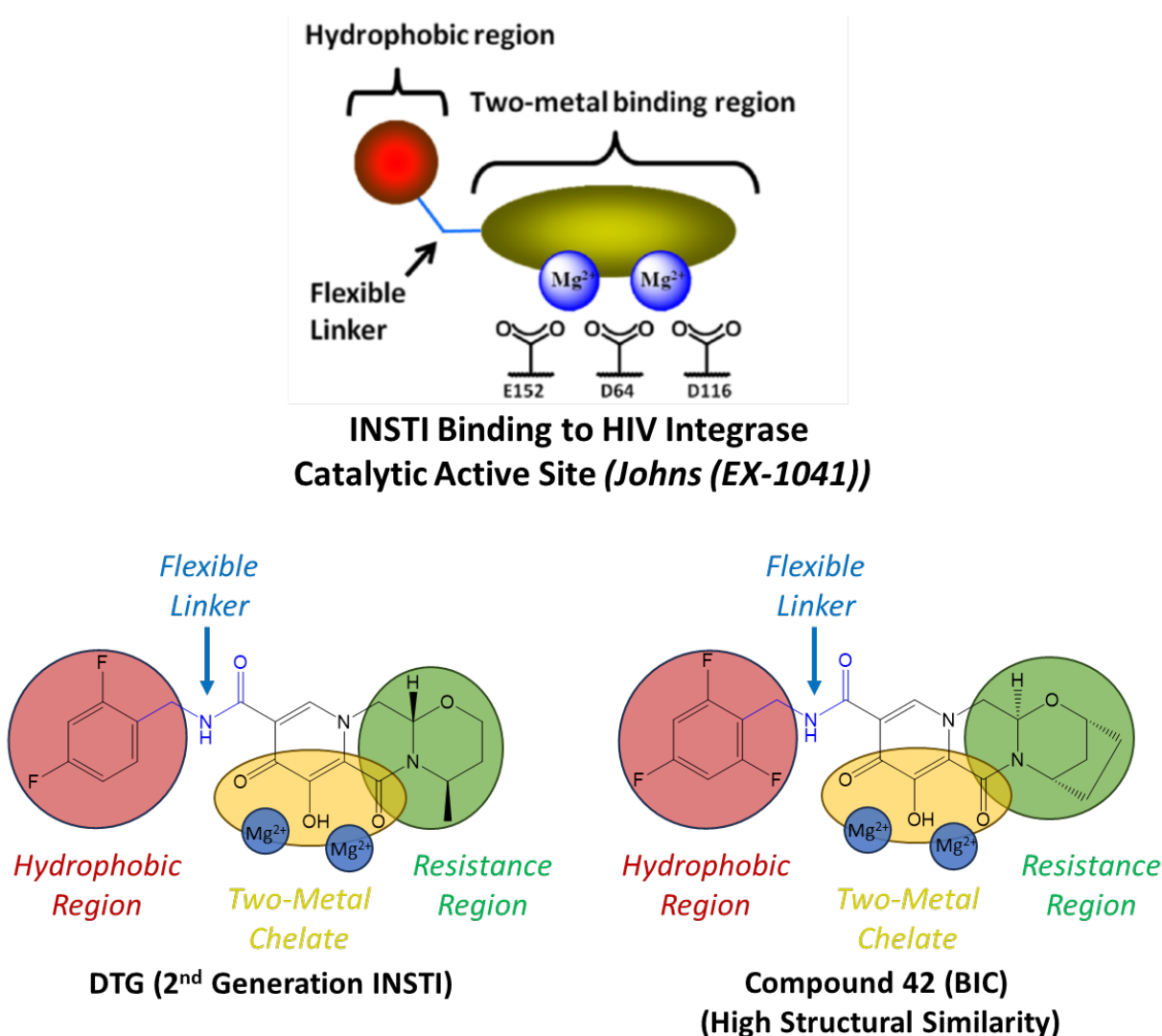
147. These similarities include an identical metal chelate region (5-6 arrangement as discussed above; black), an identical linker (blue), a structurally similar fluoro-substituted phenyl hydrophobic region (red) and a structurally similar 6-membered aминаl ring system (green) (previously designed by GSK and Shionogi to avoid cross-resistance).⁶

148. In fact, the only structural differences between DTG and BIC are: (1) the addition of a fluorine atom to the phenyl group (red) in DTG to provide three fluorine atoms on BIC compared to two fluorine atoms on the phenyl group (red) in DTG; (2) in the resistance region,

⁶ WO '764 and the '385 patent further disclosed a number of compounds structurally related to DTG along with their sodium salts in solid form, e.g., in Examples Z-1, Z-4, Z-8, Z-9, and Z-38. *See e.g.*, WO '764 at 120-28 (DEFS_BIC_00000423-31) (Compounds Z-1 - Z-3, Z-18, Z-38, Z-49, Z-52, ZZ-4, ZZ-5, Z-29, Z-47, ZZ-9, ZZ-12, ZZ-15 - ZZ-17), 128-30 (DEFS_BIC_00000431-33) (sodium salt of Z-1), 136-38 (DEFS_BIC_00000439-41) (sodium salt of Z-4), 141-44 (DEFS_BIC_00000444-47) (sodium salts of Z-8 and Z-9), 180-84 (sodium salt of Z-38) ((DEFS_BIC_00000483-87). *See* Section IX.D.

the addition of a single carbon atom to connect the C-4 methyl group of DTG to the ring carbon adjacent to oxygen in DTG to form the two-carbon bridge in BIC (green bold wedges); and (3) the change of the absolute stereochemistry of the methyl (DTG) and methylene (BIC) groups attached to the 6-membered aminal (green; DTG dashed wedge, BIC bold wedges).

149. The following illustration shows why a POSA would have expected BIC and DTG (structures realigned to fit the binding model) to provide similar anti-HIV benefits in view of the two-metal binding model that was well known in the art prior to November 9, 2015.⁷



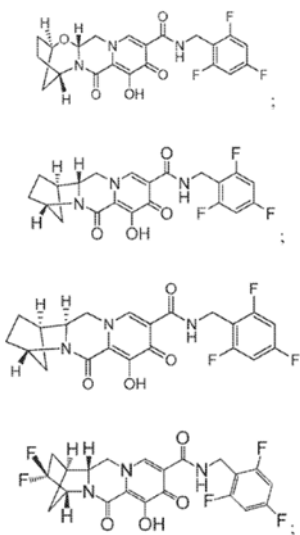
⁷ The chemical structures of DTG and BIC have been reoriented to correspond with the binding model in Johns (DEFS_BIC_00004995-5010).

150. Given that DTG and BIC were both known INSTIs and would have been expected to align with the INST in a similar fashion, their overall structural similarities would have provided a POSA with the expectation that BIC would have physicochemical and biological properties similar to DTG. This includes a similar binding mode to the active site of INST (yellow above), and an expected high genetic barrier to resistance and an ability to maintain activity against INST mutations in view of its structurally similar “resistance region” (green).⁸

C. Motivation to Select Bictegrovir from WO '323

151. In particular, WO '323 claims compound **42** (BIC) in a small group of seven INSTI compounds. WO '323 (DEFS_BIC_00002214-474) at 240-41 (DEFS_BIC_00002454-55) (claim 32) (annotated below to provide compound numbers from the specification).

32. A compound of claim 1 selected from:

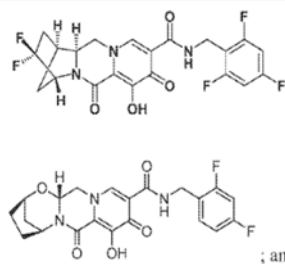


Compound 42 (bictegrovir)
(WO '323, 99:8-13)

Compound 41
(Id. at 95:11-15)

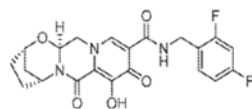
Compound 55
(Id. at 118:3-10)

Compound 98
(Id. at 193:23-194:2)



Compound 83
(Id. at 161:6-15)

Compound 2
(Id. at 45:22-46:1)



Compound 3
(Id.)

⁸ A POSA would have further appreciated that the conversion of DTG's C-4 methyl group (*see* Johns (DEFS_BIC_00004995-5010) at 5906 (DEFS_BIC_00005000) (Figure 4) (crystal structure of DTG sodium)) to a two-carbon bridge (as in compound **42**) would be expected to lock the methyl carbon substituent into the *axial* position deemed important to the potency of DTG itself. This would bolster a POSA's expectation that compound **42** would present a similar structure and therefore exhibit similar biological properties, i.e., to maintain (and perhaps improve upon) the high genetic barrier to resistance already observed for DTG.

152. In my opinion, a POSA would have been particularly drawn to this small group of compounds as a subclass of Gilead's Formula (I) INSTIs and considered them to be of particular importance. Further details from the WO '323 specification add to the POSA's motivation to focus on BIC.

153. First, each of the above seven INSTI compounds demonstrated antiviral activity in an assay utilizing HIV-infected MT4 cells, an established metric indicating each compound was potentially useful for "treating the proliferation of the HIV virus, treating AIDS, or delaying the onset of AIDS or ARC symptoms." WO '323 (DEFS_BIC_00002214-474) at 212-16 (DEFS_BIC_00002426-30). Each compound was also found to be particularly potent in the assay. The specification reports each producing EC₅₀ values in the range of 1.5–2.5 nM, placing them as among the most potent compounds studied. *Id.* (EC₅₀ of all tested compounds ranged from 1.5–422 nM).

154. Second, WO '323 discloses a pharmacokinetics (PK) study of only 11 compounds, including all seven of the compounds of claim 32, after IV administration of each compound to beagle dogs. *See id.* at 222-24 (DEFS_BIC_00002436-38) (including Table 4 below (IV study emphasized in blue; oral administration study highlighted in yellow; claim 32 compounds emphasized in red)).

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

IV Administration  Oral Administration

155. Here, the eleven compounds were first assessed for clearance (CL), steady state volume of distribution (V_{ss}), and mean residence time (MRT) after IV administration. As explained above (*see supra* ¶ 83), a compound's half-life (*t*_{1/2}) is directly linked to its volume of distribution (V) and its clearance (CL) according to the following equation:

$$t_{1/2} = \frac{(0.693 \times V)}{CL}$$

Using the CL and V_{ss} data from Table 4, a POSA would have calculated the following half-lives for each tested compound (the five compounds having the longest *t*_{1/2} (h) values emphasized in bold).

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

The compounds providing the longest half-lives (compounds **2**, **3**, **41**, **42**, and **47**) also showed the longest mean residence time (**MRT**) according to Table 4 (above).

156. As explained above in Section IX.D., a POSA would have appreciated that one important goal of INSTI development was to maintain once-a-day administration (like EVG and DTG before), preferably without the need for a pharmacokinetic booster (i.e., COBI as used with EVG in Stribild®). That person would have considered $t_{1/2}$ and **MRT** as important to that assessment and would have preferred compounds with the longest $t_{1/2}$ and largest **MRT**. The longest $t_{1/2}$ and highest **MRT** values from Table 4 are compounds **41**, **42**, and **47**, and a POSA would have preferred them for further study (with potentially also compounds **2** and **3**). Indeed, the remaining compounds **98**, **83**, **55**, **77**, **7**, and **8** provided significantly shorter half-lives ($t_{1/2}$ = 1.2–2.9 h) and smaller **MRT** values (2.2–4.2 h), and therefore would have been viewed by a POSA as less favorable for once-a-day administration.

157. Third, in the same PK study, only compounds **2**, **3**, **41**, **42**, and **47**, i.e., those with the longest $t_{1/2}$ and largest **MRT**, were investigated further in an oral administration study designed to assess oral bioavailability (**F**(%)), peak plasma concentration (**C**_{max}), and total plasma exposure (**AUC**). See WO '323 (DEFS_BIC_00002214-474) at 223-24 (DEFS_BIC_00002437-38) (Table 4) (annotated above in yellow); see also *id.* at 222

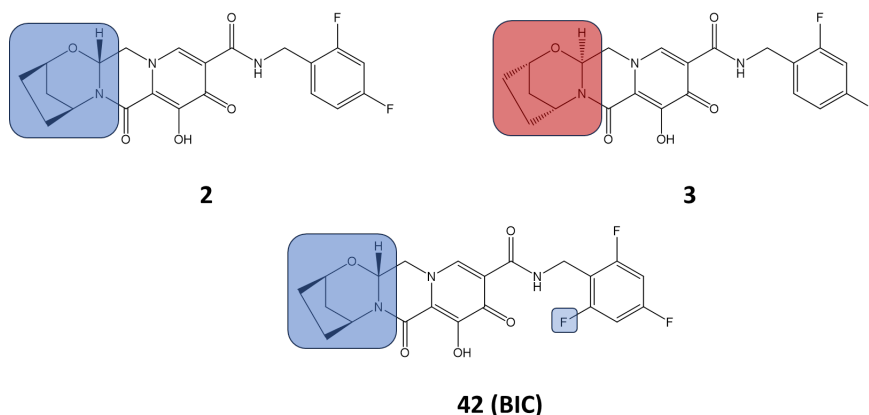
(DEFS_BIC_00002436) (compounds were administered orally as an aqueous suspension with 0.1% Tween 20 and 0.5% HPMC LV100 in Di Water at 1 mg/kg). The tested compounds provided an **F(%)** in the range of 10.7–40.7%, a **C_{max}** in the range of 1.2–7.8 mM, and an **AUC** in the range of 9.2–66.1 mM*h. *Id.* For once-a-day oral administration, a POSA would have desired compounds with higher **F(%)**, **C_{max}** and **AUC** values, given that these values would have established higher concentrations of the compound in the bloodstream. Of the five compounds tested, compounds **42** (BIC) and **2** provided the most desirable **F(%)**, **C_{max}**, and **AUC**. As such, they would have been considered superior candidates for once-a-day oral administration based on their greater bioavailability and the ability to deliver the highest blood concentrations for the longest periods of time among the tested compounds.

158. In view of the PK data provided in Table 4, a POSA would have identified compound **42** (BIC) as a particularly attractive compound for further study. It provided the longest half-life (**t_{1/2}**) and **MRT** of all compounds tested, and provided good oral bioavailability (similar to that of DTG in Johns; *see* Johns at 5905 (DEFS_BIC_00005003) (Table 6) (*supra*) (**F(%)** for DTG = 25–35)), along with elevated **C_{max}**, and **AUC** values, all desirable for a once-a-day INSTI.⁹ As such, compound **42** along with compound **2** would have been identified as the

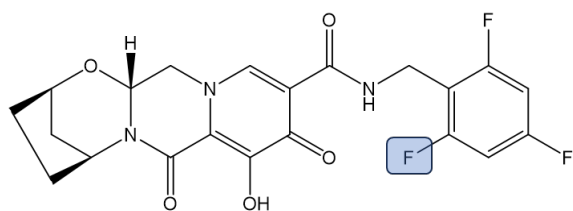
⁹ A POSA would have reasonably expected that the stereochemistry of the bicyclic “resistance region” (leftmost ring in claim 32) of compound **42** (BIC) would be preferred over the opposite stereochemistry. A POSA’s expectation in this regard comes from the comparison of compound **2** and its enantiomer compound **3**. Here, compound **2** (same stereochemical configuration as Compound **42** (BIC)) provided superior **CL** and **MRT**, a superior **t_{1/2}**, and far superior **F (%)**, **C_{max}**, and **AUC** as compared to its enantiomer **3**, and a POSA would recognize the **2** and **42** differ only by the presence of three fluorine atoms attached to the phenyl ring in **42** compared to only two fluorine atoms present in **2**.

best candidates for an INSTI intended for oral administration once-daily (as was previously discovered for DTG). In my opinion, a POSA would have viewed compound **42** as providing a distinct benefit over compound **2** in terms $t_{1/2}$ and **MRT**, while compound **2** would have been viewed as superior in terms of **F(%)** and resultant **C_{max}** and **AUC**. As such, a POSA would have selected each of these compounds based on their distinct respective advantages, but would have dismissed compounds **3**, **41**, and **47** in view of their sub-optimal results in the oral administration experiments from WO '323.

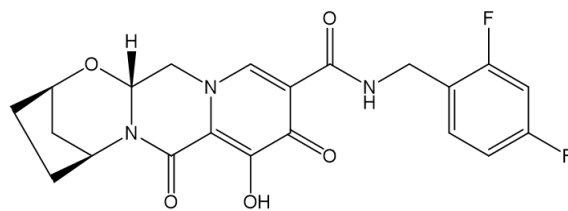
159. In particular, based on its combination of beneficial PK properties, a POSA would have selected compound **42** (BIC) from among the eleven compounds tested in Table 4 and the seven compounds of claim 32 (and also from among the compounds disclosed in WO '323) for once-a-day administration in the clinic. In my opinion, the fact that a POSA may also have investigated compound **2** does not detract from a POSA's motivation to select compound **42** (BIC) for the same developmental purpose. In fact, a POSA would have considered compounds **2** and **42** to be quite similar when considering their overall balance of relevant PK properties. Moreover, as stated previously, a POSA would have appreciated that these compounds have a large degree of structural similarity, differing only by an additional fluorine atom for compound



42 (as shown below; extra (third) fluorine group highlighted in blue), compared to compound **2**, which contains two fluorine atoms in the benzene ring.



Compound 42 (BIC)



Compound 2 (difluoro analogue)

As shown in Table 4, the IV PK data suggested that compound **42** would be superior based on its longer half-life and mean residence time as compared with Compound **2** ($t_{1/2}$ = 5.2 h vs. 4.6 h; **MRT** = 7.1 h vs. 6.5 h), whereas the data indicated better oral PK properties for compound **2** (**F** (%) = 44.7 vs. 28.0; **C_{max}** = 7.8 vs. 4.5; **AUC** = 66.1 vs. 28.6).

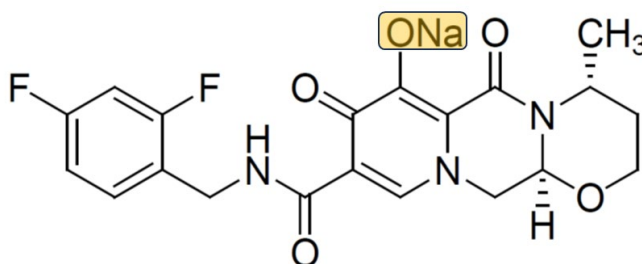
160. As such, it is my opinion that the POSA would have selected compound **42** (BIC) from among the INSTI compounds from WO '323 as one of the best compounds for once-a-day administration clinical studies. And given its beneficial properties, including low nanomolar potency, longer half-life, larger mean residence time, and good oral bioavailability, a POSA would have reasonably expected that compound **42** (BIC) would be a successful INSTI having advantages similar to structurally related DTG. As such, a POSA would have considered compound **42** (BIC) as a very promising INSTI for use in the treatment of HIV infection, and thus an obvious selection from among the INSTI compounds disclosed in WO '323.

D. Motivation to Select Bictegravir Sodium

161. WO '323 defines “pharmaceutically acceptable salt” as “a salt that is pharmaceutically acceptable and that possesses (or can be converted to a form that possesses) the desired pharmacological activity of the parent compound.” WO '323 (DEFS_BIC_00002214-474) at 14:16-18. This includes “salts derived from an appropriate base, such as an alkali metal (for example, sodium).” *Id.*; see also *id.* at 15:18-20 (metal salts typically are prepared by

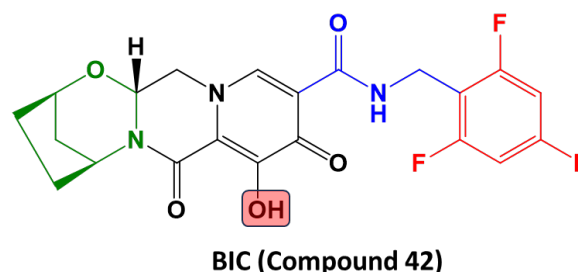
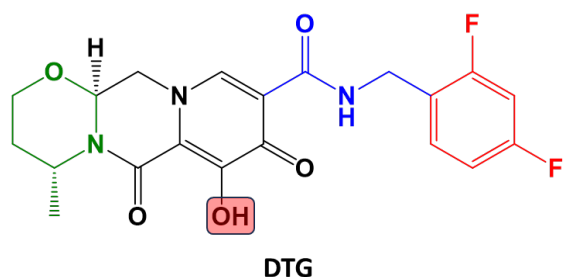
reacting the metal hydroxide with a compound of this invention, examples being salts containing Li^+ , Na^+ , and K^+).

162. DTG sodium was the preferred form of DTG according to WO '351, and both TIVICAY[®] and TRIUMEQ[®] were marketed prior to 2015 with DTG sodium. WO '351 (BICANDA01155483-513) at 5:10–27;



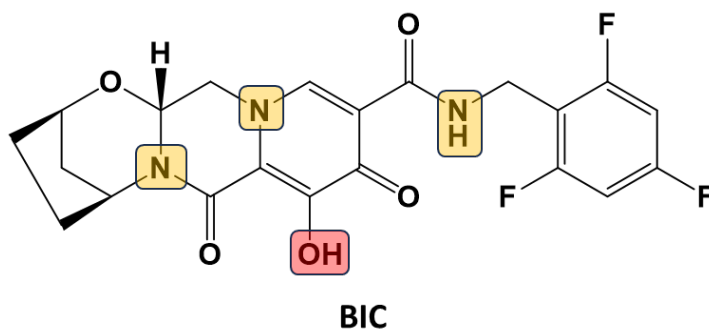
Tivicay Label (DEFS_BIC_00000659-695) at 14 (DEFS_BIC_00000672); Triumeq Label (DEFS_BIC_00002005-47) at DEFS_BIC_00002021-22; *see also* WO '351 (BICANDA01155483-513) at 4:12–25 (pointing to the WO 2006/116764 (“WO '764”) (DEFS_BIC_00000302-584) as providing procedures for preparing DTG and its pharmaceutically acceptable salts); WO '253 (DEFS_BIC_00000585-645) at 16-22 (DEFS_BIC_00000602-08) (confirming the position of sodium in DTG sodium (as preferred by WO '351) and providing synthetic methods using sodium hydroxide (NaOH)); WO '764 (DEFS_BIC_0000302-584) at 128-30 (DEFS_BIC_00000431-33) (confirming the same position of sodium for a structurally related sodium salt and providing synthetic methods using sodium hydroxide (NaOH)).

163. As shown below, DTG and BIC share significant structural similarity, including an identical metal chelation site (black) containing an acidic hydroxy group (emphasized in red shading).



It is this hydroxy group that interacts with a sodium base (NaOH in WO '764 (DEFS_BIC_00000302-584)) to form DTG sodium as preferred by WO '351 and as used in the approved DTG drug products.

164. A POSA would have known that the hydrogen atom in the hydroxy group of DTG (highlighted in red above) would be the most acidic proton in the molecule, and therefore would serve as the basis of the derived salt. A POSA would further understand that the hydroxy group (emphasized below in red shading) was the only reasonable functionality for salt formation as there are no suitable basic sites for conjugate acid salt formation, i.e., no suitably basic functionalities (because of the resonance available to each of the nitrogen atoms present in both BIC and DTG (emphasized below in yellow shading)).



165. That person would also have expected the hydroxy groups on DTG and BIC to have similar properties, including similar acidity (both considered weak acids), because each of the hydroxyls would exist in a similar chemical environment in the two compounds. Each would therefore be expected to form sodium salts (e.g., from NaOH) in the same way. A POSA would

have also assumed that BIC would have a similar acidity to that of DTG, each expected to have a $pK_a \sim 9-10$ (or slightly lower) based on a $pK_a \sim 10$ for phenol and a $pK_a \sim 9$ for 2,4-pentanedione (see Sections IX.C.1–2, ¶¶ 89-96 above). Indeed, the structural differences between DTG and BIC are distal from their common hydroxyl group and therefore would have been expected to have minimal impact on acidity, pK_a and the ease of salt formation. Therefore, a POSA would have reacted compound **42** (BIC) with the strong base NaOH and reasonably expected the formation of a stable (and irreversible) salt in direct analogy to DTG sodium as used in Tivicay[®].

166. In sum, 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[®]. Indeed, a POSA would have considered sodium salt formation to be a much-preferred option (over other salts disclosed in WO '323) for providing a stable (and irreversible) salt with BIC due to the success that had been achieved with the sodium salt of DTG.

167. Thus, a POSA would have selected sodium from among the potential salts described in WO '323 and would have specifically prepared BIC sodium (from NaOH) from among other possibilities given the expectation that the sodium salt would be preferable over the other options given the success of the sodium salt with the closely related structure of DTG. Based on the high degree of structural similarity with DTG, and the improved solubility property of DTG 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. See Johns (DEFS_BIC_00004995-5010) at 5909 (DEFS_BIC_00005003) (characterizing DTG sodium as a more soluble salt of DTG's acidic hydroxyl moiety); see also Section IX.D above (describing further structurally similar

compounds from WO '764 and WO '253 prepared as solid (e.g., crystalline) sodium salts). As such, a POSA would have considered BIC sodium to be an obvious choice for inclusion into a composition for oral administration such as a tablet composition.

168. In addition, Paulekuhn provides a survey on the frequency of different pharmaceutically acceptable counterions appearing in FDA-approved drugs from pre-1982 to 2006. This includes pharmaceutically acceptable cations, of which sodium made up 75.3% of the cations used in APIs overall (62.5 % from 2002–2006). Paulekuhn (DEFS_BIC_00000266-73) at 6667 (DEFS_BIC_00000268). The sodium cation also accounted for 65.3% of all salts used in oral formulations overall. *Id.* at 6668-69 (DEFS_BIC_00000269-70). As such, a POSA would have known 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 the sodium salt of DTG was a preferred salt.

169. Further, Bowker discusses the importance of pK_a when selecting potential salt forming counterions, including cations for acidic drugs, and further explains the need for a pK_a difference of at least three units between the ionizable group, e.g., hydroxyl group, and the base employed for deprotonation, i.e., salt formation. Bowker (DEFS_BIC_00000807-837) at 165-66 (DEFS_BIC_00000813-14). This represents a difference of acidity of at least three orders of magnitude. A ≥ 3 difference in pK_a was said to be especially important for particularly weak acids to prevent the salt from equilibrating with the free acid (protonated form) in solution. *Id.* Said another way, this is the pK_a difference required to form a stable (i.e., irreversible) salt.

170. Predicting a pK_a of ~9–10 for DTG and BIC (or slightly lower), a POSA would have looked primarily to bases with a pK_a of ~12 or greater, and especially to bases with an even higher pK_a to provide greater confidence of forming an irreversible salt, i.e., that would not undergo a reverse reaction to regenerate the starting acid and base, or a mixture of both the

product salt, and the starting acid and base in solution. Even for a weak acid having of pK_a of ~ 8.5 , a POSA would have looked to pK_a difference >3 (i.e., bases with a $pK_a \geq 11.5$) to ensure stability and irreversibility. Of the available pharmaceutically acceptable cations meeting this difference, a POSA would have nonetheless selected sodium hydroxide (NaOH) and potentially also potassium hydroxide (KOH) as the most suitable bases for salt formation.¹⁰

171. While a POSA may have considered both of these options, they would have been especially drawn to sodium (from NaOH) as the cation for BIC, given that it had already been selected (and preferred) for the structurally similar DTG, and because of the understanding of the POSA that sodium was the most common cation utilized for salt formation with acidic (or weakly acidic, such as DTG and BIC) APIs.

172. Thus, a POSA would have been motivated to select the sodium cation (and NaOH as a base) to prepare a salt of BIC. That person 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 pK_a difference between BIC and sodium hydroxide that would have been expected to provide the formation of an irreversible (and stable) salt.

173. In sum, it is my opinion from the viewpoint of a POSA that sodium would have been the most preferred option for salt formation with BIC, and that BIC sodium would have been preferred over BIC free acid in view of, e.g., its expected increased solubility in aqueous environments (as acknowledged by Johns for DTG), which would have been viewed as a benefit for both oral administration and drug absorption. As discussed above, a POSA would have considered BIC sodium to be an obvious salt to be used in oral dosage forms, e.g., tablets, useful

¹⁰ If a POSA employed a less conservative ≥ 2 difference in pK_a (i.e., bases with a $pK_a \geq 10.5$), contrary to the disclosures of Bowker for weak acids, it remains my opinion that sodium hydroxide (NaOH) and potentially also potassium hydroxide (KOH) would be the most suitable bases.

for treating of HIV infection in view of the combination of WO '323 and WO '351, considered in light of the knowledge of a POSA discussed in Section IX.

E. Motivation to Select TAF Fumarate and Hemifumarate, and FTC Free Base

174. As shown in Sections VI.B-C, each of the '802 and '846 Asserted Claims is directed to a tablet containing each of a compound of Formula I (i.e., BIC), tenofovir alafenamide (TAF), and emtricitabine (FTC), each of which may be present as a pharmaceutically acceptable salt thereof. Asserted Claims 2–8 of the '802 patent specifically require BIC as a salt and specifically a sodium salt (claims 2, 4, 5, 8), TAF as a salt and specifically TAF fumarate and TAF hemifumarate (claims 4, 5, 8), and emtricitabine as free base (claims 5, 8). Asserted Claims 2–3 of the '846 patent require BIC as a salt (claim 2) and specifically a sodium salt (claim 3), TAF as a salt (claim 2) and specifically TAF hemifumarate (claim 3), and emtricitabine as free base (claim 2).

175. WO '351 (discussed above) discloses pharmaceutical combinations containing the “second generation” INSTI DTG along with the nucleotide reverse transcriptase inhibitor (NtRTI) tenofovir and prodrugs thereof (TDF and TAF) and the nucleoside reverse transcriptase inhibitor (NRTI) FTC, including pharmaceutical compositions containing each compound, where solid oral dosage forms are preferred, and tablets are particularly preferred. WO '351 (BICANDA01155483-513) at BICANDA01155483 (Abstract), 6:24-32 (describing FTC as an NRTI), 9:4-16 (describing tenofovir as an NtRTI), 23:6-8 (stating a particular preference for tablet dosage forms). In a particularly preferred embodiment, the pharmaceutical composition comprises 40 mg to 60 mg of DTG, 150 to 250 mg FTC, 5 mg to 42 mg tenofovir (in particular TAF), and pharmaceutical excipients. *Id.* at 19:3-12. This includes a specifically preferred embodiment where the composition contains about 50 mg DTG, about 200 mg FTC and about 25 mg of tenofovir (in particular TAF). *Id.* at 19:30-20:12.

176. WO '351 also states a particular preference for DTG as a sodium salt, FTC in the form of its free base, i.e., not in the form of an acid addition salt, and the tenofovir prodrug TAF present in the form of its hemifumarate or fumarate, especially its hemifumarate. WO '351 (BICANDA01155483-513) at 5:22-27 (DTG), 8:10-11 (FTC), 13:16-18 (TAF).

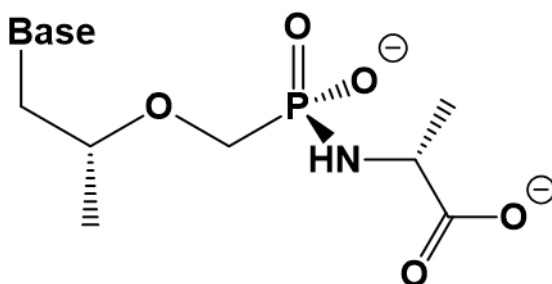
177. A POSA therefore would have appreciated from WO '351 that FTC as free base and TAF as hemifumarate or fumarate, and especially TAF hemifumarate, as required by one or more of Asserted Claims 4, 5, and 8 of the '802 patent and Asserted Claims 2-3 of the '846 patent, were well-known and preferred options for these compounds. In my opinion, 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. Notably also, WO '323 describes pharmaceutical compositions containing an INSTI, e.g., compound **42** (BIC) and its sodium salt as discussed above, along with an NRTI such as FTC and an NRTI such as TAF fumarate. WO '323 (DEFS_BIC_00002214-474) at 37:7-11, 38:13-17 (NRTIs), 38:18-21 (NtRTIs), 39:25-27 (disclosing an embodiment where the INSTI, e.g., compound **42** (BIC), is combined with two additional therapeutic agents). Thus, a POSA would have also selected FTC free base and TAF as a fumarate or hemifumarate (and especially TAF fumarate) to combine into a single tablet dosage form along with BIC sodium (as discussed in the preceding section) in view of the combination of WO '323 and WO '351, considered in light of the knowledge of a POSA discussed in Section IX.

178. In sum, it is my opinion that a POSA would have been particularly motivated to prepare a single tablet containing BIC sodium, TAF fumarate or hemifumarate, and FTC free base as covered by or required by one or more of '802 and '846 Asserted Claims. A POSA would have expected success in the preparation of such a tablet at least in view of Gilead's admission in WO '323 that methods for actually preparing single dosage units such as tablets are

“known, or will be apparent, to those skilled in this art.” WO '323 (DEFS_BIC_00002214-474) at 36:12-18. In view of the analyses and opinions provided above, a POSA would have considered it obvious to prepare a tablet composition containing BIC sodium, TAF fumarate or hemifumarate, and FTC free base.

F. Degradation of Tenofovir Alafenamide in Basic Environments

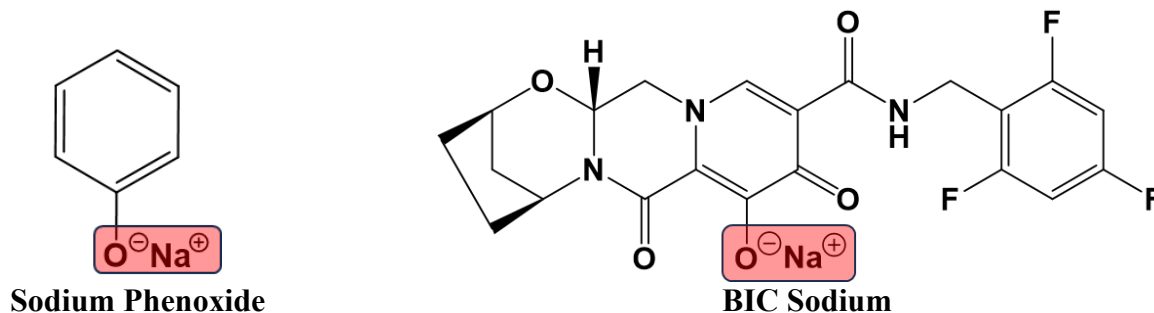
179. As explained in Section IX.E.1, a POSA would have had a high expectation that TAF's isopropyl ester group would have hydrolyzed to its corresponding carboxylic acid under basic conditions, which would then react further to provide the compound TFV-Alanine (GS-7160).



TFV-Alanine (GS-7160)

As hydrolysis of an ester under basic conditions is an irreversible process, the above product would not have converted back to TAF. Hydrolysis of TAF's isopropyl ester therefore would have provided a degradation mechanism that would remove TAF's function as a prodrug capable of absorption into the bloodstream and into cells (where it was known to convert to tenofovir (TFV) to provide its HIV reverse transcriptase inhibitory function). As such, a POSA would have known that base-mediated hydrolysis was a risk that could reduce the utility of TAF as a prodrug for the treatment of HIV infection with TFV, especially if the degradation of TAF occurred prior to administration to a patient.

180. A POSA would have expected that bicitegravir (BIC) would have a $pK_a \sim 9-10$ (or slightly lower) and would therefore form a stable sodium salt upon reaction with sodium hydroxide ($pK_a > 14$). See Section X.C. The resultant BIC sodium (below right) is an ionic salt and therefore a basic compound having an electron rich hydroxide ion similar in both its pK_a and reactivity to that of sodium phenoxide (below left).



As such, BIC sodium would have been capable of acting as a nucleophile itself, and also capable of providing hydroxide ion (OH^-) in the presence of water through conversion back to BIC free acid.¹¹

181. In my opinion from the viewpoint of a POSA, BIC sodium therefore would have been seen as capable of conversion of the isopropyl ester present in TAF to the corresponding acid, thereby destroying the prodrug and its accompanying benefits (especially in the presence of water). A POSA would have expected for this to occur in aqueous solution, but also in the solid state albeit at a slower rate. Accordingly, I believe a POSA would have been motivated to keep BIC sodium and TAF (or its fumarate/hemifumarate) separate from one another so as to reduce the risk of TAF degradation.

¹¹ Though the equilibrium between BIC sodium and water ion favors these reactants, a POSA would understand that an equilibrium would be established with some amount of both BIC free acid and hydroxide ion, making a strong base available for the hydrolysis of the TAF isopropyl ester as described above.