

Filed on behalf of Petitioner CIPLA LIMITED

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CIPLA LIMITED

Petitioner

v.

GILEAD SCIENCES, INC.,

Patent Owner

Case No.: IPR2025-00033

U.S. Patent No. 11,744,802

Issued: September 5, 2023

Title: THERAPETUTIC COMPOSITIONS FOR TREATMENT OF HUMAN
IMMUNODEFICIENCY VIRUS

PETITION FOR *INTER PARTES* REVIEW

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<u>Exhibit No.</u>	<u>Description</u>
EX-1001	U.S. Patent No. 11,744,802 (“the ’802 Patent”)
EX-1002	U.S. Patent No. 11,744,802 File History (“the ’802 File History”)
EX-1003	Declaration of Prasanna Jagannathan
EX-1004	Declaration of Jeffrey Winkler
EX-1005	WO 2014/100323 A1 (“WO ’323”)
EX-1006	WO 2015/022351 A1 (“WO ’351”)
EX-1007	U.S. Patent Publication 2015/231079 (“US ’079”)
EX-1008	Michael J. Bowker, “A Procedure for Salt Selection and Optimization” <i>in</i> HANDBOOK OF PHARMACEUTICAL SALTS: PROPERTIES, SELECTION, AND USE 161–89 (P. Heinrich Stahl & Camille G. Wermuth eds., 2002) (“Bowker”)
EX-1009	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”)
EX-1010	Ruane et al., “Antiviral Activity, Safety, and Pharmacokinetics/Pharmacodynamics of Tenofovir Alafenamide as 10-Day Monotherapy in HIV-1-Positive Adults,” 63 J. ACQUIR. IMMUNE DEFIC. SYNDR., 449–55 (2013) (“Ruane”)
EX-1011	U.S. Patent No. 10,58,846 (“the ’846 Patent”)
EX-1012	Complaint for Patent Infringement, filed in <i>Gilead Sciences, Inc. v. Lupin Ltd., Laurus Labs Limited, and Cipla Limited</i> , No. 22-cv-00165 (D.Del.) (Docket Entry 1).
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EX-1014	Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC), Guidelines for the Use of Antiretroviral Agents

	in HIV-I-Infected Adults and Adolescents, Department of Health & Human Services (revised Apr. 8, 2015) (“2015 DHHS Guidelines”)
EX-1015	Highlights and Prescribing Information on Truvada, revised July 2012 (“Truvada 2012 Label”)
EX-1016	Highlights and Prescribing Information on Isentress, revised October 2007 (“Isentress Label”)
EX-1017	Dorothy E. Dow & John A. Bartlett, “Dolutegravir, the Second-Generation of Integrase Strand Transfer Inhibitors (INSTIs) for the Treatment of HIV,” 3 INFECTIOUS DISEASES & THERAPY 83–102 (2014) (“Dow”)
EX-1018	Serrao et al., “Raltegravir, elvitegravir, and metoogravir: the birth of the “me-too” HIV-1 integrase inhibitors,” 6 RETROVIROLOGY, Art. 25, 1–14 (2009) (“Serrao”)
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EX-1026	Noemi Astuti & Franco Maggiolo, “Single-Tablet Regimens in HIV Therapy,” 3 INFECTIOUS DISEASES & THERAPY 1–17 (2014) (“Astuti”)
EX-1027	Llibre et al., “Once-Daily Single-Tablet Regimens: A Long and Winding Road to Excellence in Antiretroviral Treatment,” 14 AIDS REVIEWS 168–78 (2012) (“Llibre”).
EX-1028	Mathias et al., “Bioequivalence of the Emtricitabine/Rilpivirine/Tenofovir Disoproxil Fumarate Single

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EX-1029	ClinicalTrials.gov, NCT02275065 Protocol, Study to Evaluate Safety, Pharmacokinetics, and Antiviral Activity of Bictegravir (GS-9883) in Human Immunodeficiency Virus (HIV)-1 Infected Participants, https://clinicaltrials.gov/study/NCT02275065 (February 6, 2015) (“NCT ’065 February 2015”)
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EX-1032	Highlights and Prescribing Information on Complera, revised and issued August 2011 (“Complera Label”)
EX-1033	Günthard et al., “Antiretroviral Treatment of Adult HIV Infection 2014 Recommendations of the International Antiviral Society-USA Panel”, 312(4) JAMA 410–25 (2014) (“Günthard”)
EX-1034	Press Release, Gilead, “Gilead Announces Phase 3 Result for Investigational Once-Daily Single Tablet HIV Regimen Containing Tenofovir Alafenamines (TAF)” (February 26, 2015) (“Gilead February 2015 Press Release”)
EX-1035	ClinicalTrials.gov, NCT02397694 Protocol, Safety and Efficacy of Bictegravir + Emtricitabine/ Tenofovir Alafenamide Versus Dolutegravir + Emtricitabine/ Tenofovir Alafenamide in HIV-1 Infected, Antiretroviral Treatment-Naive Adults, https://clinicaltrials.gov/study/NCT02397694 (March 20, 2015) (“NCT ’065 March 2015”)
EX-1036	Press Release, Gilead, “Gilead’s Investigational Fixed-Dose Combination of Emtricitabine/Tenofovir Alafenamide (F/TAF) Meets Primary 48-Week Objective in Phase 3 Study” (Sept. 2, 2015) (“Gilead September 2015 Press Release”)
EX-1037	WO 2015/196116 (WO ’116)
EX-1038	US Patent Publication 2016/0016973 (US ’973)
EX-1039	Tsiang et al., “Antiviral Activity of Bictegravir (GS-9883), a Novel Potent HIV-1 Integrase Strand Transfer Inhibitor with an Improved Resistance Profile,” 60(12) ANTIMICROBIAL AGENTS AND CHEMOTHERAPY 7086–97 (2016) (“Tsaing”)
EX-1040	U.S. Patent 10,548,846 File History (“the ’846 file history”)

EX-1041	Johns et al., “Carbamoyl Pyridone HIV-1 Integrase Inhibitors 3. A Diastereomeric Approach to Chiral Nonracemic Tricyclic Ring Systems and the Discovery of Dolutegravir (S/GSK1349572) and (S/GSK1265744),” 56 J. MEDICINAL CHEMISTRY 5901–16 (2013) (“Johns”)
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EX-1043	Sabin et al., “Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration,” 371 LANCET 1417–26 (2008) (“Sabin”)
EX-1044	Press Release, Gilead, “Gilead Announces Phase 3 Result for Investigational Once-Daily Single Tablet HIV Regimen Containing Tenofovir Alafenamide (TAF)” (November 5, 2015) (“Gilead November 2015 Press Release”)
EX-1045	Stellbrink et al., “Dolutegravir in Antiretroviral-naïve Adults with HIV-1: 96-week Results from a Randomized Dose-ranging Study,” 27 AIDS 1771–78 (2013) (“Stellbrink”)
EX-1046	Highlights and Prescribing Information on Epzicom, © 2004 (“Epzicom Label”)
EX-1047-A	Benjamin E. Blass, “Drug Discovery and Development: An Overview of Modern Methods and Principles” <i>in</i> BASIC PRINCIPLES OF DRUG DISCOVERY AND DEVELOPMENT 1–34 (Elsevier Sci. & Tech., 2015), published April 27, 2015 (“Blass Chapter 1”)
EX-1047-B	Benjamin E. Blass, “Medicinal Chemistry” <i>in</i> BASIC PRINCIPLES OF DRUG DISCOVERY AND DEVELOPMENT 203–43 (Elsevier Sci. & Tech., 2015), published April 27, 2015 (“Blass Chapter 5”)
EX-1048	Chen et al., “Prediction of Absolute Hydroxyl pK_a Values for 3-Hydroxypyridin-4-ones,” 3 J. PHYSICAL CHEMISTRY LETTERS 2980–85 (2012) (“Chen”)
EX-1049	Bastin et al., “Salt Selection and Optimisation Procedures for Pharmaceutical New Chemical Entities, 4 ORGANIC PROCESS RSCH. & DEV. 427–35 (2000) (“Bastin”)
EX-1050	James Wells, “Pharmaceutical Preformulation: The Physicochemical Properties of Drug Substances” <i>in</i> 2

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EX-1051	Berge et al., “Pharmaceutical Salts,” 68 J. PHARM. SCI. 1–19 (1977) (“Berge”)
EX-1052	WO 2006/116764 (“WO ’764”)
EX-1053	Frederick G. Bordwell, “Equilibrium Acidities in Dimethyl Sulfoxide Solution,” 21 ACCT. CHEM. RSCH. 456–63 (1988) (“Bordwell”)
EX-1054	Highlights and Prescribing Information on Truvada, © 2004, issued July 2004 (“Truvada Label”)
EX-1055-A	Michael R. Franklin & Donald N. Franz, “Chapter 57: Drug Absorption, Action, and Disposition,” <i>in</i> 21 REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY 1142–70 (Lippincott Williams & Wilkins ed., 2006) (“Remington Chapter 57”)
EX-1055-B	Paul M. Beringer & Michael E. Winter, “Chapter 59: Clinical Pharmacokinetics and Pharmacodynamics,” <i>in</i> 21 REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY 1191–1205 (Lippincott Williams & Wilkins ed., 2006) (“Remington Chapter 59”)
EX-1055-C	Raymond E. Galinsky & Craig K. Svensson, “Chapter 58: Basic Pharmacokinetics and Pharmacodynamics,” <i>in</i> 21 REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY 1171–90 (Lippincott Williams & Wilkins ed., 2006) (“Remington Chapter 58”)
EX-1055-D	“Chapter 17: Ionic Solutions and Electrolytic Equilibria,” <i>in</i> 21 REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY 231–49 (Lippincott Williams & Wilkins ed., 2006) (“Remington Chapter 17”)
EX-1055-E	Alfonso R. Gennaro, “Chapter 25: Organic Pharmaceutical Chemistry,” <i>in</i> 21 REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY 386–409 (Lippincott Williams and Wilkins ed., 2006) (“Remington Chapter 25”)
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EX-1056	Zolopa et al., “Activity of Elvitegravir, a Once-Daily Integrase Inhibitor, against Resistant HIV Type 1: Results of a Phase 2, Randomized, Controlled, Dose-Ranging Clinical Trial,” 201 J. INFECTIOUS DISEASES 814–22 (2010) (“Zolopa”)

EX-1057	U.S. Patent No. 8,129,385 (“the ’385 Patent”)
EX-1058	U.S. Patent No. 7,390,791 (“the ’791 Patent”)
EX-1059	U.S. Patent No. 8,754,065 (“the ’065 Patent”)
EX-1060	Memorandum from Katherine K. Vidal, Director of the United States Patent and Trademark Office, to Members of the Patent Trial and Appeal Board, Interim Procedure for Discretionary Denials in AIA Post-Grant Proceedings with Parallel District Court Litigation (June 21, 2022) (“Vidal Memo”)
EX-1061	Press Release, Gilead, “Gilead Presents Preliminary Data on Bictegravir, an Investigational Integrase Strand Transfer Inhibitor for the Treatment of HIV” (June 20, 2016) (“Gilead 2016 Press Release”)

Petitioner Cipla Limited (“Petitioner;” “Cipla”) requests *inter partes* review (“IPR”) and cancellation of claims 1–13 (“Challenged Claims”) of U.S. Patent No. 11,744,802 (“the ‘802 Patent”) assigned to Patent Owner Gilead Sciences, Inc. (“Gilead”). The Challenged Claims should not have been allowed.

I. INTRODUCTION

The Challenged Claims cover a single pharmaceutical tablet with three antiretroviral drugs selected from two different drug classes. Each of these three drugs, when taken together, were known to suppress replication of the human immunodeficiency virus (HIV) well before the priority date (November 9, 2015; “Effective Date”).

The first drug is named “a compound of Formula (I),” and is a “second generation” integrase strand transfer inhibitor (“INSTI”), now known as bictegravir (“BIC”). The others are tenofovir alafenamide fumarate (“TAF”) and emtricitabine (“FTC”), a pair of nucleoside/nucleotide reverse transcriptase inhibitors (“N(t)RTIs”). When these drugs are combined in a single tablet, it becomes a complete antiretroviral therapy (“ART”) regimen in one tablet. A single tablet ART regimen taken once-a-day was a well-known and ideal way to improve patient adherence to a lifetime of ART. And, single tablets containing complete INSTI/N(t)RTI regimens were successfully marketed by Gilead (and its competitors) years before the priority date of the ‘802 Patent (“Effective Date”).

Prior to the Effective Date, other pharmaceutical companies began filing patent applications directed to single tablet regimens quite similar to those of the Challenged Claims. These included single tablets with ViiV Healthcare’s (“ViiV”) “second generation” INSTI dolutegravir (“DTG”) combined with Gilead’s N(t)RTI pair TAF/FTC. Commercializing such tablets in the U.S., however, was near impossible because ViiV’s DTG and tablets with Gilead’s N(t)RTI pair of TAF/FTC were protected by U.S. patents and would be for many years to come.¹

As this Petition explains, physicians understood that an improved single tablet ART regimen, one combining a “second generation” INSTI with the N(t)RTI pair of TAF/FTC was highly desirable. Though other single tablet INSTI/N(t)RTI regimens were recommended and available, physicians elected to prescribe ViiV’s DTG in one tablet with another FDA-approved Gilead N(t)RTI pair in another, even though this desirable regimen was less convenient and more expensive. The Challenged Claims embrace (exactly) the desire for a single tablet regimen with a “second generation” INSTI combined with Gilead’s improved N(t)RTI pairing of

¹ See EX-1057, 177:40–180:42 (claims covering DTG; expiry ~2026); EX-1059, 37:1–40:43 (claiming TAF and TAF fumarate; expiry ~2021); EX-1060, 11:54–13:21 (claiming TAF hemifumarate; expiry ~2032); EX-1030, 15 (Gilead patents to TAF/FTC tablets; expiry ~2022).

TAF/FT. The claimed tablets represent the combination of a Gilead owned INSTI and N(t)RTI pair. They are the product of common sense, ordinary creativity, and routine experimentation, fueled (of course) by a significant profit motive.

Simply put, the Challenged Claims are not the product of an innovation that justifies the exclusive rights afforded by the patent laws. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 427 (2007). They represent a predictable combination of known anti-HIV drugs that evolved from well-known design incentives and a recognized market need in the pharmaceutical industry. *Id.* at 417. Such ordinary innovation does not deserve patent protection.

II. MANDATORY NOTICES

A. Real Parties-In-Interest

For the purposes of this petition, the real party-in-interest is Cipla Limited.

B. Related Matters

Petitioner and Gilead are involved in an action that has been pending since May of 2022, brought by Gilead pursuant to the Hatch-Waxman Act in the District of Delaware. *Gilead Sciences, Inc. v. Lupin Ltd., Laurus Labs Ltd., and Cipla Limited*, C.A. No. 22-cv-00615 (MN). The '802 Patent was first asserted against Cipla in that action on November 16, 2023. EX-1013.

No prior IPR petition for the '802 Patent has been filed.

C. Identification of Counsel and Service Information

Petitioner provides the following designation of counsel:

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D. Power of Attorney

A power of attorney is filed herewith.

III. REQUIREMENTS FOR REVIEW

Petitioner certifies that the '802 Patent is available for IPR, and that it is not barred or estopped from requesting IPR of any Challenged Claim on any permissible patentability challenge. Petitioner requests claim cancellation under the following grounds:

Ground	Claims	Basis ²	References
1	1–13	103	WO '323, WO '351
2	1–13	103	WO '323, WO '351, Bowker, Paulekuhn
3	1–13	103	WO '323, WO '351, US '079

IV. RELEVANT BACKGROUND TO THE '802 PATENT

Petitioner submits this section to provide an overview of the “shared knowledge” that the *KSR* court advised must “define a new threshold from which innovation starts once more.” *KSR*, 550 U.S. at 427. This section relies upon analyses and opinions from the declarations of two qualified experts to provide foundational support for this “shared knowledge”: Dr. Prasanna Jagannathan of Stanford University (Ex-1003) and Dr. Jeffrey Winkler of the University of Pennsylvania (Ex-1004).

² These references and others discussed herein qualify as prior art under AIA 35 U.S.C. § 102.

The references and expert commentary summarized in this section are not, however, relied upon by Petitioner to establish disclosure of any Challenged Claim elements. Petitioner submits that this context, largely absent from the original prosecution, establishes multiple motivations for combining the prior art in Grounds 1–3, in addition to establishing factual bases for a reasonable likelihood of success.

A. Treatment of HIV Infection Before the Effective Date³

The use of multiple antiretroviral drugs to treat HIV-1 infection had “dramatically reduced HIV-associated morbidity and mortality” well before the Effective Date. EX-1014, 13. HIV-1 infection was (by then) “a chronic, manageable condition” as opposed to a “death sentence.” *Id.*, *see also* EX-1003, ¶¶ 48–51 (citing EX-1014, 13–14, 70). This initial success shifted clinical attention toward drug regimens that “optimize tolerability, long-term safety, and durable efficacy.” EX-1024, 52; *see also* EX-1003, ¶¶ 66–68. Approved antivirals for HIV-1 treatment included INSTIs and N(t)RTIs, as well as antiretrovirals from other drug classes. *Id.* at ¶ 50 (citing EX-1014, 70, 268–80 (Appendix B, Tables 1–6)). Approved antiretroviral drugs and ART combinations were available in the

³ *See generally* EX-1003, ¶¶ 48–60.

U.S. at a wide range of wholesale cost, with higher costs impacting long-term patient adherence. *Id.* at ¶ 60 (citing EX-1014, 56-57, 204–07).

The standard of care for ART was well defined by guidelines from the Department of Health and Human Services (“DHHS”). EX-1014. These guidelines (updated in April 2015; “2015 DHHS Guidelines”) were prepared by recognized independent experts in the field and were readily accessed (and followed) by physicians treating HIV-1 infection. EX-1003, ¶¶ 48–49 (citing EX-1014, 2). The 2015 DHHS Guidelines recommended five ART regimens for new patients, each with a “backbone” of two N(t)RTIs, combined with a third “anchor” drug selected from the INSTI and protease inhibitor (“PI”) classes. EX-1003, ¶¶ 52–53 (citing EX-1014, 70, and 166–67). Regimen selection was “individualized,” based several factors, including virologic efficacy, pill burden, comorbid conditions, and cost. EX-1003, ¶ 52 (citing EX-1014, 70).

The common backbone of four of the recommended ART regimens was Gilead’s approved N(t)RTI pair of tenofovir disoproxil fumarate (“TDF”) (300 mg) and FTC (200 mg). EX-1014, 70. The anchor for this backbone could be selected from among: (1) Merck’s INSTI raltegravir (“RAL”) (400 mg in Isentress® - approved 2007), (2) Gilead’s INSTI elvitegravir (“EVG”) (150 mg in Stribild® - approved 2012), and (3) ViiV Healthcare’s (“ViiV”) INSTI dolutegravir (“DTG”) (50 mg in Tivicay® - approved 2013) or (4) the PI darunavir. EX-1003,

¶¶ 52–54 (citing EX-1014, 70, 268-270, EX-1054, 16; EX-1015, 3–4, EX-1016, 1; EX-1019, 1). The fifth regimen (Triumeq[®] - approved 2014) combined ViiV’s DTG (50 mg) (approved in 2013 as Tivicay[®]) with its N(t)RTI backbone of abacavir (“ABC”) (600 mg) and lamivudine (“3TC”) (300 mg) (Epzicom[®] - approved 2004). EX-1003, ¶¶ 55–56 (citing EX-1014, 279; EX-1022, 1, 14; EX-1024, 1, 17–18).⁴

The 2015 DHHS Guidelines preferred INSTI-based regimens due to the higher virologic efficacy and improved safety profile of the INSTI class. EX-1003, ¶¶ 58–59 (citing EX-1014, 78–79, 92–94). Two of the recommend ART regimens were available in a single tablet containing commonly owned INSTI anchors and N(t)RTI backbones: Gilead’s Stribild[®] and ViiV’s Triumeq[®]. EX-1003, ¶ 55; EX-1014, 279. The other recommended regimens required administration of two tablets, individually marketed by competing companies (Merck’s Isentress[®] + Gilead’s Truvada[®] or ViiV’s Tivicay[®] + Gilead’s Truvada[®])

⁴ Petitioner recognizes there are many acronyms for the FDA-approved antiretroviral drugs and other terms relevant to the art. Petitioner adopts industry-recognized acronyms herein, and a useful key for all of them can be found at the end of the 2015 DHHS Guidelines. *See* EX-1014, 264-265.

notwithstanding that single tablet regimens we considered ideal. EX-1003, ¶ 57; EX-1014, 70, 268–69 (Table 1), 279–280 (Table 4).

B. The Evolution of INSTIs⁵

1. First Generation INSTIs.

Merck’s RAL was the first FDA-approved INSTI (approved as Isentress® in 2007) which required twice-daily (BID) dosing for a daily dose of 800 mg (taken without regard to food), and so its DHHS-recommended combination with TDF/FTC required three separate tablets per day (BID dosing of Merck’s Isentress® and once-daily (QD) dosing of Gilead’s Truvada®). EX-1003, ¶¶ 54, 57; EX-1004, ¶¶ 53–54 (citing EX-1016, 1, 7); EX-1014, 70, 268–69 (Table 1), 279–80 (Table 4); EX-1015, 1; EX-1016, 1; EX-1017, 85–86.

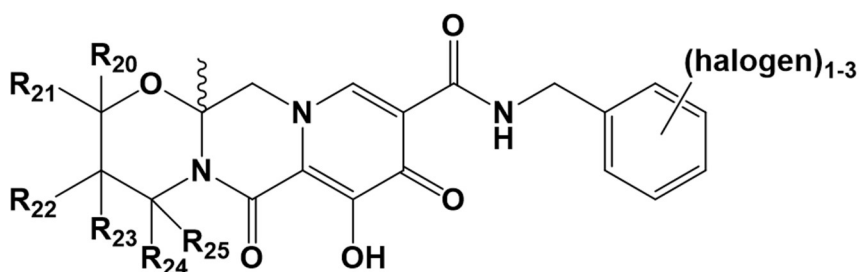
Gilead’s EVG (approved in 2012 as a component of Stribild®) was considered a “first generation” INSTI, similar to RAL, because it had a similar low genetic barrier to resistance resulting in activity loss toward HIV integrase (“INST”) mutants, along with cross-resistance to INST mutants. EX-1003, ¶¶ 54 (citing EX-1023, 506), 60–61; EX-1004, ¶¶ 58–60 (citing EX-1017, 83; EX-1018, 3–5, 9–11); EX-1041, 5901–02. The single tablet Stribild® combined Gilead’s

⁵ See generally EX-1003, ¶¶ 51–53; EX-1004, ¶¶ 53–74.

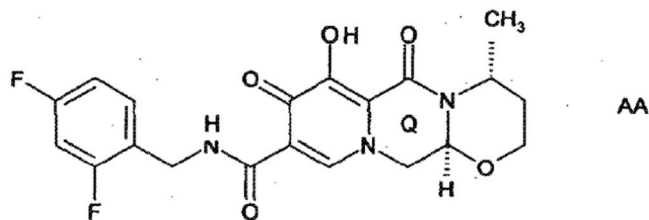
EVG with its N(t)RTI pair of TDF/FTC, which required its pharmacokinetic (“PK”) booster cobicistat for increased EVG exposure and QD dosing (with food). EX-1003, ¶ 63 (citing EX-1019, 2, 22–23; EX-1030, 3); EX-1004, ¶ 53–54 (citing EX-1019, 1, 22–23). Stribild® was not an option for patients having impaired renal function (creatinine clearance (CrCl) < 70 mL/min). EX-1003, ¶¶ 57 (citing EX-1014, 70), 63 (citing EX-1019, 3, 6). Accordingly, there was an established need in the art for a next generation of INSTIs that could avoid cross-resistance and thus improve activity toward RAL and EVG resistant mutants. EX-1003, ¶ 54; EX-1004, ¶ 60; (citing EX-1018, 4).

2. “Second Generation” INSTIs

A new and improved structural class of INSTIs meeting these needs was first disclosed in 2006. EX-1004, ¶ 61 (citing EX-1052, 2–11 (disclosing compound genera and subgenera)). Generic claims to those INSTIs were patented in 2012, including a subgeneric claim covering DTG, as follows:



U.S. 8,129,385 (EX-1058) – Claim 2



DTG (Compound AA from EX-1021)

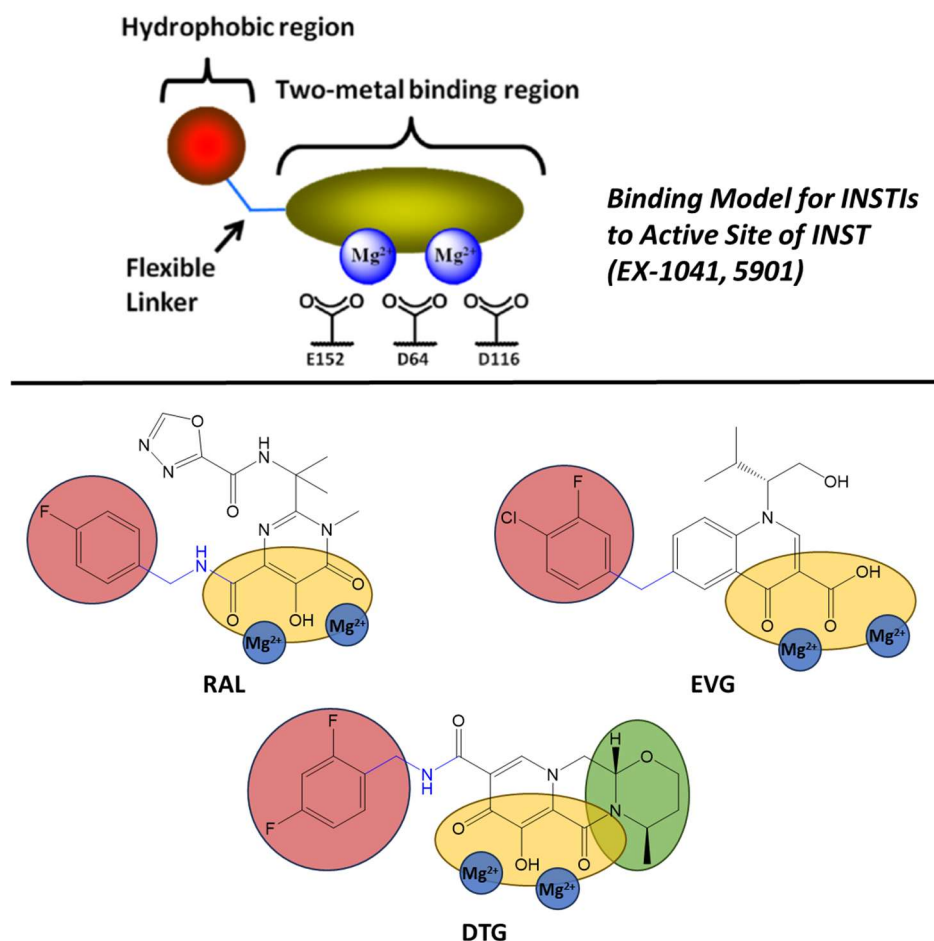
EX-1004, ¶ 61 (citing EX-1057, 177:40–178:36 (claims 1–2 covering DTG)); *see also* EX-1021, 2, 7, 16–22 (synthesis of Compound AA (DTG) and its sodium salt).

This new INSTI class was designed for more optimal binding to the active site of INST. EX-1041, Abstract. DTG was selected from the class after extensive structure activity relationship (SAR) research and pharmacokinetic evaluation had established: a low nanomolar activity ($IC_{50} = 1.7$ nM); maintained activity toward several INST mutants; a long half-life ($t_{1/2} = 5.2$ -6.2 h); and good oral bioavailability ($F\% = 25$ -35%).⁶ EX-1004, ¶¶ 63, 67–68 (citing EX-1041, 5905–08 (Tables 1–4, Figure 4), 5909–10 (Figure 6 and Table 4), 72). DTG also did not require co-administration with a PK booster (as required for Gilead’s EVG) and

⁶ For a tutorial on relevant background concepts in medicinal chemistry discussed herein, *see* EX-1004, ¶¶ 17–35 (citing EX-1047A, EX-1047B, EX-1055-A, EX-1055-B, EX-1055-C).

could be given without regard to food. EX-1003, ¶¶ 55–56 (citing EX-1023, 506, 518; EX-1017, 83), 65; EX-1004, ¶¶ 55, 69–71 (citing EX-1041, 5910, EX-1023, 506; EX-1017, 83).

DTG was a significant improvement over the “first generation” INSTIs EVG and RAL, leading to its identification as the first FDA-approved “second generation” INSTI. EX-1003, ¶ 56; EX-1004, ¶¶ 70–72 (citing EX-1018, 4 (Figure 2), EX-1017, 83, EX-1023, 506). The improvements were due to a novel scaffold for binding to INST (yellow), a relocated hydrophobic region (red), a flexible linker (blue), and an expanded tricyclic ring system (green) to avoid cross-resistance, depicted as follows:



EX-1004, ¶¶ 70–72 (further emphasizing DTG’s novel structural elements).

Though DTG was available in a DHHS-recommended single tablet combined with ABC/3TC (ViiV’s Triumeq®), this regimen was far from ideal.

EX-1003, ¶ 61 (citing EX-1024, 1). It required screening patients for a particular genetic allele (HLA-B5707) due to a life-threatening hypersensitivity to ABC in HLA-B5707 positive patients. EX-1003, ¶¶ 57 (citing EX-1014, 70); *see also id.* at ¶ 61 (citing EX-1024, 1; 1014, 92) (ABC hypersensitivity also required discontinuation for some HLA-B5701negative patients). ABC was also known to

exacerbate hepatitis B (HBV) infection in co-infected patients, and its long-term use was potentially associated with heart attacks. *Id.*

These complications were not an issue with Gilead's TDF/FTC backbone, which was instead known to be active against both HIV-1 and HBV. EX-1003, ¶¶ 61–62 (citing EX-1014, 92). For these reasons, physicians opted to prescribe ViiV's DTG (Tivicay[®]) with Gilead's TDF/FTC (Truvada[®]) as separate tablets once daily. EX-1003, ¶¶ 62, 65–66. This was a physician-preferred regimen despite the availability of DHHS-recommend single tablet regimens offered by each company (Triumeq[®] and Stribild[®]), and despite the improved tolerability, patient adherence, long-term safety, and lower cost that single tablet regimens offered. *Id.*

C. Known Complications with TDF Solved by TAF⁷

By 2014, TDF was known to be associated with nephrotoxicity, as well as a “decline in bone mineral density (BMD) relative to some other NRTIs.” EX-1003, ¶ 69 (citing EX-1014, 80; EX-1025, 53). These concerns were allayed with the advent of Gilead's new prodrug form of tenofovir: tenofovir alafenamide (“TAF”). TAF was also known to be active against HIV-1 at 1/10th the dose of TDF (25 mg vs. 300 mg). EX-1003, ¶ 70 (citing EX-1025, 52-53, 57; EX-1026,

⁷ See generally EX-1003, ¶¶ 69–72.

11; 1010, 449, 454). Also in 2014, Gilead announced it sought FDA approval for an improvement to Stribild[®] where TDF would be replaced with TAF. EX-1003, ¶ 71 (citing EX-1030, 3; EX-1034; EX-1025, 53). This improved single tablet (Genvoya[®]) was approved by the FDA on November 5, 2015. EX-1003, ¶ 72 (citing EX-1044, 1). Nonetheless, Genvoya[®] still included EVG (with its known resistance issues) and required the PK booster cobicistat (“COBI”). *Id.*

D. Market Demand for a State-of-the-Art Single Tablet with a Commonly Owned INSTI anchor and an Updated N(t)RTI Backbone⁸

Though physicians preferred to prescribe ViiV’s Tivicay[®] (DTG) with Gilead’s Truvada[®] (TDF/FTC) as separate tablets, this regimen was also more expensive than available single tablet regimens. EX-1003, ¶ 66 (citing EX-1014, 205–06). The prospect of a single tablet with a commonly owned “second generation” INSTI anchoring Gilead’s improved TAF/FTC backbone would have provided a significant financial opportunity for Gilead. EX-1003, ¶¶ 76–79 (citing EX-1030, 6, 30–31, 34, 129–30).

Such a single tablet would have also offered a potentially lower cost alternative to the physician-preferred two tablet regimen of Tivicay[®] and Truvada[®]. EX-1003, ¶ 66. Gilead also announced in 2014 that its product sales

⁸ See generally EX-1003, ¶¶ 70–76.

would be limited if physicians did not see the benefit of its HIV products. EX-1003, ¶ 76 (citing EX-1030, 6, 30–31). It further acknowledged that ViiV’s Tivicay[®] and Triumeq[®] could adversely impact its own sales. EX-1003, ¶ 77 (citing EX-1030, 34).

In view of the above considerations, a POSA would have recognized a clinical and a market need for a single tablet with a “second generation” INSTI similar to DTG (e.g., a “me too” DTG) anchoring Gilead’s new and improved TAF/FTC backbone. EX-1003, ¶ 78. Such a tablet (with the new form of tenofovir) would have allowed for smaller/lighter single tablets, in addition to improved convenience and patient adherence. EX-1003, ¶¶ 78,79; 171–73.

E. Routine Dose Ranging Studies in Clinical Trials⁹

Prior to the Effective Date, scientists in the field routinely determined effective doses of antiviral drugs with dose ranging studies in HIV infected patients. EX-1003, ¶¶ 80–96. Gilead’s WO ’323 (EX-1005) confirms that appropriate dosages of antiretroviral compounds “can be readily determined by [a POSA],” and that “therapeutically effective amount[s] can be determined routinely by [a POSA] having regard to their own knowledge, the state of the art, and this

⁹ See generally EX-1003, ¶¶ 80–96.

disclosure.” EX-1003, ¶¶ 80–82 (citing EX-1005, 16:8–32, 35:8–23); EX-1005, 16:19–21, 36:31–37;5.

As Dr. Jagannathan explains, notable published examples of dose ranging clinical studies include a Phase II study of ViiV’s INSTI DTG in combination with TDF/FTC or ABC/3TC, where 78–88% of patients receiving 10, 25, and 50 mg of DTG maintained viral suppression (HIV-1 RNA < 50 copies/mL along with substantial increases in CD4+ cell counts) after 96 weeks. EX-1003, ¶¶ 80–81, 84–85 (citing EX-1045, 1771–72, 1774, 1776). Although a 50 mg dose of DTG was later selected for Phase III trials, both the 10 mg and 25 mg doses were also efficacious. EX-1003, ¶¶ 82, 86–88 (citing EX-1045, 1776).

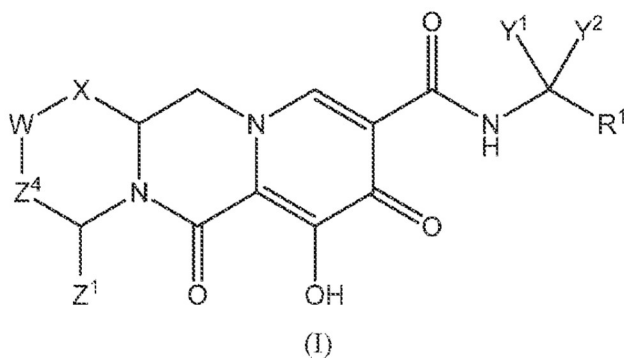
Another routine dose ranging study was the Phase II study of Gilead’s INSTI EVG, where over 90% of patients receiving 50 and 125 mg doses (combined with ritonavir) showed significant reductions in viral load after 48 weeks. EX-1003, ¶¶ 89–92 (citing EX-1056, 814–15, 818, 820–21). Another example available to the POSA was a clinical protocol studying Gilead’s compound “GS-9883” in HIV-1 infected patients at once-daily doses of 5, 10, 25, 50, and 100 mg. EX-1003, ¶¶ 94–95 (citing EX-1029, 7–9). In a later Phase 2 protocol, 75 mg of GS-9883 was selected as the experimental dose, to be given in combination with 25 mg TAF and 200 mg FTC. EX-1003, ¶¶ 93, 95 (citing EX-1035, 3).

V. PRIOR ART ASSERTED IN GROUNDS 1–3

The following sections explain advances disclosed in the prior art available prior to the Effective date, including Gilead’s own disclosure of combinations of its next generation INSTIs with its improved N(t)RTI backbone of TAF and FTC. *See also* EX-1003, ¶¶ 124–155, Appendix B; EX-1004, ¶¶ 49, 52, 73–74, 78–81, 86, 88, 93–94.

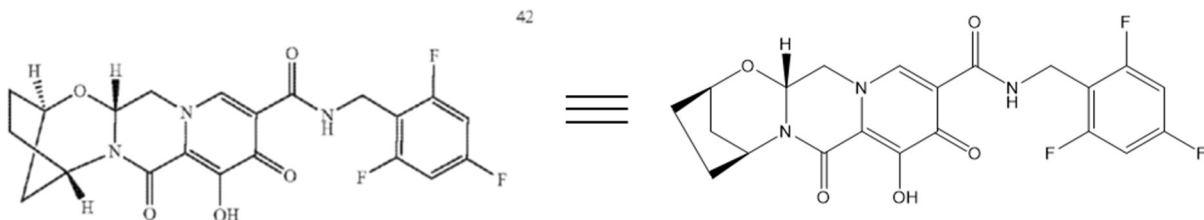
A. WO ’323 (EX-1005)¹⁰

Gilead’s WO ’323 disclosed a new family of INSTIs of “Formula (I),” as well as their “use in the treatment of [HIV].” EX-1005, Abstract, 3:8–12, 5:14–22, 6:3–10, 212:23–26. Formula (I) was identified by the following structure:



¹⁰ *See also* EX-1003, ¶¶ 126–45; EX-1004, ¶¶ 78–87.

Id. at 3:13–5:10. An exemplified Formula (I) INSTI compound was compound 42, which is now known as bicitegravir (BIC).¹¹



Compound 42 (BIC)

EX-1005, 99:8–101:25, 223–24.

WO '323 claimed compound 42 (BIC) in a Markush group including 6 structurally related compounds and disclosed it as one of 5 compounds that progressed into oral administration studies in dogs. EX-1003, ¶ 131; EX-1004, ¶ 78; EX-1005, 222:1–224; 240–241 (claim 32). WO '323 also claimed a therapeutically effective amount of compound 42 (or pharmaceutically acceptable salt thereof) in pharmaceutical compositions, including those containing one or more additional anti-HIV agents, e.g., N(t)RTIs. *Id.* at 241 (claim 33 (depending from claim 32)) and dependent claims 35–36). It also claimed methods for treating HIV infection with a “therapeutically effective amount” of a pharmaceutical

¹¹ See EX-1039. Petitioner recognizes that the name “bicitegravir” was not publicly disclosed until June 2016. EX-1061. The name is employed here as a naming convention for the convenience of the reader.

composition, including in combination with, e.g., N(t)RTIs. *Id.* at 241–42 (claim 37 (depending from claim 33) and dependent claims 39–40).

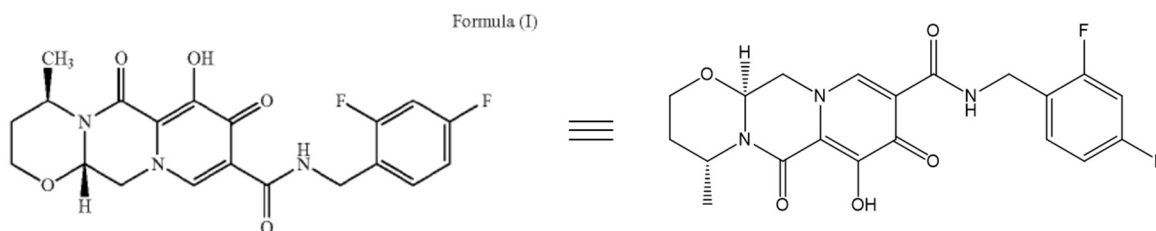
Moreover, WO '323 described pharmaceutical combinations containing an INSTI compound with one or more additional therapeutic agents, mixed with pharmaceutically acceptable carriers, diluents, or excipients, including combinations with two additional agents. EX-1005, 37:7–21, 39:25–27, 37:20–39:22. The INSTI (or a pharmaceutically salt thereof, e.g., sodium) and additional agents, including the N(t)RTIs TAF fumarate and FTC, were present in therapeutically effective amounts. *Id.* at 14:18–22; 37:7–19; 38:13–17, 38:19–21. Importantly, these pharmaceutical combinations explicitly included “unitary dosage forms for simultaneous administration, for example as a solid dosage form for oral administration[,]” where tablets were disclosed as a single dosage unit. *Id.* at 40:18–20 (emphasis added).

WO '323 also taught that therapeutically effective amounts of each drug for treating HIV infection included those alleviating HIV symptoms or preventing their appearance, reducing HIV viral load, or preventing it from reaching detectable levels. EX-1005, 16:8–32, 35:8–23, 36:31–37:5. Appropriate dosages for Gilead’s new INSTIs in pharmaceutical compositions included those in the range of “about 25 mg to about 500 mg,” including “about 25 mg, 50 mg, [and] 100 mg” *Id.* at 35:9–23.

B. WO '351 (EX-1006)¹²

Ratiopharm's WO '351 disclosed pharmaceutical combinations comprising the INSTI DTG combined with FTC and “tenofovir or a prodrug thereof” to treat HIV infection. EX-1006, Abstract, 3:22–26, 4:1–9, 6:24–32, 9:4–25. The combinations were administered once daily “preferably [as] a solid oral dosage form ... in particular a tablet.” *Id.* at 7:27–28, 23:6–8. WO '351 also confirms that dosage forms should be of “comfortable size” to improve patient compliance. *Id.* at 3:4–6.

DTG was disclosed with the following structure:



EX-1006, 4:12–18, 4:22–25 (DTG synthesis provided in EX-1021 and EX-1052).

¹² See also EX-1003, ¶¶ 146–52; EX-1004, ¶¶ 73–74, 89, 100–01.

¹³ Right structure represents DTG in same orientation as BIC in '802 patent claim 1. EX-1004, ¶ 51.

Specific pharmaceutical combinations included a total drug weight of 192–326 mg per day, including ~275 mg arising from a combination of about 50 mg DTG, about 25 mg of TAF, and about 200 mg of FTC. EX-1006, 19:30–20:2. DTG sodium, TAF hemifumarate, and FTC free base were described as particularly preferred. *Id.* at 5:22–27, 13:16–18, 8:10–11. WO '351 also provided preferred ranges for common inactive excipients to be used in unit dose combinations with all three drugs. *Id.* at 20:29–22:25.

C. US '079 (EX-1007)¹⁴

Cipla's US '079 confirmed that available drug regimens were “far from ideal” due to patients developing “resistance to one or more of antiretroviral medications.” EX-1007, [0005], [0012]. It also taught that anti-retroviral combinations “administered in a single unit dosage form may result in increased patient compliance as the pill burden is reduced and dosing schedules are simplified.” *Id.* at [0013], [0022]–[0023].

US '079 disclosed a preference for tablet formulations due to “greater stability, less risk of chemical interaction between different medicaments, smaller bulk, accurate dosage, and ease of production.” EX-1007, [0070], [0078]–[0079] (single, bilayered, or multilayered tablets). US '079 provided Example 7 where

¹⁴ See also EX-1003, ¶¶ 153–55.

DTG (50 mg), TDF (300 mg), and FTC (200 mg) were combined into a single tablet that included additional excipient amounts, to provide an uncoated total weight of 1030 mg, and coated total weight of 1055 mg. *Id.* at [0129]–[0130].

D. Bowker (EX-1008)¹⁵

Bowker discloses the importance of the acid dissociation constant (“ pK_a ”) when selecting salt forming counterions, e.g., cations for free acid drugs. EX-1008, 165–66. Bowker teaches that “there should be a minimum difference of [~ 3] units between the pK_a value of the ionizable group and a possible counter-ion.” *Id.* at 166. This requirement is said to be especially important for particularly weak acids. *Id.*

E. Paulekuhn (EX-1009)¹⁶

Paulekuhn identifies trends in pharmaceutical salt selection “over the past 25 years,” with a focus on approved drugs listed in the Orange Book. EX-1009, 6665. Paulekuhn explains that salt formation is “a well-known technique to modify and optimize the physicochemical properties of an ionizable research and development compound,” and that “salt formation is almost the only chemical technique

¹⁵ See also EX-1003, ¶ 228–29; EX-1004, ¶¶ 48–49, 94.

¹⁶ See also EX-1003, ¶ 228–29; EX-1004, ¶¶ 52, 93.

available to change aqueous solubility and dissolution rate without changing the API molecule.” *Id.*

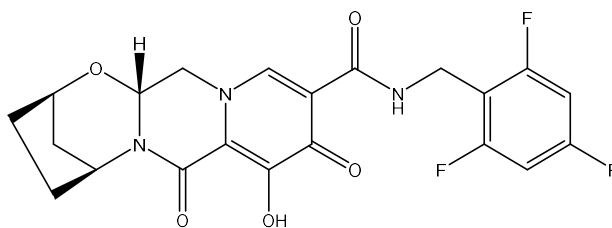
Paulekuhn summarizes the cationic counterions used in FDA-approved acidic drugs, noting that “the sodium ion strongly dominates with an incidence of 75.3% over the entire period.” EX-1009, 6665; EX-1004, ¶ 52. This trend was similar in oral formulations where sodium was used ~65% of the time. *Id.* at 6669 (Table 5); EX-1004, ¶ 52.

VI. THE '802 PATENT (EX-1001)

The '802 Patent issued on September 5, 2023, from U.S. Appl. No. 17/738,803 filed on May 6, 2022.

A. The '802 Specification¹⁷

The '802 specification identifies solid oral dosage forms containing an INSTI named “Formula I” (BIC), TAF, and FTC, or their pharmaceutically acceptable salts. EX-1001, 2:41–57, 4:66–5:4.



Formula I (BIC)

¹⁷ See also EX-1003, ¶¶ 97–109.

EX-1001, 2:41–57, 5:11–64, 5:14–16.

The specification identifies BIC (disclosed as compound 42 in WO '323 (EX-1005)) as a potent INSTI with *in vitro* activity against wild type HIV-1. *Id.* at 5:1–16. It further identifies TAF (typically in hemifumarate form) and FTC (free base) as known N(t)RTIs and acknowledges that FTC (200 mg) was (at the time) part of Gilead's FDA approved single tablets Truvada[®], Atripla[®], Stribild[®], and Complera[®]. *Id.* at 6:37–60, 7:4–20, 7:56–8:13.

The specification discloses “fixed dose combination” tablets incorporating BIC, TAF, and FTC, including specific examples of “bilayer tablets.” EX-1001, 4:15–25; 49:59–64, 58:29–66:66. It states that “the inventors have found that the use of fixed dose combinations may assist in optimizing pharmacokinetic properties ... particularly the total exposure of Formula (I) ... [, and that they] may affect the dissolution of ... active ingredients within the dosage form, and [are] therefore likely to have an impact on in vivo pharmacokinetics” *Id.* at 9:44–58. The dissolution of BIC is said to “var[y] depending on whether the tablet is in a fixed dose combination formulation [with TAF and FTC] and/or whether the tablet is a monolayer or multilayer tablet.” *Id.* at 9:51–63. The inventors also observed that the “presence of certain excipients ... (or absence of others) affects the dissolution profile of one or more active ingredients” *Id.* at 9:63–66.

One of the “bilayer tablet” examples (Tablet F2) segregates BIC sodium (78.7 mg) from TAF hemifumarate (28.1 mg)/FTC (200 mg) using separate layers (with specific excipients in each layer). EX-1001, 58:29–59:8. Tablet F2 reportedly provided a ~30% enhancement in BIC exposure in the blood of patients compared to patients administered BIC sodium as a single tablet (with different excipients) (Tablet F1) and TAF hemifumarate/FTC in a separate tablet (with its own excipients) (Tablet F3). *Id.* at 60:1–61:38; 57:60–58:17 (Tablet F1); 59:14–45 (Tablet F3); *see also* EX-1003, ¶ 109.

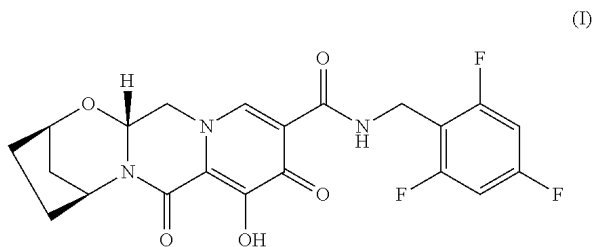
B. Challenged Claims¹⁸

The '802 Patent contains thirteen claims. EX-1001, 77:28–78:40.

Independent claim 1 covers the following (annotated to separate its elements):

1[pre] A tablet comprising

1[a] 50 mg of the compound of Formula I:



or a pharmaceutically acceptable salt thereof,

[1b] 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and

¹⁸ *See also* EX-1003, ¶ 110.

[1c] 200 mg emtricitabine or a pharmaceutically acceptable salt thereof.

The dependent claims narrow the claimed tablet to require a BIC salt (claims 2, 4), a TAF salt (claims 3–4), FTC free base (claims 4, 8), 52 mg of BIC sodium (claims 5, 8), TAF fumarate (claim 6), and 28 mg TAF hemifumarate (claims 7–8).

Additional dependent claims limit total tablet weights in various ways (claims 9–13). No claim of the '802 patent is limited to a multilayer tablet.

C. Prosecution History

The '803 application was the third continuation in a family beginning with U.S. Appl. No. 15/346,335 (“the '335 application;” issued as the '846 Patent (EX-1011)). EX-1001, (63); EX-1002, 1–8, 10. Both applications claimed priority to the Effective Date. *Id.* at 1:5–16; EX-1011, 1:5–12.

1. The '846 Patent

During prosecution of the prior '335 application, Gilead responded to a restriction requirement by amending previously filed claims and presenting claims essentially identical to the Challenged Claims. EX-1040, 1479–84; *cf.* EX-1001, 77:28–78:40. The examiner rejected the amended claims over two published applications to Carra et al. EX-1040, 1493–98 (*see* 1496–97). Gilead responded by amending claim 1, limiting it to “a multilayer tablet” having “a total weight of less than about 1000 mg.” *Id.* at 1518–24 (*see* 1519, 1522) (emphasis in original). Gilead argued that a “*bilayer tablet formulation* of ([BIC], [TAF] and [FTC])

results in approximately 30% higher total [BIC] exposure” compared to a single agent formulation of BIC, when co-administered with a separate tablet with TAF and FTC. *Id.* at 1523–24 (citing EX-1040, 96 (paragraph [0317] on bilayer tablet F2) (emphases added)).

The examiner again rejected the pending claims over the Carra applications and Dahl (US 2007/0016973) and found the alleged unexpected results not commensurate with the claims. EX-1040, 1535–40. Gilead disputed the examiner’s characterization, asserting “the unexpected results are associated with the *combination* of [BIC, TAF, and FTC], *not the specific amounts.*” *Id.* at 1556 (citing EX-1040, 96 (paragraph [0317]; Tablet F2)) (emphasis added). Gilead also urged disqualification of the Carra applications as prior art. *Id.* at 1555.

In the final Notice of Allowance, the examiner agreed that the Carra applicants were not prior art. *Id.* at 1890. She 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.” *Id.* at 1890–91. The examiner also accepted Gilead’s allegation of a 30% higher exposure of BIC when administered in a fixed dose combination as opposed to a separate tablet. *Id.* at 1891.

2. The '802 Patent¹⁹

On March 31, 2022, Cipla informed Gilead that it sought FDA approval for a competitive product to Biktarvy[®] (single tablet with BIC/TAF/FTC) that would not infringe the multilayer tablet claims of the '846 Patent. EX-1012, ¶¶ 82–83. The '803 application was filed a month later. EX-1001, (21)-(22). Gilead then filed a preliminary amendment to present claims similar to the '335 application claims before the “multilayer” amendment. EX-1002, 137–40 (*see* claims 52–64); *cf.* EX-1040, 1479–84 (*see* claims 1–5, 26–27). Although the examiner previously disqualified the Carra application during prosecution of the parent '846 Patent, she again rejected the broader tablet claims over those applications. EX-1002, 161–71; *cf.* EX-1040, 1496–97, 1535–39. Gilead (as it had before) urged disqualification of these applications (*see* EX-1002, 244–49) and the broader claims were allowed shortly thereafter (*id.* at 769–76).

In the final Notice of Allowance, the examiner identified WO '323 as “the next closest prior art,” and again found (in error) that WO '323 only disclosed administering BIC “*at a different time* than additional drugs such as tenofovir and emtricitabine.” EX-1002 at 1051–52 (emphasis added); *cf.* EX-1040, 1890–91.

¹⁹ *See also* EX-1003, ¶ 111–19.

Though not argued by Gilead during prosecution, the examiner repeated *verbatim* her unexpected results findings when allowing the '846 Patent claims. *Id.*

D. Person Having Ordinary Skill in the Art (“POSA”)²⁰

Petitioner believes a POSA (or “skilled artisan”) is an M.D. or a Ph.D. with at least three years of work experience with HIV therapy and clinical investigations, drug development, medicinal chemistry, pharmaceuticals, pharmacokinetics, and/or pharmaceutical formulations prior to the Effective Date. EX-1003, ¶ 40; EX-1004, ¶¶ 17–19. Petitioner also submits that the POSA focused in one area would also consult with a collaborative team of skilled artisans in related fields, including other POSAs (as defined above) with different skill sets, particularly in drug development and medicinal chemistry. EX-1003, ¶ 41–45; EX-1004, ¶ 18–19.

Further, the POSA skilled in HIV clinical therapy and/or drug development would be familiar with the HIV pharmaceutical and treatment market, and particularly aware of the financial impact of developing a single tablet ART regimen desired by physicians prior to the Effective Date. EX-1030, 30-31 (Gilead 10-K stating that “if we do not introduce new products to market or increase sales

²⁰ See also EX-1003, ¶¶ 37–44; EX-1004, ¶¶ 17–19.

of our existing products, we will not be able to increase or maintain our total revenues nor continue to expand our R&D efforts.”); EX-1003, ¶ 42.

VII. CLAIM CONSTRUCTION²¹

Petitioner relies upon the ordinary meaning of claim terms. No Challenged Claim requires that the claimed amounts of any drug be therapeutically effective. *See United Therapeutics Corp. v. Liquidia*, 74 F.4th 1360, 1368-70 (Fed. Cir. 2024).

Where claims refer to “*a pharmaceutically acceptable salt thereof*,” Petitioner adopts the specification’s description that the amount of that salt is one that provides the desired amount of the free acid (or base) form of the compound. EX-1001, 6:4–28; 7:22–48; 8:22–36.

VIII. THE PETITION SHOULD NOT BE DENIED UNDER 35 U.S.C. § 325(d)

The Board’s *Advanced Bionics* decision presents a two-part test for assessing whether a Petition can be denied under Section 325(d). *Advanced Bionics, LLC v. Med-El Elektromedizinische Gerate GmbH*, IPR2019-01469, Paper 6, at *8 (P.T.A.B. Feb. 13, 2020). Each part of the test is analyzed using three factors (known as the *Becton-Dickinson* factors). *Id.* at *8–10 (Part One

²¹ *See also* EX-1003, ¶¶ 120–23.

factors (i)–(iii), 17–18 (Part Two factors (iv)–(vi)). For the reasons explained below, the Board should not deny the Petition under Section 325(d).

A. Advanced Bionics Part One

When considering *Beckton-Dickinson* factors (i)–(iii), Petitioner respectfully submits that Part One of the *Advanced Bionics* test is not satisfied for all references relied upon in Grounds 1–3.

Assessing Part One as applied to Ground 1, Petitioner acknowledges that WO '323 and WO '351 were presented to the Office in an IDS along with ~180 additional documents (Part One factor (i)). EX-1002, 595–609 (*see* 598). Since Part One as applied to Ground 1 is satisfied, Petitioner analyzes Ground 1 under Factor Two below.

As for Grounds 2–3, the additional prior art was not presented to the Office (Part One factor (i)) and is materially different from (and non-cumulative to) references actually presented (Part One factor ii). The Bowker and Paulekuhn references in Ground 2 are not like any references originally presented to the Office, as no submitted references provided strategies for salt selection or preferred salts for weakly acidic drugs like BIC and DTG (Part One factors (i)–(ii)). There is also no overlap between any argument made before the Office and Petitioner's reliance upon the above concepts in Ground 2 (Part One factor (iii)). *See* Sections V.D–E, IX.B.

Additionally, US '079 (Ground 3) describes a specific tablet containing DTG (50 mg) with Gilead's TDF (300 mg)/FTC (200 mg) backbone, along with specific excipients to provide a total coated tablet weight of 1055 mg. EX-1003, ¶¶ 75, 155. The references presented to the Office do not disclose single tablets with the same level of formulation detail as US '079 (Part One factors (i)-(ii)), that Petitioner specifically relies upon herein. Sections V.C, IX.C.

The Board should therefore not deny institution of Grounds 2–3 because Part One of *Advanced Bionics* is not satisfied as to Bowker and Paulekuhn, or US '079.

B. Advanced Bionics Part Two

No reference that supports Grounds 1–3 was the basis for a substantive rejection during examination (Part Two factor (iv)). See Section VI.C.2. The examiner only mentioned WO '323 to be the “the next closest prior art” after disqualifying the Carra applications, as she had done during the parent '846 prosecution. EX-1002, 1046–53; cf. EX-1040, 1890–91.

Petitioner respectfully submits that the examiner did not appreciate highly relevant disclosures from WO '323 when granting allowance (Part Two factor (v)). EX-1002, 1051–52; EX-1003, ¶¶ 117–19. WO '323 is not limited to administration of Formula I (BIC) *at a different time* than additional drugs such as tenofovir or emtricitabine. *Id.* WO '323 specifically discloses single compositions for *simultaneous administration*, e.g., solid oral dosage forms containing

therapeutically effective amounts of BIC (compound 42) and additional anti-HIV drugs such as TAF fumarate and FTC. EX-1005, 37:7–38:2, 38:13–21; EX-1003, ¶¶ 137–38. Such single compositions would necessarily administer all compounds *at the same time*, not different times. The examiner’s reading of ’WO 323 was plainly incorrect²², and this error was material to patentability, as evidenced by Grounds 1-3 herein. *See e.g.*, Sections V.A, IX.A-C.

This Petition also provides additional evidence in the form of two expert declarations not before the Office that provide important context including background art and motivations never presented to the Office. *See e.g.*, EX-1003, ¶¶ 48–96; EX-1004, ¶¶ 24–77; *cf.* EX-1002, IDSs at 595–609, 782–94, 810–13, 971–74. This evidence provides important context that accurately summarizes the prior art, and a POSA’s motivations to arrive at the Challenged Claims with a reasonable expectation of success. *See e.g.*, EX-1003, Section IX; EX-1004, Section VI.

²² Gilead also did not advise the examiner (when the ’802 prosecution was pending) that WO ’323 is related to US Patent 9,216,996, a patent that Gilead had represented to the Food and Drug Administration (in March of 2018) covers Biktarvy®, a single, bi-layered tablet with all three claimed ingredients.

Petitioner respectfully submits that, should Part One of *Advanced Bionics* be satisfied for each reference in Grounds 1–3 (as to all Challenged Claims), Part Two nonetheless supports institution. The Board should therefore not deny the Petition under Section 325(d).

IX. CLAIMS 1–13 OF THE '802 PATENT ARE OBVIOUS

The elements that generally govern an objective obviousness analysis, as set forth by the Supreme Court in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17–18 (1966) and *KSR*, 550 U.S. at 406–07, are well known, and need not be repeated here.

For composition claims in the pharmaceutical context, “structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make ... [the] claimed compositions, creates a *prima facie* case of obviousness” *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc). The functional and pharmaceutical properties of prior art compositions and the compounds contained therein are also relevant to obviousness. *Unigene Laboratories, Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1361–62 (Fed. Cir. 2011). The discovery of an optimum value of a result effective variable generally qualifies as a skill available to a POSA. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1368 (Fed. Cir. 2007).

A. Ground 1: Obviousness over WO '323 and WO '351

The disclosures of WO '323 and WO '351 from Sections V.A–B are incorporated herein. *See also* EX-1003, ¶¶ 126–52, Appendix B; EX-1004, ¶¶ 73–74, 78–79, 83, 89, 100–103.

1. Motivation to Combine WO '323 and WO '351

Each of WO '323 and WO '351 disclosed tablets containing an INSTI (BIC or DTG) as an “anchor” for, e.g., the N(t)RTI “backbone” of TAF/FTC, and their use in treating HIV-1 infection. EX-1005, 36:12–18, 37:7–21, 37:7–19, 38:19–21, 39:25–27, 40:18–20, 240–42; EX-1006, Abstract, 3:22–26, 4:1–9, 6:24–32, 7:27–28, 9:4–25; *see also* EX-1003, Appendix B, claim 1. Both references are in the same “field of endeavor” as the '802 Patent, which discloses and claims single tablets containing the INSTI BIC (Formula (I) in the '802 Patent) as an anchor for TAF/FTC. EX-1001, 77:28–78:40. As such, WO '323 and WO '351 are analogous art and properly combinable for the purposes of the following analysis. *In re Biggio*, 381 F.3d 1320, 1325–26 (Fed. Cir. 2004).

A POSA would have further considered the combined disclosures of WO '323 and WO '351 for at least three additional reasons, as explained below.

a) Design Need and Market Pressure for a Single Tablet Regimen Combining FTC/TAF with a Commonly Owned “Second Generation” INSTI.

Although single tablets s containing INSTIs anchoring N(t)TRI pair were DHHS-recommended ART regimens (*i.e.* Gilead’s Stribild® and Viiv’s Triumeq®)

physicians elected to prescribe the “second generation” INSTI DTG in one tablet (Viiv’s Tivicay®) with a second tablet containing TDF/FTC (Gilead’s Truvada®). *See* Section IV.B.2, IV.D; EX-1003, ¶¶ 66, 162. Though less convenient and not ideal for patient safety and adherence, this two-tablet regimen was among the five DHHS-recommended ART regimens available prior to the Effective Date. EX-1003, ¶ 52; EX-1014, 70, 82.

In 2014, Gilead reported on a Phase 3 trial where single tablets combining TAF (Gilead’s improvement over TDF) and FTC had met its primary objective for treating HIV-1, where TAF demonstrated high antiviral efficacy at doses less than 1/10th of TDF (e.g., 25 mg TAF as opposed to 300 mg TDF) and also improved kidney and bone safety. *See* Section IV.C; EX-1003, ¶ 70; EX-1025, 52–53, 57; EX-1030, 3; EX-1036, 1–2. Gilead also published its own new class of INSTIs in WO ’323, which included compound 42 (BIC), and their combination with additional anti-HIV agents such as TAF fumarate and FTC in a single composition, preferably as a unit dosage forms, e.g., tablets. *See* Section V.A; EX-1003, ¶¶ 126–29, 133; EX-1004, ¶ 74.

By 2014, there was also a well-established design trend in the HIV market to provide single tablet ART regimens to HIV infected patients. *See* Section IV.D; EX-1003, ¶¶ 77–79; EX-1030, 3 (Gilead declaring single tablet regimens to be “critical for the successful management of the disease,” and that it is “focused on

the development of new HIV medicines and co-formulation of products into complete regimens.”); EX-1023, 506 (commenting on development of DTG as a once-a-day INSTI), EX-1025, 52 (discussing single tablet regimens using TAF); EX-1026, 1–2 (noting “the most advanced regimens used nowadays involve a single pill administered daily.”); EX-1027, 168 (noting that “once-daily single-tablet regimens represent the paramount simplification of antiretroviral treatment achieved so far.”). And, if that single tablet could be given once-a-day (QD), it would have been considered ideal. *See* Section IV.D; EX-1003, ¶¶ 77–78, 171.

Moreover, though other pharmaceutical companies published on single compositions containing ViiV’s DTG with Gilead’s TAF/FTC pair, a POSA would have appreciated that a single tablet INSTI/N(t)RI regimen would be more efficiently and expeditiously evaluated and brought to market with a different INSTI (having improved biological properties similar to DTG) that was commonly owned with TAF/FTC. EX-1003, ¶¶ 73–75.

As such, a POSA would have been motivated by the recognized clinical need for a single tablet QD regimen with a “second generation” INSTI anchoring the proven efficacy and safety of TAF/FTC. *Id.* With the remarkable success of single tablet regimens marketed before the Effective Date, the financial benefit for developing such a single tablet regimen would have been substantial. *See* Section IV.D; EX-1003, ¶¶ 76–79; EX-1030, 6 (noting sales of Gilead’s antiviral products

were \$22.8 billion in 2014). Indeed, Gilead had recognized the need to provide such regimens, and its INSTI BIC provided a means to achieve exactly that. EX-1003, ¶¶ 77–78, 170; EX-1030, 34 (recognizing that ViiV’s “single-tablet triple-combination antiretroviral regimen” Triumeq®, launched in late 2014, “could adversely impact sales of our HIV products.”).

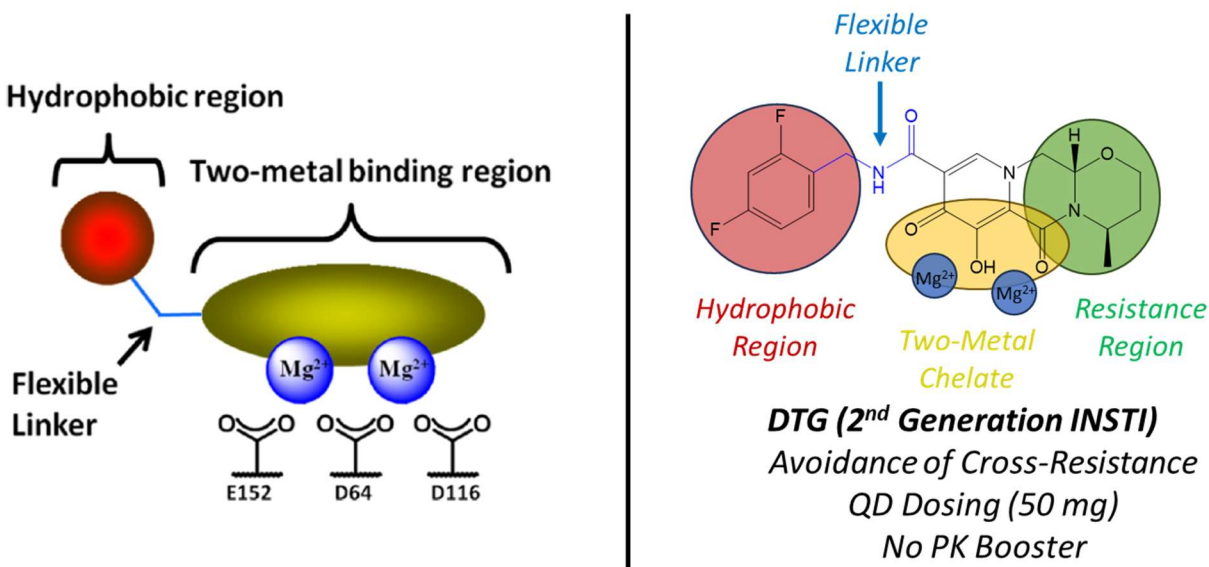
b) Gilead’s “Me-Too” INSTI with Structural and Functional Similarity to ViiV’s DTG

WO ’351 disclosed pharmaceutical compositions containing therapeutically effective amounts of the “second generation” INSTI DTG combined with therapeutically effective amounts of TAF and FTC, with a preference for solid oral dosage forms such as tablets. *See* Section V.B; EX-1006, Abstract, 3:22–26, 17:27–28, 23:6–8; EX-1003, Appendix B. Specifically disclosed is a composition combining the FDA-approved doses of DTG (50 mg) and FTC (200 mg), with a highly efficacious dose of TAF (25 mg) and additional excipients. *See* Section V.B; EX-1006, 19:30–20:2; EX-1003, ¶¶ 53–55, 70–72, Appendix B.

DTG was considered the first FDA-approved “second generation” INSTI, based on its ability to provide once-a-day administration without a PK booster (in ART naïve patients), its high genetic barrier to resistance, and its avoidance of cross-resistance with “first generation” INSTIs RAL and EVG. *See* Section IV.B; EX-1003, ¶¶ 55–56; EX-1004, ¶ 71; EX-1017, 83; EX-1023, 506; EX-1014, 70; EX-1041, 5901–02, 5909–10. A POSA also knew that DTG was marketed alone

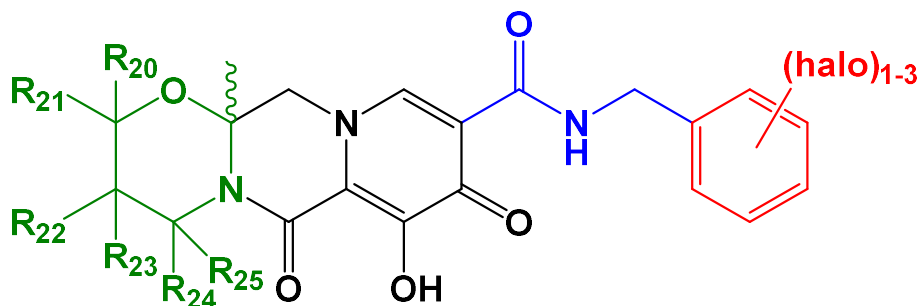
as Tivicay[®] and in combination with ABC/3TC in the single tablet Triumeq[®]. EX-1003, ¶ 55; EX-1022, 1; EX-1024, 1; *see also* EX-1001, 8:65–9:4.

The POSA would have readily appreciated the critical structural elements of DTG that provided key improvements over RAL and EVG, including a tricyclic ring system delivering an improved resistance profile and the avoidance of cross-resistance toward RAL/EVG mutants. *See* Section IV.B; EX-1004, ¶¶ 62, 70–72. These important structural features are highlighted below in view of the known binding model for INSTIs in the active site of INST. *Id.*; *see also* EX-1041, 5901.



As illustrated above, DTG contains a hydrophobic region (red) and a two-metal binding (or chelate) region known to impart low nanomolar (nM) potency against INST, along with a resistance region (green) providing its improved resistance profile vis-à-vis RAL and EVG. EX-1003, ¶¶ 178–79; EX-1004, ¶¶ 68–70, 72, 77; EX-1041, 5901–02, 5905, 5908 (Tables 2 and 4), 5909 (Figure 6). DTG was also

protected by the '385 Patent which issued in 2012 and is enforceable until at least 2026. EX-1057, (22), (45). The '385 patent claims the following genus covering DTG (highlighted to emphasize the important structural features shown directly above):²³

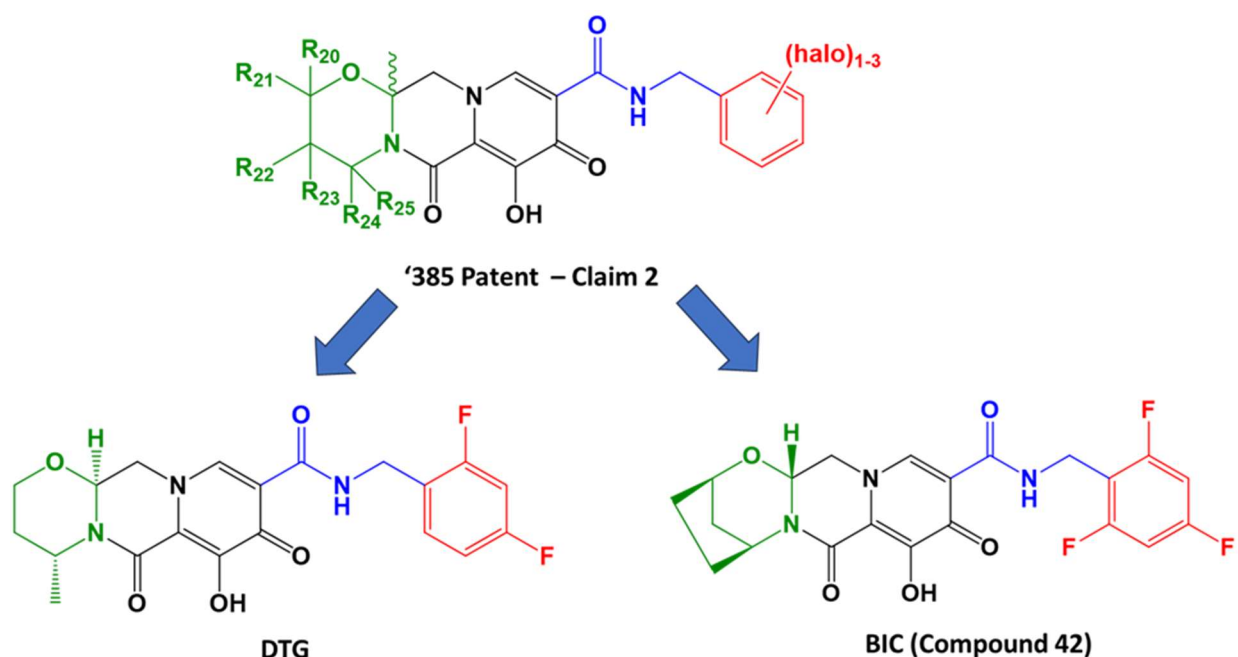


'385 patent, Claim 2

EX-1057, 178:34–36 (claim 2), 177:40–178:33 (defining variables R₂₀–R₂₅ as including hydrogen and (C1–C8)-alkyl); EX-1004, ¶¶ 61, 74.

A POSA would have recognized that some of the INSTIs from WO '323, especially compounds 42 (BIC) and 2, bear significant structural similarities to DTG from WO '351. EX-1003, ¶¶ 178–79; EX-1004, ¶¶ 74–77, 84–85, 90. The following illustration compares DTG and compound 42 (BIC) in view of claim 2 of '385 patent to emphasize their high degree of structural similarity:

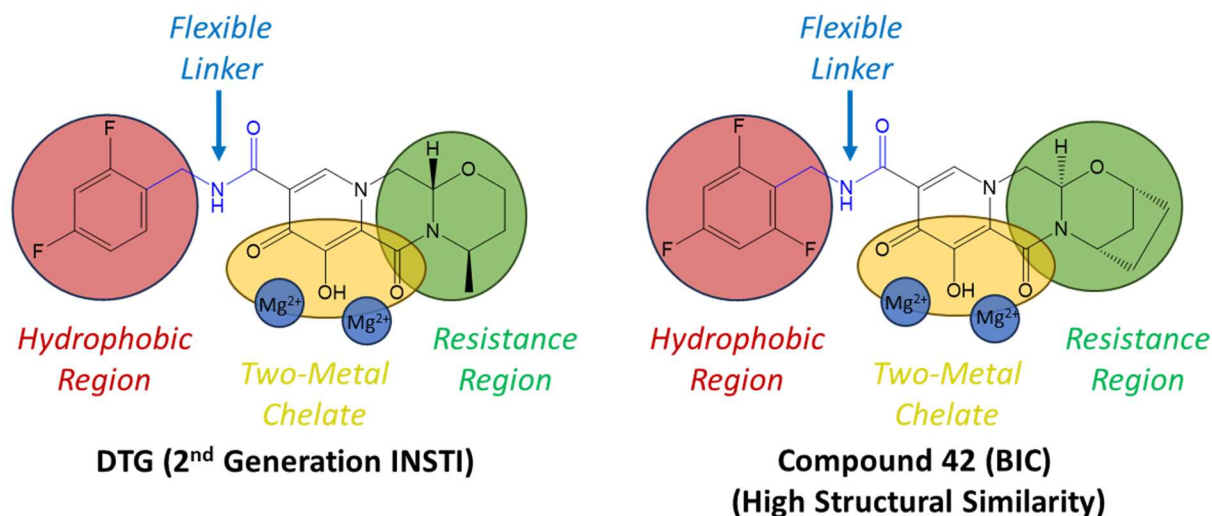
²³ Structural orientation of Claim 2 genus presented in view of the configuration for BIC in the challenged claims. EX-1004, ¶ 61.



EX-1003, ¶ 178; EX-1004, ¶¶ 74–77, 90–91. A POSA would have readily appreciated that DTG and compound 42 (BIC) contain identical metal chelate regions (black) and linkers (blue), similar hydrophobic fluoro-substituted phenyl rings (red), and similar 6-membered heterocyclic rings (green). *Id.* Indeed, the only differences between the compounds are: (1) BIC's additional fluorine atom (red), (2) an additional connection from DTG's methyl group (green dashed wedge) to the 6-membered heterocycle (green), i.e., a two-carbon bridge, and (3) its different stereochemical configuration (green dashed wedge for DTG; green bold wedges for BIC). EX-1003, ¶ 178; EX-1004, ¶¶ 74–77.

Given that DTG and compound 42 (BIC) were known INSTIs with activity against HIV-1 replication (*see* Sections IV.B, V.A), their close structural similarity would have provided a POSA with a high expectation of similar physicochemical

and biological properties, including acidity, binding mode to the active site of INST (below), and maintained activity toward RAL/EVG resistant INST mutants. EX-1003, ¶¶ 178, 192–94, 197; EX-1004, ¶ 77; EX-1041, 5905 (Table 2), 5906 (Figure 4); EX-1005, 212–16 (Table 1).



As such, a POSA would have considered Gilead's BIC a “me too” INSTI of DTG and thus essentially interchangeable with DTG in ART regimens, including in single tablets containing Gilead's improved N(t)RTI backbone TAF/FTC. EX-1003, ¶¶ 178, 192–94; EX-1004, ¶ 77.

This expected interchangeability would have provided a POSA with additional motivations to combine WO '323 and WO '351 and provide solid oral dosage forms with BIC anchoring TAF/FTC. EX-1003, ¶¶ 167–68. As discussed below, a POSA would have expected BIC to be a once-a-day (QD) INSTI based on its pharmacokinetic (PK) properties. *See also* EX-1003, ¶ 192; EX-1004, ¶ 85.

c) The Need for Smaller Tablets

Gilead's Stribild[®] and ViiV's Triumeq[®] products were known to contain 800 mg and 950 mg of total active drugs respectively. EX-1003, ¶ 170–71; EX-1019, 22–23; EX-1024, 17–18. A POSA would have appreciated that Gilead's improved N(t)RTI pair TAF/FTC would permit a reduction in the total drug weight, i.e., by 275 mg, as disclosed in WO '351. *See* Section IV.C; EX-1003, 69–70, 171; EX-1006, 19:4–25:7–9 (*cf.* DTG (50 mg)/TDF (300 mg)/FTC (200 mg) and DTG (50 mg)/TAF (25 mg)/FTC (200 mg) compositions). This change alone would have provided an overall lower tablet weight, which was preferred to improve patient adherence. EX-1003, ¶¶ 213–15 (citing EX-1014, 188; EX-1042, 3). The POSA therefore would have recognized that single tablets with a “second generation” INSTI anchoring TAF/FTC would be significantly smaller than Stribild[®] and Triumeq[®]. EX-1003, ¶¶ 172, 211–15.

In summary, the POSA would have had several good reasons to combine WO '323 and WO '351 for the purpose of making single tablets combining a therapeutically effective amount of compound 42 (BIC) with 25 mg TAF and 200 mg FTC.

2. Differences between WO '323/WO '351 Combination and the Challenged Claims

Based on the disclosures from WO '323 and WO '351 summarized in Sections V.A–B, their combination discloses each element of the challenged

claims, including a **tablet (1[pre])** containing **50 mg BIC** or its **pharmaceutically acceptable salt** (e.g., BIC sodium) (**1[a]**), **25 mg TAF** or a **pharmaceutically acceptable salt** (e.g., TAF fumarate and hemifumarate) (**1[b]**), and **200 mg FTC** free base (non-salt form) (**1[c]**). *See also* EX-1003, ¶¶ 183–85, 190, Appendix B.

In particular, WO '323 discloses solid unitary dosage forms for oral administration, e.g., tablets (**1[pre]**). EX-1005, 5:14–22, 12:18–20, 36:11–23, 37:7–21, 39:25–27, 40:18–20, 240–42. It discloses and claims BIC as compound 42 including pharmaceutically acceptable salts, e.g., sodium salts, and discloses 50 mg as an appropriate therapeutically effective amount (**1[a]**). EX-1005, 5:23–6:8, 14:16–15:20, 35:11–17, 35:8–17, 36:12–15, 36:18–21, 37:7–19, 98:8–101:25, 240–42. It further discloses INSTIs such as compound 42 (BIC) combined in a single composition with, e.g., two other anti-HIV agents, including the N(t)RTIs TAF fumarate (**1[b]**) and FTC (**1[c]**). EX-1005, 12:18–20, 16:8–21, 37:7–21, 38:13–21, 40:18–22, 241–42. WO '351 specifically discloses single compositions combining TAF (25 mg)/FTC (200 mg) (**1[b]-1[c]**) with 50 mg of the structurally similar INSTI DTG (**1[a]**) and prefers tablets (**1[pre]**). EX-1006, Abstract, 1:3–7, 2:15–16, 3:15–16, 3:23–26, 4:1–15, 5:22–27, 6:24–32, 8:10–11, 9, 12:21–13:13, 13:16–18, 17:27–28, 19:3–12, 19:30–20:6, 23:6–8.

The differences between the asserted combination and the Challenged Claims reside in a specific disclosure of a single tablet containing each of 50 mg

BIC (or 52 mg BIC sodium), 25 mg TAF (or TAF fumarate or 28 mg TAF hemifumarate), and 200 mg FTC (free base) (claims 1–8), total tablet weights <1000 mg (claims 9–11), and BIC weight percents <15% of the tablet weight (claims 12–13). EX-1003, ¶¶ 186–87, 190.

As discussed below, a POSA would have been motivated to select a therapeutically effective amount of BIC (and BIC sodium) from the INSTI compounds from WO '323 and combine it with TAF (25 mg)/FTC (200 mg) in a single tablet. The therapeutically effective amount of BIC (and BIC sodium) would have been identified through routine experimentation, and so the claimed 50 mg BIC (52 mg BIC sodium) are not patentably significant. That person would have a reasonable expectation of success in making the claimed tablets given the advanced state of tablet formulations and routine tablet formulation considerations at the time. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1068–69 (Fed. Cir. 2012); *Amgen Inc. v. F. Hoffmann-La Roche*, 580 F.3d 1340, 1362 (Fed. Cir. 2009).

3. Obviousness Analysis

a) Claim 1

Claim 1 recites a tablet with 50 mg BIC, 25 mg TAF, and 200 mg FTC, each of which may be present as a pharmaceutically acceptable salt. EX-1001, 77:23–78:4. Each limitation is disclosed by the WO '323/WO '351 combination. *See*

Section IX.A.1. The following sections provide additional motivation for making the tablet of claim 1 with a reasonable expectation of success.

i. Selection of BIC (Compound 42)²⁴

WO '323 discloses BIC (compound 42) along with ~100 other INSTI compounds. *See* Section V.A. As explained below, the publication specifically directed a POSA to select compound 42 (BIC) as an INSTI anchor in single tablet regimens containing an N(t)RTI backbone, e.g., TAF/FTC as disclosed in WO '351.

First, the INSTI compounds disclosed in WO '323 demonstrated antiviral activity *in vitro*, an established metric indicating their potential utility for “treating the proliferation of the HIV virus, treating AIDS, or delaying the onset of AIDS or ARC symptoms.” EX-1005, 212:24–26. Several compounds, including compound 42 (BIC), were found to be particularly active at suppressing HIV replication, i.e., **EC₅₀** values in the range of 1.5–2.5 nM, placing them as among the most active compounds studied. EX-1005, 212:5–216 (Table 1- reporting **EC₅₀** values in the range of 1.5–422 nM; compound 42 (BIC) = 2.5 nM); EX-1003, ¶ 191; EX-1004, ¶¶ 78–79; *see also* EX-1004, ¶¶ 27–28 (tutorial on *in vitro* and *in vivo* screening).

²⁴ *See generally* EX-1003, ¶¶ 119, 190–91; Ex-1004, ¶¶ 78–87.

Second, only 11 INSTI compounds were studied *in vivo* to assess PK properties after IV administration to dogs. EX-1005, 222–24 (Example 107 and Table 4); EX-1003, ¶¶ 131–33, 191–92; EX-1004, ¶¶ 83–84. A POSA would have appreciated that QD administration was an important goal for ART regimens and INSTI development specifically. EX-1003, ¶¶ 192–93, EX-1004, ¶ 82. As such, that person would have desired INSTI compounds with longer half-lives ($t_{1/2}$) and residence times (**MRT**) in the body.²⁵ EX-1003, ¶¶ 191–92; EX-1004, ¶ 82; *see also* EX-1004, ¶¶ 29–35 (tutorial on ADME and PK principles). Dr. Winkler calculated the expected half-lives for the 11 compounds tested *in vivo* by IV administration based on their clearance (**CL**) and distribution (**V_{ss}**) data, which are provided in the following table:

Compound	Expected $t_{1/2}$ (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

²⁵ According to WO '323, lower clearance values (**CL**) combined with larger distribution values (**V_{ss}**) provide longer elimination half-lives ($t_{1/2}$). EX-1005, 223:11–15.

3	~3.4
2	~4.6

EX-1004, ¶¶ 33–34 (explaining calculation), 81 (calculation). As shown, compounds 41, 42 (BIC), and 47 had the longest expected half-lives (~5.0-5.2 h), with compounds 2 and 3 being shorter (~4.6 and ~3.4 h), and the remaining compounds being significantly shorter (~1.2–2.9 h). Compounds 41, 42, and 47 also provided the longest residence times (**MRT**). *Id.* at ¶¶ 81–82; *see* EX-1005, Table 4 (MRT = 7.1–7.5 h). Considering the goal of QD administration, a POSA would have been particularly interested in compounds 41, 42, and 47 based upon the IV data. EX-1003, ¶¶ 191–92; EX-1004, ¶ 82.

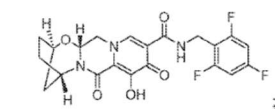
Compounds 41, 42, and 47 were then selected by the applicant (along with compound 2 and 3) for an oral study designed to assess oral bioavailability (**F(%)**), peak plasma concentration (**C_{max}**), and total plasma exposure (**AUC**). EX-1005, Table 4; EX-1003, ¶¶ 132–35, 191–92; EX-1004, ¶¶ 80, 83. For oral administration, a POSA would have desired compounds with a higher **F(%)**, along with a larger **C_{max}** and **AUC**, as they would be absorbed more readily to provide higher concentrations in the blood – important elements for oral QD administration. EX-1003, ¶¶ 191–92; EX-1004, ¶¶ 32, 35 (tutorial on **F(%)**, **C_{max}**, and **AUC**), 83. Compounds 42 and 2 provided significantly better **F(%)**, **C_{max}** and **AUC** compared with the other three compounds studied. EX-1004, ¶ 83; EX-1003, ¶ 132-133. Compounds 42 and 2 therefore would have been particularly

preferred compounds for QD oral administration based on their greater ability to maintain appropriate drug concentrations for longer periods of time. EX-1004 at ¶ 83; EX-1003, ¶¶ 133-134, 191-92.

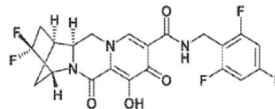
A POSA would have identified compound 42 (BIC) as particularly attractive based on its long expected $t_{1/2}$ (the longest of all tested compounds) and long **MRT**, combined with its good oral bioavailability (**F (%)**) and resultant **C_{max}** and **AUC** (only compound 2 provided better results in the oral study). EX-1003, ¶¶ 133-134, 191-92; EX-1004, ¶¶ 80-84. A POSA also would have preferred compound 42 over its enantiomer (not tested orally) given that compound 2 (same stereochemical configuration as compound 42 (blue below)) provided substantially better $t_{1/2}$, **MRT**, **F (%)**, **C_{max}** and **AUC** values than its enantiomer 3 (red below). EX-1004, ¶ 77, n. 3.

Claim 32 from WO '323 describes a Markush group made of compound 42 (BIC) and six other INSTI compounds tested *in vivo*, as follows:

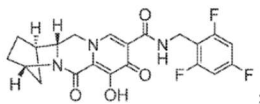
32. A compound of claim 1 selected from:



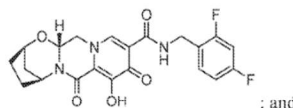
Compound 42 (bictegravir)
(WO '323, 99:8-13)



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

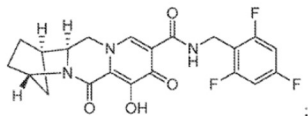


Compound 41
(*Id.* at 95:11-15)

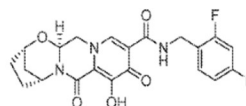


Compound 2
(*Id.* at 45:22-46:1)

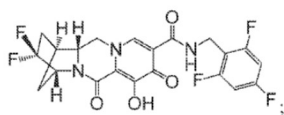
; and



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



Compound 3
(*Id.*)



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

EX-1005, 240–41 (annotated to provide compound numbers). A POSA would have understood the applicant's decision to claim this small group to indicate that they were particularly important. EX-1003, ¶ 145; EX-1004, ¶ 78. The *in vivo* studies described above make this selection readily apparent and provide the POSA with motivation to specifically select compound 42 from this small group. EX-1003, ¶¶ 131–34; EX-1004, ¶¶ 80–84.

Claim 33 describes a pharmaceutical composition comprising a compound of claim 32, or a stereoisomer or pharmaceutically acceptable salt thereof, along with a carrier, diluent, or excipient. EX-1005, 241. Claims 35–36 then allow for the composition to comprise one or more additional anti-HIV agents including N(t)RTIs, where TAF fumarate and FTC are N(t)RTIs disclosed in the specification. *Id.*

In sum, a POSA would have selected compound 42 (BIC) from among the ~100 compounds disclosed in WO '323, including from the eleven compounds tested in Example 107, and from the seven compounds in claim 32, as a prime candidate for oral administration, e.g., in a single tablet containing a therapeutically effective amount combined with Gilead's improved N(t)RTI pair of TAF (25 mg)/FTC (200 mg) described in WO '351 (*see* EX-1006, 19:30–20:2). EX-1003, ¶¶ 191–92; EX-1004, ¶¶ 83–87. Indeed, such a tablet represents nothing more than a predictable combination of known anti-HIV compounds with no change in their well-known functions as INSTIs as anchors for N(t)RTI backbones. *KSR*, 550 U.S. at 415–18.

As such, the POSA would have selected an appropriate therapeutically effective amount of compound 42 (BIC) and prepared oral compositions, and preferably single tablets, containing appropriate therapeutically effective amounts TAF and FTC as suggested by WO '323. EX-1003, ¶¶ 186, 191–94; EX-1005, 16:19–21, 35:16–17; 36:13; 37:7–12, 38:14, 38:19–20, claim 36 (when depending from claim 32). TAF (25 mg) and FTC (200 mg) (combined with DTG (50 mg) as disclosed by WO '351 were known to be therapeutically effective amounts. EX-1003, ¶¶ 193–94; EX-1004, ¶¶ 100–03; EX-1006, 5:22–27; 19:30–20:2, 23:6–8; EX-1005, 37:7–11, 38:13–17, 38:18–21; 39:25–27. All that remains is a POSA's

determination of an appropriate amount of BIC to use in a single tablet with TAF (25 mg)/FTC (200 mg).

ii. Selection of BIC 50 mg, 25 mg TAF, and 200 mg FTC in a Single Tablet.

WO '323 discloses INSTI doses in the range of about “25 mg to about 500 mg,” and specific doses such as 25, 50, and 100 mg. EX-1005, 35:14–23; EX-1003, ¶ 143, 194. It further states that “therapeutically effective amount[s] can be determined routinely by [a POSA] having regard to their own knowledge, the state of the art, and this disclosure,” and that such amounts depend on compound activity, length of action, rate of excretion, and drug combinations, along with patient age, body weight, and disease severity. EX-1005, 16:8–32, 16:19–21, 36:31–37:5; *see also* Section IV.E; EX-1003, ¶¶ 77–79, 139–43.

A POSA would have recognized that compound 42 (BIC) provided low nanomolar (nM) anti-HIV activity ($EC_{50} = 2.5$ nM), slow excretion ($CL = 0.020$ L/h/kg), and long length of action ($t_{1/2} \sim 5.2$ h; $MRT = 7.1$ h) as compared to other INSTI compounds tested in WO '323. EX-1003, ¶¶ 128–134, 175; EX-1004, ¶¶ 84–86. In view of these improved properties and its good oral bioavailability ($F\% = 28$), a POSA would have expected a therapeutically effective amount in the lower end of the ~25–500 mg range, e.g., 25–100 mg. EX-1003, ¶¶ 143–44, 176–77. The disclosed 50 mg dose falls squarely within that smaller range. EX-1005, 35:14–23. A therapeutically effective dose would have been expectedly even

lower for children and low weight adults, and patients with less severe HIV-1 infection (e.g., lower viral loads) or no HIV-1 infection at all (e.g., viral loads undetectable in the blood). EX-1003, ¶¶ 143–44, 176–77; EX-1005, 16:8–32 (definition of “treatment”). As such, a POSA would have been particularly interested in selecting lower amounts of compound 42 (BIC), e.g., 50 mg, as a therapeutically effective amount for treatment. EX-1003, ¶¶ 143–44, 176–77.

A POSA also would have arrived at the 50 mg dose of BIC using routine clinical dose ranging studies. EX-1003, ¶¶ 195–96; *see also* EX-1003, ¶¶ 80-96; EX-1045 and EX-1056 (disclosing routine dose ranging studies for INSTIs DTG and EVG respectively, where doses well below the FDA-approved dose provided significant reductions in viral load and significant increases in CD4+ cell counts); EX-1029 and EX-1035 (disclosing ongoing dose ranging and Phase II studies involving Gilead’s GS-9883, where a compromise between 50 mg and 100 mg was selected as an experimental dose for Phase II studies). Indeed, given that multiple doses of DTG and EVG were found effective for reducing viral load, the POSA would have reasonably expected that multiple compound 42 (BIC) doses in the lower end of the WO ’323 range would be effective for the same. EX-1003, ¶¶ 195–96.

In view of this knowledge, a POSA would have routinely determined a therapeutically effective dose for compound 42 (BIC) suitable to reduce viral load,

or at least prevent HIV-1 from reaching detectable levels in the blood. Because routine experimentation would have led to 50 mg as a therapeutically effective dose, that dose would have been obvious. *Pfizer* 480 F.3d at 1368; *In re Boesch*, 617 F.2d 272, 276 (C.C.P.A.).

As discussed above, DTG and BIC would have expectedly shared biological properties due to their structural similarity. The data in the prior art confirms these expectations. EX-1003, ¶¶ 191–92 (citing EX-1004, ¶¶ 67–68, 80–81); EX-1041, 5905 (Table 3), 5909 (Table 6). Both compounds had similar anti-HIV activity ($IC_{50(DTG)} = 1.7$ nM; $EC_{50(BIC)} = 2.5$ nM), half-life ($t_{1/2}$) (DTG = 5.2–6.2 h; BIC = 5.2 h). EX-1003, ¶ 197; EX-1004 ¶¶ 67–68. Both compounds also had similar oral bioavailability (F%) (DTG = 25–35; BIC = 28). *Id.* Based on this data, a POSA would have reasonably expected to identify 50 mg as a therapeutically effective amount using routine dose ranging studies. *Id.* As such, that person would have also reasonably expected the claimed tablet to effect “treatment” according to the ’802 Patent, which includes simply preventing or reducing the risk of HIV-1 infection altogether. EX-1001, 57:33–52; EX-1003, ¶ 199.

As such, a POSA would have been motivated to prepare a tablet containing BIC (50 mg)/TAF (25 mg)/FTC (200 mg), e.g., by replacing the 50 mg DTG in the composition DTG (50 mg)/TAF (25 mg)/FTC (200 mg) from WO ’351 with a therapeutically effective amount of BIC (e.g., 50 mg). EX-1003, ¶¶ 198–99. In so

doing, that person would have resolved all differences between the WO '323/WO '351 combination and claim 1 and prepared the claimed tablet with a reasonable expectation of success. EX-1003, ¶¶ 199–200; *see also* EX-1005, 36:15–17 (“actual methods for preparing such dosage forms [(e.g., tablets)] are known, or will be apparent to those skilled in the art”); EX-1001, 54:37–51 (“[T]ableting methods are well known in the art or pharmacy”). That is all the law requires. *Amgen*, 580 F.3d at 1362.

Claim 1 is therefore *prima facie* obvious over the WO '323/WO '351 combination. EX-1003, ¶ 200.

b) Claims 2–8²⁶

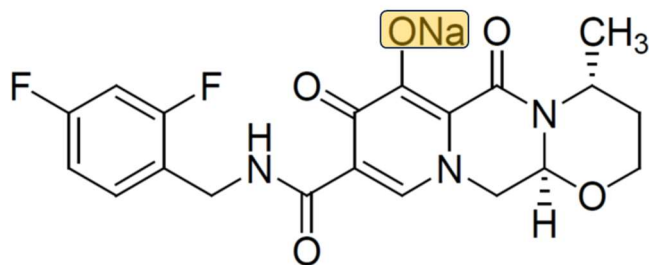
Claims 2–4 are similar in scope to claim 1 but limit Formula (I) (BIC) in **1[a]** to a pharmaceutically acceptable salt thereof (claims 2, 4), TAF in **1[b]** to a pharmaceutically acceptable salt thereof (claims 3, 4), and FTC in **1[c]** as a free base (claim 4). Claims 5 also depend from claim 1 and requires 52 mg BIC sodium, whereas claims 6–7 require TAF fumarate (claim 6) or TAF hemifumarate

²⁶ For a tutorial on the acidity, pK_a , the strong base sodium hydroxide (NaOH), and salt selection concepts discussed in this section, *see* EX-1004, ¶¶ 36–52 (citing e.g., EX-1049, EX-1050, EX-1051, EX-1053, EX-1055-D, EX-1055-E, EX-1055-F).

(claim 7). Claim 8 then calls for 52 mg of BIC sodium, 28 mg of TAF hemifumarate, and 200 mg FTC (as free base).

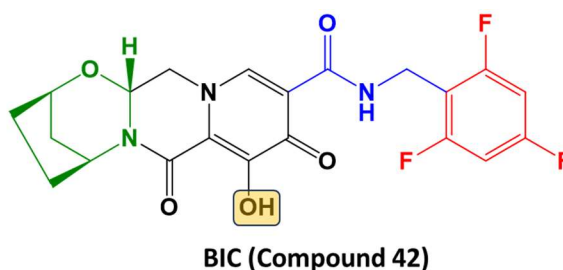
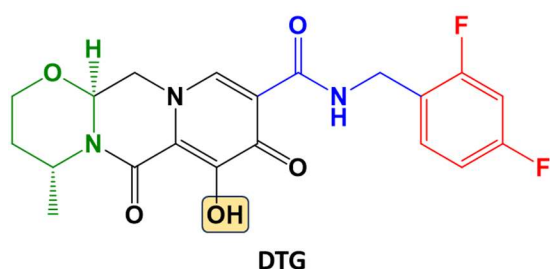
As explained for claim 1, a POSA would have specifically selected BIC from the INSTI compounds disclosed in WO '323. Claim 33 (depending from claim 32) provides for pharmaceutically acceptable salts of BIC as one of two options, the other being BIC free acid. EX-1005, 240–41. Based on the expectation of higher solubility for pharmaceutically acceptable salts, and especially the enhanced solubility of DTG sodium from WO '351, a POSA would have been directed to BIC salts over its free acid forms. EX-1003, ¶¶ 202–24; EX-1004, ¶¶ 88–98. That is all that is required to meet the limitation to BIC salts in claims 2 and 4.

Moreover, WO '323 defines “pharmaceutically acceptable salt” as including “salts derived from an appropriate base, such as an alkali metal (for example, sodium),” which are typically prepared by reacting the metal hydroxide with a compound of this invention, examples being Li^+ , Na^+ , and K^+ salts. EX-1004, ¶ 88; EX-1005, 14:14–22; 15:17–20. DTG sodium was preferred over DTG free acid by WO '351. EX-1004, ¶ 89; EX-1006, 5:10–27. DTG was also marketed as a sodium salt in Tivicay[®] and Triumeq[®] prior to the Effective Date. EX-1004, ¶ 89; EX-1022, 14 (Section 11); EX-1024, 17–18 (Section 11).



DTG Sodium from Tivicay[®] and Triumeq[®] Labels

Again, DTG and BIC share significant structural similarity, including an identical metal binding site (black) containing an aromatic hydroxy group (-OH group; emphasized below in yellow).



EX-1004, ¶ 90. It is this hydroxy group that interacts with sodium hydroxide (NaOH) to provide DTG sodium. *Id.*; see also EX-1006, 4:12–25 (identifying two prior publications with procedures for making DTG sodium from DTG and NaOH, e.g., in EX-1021, 22:4–12)

A POSA would have known that DTG's hydroxy group was the only reasonable functionality for salt formation and would have immediately appreciated the same for Compound 42 (BIC). EX-1004, ¶ 91. That POSA would have expected these hydroxy groups to have similar properties, including a similar

acidity (both considered weak acids). *Id.* (POSA would have considered DTG and BIC to be weak acids ($pK_a \sim 9-10$ (or slightly lower)); *see also* ¶¶ 47 (connecting core structure of BIC with phenol and for 2, 4-pentanedione), 38–46 (discussing acidity and noting $pK_a \sim 10$ for phenol and a $pK_a \sim 9$). The hydroxy groups would also form sodium salts (e.g., from NaOH) in the same way. EX-1004, ¶ 91; *see also* ¶¶ 47–51 (discussing salt formation for weakly acidic drugs). Indeed, the structural differences between DTG and BIC are distal from their mutual hydroxy group and would be expected to have a minimal impact on acidity and salt formation. *Id.*

As such, a POSA would have been specifically motivated to prepare a pharmaceutically acceptable salt of Compound 42 (BIC) with the alkali metal Na^+ using NaOH (just as for DTG sodium) and expected a stable (and irreversible salt). EX-1004, ¶ 92.

Pharmaceutically acceptable salts of Formula (I) (BIC) as generally required by claims 2 and 4, and BIC sodium as specifically required by claims 5 and 8 would have been obvious choices to anchor Gilead's preferred backbone of TAF/FTC. EX-1003, ¶¶ 204–09; EX-1004, ¶ 98. The 52 mg dose is the weight of BIC sodium equivalent to 50 mg of BIC free acid. EX-1003, ¶ 207.

Regarding claims 3–8, WO '351 also disclosed TAF fumarate and TAF hemifumarate (especially TAF hemifumarate) and FTC free base as particularly

preferred options for the single composition containing DTG (50 mg)/TAF (25 mg)/FTC (200 mg) described therein. EX-1003, ¶¶ 206–07; EX-1004, ¶¶ 100–02; EX-1006, 8:10–11, 13:16–18, 19:30–20:2. WO '323 further identified TAF fumarate and FTC (as free base) as N(t)TRIs for the compositions containing an INSTI, preferably compound 42 (BIC), disclosed and claimed therein. EX-1003, ¶ 194; EX-1005, 38:18–21, 241 (claims 33 and 36). As such, a POSA would have been motivated to include a pharmaceutically acceptable salt of TAF, and especially TAF fumarate (claim 6) and TAF hemifumarate (claims 7–8), and FTC free base into a single tablet composition (claims 5, 8). EX-1003, ¶¶ 194–95. The 28 mg of TAF hemifumarate required by claims 7–8 is equivalent to 25 mg of TAF. EX-1003, ¶ 207.

A POSA would have expected success in making the tablets of claims 2–8, and reasonably expected these tablets to be effective for HIV-1 treatment for the same reasons as claim 1. *See* Section IX.A.3; EX-1003, ¶ 208. These claims fail to provide any patentable distinction over claim 1 and are *prima facie* obvious for the same reasons (and additional reasons presented herein). EX-1003, ¶ 209.

c) Claims 9–11

Claims 9–11 depend from claim 1 recite a total tablet weight of less than 1000 mg, less than 800 mg, and less than 730 mg., respectively.

WO '351 discloses tablets with a total amount of DTG, TAF, and FTC in the range of 192–326 mg per day, including specific compositions having total drug weight of 275 mg. EX-1003, ¶ 211; EX-1006, 17:17–18, 19:5–12. These are substantially less than the drug weight in the single tablet products Triumeq® (50 mg DTG/600 mg ABC/300 mg 3TC) and Stribild® (150 mg EVG/150 mg COBI/300 mg TDF/200 mg FTC). EX-1003, ¶ 171; EX-1019, 22 (Stribild®); EX-1024, 17 (Triumeq®).

A POSA would have been motivated to prepare smaller single tablets for ART for patient adherence. *See* Section IX.A.1.c; EX-1003, ¶¶ 171–72, 211–16.

Given the significantly smaller amount of total drugs in the obvious tablet of claim 1 (also 275 mg as 50 mg BIC/25 mg TAF/200 mg FTC), a POSA would have known and appreciated that significantly smaller tablets were accessible. EX-1003, ¶¶ 211–16. In particular, that person would have known that less excipients would be required to prepare pharmaceutically acceptable tablet having a total drug weight of 275 mg compared to tablets such as Triumeq® and Stribild® with significantly larger total drug weights. *Id.* at ¶ 171. And that person POSA would have expectedly provided significantly smaller tablets for the obvious tablet called for by claim 1. EX-1003, ¶¶ 214–15.

Indeed, a POSA would have ~725 mg of excipients to work with for a <1000 mg tablet (claim 9), ~525 mg for an <800 mg tablet (claim 10), and ~465 mg for a

<730 mg tablet. *Id.* Given these large amounts of available excipients compared the 275 mg total drug weight, a POSA certainly would have expected success in making a pharmaceutically acceptable tablet with a total weight <730 mg, as covered by each of claims 9-11. *Id.*

Moreover, WO '351 describes “suitable pharmaceutical excipients,” e.g., glidants, fillers, disintegrants, binders, lubricants, and surfactants, and particularly preferred ranges for each. EX-1003, ¶¶ 211–12; EX-1006, 20:29–22:25. Applying the particularly preferred ranges for each excipient combined with the 275 mg total drug weight from claim 1, would have provided a tablet with a total weight of ~330 mg to ~410 mg. *Id.* These total weights fall well below the total weights required by claims 9–11. EX-1003, ¶¶ 214–15; *see also* EX-1005, 36:15–21 (Gilead admitting that “[a]ctual methods of preparing such dosage forms are known, or will be apparent, to POSAs,” and would have been “prepared by methodologies well known in the pharmaceutical art”).

A POSA would have expected success in making the tablets of claims 9-11, and reasonably expected them to be effective for treating HIV-1 for the same reasons as claim 1. *See* Section IX.A.3; EX-1003, ¶ 215; EX-1005, 36:15–21. These claims fail to provide any patentable distinction over claim 1 and are *prima facie* obvious for the same reasons (and additional reasons presented herein). *See* Section IX.A.3; EX-1003, ¶ 216.

d) Claims 12–13

Claims 12–13 each respectively limit the tablet of Claim 1 to one containing less than 15% and less than 11% of Formula (I) (BIC) or a pharmaceutically acceptable salt thereof. EX-1001 78:35–40. These limitations fail to provide any patentable distinctions over claim 1. In fact, tablets containing 50 mg of BIC (or an equivalent amount of a salt form), along with 25 mg TAF and 200 mg FTC, with total weights of 1000 mg, 2000 mg and even 4000 mg would contain less than the claims percentages. EX-1003, ¶ 218 (1000 mg tablet contains 5% BIC; 2000 mg tablet contains 2.5% BIC; 4000 mg tablet contains 1.25% BIC). Thus, even tablets of claim 1 containing a large and unnecessary amount of excipients meet the limitations of claims 12–13.

A POSA would have expected success in making the tablets of claims 12–13, and reasonably expected them to be effective for treating HIV-1 for the same reasons as claim 1. *See* Section IX.A.3; EX-1003, ¶ 219. These claims fail to provide any patentable distinction over claim 1 and are *prima facie* obvious for the same reasons (and additional reasons presented herein). *See* Section IX.A.3; EX-1003, ¶ 220.

B. Ground 2: WO '323, WO '351, Bowker, and Paulekuhn

Ground 1 establishing obviousness over WO '323 and WO '351 is incorporated herein as starting point for Ground 2. Bowker is a chapter from a

handbook pertaining to selection of pharmaceutical salts, and Paulekuhn addresses the relative frequency pharmaceutical salts in FDA-approved drugs. Both references, in addition to WO '323 and WO '351, are analogous art and are properly combinable for the purposes of the following analysis. *In re Biggio*, 381 F.3d at 26.

DTG and compound 42 (BIC) bear a close structural similarity, including an expected similar acidity of their aromatic hydroxyl groups (expected pK_a of ~9–10 (or slightly lower)). See Section IX.A.1.b; EX-1004, ¶¶ 90–92. A POSA would have known from Paulekuhn that sodium was far and above the most common cation to use with acidic drugs. EX-1009, 6665, 6668–69 (sodium salts made up 75.3% of all salts, including 65.3% of salts in oral compositions); EX-1003, ¶ 228; EX-1004, ¶ 93; see also EX-1004, ¶ 52 (discussing frequency of pharmaceutically acceptable counterions in FDA-approved drugs from 2006 and prior).

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., hydroxy group, and the base employed for deprotonation, i.e., salt formation. EX-1008, 161, 165–66; EX-1003, ¶ 228; EX-1004, ¶¶ 94, 94, 48–49. A ≥ 3 pK_a difference was especially important to form stable (irreversible) salts of particularly weak acids. EX-1008, 161, 165–66; EX-1004, ¶¶ 48–49, 94; EX-

1003, ¶ 228. When considering salts for BIC, a POSA would have especially identified bases with a $pK_a > 12$ to allow stable salt formation. EX-1003, ¶ 228; EX-1004, ¶ 95; *see also* EX-1004, ¶¶ 48–51 (discussing concepts on salt selection for drug candidates).

Of the available pharmaceutically acceptable cations, the most suitable bases were sodium and potassium hydroxide (NaOH and KOH). EX-1003, ¶ 228; EX-1004, ¶ 95. And a POSA would have selected NaOH because sodium was the most commonly used counterion for salt formation and was well-suited for the aromatic hydroxyl group on BIC. EX-1003, ¶¶ 202–04, 228; EX-1004, ¶¶ 96–97. A POSA would have been especially drawn to sodium (from sodium hydroxide (NaOH)), given that it was preferred by WO '351 for structurally similar DTG, and was used in Tivicay[®] and Triumeq[®]. EX-1003, ¶¶ 202–04, 228; EX-1004, ¶¶ 89–92. A POSA would have expected success in making BIC sodium given the >3 pK_a difference between BIC and NaOH. EX-1003, ¶ 228; EX-1004, ¶¶ 97–98.

All claims requiring BIC sodium (claims 5 and 8) are *prima facie* obvious over WO '323 and '351, in view of Bowker and Paulekuhn. EX-1003, ¶¶ 228–29. Claims generally allowing for BIC as a pharmaceutically salt (1–4, 6–7, 9–13) are also *prima facie* obvious for the same reasons. *Id.*; *see also* Section IX.A.3.a.i-ii (reasonable expectation of success in making claimed tablets).

C. Ground 3: WO '323, WO '351, and US '079

Ground 1 establishing obviousness over WO '323 and WO '351 is incorporated herein as starting point for Ground 3.

US '079, like WO '323 and WO '351, relates to single tablets for treating HIV-1 infection. EX-1007, Abstract, [0129]–[0130]. It is therefore analogous art and properly combinable for the purposes of the following analysis. *In re Biggio*, 381 F.3d at 26.

US '079 prefers tablets due to *inter alia* their greater stability, smaller bulk, and ease of production. EX-1003, ¶ 223; EX-1007, [0078]–[0079]. US '079 exemplifies a tablet containing 50 mg DTG, 300 mg TDF, and 200 mg FTC (total drug weight 550 mg), a total uncoated tablet weight of 1030 mg and a coated weight of 1055 mg. EX-1003, ¶ 223; EX-1007, [0129].

As discussed in Ground 1, it would have been obvious to prepare the tablet of claim 1 with 50 mg BIC, 25 mg TAF, and 200 mg FTC. EX-1003, ¶¶ 224–27. Such a tablet would have contained half of the drug weight of the aforementioned tablet from US '079. *Id.* at ¶ 226. Preparing a similar tablet with BIC (50 mg) in place of DTG (50 mg) and TAF (25 mg) in place of TDF (300 mg) (an obvious choice as discussed upon Ground 1), would have provided an uncoated weight 755 mg and a coated weight of 780 mg. *Id.* at ¶¶ 223–25. These obvious tablets

already fall within the scope of claims 11 (<1000 mg) and 12 (<800 mg). *Id.* at ¶ 226; EX-1001, 78:33–37.

A POSA would have immediately appreciated that excipient amounts in such a tablet could be reduced significantly, potentially in half, and would have been motivated to further reduce excipient weight in view of the lower drug weight (275 mg vs. 550 mg in US '079), and the desirability for smaller tablets to enhance patient compliance (easier to swallow, etc.). EX-1003, ¶¶ 213, 225. Even small reductions of excipients amounts (e.g., from 375 mg to 320 mg) would have provided a tablet weight <730 mg, as covered by each of claims 9–11. EX-1003, ¶¶ 213–15; EX-1001, 78:28–33. A POSA would have expected success in making the single tablet of claim 1 (275 mg total drug) weighing less than 730 mg for the same reasons as claims 1, given that a single tablet containing twice the drug content (550 mg as DTG/TDF/FTC) having a total coated weight of 1055 mg was disclosed in US '079. *Id.* at ¶¶ 214–15.

Claims 9–11 are *prima facie* obvious over WO '323 and WO '351 for the reasons provided in Ground 1, further in view of US '079 as discussed herein. The remaining claims generally allow for tablet weights <730 mg (claims 1–8 and 12–13) and are *prima facie* obvious for the same reasons. EX-1003, ¶¶ 215–20; *see also* Section IX.A.3.a.i-ii (reasonable expectation of success in making the claimed tablets).

X. SECONDARY CONSIDERATIONS

Petitioner submits that the examiner erred in her assessment (when allowing the Challenged Claims) that a ~30% increase in BIC exposure from a specific bilayer tablet (with specific excipients and excipient amounts) supported issuance. EX-1040, 1891 (noting ~30% increase in BIC exposure in reasons for allowance). To be accorded any weight, there must be a nexus between an allegedly unexpected result and the “merits of the claimed invention.” *In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995). The Challenged Claims broadly cover any tablet, they are not limited to bilayered tablets with specific excipients in specific amounts. EX-1001, 77:28–78:40. Accordingly, the alleged ~30% increase is not commensurate in scope with the broadly issued tablet claims. *Id.*

Moreover, Gilead argued that a bilayer tablet (Tablet F2) produced the alleged ~30% increase in BIC exposure during prosecution of the '846 Patent, not the '802 Patent. EX-1040, 1523–24; *cf.* EX-1002, 244–49. Tablet F2 segregated BIC from TAF and FTC by isolating BIC in one layer with specific excipients in specific amounts, while keeping TAF and FTC in their own layer with different amounts of excipients. EX-1002, 86 at [0305]–[0306] (Tablet F2), 88–89 at [0316]–[0317] (BIC exposure for Tablet F2 compared to co-administered Tablets F1 and F3). Gilead also affirmatively admits (in the '802 specification) that both tablet construction (monolayer vs. multilayer) and certain excipients used in a

formulation (and the lack of others) may affect drug dissolution, which likely impacts *in vivo* pharmacokinetics. EX-1001, 9:53–66.

Only bilayer Tablet F2 (with its specific excipients in specific amounts) provided the alleged ~30% exposure increase. EX-1003, ¶¶ 107. As Dr. Jagannathan explains, WO '323 discloses unitary dosage forms for simultaneous administration, e.g., tablets containing BIC combined with N(t)RTIs such as TAF and FTC,” leaving very little that is not in the prior art. EX-1003, ¶¶ 227; *see also id.* at ¶¶ 232-33.

There was, therefore, no evidence presented during prosecution of the '802 that tablets without segregation of BIC from TAF/FTC through layering (with specific excipients in specific amounts in each layer) would experience a BIC exposure increase. Accordingly, the alleged ~30% increase in BIC exposure is not commensurate in scope with the Challenged Claims, which do not require tablets that segregate the claimed APIs by layering. *See In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011). And, given the specific (and unclaimed) characteristics of bilayer Tablet F2, there is no nexus between applicant’s allegations and the Challenged Claims. *Id.* (holding secondary consideration resulting from something other than what is both claimed and novel in the claim have no nexus to the merits of the claimed invention.).

XI. THE PETITION SHOULD NOT BE DENIED UNDER *FINTIV*.

Petitioner submits that compelling, meritorious challenges of obviousness have been asserted herein, with evidence that, if unrebutted in trial, would plainly lead to a conclusion that one or more claims are unpatentable by a preponderance of the evidence. EX-1060 (Director Vidal June 21, 2022, memorandum), 3–5.

The tablets of the Challenged Claims are (at best) the product of ordinary innovation, which is not sufficient for patent protection. *KSR*, 550 U.S. at 427.

The simple combination of three known antiretroviral drugs in a single tablet had been (repeatedly) accomplished by Gilead (and others) well before the Effective Date. At the very least, Petitioner has presented a compelling and meritorious challenge to the broadest claim – independent claim 1. That is all that is required to avoid discretionary denial under *Fintiv*.

XII. CONCLUSION

The Challenged Claims are the result of ordinary innovation and should not be the subject of exclusive rights under the patent laws. Petitioner therefore respectfully requests institution of *inter partes* review of the Challenged Claims.

Date: October 28, 2024

Respectfully submitted,

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CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24(d), Petitioner hereby certifies, in accordance with and reliance on the word count provided by the word-processing system used to prepare this petition, that the number of words in this paper is 13,889 inclusive of figures and footnotes. Pursuant to 37 C.F.R. § 42.24(d), this word count excludes the cover page, table of contents, table of authorities, mandatory notices under § 42.8, certificate of service, certificate of word count, and list of exhibits.

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CERTIFICATION OF SERVICE

The undersigned hereby certifies that this “PETITION FOR *INTER PARTES* REVIEW UNDER 35 U.S.C. §§ 311-319 AND 37 C.F.R. § 42.100 *ET SEQ.*” with an accompanying Power of Attorney, List of Exhibits, and Exhibits 1001-1061 were served in their entirety this 28th day of October, 2024 on the Patent Owner by service via overnight delivery to the correspondence address of record for the ‘802 Patent:

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