

IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE

VIIV HEALTHCARE COMPANY,  
SHIONOGI & CO., LTD. and VIIV  
HEALTHCARE UK (NO. 3) LIMITED,

Plaintiffs,

V.

GILEAD SCIENCES, INC.,

Defendant.

C.A. No. 18-224 (CFC) (CJB)

REBUTTAL EXPERT REPORT OF DAVID W. C. MACMILLAN, PH.D.

January 10, 2020

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**REBUTTAL EXPERT REPORT OF DAVID W. C. MACMILLAN, PH.D.**

**I. PERSONAL BACKGROUND**

1. I am currently the James S. McDonnell Distinguished University Professor of Chemistry, as well as the Director of the Merck Center for Catalysis at Princeton University, where I have been employed since September 2006. I was also the Chairman of the Department of Chemistry at Princeton University from 2010 to 2015. My research program is centered on chemical synthesis, which is an organic chemistry specialty consisting of new reaction development and molecular construction, with an emphasis on applications in the pharmaceutical sciences, especially medicinal chemistry and process chemistry.

2. I earned my Ph.D. in organic chemistry at the University of California at Irvine in 1996, where Professor Larry E. Overman, Ph.D., supervised my doctoral research. Subsequently, I attended Harvard University where Professor David A. Evans, Ph.D., supervised my postdoctoral research.

3. I began my independent research career in July 1998 as an Assistant Professor at the University of California at Berkeley. After only two years at Berkeley, I was offered in 2000 a tenured professorship as an Associate Professor of Chemistry.

4. In June 2000, the California Institute of Technology (Caltech) recruited me and I joined their faculty. Caltech, in 2002, promoted me to Full Professor in Chemistry after my fourth year of independent research, a position that is typically awarded after 15 years of independent research.

5. After five years of independent research, I was again promoted in 2003 as the Earle C. Anthony Professor of Chemistry at Caltech, a position that usually takes 25 years to obtain.

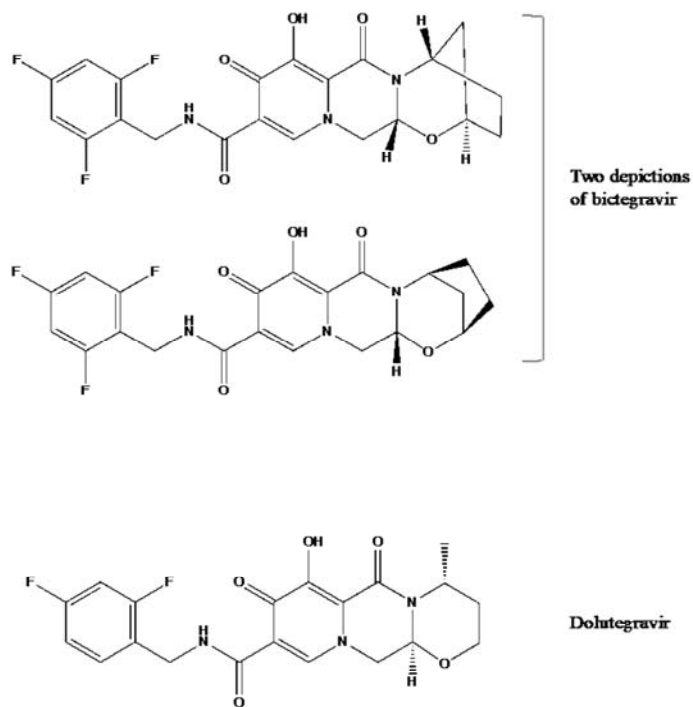
**A. Bictegravir's Ethylene Bridge is Substantially Different than Dolutegravir's (and Its Stereoisomers') Methyl Substituent**

107. Dr. Wipf opines that bictegravir's A-ring ethylene bridge is insubstantially different from the claim 6 compounds' methyl substituent at the 4-position on the oxazine ring. *See* Wipf. Rpt. ¶ 362. I disagree. A bridge, and the resulting bridged ring system, is a unique structural feature that a person of skill in the art—a chemist—would view as significantly different from a terminal methyl group.

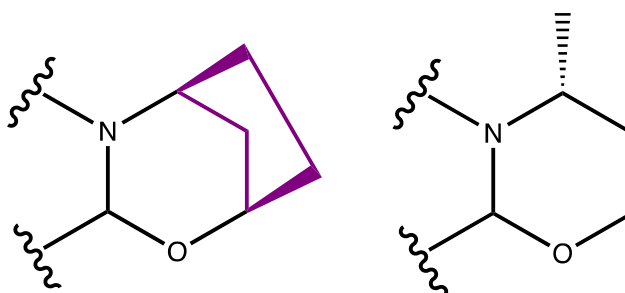
108. A bridged ring system—the system created by the substitution of bictegravir's ethylene bridge—is a unique bicyclic group in many ways. First, differently from dolutegravir, bictegravir has four rings, as opposed to dolutegravir's three rings.<sup>2</sup> Second, bictegravir's ethylene bridge connects at non-neighboring atoms, making it a bridged ring system and part of the core multi-cyclic framework. Bridging a ring—such as with the ethylene bridge in bictegravir—adds three-dimensionality to the ring system.

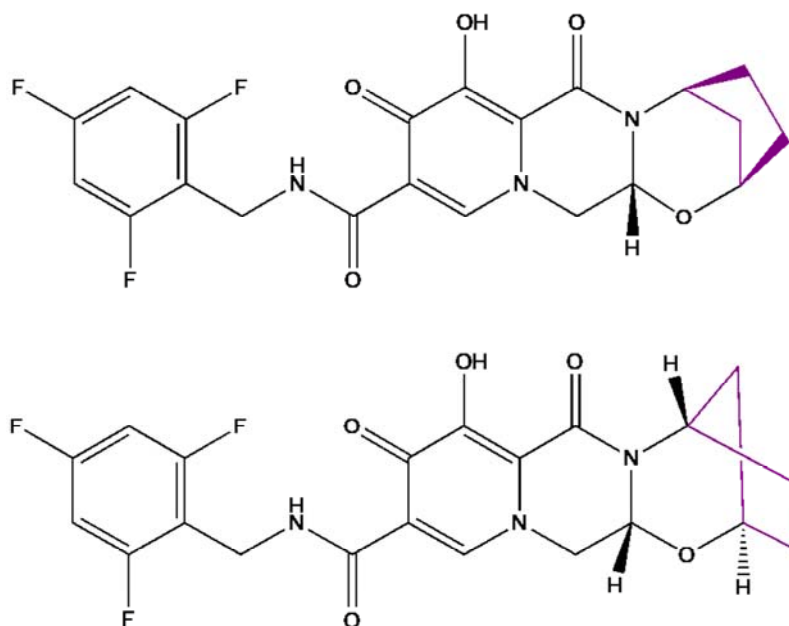
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<sup>2</sup> I note that prior art publications disclosed core structures with two fused rings that are similar in structure to dolutegravir. In that way, the prior art to dolutegravir has two-ringed structures, dolutegravir has a three-ringed structure, and bictegravir is a four-ringed structure. *See* WO 2005/016927 A1, Abstract, Examples 377 and 378. Moreover, bictegravir's fourth ring is unique because it is bridged, making its fourth ring perpendicular to the rest of the structure and overall increasing the three-dimensionality of the structure.



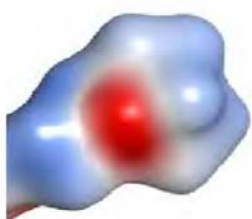
109. I have drawn and colored bicitegravir's fourth ring in purple below.



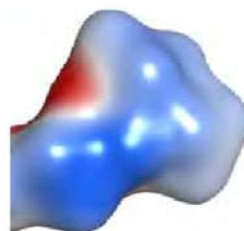


110. Chemists use a shorthand to represent three-dimensional structures on a two-dimensional page. This has the effect to the mind's eye that the structures are flattened even though they exist in highly different spatial arrangements. Indeed, if we draw the bridged ring of bicitragravir in a three-dimensional perspective and compare it to the monocyclic ring of dolutegravir, also in three-dimensional format, it is much more obvious the degree of volume and spatial differences between the two molecules. See Expert Report of Charles H. Reynolds adapted from Figures 2, 3 ("Reynolds Rpt.").

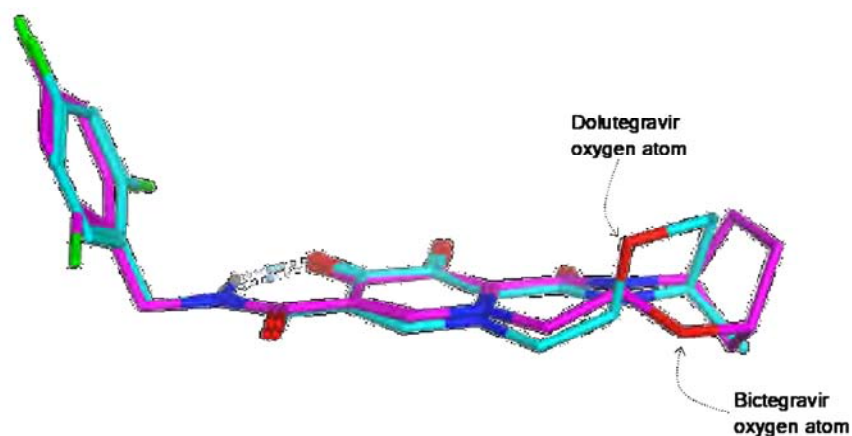
Bicitragravir A-ring and dolutegravir A-ring in same orientation



*Bicitragravir bridged bicyclic A-ring: more spherical, distributed positive charge, oxygen in lower middle*



*Dolutegravir monocyclic methyl-substituted A-ring: more planar, concentrated positive charge, oxygen in upper left*



111. As I discussed above, there are multiple types of bicyclic ring systems—dolutegravir contains only fused rings, which are very common in small molecules and drug development. However, bridges are rare in drug development and particularly in anti-infectives, which includes antivirals like bictegravir. In fact, a January 2016 publication found that only 13 anti-infective drugs, or about 1.4% of all anti-infective drugs, have bridged rings. See Fei Mao et al., *Chemical Structure-Related Drug-Like Criteria of Global Approved Drugs*, 21 Molecules 5, 8 (2016). This highlights how substantially different bridged systems are from even other bicyclic systems, not to mention a mono-substituted A-ring system like dolutegravir.

Table 2. Number of drugs containing non-aromatic rings or bridge rings in the whole database and five sub-databases.

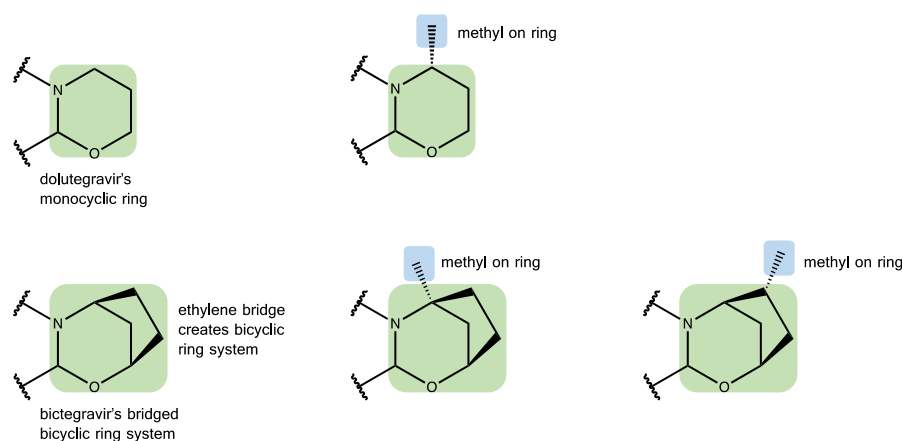
| Number of Non-Aromatic Rings | All Drugs | Oral Drug | CNS Drugs | Cardiovascular Drugs | Anti-Infective Drugs | Anti-Cancer Drugs |
|------------------------------|-----------|-----------|-----------|----------------------|----------------------|-------------------|
| 0                            | 2985      | 435       | 416       | 466                  | 372                  | 182               |
| 1                            | 2164      | 343       | 443       | 332                  | 293                  | 117               |
| 2                            | 854       | 147       | 199       | 138                  | 140                  | 61                |
| 3                            | 258       | 47        | 29        | 35                   | 60                   | 31                |
| >3                           | 464       | 55        | 8         | 33                   | 27                   | 43                |
| bridge rings                 | 166       | 24        | 27        | 17                   | 13                   | 8                 |

**Table 4.** The proportion of drugs containing only aromatic rings, only non-aromatic rings, both aromatic and non-aromatic rings, no rings and bridge rings in the whole database and five sub-databases.

| Classes <sup>a</sup> | Only Aromatic Rings               | Only Non-Aromatic Rings | Both Aromatic and Non-Aromatic Rings | No Rings | Bridge Rings |
|----------------------|-----------------------------------|-------------------------|--------------------------------------|----------|--------------|
| All drugs            | 37.5 (12.1, 16.5) <sup>b</sup>    | 12.4                    | 42.0 (11.1, 11.8) <sup>c</sup>       | 5.8      | 2.4          |
| Oral drug            | 36.9 (11.1, 15.9) <sup>b</sup>    | 11.1                    | 45.2 (11.6, 12.4) <sup>c</sup>       | 4.1      | 2.3          |
| CNS drugs            | 31.7 (8.8, 18.3) <sup>b</sup>     | 7.0                     | 53.6 (12.0, 17.4) <sup>c</sup>       | 5.3      | 2.4          |
| Cardiovascular drugs | 42.0 (14.1, 17.3) <sup>b</sup>    | 7.3                     | 45.3 (12.8, 12.3) <sup>c</sup>       | 3.6      | 1.7          |
| Anti-infective drugs | 37.8 (10.5, 17.3) <sup>b</sup>    | 15.9                    | 41.5 (13.0, 11.9) <sup>c</sup>       | 3.3      | 1.4          |
| Anti-cancer drugs    | 30.1 (9.5, 7.7, 7.9) <sup>d</sup> | 13.3                    | 43.7 (6.6, 6.8, 5.0) <sup>e</sup>    | 11.1     | 1.8          |

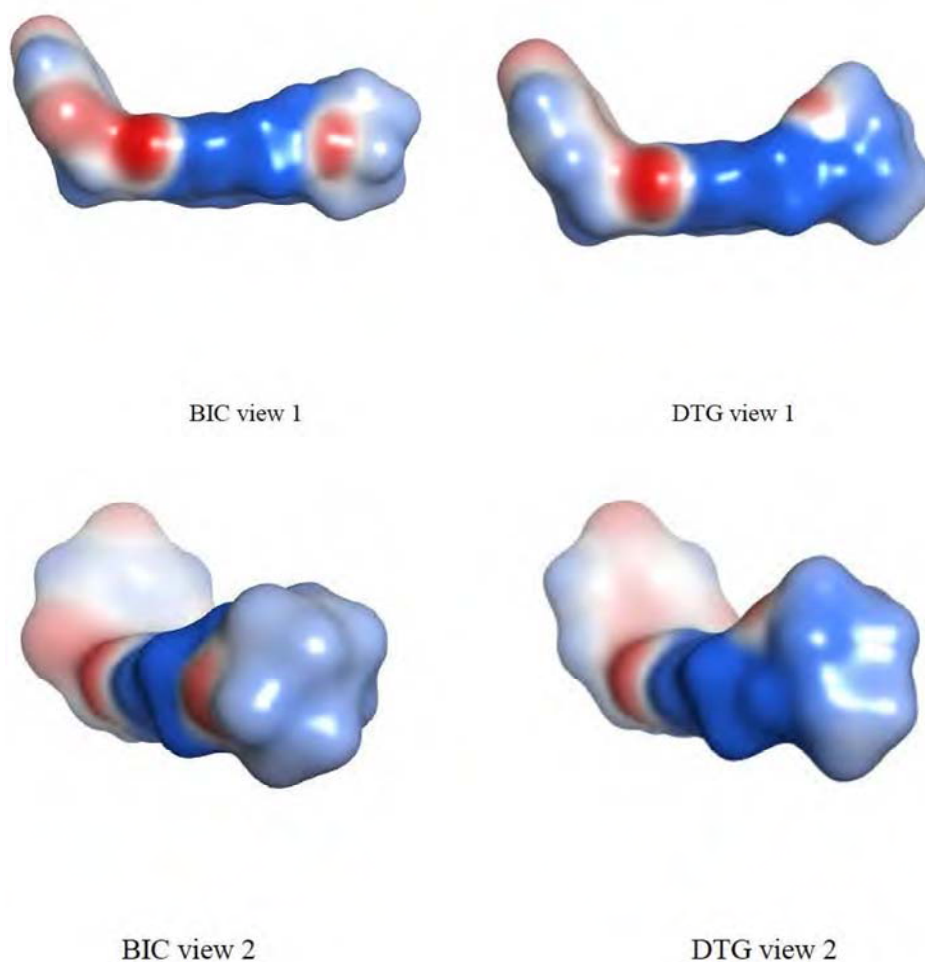
<sup>a</sup> The captions in each row represent drugs containing different rings; <sup>b</sup> The numbers in brackets represents the proportions of drugs with one aromatic ring and two aromatic rings, sequentially; <sup>c</sup> The numbers in brackets represents the proportions of drugs with one aromatic ring and one non-aromatic ring, two aromatic rings and one non-aromatic ring, sequentially; <sup>d</sup> The numbers in brackets represents the proportions of drugs with one aromatic ring, two aromatic rings and three aromatic rings, sequentially; <sup>e</sup> The numbers in brackets represents the proportions of drugs with two aromatic rings and one non-aromatic ring, two aromatic rings and two non-aromatic rings, two aromatic rings and three non-aromatic rings, sequentially.

112. This is unsurprising. Bridges typically have different properties than non-bridged ring systems or even fused ring systems, and bictegavir's bicyclic ring system created by its ethylene bridge is fundamentally different than dolutegavir's oxazine monocyclic ring with a methyl substituent.<sup>3</sup>



<sup>3</sup> I am using the term ethylene bridge because ViiV has approached the comparison of bictegavir and dolutegavir from the position that bictegavir has a six-membered oxazine ring with an ethylene bridge. However, chemists could also, and would often, view bictegavir as actually having an oxazepine (seven-membered) ring system with a methylene bridge. This property of bictegavir makes it even more different from dolutegavir. Bictegavir can be described as having a different base A-ring than dolutegavir does (six-membered versus seven-membered) and has an additional ring as part of its core structure. Dolutegavir cannot be described as having anything other than a six-membered base A-ring. The fundamental attribute of a bridged ring system is that it is its own molecular entity. It looks and behaves as a five-, six-, and seven-membered ring system all at the same time. Meaning, it functions as a three-dimensional bicyclic structure.

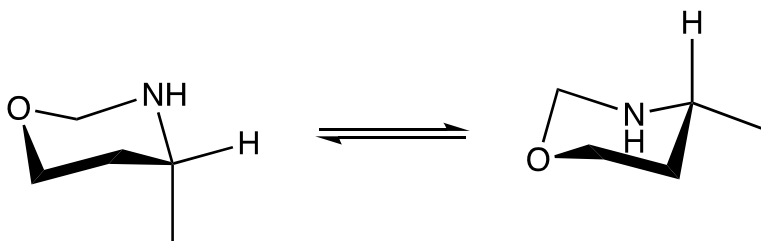
113. *Electronics:* Bictegravir and dolutegravir have different electronics at the A-ring due to the difference between bictegravir's ethylene bridge and dolutegravir's methyl substituent. This is shown from the difference in electrostatic surfaces for the bound ligands, bictegravir and dolutegravir, in the integrase pocket. See Reynolds Rpt. ¶¶ 55-57 (and images included therein). In the below images from Dr. Reynolds's Report, the red portions indicate areas (atoms) with negative partial charges and the blue areas indicate atoms with positive partial charges. A more "intense" blue indicates more positive charge.



114. First, the top view (view 1) shows that the location of the oxygen and the accompanying negative charge is in a completely different location and therefore that negative charge (and the oxygen) will interact differently not only with the integrase pocket but also with

other targets in the body. Second, on the A-ring it is clear that the globularity/spherical nature of bictegavir's ethylene bridge and bridged bicyclic system is significant, as opposed to dolutegavir that has an "edge" (the methyl group) sticking out from a plane (the oxazine ring). Therefore, it is clear that the shapes of these two molecules' A-rings are different. This will significantly impact how bictegavir and dolutegavir interact with the integrase pocket and with other targets in the body. Third, the electrostatic surfaces show a difference in positive charge distribution over bictegavir's bridged bicyclic system—the more even and muted blue that is easiest to see in view 2—that is likely caused by a delocalization of the positive charge around that system. This is in contrast to dolutegavir, where the positive charge appears to be localized in certain areas, showing larger blue contrasts on the edges of its A-ring.

115. *Conformation:* As discussed above, molecules can take on different ring conformations. In particular, dolutegavir can take on two different ring conformations, and can flip between the two.



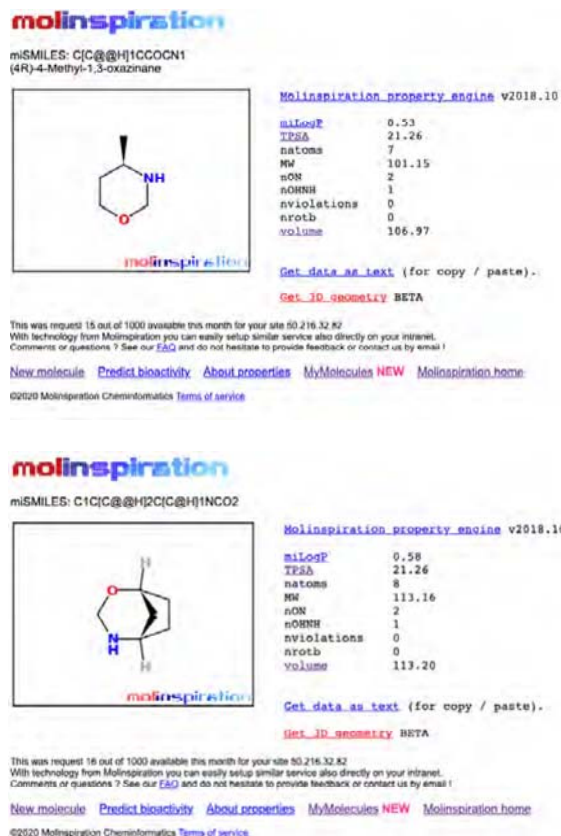
As shown above, dolutegavir exists in two different chair conformations: one where the methyl group is axial (left) and one where it is equatorial (right). This is in contrast to bictegavir. Bictegavir can only exist in a single conformation because the bridge locks the A-ring portion of the molecule into a single, bis-axial conformation. This is important for a number of reasons. First, the potency of a molecule is related to the conformation in which the molecule binds to the active site of the enzyme. When a molecule has multiple conformations, typically one of those conformations is the potent binder while the other conformations are less potent. As such, the

more conformations that are available to a given molecule at room temperature, the larger the negative impact on potency. In a molecule that has a locked conformation, it can only bind in one orientation and as such cannot lose potency as a function of less active conformations (as they do not exist). In this case, this difference in potency could be seen in the potency against resistant mutants as well, where the active site of the enzyme has been changed.

116. Second, molecules which have multiple conformations therefore have multiple orientations or pathways by which they can undergo metabolism *in vivo*. In contrast, a molecule which has a locked conformation can only undergo metabolism from the conformation in which it permanently resides. Some metabolic pathways require that hydrogens on the molecule be in a specific spatial or electronic configuration. *See* Frans M. Belpair & Marc G. Bogaert, *The Fate of Xenobiotics in Living Organisms*, in *THE PRACTICE OF MEDICINAL CHEMISTRY*, 608-09, 593-614 (Camille Georges Wermuth ed., 1st ed. 1996). The existence of multiple conformations allows those hydrogens to achieve multiple spatial or electronic configurations thereby enabling metabolism to happen more readily. In contrast, a molecule with a locked conformation has hydrogens which are in a set spatial and electronic configuration, which often can lead to diminished metabolism due to the hydrogens in question being less available to *in vivo* oxidation. As discussed more below, bictegravir is metabolized more slowly than dolutegravir.

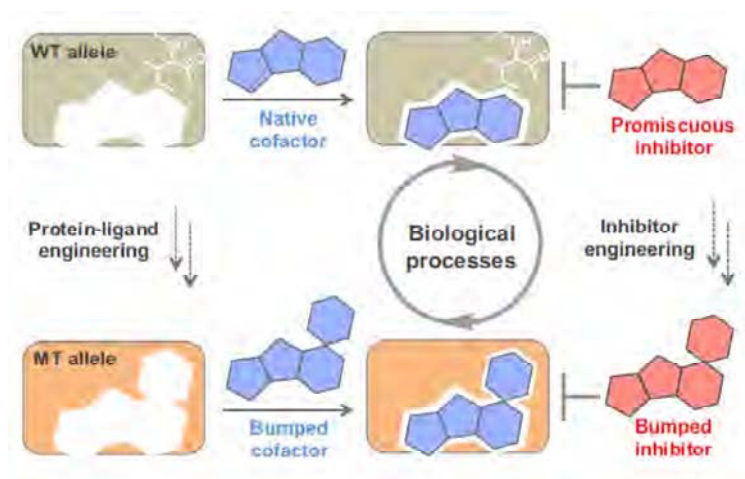
117. *Volume and globularity*: Bictegravir's A-ring with an ethylene bridge has a different volume than dolutegravir's ring with a single methyl substituent. This change in volume is caused solely by the difference between bictegravir's ethylene bridge and dolutegravir's A-ring methyl substituent. Dr. Wipf's report attempts to minimize the difference in volume between bictegravir's A-ring bridge and dolutegravir's A-ring methyl substituent by providing the difference in molar volume for the *entire molecule*. *See* Wipf Rpt. ¶ 282. However,

bictegravir's A-ring has a different volume, caused by its different bridged structure, than dolutegravir—an increase in volume of 6%. *See* Wipf Rpt. Ex. 7 at 2-3 (below). I have used the same program as Dr. Wipf to calculate various properties for bictegravir's ethylene bridge creating a bridged bicyclic A-ring and dolutegravir's methyl substituted monocyclic A-ring. All of my Molinspiration screenshots are included in Exhibit C.



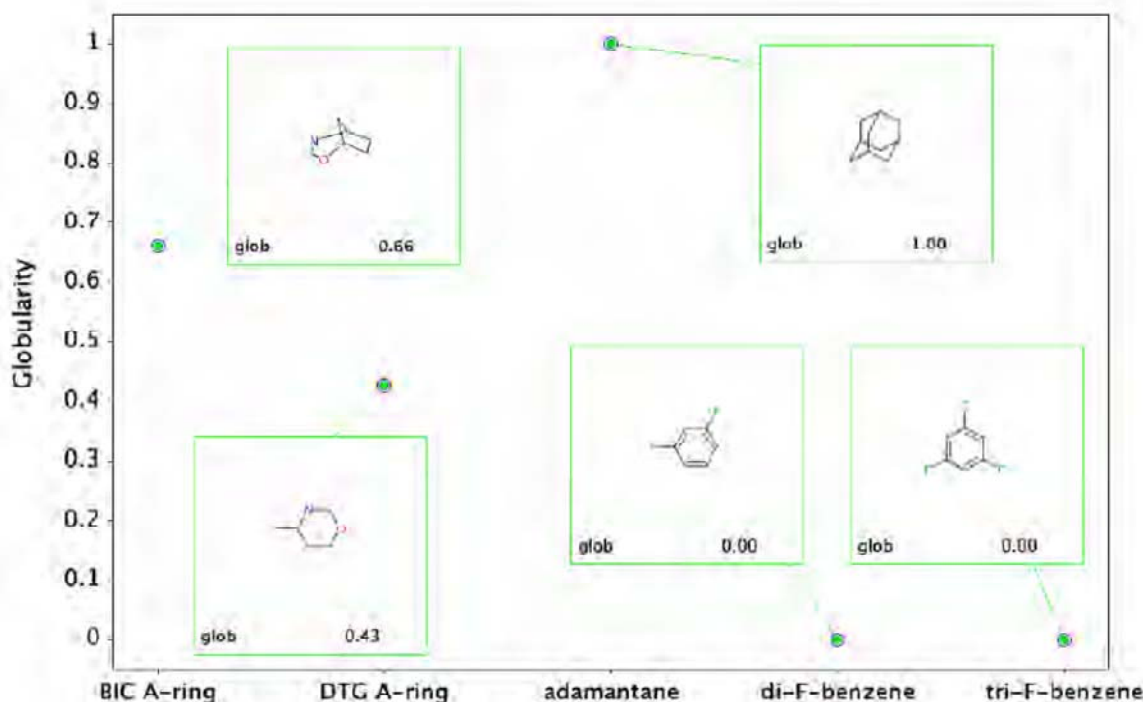
118. This number may seem small, but as illustrated by the bump-hole concepts, which has become an important field of research over the last 20 years and has been exploited extensively by biologists and chemists alike, a change in a molecule's volume by 6% is significant. *See* Kabirul Islam, *The Bump-and-Hole Tactic: Expanding the Scope of Chemical Genetics*, 25 Cell Chem. Biology 1171-84 (2018) (describing how addition of a small “bump” in a molecule can fill a corresponding hole in an enzyme) (“Islam 2018”). In fact, this bump-hole

process is exemplified in Islam 2018 with the addition of a fourth ring—just as bictegravir’s ethylene bridge added a fourth ring to the integrase inhibitor structure. *See id.* at Fig. 1 (below).



119. Moreover, bictegravir’s A-ring has a different type of volume than dolutegravir’s.

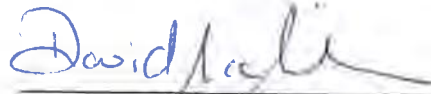
Dolutegravir is more planar (flatter) than bictegravir. This means that it will interact differently with enzymes and targets than bictegravir’s more spherical A-ring. Consistent with and supporting my opinion that bictegravir and dolutegravir have a different three-dimensional volume, I understand that they also have a different “globularity.” Reynolds Rpt. ¶¶ 78-81. Bictegravir is much more globular (spherical) than dolutegravir. *See id.* at Fig. 12 (below). This means it will behave more as a sphere when interacting with the active site of an enzyme. The figure below plots bictegravir’s A-ring against dolutegravir’s A-ring and a known highly-globular ring system, adamantane. The closer the value of the ring is to 1, the more globular (or spherical) the ring system is. Bictegravir’s bridged bicyclic ring system has a much higher globularity value than dolutegravir’s more planar monocyclic ring system.



120. The significance of this difference in structure, volume, and globularity is supported by the modeling and conclusions of Dr. Reynolds, and was recognized by the researchers who conducted the experiments and provided the data to Dr. Reynolds. Reynolds Rpt. ¶¶ 41-43, 54-55, 62; Dec. 13, 2019 E-mail from Peter Cherepanov to Chuck Reynolds, BICVHIVUS3029295 (“Cherepanov E-mail”). In his e-mail, Dr. Cherepanov concludes that bictegravir’s “more intimate contacts via its extended structure” (caused by bictegravir’s ethylene bridge) causes “better performance of the compound.” Cherepanov E-mail.

121. *Orientation/Three-Dimensionality*: Bictegravir’s ethylene bridge on the A-ring has the opposite stereochemistry as dolutegravir’s methyl substituent. While Dr. Wipf seeks to minimize this difference, *see* Wipf Rpt. ¶¶ 300-03, 321, the stereochemical orientation of a compound is very important. As an example, imagine waking up in the morning and putting your right foot into your left shoe. It might still “work,” but it does not fit or work correctly. In medicine, thalidomide is just one example of how stereochemistry can greatly affect the

January 10, 2020

A handwritten signature in blue ink, appearing to read "David W. C. MacMillan", written over a horizontal line.

David W. C. MacMillan

IN THE UNITED STATES DISTRICT COURT  
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VIIV HEALTHCARE COMPANY,  
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HEALTHCARE UK (NO. 3) LIMITED,

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GILEAD SCIENCES, INC.,

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C.A. No. 18-224 (CFC) (CJB)

## SUPPLEMENTAL REBUTTAL EXPERT REPORT OF DAVID W. C. MACMILLAN

March 25, 2020

**SUPPLEMENTAL REBUTTAL EXPERT REPORT OF DAVID W. C. MACMILLAN**

1. As set forth in my November 15, 2019 Opening Report on Invalidity, my January 10, 2020 Rebuttal Report on Non-Infringement, and my February 7, 2020 Reply Report on Invalidity, I have been retained as an expert witness on behalf of Gilead Sciences, Inc. in this litigation. I hereby incorporate those reports as if fully set forth herein.

2. On January 30, 2020 (updated version of Cook 2020 published February 14, 2020), two articles were published in *Science* that relate to two of the compounds at issue in this litigation: bictegravir (BIC) and dolutegravir (DTG). See Nicola J. Cook et al., *Structural basis of second-generation HIV integrase inhibitor action and viral resistance*, 367 (6479) SCIENCE 806-810, 1-4 (2020) (“Cook 2020”); Dario Oliveira Passos et al., *Structural basis for strand-transfer inhibitor binding to HIV intasomes*, 367 (6479) SCIENCE 810-814, 1-4 (2020) (“Passos 2020”). Neither article was available to me when I submitted my Rebuttal Report on Non-Infringement. Because those articles directly relate to the differences between BIC and DTG, one of the issues in this litigation, I have reviewed the articles. They are consistent with and support the opinions I set forth in my Rebuttal Report on Non-Infringement.

3. Cook 2020, written by Peter Cherepanov, Alan Engelman, and others, was published online ahead of print in *Science* on January 30, 2020, and officially published in *Science* on February 14, 2020. It presents the cryo-electron microscopy structures of BIC and DTG bound to HIV integrase. Cook 2020 at 2. As the authors state, “[t]he inhibitors were defined particularly well in density maps,” which allowed them to determine that “DTG and BIC intimately contact the backbone atoms of Asn<sup>117</sup> and Gly<sup>118</sup> ... making 8 and 12 contacts, respectively, with interatomic distances  $\leq 5$  Å.” *Id.* at 1-2. The region of integrase that contains

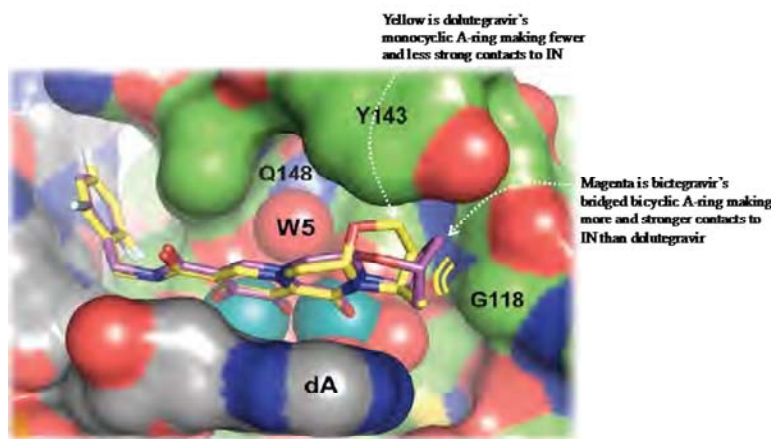
Asn117 and Gly118 is called the  $\beta 4$ - $\alpha 2$  connector or loop. BIC makes three contacts  $\leq 4 \text{ \AA}$  with the  $\beta 4$ - $\alpha 2$  connector, while DTG has no contacts  $\leq 4 \text{ \AA}$ . *Id.* at 2.

4. The contacts that BIC and DTG make with the backbone of Asn117 and Gly118 are “van der Waals” or “dispersion forces.” “Dispersion forces are typically of short range relative to, for example, electrostatic forces. ... [T]heir strength increases sharply as the intervening distance decreases.” Charles M. Roth et al., *Van der Waals Interactions Involving Proteins*, 70 BIOPHYSICAL JOURNAL 977-987, 978 (1996). The Cook 2020 authors highlight the  $\leq 4 \text{ \AA}$  contacts of BIC because those contacts are stronger, different, and better than DTG’s contacts with the  $\beta 4$ - $\alpha 2$  connector. Moreover, Cook 2020 demonstrates why an integrase inhibitor’s contacts with that region of the molecule are important. Cook 2020 studied a truncated version of DTG with no A-ring and found that it was approximately 80 times less effective against the HIV-1 G140S and Q148H double mutant. Cook 2020 at 2. The authors consider “contacts with the  $\beta 4$ - $\alpha 2$  connector as a crucial feature of the second-generation INSTIs.”<sup>1</sup> *Id.* BIC makes 50% more contacts with the  $\beta 4$ - $\alpha 2$  connector than DTG, and three of BIC’s contacts are significantly shorter and therefore stronger than DTG’s. *See id.*; *see also* March 25, 2020 Suppl. Rebuttal Expert Report of Charles H. Reynolds ¶¶3-9, 10-12, Figs. 2 & 3, Appendix A (showing the contacts that BIC and DTG make with the  $\beta 4$ - $\alpha 2$  connector and

<sup>1</sup> The authors determined that certain IN mutation amino acid substitutions perturb magnesium ion coordination in the IN active site. Cook 2020 at Abstract. Therefore, compounds that interact with integrase in ways beyond metal chelation maintain more activity even when the  $\text{Mg}^{2+}$  coordination is disturbed. Cook 2020 identified that additional long-range interactions from IN mutation substitutions could further impact the metal-chelating region. *Id.* at 4. Moreover, the Cook 2020’s conclusions about why  $\beta 4$ - $\alpha 2$  contacts are important for maintaining activity against the G140S/Q148H mutant could be extended to the G140S/Q148R mutant and explain bicitegravir’s better performance against that mutant compared to dolutegravir. *See* MacMillan Rebuttal Rpt. ¶ 136; Rebuttal Expert Report of Douglas D. Richman, ¶ 160; Manuel Tsiang et al., *Antiviral Activity of Bicitegravir (GS-9883), a Novel Potent HIV-1 Integrase Strand Transfer Inhibitor with an Improved Resistance Profile*, 60 Antimicrobial Agents & Chemotherapy 7086, Table 6 (2016).

highlighting the additional and stronger contacts that BIC makes with integrase compared to DTG).

5. The Cook 2020 authors highlighted this phenomenon with a picture in Figure 2(C) as annotated below:



The authors described this picture as the “Superposition of BIC-bound (magenta) and DTG-bound (yellow) structures, with protein and DNA shown in space-fill mode. Yellow lines accentuate proximity to the IN  $\beta 4$ - $\alpha 2$  connector.” Cook 2020 at 3, Fig. 2(C). The picture is clear: the yellow lines *accentuate* the proximity of the integrase inhibitors to the IN  $\beta 4$ - $\alpha 2$  connector and highlight BIC’s closer and more numerous contacts with that location on SIV. This is not an insubstantial difference between these contacts—in fact, BIC’s additional and stronger contacts in this region are reflective of the different shape, orientation, and volume of BIC’s bridged-bicyclic A-ring system created by its ethylene bridge. BIC’s improved contacts in this region are also consistent with its longer dissociation half-life from the G140S/Q148H HIV-1 Integrase-DNA Complex, *see* Kirsten White et al., *Bictegravir Dissociation Half-life from HIV-1 G140S/Q148H Integrase-DNA Complexes*, CROI Poster No. 497 at Table 4 (Feb. 13-16, 2017), and the conclusion that “BIC is better than DTG” in terms of its ability “to broadly inhibit the

known IN mutants,” Steven J. Smith et al., *Efficacies of Cabotegravir and Bictegravir against drug-resistant HIV-1 integrase mutants*, 15(37) *Retrovirology* 1-18, 11 (2018) (“Smith 2018”).

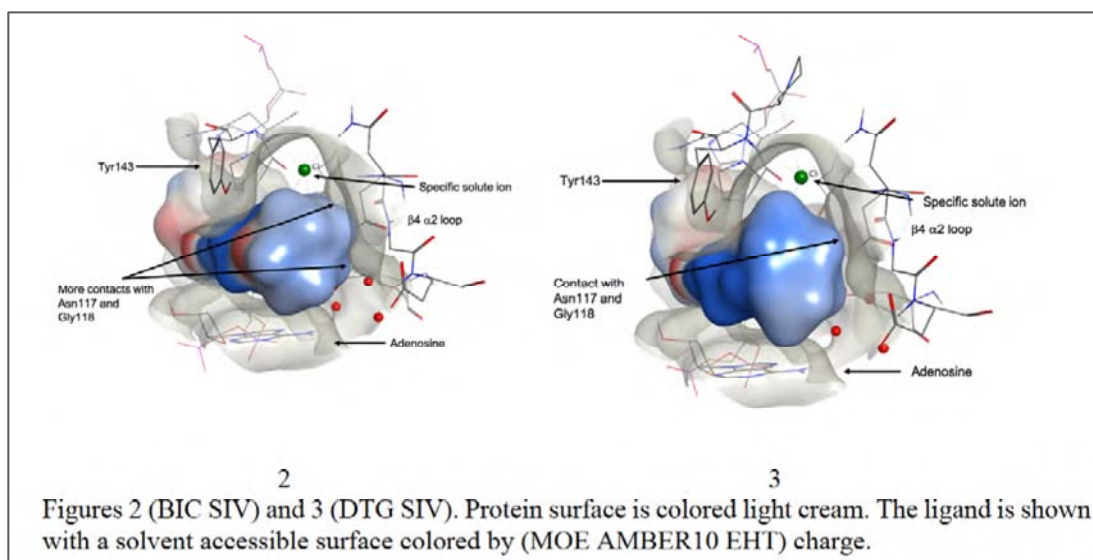
6. Similarly, the picture above highlights the structural differences between BIC and DTG at the A-ring region. The oxygen atoms are in two completely different locations, the orientation of the six-membered ring is completely different, and BIC’s bridged-bicyclic ring system terminates in a fourth ring: a cyclopentyl that interacts with integrase more and more strongly than DTG’s three-ringed system. The volume and orientation of BIC’s bridged-bicyclic A-ring are important because BIC’s different volume and orientation affect its interactions with (SIV) integrase compared to DTG, and these different interactions help explain meaningful experimental differences between the two compounds. This example shows that enzyme-substrate interactions can be highly specific. A few structural changes impact the way the substrate contacts and binds with the enzyme and, ultimately, how it performs as a broadly effective inhibitor. This is consistent with, and supports, the opinions I set forth in my Rebuttal Report on Non-Infringement. *See* MacMillan Rebuttal Rpt. ¶¶107-112, 114-115, 117-128, 133-136, 139, 145-148, 164.

7. My understanding of the Cook 2020 article and the difference in number of contacts between BIC and SIV integrase and DTG and SIV integrase is confirmed by an e-mail between Dr. Peter Cherepanov, one of the authors of the Cook 2020 paper, and Dr. Charles Reynolds. *See* March 20, 2020 E-mail between Peter Cherepanov and Charles Reynolds (“March 20 Cherepanov E-mail”). In it, Dr. Cherepanov confirmed that BIC has more intimate contacts than DTG with the  $\beta$ 4- $\alpha$ 2 connector (“loop” in the e-mail) and that those “more intimate contacts with integrase backbone explain improved resistance profile of BIC vs DTG, which was shown by Hughes’ lab.” *Id.* Dr. Cherepanov’s understanding of the difference between BIC’s and DTG’s

contacts with the  $\beta 4$ - $\alpha 2$  connector and BIC's improved resistance profile compared to DTG are consistent with and support the opinions I set forth in my Rebuttal Report. *See* MacMillan Rebuttal Rpt. ¶¶107-112, 114-115, 117-128, 133-136, 139, 145-148, 164.

8. As discussed in my Rebuttal Report on Non-Infringement, I understand that Gilead asked an expert in molecular modeling, Dr. Reynolds, to evaluate the interaction of BIC and DTG with HIV-1 (and SIV) integrase. MacMillan Rebuttal Rpt. ¶145. While I do not regularly conduct the type of modeling simulations that Dr. Reynolds does and did for his supplemental report, I have extensive experience reviewing and using modeling data and crystal structure data in my work. I reviewed Dr. Reynolds' Supplemental Rebuttal Report and it supports my opinion that BIC and DTG are substantially different chemical structures and make substantially different contacts with the target enzyme.

9. Dr. Reynolds reviewed the recently-published final structures of BIC and DTG bound to SIV-integrase. Dr. Reynolds concluded that BIC makes more contacts with the main chain of Asn117 and Gly118 and that three of BIC's contacts are substantially closer than DTG's. Reynolds Suppl. Rebuttal Rpt. ¶¶3-10, 12, Figs. 2 & 3, Appendix A.



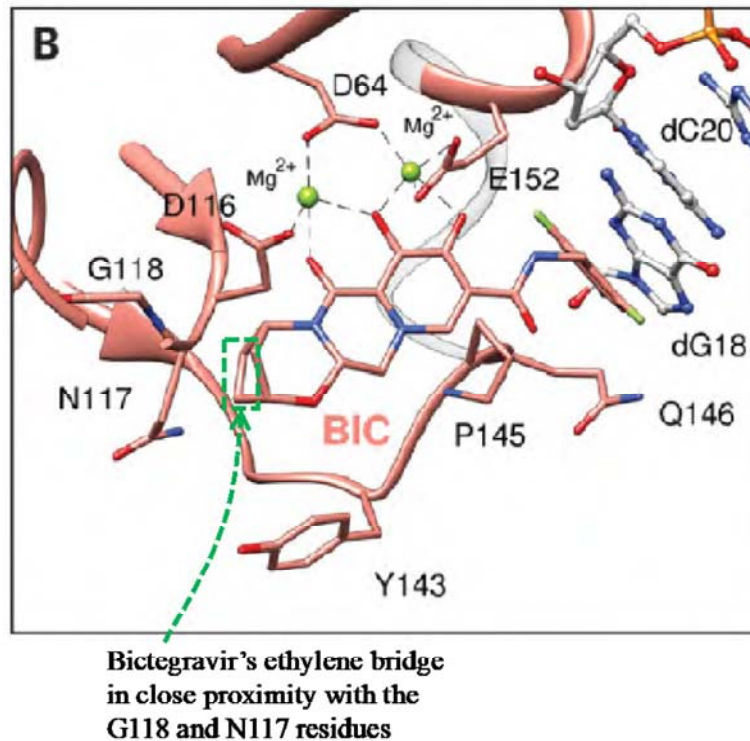
10. Moreover, Dr. Reynolds identifies that, at certain positions, all of BIC's contacts with the  $\beta$ 4- $\alpha$ 2 connector are closer than DTG's. *Id.* at ¶9. Further, Dr. Reynolds demonstrates that it is BIC's bridged-bicyclic ring system (and the ethylene bridge itself) that cause the closer and additional contacts with the  $\beta$ 4- $\alpha$ 2 connector and that makes it different from DTG. *Id.* at ¶¶9-11. Lastly, Dr. Reynolds concludes that, in light of the Cook 2020 article, Dr. Cherepanov's statement that "BIC makes more intimate contacts via its extended structure" is comparing BIC and DTG. *Id.* at ¶¶10-11 (quoting Cherepanov email to Reynolds); *see also* March 20 Cherepanov E-mail. Dr. Reynolds' opinions and conclusions are consistent with and support my opinions. The substantial differences in the chemical structure of BIC and DTG that are noted in this supplemental report and my Rebuttal Report on Non-Infringement influence the volume, conformation, and spatial orientation of these molecules and the interaction of these molecules with the integrase enzyme.

11. The Passos 2020 article recognizes BIC as "the most broadly potent of all clinically approved INSTIs." Passos 2020 at 1. This statement includes DTG.<sup>2</sup> As noted by the Passos 2020 authors, "[s]mall chemical modifications can markedly affect drug potency, as demonstrated previously for compounds targeting reverse transcriptase [ ] or protease." Passos 2020 at 2. The structural differences between BIC and DTG, which I would not characterize as "small," do affect drug potency against HIV-1 integrase-resistant mutants and also affect drug potency against various other non-desired targets in the body, pharmacokinetics, crystal structure

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<sup>2</sup> This statement by the Passos 2020 authors cites to the Smith 2018 article. This demonstrates that persons of skill in the art have reviewed and relied on the Smith 2018 article for its teachings that "BIC is better than DTG" in its ability "to broadly inhibit the known IN mutants." Smith 2018 at 11.

and packing, and numerous other drug properties, as I noted in my Rebuttal Report on Non-Infringement at ¶¶80, 89-94, 118-127, 129, 134-136, 140-153.



12. Passos 2020 depicts the binding mode of BIC in the HIV intasome (Figure 2(B)).

This Figure highlights the unique shape of BIC and its proximity to the G118 and N117 residues of the  $\beta 4$ - $\alpha 2$  connector which is caused by BIC's unique bridged-bicyclic system. I have annotated the Figure above to highlight that it is BIC's ethylene bridge that is closest to the  $\beta 4$ - $\alpha 2$  connector. Passos 2020's Figure 2(B) and statements about BIC being the most broadly potent currently-available integrase inhibitor, support my opinions that BIC is substantially different from DTG because of its structure, volume, orientation, conformation, interaction with enzyme targets, and potency in *in vitro* assays.

13. Overall, the Cook 2020 and Passos 2020 papers support my opinion that BIC is substantially different from DTG in its structure, volume, orientation, conformation, interaction

with enzyme targets, potency in *in vitro* assays, crystal structures, dissociation kinetics, and pharmacokinetics.

14. I reserve the right to revise, further supplement, and/or amend my opinions to address any new opinions advanced by Plaintiffs' expert witnesses. I further reserve the right to address additional evidence, articles, testimony, and/or data that are published in the literature or otherwise become available to me after the date of this report, up to and including at trial.

March 25, 2020

  
David W. C. MacMillan