

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

DECLARATION OF PRASANNA JAGANNATHAN, M.D.

TABLE OF CONTENTS

I.	QUALIFICATIONS AND EXPERIENCE	1
II.	SCOPE OF WORK.....	9
III.	LEGAL STANDARDS.....	11
	A. Obviousness.....	11
IV.	THE LEVEL OF ORDINARY SKILL.....	14
V.	COMMON KNOWLEDGE AND WELL-KNOWN TECHNICAL PRINCIPLES IN THE ART	18
	A. Treating HIV-1 Infections prior to November 9, 2015	18
	B. Available Regimens Anchored by INSTIs in 2015.....	27
	C. Growing Concerns over Long Term Use of TDF	33
	D. The HIV Treatment Market in 2015.....	35
	E. Routine Dose Ranging Studies in Clinical Trials.....	39
VI.	OVERVIEW OF THE '802 PATENT.....	50
	A. The Specification of the '802 Patent.....	50
	B. The Claims of the '802 Patent.....	58
	C. The Prosecution History of the '802 Patent.....	59
VII.	CLAIM CONSTRUCTION	64
VIII.	THE PRIOR ART DISCLOSES OR SUGGESTS MOST ELEMENTS OF THE CHALLENGED CLAIMS	65
	A. Disclosures and Suggestions to a POSA from WO '323 (EX-1005).....	66
	B. Disclosures and Suggestions to a POSA from WO '351 (EX-1006).....	80

C.	Disclosures and Suggestions to a POSA from US '079 (EX-1007).....	84
IX.	OBVIOUSNESS ANALYSIS	87
A.	By November 9, 2015, a POSA had Several Reasons to Prepare Tablets containing Compound 42 (BIC), TAF, and FTC.	90
1.	The Combination of WO '323 and WO '351	98
2.	The Combination of WO '323 and WO '351 with US '079	103
B.	Combining WO '323 and WO '351 Leaves Minor Differences Between the Challenged Claims and the Prior Art	105
1.	A POSA Combining WO '323 and WO '351 would have been Motivated to Arrive at These Differences with a Reasonable Expectation of Success	108
a.	Claim 1	108
b.	Claims 2–8	116
c.	Claims 9–11	121
d.	Claims 12–13	125
C.	Adding '079 to the Combination of WO '323 and WO '351 renders Tablet Size as the Only Difference	127
D.	The Combination of WO '323 and WO '351 with Bowker and Paulekuhn Bolsters a POSA's Motivation to Select BIC Sodium with a Reasonable Expectation of Success.	129
E.	Secondary Considerations	131
X.	SUPPLEMENTATION	133

I, Prasanna Jagannathan, M.D., hereby declare as follows:

I. QUALIFICATIONS AND EXPERIENCE

1. I am an Internal Medicine and Infectious Diseases Board-Certified physician and an Associate Professor of Medicine (Infectious Diseases) and of Microbiology and Immunology at Stanford University School of Medicine. A copy of my Curriculum Vitae is attached to this declaration as **Appendix A**.

2. I received my B.A. in Religious Studies from the University of California, Berkeley in 1998 and my M.D. from Harvard Medical School in 2005. As a medical student at Harvard, I trained in outpatient HIV medicine through a longitudinal 2-year clerkship with Dr. Laura Kogelman at Tufts New England Medical Center Infectious Diseases Clinic, and spent 2 months working at McCord Hospital in Durban, South Africa, learning inpatient and outpatient HIV medicine. I completed post-doctoral training in internal medicine, infectious diseases, and immunology at the University of California, San Francisco (UCSF), was Chief Resident of Internal Medicine at San Francisco General Hospital, and also trained in inpatient and outpatient HIV management. I joined the faculty at UCSF as an Assistant Professor of Medicine in 2012, and completed the Advanced Training in Clinical Research Certificate Program at UCSF in 2014.

3. Clinically, while at UCSF, I was an Adult Infectious Diseases and HIV specialist, where I gained 7 years of experience providing HIV primary care at Ward

86, San Francisco General Hospital, and 5 years of experience as an attending physician on the joint inpatient infectious diseases/HIV consultation service.

4. Ward 86 at San Francisco General Hospital was established in 1983, and, as one of the first outpatient clinics devoted to caring for people living with HIV in the world, is one of the premier clinical and academic training centers for care of HIV-infected individuals. As an attending inpatient and outpatient clinician at Ward 86, I cared directly for or supervised the care of many patients receiving multiple approved drugs and drug regimens in the United States for the treatment of HIV infection. I regularly prescribed (and still prescribe to this day) highly active antiretroviral therapy (HAART or simply ART) to treatment-naïve and treatment-experienced individuals living with HIV/AIDS. These ART therapies employed a “cocktail” of antiretroviral medications that inhibit different targets of the HIV viral lifecycle, including medications that target HIV viral proteins such as reverse transcriptase, protease, and integrase, among others.

5. Typically, the ART cocktail I regularly prescribed (and still currently prescribe) contained a “backbone” of two nucleos(t)ide reverse transcriptase inhibitors (N(t)RTIs), and an “anchor” medication from another antiviral class. In the 2014–2015 timeframe, this anchor medication included an integrase inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a protease

inhibitor (PI).¹ When prescribing these medications, clinicians (including myself) had to consider the complex nature of the infection; medical co-morbidities such as chronic kidney or liver disease; co-infections such as hepatitis or tuberculosis; tolerability and safety profile of the medications; and concomitant medications that could present important drug-drug interactions with antiretroviral medications. We typically sought ART regimens that had the following characteristics: 1) high virologic efficacy; 2) good safety profile; 3) minimal drug-drug interactions; and 4) minimal pill burden.

6. Over 15 years as a medical student, trainee, and eventual attending physician in HIV medicine at UCSF, I witnessed and was a part of the remarkable transformation of HIV management from a terminal illness to a chronic, manageable disease. By 2015, a majority of my patients were on an ART regimen consisting of two nucleos(t)ide reverse transcriptase inhibitors (N(t)RTIs) and an integrase inhibitor (INSTI), as such regimens met many of the desirable characteristics described above.

7. While at UCSF, I taught courses to medical students, residents, and fellows at UCSF in HIV medicine from 2009-2016 and, from 2015–2016, I was the

¹ 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”)

Associate Director of Education in the Division of HIV, Infectious Diseases, and Global Medicine. In this capacity, I was responsible for training the next generation of medical students, interns, residents, and infectious diseases/HIV fellows in the care and management of patients with HIV. This included teaching the Department of Health and Human Services Guidelines for the care and management of HIV-positive patients, including the rationale for using particular medications for the care of treatment naïve and treatment-experienced HIV-infected patients. By 2015, several of the recommended first line therapies that I prescribed and recommended others to prescribe included integrase inhibitors in combination with nucleos(t)ide reverse transcriptase inhibitors to provide the benefits described above.

8. From 2013–2018, I was an invited speaker to the annual UCSF-led “Medical Management of HIV/AIDS and Hepatitis” course in San Francisco. This course provided the active, intermediate-to-advanced clinician with a comprehensive review of the science of HIV and key co-infections including Hepatitis B and C. In this course, I gave well-received talks on “Updates in HIV Primary Care” and “Health and Well-being in Persons living with HIV and AIDS,” and served on an antiretroviral therapy panel where we would consider complex therapeutic cases among newly diagnosed or treatment-experienced patients with HIV.

9. As a trainee and Assistant Professor at UCSF, I was the recipient of many awards, including the Julius R. Krevans Award for Clinical Excellence at San Francisco General Hospital, the T.E.A.C.H. Graduation Teaching Award, and the Hellman Fellowship, among others.

10. In 2017, I was recruited to a tenure-track faculty position at Stanford University in the Department of Medicine, Division of Infectious Diseases and Geographic Medicine. While at Stanford, I have spent 80% of my time conducting research, 10% of my time as a clinician, and 10% of my time on teaching. The main focus of my current research program relates to the study of host immune responses to malaria and other infectious diseases.

11. My research leverages patient samples collected from cohort studies and clinical trials to perform in depth immune profiling and *in vitro* mechanistic studies. I also conduct and lead clinical trials to test agents capable of enhancing naturally acquired immunity to malaria and SARS-CoV-2. My research is predominantly funded by the United States National Institutes of Health and the Gates Foundation.

12. Clinically, at Stanford, I attend on the inpatient Infectious Diseases consultation unit at Stanford University Medical Center. In this role, I provide consultative services for patients with HIV and other communicable diseases. I

became a tenured Associate Professor of Medicine and of Microbiology and Immunology at Stanford in August of 2024.

13. I have published more than 110 peer-reviewed publications, mostly related to studies of malaria, HIV, SARS-CoV-2, and studies of the host immune response to infection. These papers have been published in many highly regarded scientific journals, including the *Lancet*, *New England Journal of Medicine*, *Nature Immunology*, and *Science Translational Medicine*. Relevant to the current case, I have authored or co-authored several articles relating to either HIV or HIV-malaria interactions, including “Piperaquine Exposure Is Altered by Pregnancy, HIV, and Nutritional Status in Ugandan Women” (PMID 33020153); “Predicting optimal dihydroartemisinin-piperaquine regimens to prevent malaria during pregnancy for HIV-infected women receiving efavirenz” (PMID 29272443); “Intermittent Preventive Treatment with Dihydroartemisinin-piperaquine for the Prevention of Malaria among HIV-infected Pregnant Women” (PMID 28329368); “Comparisons of CD8⁺ T cells specific for human immunodeficiency virus, hepatitis C virus, and cytomegalovirus reveal differences in frequency, immunodominance, phenotype, and interleukin-2 responsiveness” (PMID 19129459); “Limitations in knowledge of HIV transmission among HIV-positive patients accessing case management services in a resource-poor setting” (PMID 16971286).

14. I am an investigator, including the principal investigator, in several clinical trials. For instance, I am the Principal Investigator of an ongoing NIH-sponsored clinical trial assessing the impact of early life malaria chemoprevention on infant immune development (NCT04978272), where I lead all aspects of this trial including protocol development and investigational new drug (IND) submissions to the Food and Drug Administration (FDA), where we present study protocols to the FDA for consideration prior to dosing of investigational new drugs. As Principal Investigator, I also work on communications with the FDA and assessments of clinical trial data (safety, tolerability, and efficacy).

15. I am also a co-investigator of a clinical trial of antimalarial chemoprevention in pregnant women (NCT 04336189). Previously, I was a key co-investigator on three completed clinical trials of antimalarial chemoprevention in HIV-infected and uninfected Ugandan pregnant women and their infants (NCT02163447; NCT 02282293; NCT 02793622), and performed the primary biostatistical analyses for these studies. In all, I have been a co-investigator or principal investigator for 5 clinical trials. As an investigator, I took on a variety of roles – development of study protocols and standard operating procedures; preparation of statistical analysis plans; statistical analyses; ancillary analysis of patient samples and data; and write-up of results.

16. Additionally, I have been recently testing novel immune-modulating and anti-viral therapeutics for the treatment of COVID-19. I was co-Principal Investigator of a single site clinical trial of Peginterferon Lambda in outpatients with COVID-19 at Stanford University (NCT 04331889). In this role, I led all aspect of this trial, including protocol development, IND submission, FDA communications, assessments of trial data (safety, tolerability, and efficacy), and write-up and submission of the final study. I was also a co-investigator on a completed trial of favipiravir for COVID-19 (NCT 04346628), and am a co-investigator for a clinical trial of Paxlovid for individuals with long-COVID (NCT 05576662). I am also a study investigator for the NIH-sponsored multicenter ACTG ACTIV-2 protocol (NCT 04518410). ACTIV-2 is an outpatient adaptive trial protocol that includes both phase 2 and phase 3 evaluations of multiple promising investigational agents for treating early, symptomatic COVID-19 both in the US and internationally. Specifically, I served as one of the ACTIV-2 study leads for SNG001, an inhaled formulation of beta interferon, for treatment of COVID-19, and in this role was responsible for protocol development, development of standard operating procedures, assessments of trial data, and write-up and presentation of trial results.

17. In the above clinical studies, I worked directly with those skilled in the art of formulation science and pharmacology to assess optimal dosing regimens (e.g., administration route, dose determination, and dosing frequency).

II. SCOPE OF WORK

18. I have been retained by Cipla Limited (“Cipla”) to provide and/or review the materials I discuss in this declaration, to provide my expert opinion in relation to what a person of ordinary skill in the art in relation to U.S. Patent No. 11,744,802 (“the ’802 Patent”) would have understood, and the actions that this hypothetical skilled scientist would have undertaken prior to November 9, 2015, given the state of the art and accumulated knowledge at the time. In particular, I understand that Cipla is filing a petition with the United States Patent and Trademark Office (“USPTO”) for *Inter Partes* Review (“IPR”) of the ’802 Patent. Cipla retained me as an expert to provide my analysis and opinion concerning the use of anti-viral agents to treat HIV infections, including the use of such agents in solid oral dosage forms, such as single tablets containing more than one anti-viral agent for use in ART therapy.

19. My opinions are based on my skills, knowledge, training, education, and experience with treating persons infected with HIV, in addition to my experience in the design and implementation of clinical trials in the area of infectious disease. The clinical trials that I have participated in included consulting with pharmaceutical formulation teams to understand the dosage forms used in the clinical trials in which I have been involved.

20. In addition to the '802 Patent, I have reviewed the record of the exchanges occurring between the USPTO and the applicant as that patent was originally examined. I have also reviewed many other documents that I understand to be prior art to the '802 Patent in arriving at my opinions.

21. I have also reviewed and considered the expert declaration of Jeffrey D Winkler, Ph.D. in its entirety (Winkler Declaration (EX-1004)), and understand that Dr. Winkler provides analyses and opinions for the standpoint of a person of ordinary skilled in the art of medicinal chemistry and drug development. To the extent I rely on the Winkler Declaration to support my own analyses and opinions, I cite to and summarize his own analyses and opinions herein.

22. I am being compensated for the time spent working on this matter at my usual and customary hourly rate of \$800 per hour. My compensation is not dependent upon the outcome of, or my testimony in, the present proceeding. I have no other financial interest in the outcome of this proceeding.

23. This declaration sets forth the substance of the facts and opinions on which I base my testimony herein. I understand that this declaration will be filed as evidence in an IPR before the Patent Trial and Appeal Board at the USPTO, and acknowledge that I may be subject to cross-examination in this case and that cross-examination will take place within the United States. If cross-examination is

required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

III. LEGAL STANDARDS

24. I am not an attorney and have no formal training in patent law. I do not profess to be an expert in patent law. Accordingly, in preparing this declaration, I have been informed by counsel of the legal standards that are applicable to the patentability of patent claims in general. I have assumed these legal standards to be accurate.

25. A summary of these legal standards, as I understand them, and that I have applied in my analysis, are provided in this section.

A. Obviousness

26. I understand that a patent claim is obvious under Section 103 of the Patent Act (35 U.S.C. §103) if the differences between the subject matter sought to be patented and the prior art are such that the claimed subject matter as a whole would have been obvious to person of ordinary skill in the art (“POSA”) at the time the alleged invention was made. For the purposes of my analysis, I assume this timeframe to be on or before November 9, 2015.

27. I understand that the following factors must be considered in determining obviousness: (1) the scope and content of the prior art; (2) the difference or differences, if any, between the claimed subject matter and the prior art; (3) the

level of ordinary skill in the art at the time of the alleged invention; and (4) additional “secondary considerations,” if any, that indicate whether the alleged invention was obvious or not obvious. I further understand that evidence of “secondary considerations” may be advanced by a patent owner, if available, and that such evidence can overcome an initial showing of obviousness.

28. I understand a patent claim would have been obvious if all the claim elements were known in or suggested by prior art references, where a POSA would have had reason(s) to combine the teachings or suggestions from that art based on the references themselves and the background knowledge available to a POSA, so as to arrive at the claimed subject matter with a reasonable expectation of success.

29. I further understand that no guarantee or absolute predictability of success is required to establish obviousness. As such, obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art, so long as the prior art establishes a reasonable probability that a POSA could have made the subject matter embraced by a claim such that it would have worked for its intended purpose.

30. I understand that a conclusion of obviousness can be based on a single prior art reference or a combination of two or more prior art references. Where the POSA would have arrived at the claimed invention by selecting and/or modifying prior art disclosures and had a good reason (i.e., motivation) to do so with a

reasonable expectation of success, the invention as claimed would have been obvious.

31. While I appreciate that the prior art references themselves may provide a POSA with a teaching, suggestion, or motivation to modify or combine them, I understand that motivation can also be based on the ordinary skill, ordinary creativity, and common sense of the POSA.

32. As I understand the law, an obviousness analysis considers the inferences and creative steps a POSA would employ under the circumstances, e.g., a need or problem to be solved in the field at the time of invention. I further understand that a need or a problem in the art can provide a motivation to modify and/or combine teachings and suggestions from the prior art.

33. I further understand that the law allows consideration of demands known to the design community or present in the marketplace. When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. As such, economic influences may also provide a motivation to combine prior art references. Moreover, I understand that when there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a POSA would have good reason to pursue the known options within his or her technical grasp. I understand such circumstances may lead to solutions that are not deemed inventive.

34. I further understand that obviousness requires a POSA to have a reasonable expectation of success when modifying the prior art in a particular way, e.g., if a POSA can implement a predictable variation of a known method using common sense or the teachings of another reference to arrive at the claimed invention, a patent claim is likely obvious.

35. I also understand that in determining the obviousness or non-obviousness of the subject matter of an alleged invention, secondary considerations such as unexpected results, long felt but unsolved needs, failure of others, commercial success, etc., to the extent they exist, should be considered. I am informed that secondary considerations are relevant where there is a nexus between the evidence and the merits of the claimed invention, and where the asserted secondary considerations are commensurate in scope with the claimed invention, and not just directed to one particular embodiment of a broader patent claim.

36. I am informed that the patent owner bears the burden to establish any secondary considerations indicating non-obviousness.

IV. THE LEVEL OF ORDINARY SKILL

37. This declaration refers throughout to a person of ordinary skill, or a “POSA.” As I understand the law, this is a hypothetical person who is presumed to have a comprehensive knowledge of the available prior art and a level of skill commensurate with a typical practitioner in the relevant field at the time the patent

application at issue was originally filed. For the '802 Patent, I understand that date to be November 9, 2015.

38. I understand that a POSA is a person of ordinary creativity. He or she generally thinks along the line of conventional wisdom in the art and is not one who undertakes to innovate. However, when another work is available for use by the POSA, I understand the law recognizes that design incentives and market forces can also prompt that POSA to seek variations of that work in the same field.

39. In determining the level of skill of a POSA, I understand that I may consider the following factors: (1) the type of problems encountered in the art; (2) the prior art solutions to those problems; (3) the rapidity with which innovations are made; (4) the sophistication of the technology; and (5) the educational level of active workers in the field.

40. In my opinion, a POSA in the field of the '802 Patent, as of November 9, 2015, would have 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. The POSA could hold a B.S. or master's degree, so long as that person had at least five years of work experience in one or more of the above fields.

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

42. In my opinion, a POSA skilled in HIV therapy and clinical investigations, and/or HIV drug development would also be familiar with the HIV pharmaceutical market and HIV treatment market in the United States. In particular, it is my opinion that the POSA would be aware of the substantial financial implications of developing a single tablet containing a complete regimen for the treatment of HIV, including tablets containing a second generation INSTI that anchors a pair of N(t)RTIs such as the well-known pairing of emtricitabine (FTC) and tenofovir (TFV).

43. As I explain later in this declaration, a POSA would have known that the combination of a state-of-the-art second generation INSTI with emtricitabine and tenofovir was a popular, and recommended, dosing regimen to treat patients infected with HIV-1 prior to November 9, 2015. However, that person would have also known at the time that physicians electing to use this combination were required to prescribe two separate tablets – for example, the second generation INSTI

dolutegravir (DTG) in one tablet, and FTC and TFV (as tenofovir disoproxil fumarate (TDF)) in another. This was at least because different pharmaceutical companies owned the marketing and patent rights to DTG and the FTC/TDF combinations, such that no single tablet regimen containing each of the active ingredients was available.

44. In my opinion, the POSA would also be familiar with the pharmaceutical market in the United States. In particular, it is my opinion that the POSA would be aware of the substantial financial implications of developing a single tablet containing a complete regimen for the treatment of HIV, including tablets containing a second generation INSTI that anchors a pair of N(t)RTIs such as the well-known pairing of emtricitabine (FTC) and tenofovir (TFV). As I explain later in this declaration, a POSA would have known that the combination of a state-of-the-art second generation INSTI with emtricitabine and tenofovir was a popular, and recommended, dosing regimen to treat patients infected with HIV-1 prior to November 9, 2015.

45. However, that person would have also known at the time that physicians electing to use this combination were required to prescribe two separate tablets – for example, the second generation INSTI dolutegravir (DTG) in one tablet, and FTC and TFV (as tenofovir disoproxil fumarate (TDF)) in another. This was at least because different pharmaceutical companies owned the marketing and patent

rights to DTG and the FTC/TDF combinations, such that no single tablet regimen containing each of the active ingredients was available.

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

47. On the basis of my personal knowledge and experience, I am very familiar with the knowledge and practice available to a POSA prior to November 9, 2015.

V. COMMON KNOWLEDGE AND WELL-KNOWN TECHNICAL PRINCIPLES IN THE ART

A. Treating HIV-1 Infections prior to November 9, 2015

48. The state of the art in HIV antiretroviral therapy (ART) was guided by comprehensive guidelines issued by the Department of Health and Human Services (DHHS), which were updated annually, including guidelines from April of 2015 (“2015 DHHS Guidelines”) that were publicly available prior to November 9, 2015.² The 2015 DHHS Guidelines were issued by a panel of recognized experts in the field, who had reviewed countless clinical studies to guide physicians concerning

² See 2015 DHHS Guidelines (EX-1014).

the optimal use of the ART therapies available at the time.³ In my experience, practitioners in the HIV treatment space would immediately access these guidelines, including updates to the guidelines, upon their publication. In my clinical practice, I would have accessed the 2015 DHHS guidelines immediately after issuance in providing care to my patients, and in my opinion a POSA would have done the same.

49. The 2015 DHHS Guidelines provide detailed recommendations for the treatment of antiretroviral-naïve patients, including the preferred initial combination regimens and specific considerations for various antiretroviral components.⁴ In my experience, physicians treating HIV infections prior to November 9, 2015 were aware of, and followed, these guidelines.

50. The 2015 DHHS Guidelines established that more than 25 antiviral drugs in 6 different drug classes had been approved by the FDA for the treatment of HIV infection prior to November 9, 2015.⁵ These different classes of approved antiviral agents were known to interfere with the ability of the virus to replicate itself by inhibiting different viral enzymes or proteins. Classes of approved agents at the time included: integrase inhibitors (INSTIs), nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs and NtRTIs, collectively N(t)RTIs), non-nucleoside

³ *Id.* at 13–14.

⁴ EX-1014 at 70.

⁵ *Id.*

reverse transcriptase inhibitors (NNRTIs), fusion inhibitors, CCR5 antagonists, and protease inhibitors (PIs).⁶

51. The 2015 DHHS Guidelines emphasized that viral suppression required the use of a combination of antiretroviral agents given at the same time. The recommended regimens at the time required the use of at least three antiretroviral drugs from at least two different drug classes as the best way to achieve viral suppression.⁷

52. The 2015 DHHS Guidelines provided five recommended antiretroviral therapy (ART) options for patients who had not yet been administered any antiretroviral drugs.⁸ Four of the recommended regimens were directed the use of an integrase strand transfer inhibitor (INSTI) as the anchor drug, with the other employing a protease inhibitor as the anchor.⁹ The 2015 DHHS Guidelines state that the selection of options should be “individualized on the basis of virologic efficacy, potential adverse effects, pill burden, dosing frequency, drug-drug interaction potential, a patient’s resistance test results and comorbid conditions, and cost.”¹⁰ These available options had dramatically reduced both morbidity and mortality

⁶ EX-1014 at 70, 268–280 (DHHS Appendix B, Tables 1–6).

⁷ *Id.* at 43.

⁸ *Id.* at 72–73 (Table 6).

⁹ *Id.* at 72 (Table 6).

¹⁰ *Id.* at 70 (fourth bullet point in “Panel’s Recommendations”).

associated with HIV infection.¹¹ As such, prior to November 9, 2015, HIV infection was considered a chronic, but manageable, condition.¹²

53. Each of the recommended regimens discussed in the preceding paragraph included the administration of two nucleoside/tide reverse transcriptase inhibitors (N(t)RTIs), frequently referred to as the “backbone” of a given regimen.¹³ One well known and frequently used N(t)RTI backbone was tenofovir disoproxil fumarate (TDF) paired with emtricitabine (FTC).¹⁴ This N(t)RTI pair was made available in the single tablet combination Truvada[®] (300 mg TDF; 200 mg FTC) that was first approved in 2004 to be given in combination with other antiretroviral agents to treat HIV infection.¹⁵ Another N(t)RTI pairing (or backbone) was the combination of abacavir (ABC) with lamivudine (3TC), also approved in 2004 in the single tablet combination Epzicom[®] (600 mg ABC; 300 mg 3TC) to be given in combination with other antiretroviral agents for the treatment of HIV infection¹⁶.

¹¹ EX-1014 at 13.

¹² *Id.*

¹³ *See, e.g., id.* at 166–67.

¹⁴ EX-1014 at 271; *see also* Highlights and Prescribing Information on Truvada, © 2004, issued July 2004 (“Truvada 2004 Label”) (EX-1054)

¹⁵ EX-1054 at 16 (Indications and Usage); *see also* Highlights and Prescribing Information on Truvada, revised July 2012 (“Truvada 2012 Label”) (EX-1015) at 3–4 (Indications and Usage) (adding indication for pre-exposure prophylaxis (PrEP)).

¹⁶ EX-1014 at 270; *see also* Highlights and Prescribing Information on Epzicom, © 2004 (“Epzicom Label”) (EX-1046) at 10–11.

54. Prior to November 9, 2015, there were also three approved INSTIs to choose from for combination with an N(t)RTI backbone: raltegravir (RAL), elvitegravir (EVG), and dolutegravir (DTG).¹⁷ The first two INSTIs that were approved to treat HIV infection were RAL and EVG.¹⁸ RAL was approved in 2007.¹⁹ RAL was available in a 400 mg tablet (Isentress®), which was given twice daily (BID) for a total daily dose of 800 mg.²⁰ EVG approval followed in 2012, and it was recognized as a “me too” INSTI, similar to RAL.²¹ EVG (150 mg) was available in a single tablet combination (Stribild®) with the N(t)RTI backbone of FTC (200 mg) and TDF (300 mg), where an additional pharmacokinetic booster - cobicistat (COBI) (150 mg) - allowed for administration once daily.²² Though effective against HIV infection, both RAL and EVG were recognized as having a “low genetic barrier to resistance and [were] associated with cross-resistance”

¹⁷ 2015 DHHS Guidelines (EX-1014) at 279 (App. B, Table 4).

¹⁸ Shah et al., “Dolutegravir: A New Integrase Strand Transfer Inhibitor for the Treatment of HIV,” 34(5) PHARMACOTHERAPY 506–20 (2014) (“Shah”) (EX-1023) at 506 (abstract).

¹⁹ Highlights and Prescribing Information on Isentress, revised October 2007 (“Isentress Label”) (EX-1016).

²⁰ *Id.* at 1.

²¹ Serrao et al., “Raltegravir, elvitegravir, and metoogravir: the birth of the “me-too” HIV-1 integrase inhibitors,” 6 RETROVIROLOGY, Art. 25, 1–14 (“Serrao”) (EX-1018) at 4; Highlights and Prescribing Information on Stribild, revised and issued August 2012 (“Stribild Label”) (EX-1019) at 1.

²² Stribild Label (EX-1019) at 1.

toward one another.²³ In other words, both RAL or EVG have been shown to be prone to the development of resistance in the setting of poor treatment adherence or in the absence of other active antiretroviral drugs, with resistance to RAL also conferring resistance to EVG and vice versa.²⁴

55. DTG was approved by the FDA in 2013 as a single tablet containing the sodium salt of DTG (equivalent to 50 mg DTG), known as Tivicay[®].²⁵ DTG was considered the first so-called “second generation” INSTI.²⁶ It provided a longer half-life than EVG and RAL, which allowed it to be given once a day; and was reported to combine “the advantages of both [RAL and EVG]: it is well-tolerated and can be given once/day without the use of a booster, thus limiting the number of significant drug-drug interactions.”²⁷ As a further benefit, DTG was recognized to have “a higher genetic barrier to resistance compared with [RAL],”²⁸ and allowing use in patients that developed resistance to RAL and EVG therapies. The manufacturer of

²³ Shah (EX-1023) at 506.

²⁴ *Id.*

²⁵ 2015 DHHS Guidelines (EX-1014) at 279 (App. B, Table 4); *see also* Highlights and Prescribing Information on Tivicay, © 2013, revised August 2013 (“Tivicay Label”) (EX-1022) at 1.

²⁶ Shah (EX-1023) at 506; 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-1017) at 83 (Abstract); Winkler Declaration (EX-1004) at ¶ 71.

²⁷ Shah (EX-1023) at 518.

²⁸ *Id.*

both Tivicay[®] and Epzicom[®] (ViiV Healthcare (“ViiV”) and GlaxoSmithKline (“GSK”)) also offered a single tablet with DTG combined with the N(t)RTI backbone of ABC and 3TC in the single tablet Triumeq[®] (50 mg DTG; 600 mg ABC; 300 mg 3TC), approved in 2014.²⁹

56. In sum, prior to November 9, 2015, DTG was considered a “second generation” INSTI with a longer half-life than EVG and RAL, which allowed it to be given once-a-day.³⁰ DTG also combined the advantages RAL and EVG in that it was well-tolerated and allowed once-a-day administration without a booster, thus limiting the number of significant drug-drug interactions.³¹ It also provided a higher genetic barrier to resistance compared with RAL and EVG.³² At this time, DTG was also available in the U.S. as a single active agent in the product Tivicay^{®33}, and in a single tablet in combination with ABC/3TC in the product Triumeq^{®34}.

²⁹ 2015 DHHS Guidelines (EX-1014) at 279 (App. B, Table 4); *see also* Highlights and Prescribing Information on Triumeq, © 2014, revised and issued August 2014 (“Triumeq Label”) (EX-1024) at 1.

³⁰ Shah (EX-1023) at 506.

³¹ *Id.* at 518.

³² *Id.*

³³ 2015 DHHS Guidelines (EX-1014) at 279 (App. B, Table 4); *see also* Tivicay Label (EX-1022) at 1, 14.

³⁴ 2015 DHHS Guidelines (EX-1014) at 279 (App. B, Table 4); *see also* Triumeq Label (EX-1024) at 1, 17–18.

57. Specific preferred initial regimens for antiretroviral-naïve patients in the 2015 DHHS Guidelines³⁵ included:

a. Integrase Strand Transfer Inhibitor (INSTI)-Based Regimens

- i. Dolutegravir (DTG) + Abacavir/Lamivudine (DTG/ABC/3TC)
single pill fixed dose combination: Recommended for patients who test negative for the HLA-B*5701 allele. One pill given once daily.
- ii. Dolutegravir (DTG) + Tenofovir/Emtricitabine (TDF/FTC).
Two pills given once daily
- iii. Elvitegravir/Cobicistat/Tenofovir/Emtricitabine (EVG/c/TDF/FTC): Only recommended for patients with a creatinine clearance (CrCl) of ≥ 70 mL/min. One pill given once daily
- iv. Raltegravir (RAL) + Tenofovir/Emtricitabine (TDF/FTC). Two pills twice a day (RAL), one pill once a day (TDF/FTC).

b. Protease Inhibitor (PI)-Based Regimens:

- i. Darunavir/Ritonavir (DRV/r) + Tenofovir/Emtricitabine (TDF/FTC). 2 pills once a day.

³⁵ EX-1014 at 70 (providing summary of the Panel's Recommendations).

58. Each of the available options for an anchor to the recommended N(t)RTI backbones had both advantages and disadvantages, but employing an INSTI as the anchor drug was a preferred strategy prior to November 9, 2015, among the choices available.³⁶ The 2015 DHHS Guidelines provided that “for most patients, an INSTI-containing regimen will be highly effective, have few adverse effects,” and (when using RAL or DTG) have no CYP 3A4-associated drug interactions.³⁷

59. The preference for INSTI-based regimens over other types of ART regimens prior to November 9, 2015 was driven by several factors, which are outlined in alphabetical order in Table 8 of the 2015 DHHS Guidelines.³⁸ To briefly summarize, the advantages of INSTI-based regimens such as DTG regimens included:

a. Higher Barrier to Resistance:

Dolutegravir (DTG): Exhibited a higher barrier to resistance compared to Elvitegravir (EVG) and Raltegravir (RAL), making it a robust option for initial therapy.

b. Favorable Dosing Schedules:

Dolutegravir (DTG) and Elvitegravir/Cobicistat (EVG/c): Both drugs were available in once-daily dosing formulations, improving patient adherence.

³⁶ 2015 DHHS Guidelines (EX-1014) at 70 (second bullet under “Integrase Strand Transfer Inhibitor-Based Regimens.”).

³⁷ 2015 DHHS Guidelines (EX-1014) at 78-79.

³⁸ *Id.* at 92–94.

c. Minimal Food Requirements:

Dolutegravir (DTG) and Raltegravir (RAL): These drugs did not have significant food requirements, making administration simpler for patients.

d. Fewer Drug-Drug Interactions:

Dolutegravir (DTG) and Raltegravir (RAL): These drugs had fewer interactions with the cytochrome P450 (CYP3A4) enzyme system, reducing the risk of adverse interactions with other medications. In contrast, Elvitegravir (EVG) interacts with CYP3A4, requiring pharmacologic boosting with Cobicistat.

60. The 2015 DHHS Guidelines also provided a summary of the wholesale cost at the time for preferred regimens.³⁹ The guidelines recommend that providers “remain informed of current insurance and payment structures,” as cost was understood to have an impact on long term adherence to any selected regimen.⁴⁰

B. Available Regimens Anchored by INSTIs in 2015

61. The choices available to physicians among the regimens anchored by an INSTI presented different advantages and disadvantages themselves. Dolutegravir (DTG) as an anchor provided numerous advantages, including no food requirement, no CYP3A4 interactions, and a high barrier to resistance.⁴¹ The oral absorption of DTG, however, potentially could be reduced in patients taking

³⁹ *Id.* at 204–07 (Table 16).

⁴⁰ *Id.* at 204.

⁴¹ 2015 DHHS Guidelines at 92 (Table 8).

antacids, or calcium or magnesium supplements.⁴² In addition, the single tablet Triumeq[®] containing DTG (50 mg) as anchor and the N(t)RTI backbone ABC (600 mg) and 3TC (300 mg)⁴³ was not ideal. For example, ABC was known to induce life-threatening hypersensitivity in individuals bearing the HLA-B5701 allele, which required screening prior to prescription.⁴⁴ Moreover, according to the 2014 Triumeq[®] Label, hypersensitivity to ABC was known as a multi-organ clinical syndrome, where hypersensitivity required discontinuation of Triumeq[®] regardless of HLA-B5701 status.⁴⁵ In addition, the ABC/3TC backbone, including as used in Triumeq[®], did not provide adequate therapy for hepatitis B virus (HBV infection). On this basis, the ABC/3TC backbone, and thus the Triumeq[®] single tablet regimen, was not recommended in patients co-infected with HIV and HBV.⁴⁶ On the other hand, the TDF/FTC backbone was known to be active against both HIV and HBV and was therefore more suitable (over ABC/3TC) for use in an ART regimen in HIV/HBV co-infected individuals.⁴⁷ At the time, there were also lingering questions about the long-term safety of ABC administration, given reports suggesting that long

⁴² *Id.*

⁴³ Triumeq Label (EX-1024) at 1.

⁴⁴ 2015 DHHS Guidelines (EX-1014) at 92.

⁴⁵ Triumeq Label (EX-1024) at 1.

⁴⁶ *Id.*

⁴⁷ 2015 DHHS Guidelines at 92 (Table 8) (noting the combination is active against HBV/HIV co-infected patients.)

term ABC use may be associated with a higher risk of myocardial infarction (MI; e.g. heart attacks).⁴⁸

62. Each of the above concerns with the ABC/3TC backbone could be allayed by giving DTG with a TDF/FTC backbone instead, given the benefits of the latter backbone. However, as DTG was manufactured by VIIV healthcare and TDF/FTC was manufactured by Gilead, no single tablet regimen with DTG combined with TDF/FTC was available. As a result, many clinicians (including myself) routinely prescribed the DHHS recommended regimen of DTG with TDF/FTC as two separate pills once daily for newly infected patients.

63. As discussed above, elvitegravir/cobicistat (EVG/c) (150 mg; 150 mg) was also available in a single tablet with TDF/FTC (300 mg; 200 mg) (Stribild®).⁴⁹ Stribild® however required patients to have a creatinine clearance (CrCl) of ≥ 70 mL/min due to cobicistat (COBI) resulting in increases in serum creatinine concentrations.⁵⁰ Increasing serum creatinine can be a marker of impaired kidney function.⁵¹ Thus, in individuals with CrCl of < 70 mL/min, this regimen is not

⁴⁸ See generally 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) (EX-1043).

⁴⁹ Stribild Label (EX-1019) at 22-23; see also Gilead, 2014 Form 10-K (“Gilead 2014 10-K”) (EX-1030) at 3 (listing ingredients).

⁵⁰ Stribild Label (EX-1019) at 3.

⁵¹ *Id.*

recommended. In clinical trials, co-administration of COBI with TDF led to discontinuation of Stribild[®] in some patients due to renal impairment (CrCl of <70 mL/min) and proximal renal tubular dysfunction.⁵² As such, according to its 2012 Label, Stribild[®] “should not be initiated in patient with an estimated [CrCl] below 70 mL per min.”⁵³ Also, as discussed above, EVG has a low genetic barrier to resistance, thereby being prone to the development of resistance in the setting of poor treatment adherence or the absence of other active antiretroviral drugs.

64. Raltegravir (RAL) was another option, and it was known for its long post-marketing experience, which did not include the need to administer with food, and it had no CYP3A4 interactions.⁵⁴ However, it required twice-daily dosing and also had a low genetic barrier to resistance compared to boosted PI- or DTG-based regimens.⁵⁵

65. As such, as of November 9, 2015, the state-of-the-art approach to HIV antiretroviral therapy for treatment-naïve patients prominently featured INSTI-based regimens. Of the INSTI-based regimens available at that time, dolutegravir (DTG)-based regimens were widely being adopted by clinicians given several advantages

⁵² *Id.* at 6.

⁵³ *Id.*

⁵⁴ 2015 DHHS Guidelines at 92 (Table 8)

⁵⁵ *Id.*

over other INSTI-based regimens, including a higher genetic barrier to resistance vis-à-vis RAL and EVG, and once-a-day dosing without a pharmacokinetic booster.

66. In sum, many physicians (including myself) elected to prescribe the second generation INSTI DTG as the anchor in one tablet, with the N(t)RTI backbone TDF/FTC in a separate tablet. This required prescribing two separate tablets, one (DTG) with an average wholesale cost in 2015 of \$1,581.69 per month; and the other (TDF/FTC) with an average wholesale cost of \$1,539.90 per month.⁵⁶ In 2015, both tablets together were more expensive than available single tablet regimens.⁵⁷ Even though giving two tablets was less convenient and more expensive than administering a single tablet regimen, it was (in my experience) the preferred option at the time. Giving DTG as one tablet and FTC/TDF in another did not require screening for hypersensitivity reactions, contained two agents (FTC and TDF) that would not cause severe exacerbations of HBV in co-infected patients and instead was known to be beneficial in HBV treatment, avoided the need for a pharmacokinetic booster, and provided a higher genetic barrier to resistance to integrase inhibition compared with both EVG and RAL.⁵⁸

⁵⁶ 2015 DHHS Guidelines (EX-1014) at 206 (listing monthly DTG – Tivicay[®] price at \$1,581.68); and 205 (listing monthly TDF/FTC-Truvada[®] price at \$1,539.90)(Table 16).

⁵⁷ *Id.* at 206 (listing monthly cost of available single tablet regimens ranging from \$2,551.99 to \$2,948.70).

⁵⁸ *Id.* at 81–82 (Listing Panel’s Recommendations).

67. By November 9, 2015, a fixed dose, single tablet was recognized by many to be ideal for ART therapy.⁵⁹ According to Gilead in 2014, “[s]ingle tablet regimens allow patients to adhere to a fully suppressive course of therapy more easily and consistently, which is critical for the successful management of the disease.”⁶⁰ I agree with this statement, and it is my opinion that the POSA in this time frame would have agreed as well, given their access to the publicly available information discussed herein.

68. In addition, the 2015 DHHS Guidelines noted (and I agree) that successful treatment of HIV infection requires consideration of many factors, including “patient tolerance of pill number, size and frequency.”⁶¹ And, it has been recognized for some time now that the size and shape of a tablet (or capsule) does have an influence on patient compliance with medication regimens.⁶²

⁵⁹ Noemi Astuti & Franco Maggiolo, “Single-Tablet Regimens in HIV Therapy,” 3 *INFECTIOUS DISEASES & THERAPY* 1–17 (2014) (“Astuti”) (EX-1026) at 1-3; 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-1027) at 168.

⁶⁰ Gilead 2014 10-K (EX-1030) at 3.

⁶¹ 2015 DHHS Guidelines (EX-1014) at 188 (discussing interventions to improve adherence to ARV treatments).

⁶² DEPARTMENT OF HEALTH AND HUMAN SERVICES, CENTER FOR DRUG EVALUATION AND RESEARCH (CDER), “Guidance for Industry: Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules,” (June 2015) (“June 2015 CDER Guidance”) (EX-1042) at 6.

C. Growing Concerns over Long Term Use of TDF

69. The use of TDF (one ingredient of the N(t)RTI backbone TDF/FTC) was also the subject of growing concern prior to November 9, 2015.⁶³ Clinical trial data from 2014 recognized that the long term use of TDF has been associated with nephrotoxicity (impaired kidney function), and had also been shown to “result in a greater decline in bone mineral density (BMD) relative to some other NRTIs.”⁶⁴ To address these concerns, tenofovir alafenamide (TAF), a different pro-drug form of tenofovir, was being tested in patients in clinical studies sponsored by Gilead.⁶⁵

70. In September of 2014, clinical data was published by Gilead showing TAF, when compared to TDF in a similar treatment arm, had produced “5-to-7-fold higher” concentrations of tenofovir in cells where the virus tends to replicate.⁶⁶ In this study, treatment-naïve patients given a single tablet of EVG/COBI/TAF/FTC experienced “significantly smaller changes in estimated creatinine clearance, renal tubular proteinuria, and bone mineral density” than those patients who received

⁶³ 2015 DHHS Guidelines (EX-1014) at 80 (noting that clinical study “participants receiving TDF/FTC experienced significantly greater decline in bone mineral density” as compared to other NRTI combinations).

⁶⁴ Sax et al., “Tenofovir Alafenamide Vs. Tenofovir Disoproxil Fumarate in Single Tablet Regimens for Initial HIV-1 Therapy: A Randomized Phase 2 Study,” 67(1) J. ACQUIRED IMMUNE DEFICIENCY SYNDROMES 52–58 (2014) (“Sax”) (EX-1025) at 53.

⁶⁵ *Id.*

⁶⁶ *Id.* at 57.

EVG/COBI/TDF/FTC.⁶⁷ Another 2014 paper also recognized that “a 25 mg dose of TAF has shown greater [antiretroviral activity] than a standard 300 mg dose of TDF,” and further noted that “[t]he possibility to use small doses of TAF instead of TDF could further widen the [single tablet regimen] options”^{68,69}

71. And, in the same year, Gilead announced that it had filed a new drug application with the FDA seeking approval to sell a once-daily single tablet regimen with EVG, COBI, FTC, and a 10 mg dose of TAF (in place of the 300 mg of TDF that had already been approved in Gilead’s Stribild®).⁷⁰ In a February 26, 2015 press release, Gilead’s Executive Vice President, Research and Development and Chief Scientific Officer announced “[w]e look forward to the opportunity to offer patients this and other next-generation, TAF-based therapies that have the potential to improve HIV treatment.”⁷¹ The PK booster (COBI) in this tablet was also shown to increase the bioavailability of TAF, so 10 mg of TAF in this single tablet was

⁶⁷ *Id.* at 52.

⁶⁸ Noemi Astuti & Franco Maggiolo, “Single-Tablet Regimens in HIV Therapy,” 3 INFECTIOUS DISEASES & THERAPY 1–17 (2014) (“Astuti”) (EX-1026) at 11.

⁶⁹ 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-1010) at 449, 454 (1/10th dose disclosure).

⁷⁰ Gilead 2014 10-K (EX-1030) at 3.

⁷¹ EX-1034 a (2/26/15 Press Release with Phase 3 results).

reported to be “equivalent to the 25-mg dose of TAF” without the PK booster COBI.⁷²

72. This single tablet regimen became known as Genvoya[®], and it was approved on November 5, 2015.⁷³ The use of cobicistat, however, was recognized as important to increase EVG bioavailability, and not TAF bioavailability. As such, a POSA would have recognized that larger doses of TAF, e.g., 25 mg, would expectedly be required for single tablets containing an unboosted INSTI such a DTG.

D. The HIV Treatment Market in 2015.

73. As discussed above, clinicians prior to November 9, 2015 (including myself) would have preferred having the option to prescribe a fixed dose, single tablet combination therapy combining DTG with TAF/FTC, given the aforementioned advantages of DTG over so-called “first generation” INSTIs EVG and RAL. But such a tablet was not available at that time, in large part because different pharmaceutical companies, i.e., ViiV and Gilead, owned the rights to DTG and TDF (and TAF) respectively. In my opinion, a POSA at the time would have also recognized, despite the available options, there remained a clinical need for a simplified complete regimen with a second generation INSTI that could be dosed

⁷² Sax (EX-1025) at 53.

⁷³ Gilead 11/5/15 Press Release (EX-1044) at 1.

once a day without a PK booster to anchor the proven N(t)RTI pairing of tenofovir and emtricitabine, which had evolved away from TDF and toward the safer tenofovir prodrug TAF.

74. Based on my review of certain patent literature that was available to the POSA prior to November 9, 2015, other pharmaceutical companies also recognized the clinical need for a single tablet with a second generation INSTI (such as DTG) anchoring the N(t)RTI pair of tenofovir and emtricitabine.

75. One example of this is a Cipla patent application published on August 20, 2015 that disclosed and claimed single tablets with 50 mg of DTG coupled with the N(t)RTI pair of TDF (300 mg) and FTC (200 mg).⁷⁴ Another patent application from a different company published in February of 2015 and disclosed and claimed single tablets where DTG is combined with FTC and “tenofovir or a prodrug thereof.”⁷⁵ In my opinion, both of these publications confirm that pharmaceutical companies were aware of, and actively pursuing, a single tablet option with the INSTI DTG anchoring the emtricitabine and tenofovir N(t)RTI pair prior to November 9, 2015. I provide a more detailed analysis of these particular publications later in this declaration.

⁷⁴ U.S. Patent Publication 2015/231079 (“US ’079”) (EX-1007) at ¶ 117.

⁷⁵ WO 2015/022351 A1 (“WO ’351”) (EX-1006) at [57].

76. I have also been provided, and have reviewed, a document which I understand is the 2014 10-K filing by Gilead.⁷⁶ Gilead’s 2014 10-K was signed by Gilead’s CEO on February 25, 2015, was made publicly available prior to November 9, 2015, and therefore would have been accessible to a POSA.⁷⁷ This document attests to the financial performance of Gilead in the 2014 fiscal year (ending December 31, 2014).⁷⁸ Here, Gilead reported that sales associated with its antiviral products were \$22.8 billion – which was 91% of the company’s total revenues during the year ending December 31, 2014.⁷⁹ Gilead also announced that HIV-related products “accounted for more than 40% of [its] total product sales[,]” and candidly recognized that “[i]f physicians do not see the benefit of our HIV products, the sales of our HIV products will be limited.”⁸⁰ And, Gilead cautioned that “if we do not introduce new products to market or increase sales of our existing products, we will not be able to increase or maintain our total revenues nor continue to expand our R&D efforts.”⁸¹

77. Gilead’s 2014 10-K further acknowledged that the competitive environment for a single tablet regimen was substantial in 2015, and recognized that

⁷⁶ Gilead 2014 10-K (EX-1030).

⁷⁷ *Id.* at 129–30.

⁷⁸ *See generally id.*

⁷⁹ *Id.* at 6.

⁸⁰ *Id.* at 30.

⁸¹ *Id.* at 31.

DTG, “an integrase inhibitor, launched in 2013 by ViiV, and Triumeq® [DTG/ABC/3TC], a single tablet antiretroviral regimen, launched in the third quarter by ViiV, could adversely impact sales of our HIV products.”⁸²

78. In my opinion, given the available clinical information, a POSA would have recognized the clinical need for a simple and complete HIV regimen, given in a single tablet, containing a “second generation” INSTI as the anchor drug, combined with the proven and preferred N(t)RTI pairing of a tenofovir prodrug and FTC vis-à-vis the less preferred pairing of ABC/3TC. Again, a single tablet combination of the “second generation” INSTI DTG with a tenofovir prodrug and FTC was not available at the time. A POSA would have further appreciated that this much needed combination would be achieved more efficiently and expeditiously by utilizing an INSTI similar to DTG but owned by Gilead, such that a single pharmaceutical company would be able to evaluate and potentially market the single tablet combination.

79. The POSA would have also understood, based on Gilead’s 2014 10-K, the beneficial market opportunity that such a fixed dose single tablet would offer. That person would have appreciated that large sums of revenue were earnable through the introduction of a single tablet using a tenofovir prodrug (preferably TAF

⁸² *Id.* at 34.

over TDF) and FTC as an N(t)RTI backbone, anchored by a second generation INSTI. This would have provided a single tablet regimen having at least an equivalent level of inhibitory action toward HIV integrase as DTG along with a similarly high genetic barrier to resistance, which allowed for once-a-day administration without the need for a pharmacokinetic booster like COBI. Based on such a design need and market opportunity, a POSA would have unquestionably been motivated to access and prepare this simplified and preferred treatment regimen.

E. Routine Dose Ranging Studies in Clinical Trials

80. Dose ranging studies are, in my experience, a relatively common way to determine an appropriate dose for an antiretroviral drug. For example, a patent application owned by Gilead, WO '323, which was published in June of 2014 (discussed below in Section VIII.A) explains that the compounds it discloses (which are INSTI compounds), were used within a pharmaceutical composition. Further, the INSTI compounds were reported to be used in an amount which is effective to treat a particular disease of interest, i.e., a “therapeutically effective amount.” The same document explains that “treatment” is defined to include “the administration

of a compound or composition according to the present inventions to alleviate or eliminate symptoms of HIV infection and/or to reduce viral load in a patient.”⁸³

81. In further regard to pharmaceutical compositions, WO '323 states that the activity of the disclosed compounds “can be determined by one skilled in the art” and also that “[a]ppropriate concentrations and dosages can be readily determined by one skilled in the art.”⁸⁴ I agree with this general proposition, and it is my opinion that the POSA would agree as well.

82. WO '323 further states a “therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to their own knowledge, the state of the art, and this disclosure[,]” including considerations of the activity of the specific compound employed; the metabolic stability and length of action of the compound; the age, body weight, general health, sex, and diet of the patient; the mode and time of administration; the rate of excretion; the drug

⁸³ WO 2014/100323 A1 (“WO '323”) (EX-1005) at 16:8–32 (also noting that the term “treatment” encompasses administration post-exposure to the virus but before the appearance of symptoms of the disease, and/or prior to the detection of the virus in the blood, to prevent symptoms and/or to prevent the virus from reaching detectable levels in the blood, and also the administration to prevent perinatal transmission of HIV from mother to baby); *see also* '802 Patent (EX-1001) at 57:32–44 (providing similar goals for “treatment” including preventing or reducing the risk of developing the disease in a subject that may be exposed to or predisposed to the disease but does not yet experience or display symptoms).

⁸⁴ EX-1005 (WO '323) at 35:8–23 (further disclosing pharmaceutical compositions containing an INSTI compound in the amount of about 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg or about 500 mg).

combination; the severity of the particular disorder or condition: and the subject undergoing therapy.⁸⁵

83. In my experience, these are also accurate statements, and it is my opinion that a POSA would agree. Once the anti-viral activity of a compound is established, appropriate amounts of that compound for oral administration can be readily determined by the POSA using routine pre-clinical and clinical experimentation. I provide some examples of such routine practices below in the context of treating HIV.

84. Relevant to the field of ART where an INSTI anchors a preferred backbone such as tenofovir and emtricitabine is an article authored by Stellbrink et al. and published in 2013 that presented results of a dose ranging clinical study for DTG (called SPRING-1) to evaluate efficacy and safety/tolerability.⁸⁶ In the SPRING-1 study, treatment naïve adults with HIV received DTG at a dose of 10, 25 or 50 mg in combination with one of two NRTIs backbones (tenofovir/emtricitabine or abacavir/lamivudine), with a control arm of 600 mg efavirenz (EFV) once daily

⁸⁵ *Id.* at 16:19–21, 36:31–37:5; *see also* '802 Patent (EX-1001) at 57:45–52 (defining “effective amount” to include the “amount of the compound that, when administered to a subject for treating a disease, is sufficient to effect such treatment of the disease[,]” which considers factors such as “the compound [itself], the disease and its severity, and the age, weight, etc. of the subject to be treated.”

⁸⁶ 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-1045) at 1771 (Objective).

combined with the same backbones.⁸⁷ Stellbrink describes DTG as a new potent INSTI with low nanomolar activity that is suitable for once-daily unboosted dosing, and that retains activity against most isolates carrying major integrase resistance mutations to RAL and/or EVG.⁸⁸ The primary goal of SPRING-1 study was to select a dose for Phase III development.⁸⁹

85. Initial analyses from SPRING-1 established “a rapid antiviral response to DTG” and that “93% of participants who received DTG achieved HIV-1 RNA less than 50 copies/ml by 16 weeks,” and this suppression rate “was generally sustained up to 48 weeks,” in each treatment group receiving each of the three dosage amounts.⁹⁰ After 96 weeks in the study, 88% of the patients taking 50 mg DTG had maintained viral suppression, while 79% and 78% of those taking 10 mg and 25 mg respectively maintained viral suppression, i.e., HIV-1 RNA less than 50 copies/ml as shown in the Figure 1 below.⁹¹

⁸⁷ Stellbrink (EX-1045) at 1772.

⁸⁸ *Id.*

⁸⁹ *Id.*

⁹⁰ *Id.*

⁹¹ *Id.* at 1776.

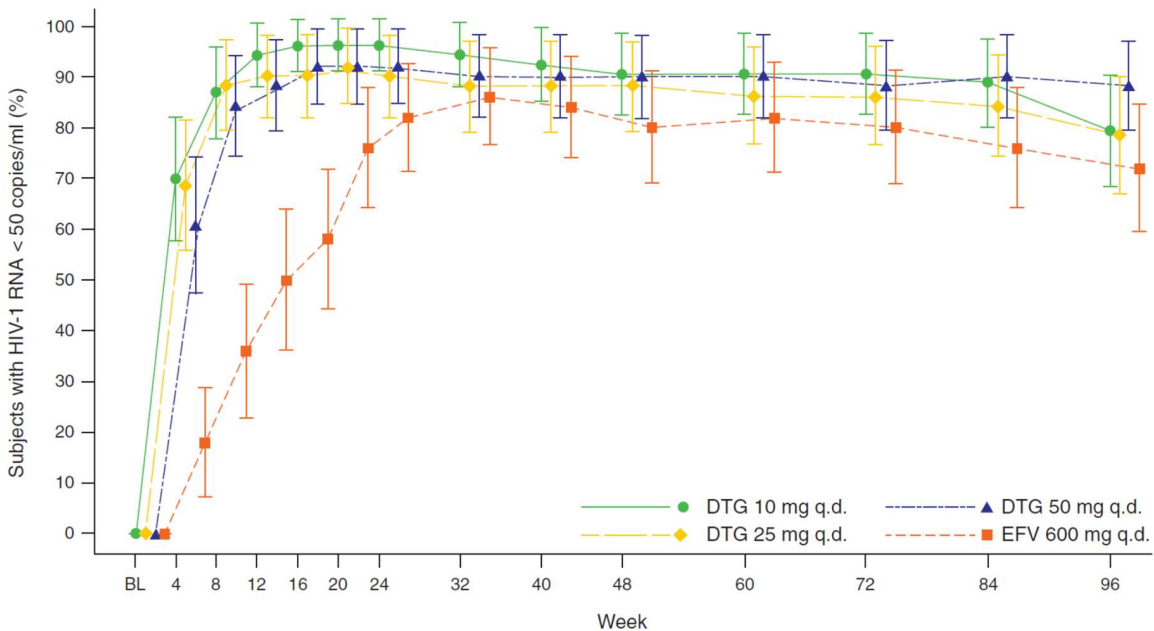


Fig. 1. Proportion of participants with plasma HIV-1 RNA less than 50 copies/ml as determined using the time to loss of virologic response algorithm. Error bars indicate 95% confidence intervals, which were derived using the normal approximation. BL, baseline; DTG, dolutegravir; EFV, efavirenz; q.d., once daily.

Also, there were no protocol-defined virologic failures (PDVFs), here a confirmed viral load ≥ 400 copies/ml between 48 weeks and 96 weeks on any treatment arm.⁹² Median CD4 cell counts also increased from baseline to week 96 in all treatment groups and were numerically greater at each dose relative to EFV.

86. As shown in Figure 2 below, the largest increase in CD4+ cell count was achieved with 25 mg of DTG, though all doses of DTG provided statistically similar results.

⁹² *Id.* at 1774, 1776.

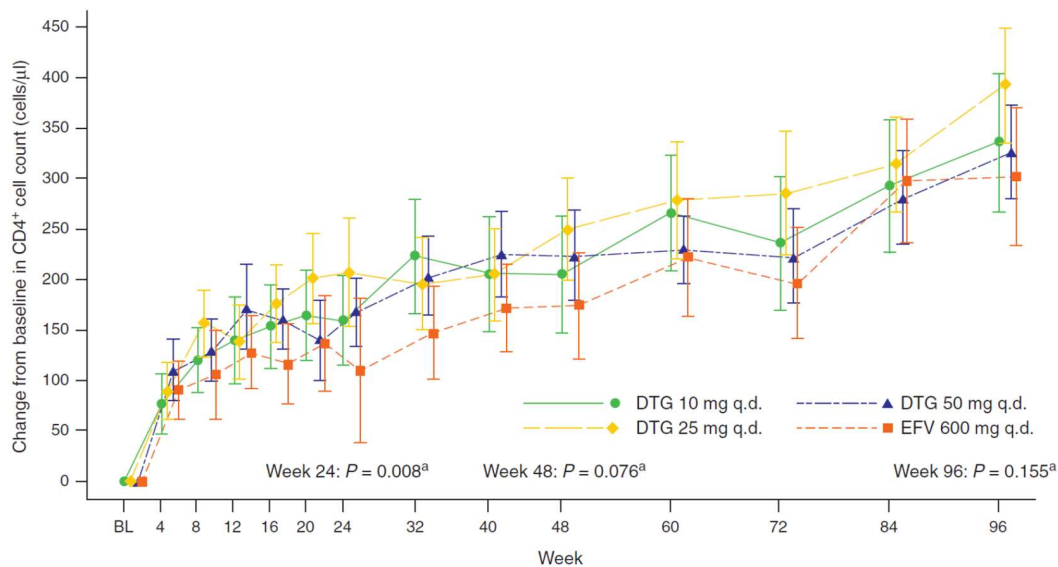


Fig. 2. Median (95% confidence interval) change from baseline in CD4⁺ cell counts. BL, baseline; DTG, dolutegravir; EFV, efavirenz; q.d., once daily. ^a*P* value determined for all DTG doses vs. EFV using the Wilcoxon two-sample test.

87. The 50 mg dose was selected for Phase III trials because it was the “maximum tolerated dose to compensate for potential reductions in exposure caused by drug interactions without the need for dose adjustment, specifically in the treatment-experienced, INSTI-naïve patient population.”⁹³ Nonetheless, the 10 mg and 25 mg DTG doses with two N(t)RTIs were also efficacious through 96 weeks and did not allow for the emergence of HIV integrase mutations.

88. As such, this routine clinical investigation to determine effective doses of DTG established that not only a 50 mg dose was efficacious, but that a dose five times lower (10 mg) had (among other things) provided a similar reduction in viral load, i.e., <50 copies HIV-1 RNA, throughout the 96-week study.

⁹³ *Id.* at 1776.

89. Another example of a routine dose ranging study, this time for the INSTI EVG, was summarized by Zolopa et al., an article published in 2010, including authors Zhong, Chuck, Enejosa, Kearny, and Chaeng from Gilead Sciences.⁹⁴ In this Phase II study, patients received nucleoside or nucleotide reverse transcriptase inhibitors (N(t)RTIs) combined with once-daily elvitegravir at a dose of 20 mg, 50 mg, or 125 mg, along with 100 mg of ritonavir.⁹⁵

90. Zolopa notes a small monotherapy study of EVG involving treatment-naïve and treatment-experienced subjects where all evaluated doses produced significant decreases in HIV RNA level, including all subjects treated once-daily with a dose of 50 mg EVG and 100 mg ritonavir where the mean reduction in HIV RNA level was $-2.0 \log_{10}$ over a 10-day period.⁹⁶ Thereafter, an active-controlled, dose-ranging, 48 week, phase 2 study was conducted in the United States where ritonavir-boosted EVG (EVG/r with EVG at a dose of 20 mg, 50 mg, and 125 mg per day, combined with 100 mg ritonavir) was compared with a ritonavir-boosted comparator protease inhibitor (CPI/r) in combination with optimized background therapy (OBT) in HIV-1-infected treatment-experienced subjects.

⁹⁴ 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-1056).

⁹⁵ EX-1056 at 1, 814–15 (100 mg ritonavir boosted the systemic exposures by ~20-fold).

⁹⁶ *Id.* at 815.

91. After review of interim data at week 8, the EVG 20 mg arm was discontinued because it was associated with a higher rate of virologic failure, i.e., PDVF. In an intent-to-treat analysis of the primary endpoint (time-weighted average change from baseline in HIV RNA level through week 24), compared to the CPI/r arm ($-1.19 \log_{10}$ copies/mL), the elvitegravir 50 mg arm was noninferior ($-1.44 \log_{10}$ copies/mL), and the elvitegravir 125 mg arm was superior ($-1.66 \log_{10}$ copies/mL), with no difference in adverse events between EVG arms. Subjects given elvitegravir 50 mg or 125 mg had a 2-week virologic response similar to that observed in the monotherapy study and greater than that observed for patients given CPI/r ($-1.79 \log_{10}$ copies/mL for EVG 50 mg and $-2.07 \log_{10}$ copies/mL for EVG 125 mg compared with $-1.08 \log_{10}$ copies/mL in the CPI/r arm).⁹⁷ Over 90% of subjects who received EVG at a dose of 50 mg or 125 mg showed a reduction in HIV RNA of at least 1 $\log_{10}$ copies/mL by week 24.⁹⁸

92. In view of these and other results, Zolopa states that “once-daily administration of elvitegravir was well-tolerated and produced rapid virologic suppression that was durable when the drug was administered with active

⁹⁷ *Id.* at 818 (also noting that the difference in mean change from baseline in HIV RNA level between the EVG 50 mg and 125 mg arms did not reach statistical significance).

⁹⁸ *Id.*

background therapy[.]”⁹⁹ and that “[t]his study clearly demonstrates the importance of using at least 1 fully active drug to support the potent antiviral activity of an integrase inhibitor, such as elvitegravir, in producing a durable virologic response.”¹⁰⁰ Overall, EVG at a dose of 125 mg provided slightly better efficacy than EVG at a dose of 50 mg, which are lower than the 150 mg EVG in the FDA approved Stribild product.¹⁰¹ In sum, the dose ranging study described in Zolopa provided another example where more than one dose provided efficacy (reduction in HIV viral load) compared with a comparator regimen. Here, however, a lower dose (20 mg) had provided PAVFs and was dropped from the study.

93. Further, prior to November 9, 2015, Gilead was also actively (and publicly) pursuing a new ART regimen, combining an investigational drug along with 25 mg of TAF and 200 mg of FTC.¹⁰² The protocol for a clinical study exploring the dosing level for such a tablet was first published on March 20, 2015, seeking participants in a clinical trial studying two different drug regimens in

⁹⁹ *Id.* at 820–21.

¹⁰⁰ *Id.* at 821.

¹⁰¹ Stribild Label (EX-1019) at 22-23.

¹⁰² 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> (Version 1: March 20, 2015) at p. 2 (EX-1035).

separate patient groups.¹⁰³ One group of patients (the active comparator arm) would be given tablets with the “second generation” INSTI DTG (50 mg) anchoring an N(t)RTI pair of TAF (25 mg) and FTC (200 mg).¹⁰⁴ The other group of patients (the treatment arm) would be given tablets with the same N(t)RTI pair, anchored by 75 mg of a compound called (at the time) “GS-9883.”¹⁰⁵

94. Another protocol using the same study drug “GS-9883”, described as a “a Phase 1b” study, was earlier published by Gilead on February 6, 2015.¹⁰⁶ This study was divided into four different groups, all of which were given (in a randomized and placebo controlled manner) either 5, 10, 25, 50, or 100 mg of GS-9883 once daily.¹⁰⁷ The study lasted for up to 11 days, and the ability of each dose to reduce the amount of virus was measured at day 11 (DAVG₁₁ in plasma HIV-1 RNA (log₁₀ copies/mL)).¹⁰⁸ A POSA would understand a study of this nature to be a dose ranging study, and another example of the sort of clinical study that was

¹⁰³ EX-1035 at 3 (Arms and Interventions).

¹⁰⁴ *Id.*

¹⁰⁵ *Id.*

¹⁰⁶ 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> (Version 7: February 6, 2015) at p. 2 (EX-1029).

¹⁰⁷ *Id.* at 7–8 (Arms and Interventions table defining cohorts 1–4).

¹⁰⁸ *Id.* at 9.

routinely employed at the time to determine appropriate concentrations and dosages for an anti-viral therapy at the time.

95. While it appears that a 75 mg dose of GS-9883 was selected for use in a phase 2 study (EX-1035), a POSA would have expected that a phase 2 study dose may not necessarily represent the most effective, or final dose to be used in a subsequent Phase 3 trial, especially when measuring viral suppression. Depending on the results of the pending routine studies, a dose of 50 mg (and lower) may have also provided significant reductions in HIV RNA counts, just as had been shown for DTG. In other words, it is my opinion that the POSA would understand that a 50 mg dose of the study drug may have sufficiently reduced viral load in the Phase 1b study, since doses lower than the final chosen INSTI dose had done so in the Stellbrink and Zolopa studies.

96. The studies above also confirm that statements made by Gilead scientists in WO '323 (published in June of 2014), were accurate, including that the activity of anti-HIV compounds would have been readily determined by POSAs prior to November 9, 2015, and that appropriate concentrations and dosages of such compounds, including therapeutically effective amounts, also would have been “readily determined” by a POSA.¹⁰⁹ In my opinion, the POSA would have had the

¹⁰⁹ WO '323 (EX-1005) at 35:8–23 (further disclosing pharmaceutical compositions

tools and guidance needed to routinely determine efficacious doses of an anti-viral drug, and specifically an anti-HIV INSTI paired with an N(t)RTI combination, where efficacy was measured in terms of a percentage of patients having <50 copies/mL of HIV RNA after a certain number of days receiving the dose (*see* Stellbrink), or a reduction in HIV RNA levels after a certain number of days receiving the dose (DAVG) (*see* Zolopa and NCT02275065).

VI. OVERVIEW OF THE '802 PATENT

A. The Specification of the '802 Patent.

97. The '802 Patent issued on September 5, 2023. Its abstract summarizes its content as providing “a solid oral dosage form,” with three anti-viral compounds, or pharmaceutically acceptable salts of each compound.¹¹⁰

98. The “Background” section of the patent recognizes that the standard of care for the treatment of patients with AIDS was to administer a combination of multiple types of antiretroviral agents to “suppress viral replication to below detectable limits, increase CD4 cell counts, and halt disease progression.”¹¹¹ The same section identifies the DHHS treatment guidelines, which provide that

containing an INSTI in the amount of about 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg or about 500 mg).

¹¹⁰ '802 Patent (EX-1001) at [57].

¹¹¹ *Id.* at 1:31–35.

“achievement of viral suppression requires the use of combination therapies, i.e., several drugs from at least two or more drug classes.”¹¹²

99. The “Summary” part of the ’802 Patent begins by identifying the disclosed oral dosage form as containing “a compound of Formula I,” combined with both tenofovir alafenamide and emtricitabine.¹¹³ This section lists several different aspects of the dosage forms, which (basically) includes various tablet configurations with 50 mg of “Formula I,” and others with 75 mg of the same compound, both combined with emtricitabine and tenofovir alafenamide.¹¹⁴

100. The “Detailed Description” section of the ’802 Patent begins with an explanation that the first compound, “Formula I,” is a “potent HIV integrase inhibitor” (INSTI) (hereafter, referred to as “BIC”).¹¹⁵ The second and third compounds are described as both nucleotide (tenofovir alafenamide)(“TAF”) and nucleoside (emtricitabine)(“FTC”) reverse transcriptase inhibitors (N(t)RTIs).¹¹⁶ The patent explains that each of the active ingredients had been independently established as effective in suppressing HIV infection in patients.¹¹⁷ It also reports that FTC was (at the time) “a part of” several FDA approved single regimen dosage

¹¹² *Id.* at 1:46–51.

¹¹³ *Id.* at 2:36–40.

¹¹⁴ *Id.* at 2:41–4:31.

¹¹⁵ *Id.* at 5:14–16.

¹¹⁶ *Id.* at 6:37–7:17.

¹¹⁷ *Id.* at 4:66–8:49.

forms.¹¹⁸ Each of the approved single regimen dosage forms included 200 mg of FTC and 300 mg of tenofovir disoproxil fumarate, in addition to other active ingredients, all in the same tablet.¹¹⁹

101. After identifying three active ingredients, the '802 Patent states that the applicants “have successfully formulated [BIC], [FTC] and [TAF] in a single, stable dosage form that is pharmacologically efficacious and physically acceptable.”¹²⁰ The patent also states that the oral dosage forms that are the subject of the patent are intended for use in humans, and so “they must be of an appropriate size and weight for oral human administration,” which is defined as weighing less than 1.5 grams, in addition to being efficacious.¹²¹

102. The '802 Patent also identifies the FDA-approved single regimen dosage form TRIUMEQ[®] as a tablet containing 50 mg of dolutegravir (DTG) and two N(t)RTIs (abacavir (ABC) (600 mg) and lamivudine (3TC) (300 mg)).¹²² TRIUMEQ[®] is said to contain 950 mg of combined active ingredients and a total

¹¹⁸ *Id.* at 8:4–13 (referring to TRUVADA[®], ATRIPLA[®], STRIBILD[®] and COMPLERA[®]).

¹¹⁹ *Id.*

¹²⁰ *Id.* at 8:41–54.

¹²¹ *Id.* at 8:54–60.

¹²² *Id.* at 8:65–9:4.

weight more than 1000 mg “due to excipient amounts required to make a pharmaceutically acceptable tablet.”¹²³

103. The '802 patent states that its inventors “found that the use of fixed dose combinations *may assist* in optimizing pharmacokinetic properties, particularly the total exposure of the compound of Formula (I) [(BIC)] or a pharmaceutically acceptable salt thereof” in patients taking the different types of dosage forms disclosed.¹²⁴ The patent also states the following:

In certain embodiments, the use of a fixed dose combinations, e.g., multilayer tablets, *may affect* the dissolution profile of one or more of the active ingredients within the dosage form, and is therefore likely to have an impact on the in vivo pharmacokinetics of the dosage form. In particular, it has been observed that the dissolution of the compound of Formula I (e.g., as Formula II) varies depending on whether the tablet is in a fixed dose combination formulation with tenofovir alafenamide and emtricitabine *and/or whether the tablet is a monolayer or multilayer tablet*. It has also been observed that the presence of *certain excipients in the multilayer tablet formulation (or absence of others)* affects the dissolution profile of one or more of the active ingredients within the dosage form.¹²⁵

The '802 Patent then catalogs multiple configurations of various “embodiments” of tablets in several subsequent columns and pages of the specification.¹²⁶

¹²³ *Id.*

¹²⁴ *Id.* at 9:44-53 (emphasis added).

¹²⁵ *Id.* at 9:53-66 (emphasis added)

¹²⁶ *Id.* at 8:61–55:25.

104. Beginning at column 57, the patent provides specific examples of the tablets that were used in experiments that are also disclosed. The first, “F1,” is a “single agent tablet,” containing only one active ingredient – 75 mg BIC (78.7 mg as sodium salt) –along with the excipients microcrystalline cellulose, lactose monohydrate crospovidone and sodium stearyl fumarate in specific amounts.¹²⁷

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

*Equivalent to 75 mg of the Compound of Formula I

**Intergranular: 2.25 mg (0.75%); Extragranular: 2.25 mg (0.75%)

105. Another type of tablet, “F3,” named a “fixed dose combination” tablet, contains a mixture of 200 mg FTC and 25 mg TAF (28 mg as hemifumarte salt) in a single non-layered tablet with the excipients microcrystalline cellulose, croscarmellose sodium and magnesium stearate in specific amounts.¹²⁸

¹²⁷ *Id.* at 57:60–58:27.

¹²⁸ *Id.* at 59:14–45.

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

106. A third type of tablet is identified as a “Bilayer Tablet,” which contains BIC in either 75 mg (78.7 mg as sodium salt) (“F2”) or 50 mg (52.5 mg as sodium salt) (“F7”), where the BIC is segregated into one layer, and 200 mg FTC and 25 mg TAF (28 mg as hemifumarte salt) are segregated into another layer, each containing microcrystalline cellulose, croscarmellose sodium and magnesium stearate in specific amounts.¹²⁹ The 75 mg and 50 mg BIC bilayer tablets, identified as “F2” and “F7” are as follows:

¹²⁹ *Id.* at 57:54–59:37 (“F2”); 66:33–67:5 (“F7”)

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

*Equivalent to 75 mg of the Compound of Formula I
**Equivalent to 25 mg tenofovir alafenamide
***Intergranular: 212.5 mg (29.1%); Extragranular: 2.65 mg (0.4%)
[†]Intergranular: 2.65 mg (0.4%); Extragranular: 2.65 mg (0.4%)
^{††}Intergranular: 2.83 mg (0.4%); Extragranular: 2.83 mg (0.4%)

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

*Equivalent to 50 mg of the Compound of Formula I
**Equivalent to 25 mg tenofovir alafenamide

107. Only the Bilayer Tablet F2 is reported by the '802 patent as providing a total exposure of BIC in the blood of patients enrolled in a PK study that “was approximately 30% higher when dosed in the bilayer tablet formulation F2,” as compared to the dosing the same amount of BIC, administered in its own single agent tablet (F1) co-dosed with the tablet containing TAF and FTC (F2).¹³⁰

108. In a second PK study (Example 9) a similar comparison was made, except using a Bilayer Tablet with 50 mg of BIC combined with FTC and TAF (“F7”) in one treatment arm, to assess the BIC exposure from that tablet compared with the co-administration of Tablets F1 and F3.¹³¹ Total exposure when using Bilayer Tablet F7 is also disclosed, and the patent reports that the data “were consistent with the modeling of earlier clinical data confirming that these exposures provided antiviral efficacy.”¹³²

109. Based on my review of the '802 Patent, the only tablet that produces what the applicants report as an “approximately 30% higher” exposure of BIC is Tablet F2 with 75 mg of BIC (75.7 mg as sodium salt), where BIC is segregated in its own layer with specific amounts of excipients, and FTC and TAF are in another layer with different amounts of excipients.

¹³⁰ *Id.* at 60:43–61:29 (Example 3).

¹³¹ *Id.* at 68:50–73:4) (Example 9).

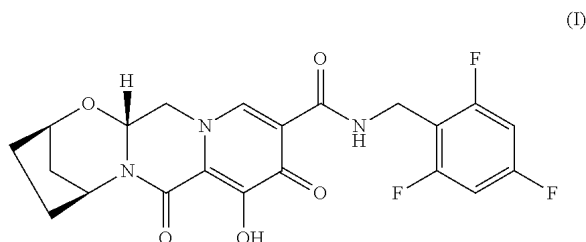
¹³² *Id.* at 70:14–65.

B. The Claims of the '802 Patent.

110. Claims 1–13 of the '802 Patent are the focus of my analysis, and are challenged by Cipla's Petition. Each of those claims are as follows (claim 1 annotated to identify its separate elements):

1. **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

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

2. The tablet of claim 1, wherein the tablet comprises 50 mg of the compound of Formula I as a pharmaceutically acceptable salt thereof.
3. The tablet of claim 1, wherein the tablet comprises 25 mg tenofovir alafenamide as a pharmaceutically acceptable salt thereof.
4. The tablet of claim 1, wherein the tablet comprises 50 mg of the compound of Formula I as a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide as a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine.
5. The tablet of claim 1, wherein the tablet comprises 52 mg of the sodium salt of the compound of Formula I.

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

C. The Prosecution History of the '802 Patent.

111. I have reviewed what I understand to be the record of correspondence between the applicants for the '802 Patent and the USPTO, a collection of documents I understand is referred to as a "prosecution history." I understand that the application that led to the '802 Patent was filed on May 6, 2022, and that it claims priority to a provisional application that was filed several years earlier, on November

9, 2015. For the purposes of my analysis, I have been asked to assume that the '802 is entitled to this priority date.

112. The application filed on May 6, 2022 listed a total of 51 claims, and I have reviewed those claims.¹³³ Initially, the applicants claimed its tablets by describing a variety of different kinds of solid oral dosage forms. For example, the applicants claimed a “solid oral dosage form” (claim 1) a “coated tablet” (claim 7), a “tablet” (claim 8), a “multilayer tablet” (claim 16), and methods for making the same kinds of tablets.¹³⁴

113. The applicant however filed an amendment to the original 51 claims on August 19, 2022, cancelling all of them.¹³⁵ In their place, the applicant presented a new set of claims for examination, narrowed to only “a tablet,” and claim 52 is an example, as follows:¹³⁶

¹³³ '802 Patent File History (EX-1002) at 107–12.

¹³⁴ *Id.*

¹³⁵ *Id.* at 137.

¹³⁶ *Id.* at 139.

1-51. (Canceled)

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

(I)



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

114. The examiner rejected these claims on December 6, 2022, explaining that two of Gilead's patent publications ("the Carra references;" EX-1038 and EX-1039) rendered the claims under examination anticipated, where the combination with another Gilead publication rendered the claims obvious.¹³⁷

115. The examiner also rejected the same claims as not patentably distinct from the claims 1-10 of U.S. Patent No. 10,548,846.¹³⁸ As I understand this rejection, it was based on obviousness-type double patenting, which prohibits the extension of the term of an issued patent by claiming, in a later filed application, essentially the same invention.

¹³⁷ *Id.* at 163–71 (December 6, 2022 Office Action at 2–4).

¹³⁸ *Id.* at 170 (December 6, 2022 Office Action at 9).

116. In response to the examiner's rejections, Gilead explained first that the Carra references were not prior art.¹³⁹ Gilead also filed a terminal disclaimer to the '846 patent.¹⁴⁰ My understanding of a terminal disclaimer is that Gilead agreed that any new patent claims issuing from the pending prosecution would expire on the same day as the '846 patent.

117. On June 30, 2023, the USPTO examiner allowed the claims of the '802 Patent.¹⁴¹ In the Notice of Allowance, the examiner first explains that publications from "Carra et al." were published after "the effective filing date of the instant application and have a common assignee."¹⁴² I understand this means those reference are not prior art to the '802 Patent.

118. The examiner states that "[t]he next closest prior art of WO2014/100323 comprises administering the compound of Formula 1 at a different time than additional drugs such as tenofovir or emtricitabine."¹⁴³ The examiner then concludes that the prior art "does not teach all three drugs within the same tablet."¹⁴⁴ The examiner also notes in her "reasons for allowance" that "[a]pplicants have

¹³⁹ *Id.* at 244–49 (April 5, 2023 Response to December 6, 2022 Office Action at 1–6).

¹⁴⁰ *Id.* at 248 (April 5, 2023 Response to December 6, 2022 Office Action at 5).

¹⁴¹ *Id.* at 1046.

¹⁴² *Id.* at 1051 (June 30, 2023 Notice of Allowance at 2).

¹⁴³ *Id.*

¹⁴⁴ *Id.*

shown a 30% higher exposure of [BIC] in a fixed dose combination of [the three active ingredients] relative to its exposure when co-administered as a single agent of [BIC] with a fixed dose combination of [FTC and TAF].”¹⁴⁵ As I have explained in Section VI.A., the ’802 specification ascribes a 30% higher exposure of BIC only to Tablet F2, which is a bilayer tablet containing 75 mg of BIC (78.7 mg sodium salt) contained in one layer with specific amounts of excipients, with both TAF and FTC in another layer with different amount of excipients.¹⁴⁶

119. I provide my detailed analysis and review of WO 2014/100323 (EX-1005) later in this declaration, but it is my opinion that the examiner was mistaken in her conclusion that that this reference only discloses administering the compound of Formula I at a different time than additional drugs such as tenofovir or emtricitabine. That reference does in fact disclose embodiments where Formula (I), e.g., compound 42 (BIC), is combined with additional therapeutic agents in the same dosage form, as follows (red underlying added):¹⁴⁷

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

20

¹⁴⁵ *Id.* at 1051–52 (June 30, 2023 Notice of Allowance at 2–3).

¹⁴⁶ *Id.* at 59:47–64:16 (F2 PK Study).

¹⁴⁷ WO ’323 (EX-1005) at 40:18–20 (emphasis added); *see also* 37:13-21.

In other parts of this reference, combination dosage forms containing two additional therapeutic agents, e.g., anti-HIV agents including the N(t)RTIs FTC and TAF are disclosed.¹⁴⁸ Such combinations containing compound **42** (BIC) and N(t)RTIs are then claimed in a single “pharmaceutical composition,” including for treating HIV infection in a human.¹⁴⁹ As detailed below, this clear disclosure of combination dosage forms, e.g., tablet, forms the basis for my analyses and opinions as to obviousness below.

VII. CLAIM CONSTRUCTION

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

121. I understand that the plain and ordinary meaning should be apparent from the content of the '802 Patent, and (if necessary) the record of correspondence between the applicant and the USPTO, which I understand to be the intrinsic record. I have followed these principles in my analysis to the extent necessary throughout this declaration.

¹⁴⁸ *Id.* at 37:20–38:2, 39:25-27.

¹⁴⁹ *Id.* at 241 (Claims 33 (depending from claim 32) and claims 35-36); *see also id.* at 241-242 (Claim 37 (treating HIV infection by administering pharmaceutical composition of claim 33) and claims 39-40).

122. Claims 1–4, and 12–13 (above) refer to “a pharmaceutically acceptable salt” of the active ingredients that are identified. The ’802 Patent explains that the amount of “pharmaceutically acceptable salt” is the amount of the salt that provides for the same amount of the recited compound in its free acid, or base, form.¹⁵⁰ In my analysis, I have applied this definition to all claims that recite an amount of “a pharmaceutically acceptable salt thereof.”

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

VIII. THE PRIOR ART DISCLOSES OR SUGGESTS MOST ELEMENTS OF THE CHALLENGED CLAIMS

124. I have reviewed in detail the three patent application publications that I discuss in this section. I understand each of these publications qualify as prior art to the ’802 Patent. As I explain in more detail below, it is my opinion that nearly all recited elements of the Challenged Claims are disclosed (or at least suggested) to a POSA in these three references.

125. I have also prepared a table that provides specific cites showing where in each reference discloses elements of Challenged Claims and have attached that table as **Appendix B** to this declaration.

¹⁵⁰ ’802 Patent (EX-1001) at 6:4–28; 7:22–48; 8:22–36.

A. Disclosures and Suggestions to a POSA from WO '323 (EX-1005)

126. WO '323 is a patent application filed on behalf of Gilead that published on June 26, 2014.¹⁵¹ Its abstract summarizes the application as one that discloses compounds “for use in the treatment of human immunodeficiency virus (HIV) infection,” as well as methods for preparing those compounds, “as well as pharmaceutical compositions comprising such compounds.”¹⁵²

127. WO '323 discloses a family of compounds, named as compounds “of Formula (I),” which may have antiviral activity, and which “may be used to inhibit the activity of HIV integrase and may be used to reduce HIV replication.”¹⁵³ WO '323 then discloses ~100 particular examples of Formula (I) compounds, which include detailed methods for preparing them.¹⁵⁴ Following the examples, a table (Table 1) reports results of an antiviral assay performed on each exemplary compound.¹⁵⁵

128. This assay details the impact of these different compounds on infectivity of HIV in a cell line known to be permissive for HIV replication. The table reports half maximal effective concentrations (EC₅₀; drug concentration that

¹⁵¹ WO '323 (EX-1005).

¹⁵² *Id.* at [57].

¹⁵³ *Id.* at 3:8–12.

¹⁵⁴ *Id.* at 43:15–212:3

¹⁵⁵ *Id.* at 212:5–216.

inhibits 50% of the virus) for the compounds in the range of 1.5 to 422 nM. Compounds with lower EC₅₀ would be understood by a POSA to have more potent anti-HIV activity.¹⁵⁶ A POSA would have appreciated that a majority of the exemplary compounds exhibited good to excellent anti-HIV activity, with ~50% having an EC₅₀ of ≤5 nM, and ~30% having an EC₅₀ ≤2.5 nM. And given the INSTI function of these compounds, a POSA would have recognized that their anti-HIV activity was the result of HIV integrase inhibition. Moreover, WO '323 states that these compounds “may be useful for treating the proliferation of the HIV virus, treating AIDS, or delaying the onset of AIDS or ARC symptoms.”¹⁵⁷

129. A second table (Table 2) reports results from another assay, designed to assess pregnane X receptor (PXR) activation as a tool to evaluate induction of cytochrome P450 3A (CYP3A).¹⁵⁸ CYP3A is a critical enzyme, known to the POSA to be implicated in drug metabolism. The table reports the %E_{max}, or percent effective concentration in relation to PXR activation with a positive control. PXR activation within a subset (75) of the ~100 examples tested for anti-HIV activity is reported.¹⁵⁹ The large majority of the tested compounds provided an EC₅₀ in the activity assay < 10 nM, while most compounds providing an EC₅₀ > 10 nM were

¹⁵⁶ See also Winkler Declaration (EX-1004) at ¶¶ 27, 79.

¹⁵⁷ WO '323 (EX-1005) at 212.

¹⁵⁸ *Id.* at 217–19.

¹⁵⁹ *Id.* at 216:1–219.

excluded. The ~75 compounds tested provided an %E_{max} within the range from 0% to 123%, with lower values in this table representing more desirable compounds.

130. Next, WO '323 reports a third table (Table 3) disclosing a compound's ability to inhibit the organic cation transporter OCT2. OCT2 is thought to be important in the renal excretion of cationic drugs; inhibitors of OCT2 may decrease OCT2-dependent renal clearance of other drugs, thus resulting in important drug-drug interactions.¹⁶⁰ Table 3 reports results from a smaller subset of compounds (23 of the ~100 examples).¹⁶¹ The table reveals a range of inhibitory concentrations (IC₅₀) from 42 to 10000 nM, with lower values in this table representing more desirable compounds.

131. Following the above *in vitro* assays, a series of *in vivo* experiments were performed on an even smaller subset of selected compounds (11 of the ~100 examples) to assess the pharmacokinetic properties of the subset.¹⁶² Each of the 11 compounds were administered to beagle dogs intravenously, and then a subset of 5 of those compounds were also administered orally.¹⁶³

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

¹⁶⁰ *Id.* at 220–21.

¹⁶¹ *Id.*

¹⁶² *Id.* at 222.

¹⁶³ *Id.* at 222:1–224 (including Table 4).

pharmacokinetics in the IV study. Specifically, as shown in the leftmost columns in Table 4 (annotated below), these compounds provided lower clearance (**CL**) values and a longer mean residence times (**MRT**) as compared with the 6 other compounds tested.¹⁶⁴

Table 4

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

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

¹⁶⁴ *Id.* at 223–24 (Table 4 (annotated in green to emphasize the 5 compounds selected for oral administration)).

compared to the remaining 6 compounds when administered intravenously (*see* expected $t_{1/2}$ below).¹⁶⁵

Compound	Half-Life ($t_{1/2}$) (h)
98	~2.4
83	~1.6
55	~2.9
77	~1.5
41	~5.1
42	~5.2
47	~5.0
8	~1.2
7	~1.6
3	~3.4
2	~4.6

Notably, compounds **41**, **42**, and **47** provided longer expected half-lives than compounds **2** and **3** (~5.0-5.2 h versus ~3.4-4.6 respectively), though the Gilead inventors selected each of these compounds for the oral study.¹⁶⁶

133. Table 4 reports results from the oral study including **F%**, or the fractional percentage of the drug dosage that reaches the therapeutic site of action (i.e., oral bioavailability), as well as the maximum plasma concentration (**C_{max}**) and area under curve (**AUC**) for compounds **2**, **3**, **41**, **42**, and **47**.¹⁶⁷ Among the tested

¹⁶⁵ Winkler Declaration (EX-1004) at ¶¶ 80–81.

¹⁶⁶ *See also* Winkler Declaration (EX-1004) at ¶ 81.

¹⁶⁷ WO '323 (EX-1005) at 223–24 (Table 4, right three columns).

compounds administered orally, compounds **42** and **2** had the highest oral bioavailability (**F%**), **C_{max}**, and **AUC** values.¹⁶⁸

134. A POSA would have understood from WO '323 that the Gilead inventors progressively narrowed the ~100 exemplary compound tested in the HIV activity assay (Example 104) based on their activity, data from PXR assay (Example 105; 75 of ~100 compounds tested) and OCT assay (Example 106; 23 of ~100 compounds tested), followed by an *in vivo* IV study (11 of ~100 compounds tested), and finally an *in vivo* oral study (5 of ~100 compounds tested) (Example 107). That POSA would have appreciated that Gilead used these assays to hone in on the most desirable INSTI compounds for treating the proliferation of the HIV virus, treating AIDS, or delaying the onset of AIDS or ARC symptoms upon oral administration. In my opinion, this was not surprising given that oral administration e.g., single tablet regimens for ART, had long been favored for HIV treatment.¹⁶⁹ And based on the half-lives (**t_{1/2}**), **F%**, **C_{max}**, and **AUC** values reported in Table 4 (above), the POSA would have specifically selected compounds **42** and **2** for further study, e.g., in the clinic.¹⁷⁰

¹⁶⁸ See also Winkler Declaration (EX-1004) at ¶¶ 83–84.

¹⁶⁹ See e.g., Section V.B, ¶¶ 66–68.

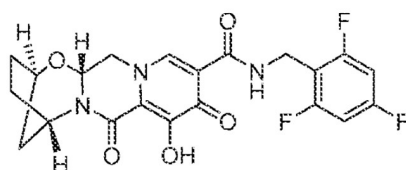
¹⁷⁰ See also Winkler Declaration (EX-1004) at ¶¶ 84–85.

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

Example 42

Preparation of Compound **42**

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



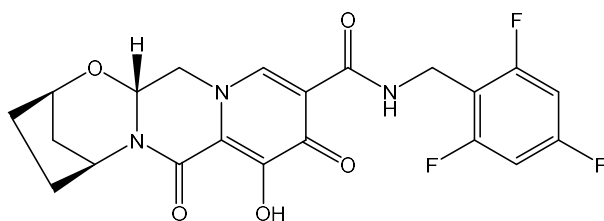
42

I understand that this “Compound 42”¹⁷¹ corresponds to Gilead’s compound with code name “GS-9883” and is now known as bictegravir (BIC).¹⁷² Dr. Winkler provides different structural orientations for compound **42**, including the following structure that corresponds to Formula (I) in the Challenged Claims.¹⁷³

¹⁷¹ WO '323 (EX-1005) at EX-1005 at 99:8–101:25. (the chemical structure on the right is also bictegravir, drawn in a different orientation).

¹⁷² See 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) (EX-1039) at 7086. This later correlation between compound **42**, GS-9883, and BIC does not factor into the analysis and opinions set forth herein.

¹⁷³ Winkler Declaration (EX-1004) at ¶ 74.



Compound 42 (BIC)

Dr. Winkler also identifies the chemical structure of compound **2** and notes its close structural similarity to compound **42**.¹⁷⁴

136. WO '323 confirms that “[a] goal of antiretroviral therapy is to achieve viral suppression of in the HIV infected patient,” and it refers to the 2013 version of DHHS treatment guidelines.¹⁷⁵ WO '323 also notes that “achievement of viral suppression requires the use of combination therapies, i.e., several drugs from at least two or more drug classes,” and that drug regimen choices are complicated where patients are receiving treatment for other medical conditions, as “the potential for drug interaction is a criterion for selection of a drug regimen.”¹⁷⁶ On this basis, WO '323 reported that a need existed (at the time) “for antiretroviral therapies having a decreased potential for drug interactions,” and “for new agents that inhibit

¹⁷⁴ Winkler Declaration (EX-1004) at ¶¶ 85 (Table 4 analysis and structural comparison of compounds **42** and **2** showing identical structures except for an additional fluorine atom on the phenyl ring of compound **42**).

¹⁷⁵ WO '323 (EX-1005) at 2:22–3:6.

¹⁷⁶ *Id.* at 2:22–3:2.

the replication of HIV” while also reducing drug interactions “when co-administered with other drugs.”¹⁷⁷

137. WO '323 also discusses “combination therapy,” and states that one embodiment of the inventions disclosed in the publication involves administering a therapeutically effective amount of “a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents.”¹⁷⁸ The publication then details what it means by such “additional therapeutic agents” by listing multiple classes of antiretroviral compounds, including the NRTI emtricitabine (FTC) and the NtRTI tenofovir alafenamide fumarate (TAF), among the list.¹⁷⁹

138. WO '323 further notes that when “a compound disclosed herein is combined with one or more additional therapeutic agents,” the administration can be “as a simultaneous or sequential regimen.”¹⁸⁰ The same combinations are, in certain embodiments, “*in a unitary dosage form* for simultaneous administration to a patient, for example as a solid dosage form for oral administration[.]”¹⁸¹ and WO

¹⁷⁷ *Id.* at 3:2–6.

¹⁷⁸ *Id.* at 37:7–12.

¹⁷⁹ *Id.* at 37:20–39:23 (emtricitabine at 38:14; tenofovir alafenamide fumarate at 38:19–20; dolutegravir at 38:28).

¹⁸⁰ *Id.* at 40:13–15.

¹⁸¹ *Id.* at 40:18–20 (emphasis added).

'323 identifies a tablet as a single dosage unit.¹⁸² In my opinion, a POSA would have understood from WO '323 that an INSTI compound, especially one with good oral bioavailability. e.g., compound **42** (*supra*), would be an optimal choice for combination with additional anti-HIV compounds such as FTC and TAF fumarate into a single oral dosage, including in a tablet, allowing for simultaneous administration. Such dosage forms contained therapeutically effective amounts of each anti-HIV agent.¹⁸³

139. Importantly, WO '323 also confirms that a skilled artisan, “[f]or purposes of administration,” may prepare pharmaceutical compositions where compounds are mixed with acceptable carriers, diluents, or excipients “in an amount which is effective to treat a particular disease or condition of interest.”¹⁸⁴ WO '323 reports that “the activity of compounds of Formula (I) can be determined by one skilled in the art,” and it notes in particular that the *in vitro* and *in vivo* examples (discussed above) can be used to assess activity.¹⁸⁵

140. Upon determining activity, WO '323 states with regards to pharmaceutical compositions that “[a]ppropriate concentrations and dosages can be

¹⁸² *Id.* at 36:9–15.

¹⁸³ *Id.* at 37:7–21.

¹⁸⁴ *Id.* at 35:9–23

¹⁸⁵ *Id.* at 35:14–16.

readily determined by one skilled in the art.”¹⁸⁶ It also states that a “therapeutically effective amount can be determined routinely by [a POSA] having regard to their own knowledge, the state of the art, and this disclosure.”¹⁸⁷ A POSA would have appreciated that “a tablet [which] may be a single dosage unit”¹⁸⁸ would have been suitable, and in fact preferred for oral administration..

141. In my experience, these are accurate observations, and the POSA would agree. Once the anti-HIV activity of a compound is established, an appropriate (or therapeutically effective) amount of that compound for treating HIV¹⁸⁹ (e.g., by oral administration) can be readily determined by the POSA using routine pre-clinical and clinical experimentation, e.g., the beagle dog studies from Example 107 in the WO ’323 patent. *See e.g.*, Section V.E (discussing routine dose ranging studies for the INSTIs DTG and EVG, where doses that reduced HIV viral load were identified and considered efficacious). This would have included, of course, the preparation

¹⁸⁶ *Id.* at 35:16–17.

¹⁸⁷ *Id.* at 16:19–21; *see also id.* at 36:31–37:5 (noting that a therapeutically effective amount considers factors such as the activity of the specific compound employed; the metabolic stability and length of action of the compound; the age, weight, general health, sex, and diet of the patient of the patients; the mode and time of administration; the rate of excretion; the drug combination; the severity of the particular disorder or condition; and the subject undergoing therapy).

¹⁸⁸ *Id.* at 36:13.

¹⁸⁹ As noted in Section V.E, treatment in WO ’323 includes preventing the appearance of symptoms and/or preventing viral load from reaching detectable levels post-exposure to the HIV virus. *See* WO ’323 (EX-1005) at 16:22–32.

of a tablet containing an appropriate (or therapeutically effective) amount of a disclosed INSTI compound for “treatment” as defined in WO ’323¹⁹⁰, which “may be a single dosage unit.”¹⁹¹ According to WO ’323, such a composition would have also been readily “prepared by methodologies well known in the pharmaceutical art.”¹⁹²

142. WO ’323 also discloses combination therapy for the treatment of HIV infection where a “therapeutically effective amount of a compound disclosed herein[, e.g., INSTI compound **42** that a POSA would have preferred for oral administration], or a pharmaceutically acceptable salt thereof” is administered in combination with a “therapeutically effective amount of one or more additional therapeutic agents[,]” including in a single composition containing each agent and a pharmaceutically acceptable carrier, diluent or excipient.^{193,194,195} Thus, a POSA would have understood WO ’323 to disclose single tablets containing a

¹⁹⁰ *Id.* at 36:31–37:5.

¹⁹¹ *Id.*

¹⁹² *Id.* at 36:22–23.

¹⁹³ *Id.* at 37:7–16.

¹⁹⁴ *Id.* at 16:8–21 (defining “therapeutically effective amount” as “an amount . . . sufficient to effect treatment of disease-states conditions or disorders for which the compounds have utility,” which can be “determined routinely by one of skill in the art having regard to their own knowledge, the state of the art, and this disclosure.”).

¹⁹⁵ *Id.* at 16:22–32 (defining “treatment” to mean “the administration of a compound or composition according to the present invention to alleviate or eliminate symptoms of HIV infection and/or to reduce viral load in a patient.”).

therapeutically effective amount of an INSTI, e.g., preferred compound **42**, and therapeutically effective amounts of anti-HIV agents such as FTC and TAF fumarate.

143. WO '323 discloses therapeutically effective amounts in the range of “about 25 mg to about 500 mg,” including specific doses of 25 mg, 50 mg, and 100 mg.¹⁹⁶ A POSA would have known and expected from WO '323 that: (1) more active compounds of Formula (I) (smaller EC_{50} values) would be orally administrable at lower doses within this range, (2) compounds having lower clearance rates (CL) and longer residence times (MRT) (and longer half-lives ($t_{1/2}$)) would be orally administrable at lower doses within this range, and (3) that compounds with higher oral bioavailability ($F\%$) would be orally administrable at lower doses within this range. That person also would have agreed with Gilead’s statement in WO '323 that factors such as the age and weight of the patient and the severity of the disease to be treated would have an impact on dose, e.g., lower doses within the “about 25 mg to about 500 mg” range would be appropriate and therapeutically effective in children and lower weight individuals, and also patients with less severe conditions, e.g., those exposed to HIV-1 but without symptoms and/or without detectable levels of HIV in the blood.

¹⁹⁶ *Id.* at 35:16–23.

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

145. In the claims set forth at the end of WO ’323, claim 32 lists compound **42** as the first among a group of 7 structurally related compounds of Formula (I).¹⁹⁷ Notably, four of the seven compounds are those tested in the oral administration assay in Example 107.¹⁹⁸ Claim 33 then refers to the compounds of claim 32, as part of “[a] pharmaceutical composition comprising a compound” of claims 1–32, “or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.”¹⁹⁹ Claims 34 and then 35 (in sequence) then recite the further addition of “one or more additional therapeutic agents” and “anti-HIV agents”

¹⁹⁷ *Id.* at 240–41.

¹⁹⁸ *See* Winkler Declaration (EX-1004) at ¶ 78 (correlating to compounds of claim 32 with compound numbers, which include orally tested compounds **2**, **3**, **41**, and **42**).

¹⁹⁹ WO ’323 (EX-1005) at 241.

respectively to the pharmaceutical compositions of claim 33, which includes compositions containing a compound of claim 32.²⁰⁰ Finally, claim 36, incorporates claim 35, and recites several classes of HIV agents from which additional agents are selected, including the classes of NRTIs and NtRTIs that contain emtricitabine (FTC) and TAF fumarate according to the specification (*supra*).²⁰¹

B. Disclosures and Suggestions to a POSA from WO '351 (EX-1006)

146. WO '351 (EX-1006) is a patent application filed by Ratiopharm GMBH, a pharmaceutical company in Denmark, that published on February 19, 2015.²⁰² The abstract²⁰³ provides a concise summary of its content, as follows:

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

As can be seen, applicant Ratiopharm disclosed the combination of the “second generation” INSTI DTG with emtricitabine and tenofovir (or a prodrug of tenofovir) for use as a medication for the treatment of HIV.²⁰⁴ The application also discusses the results from a phase 3 clinical study (published in 2013), where DTG (50 mg)

²⁰⁰ *Id.*

²⁰¹ *Id.*

²⁰² WO '351 (EX-1006).

²⁰³ *Id.* at [57].

²⁰⁴ *Id.*

was compared to “first generation” INSTI raltegravir (RAL) (400 mg), both in further combination with one of two known N(t)RTI-backbones.²⁰⁵ WO ’351 reports that the study found DTG to be a “suitable alternative to” RAL, but that the combinations in the clinical study “seem to be improvable in view of their effic[a]cy and/or safety.”²⁰⁶

147. WO ’351 then specifically discloses pharmaceutical combinations employing DTG as the anchor drug, with the N(t)RTI backbone of FTC and “tenofovir or a prodrug thereof,” e.g., TAF, including combinations with specific amounts of each compound for the treatment of HIV infection.²⁰⁷ When identifying DTG, the publication includes pharmaceutically acceptable salts, and particularly prefers the sodium salt.²⁰⁸ The salt form of TAF is preferably a “hemifumarate or fumarate” salt, and “especially the hemifumarate, and FTC is preferably used in its free base form.”²⁰⁹

²⁰⁵ *Id.* at 2:14–21.

²⁰⁶ *Id.* at 2:21–26.

²⁰⁷ *Id.* at 3:22–26 (amounts of compounds taken together are effective to treat HIV infection in a human); *see also id.* 4:1–9 (DTG is an INSTI) 6:24–32 (FTC is an NRTI), 9:4–25 (TFV and its prodrugs are NtRTIs).

²⁰⁸ *Id.* at 4:22–25 (the term “dolutegravir” comprises all the pharmaceutically acceptable salts thereof; dolutegravir can be obtained according to procedures outlined in WO 2006/116764 or WO 2010/068253), 5:21–27 (dolutegravir sodium salt particularly preferred).

²⁰⁹ *Id.* at 5:22–27 (DTG sodium), 13:16–18 (TAF fumarate or hemifumarate), 8:10–11 (emtricitabine free form).

148. The pharmaceutical combinations of WO '351 are administered once daily “preferably [as] a solid oral dosage form ... in particular a tablet.”²¹⁰ Specific pharmaceutical combinations include those containing about 50 mg DTG, about 200 mg of FTC, and about 25 mg of the prodrug tenofovir alafenamide (TAF).²¹¹

149. The total amount of active ingredients of the compositions disclosed in WO '351 that use TAF as the tenofovir prodrug are reported as preferably in the range of 192–326 mg per day,²¹² which covers particular embodiments with 50 mg DTG, 25 mg TAF, and 200 mg FTC, i.e., 275 mg of total active ingredients.²¹³

150. WO '351, consistent with similar teachings in WO '323, generally discloses the preparation of pharmaceutical compositions,²¹⁴ which includes the use of excipients “with which the person skilled in the art is familiar, such as those which are described . . . in the US Pharmacopeia (USP).”²¹⁵ WO '351 also lists six categories of excipients commonly used to prepare such compositions, which are taught to be present in certain ranges of amounts, each based on the total weight of the oral dosage form.²¹⁶ As explained further below, pharmaceutical tablets

²¹⁰ *Id.* at 17:27–28, 23:6–8 (emphasis added).

²¹¹ *Id.* at 19:30–20:2.

²¹² *Id.* at 17:17–18, 19:5–12.

²¹³ *Id.* at 19:30–20:2.

²¹⁴ WO '323 (EX-1005) at 35–36.

²¹⁵ WO '351 (EX-1006) at 20:24–27.

²¹⁶ *Id.* at 20:29–23:17.

containing 275 mg of total active ingredients and excipient amounts in the preferred ranges disclosed in WO '351 provide total tablet weights less than 730 mg, where the INSTI DTG is present in an amount less than 15% and less than 11% of the total weight of the tablet.

151. WO '351 also reports on the results of a pre-clinical study testing the anti-viral activity of three compositions, comparing the “second generation” INSTI DTG (50 mg) coupled with two different N(t)RTI pairs.²¹⁷ In one part of the study, two compositions using DTG (50 mg) as an anchor for the N(t)RTI pair of FTC (200 and 100 mg) and TDF (300 and 150 mg) are used.²¹⁸ The study also used a comparator composition (named “Trii-572”) that uses DTG (50 mg) to anchor the N(t)RTI pair of lamivudine (300 mg) and abacavir (600 mg).²¹⁹

152. All three compositions were tested in CEM-M7 cells infected with HIV-1 NL4-3 (wild type) and dolutegravir resistant HIV-1 R263K.²²⁰ The combinations using DTG to anchor the N(t)RTI pair of FTC + TDF are reported to “show[] unexpected and significantly better anti-viral activity than the combination

²¹⁷ *Id.* at 25:1–13.

²¹⁸ *Id.* at 25:7–13.

²¹⁹ *Id.* at 25:4–5.

²²⁰ *Id.* at 23:19–24:13.

of the product Trii-572,” the latter of which is said to be “promising in clinical trials and expected to be launched in the future.”²²¹

C. Disclosures and Suggestions to a POSA from US '079 (EX-1007)

153. US '079 (EX-1007) is a patent application filed by Cipla that was published on August 20, 2015. It claims priority to an application filed in India on October 23, 2012, and is drawn generally to pharmaceutical compositions that combine an INSTI with at least one other anti-HIV drug compound in a single oral dosage form.²²²

154. US '079 confirms that scientists in this time frame knew that for the successful treatment of HIV infection, it was necessary to administer “a combination of antiretroviral drugs (ARV) taken together.”²²³ US '079 also observes that the available drug regimens at the time were “far from ideal,” due to HIV strains in patients developing “resistance to one or more of antiretroviral medications.”²²⁴ US '079 emphasizes that successful therapy depends upon adherence by patients to the prescribed regimen, and that “the combination of antiretroviral drugs administered

²²¹ *Id.* at 25:15–26:15.

²²² US '079 (EX-1007) at 2, ¶ [0029].

²²³ *Id.* at 1, ¶ [0005].

²²⁴ *Id.* at 1, ¶ [0012].

in a single unit dosage form may result in increased patient compliance as the pill burden is reduced and dosing schedules are simplified.”²²⁵

155. US '079 prefers that the pharmaceutical composition comprises dolutegravir (DTG), tenofovir (TFV) and emtricitabine (FTC) or lamivudine (3TC) with one or more pharmaceutically acceptable excipients, where DTG is preferably present in the range of 25 to 50 mg.²²⁶ It then discloses an example of this embodiment (Example 7)²²⁷ which (in a single tablet) combines the INSTI DTG with tenofovir and emtricitabine, as follows:

²²⁵ *Id.* at 2, ¶ [0022].

²²⁶ *Id.* at 3, ¶¶ [0044, 0055]

²²⁷ *Id.* at 9–10, ¶ [0129].

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

A POSA would have appreciated that this single tablet includes DTG (50 mg) as an anchor to the DHHS preferred N(t)RTI backbone of FTC (200 mg) + TDF (300 mg), each in an amount approved by the FDA in different drug products, e.g., 50 mg DTG in Tivicay® and Triumeq®, 300 mg TDF and 200 mg FTC in Truvada® and Stribild®, and therefore considered preferred by the POSA.²²⁸ The total uncoated weight of this particular tablet is 1030 mg, and roughly half (550 mg) of the tablet weight is attributable to the three active ingredients. Here, the INSTI DTG is present in an amount or ~5% of the total tablet weight, which is less than 15% and less than 11%

²²⁸ See Section V.A–B.

of the total weight of the tablet. This tablet also combines all three active ingredients together in a dry mix of excipients before a binder is added, followed by blending and lubrication before being compressed into a tablet and then coated.²²⁹ The final coated tablet weighs 1055 mg.²³⁰ As explained below, a POSA would have known that the total weight of this tablet would be reducible if the total active ingredient weight was reduced. As such, a POSA motivated to replace 300 mg of TDF with 25 mg of TAF, e.g., as disclosed and preferred in WO '351, would have expected for a significant reduction in total tablet weight based on a lowering of active ingredient weight from 550 mg to 275 mg, which would allow for less excipients than the tablet of Example 7.

IX. OBVIOUSNESS ANALYSIS

156. I have set forth in Section III of this declaration my understanding of the legal requirements that pertain to an assessment of whether a patent claim is considered obvious, and therefore not patentable. The following analysis is conducted in consideration of those requirements, including whether a POSA would have been motivated to combine the disclosures of certain references to arrive at the tablets of the Challenged Claims with a reasonable expectation of success.

²²⁹ *Id.* at 10, ¶ [0130].

²³⁰ *Id.* at 9, ¶ [0129].

157. I provide a summary of the background scope and content of the prior art in Section V (*supra*). I further provide a summary of WO '323, WO '351, and US '079 in Section VIII which alone and/or in combination disclose (or at least suggest) each element of the Challenged Claims. In my opinion, a POSA would have been motivated to arrive at the tablets of the Challenged Claims with a reasonable expectation of success based on the combination of WO '323, WO '351, optionally in further combination with US '079, that person's common knowledge, routine practices in the art, and the general state of the art as discussed in Section V. Again, I provide in **Appendix B** a detailed summary table containing specific citations for where, in each reference, the claim elements are generally or specifically disclosed. The following analysis is conducted from the standpoint of a POSA prior to November 9, 2015, as defined in Section IV above. For the avoidance of doubt, each of Sections III–V and VIII are also incorporated herein.

158. In this Section, I provide analyses and opinions concerning any differences between the subject matter of the Challenged Claims patent and the specific combinations of WO '323 and WO '351, and WO '323, WO '351, and US '079. I also provide analyses and opinions for the combination of WO '323, WO '351 with additional publications (Bowker and Paulekuhn) based upon Dr. Winkler's opinions on the selection of the sodium salt of compound **42** (BIC) from WO '323. I further provide analyses and opinions to support that a POSA, given the

scope and content of art available prior to November 9, 2015, had many motivations to combine the teachings of WO '323, WO '351, and optionally US '079 (summarized in Sections VIII.A–C above), to achieve these differences and arrive at the subject matter of the Challenged Claims.

159. This section further contains my opinions concerning whether the POSA, prior to November 9, 2015, would have reasonably expected to succeed in preparing tablets that meet the limitations of the Challenged Claims (as arranged in the claims) in light of the combination of WO '323 and WO '351 and optionally U.S. '079.

160. Finally, this section addresses a POSA's motivation to select compound **42** (BIC) and especially its sodium salt for combination with TAF fumarate or hemifumarate, and FTC free base in a single tablet in the amounts recited in the Challenged Claims. To support some of my opinions, I rely on the analyses and opinions of Dr. Jeffrey Winkler (EX-1004) relating to *inter alia* structural and biological similarities between compound **42** (BIC) and DTG, the selection of compound **42** (BIC) from WO '323 from the perspective of an ordinarily skilled medicinal chemist, and the specific selection of sodium as a pharmaceutically acceptable salt for compound **42** (BIC) based upon its structural similarity to DTG, and optionally additional prior art disclosures, i.e., Bowker and Paulekuhn, on salt

selection for weakly acidic compounds such as DTG and compound **42** (BIC) and the prevalence for sodium salts in FDA-approved drugs.²³¹

161. As I explain below, it is my professional opinion from the viewpoint of a POSA, prior to November 9, 2015, that no claim of the '802 Patent is patentable under the law of obviousness, when considered in the context of the analysis I present in this declaration.

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

162. I have explained in some detail in Section V.B above that, prior to November 9, 2015, several physicians (including myself) were prescribing the “second generation” INSTI DTG in a single tablet (Tivicay®), and combining that tablet with another prescription for the N(t)RTI pair of emtricitabine (FTC) and tenofovir disoproxil (TDF) in a second tablet (Truvada®).²³² The N(t)RTI pair of FTC and TDF was a backbone recommended by DHHS, and was preferred over the N(t)RTI pair of ABC/3TC at the time for the reasons I have already explained above (Section V.B).

²³¹ See generally Winkler Declaration (EX-1004) at Sections V.C.2 and V.D.

²³² Section V.B, ¶¶ 66. This particular regimen was also specifically recommended by the 2015 DHHS Guidelines. See EX-1014 at 82 (“On the basis of clinical trial data, the Panel categorizes DTG in combination with either ABC/3TC or TDF/FTC as a Recommended regimen in ART-naïve patients.”).

163. In addition, as explained in Section V, DTG was preferred over the approved “first generation” INSTIs RAL and EVG because it offered the combination of once-a-day dosing without the need for a pharmacokinetic booster such as COBI, a higher genetic barrier to resistance to mutation than RAL and EVG, and maintained activity toward mutated strains of HIV integrase including those with known resistance to RAL and EVG.²³³ The use of TAF as an improvement over TDF that would be administered at ~10 times lower dose was also well known at the time.²³⁴

164. The only single tablet regimen containing the preferred INSTI DTG available prior to November 9, 2015 was Triumeq[®], a product that combined DTG with the N(t)RTI backbone ABC/3TC. Triumeq[®] required screening patients for the HLA-B5701 allele, as patients with this allele could experience severe hypersensitivity reactions due to ABC.²³⁵ As Triumeq[®] was not active against HBV, treatment could also result in severe acute exacerbation of hepatitis B (HBV) in patients co-infected with HIV and HBV.²³⁶ As explained above, the 2015 DHHS Guidelines included the combination of DTG with TDF/FTC (administered as two separate tablets) as an option, as this combination was known to provide fewer

²³³ See e.g., Section V.B, ¶¶ 65–66 (DTG was the preferred INSTI).

²³⁴ See e.g., Section V.C, ¶¶ 69–72 (benefits of TAF over TDF were known).

²³⁵ See Section V.B, ¶ 61.

²³⁶ *Id.*

treatment complications than the Triumeq[®] combination, and had become the preferred combination by physicians.²³⁷

165. Further, prior to November 9, 2015, a single tablet regimen that also employed TAF paired with FTC as the N(t)RTI backbone would have been recognized by the POSA as an improvement over TDF.²³⁸ TAF had (by then) been recognized as a safer prodrug of tenofovir, which would be dosed in a much lower daily amount than TDF (25 mg vs. 300 mg). TAF was also reported to have a reduced effect on serum creatinine and is associated with reduced tubular proteinuria, both important clinical markers of chronic kidney disease, as well as significantly smaller changes in bone mineral density.^{239,240} Indeed, the POSA would have known that a fixed dose co-formulated tablet using TAF and FTC was in Phase 3 clinical trials prior to November 9, 2015,²⁴¹ and that TDF had already

²³⁷ See Section V.A, ¶¶ 57–59; and Sections V.B, ¶¶ 65–68.

²³⁸ See Section V.C. ¶¶ 69–72.

²³⁹ Astuti (EX-1026) at 11 (noting that “a 25 mg dose of TAF has shown greater [antiretroviral activity] than a standard 300 mg dose of TDF,” and recognizing “[t]he possibility to use small doses of TAF instead of TDF could further widen the [single tablet regimen] options” and confirming that studies substituting in TAF with other single table regimens were under way).

²⁴⁰ Sax (EX-1025), 55, 57.

²⁴¹ 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 Sept. 2, 2015 Press Release”) (EX-1036) (announcing that a pending Phase 3 clinical study evaluating its fixed-dose combination of FTC and TAF had met its 48 week objective).

been replaced with TAF to provide an improved single tablet regimen over Stribild[®] known as Genvoya[®].²⁴²

166. Gilead had also announced in September of 2015 that it had filed two additional drug applications seeking approval to use TAF in place of TDF in other single table regimens, along with a third investigation using TAF in yet another single regimen tablet.²⁴³ The POSA also would have also understood that the N(t)RTI pair of TAF/FTC anchored by an INSTI in a single tablet that could be given once-a-day without the need for a pharmacokinetic booster, would have provided a simpler, more convenient and safer dosage regimens than the ART regimens employing TDF/FTC combinations recommended by DHHS at the time , including the RAL + TDF/FTC (in 2 separate tablets) and EVG + TDF/FTC + COBI in the single tablet Stribild[®].^{244,245}

167. In my opinion, prior to November 9, 2015, a POSA would have recognized the need for a single tablet regimen containing a “second generation”

²⁴² Ex-1044 (Gilead 11/5/15 Press Release announcing approval of Genvoya)

²⁴³ Gilead September 2, 2015 Press Release (EX-1036) at 2 (describing the filing of NDAs with the FDA “for two other TAF-based HIV medicines,” and another “TAF-based regimen” with darunavir that was under investigation).

²⁴⁴ See Section V.A, ¶ 57; V.B, ¶ 66.

²⁴⁵ See Gilead 2014 10-K (EX-1030) at 3 (Gilead itself acknowledging that “single tablet regimens allow patients to adhere to a fully suppressive course of therapy more easily and consistently, which is critical for the successful management of the disease.”).

INSTI like DTG or a structurally related analogue, in combination with the N(t)RTI pair of FTC and tenofovir (as TAF), which would have allowed for a more convenient, simplified, and safer regimen for treating HIV-1 infection, and that would have improved patient adherence over the two tablet regimen recommended by the DHHS at the time.²⁴⁶ That person would have been particularly motivated, in view of design needs and market forces, to identify a “second generation” INSTI similar to DTG that was combinable with FTC and tenofovir (as TAF) in a single tablet to achieve the aforementioned benefits of convenience, increased safety, and improved patient adherence. A POSA would have appreciated that such a tablet would have been provided more efficiently and expeditiously if a single entity owned the rights, e.g., patent and marketing rights, to all three active ingredients.²⁴⁷

168. In my opinion, the need for a single tablet regimen with an N(t)RTI backbone of TAF/FTC, combined with a “second generation” INSTI having a higher genetic barrier to resistance than RAL and EVG given once daily without the need for a pharmacokinetic booster, would have motivated the POSA to prepare a single tablet with appropriate amounts, i.e., therapeutically effective amounts, of TAF, FTC, and a “second generation” INSTI similar to DTG for the treatment of HIV-1

²⁴⁶ See Section V.B, ¶¶ 67-68; Section VIII.C, ¶ 154.

²⁴⁷ See Section V.D, ¶¶ 76-79.

infection.²⁴⁸ Moreover, as explained above, a POSA additionally would have been motivated to prepare single tablet combining TAF and FTC with a commonly owned INSTI, i.e., one owned by Gilead, such that a single tablet regimen would have been provided to the public more efficiently and expeditiously than a single tablet containing, e.g., DTG (owned by ViiV) and TAF/FTC (owned by Gilead).²⁴⁹

169. As I also explain in Section V.D., my review of the patent literature confirms that at least two other pharmaceutical companies (Ratiopharm and Cipla) had already recognized the need for combining the “second generation” INSTI DTG with FTC and tenofovir (as TDF and TAF) in a single tablet, and had filed patent applications on the same.²⁵⁰ These applications, however, utilized DTG in combination with TDF (or TAF) and FTC, i.e., a combination that would have required the approval of competing pharmaceutical companies for any potential clinical evaluation or marketing to occur. Otherwise, such a combination would have to be delayed until the expiration of patents covering DTG (owned by ViiV), and TDF (or TAF) and FTC (owned by Gilead).

170. In this sense, it is important to reiterate that Gilead, in 2014, publicly acknowledged that Triumeq[®], a single tablet with DTG paired with N(t)RTI

²⁴⁸ See Sections V.E (dose ranging studies) and VIII.A, ¶¶ 140-142 (Gilead’s definitions of appropriate and therapeutically effective amounts in WO ’323).

²⁴⁹ See Section V.D, ¶¶ 76–79.

²⁵⁰ See Section V.D, ¶¶ 74–75.

backbone of ABC/3TC drugs, “could adversely impact sales of our HIV products[,]”²⁵¹ confirming a recognized need for POSAs working in the field to identify a similar single tablet containing a structurally similar “second generation” INSTI with the DHHS and physician preferred backbone of tenofovir and emtricitabine, and specifically the known improved backbone of TAF/FTC.

171. Prior to November 9, 2015, it had also been recognized that long term patient compliance and adherence to an ART drug combination would have been enhanced by the availability of a single tablet taken once-a-day.²⁵² In my opinion, the POSA would have also understood that a single tablet with a “second generation” DTG analog combined with TAF/FTC would benefit patients if it could be made smaller in size than other available single tablet regimens employing an INSTI combined with an N(t)RTI pair of ingredients, such as Stribild[®] and Triumeq[®] containing total active ingredient amounts of 800 mg (when considering COBI) and 950 mg respectively. The 2015 DHHS Guidelines also included oral dosage form size as a factor that is important to consider when individualizing a treatment plan

²⁵¹ Gilead 2014 10-K (EX-1030) at 34.

²⁵² See *e.g.*, *id.* at 3; see also Shah (EX-1023) at 506 (“Patients with HIV infection prefer once/day regimens, especially single-tablet regimens.”); Sax (EX-1025) at 52 (“Single-tablet regimens (STRs) represent a simple and convenient way for patients to maximize adherence and to control their HIV for many years.”).

to which a patient can commit.²⁵³ A POSA would have appreciated that smaller tablet sizes would be achievable simply by substituting the approved 300 mg dose of TDF with a significantly lower dose of TAF (i.e., 25 mg), because this change alone would reduce total API content by 275 mg.

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

173. In sum, based on my personal experience as well as my consideration of the material cited herein, the POSA prior to November 9, 2015 would have recognized a need for a simplified, single tablet regimen that provided a “second generation” INSTI (i.e., a once-a-day unboosted INSTI with a high genetic barrier to resistance), anchoring the N(t)RTI backbone of TAF/FTC. Moreover, in my

²⁵³ 2015 DHHS Guidelines (EX-1014) at 188 (stating that it is important to consider the patient’s daily schedule and “patient tolerance of pill number, size and frequency,” when devising a successful treatment design to which a patient can commit) (emphasis added).

opinion, the remarkable commercial success of other single tablet regimens marketed by that time would have provided the POSA (and Gilead itself) with a substantial underlying financial motivation to direct significant resources to offer such a tablet. Indeed, Gilead understood (at the time) that its HIV products “primarily compete with the fixed-dose combination products in the nucleotide/nucleoside reverse transcriptase inhibitors (NTRI) class,” and so a POSA would have been acutely aware of the need to develop an INSTI similar to DTG that could be used with Gilead’s leading N(t)RTI combination of TAF and FTC.²⁵⁴

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

174. A POSA would have recognized that the above needs for a single tablet regimen containing a “second generation” INSTI combined with TAF and FTC were already being addressed by WO ’323 and WO ’351.²⁵⁵ Indeed, these published patent applications filed by pharmaceutical companies, were directed to pharmaceutical compositions and methods for treating HIV infections with an INSTI compound combined with other anti-HIV compounds, including in a single dosage form.²⁵⁶ One (WO ’351) disclosed a single composition with 50 mg of DTG (preferably as DTG sodium), 25 mg of TAF (preferably as TAF fumarate or TAF

²⁵⁴ Gilead 2014 10-K (EX-1030) at 9.

²⁵⁵ See Section VIII.A, ¶¶ 137-38 (providing summary of WO ’323 (EX-1005); and Section VIII.B, ¶¶ 148-149 (providing summary of WO ’351 (EX-1006)).

²⁵⁶ *Id.*

hemifumarate), and 200 mg of FTC (preferably as a free base), and the other (Gilead's WO '323) disclosed a family of INSTI compounds which included compound **42** (BIC), along with compositions (including unit dosage forms such as tablets) containing a therapeutically effective amount of the INSTI compound, e.g., compound **42**, combined with therapeutically effective amounts one or more, such as two, anti-HIV agents, such as the NRTI FTC and the N(t)RTI TAF fumarate. These therapeutically effective amounts for the INSTIs disclosed in WO '323, e.g., compound **42**, include doses in the range of 25 mg to 500 mg, including specific doses 25 mg, 50 mg, and 100 mg.²⁵⁷

175. As I explain above in Section VIII.A, Gilead's WO '323 disclosed ~100 INSTI compounds sharing structural attributes to DTG, all of which were progressively narrowed through *in vitro* and *in vivo* screening to only five compounds given orally to beagle dogs.²⁵⁸ Two of those five compounds, i.e., compounds **42** and **2**, were shown to be markedly more orally bioavailable, and provided significantly higher $C_{\max}$ and AUC compared the other three.²⁵⁹ Compound **42** also provided longest half-life ($t_{1/2}$) and mean residence time (MRT) of the compounds tested, and compound **2** provided the largest oral bioavailability

²⁵⁷ See Section VIII.A. at ¶ 143-144.

²⁵⁸ WO '323 (EX-1005) at 222-24.

²⁵⁹ *Id.* at 223-24 (Table 4); see also Section VIII.A, ¶¶ 132-34; Winkler Declaration (EX-1004) at Section VI.A., ¶¶ 83-84.

(F%), C_{max} and AUC.²⁶⁰ Based on these more optimal pharmacokinetic properties, a POSA would have specifically selected compound **42** (along with compound **2**) from among the INSTI compounds disclosed in WO '323 as prime candidates for once-a-day administration.²⁶¹ After selection of compound **42**, in my professional opinion, its appropriate concentrations and dosages in a pharmaceutical composition, including therapeutically effective amounts for treating HIV, would have been routinely determined by a POSA, who would have considered and tested dosages in WO '323 such as 25 mg, 50 mg, and 100 mg.²⁶²

176. Indeed, a POSA would have known and expected from WO '323 itself that more active compounds of Formula (I) for WO '323 (smaller EC₅₀ values), compounds having lower clearance rates (CL) and longer residence times (MRT) (and longer half-lives), and compounds with higher oral bioavailability (F%) would be orally administrable at lower doses within the “about 25 mg to about 500 mg” range disclosed in WO '323. Compound **42** offered the combination of lower nanomolar activity, lower CL, longer MRT, and longer expected t_{1/2} compared to many other INSTI compounds disclosed in WO '323, and so a POSA would have

²⁶⁰ WO '323 (EX-1005) at 223–24 (Table 4); *see also* Section VIII.A, ¶¶ 132–34; Winkler Declaration (EX-1004) at Section VI.A., ¶¶ 80–84.

²⁶¹ *See also* Winkler Declaration (EX-1004) at ¶¶ 82–87.

²⁶² WO '323 (EX-1005) at 19:21, 35:15–17.

known that its therapeutically dose would be significantly lower than other compounds.

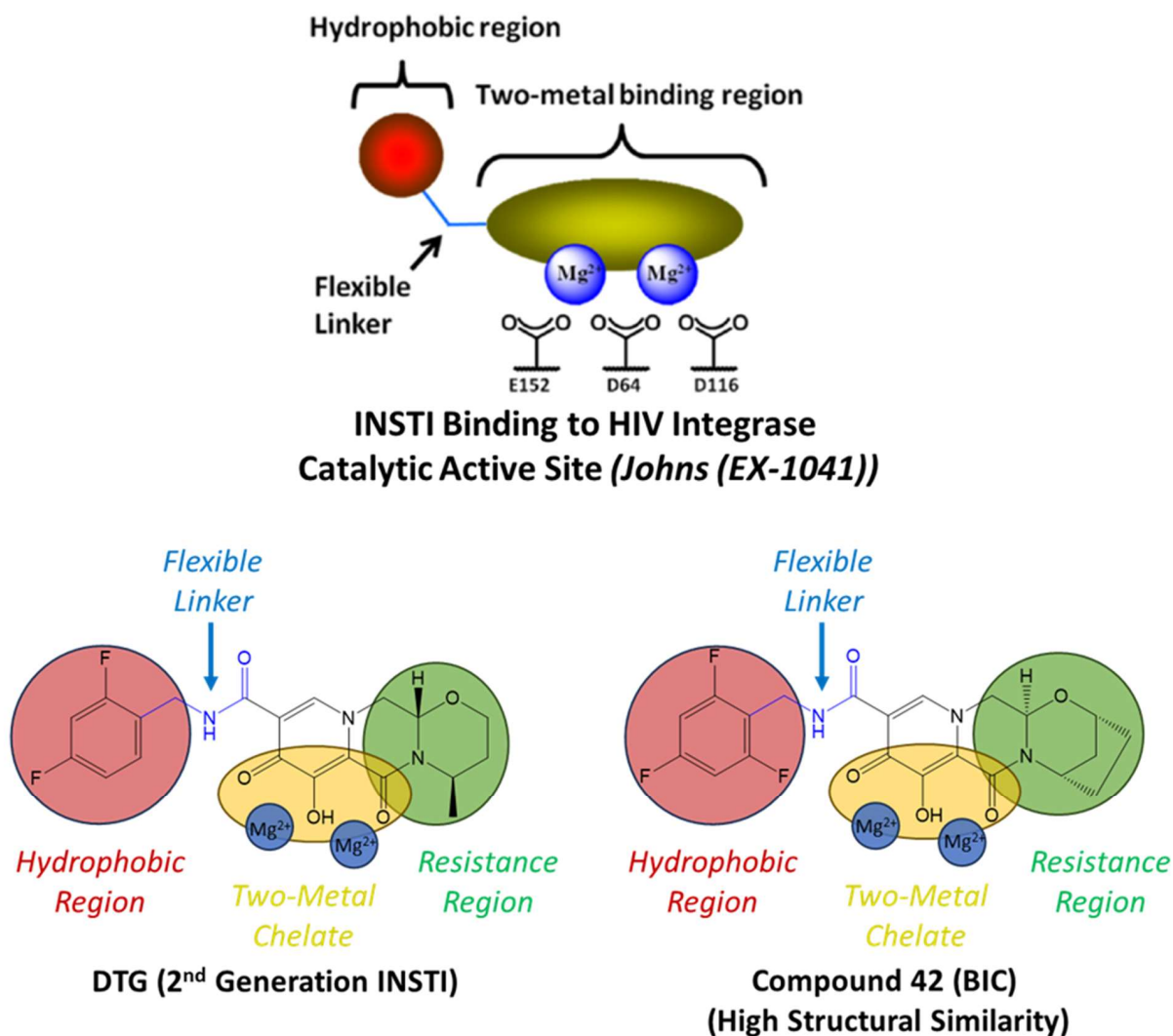
177. That POSA also would have known that factors such as the age and weight of the patient and the severity HIV to be treated would also have an impact on the dose, e.g., children and lower weight individuals would be orally administered lower doses within this range, as would patients with less severe disease states, e.g., those with exposure to the virus but without symptoms and/or without detectable levels of HIV in the blood.

178. WO '351 discloses similar pharmaceutical compositions, including tablets, where the “second generation” INSTI DTG (50 mg) is combined with TAF (25 mg) and FTC (200 mg).²⁶³ I have considered Dr. Winkler’s analyses and opinions regarding the large degree of structural similarity between compound **42** and DTG, including his opinion that an ordinarily skilled medicinal chemist would have expected that compound **42** (BIC) would have similar physicochemical and biological properties to DTG, an established, FDA approved, INSTI compound.²⁶⁴ In particular, I have considered Dr. Winkler’s specific analysis on the function of specific structural features present in both compound **42** (BIC) and DTG, that form

²⁶³ See Section VIII.B, ¶¶ 147-49.

²⁶⁴ *Id.* at ¶ 132-134; *see also* Winkler Declaration (EX-1004), Section VI at ¶¶ 74-77.

the basis of his opinion that compound **42** would provide a similar binding mode to the active site HIV integrase through a two-metal chelate, and an expected high genetic barrier to resistance and ability to maintain activity against HIV integrase in view of its structurally similar “resistance region.” For clarity, I reproduce an illustration from the Winkler Declaration (at ¶77) that I found useful to summarize his opinions.



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

179. Each of WO '323 and WO '351 include disclosures teaching the use of two (or more) and preferably three active ingredients in a single dosage form (including tablets) all designed to reduce replication of the HIV-1 virus and thus reduce viral load in HIV-1 infected patients. In my professional opinion, the POSA therefore would have had good reason to combine WO '323 and WO '351 when exploring options for a smaller, single tablet regimen compared to Triumeq® and Stribild®, that would treat HIV-1 infection with a “second generation” INSTI similar to DTG anchoring the DHHS preferred N(t)RTI backbone of emtricitabine and tenofovir, and especially a backbone of TAF/FTC.

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

180. I incorporate my discussion of WO '323 and WO '351 herein.

181. US '079 is an application filed by Petitioner (Cipla) that, like WO '323 and WO '351, seeks to solve the need in the art for a single tablet that could be given

once-a-day with a “second generation” INSTI anchoring the DHHS preferred N(t)RTI pair of emtricitabine and tenofovir.²⁶⁵ The additional disclosure of US ’079 also informs the POSA of available options for the precise amounts of additional ingredients to use when preparing such a tablet. It also discloses a preference for tablets due to their greater stability, smaller bulk, and ease of production.²⁶⁶ As discussed above in Section VIII.C, US ’079 also exemplifies a tablet containing 50 mg of “second generation” INSTI DTG as an anchor for the N(t)RTIs pair of TDF (300 mg) and FTC (200 mg) having a total API weight of 550 mg, a total uncoated weight of 1030 mg, and a coated weight of 1055 mg.²⁶⁷

182. In my opinion, the POSA would have been further motivated to combine US ’079 with both WO ’323 and WO ’351. This is because US ’079 also address the need in the art for a single tablet containing a “second generation” INSTI combined with the N(t)RTI pair of emtricitabine and tenofovir, and because it provides the POSA with additional guidance on the construction of single tablets, including the amounts of excipients contained those tablets.²⁶⁸ In essence, US ’079 independently confirms what Gilead stated in WO ’323: “[a]ctual methods of preparing such dosage forms [e.g., tablets] are known, or will be apparent, to those

²⁶⁵ US ’079 (EX-1007) at 2, ¶ [0029].

²⁶⁶ *Id.* at 5, ¶¶ [0078]–[0079] (disclosing single, bilayered or multilayered tablets).

²⁶⁷ *Id.* at 9–10, ¶ [0129] (Example 7).

²⁶⁸ *See* Section VIII.C, ¶¶ 153–55.

skilled in this art,” “[a]ppropriate concentrations and dosages [of INSTIs] can be readily determined by one skilled in the art[,]” and a “therapeutically effective amount” of compounds for treating HIV infection “can be determined routinely by one of ordinary skill in the art.”²⁶⁹ In my opinion, consistent with intent of the publications, a POSA would have been motivated to combine WO ’323, WO ’351, and US ’079 to address the need in the art for a single tablet regimen containing a “second generation” INSTI similar to DTG anchoring the N(t)RTI backbone of emtricitabine and tenofovir, and especially the TAF/FTC backbone.

B. Combining WO ’323 and WO ’351 Leaves Minor Differences Between the Challenged Claims and the Prior Art

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

184. With reference to the summary chart provided in **Appendix B** (and my summaries of WO ’323 and WO ’351 in Sections VIII.A–B and IX.A) above, the combination of WO ’323 and WO ’351 discloses the claimed tablet (*see* claim charts at **1[pre]**) containing a “second generation” INSTI compound (e.g., DTG or compound **42** (BIC)) in an amount of 50 mg including as a pharmaceutically acceptable salt thereof (e.g., DTG or BIC sodium) (*id.* at **1[a]**), TAF in an amount

²⁶⁹ WO ’323 (EX-1005) at 16:8–14, 16:19–25, 35:16–17.

of 25 mg including as a pharmaceutically acceptable salt thereof (e.g., TAF fumarate and hemifumarate) (*id.* at **1[b]**), and FTC in an amount of 200 mg or a pharmaceutically acceptable salt thereof (FTC preferred in free base (non-salt) form) (*id.* at **1[c]**).

185. WO '323 also teaches therapeutically effective amounts of it INSTI compounds, including compound **42** (BIC), in a unitary dosage form in combination with therapeutically effective amounts of other HIV agents (*id.* at **1[pre]**, **1[a]**), which include TAF fumarate (*id.* at **1[b]**) and FTC (*id.* at **1[c]**), and discloses pharmaceutically acceptable salts such as sodium salt. WO '351 specifically discloses a preference for the sodium salt of DTG, combined with a preference for TAF fumarate or hemifumarate and especially TAF hemifumarate, and FTC as free base (*id.* at **1[a]-1[c]**) and prefers tablets (*id.* at **1[pre]**).

186. WO '323 and WO '351, considered together, therefore leave only minor differences between the prior art and the claimed tablets. First, while the combination generally discloses the limitations of the Challenged Claims, it does not specifically disclose or exemplify a single tablet specifically containing 50 mg of compound **42** (BIC) (or 52 mg of its sodium salt) also containing 25 mg TAF (or its fumarate or hemifumarate salt, including 28 mg of TAF hemifumarate) and 200 mg of FTC (as free base). Second, though a POSA would have been drawn to lower doses in the range of “about 25 mg to 500 mg” based on compound **42**’s beneficial

combination of properties (*supra*), the WO '323/WO '351 combination does not specifically disclose a 50 mg dose for compound **42** (BIC) (or 52 mg its sodium salt). Third, for some of the dependent claims, the combination does not specifically disclose a compound **42** (BIC) as a sodium salt (claims 5, 8), a tablet with a total weight or less than 1000 mg, less than 800 mg, or less than 730 mg (claims 9-11), or a tablet having the required amounts of active ingredients where compound **42** (BIC) is present in less than 15% or less than 11% by weight of the total tablet (claims 12-13).

187. As I explain below, it is my opinion that a POSA would have been motivated to make each of these specific selections from the combined disclosure of WO '323 and WO '351 using their common knowledge of the art and routine methods in the art available prior to November 9, 2015. As I explain further below, that person would have also had, in my opinion, a reasonable expectation of success in making the tablets recited by the Challenged Claims, given the significantly advanced state of the art prior to November 9, 2015. And though not required by the claims, a POSA would have also reasonably expected that the claimed combination would be useful for the treatment of HIV infection.

1. **A POSA Combining WO ' 323 and WO '351 would have been Motivated to Arrive at These Differences with a Reasonable Expectation of Success**

188. My analysis below is presented in the order of the Challenged Claims, beginning with independent claim 1.

a. Claim 1

189. Claim 1 is drawn to a tablet comprising 50 mg BIC, 25 mg TAF, and 200 mg FTC, each of which may be present as a pharmaceutically acceptable salt.²⁷⁰

190. As explained in Sections VIII.A–B, IX.A.1, IX.B, and as shown in **Appendix B**, each of these limitations is disclosed by the combination of WO '323 and WO '351, except that the combination does not specifically disclose a tablet with the claimed doses of each ingredient, or the specific selection of a pharmaceutically acceptable salt of BIC (e.g., its sodium salt). WO '323 does, however, teach pharmaceutical compositions containing a therapeutically effective amount “a compound of Formula (I)” which includes embodiments containing seven discrete amounts that include 50 mg.²⁷¹ It also teaches compositions containing a therapeutically effective amount of a Formula (I) compound along with therapeutically effective amounts of one or more additional anti-HIV agents.²⁷²

²⁷⁰ '802 Patent (EX-1001) at 77:23–78:4.

²⁷¹ WO '323 (EX-1005) at 35:22–23.

²⁷² *Id.* at 37:7–13; 38:13–21.

Further, and perhaps most important to my analysis, WO '323 explicitly advises (and I agree) that “appropriate concentrations and dosages” of the compounds it discloses “can be readily determined by one skilled in the art[.]”²⁷³ and that a “therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to the own knowledge, the state of the art, and this disclosure.”²⁷⁴

191. WO '323 also provides results from relatively detailed and progressive series of *in vitro* and *in vivo* experiments that the POSA would have understood to be pre-clinical experimentation that was well-known for determining the activity of the INSTI compounds under investigation. WO '323 confirms “[t]he activity of compounds of Formula (I) can be determined by one skilled in the art, for example, as described in the Examples below,” and the POSA would have understood those examples to include the *in vitro* antiviral assay of Example 104.²⁷⁵ As explained above, WO '323 further discloses *in vivo* animal experiments that narrowed the disclosed INSTIs to only 5 compounds that progressed into oral dosing experiments.²⁷⁶ In my opinion (and in Dr. Winkler’s opinion), a POSA would have selected compound **42** (BIC) from among these compounds as a prime candidate based in its expected longer half-life ($t_{1/2}$) and mean residence time (**MRT**)

²⁷³ *Id.* at 35:16–17.

²⁷⁴ *Id.* at 16:19–21.

²⁷⁵ *Id.* at 35:14–16, 212:7–216:1.

²⁷⁶ *Id.* at 222–24 (including Table 4).

combined with its good oral bioavailability (**F%**) and promising **C_{max}** and **AUC**.²⁷⁷ That POSA would have also been motivated by the combination of WO '323 and WO '351 to select compound **42** (BIC) and include it into a single tablet in a therapeutically effective amount (that the POSA could routinely determine) combined with therapeutically effective amounts of TAF (25 mg in WO '351), and FTC (200 mg in WO '351).

192. A POSA would have appreciated that one important goal of INSTI development was to maintain once-a-day administration, and so would have preferred compounds to be both sufficiently bioavailable, and with a long enough half-life to support dosing once-a-day. Applying this criteria, the PK analysis from WO '323 also establishes to a POSA, in my opinion, that compound **42** would have been prime candidates for once-a-day administration in a tablet also containing TAF and FTC. Indeed, among those five compounds tested, compounds **2** and **42** provided the best PK properties for once daily dosing. Dr. Winkler shares my opinions,²⁷⁸ and also concludes that compound **42** bears a close structural similarity to the “second generation” INSTI DTG (disclosed in a composition comprising 50 mg, 25 mg TAF, and 200 mg FTC in WO '351) such that a POSA would have expected compound **42** (BIC) to share similar physicochemical and biological

²⁷⁷ See Section VIII.A, ¶¶ 132-134; Winkler (EX-1004) at ¶¶ 80-87.

²⁷⁸ Winkler Declaration (EX-1004), Section VI.A.

properties with DTG, including an ability for once-a-day dosing without a pharmacokinetic booster, and a higher genetic barrier to resistance to provide the ability to maintain activity toward HIV integrase mutants resistant to RAL and EVG.²⁷⁹ As such, a POSA would have been motivated to use a therapeutically effective amount of compound **42** (BIC) in the WO '351 composition containing 25 mg TAF and 200 mg FTC in the place of DTG.

193. Moreover, as I have explained in detail in Sections V.B and V.C., it is my opinion that the POSA would have recognized that the N(t)RTI pair of tenofovir and emtricitabine (as disclosed in WO '351) was a preferred backbone for ART therapy in treating HIV infections. As such, a POSA would have been motivated prepare a unit dose regimen similar to the DTG (50 mg)/TAF (25 mg)/FTC (200 mg) composition disclosed in WO '351, where DTG is replaced by a therapeutically effective amount of compound **42** (BIC). WO '351 also states a preference for single tablet compositions, and so a POSA would have been motivated to prepare this modified composition as a tablet.²⁸⁰ Moreover, the POSA would have also known that TAF (as disclosed in both WO '351 and WO '323) was a clear improvement over TDF in terms of safety profile and that TAF had proven to be therapeutically

²⁷⁹ Winkler Declaration (EX-1004), Section VI.A at ¶¶ 73–77, 87.

²⁸⁰ WO '351 (EX-1006) at 19:30–20:2, 23:6–8; *see also id.* at 5:22–27 (preference for DTG sodium), 13:16–18 (preference for TAF fumarate or hemifumarate), 8:10–11 (preference for FTC free base).

effective at a significantly lower dose (e.g., 25 mg TAF vs 300 mg TDF), and would have therefore opted for TAF over TDF.

194. In sum, the combination of WO '323 and WO '351 would have motivated a the POSA to prepare single tablets containing a therapeutically effective amount of INSTI compound **42** (BIC) and therapeutically effective amounts of TAF and FTC, i.e., 25 mg of TAF and 200 mg FTC as disclosed in WO '351. From there, as WO '323 advises (and I agree), a “therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to the own knowledge, the state of the art, and this disclosure,” meaning that therapeutically effective amounts of compound **42** (BIC) would have been determined by a POSA as a matter of routine experimentation, in view of the dose options disclosed in WO '323.²⁸¹ As explained above, a POSA would have been drawn to lower doses in the range of “about 25 mg to 500 mg” disclosed in WO '323 based on compound **42**'s beneficial combination of properties compared to many other disclosed INSTI compounds. The low end of this range includes doses in the range of 25 mg to 100 mg, and WO '323 also specifically discloses doses of 25 mg, 50 mg and 100 mg. A POSA would have been drawn to even lower amounts in the “about 25 mg to 500 mg” range in children and low weight individuals (who require less drug to achieve

²⁸¹ *Id.* at 35:16–17.

similar drug concentrations in the blood), and in patients with a lower severity of HIV-1 infection (or no detectable infection at all) who would be treatable with lower drug concentrations as well.

195. Considering the advanced state of the art by November 9, 2015, the POSA, in my opinion, would have identified specific doses and therapeutically effective amounts for compound **42** (BIC) falling in the lower end of the “about 25 mg to 500 mg,” by employing routine dose ranging studies like those discussed in Section V.E. These effective doses would have been readily incorporated into a tablet in combination with the N(t)RTI pair of TAF (25 mg)/FTC (200 mg) as disclosed by WO '351 (as a preferred alternative to 50 mg of DTG). Because the POSA would have routinely determined appropriate doses from clinical dose ranging studies, it is my opinion that the claimed 50 mg is not particularly significant, because a POSA would have arrived at that dose routinely when assessing dose levels that, e.g., provided suitable reductions in HIV RNA viral load. And again, lower doses also would expectedly be sufficient in children and low weight adults. Indeed, as explained above in Section V.E, multiple doses of the INSTI DTG were considered efficacious, including a dose five times smaller (10 mg) than the FDA approved dose of 50 mg, which like the 50 mg dose provided an HIV RNA count of <50 copies/mL in a large majority of patients at 96 weeks.

196. The same was true for Gilead's INSTI EVG, which was approved at a dose of 150 mg (when combined with COBI, TDF, and FTC) but was shown to effectively reduce viral load at lower doses, i.e., 50 mg and 125 mg.²⁸² And Gilead had also entered clinical evaluation of its compound GS-9983 (75 mg) combined with TAF (25 mg) and FTC (200 mg) after conducting a routine dose ranging study in a Phase 1b trial where GS-9883 was administered at doses including 50 mg and 100 mg. Though a 75 mg dose of GS-9883 was apparently selected as the recommended phase 2 dose, a POSA would have expected that the 50 mg dose would have also provided significant reductions in HIV RNA counts, just as had been shown for DTG and EVG. Indeed, there would be no basis to choose a 75 mg dose for phase 2 studies if a 50 mg dose failed to reduce viral load in the phase 1b study.

197. Moreover, compound 42 (BIC) provided a similar anti-HIV activity, half-life ($t_{1/2}$), and oral bioavailability (F%) to DTG, as follows²⁸³:

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

²⁸² See Section V.E (citing Zolopa (EX-1056) at 818).

²⁸³ See Winkler Declaration (EX-1004) at ¶¶ 67-68 (properties of DTG), 80-81 (properties of compound 42).

Given their substantial structural similar similarity and expectation of shared biological functions as discussed by Dr. Winkler,²⁸⁴ a POSA would not have been surprised to learn from routine dose determination studies that an effective amount of compound **42** would be similar to that of DTG.

198. Finally, as had been repeatedly shown by multiple teams of ordinarily skilled artisans prior to November 9, 2015, the development of FDA approved single tablets containing therapeutically effective amounts of three (and sometimes four) active ingredients to treat HIV-1 infection had been accomplished routinely several times.²⁸⁵

199. On these bases, is it my opinion that the POSA would have been motivated to arrive at the tablet of claim 1, and would have had a reasonable expectation of success in preparing it. Though not required, as explained in this section and above,²⁸⁶ that person would have also reasonably expected that such a tablet contained amounts of BIC, TAF, and FTC effective to reduce HIV-1 viral load in a patient. At the very least, the tablet of claim 1 would have expectedly been effective to prevent or reduce the risk of developing HIV-1 infection in patients

²⁸⁴ *Id.*

²⁸⁵ See Sections V.A. and D., *supra* (summarizing multiple FDA approved single regimen tablets with multiple APIs to treat HIV infection).

²⁸⁶ See *supra* Sections V.E. (summarizing routine dose determination and dose determination from WO '323) and VIII.A., ¶¶140-141 (appropriate dosages and therapeutically effective amounts can be routinely determined by a POSA).

exposed to the HIV virus, as covered by the term “treatment” in both WO ’323 and the ’802 Patent.²⁸⁷

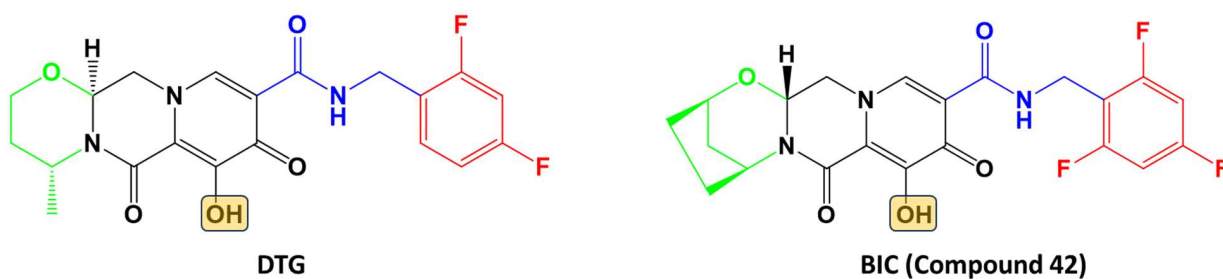
200. In my professional opinion, from the standpoint of a POSA and in view of the legal principles of obviousness above, claim 1 would have been obvious over the combination of WO ’323 and WO ’351 as informed by common knowledge and well-known technical principles discussed in Section V available prior to November 9, 2015.

b. Claims 2–8

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

²⁸⁷ See WO ’323 (EX-1005) at 16:22–32; ’802 Patent (EX-1001) at 57:32–52.

202. Dr. Winkler has conducted an analysis that focuses, from the perspective of an ordinarily skilled medicinal chemist, on what that person would have understood concerning the selection of a pharmaceutically acceptable salt of the INSTI compounds disclosed in WO '323.²⁸⁸ In particular, Dr. Winkler points to pharmaceutically acceptable salts in WO '323, including “salts derived from an appropriate base, such as an alkali metal (for example, sodium)[,]” and notes that the structurally similar INSTI DTG was preferred as a sodium salt in WO '351, that was being used in both Tivicay[®] and Triumeq[®].²⁸⁹ Dr. Winkler notes that compound **42** and DTG share an identical metal chelation binding group (black below) that contains the same acidic hydroxy group (yellow below), which was the only reasonable functionality for salt formation.²⁹⁰ I have reproduced below an illustration from Dr. Winkler’s report to summarize his analysis and opinion in this regard.²⁹¹



²⁸⁸ See generally Winkler Declaration, Section VI.B.

²⁸⁹ *Id.* at ¶¶ 88–89.

²⁹⁰ *Id.* at ¶ 90.

²⁹¹ *Id.*

203. Dr. Winkler further opines that an ordinarily skilled medicinal chemist would have expected that compound **42** (BIC) would form a sodium salt (using NaOH as base) in the same way as DTG, based on their expectedly similar low acidity (both are weak acids) and similar pKa.²⁹² He then concludes that a “POSA would have been specifically motivated to prepare a pharmaceutically acceptable salt of compound **42** (BIC) with sodium hydroxide (NaOH) to provide BIC sodium, and would have expected that it would be stable for the same reasons as the DTG sodium salt used in Tivicay®.” Dr. Winkler further opines that, “[b]ased on the high degree of structural similarity with DTG, and the improved solubility property of DTG sodium relative to the corresponding free acid, a POSA would have also expected for BIC sodium to be more soluble in an aqueous environment than BIC free acid, and thus a more suitable choice for oral administration.”²⁹³

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

²⁹² *Id.* at ¶ 91.

²⁹³ *Id.* at ¶ 92.

FTC and TAF free base and other salt forms of TAF.” I adopt his conclusions on these points for the same reasons.

205. Additionally, from the perspective of clinical practice in the relevant time frame, as I explain in Section V), among the FDA approved compounds, the “second generation” INST DTG was (in my experience) a preferred INSTI, as it was available for dosing once-a-day, without needing a booster.²⁹⁴ DTG was frequently used as a single 50 mg tablet, in combination with the N(t)RTI pair of tenofovir and emtricitabine.²⁹⁵ The single tablet containing a 50 mg dose of DTG was recognized to be effective as established during a dose-ranging clinical study, and was marketed as a sodium salt.²⁹⁶

206. Regarding pharmaceutically acceptable salts of TAF in claims 3–4 and the specific salts TAF fumarate and TAF hemifumarate in claims 6–8, these were also disclosed in WO ’351 as particularly preferred options to combine with the structurally similar INSTI DTG in a single tablet regimen.²⁹⁷ WO ’323 also identifies TAF fumarate as a salt of TAF that is suitable for use in the combinations disclosed and claimed in the reference.²⁹⁸ Moreover, Gilead’s combination product

²⁹⁴ Tivicay Label (EX-1022).

²⁹⁵ See Section V.A, ¶¶55-57.

²⁹⁶ Tivicay Label (EX-1022) at 14.

²⁹⁷ WO ’351 (EX-1006) at 13:16–18, 19:30–20:6 (Single Tablet with 50 mg DTG, 25 mg TAF, 200 mg FTC).

²⁹⁸ WO ’323 (EX-1005) at 38:19–20.

Genvoya® was approved on November 5, 2015, employing the hemifumarate salt of TAF.²⁹⁹

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

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

²⁹⁹ Gilead 11/5/15 Press Release (EX-1044) at 1.

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

c. Claims 9–11

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

211. WO '351 describes single tablet compositions where the total amount of DTG, TAF, and FTC are preferably in the range of 192–326 mg per day.³⁰⁰ The same publication discloses a preferred design with 50 mg DTG, 25 mg TAF, and 200 mg FTC, which would have a total active ingredient weight of 275 mg. WO '351 also includes a description³⁰¹ of “suitable pharmaceutical excipients,” organized into six categories, as follows:

³⁰⁰ WO '351 (EX-1006) at 17:17–18, 19:5–12.

³⁰¹ *Id.* at 20:29–30.

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

212. The total weight of each of these excipient categories, as described by WO '351, will vary within stated “preferable,” “more preferable,” and “in particular” ranges for each category.³⁰² Each of the ranges disclosed were provided as a percentage of the total weight of the composition.³⁰³ I have prepared the following chart that summarizes the amounts of the most preferred (i.e., “in particular”) ranges for each excipient category, along with the expected total weight for a composition containing 275 mg of total active ingredients (i.e., 50 mg DTG, 25 mg TAF, and 200 mg FTC) at each endpoint of these ranges as well as a midpoint for each range:

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

³⁰² *Id.* at 20:29–22:25.

³⁰³ *Id.*

Total Tablet Weight (with 275 mg total active pharmaceutical ingredient)	~330 mg – ~410 mg	~410 mg	~370 mg	~330 mg
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213. As shown above, the low end of the preferred “in particular” set of ranges produces a total weight percent of excipients of ~17% and the high end of this set of ranges produces a total weight percent of excipients of ~32%, based on the total weight of the composition.³⁰⁴ The 275 mg total weight of active ingredients makes up the rest of the total weight of these compositions: ~83 weight percent of total actives for the lower end of the excipient ranges and ~68% weight percent of total actives for the high end of the excipient ranges, based on the total weight of the composition. Accordingly, based on 275 mg of actives (i.e., 50 mg DTG, 25 mg TAF, and 200 mg FTC), the high end of the “in particular” excipient ranges disclosed by WO ’351 produces a composition with a total weight of ~410 mg and the low end of these ranges produces a composition with a total weight of ~330 mg. Choosing excipient weight percents falling in the middle of these excipient ranges produces a composition with a total weight of ~370 mg. In my experience, the smaller a tablet is, the easier it is for a patient to swallow. And, in my opinion, the POSA would understand that in the art of HIV therapy, smaller tablets could greatly improve

³⁰⁴ *Id.*

patient adherence to therapy.³⁰⁵ Further, as Gilead admits in WO '323, “[a]ctual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art,” and such tablets would be “prepared by methodologies well known in the pharmaceutical art.”³⁰⁶

214. In my opinion, a POSA working from the tablet of WO '351 containing 50 mg of INSTI DTG, 25 mg of TAF, and 200 mg FTC as a starting point, would understand that they would be able to include up to ~725 mg (total weight) of excipients and still have a tablet with a total weight less than 1000 mg (claim 9). For a tablet weighing less than 800 mg (claim 10), the same POSA would have had ~525 mg (total weight) of excipients to work with, and that POSA would have had ~465 mg (total weight) of excipients to arrive at tablet weighing less than 730 mg (claim 11).

215. Given the large amounts of available excipients relative to the 275 mg total API weight required by claims 9–11, a POSA (in my opinion) motivated to provide smaller tablets for improved convenience, safety, and patient adherence,

³⁰⁵ 2015 DHHS Guidelines (EX-1014) at 188 (discussing interventions to improve adherence to ARV treatments, including assessing tablet size); *see also* June 2015 CDER Guidance (EX-1042) at 3 (“Studies in adults evaluating the effect of tablet and capsule size on ease of swallowing suggest that increases in size are associated with increases in patient complaints related to swallowing difficulties and tablet sizes greater than approximately 8 mm in diameter.”)

³⁰⁶ WO '323 (EX-1005) at 36:15–21.

would have arrived at tablets containing 50 mg of compound **42** (BIC), 25 mg TAF, and 200 mg FTC (as already discussed above for claim 1), with a sufficient amount of excipients (~465 mg as for the similar tablet in WO '351 containing 50 mg DTG, 25 mg TAF, and 200 mg FTC) to provide a tablet weighing less than 730 mg. That POSA would have reasonably expected success in preparing such tablets using common excipients and routine techniques in the art. Again, though not required, that person would have also expected that such tablets contained amounts of compound **42** (BIC) or a sodium salt thereof), TAF (or a fumarate or hemifumarate salt thereof), and FTC (as a free base) would be effective to reduce viral load in a patient, or at the very least expectedly been effective to prevent or reduce the risk of developing HIV-1 infection in patients exposed to the HIV virus.

216. In my professional opinion, from the standpoint of a POSA and in view of the legal principles of obviousness discussed herein, claims 9–11 would have been obvious over the combination of WO '323 and WO '351 as informed by common knowledge and well-known technical principles discussed in Section V available prior to November 9, 2015.

d. Claims 12–13

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

218. As discussed for claims 9–11, a POSA would have expected success in making a tablet containing 50 mg compound **42** (BIC), 25 mg TAF, and 200 mg of FTC having a total weight of less than 730 mg (e.g., 725 mg, 650 mg, 600 mg). Each of these tablets would have contained less than 15% and less than 11% of compound **42** (BIC) or a pharmaceutically salt thereof), so long as the total weight of the tablet was greater than 375 mg and 450 mg, respectively. Indeed, even tablets with a total weight of 1000 mg or greater would have met these limitations, i.e., 50 mg BIC is 5% of a tablet weighing 1000 mg and 2.5% by weight of a tablet weighing 2000 mg.

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

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

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

221. My analysis of the combination of WO '323 and WO '351 above is incorporated into this section.

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

223. As discussed in Section VIII.C., US '079 is an application filed by Cipla that, like WO '323 and WO '351, relates to single dosage units with multiple antiretroviral compounds, used to treat HIV infection with a “second generation” INSTI anchoring at least one other antiretroviral or anti-HIV agent.³⁰⁷ US '079 discloses a preference for tablets due to their greater stability, smaller bulk, and ease of production.³⁰⁸ It also exemplifies a tablet containing 50 mg DTG as an anchor for the N(t)RTIs TDF (300 mg) and FTC (200 mg) having a total API weight of 550 mg, a total uncoated weight of 1030 mg, and a coated weight of 1055 mg.³⁰⁹

³⁰⁷ US '079 (EX-1007) at 9–10, ¶ [0129].

³⁰⁸ *Id.* at 5, ¶¶ [0078]–[0079] (disclosing single, bilayered or multilayered tablets).

³⁰⁹ *Id.* at 9–10, ¶ [0129] (Example 7).

224. As discussed in Section IX.A–B, it is my opinion that the combination of WO '323 and 'WO 351 alone would have provided the POSA with sufficient information to arrive at the tablet of claim 1 with a reasonable expectation of success – a tablet having 50 mg BIC, 25 mg TAF, and 200 mg FTC. The APIs of this tablet would weigh 275 mg, which is 275 mg less than the APIs that are included in the “Dry Mix” of excipients provided in Example 7 of US '079.

225. The total weight of this uncoated tablet modified to replace TDF with TAF (without modifying any remaining excipients) would be 780 mg. In my opinion, the POSA would have understood that excipient amounts could also be reduced to correspond with the 50% decrease in weight of the APIs. As I mentioned above, it is my opinion that the POSA would want to make the smallest tablet possible, in order to maximize patient compliance. In my opinion, this would have produced, with a reasonable likelihood of success, a tablet with all three APIs, that weighed less than 730 mg. If an acceptable tablet with a total coated weight of 1055 mg had been successfully made when containing twice as much API (as in Example 7), a POSA would have reasonably expected to succeed in making a tablet with 275 mg of total active ingredients that (when coated) that would have weighed less than 730 mg as well.

226. As such, a POSA motivated to arrive at a tablet containing 50 mg compound **42** (BIC), 25 mg TAF, and 200 mg FTC (275 mg active ingredients) with

a reasonable expectation of success (as addressed in claim 1), would have been further motivated to prepare that tablet in the smallest size (and weight possible) possible, in order to maximize patient compliance. For the same reasons, a POSA preparing a tablet like that from US '079 (modified to replace 50 mg DTG with a therapeutically effective amount of compound **42** (BIC) and 300 mg TDF with 25 mg of TAF) would have reasonably expected to succeed in making the tablet of claim 1 that (whether coated or uncoated) would weigh less than 730 mg. And as explained above, that tablet would have contained less than 15% and less than 11% of compound **42** (BIC) based on total tablet weight, as required by claims 12–13.

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

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

228. Again, I have reviewed and considered Dr. Winkler's analysis and opinions on the specific selection of compound **42** as a sodium salt (BIC sodium).³¹⁰

³¹⁰ Winkler Declaration (EX-1004), Section VI.B.

Part of Dr Winkler's analysis and opinion in this regard relies on additional disclosures from Bowker (EX-1008) and Paulekuhn (EX-1009).³¹¹ I understand that Dr. Winkler includes these disclosures to provide additional bases for concluding that compound **42** (BIC) as a sodium salt was a clearly preferred selection over compound **42** (BIC) free acid and other pharmaceutically acceptable salts disclosed in WO '323.³¹² This is because, according to Dr. Winkler, an ordinarily skilled medicinal chemist would have known from Paulekuhn that "sodium was far and above the most common cation to use with acidic drugs, including weakly acidic drugs like DTG and BIC," and that POSA would have known from Bowker that the preparation of compound **42** (BIC) sodium salt (from NaOH) would provide a pKa difference (i.e., ≥ 3 units) necessary to form a stable (i.e., irreversible) salt.³¹³ As stated by Dr. Winkler, "[a POSA] would have expected success making BIC sodium given the structural similarities between BIC and DTG, the preference for DTG sodium in WO '351, and the expected >3 pKa difference between BIC and sodium hydroxide that would have expectedly provided the formation of an irreversible (and stable) salt."³¹⁴

³¹¹ *Id.* at ¶¶ 93–94.

³¹² *Id.* at ¶ 97-98.

³¹³ *Id.* at ¶¶ 93–95.

³¹⁴ *Id.* at ¶ 97.

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

E. Secondary Considerations

230. As noted above in Section III, I understand that a determination of obviousness also involves an inquiry into secondary considerations of non-obviousness, should such secondary considerations exist.

231. I also understand that secondary considerations are intended to be an objective analysis, including whether the claim generated an unexpected result commensurate with its scope. I also understand that there must be a nexus (or causal link) between evidence of an unexpected result and the claimed invention, and that this nexus should involve an aspect of the claim that is not already in the prior art.

232. With regard to the prior art, I have explained herein that the combination of WO '323 and WO '351 discloses nearly every limitation of the claims of the '802 Patent. As I also have explained, after granting allowance of the

patent claims, the examiner of that patent considered WO '323 to be the closest prior art to the patent claims the examiner was (at the time) examining, but that it did not disclose any pharmaceutical compositions for simultaneous administration of Formula (I), e.g., compound **42** (BIC) with N(t)RTIs such as TAF and FTC. In my opinion, the examiner clearly missed disclosures from WO '323 that did in fact disclose such single oral dosage forms, e.g., tablets, for this exact purpose.³¹⁵

233. Indeed, as explained above, WO '323 discusses “combination therapy,” including combination of a disclosed INSTI compound, e.g., compound **42** (BIC), and N(t)RTIs, where the NRTI FTC and the NtRTI TAF fumarate are among the list,³¹⁶ including compositions that are, in certain embodiments, “*in a unitary dosage form* for simultaneous administration to a patient, for example as a solid dosage form for oral administration.”³¹⁷

234. I note that in the '802 specification, the Patent Owner does report that BIC exposure was enhanced by approximately 30% when BIC was in one layer of a bilayered tablet (with specific amounts of excipients) and TAF/FTC in a separate layer (Tablet F2) as opposed to a single agent tablet (with different excipients and excipient amounts) (Tablet F2) co-administered with TAF/FTC tablet (with its own

³¹⁵ WO '323 (EX-1005), 37:13-19, 39:25-27, 40:18–20.

³¹⁶ *Id.* at 37:20–39:23 (emtricitabine at 38:14; tenofovir alafenamide fumarate at 38:19–20).

³¹⁷ *Id.* at 40:18–20 (emphasis added).

excipients and amounts) (Tablet F3). In my opinion, the ~30% increase attributed to bilayer Tablet F2 is not attributable to the tablets of the Challenged Claims. The Challenged claims require 50 mg of BIC (or an equivalent amount of its salt), are not limited to a bilayer tablets, or any separation of the claimed active ingredients, and allow for any excipient or excipient combination in any amount whatsoever. As such, I do not see any connection between evidence of a ~30% exposure increase for BIC from Tablet F2 containing 75 mg of BIC (78.7 mg BIC sodium), and the Challenged Claims. Even if a connection were to exist, the ~30% exposure increase cannot be correlated to the full scope of the Challenged Claims, which allow for any type of tablet, without regard to segregating any active ingredient by layering, in addition to the use of any excipients whatsoever (or none at all).

X. SUPPLEMENTATION

235. I reserve the right to modify and/or supplement the opinions in this report as appropriate and in response to any new information provided by the Patent Owner, including any allegations of unexpected results or other secondary considerations, and any declarations or additional testimony offered by other expert witnesses.

I hereby declare that all statements made herein based upon my own knowledge and expertise are true and accurate; that all statements made herein based on information and belief are believed to be true and accurate; and further

that these statements were made with the knowledge that willfully false statements are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.



Prasanna Jagannathan, M.D.

10/23/2024

Date

Appendix A

Prasanna Jagannathan, M.D.

Updated September 13, 2024



Position: Associate Professor of Medicine, with Tenure, Division of Infectious Diseases
Associate Professor of Microbiology and Immunology

Address: BioMedical Innovations Building, Room 3456
Stanford University School of Medicine
Voice: 650-724-6353
Email: praj@stanford.edu

I. EDUCATION/TRAINING

06/13 – 06/14	University of California, San Francisco	Certificate	Advanced Training in Clinical Research
7/10 – 6/12	University of California, San Francisco	Post-doctoral Fellow	Immunology
7/09 – 6/10	University of California, San Francisco	Clinical Fellow	Infectious Diseases
6/05 – 5/08	University of California, San Francisco	Internship and Residency	Internal Medicine
08/00 – 05/05	Harvard Medical School	M.D.	
08/94 – 05/98	University of California, Berkeley	B.A.	Religious Studies

II. LICENSES, CERTIFICATION

09/11 – 12/23	Board Certification, Infectious Diseases, American Board of Internal Medicine
09/08 – 09/18	Board Certification, American Board of Internal Medicine (recert in progress)
Present	California State Medical License A99002
Present	DEA Registration

III. PROFESSIONAL APPOINTMENTS

8/1/24 – present	Stanford University	Associate Professor with Tenure	Medicine, Infectious Diseases
1/1/24 – 7/31/24		Assistant Professor, COVID Extension	
1/1/21 – 12/31/23		Assistant Professor, Reappointment	
1/1/17 – 12/31/20		Assistant Professor	
8/1/24 - present	Stanford University	Associate Professor	Microbiology and Immunology
1/1/24 – 7/31/24		Assistant Professor, COVID Extension	
1/1/21 – 12/31/23		Assistant Professor, Reappointment	
8/1/18 – 12/31/20		Assistant Professor	
9/1/23 – present	Stanford University	Woods Family Faculty Endowed Scholar in Pediatric Translational Research	Stanford Maternal and Child Health Research Institute
9/1/20 - present	Stanford University	Med Scholars Director, Immunology Scholarly Concentration	Stanford University School of Medicine
7/1/17 – present	Stanford University	Faculty Member, Immunology Program	Stanford Immunology

7/1/12 – 12/31/16	University of California, Assistant Adjunct Professor San Francisco		Medicine
6/1/08 – 6/30/09	University of California, Chief Resident San Francisco		Internal Medicine
06/03 – 06/05	Howard Hughes Medical Institute/National Institutes of Health	Research Scholar, Laboratory of Immunoregulation, NIAID	NIAID, NIH
8/1/98 – 6/04/00	Locke High School, Los Angeles, CA	9 th /10 th Grade Integrative Science Teacher	Teach for America Corps

IV. HONORS AND AWARDS

2023	Stanford Maternal and Child Health Research Institute Faculty Scholar Award
2019	Basil O'Connor Award, March of Dimes Foundation
2018	Rosenkranz Prize, Stanford University
2018	American Society of Clinical Investigation Young Physician-Scientist Award
2015	Distinguished Scholar Award, MU-UCSF-LSHTM-IDRC Young Investigator Conference, Kampala, Uganda
2014	Hellman Fellows Award, University of California, San Francisco
2011	Burroughs Wellcome Fund/American Society of Tropical Medicine and Hygiene Postdoctoral Fellowship in Tropical Infectious Diseases
2009	UCSF Medical School Graduation Teaching Award, University of California, San Francisco
2006	Julius R. Krevans Award, San Francisco General Hospital, San Francisco, CA
2004	HHMI/NIH Research Scholars Program, Continuing Support Scholarship
2001	Joan Gillespie Fellow, Division of Social Medicine, Harvard Medical School
1998	Graduation Speaker, University of California Berkeley
1998	Highest Honors, Religious Studies, University of California Berkeley

V. SCHOLARLY PUBLICATIONS

A. Peer reviewed original research articles (110 total)

1. Tong Y, Ratnasiri K, Hanif S, Nguyen AT, Roh ME, Dorsey G, Kakuru A, **Jagannathan P**, Benjamin-Chung J. Pathways through which intermittent preventive treatment for malaria in pregnancy influences child growth faltering: a mediation analysis. medRxiv [Preprint]. 2024 Jun 10:2024.06.09.24308656. doi: 10.1101/2024.06.09.24308656. PMID: 38947035; PMCID: PMC11213035. *eBiomedicine*. In Press
2. Tukwasibwe S*, Lewis SN*, Taremwa Y, Nankya FN, Musinguzi K, Chamai M, Okitwi M, Ty M, Dantzler Press K, van der Ploeg K, Nakimuli A, Colucci F, Kamya MR, Nankabirwa JI, Arinaitwe E, Greenhouse B, Dorsey G, Rosenthal PJ, **Jagannathan P**. Natural Killer cell antibody-dependent cellular cytotoxicity to *Plasmodium falciparum* is impacted by cellular phenotypes, erythrocyte polymorphisms, parasite diversity, and intensity of transmission. 2024. *Clinical and Translational Immunology*. In Press
3. Nideffer J, Ty M, Donato M, John R, Kajubi R, Ji X, Maecker H, Nankya F, Musinguzi K, Press KD, Greenhouse B, Kamya M, Feeney ME, Dorsey G, Utz P, Pulendran B, Khatri P, **Jagannathan P**. Disease Tolerance Acquired Through Repeated *Plasmodium* Infection Involves Epigenetic Reprogramming of

Innate Immune Cells. *PNAS Nexus*. 2024 Aug 6;3(8):pgae325. doi: 10.1093/pnasnexus/pgae325. PMID: 39161730; PMCID: PMC11331423.

4. Kamya MR, Nankabirwa JI, Arinaitwe E, Rek J, Zedi M, Maiteki-Sebuguzi C, Opigo J, Staedke SG, Oruni A, Donnelly MJ, Greenhouse B, Briggs J, Krezanoski PJ, Bousema T, Rosenthal PJ, Olwoch P, **Jagannathan P**, Rodriguez-Barraquer I, Dorsey G. Dramatic resurgence of malaria after 7 years of intensive vector control interventions in Eastern Uganda. *PLOS Glob Public Health*. 2024 Aug 29;4(8):e0003254. doi: 10.1371/journal.pgph.0003254. PMID: 39208072. **Member of PRISM study team, Interpretation of data, critical revision of the manuscript.*
5. Jacobson KB, Roltgen K, Lam B, Nayebare P, Kakuru A, Kizza J, Aguti M, Nankya F, Briggs J, Takahashi S, Greenhouse B, Rodriguez-Barraquer I, Ploeg Kvd, Wohlsadter J, Sigal G, Roh M, Nankabirwa JI, Cuu G, Gaw SL, Rosenthal PJ, Kamya MR, Ssewanyana I, Dorsey G, Boyd S*, **Jagannathan P***. Gestational SARS-CoV-2 infection in a Ugandan birth cohort: high incidence, mild maternal disease and evidence for an association with transient infant stunting. *American Journal of Tropical Medicine and Hygiene*. 2024. In Press. Also at medRxiv. 2023.06.16.23291450; doi:https://doi.org/10.1101/2023.06.16.23291450.
6. Chew KW, Taiwo BO, Moser C, Daar ES, Wohl DA, Ritz J, Javan AC, Li JZ, Fischer W, Greninger AL, Bausch C, Luke T, Call R, Neytman G, Giganti MJ, Fletcher CV, Hughes MD, Eron JJ, Currier JS, Smith DM; **ACTIV-2/A5401 Study Team**. Safety and Efficacy of SAB-185 for Non-hospitalized Adults with COVID-19: A Randomized Clinical Trial. *J Infect Dis*. 2024 Jul 20;jiae369. doi: 10.1093/infdis/jiae369. Epub ahead of print. PMID: 39028902. **Member of ACTIV-2/A5401 Study Team.*
7. Lee HJ, Moreira ML, Li S, Asatsuma T, Williams CG, Skinner OP, Asad S, Bramhall M, Jiang Z, Liu Z, Kerr AS, Engel JA, Soon MSF, Straube J, Barrera I, Murray E, Chen F, Nideffer J, **Jagannathan P**, Haque A. CD4⁺ T cells display a spectrum of recall dynamics during re-infection with malaria parasites. *Nature Communications*. 2024. In Press. **Interpretation of data, critical revision of the manuscript.*
8. Geng, L, Bonilla H, Hedlin H, Jacobson KB, Tian L, **Jagannathan P**, Yang PC, Subramanian AK, Liang JW, Shen S, Deng Y, Shaw BJ, Botzheim B, Desai M, Pathak D, Jazayeri Y, Thai D, O'Donnell A, Mohaptra S, Leang Z, Reynolds GZM, Brooks EF, Bhatt AS, Shafer RW, Miglis MG, Quach T, Tiwari A, Banerjee A, Lopez RN, De Jesus M, Charnas LR, Utz PJ, Singh U. Effect of Nirmatrelvir-Ritonavir versus Placebo-Ritonavir on Clinical Outcomes in Adults with Post-Acute Sequelae of SARS-CoV-2: The STOP-PASC Randomized Clinical Trial. *JAMA Intern Med*. 2024 Jun 7:e242007. doi: 10.1001/jamainternmed.2024.2007. Epub ahead of print. PMID: 38848477; PMCID: PMC11161857. **Member of STOP-PASC Study Team, critical revision of the manuscript.*
9. Keshkar-Jahromi, M, Anstrom KJ, Barkauskas C, Brown SM, Daar ES, Fischer W, Gibbs KW, Higgs ES, Hughes MD, **Jagannathan P**, LaVange L, Lindsell CJ, Nayak S, Paredes R, Parmar M, Peltan ID, Proschan M, Shotwell M, Vock DM, Yokum, Adam SJ. ACTIV Trials: Lessons Learned in Trial Design in the Setting of an Emergent Pandemic. *Journal of Clinical and Translational Sciences*. 2024. In Press. **Member of ACTIV-2/A5401 Study Team.*
10. Choudhary MC, Deo R, Evering TH, Chew KW, Giganti MJ, Moser C, Ritz J, Regan J, Flynn JP, Crain CR, Wohl DA, Currier JS, Eron JJ, Margolis D, Zhu Q, Zhon L, Ya L, Greninger AL, Hughes MD, Smith D, Daar ES, Li JZ; **ACTIV-2/A5401 Study Team**. Characterization of treatment resistance and viral kinetics in the setting of single- versus dual-active monoclonal antibodies against SARS-CoV-2. *J Infect Dis*. 2024 May 8;jiae192. doi: 10.1093/infdis/jiae192. Epub ahead of print. PMID: 38716969. **Member of ACTIV-2/A5401 Study Team.*
11. Lee JJ, Kakuru A, Jacobson KB, Kamya MR, Kajubi R, Ranjit A, Gaw SL, Parsonnet J, Benjamin-Chung J, Dorsey G, **Jagannathan P***, Roh ME*. Monthly Sulfadoxine-Pyrimethamine During Pregnancy Prevents Febrile Respiratory Illnesses: A Secondary Analysis of a Malaria Chemoprevention Trial in Uganda. *Open*

12. Reyes R, Batugedara G, Dutta P, Reers A.B., Garza R, Ssewanyana I, **Jagannathan P**, Feeney M.E., Greenhouse B, Bol S, Ay F, Bunnik EM. Atypical B Cells Consist of Subsets with Distinct Functional Profiles. iScience. 2023 Nov 20;26(12):108496. doi: 10.1016/j.isci.2023.108496. PMID: 38098745; PMCID: PMC10720271. **Obtained resources, supervised sample collection, critical revision of the manuscript.*
13. **Jagannathan P**, Chew KW, Giganti MJ, Hughes MD, Moser C, Main MJ, Monk PD, Javan AC, Li JZ, Fletcher C, McCarthy C, Wohl DA, Daar ES, Eron JJ, Currier JS, Singh U, Smith D, Fischer W, for the ACTIV-2/A5401 Study Team. Safety and Efficacy of Inhaled Interferon- β 1a (SNG001) in a Phase II Randomized Controlled Trial of Adults with Mild-to-Moderate COVID-19. eClinicalMedicine. 2023 Oct 6;65:102250. doi: 10.1016/j.eclinm.2023.102250. PMID: 37855026; PMCID: PMC10579289.
14. Kiro Singh AS, Delmastro A, Kakuru A, van der Ploeg K, Bhattacharya S, Press KD, Ty, M, de la Parte L, Kizza J, Muhindo M, Devachannee S, Gamain B, Nankya F, Musinguzi K, Rosenthal PJ, Feeney ME, Kanya M, Dorsey G, **Jagannathan P**. Malaria-Specific Type 1 Regulatory T Cells are More Abundant in First Pregnancies and Associated with Placental Malaria. EBioMedicine. 2023 Sep;95:104772. doi: 10.1016/j.ebiom.2023.104772. Epub 2023 Aug 25. PMID: 37634385; PMCID: PMC10474374.
15. Natarajan A, Fremin BJ, Schmidtke DT, Wolfe MK, Zlitni S, Graham KE, Brooks EF, Severyn CJ, Sakamoto KM, Lacayo NJ, Kuersten S, Koble J, Caves G, Kaplan I, Singh U, **Jagannathan P**, Rezvani AR, Bhatt AS, Boehm AB. The Tomato Brown Rugose Fruit Virus Movement Protein Gene Is a Novel Microbial Source Tracking Marker. Appl Environ Microbiol. 2023 Jul 5:e0058323. doi: 10.1128/aem.00583-23. Epub ahead of print. PMID: 37404180. **Obtained resources, supervised volunteer recruitment and sample collection, critical revision of the manuscript.*
16. Horwitz LI, Thaweethai T, Brosnahan SB, Cicek MS, Fitzgerald ML, Goldman JD, Hess R, Hodder SL, Jacoby VL, Jordan MR, Krishnan JA, Laiyemo AO, Metz TD, Nichols L, Patzer RE, Sekar A, Singer NG, Stiles LE, Taylor BS, Ahmed S, Algren HA, Anglin K, Aponte-Soto L, Ashktorab H, Bassett IV, Bedi B, Bhadelia N, Bime C, Bind MC, Black LJ, Blomkalns AL, Brim H, Castro M, Chan J, Charney AW, Chen BK, Chen LQ, Chen P, Chestek D, Chibnik LB, Chow DC, Chu HY, Clifton RG, Collins S, Costantine MM, Cribbs SK, Deeks SG, Dickinson JD, Donohue SE, Durstenfeld MS, Emery IF, Erlandson KM, Facelli JC, Farah-Abraham R, Finn AV, Fischer MS, Flaherman VJ, Fleurimont J, Fonseca V, Gallagher EJ, Gander JC, Gennaro ML, Gibson KS, Go M, Goodman SN, Granger JP, Greenway FL, Hafner JW, Han JE, Harkins MS, Hauser KSP, Heath JR, Hernandez CR, Ho O, Hoffman MK, Hoover SE, Horowitz CR, Hsu H, Hsue PY, Hughes BL, **Jagannathan P**, James JA, John J, Jolley S, Judd SE, Juskowich JJ, Kanjilal DG, Karlson EW, Katz SD, Kelly JD, Kelly SW, Kim AY, Kirwan JP, Knox KS, Kumar A, Lamendola-Essel MF, Lanca M, Lee-Lannotti JK, Lefebvre RC, Levy BD, Lin JY, Logarbo BP Jr, Logue JK, Longo MT, Luciano CA, Lutrick K, Malakooti SK, Mallett G, Maranga G, Marathe JG, Marconi VC, Marshall GD, Martin CF, Martin JN, May HT, McComsey GA, McDonald D, Mendez-Figueroa H, Miele L, Mittleman MA, Mohandas S, Mouchati C, Mullington JM, Nadkarni GN, Nahin ER, Neuman RB, Newman LT, Nguyen A, Nikolich JZ, Ofotokun I, Ogbogu PU, Palatnik A, Palomares KTS, Parimon T, Parry S, Parthasarathy S, Patterson TF, Pearman A, Peluso MJ, Pemu P, Pettker CM, Plunkett BA, Pogreba-Brown K, Poppas A, Porterfield JZ, Quigley JG, Quinn DK, Raissy H, Rebello CJ, Reddy UM, Reece R, Reeder HT, Rischard FP, Rosas JM, Rosen CJ, Roupheal NG, Rouse DJ, Ruff AM, Saint Jean C, Sandoval GJ, Santana JL, Schlater SM, Sciurba FC, Selvaggi C, Seshadri S, Sesso HD, Shah DP, Shemesh E, Sherif ZA, Shinnick DJ, Simhan HN, Singh U, Sowles A, Subbian V, Sun J, Suthar MS, Teunis LJ, Thorp JM Jr, Ticotsky A, Tita ATN, Tragus R, Tuttle KR, Urdaneta AE, Utz PJ, VanWagoner TM, Vasey A, Vernon SD, Vidal C, Walker T, Ward HD, Warren DE, Weeks RM, Weiner SJ, Weyer JC, Wheeler JL, Whiteheart SW, Wiley Z, Williams NJ, Wisnivesky JP, Wood JC, Yee LM, Young NM, Zisis SN, Foulkes AS. Researching COVID to Enhance Recovery (RECOVER) adult study protocol: Rationale, objectives, and design. PLoS One. 2023

17. Thaweethai T, Jolley SE, Karlson EW, Levitan EB, Levy B, McComsey GA, McCorkell L, Nadkarni GN, Parthasarathy S, Singh U, Walker TA, Selvaggi CA, Shinnick DJ, Schulte CCM, Atchley-Challenger R, Alba GA, Alicic R, Altman N, Anglin K, Argueta U, Ashktorab H, Baslet G, Bassett IV, Bateman L, Bedi B, Bhattacharyya S, Bind MA, Blomkalns AL, Bonilla H, Bush PA, Castro M, Chan J, Charney AW, Chen P, Chibnik LB, Chu HY, Clifton RG, Costantine MM, Cribbs SK, Davila Nieves SI, Deeks SG, Duven A, Emery IF, Erdmann N, Erlandson KM, Ernst KC, Farah-Abraham R, Farner CE, Feuerriegel EM, Fleurimont J, Fonseca V, Franko N, Gainer V, Gander JC, Gardner EM, Geng LN, Gibson KS, Go M, Goldman JD, Grebe H, Greenway FL, Habli M, Hafner J, Han JE, Hanson KA, Heath J, Hernandez C, Hess R, Hodder SL, Hoffman MK, Hoover SE, Huang B, Hughes BL, **Jagannathan P**, John J, Jordan MR, Katz SD, Kaufman ES, Kelly JD, Kelly SW, Kemp MM, Kirwan JP, Klein JD, Knox KS, Krishnan JA, Kumar A, Laiyemo AO, Lambert AA, Lanca M, Lee-Iannotti JK, Logarbo BP, Longo MT, Luciano CA, Lutrick K, Maley JH, Marathe JG, Marconi V, Marshall GD, Martin CF, Matusov Y, Mehari A, Mendez-Figueroa H, Mermelstein R, Metz TD, Morse R, Mosier J, Mouchati C, Mullington J, Murphy SN, Neuman RB, Nikolich JZ, Ofotokun I, Ojemakinde E, Palatnik A, Palomares K, Parimon T, Parry S, Patterson JE, Patterson TF, Patzer RE, Peluso MJ, Pemu P, Pettker CM, Plunkett BA, Pogreba-Brown K, Poppas A, Quigley JG, Reddy U, Reece R, Reeder H, Reeves WB, Reiman EM, Rischard F, Rosand J, Rouse DJ, Ruff A, Saade G, Sandoval GJ, Schlater SM, Shepherd F, Sherif ZA, Simhan H, Singer NG, Skupski DW, Sowles A, Sparks JA, Sukhera FI, Taylor BS, Teunis L, Thomas RJ, Thorp JM, Thuluvath P, Ticotsky A, Tita AT, Tuttle KR, Urdaneta AE, Valdivieso D, VanWagoner TM, Vasey A, Verduzco-Gutierrez M, Wallace ZS, Ward HD, Warren DE, Weiner SJ, Welch S, Whiteheart SW, Wiley Z, Wisnivesky JP, Yee LM, Zisis S, Horwitz LI, Foulkes AS; RECOVER Consortium. Development of a Definition of Postacute Sequelae of SARS-CoV-2 Infection. JAMA. 2023 Jun 13;329(22):1934-1946. doi: 10.1001/jama.2023.8823. PMID: 37278994; PMCID: PMC10214179. **Member of RECOVER Consortium, collected data, critical revision of the manuscript.*
18. Mwakibete L, Takahashi S, Ahyong V, Black A, Rek J, Ssewanyana I, Kamya M, Dorsey G, **Jagannathan P**, Rodríguez-Barraquer I, Tato CM, Greenhouse B. Metagenomic next-generation sequencing to characterize potential etiologies of non-malarial fever in a cohort living in a high malaria burden area of Uganda. PLOS Global Public Health. 2023;3(5):e0001675. doi: 10.1371/journal.pgph.0001675. PMID: 37134083; PMCID: PMC10156012. **Obtained resources, supervised sample collection, critical revision of the manuscript.*
19. Bender Ignacio RA, Chew KW, Moser C, Currier JS, Eron JJ, Javan AC, Giganti MJ, Aga E, Gibbs M, Tchouakam Kouekam H, Johnsson E, Esser MT, Hoover K, Neytman G, Newell M, Daar ES, Fischer W, Fletcher CV, Li JZ, Greninger AL, Coombs RW, Hughes MD, Smith D, Wohl DA; Accelerating COVID-19 Therapeutic Interventions and Vaccines (**ACTIV-2/A5401 Study Team**). Safety and Efficacy of Combined Tixagevimab and Cilgavimab Administered Intramuscularly or Intravenously in Nonhospitalized Patients With COVID-19: 2 Randomized Clinical Trials. JAMA Netw Open. 2023 Apr 3;6(4):e2310039. doi: 10.1001/jamanetworkopen.2023.10039. PMID: 37099295; PMCID: PMC10134004. **Member of ACTIV-2/A5401 Study Team.*
20. Gao F, Mallajoysula V, Arunachalam PS, van der Ploeg K, Manohar M, Röltgen K, Yang F, Wirz O, Hoh R, Haraguchi E, Lee JY, Willis R, Ramachandiran V, Li J, Kathuria KR, Li C, Lee AS, Shah MM, Sindher SB, Gonzalez J, Altman JD, Wang TT, Boyd SD, Pulendran B, **Jagannathan P**, Nadeau KC, Davis MM. Spheromers reveal robust T cell responses to the Pfizer/BioNTech vaccine and attenuated peripheral CD8⁺T cell responses post SARS-CoV-2 infection. Immunity. 2023 Apr 11;56(4):864-878.e4. doi: 10.1016/j.immuni.2023.03.005. Epub 2023 Mar 16. PMID: 36996809; PMCID: PMC10017386. **Obtained resources, supervised volunteer recruitment and sample collection, critical revision of the manuscript.*
21. Deo R, Choudhary MC, Moser C, Ritz J, Daar ES, Wohl DA, Greninger AL, Eron JJ, Currier JS, Hughes MD, Smith DM, Chew KW, Li JZ; **ACTIV-2/A5401 Study Team**. Symptom and Viral Rebound in Untreated

SARS-CoV-2 Infection. Ann Intern Med. 2023 Mar;176(3):348-354. doi: 10.7326/M22-2381. Epub 2023 Feb 21. PMID: 36802755; PMCID: PMC10052317. **Member of ACTIV-2/A5401 Study Team.*

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***Equal contribution**

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83. Kapisi J, Kakuru A, **Jagannathan P**, Muhindo MK, Natureeba P, Awori P, Nakalembe M, Ssekitoleko R, Olwoch P, Ategeka J, Nayebara P, Clark TD, Rizzuto G, Muehlenbachs A, Havlir DV, Kamya MR, Dorsey G, Gaw SL. Relationships between infection with Plasmodium falciparum during pregnancy, measures of placental malaria, and adverse birth outcomes. Malar J. 2017 Oct 5;16(1):400. doi: 10.1186/s12936-017-2040-4. PMID: 28982374. **Role: Supervised data/sample collection, data analysis and interpretation, revision of manuscript.*
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- J Med. 2016 Mar 10; 374(10):928-39. PMID: 26962728. *Role: Laboratory director for study. Performed all data analysis, interpreted results, and drafted, reviewed, and revised manuscript.*
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- therapy among Ugandan children with uncomplicated *Plasmodium falciparum* malaria. *Malar J.* 2014; 13(1):32. PMID: 24468007. **Role: Data analysis and interpretation, drafting and revision of manuscript.*
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B. Pre-prints and submitted publications (5 in Total)

113. Hamlin RE, Pienkos SM, Chan L, Stabile MA, Pinedo K, Rao M, Grant P, Bonilla H, Holubar M, Singh U, Jacobson KB, Jagannathan P, Maldonado Y, Holmes SP, Subramanian A, Blish CA. Sex differences and immune correlates of Long COVID development, persistence, and resolution. *bioRxiv* [Preprint]. 2024

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115. Rothman RL, Stewart TG, Mourad A, Boulware DR, McCarthy MW, Thicklin F, Garcia Del Sol IT, Garcia JL, Bramante CT, Shah NS, Singh U, Williamson JC, Rebolledo PA, **Jagannathan P**, Schwasinger-Schmidt T, Ginde AA, Castro M, Jayaweera D, Sulkowski M, Gentile N, McTigue K, Felker GM, DeLong A, Wilder R, Collins S, Dunsmore SE, Adam SJ, Hanna GJ, Shenkman E, Hernandez AF, Naggie S, Lindsell CJ; Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)-6 Study Group and Investigators. Effect of Montelukast vs Placebo on Time to Sustained Recovery in Outpatients with COVID-19: The ACTIV-6 Randomized Clinical Trial. medRxiv [Preprint]. 2024 May 18:2024.05.16.24307115. doi: 10.1101/2024.05.16.24307115. PMID: 38798524; PMCID: PMC11118662.

C. Peer reviewed publications, other (17 in total)

1. Boyle M, Engwerda C, **Jagannathan P**. The development of immune regulatory networks during malaria; their roles and impact on anti-parasitic vaccination and drug treatment. 2024. Nat Rev Immunol. 2024 Jun 11. doi: 10.1038/s41577-024-01041-5. Epub ahead of print. PMID: 38862638.
2. Dobbs KR, **Jagannathan P**, Dechavanne C. Editorial: Immune tolerance and human malaria. Front Immunol. 2024 Jul 4;15:1450480. doi: 10.3389/fimmu.2024.1450480. PMID: 39026667; PMCID: PMC11254803.
3. Mohandas S, **Jagannathan P**, Henrich TJ, Sherif ZA, Bime C, Quinlan E, Portman MA, Gennaro M, Rehman J, Force RMPT. Immune mechanisms underlying COVID-19 pathology and post-acute sequelae of SARS-CoV-2 infection (PASC). eLife. 2023;12:e86014. doi: 10.7554/eLife.86014. Review.
4. Tukwasibwe S, Mboowa G, Sserwadda I, Nankabirwa JI, Arinaitwe E, Ssewanyana I, Taremwa Y, Tumusiime G, Kanya MR, **Jagannathan P**, Nakimuli A. Impact of high human genetic diversity in Africa on immunogenicity and efficacy of RTS,S/AS01 vaccine. Immunogenetics. 2023 Apr 21:1–8. doi: 10.1007/s00251-023-01306-8. Epub ahead of print. PMID: 37084013; PMCID: PMC10119520. Review
5. Kakuru A, **Jagannathan P**. Can we reduce malaria in pregnancy and improve birth outcomes? Lancet. 2023 Mar 25;401(10381):973-975. doi: 10.1016/S0140-6736(23)00101-0. Epub 2023 Mar 10. PMID: 36913960. Commentary.
6. Nideffer J, **Jagannathan P**. Type I regulatory T cells in malaria: of mice and men. J Clin Invest. 2023;133(1). Epub 2023/01/04. doi: 10.1172/JCI166019. PubMed PMID: 36594472; PMCID: PMC9797330. Commentary.
7. Kakuru A, **Jagannathan P**. Malaria in 2022: Increasing Challenges, Cautious Optimism. Nat Commun. 2022 May 13;13(1):2678. doi: 10.1038/s41467-022-30133-w. PMID: 35562368; PMCID: PMC9106727. Perspective.
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- Populations. Clin Pharmacol Ther. 2021 Oct;110(4):926-940. doi: 10.1002/cpt.2238. Epub 2021 May 2. Review. PubMed PMID: 33763871; PubMed Central PMCID: PMC8518425. Review.
9. Tao K, Tzou PL, Nouhin J, Bonilla H, **Jagannathan P**, Shafer RW. SARS-CoV-2 Antiviral Therapy. Clin Microbiol Rev. 2021 Jul 28:e0010921. doi: 10.1128/CMR.00109-21. Epub ahead of print. PMID: 34319150. Review.
 10. **Jagannathan P**, Wang TT. Immunity after SARS-CoV-2 infections. Nat Immunol. 2021 Apr 19. doi: 10.1038/s41590-021-00923-3. Epub ahead of print. PMID: 33875881. Commentary.
 11. Dantzler K, de la Parte L, **Jagannathan P**. Emerging role of $\gamma\delta$ T cells in vaccine-mediated protection from infectious diseases. Clinical and Translational Immunology. 2019 Aug 28. doi: 10.1002/cti2.1072. PMID 31485329. Review.
 12. **Jagannathan P**. How does malaria in pregnancy impact malaria risk in infants? BMC Medicine. BMC Medicine. 2018 Nov 20;16(1):212. PMID 30454004. Commentary.
 13. Dantzler K, **Jagannathan P**. $\gamma\delta$ T cells in antimalarial immunity: new insights into their diverse functions in protection and tolerance. Frontiers in Immunology. 2018. Oct 23;9:2445. doi: 10.3389/fimmu.2018.02445. PMID: 30405634. Review/
 14. Harrington W, Kakuru A, **Jagannathan P**. Malaria in pregnancy shapes the development of infant immunity. Parasite Immunology. 2018 Jul 17:e12573. PMID 30019470. Review.
 15. **Jagannathan P**, Kajubi R, Aweeka FT. Response to "Antiretroviral Therapy With Efavirenz in HIV-Infected Pregnant Women: Understanding the Possible Mechanisms for Drug-Drug Interaction". Clin Pharmacol Ther. 2018 Jan 11. doi: 10.1002/cpt.963. PMID: 29322501. Commentary.
 16. Landovitz RJ, **Jagannathan P**, Bhatt A, Roland ME. Preventing HIV infection after a potential sexual exposure. Infect Med. 2007;24(6):239-243(1). Review.
 17. **Jagannathan P**, Landovitz RJ, Roland, M. Post-Exposure Prophylaxis after Sexual Exposure to Human Immunodeficiency Virus. Future HIV Therapy. 2007; 1(1):35-47. Review.

D. Book Chapters (1 in total)

1. Briggs J, Murray M, Nideffer J, **Jagannathan P**. Sex-Linked Differences in Malaria Risk Across the Lifespan. Curr Top Microbiol Immunol. 2023;441:185-208. doi: 10.1007/978-3-031-35139-6_7. PMID: 37695429.

E. Selected Conference Abstracts Not Published in Other Forms

1. Lewis SN, Tukwasibwe S, Taremwa Y, Nankya FN, Musinguzi K, Chamai M, Okitwi M, Ty M, Dantzler Press K, van der Ploeg K, Nakimuli A, Colucci F, Kamya MR, Nankabirwa JI, Arinaitwe E, Greenhouse B, Dorsey G, Rosenthal PJ, **Jagannathan P**. Evaluating the impact of natural killer cell phenotype, malaria diversity and transmission, and erythrocyte polymorphisms on antibody dependent cellular cytotoxicity. 72nd Annual American Society of Tropical Medicine and Hygiene Annual Conference. Chicago, IL. 2023.
2. Nankya F, Bach F, Press KD, Odorizzi P, Musinguzi K, Naluwu K, Ssewanyana I, Kakuru A, Kamya M, Dorsey G, Feeney M, **Jagannathan P**. Antibody and cellular responses following *in utero* malaria exposure in infants. 72nd Annual American Society of Tropical Medicine and Hygiene Annual Conference. Chicago, IL. 2023.
3. Jacobson KB, Roltgen K, Lam B, Nayebare P, Kakuru A, Kizza J, Aguti M, Nankya F, Briggs J, Takahashi S, Greenhouse B, Rodriguez-Barraquer I, Ploeg Kvd, Wohlsadter J, Sigal G, Roh M, Nankabirwa JI, Cuu G, Gaw SL, Rosenthal PJ, Kamya MR, Ssewanyana I, Dorsey G, Boyd S*, **Jagannathan P***. High rates of

- SARS-CoV-2 infection in pregnant Ugandan women and association with stunting in infancy. Malaria Gordon Research Seminar and Conference. Castelldefels, B, Spain. 2023.
4. Nideffer J, Zedi M, van der Ploeg K, Rek J, Nankya F, Musinguzi K, Boonrat P, Kamya M, Khatri P, Dorsey G, Ssewanyana I, Takahashi S, Greenhouse B, Rodriguez-Barraquer I, Roncarolo MG, **Jagannathan P**. The pediatric CD4+ T cell response to malaria. Malaria Gordon Research Seminar and Conference. Castelldefels, B, Spain. 2023.
 5. Delmastro A, Kirosingh A, Dorsey G, Rosenthal P, Kakuru A, Kamya M, Angelo M, and **Jagannathan P**. Characterizing the Transcriptomic Differences between Pregnant Women in a Malaria-Endemic Setting. Infections in Pregnancy Keystone Symposium. Santa Fe, NM, USA. 2023.
 6. **Jagannathan P**, Chew KW, Giganti MJ, Hughes MD, Moser C, Main MJ, Monk PD, Javan AC, Li JZ, Fletcher C, McCarthy C, Wohl DA, Daar ES, Eron JJ, Currier JS, Singh U, Smith D, Fischer W, for the ACTIV-2/A5401 Study Team. Safety and Efficacy of Inhaled Interferon- β 1a (SNG001) in Outpatients with COVID-19. The 30th Conference on Retroviruses and Opportunistic Infections. Seattle, WA, USA. 2023.
 7. Nideffer J, Ty M, Donato M, Rek J, Kajubi R, Ji X, Maecker H, Nankya F, Musinguzi K, Press K, Greenhouse B, Kamya M, Feeney M, Dorsey G, Utz PJ, Pulendran B, Khatri P, **Jagannathan P**. Epigenetic reprogramming of innate immune cells predicts naturally acquired immunity to malaria. EMBL Symposium: Innate Immunity in Host Pathogen Interactions. Heidelberg, Germany. 2022.
 8. Jacobson KB, Nayebara P, Kakuru A, Kizza J, Aguti M, Nankya F, Briggs J, Takahashi S, Greenhouse B, Rodriguez-Barraquer I, Nankabirwa JI, Cuu G, Gaw SL, Rosenthal PJ, Kamya MR, Ssewanyana I, Dorsey G, **Jagannathan P**. Sars-CoV-2 and malaria interactions in pregnancy and their impact on birth outcomes in Uganda. 71st Annual American Society of Tropical Medicine and Hygiene Annual Conference. Seattle, WA. 2022.
 9. Dantzler Press K, Klemm S, Muller F, Chan D, Maran MIJ, Hu Zicheng, Rek J, Nankya F, Ssewanyana I, Kamya MR, Greenhouse B, Dorsey G, Feeney M, Greenleaf W, **Jagannathan P**. Altered V δ 2+ $\gamma\delta$ T cell chromatin accessibility following *in vivo* or *in vitro* malaria exposure. 71st Annual American Society of Tropical Medicine and Hygiene Annual Conference. Seattle, WA. 2022.
 10. Tukwasibwe S, Taremwa Y, Nankya FN, Musinguzi K, Chamai M, Okitwi M, Ty M, Dantzler Press K, van der Ploeg K, Nakimuli A, Colucci F, Cose S, Rek J, Ssewanyana I, Kamya MR, Nankabirwa JI, Arinaitwe E, Greenhouse B, Dorsey G, Rosenthal PJ, **Jagannathan P**. Role of antimalarial antibodies in functional modulation of the natural killer cell response to malaria. 71st Annual American Society of Tropical Medicine and Hygiene Annual Conference. Seattle, WA. 2022.
 11. Dantzler K, Klemm S, Polidoro R, Rao A, Junquiera C, Dvorak M, Rek J, Kamya MR, Cheung P, Kuo A, Dorsey G, Feeney M, Lieberman J, Khatri P, Greenleaf W, **Jagannathan P**. Diminished V δ 2+ $\gamma\delta$ T cell cytokine production and degranulation following *in vitro* malaria exposure. 70th Annual American Society of Tropical Medicine and Hygiene Annual Conference. 2021.
 12. Ty M, De La Parte L, Rek J, Kajubi R, Kamya M, Maecker H, Greenhouse B, Feeney M, Dorsey G, Boyle M, Utz PJ, Kuo A, Khatri P, Pulendran B, **Jagannathan P**. Immunologic profiles underlying clinical states in malaria. "69th Annual American Society of Tropical Medicine and Hygiene Annual Conference. 2020.
 13. Dantzler K, Polidoro R, John R, Kamya M, Dorsey G, Feeney M, Lieberman J, **Jagannathan P**. Mechanisms driving altered V δ 2+ $\gamma\delta$ T cell function during recurrent malaria infection. Gordon Malaria Research Conference. Les Diablerets, Switzerland. 2019.
 14. De La Parte L, Ty M, Kakuru A, Muhindo MK, Kamya M, Feeney M, Dorsey G, **Jagannathan P**. "Cellular correlates of protective immunity to malaria in pregnancy." Gordon Malaria Research Conference. Les Diablerets, Switzerland. 2019.

15. Dantzler K, Polidoro R, John R, Kanya M, Dorsey G, Feeney M, Lieberman J, **Jagannathan P**. Impact of recurrent malaria on Vd2 T cell in vitro anti-parasitic activity. 67th Annual American Society of Tropical Medicine and Hygiene Annual Conference. New Orleans, LA. 2018.

VI. GRANTS

A. Current Funding

R01 AI 177377A-01A1	Jagannathan, Haque (MPI)	3/15/24-1/31/29
National Institutes of Allergy and Infectious Diseases/ National Institutes of Health		
<i>Deciphering mechanisms of CD4+ T cell- dependent clinical immunity to repeated Plasmodium infections</i>		
The major goal of this project is to determine whether clonal populations of <i>Plasmodium</i> -specific type 1 regulatory CD4+ T cells expand following <i>Plasmodium</i> infection and play a role in clinical immunity to repeated <i>Plasmodium</i> infections, combining studies in pediatric cohorts with animal models.		
Role: MPI (Contact)		
OPP 052649	Jagannathan, Nankabirwa (MPI)	10/1/23-9/30/26
Bill & Melinda Gates Foundation		
<i>Dynamics of host immunity in the setting of malaria control interventions</i>		
The major goal of this project is to determine the impact of malaria vector control interventions on naturally acquired immunity to malaria.		
Role: MPI		
U01 AI155325	Jagannathan	9/1/21-8/30/26
National Institutes of Allergy and Infectious Diseases/ National Institutes of Health		
<i>Enhancing immunity to malaria in young children with effective chemoprevention</i>		
This double blind randomized controlled trial will determine whether effective prevention of malaria with IPT during pregnancy and infancy can enhance protective immunity to malaria in children.		
Role: PI		
SPO 204247	Jagannathan, Nankabirwa (MPI)	9/1/21-2/28/25
Bill & Melinda Gates Foundation		
<i>Impact of Intermittent Preventive Therapy during Pregnancy with Dihydroartemisinin Piperazine on Incidence of Malaria in Infancy</i>		
The major goal of this project is to determine the impact of dihydroartemisinin-piperazine chemoprevention during pregnancy on the incidence of malaria in infancy.		
Role: MPI		
SPO 276613	Singh	10/12/22-06/30/24
Pfizer, Inc.		
<i>Paxlovid Treatment in PASC: Randomized Double-Blind Placebo-Controlled Pilot Trial.</i>		
Major Goals: Identify whether treatment with Paxlovid helps alleviate the symptoms of long-covid or PASC.		
Status of Support: Active		
Role: Co-I		
SPO 270519	Benjamin-Chung	07/01/22-6/30/24
Stanford Center for Innovation in Global Health		
<i>Intermittent preventive treatment for malaria in pregnancy: a potential child growth intervention</i>		
Major Goals: The major goal is to evaluate association between malaria prevention regimen in pregnancy and infant growth.		
Role: Co-I		

U01 AI150741 Greenhouse, Jagannathan, Butte (MPI) 04/01/20-03/31/25
National Institutes of Allergy and Infectious Diseases/ National Institutes of Health
Computational models of naturally acquired immunity to falciparum malaria
The major goal of this project is to broadly profile the immune systems of children and adults living in a malaria endemic area over multiple points in time and build state-of-the-art computational models of natural immunity.
Role: MPI

U01 AI165527 Pulendran, Beeson, Valim (MPI) 02/01/22-01/31/27
National Institutes of Allergy and Infectious Diseases/ National Institutes of Health
Systems biological assessment of vaccination-induced protective immunity in African children
The major goal of this project is to identify immunologic correlates of protection following vaccination with RTS,S in Malawian children
Role: Co-I

R01 AI150521 (Aide/Mayor) Aide, Mayor 06/01/20-05/31/25
National Institutes of Allergy and Infectious Diseases/ National Institutes of Health
Unravelling disease tolerance and host resistance in afebrile P. falciparum infections: a prospective study
The major goal of this project is to identify host and parasite factors that determine the outcome of asymptomatic malaria infections in Mozambican adults.
Role: Co-I

R01AI137037 Greenhouse 07/01/20-06/30/25
National Institutes of Allergy and Infectious Diseases/ National Institutes of Health
Drivers of strain-specific and strain-transcendent antimalarial immunity in childhood
The major goal of this project is to evaluate parasite and host drivers of strain-specific and strain-transcendent antimalarial immunity.
Role: Co-I

OT2HL161847-01 (Singh/Blish/Maldonado/UTZ) 10/01/2021-5/23/2025
National Institutes of Health
Researching COVID to Enhance Recovery (RECOVER) Initiative: A multi-site Observational Study of Post-Acute Sequelae of SARS-CoV-2 Infection in Adults.
Major Goals: The major goal of this project is to enroll a longitudinal observational meta-cohort to define and characterize the epidemiology, natural history, clinical spectrum, and underlying mechanisms of post-acute effects of SARS-CoV-2 infection in a diverse, adult population representative of the general COVID-19 population.
Role: Co-I

B. Pending/Submitted Funding

U01 AI Jagannathan, Kakuru 7/1/25-6/30/30
National Institutes of Allergy and Infectious Diseases/ National Institutes of Health
Protecting infants with monoclonal antibodies in the malaria vaccine era (PRIME)
The major goal of this double blind randomized controlled trial is to determine whether the antimalarial monoclonal antibody L9LS can protect infants can protect infants against malaria without diminishing subsequent malaria vaccine efficacy.
Role: MPI (Contact)

C. Past Funding

UM1AI068636 (Currier) 12/01/2020-11/30/2023

UCLA / National Institutes of Health

Leadership and Operations Center (LOC), AIDS Clinical Trials Group ACTIV-2 study (ACTG-5401)

The major goals of this COVID-19 adaptive clinical trial are to evaluate different agents for the treatment of mild to moderate SARS-CoV-2 infection in outpatients. Dr. Jagannathan serves as a co-lead for the Synairgen inhaled interferon beta agent and the MP/NVS subcutaneous DARPIN agent.

Role: Co-I

SPO 286869

Jagannathan

4/1/23-3/30/24

National Institutes of Allergy and Infectious Diseases/ National Institutes of Health

SARS-CoV-2 specific T cell responses in malaria-exposed individuals

The major goals of this grant are to compare SARS-CoV-2 specific T cell responses between North American and Ugandan adults

Role: PI

SPO 249041

Jagannathan

12/01/21-06/30/23

Innovative Medicine Accelerator Stanford ChEM-H

Impact of malaria antigen exposure on memory responses to vaccination.

Major Goals: The major goal of this project is using a human tonsil organoid system to evaluate the impact of malaria antigen exposure on vaccine responses in vitro.

Role: PI

ACTIV-2/A5401 COMOSTAT- SPO 221619

Singh

03/31/21-03/30/23

National Institutes of Health

Camostat - Adaptive Platform Treatment Trial for Outpatients with COVID-19 (Adapt Out COVID)

The major goal of this project is to evaluate novel treatments for patients with COVID-19. Stanford University is a participating site in this multi-site study.

Role: Co-I

ACTIV-2/A5401 SNG001- SPO 221627

Singh

03/31/21-03/30/23

National Institutes of Health

SNG001 - Adaptive Platform Treatment Trial for Outpatients with COVID-19 (Adapt Out COVID)

The major goal of this project is to evaluate novel treatments for patients with COVID-19. Stanford University is a participating site in this multi-site study.

Role: Co-I

ACTIV-2/A5401 AZD7442 IV & IM- SPO 220675 Singh

03/31/21-03/30/23

National Institutes of Health

AZD7442 IV & IM - Adaptive Platform Treatment Trial for Outpatients with COVID-19 (Adapt Out COVID)

The major goal of this project is to evaluate novel treatments for patients with COVID-19. Stanford University is a participating site in this multi-site study.

Role: Co-I

SPO 198287

Jagannathan (PI)

07/01/20-09/30/22

Innovative Medicine Accelerator Stanford ChEM-H

Systems immunology to identify determinants of viral shedding cessation and symptom resolution in outpatients with mild to moderate COVID- 19

The major goal of this project is to identify host signatures predictive of COVID-19 clinical outcomes

Role: PI

Gates Center for Human Systems Immunology

Jagannathan, Khatri (MPI)

10/01/19-09/30/22

Mechanisms and longevity of innate immune hyporesponsivity to malaria

The major goal of this project is to determine the duration of innate immune hyporesponsivity following resolution of infection.

Role: Co-PI

U01 AI150741-S1	Greenhouse, Jagannathan, Butte (MPI)	04/01/20-03/31/22
<i>Impact of IFN-Lambda on the host immune response to COVID-19</i>		
The major goal of this project is to broadly profile host immunity in individuals participating in a clinical trial of pegylated-lambda interferon for COVID-19.		
Role: MPI		
Gates Center for Human Systems Immunology	Schneider, Jagannathan (MPI)	10/01/19-09/30/21
<i>Measuring disease trajectories in human malaria patients</i>		
The major goal of this project is to determine whether plasma metabolomics are predictive of disease resilience following malaria infection.		
Role: Co-PI		
Stanford Women's Health/Sex Differences Center	Jagannathan, Schneider (MPI)	12/01/19-09/30/21
<i>Investigating basis of sex differences in malaria infection in humans and mice</i>		
The major goal of this project is to evaluate sex-specific differences in response to malaria infection in humans and murine models		
Role: Co-PI		
March of Dimes	Jagannathan (PI)	07/01/19–06/30/21
Identifying novel immunologic targets to reduce the burden of malaria during pregnancy and infancy		
The major goal of this project is to identify cellular and antibody repertoires correlate with protection against malaria during pregnancy and infancy.		
Role: PI		
Gates Center for Human Systems Immunology	Jagannathan, Wang (MPI)	10/01/17-09/30/19
Identifying optimal specificities and Fc domain repertoires for protective anti-malarial immunity in infants		
The major goal of this project is to test the hypothesis that specific cellular and antibody repertoires correlate with protection against malaria during pregnancy and infancy.		
Role: Co-PI		
P01 HD059454	Havlir	08/01/08 – 06/30/19
<i>Novel strategies to prevent malaria and improve HIV outcomes in Africa</i>		
The major goal of this project is to build on current knowledge to establish new approaches to reduce HIV and malaria in sub-Saharan Africa and to advance the public health approach to both diseases.		
Role: Laboratory Core Director and Co-Investigator		
Human Immunology Project Consortium	Jagannathan, Pulendran (MPI)	06/01/18-05/31/19
Systems analysis of innate responses to malaria infection		
The major goal of this pilot project is to use systems biology approaches to define molecular networks that drive the innate immune responses to malaria infection in Ugandan children.		
Role: Co-PI		
K23 AI100949	Jagannathan	07/01/12-04/30/18
Immunologic consequences of highly effective antimalarial chemoprevention		
Mentored, patient-oriented career training award to (1) to study the impact of antimalarial chemoprevention on the development of IL-10-specific counterregulatory mechanisms and malaria-specific T cell responses in children living in high endemicity settings, and (2) to determine whether these responses correlate with protection from subsequent malaria.		
Role: PI		
Stanford ITI Institute	Jagannathan	04/30/17-03/31/18
Training innate immune memories to malaria		

The major goal of this pilot project is to evaluate the impact of repeated malaria stimulation *in vitro* on innate immune function

Role: PI

Stanford Child Health Research Institute Jagannathan 01/01/17-01/01/18

Impact of DHA-PQ chemoprevention in pregnancy on transfer of antimalarial antibodies to newborns

The major goal of this project is to determine the impact of effective artemisinin-based chemoprevention in pregnancy on the generation and transfer of protective antimalarial antibodies to newborns

Role: PI

VII. CLINICAL TRIALS

A. Current Trials

1. Modifying Immunity in Children with Dihydroartemisinin-Piperaquine (MIC-DroP)

NCT 04978272

9/01/21-8/30/26

Funder: National Institutes of Allergy and Infectious Diseases/ National Institutes of Health (U01 AI155325)

This double blind randomized controlled trial will determine whether effective prevention of malaria with IPT during pregnancy and infancy can enhance protective immunity to malaria in children.

Role: PI

2. Optimal Chemopreventive Regimens to Prevent Malaria and Improve Birth Outcomes

NCT 04336189

4/01/20-3/31/25

Funder: National Institutes of Allergy and Infectious Diseases/ National Institutes of Health

This double blind randomized controlled trial is evaluating optimal chemopreventive regimens to prevent malaria in pregnancy.

Role: Co-I (MPI: Grant Dorsey, Phil Rosenthal UCSF)

3. Paxlovid Treatment in PASC: Randomized Double-Blind Placebo-Controlled Pilot Trial.

NCT 05576662

10/12/22-04/30/24

Funder: Pfizer, Inc.

Identify whether treatment with Paxlovid helps alleviate the symptoms of post-acute sequelae of COVID-19.

Role: Co-I (MPI: Linda Geng, Upinder Singh)

5. AIDS Clinical Trials Group ACTIV-2 study (ACTG-5401)

NCT 04518410

12/01/2020-11/30/2023

Funder: National Institutes of Allergy and Infectious Diseases/ National Institutes of Health

This COVID-19 adaptive clinical trial is evaluating different agents for the treatment of mild to moderate SARS-CoV-2 infection in outpatients. Dr. Jagannathan serves as co-lead for the Synairgen inhaled interferon beta agent.

Role: Co-I, SGN001 Study Lead (PI Judith Currier UCLA)

B. Past Trials

1. Single-blind Study of a Single Dose of Peginterferon Lambda-1a Compared with Placebo in Outpatients with Mild COVID-19

NCT 04331899

03/01/20 – 02/01/21

Funder: Stanford University/Quattrone Foderaro Family

24 of 32

The major goals of this study were to determine the potential efficacy of the pharmaceutical Lambda to decrease viral shedding and perhaps decrease the severity of reaction to this virus.

Role: MPI Jagannathan, Singh

2. Prevention of Malaria in HIV-uninfected Pregnant Women and Infants (PROMOTE-BC3)

NCT 02793622

6/08/16-4/14/21

Funder: Bill and Melinda Gates Foundation, National Institutes of Allergy and Infectious Diseases/ National Institutes of Health

This double blind randomized controlled trial evaluated optimal chemopreventive regimens to prevent malaria in pregnant women and the children born to them.

Role: Co-I (PI: Grant Dorsey, UCSF)

2. Reducing the Burden of Malaria in HIV-infected Pregnant Women and their HIV-Exposed Children (PROMOTE-BC2)

NCT 02282293

11/04/14-3/5/19

Funder: National Institutes of Allergy and Infectious Diseases/ National Institutes of Health

This double blind randomized controlled trial evaluated optimal chemopreventive regimens to prevent malaria in HIV-infected pregnant women and the HIV-exposed children born to them.

Role: Co-I (PI: Diane Havlir, UCSF)

3. Reducing the Burden of Malaria in HIV-uninfected Pregnant Women and Infants (PROMOTE-BC1)

NCT 02163447

6/01/14-11/14/18

Funder: National Institutes of Allergy and Infectious Diseases/ National Institutes of Health

This double blind randomized controlled trial is evaluating optimal chemopreventive regimens to prevent malaria in pregnant women and the children born to them.

Role: Co-I (PI: Grant Dorsey, UCSF)

VIII. EDITORIAL SERVICE

2022 Guest editor, PLoS Pathogens

2018- Editorial Board, BMC Medicine

Ad Hoc Journal Peer Review: Science Translational Medicine, Nature Immunology, New England Journal of Medicine, Lancet Infectious Diseases, Journal of Clinical Investigation, ELife, BMC Medicine, PLoS Pathogens, Infection and Immunity, Clinical Infectious Diseases, Journal of Infectious Diseases, Malaria Journal, International Journal of Parasitology, American Journal of Tropical Medicine and Hygiene, Parasite Immunology; Frontiers in Immunology

IX. SERVICE AS GRANT REVIEWER

2024 ad hoc reviewer, NIH Pathogenic Eukaryotes (PTHE) Study Section

2022 ad hoc reviewer, NIAID Special Emphasis Panel (ZAs11 RK-M J1 1, 2022).

2021 ad hoc reviewer, NIH CSR Special Emphasis Panel (IDIB-S90, 2021)

2021 ad hoc reviewer, NIH Collaborative Cross Mouse Model Generation and Immunoregulatory Mechanisms

2018 Early career reviewer, NIH Pathogenic Eukaryotes (PTHE) Study Section

2016 ad hoc reviewer, Department of Defense Congressionally Directed Medical Research Programs

2014 ad hoc reviewer, Medical Research Council, United Kingdom

X. UNIVERSITY ADMINISTRATIVE SERVICE

25 of 32

A. Committee Service

2024-present Reviewer, Stanford Medicine REACH (Racial Equity to Advance a Community of Health) Postbaccalaureate Program
2022-present Division representative, Department of Medicine Team Science Initiative, Stanford University School of Medicine
2021 Reviewer, Stanford ChemH Seed Grants
2021-present Reviewer, Stanford MCHRI Postdoctoral Scholars Fellowships
2020-present Member, Diversity, Equity, and Inclusion Committee, Stanford Immunology Program, Stanford University School of Medicine
2018-present Intern Selection Committee, Department of Medicine, Stanford University
2017-present Fellowship Selection Committee, Division of Infectious Diseases and Geographic Medicine, Stanford University Department of Medicine

B. Leadership roles

2022-present Chair, Community, Diversity, and Inclusion in Immunology (CDIII) Committee, Stanford Immunology Program, Stanford University School of Medicine
2019-present Director, Stanford University Scholarly Concentration in Immunology

XI. SERVICE TO PROFESSIONAL ORGANIZATIONS

A. Membership

2018- Infectious Diseases Society of America
2011- American Society of Tropical Medicine and Hygiene

B. Committee Service

2021-present Young Investigator Award Committee, American Society of Tropical Medicine and Hygiene

C. Leadership Roles

2023-2027 Elected Vice-Chair, Gordon Research Conference on Malaria
2023 Co-Chair, Bill and Melinda Gates Foundation Convening on Naturally Acquired Immunity to Malaria under Chemoprevention, London, UK

XII. PRESENTATIONS

A. Invited Presentations (since 2017)

09/2024 "New insights into regulatory responses induced by repeated Plasmodium infections in children." NIAID Malaria Research Symposium. Rockville, MD.
06/2024 "New insights into regulatory responses induced by repeated Plasmodium infections in children." University of Massachusetts Chan Medical School Department of Medicine Research Seminar Series. Worcester, MA.
10/2022 "Immunologic consequences of early life malaria exposure." University of Pennsylvania Global Parasitology Seminar Series, Philadelphia, PA.
09/2022 "New Insights into Human Immunology of Malaria". RUSH Medical Grand Rounds, Rush University, Chicago, IL
07/2022 "New Insights into Human Immunology of Malaria." Biology of Parasitism Course. Woods Hole, MA

- 03/2022 “Early immune responses have long-term associations with clinical, virologic, and immunologic outcomes in patients with COVID-19.” Stanford Department of Medicine Grand Rounds
- 08/2021 “Immunologic consequences of early life malaria exposure and prevention”. Global Health Lecture Series, Mayo Clinic, Rochester, MN.
- 10/2020 “Peg-interferon lambda for treatment of outpatients with uncomplicated COVID-19: a randomized placebo-controlled trial.” Stanford Department of Medicine Grand Rounds
- 09/2019 “Benefits and consequences of effective prevention of malaria in pregnancy”. University of Washington Global Infectious Diseases Seminar Series. Seattle, Washington.
- 10/2018 “Immunologic consequences of antimalarial chemoprevention.” Twinbrook Seminar Series, NIH/National Institutes of Allergy and Infectious Diseases, Twinbrook, MD.
- 09/2018 “Immunologic consequences of early life malaria exposure and prevention.” Microbiology and Immunology Seminar Series, University of California, Davis.

B. National and Regional Meetings

- 11/2024 “Immunoregulatory mechanisms in pediatric malaria”. 73rd Annual American Society of Tropical Medicine and Hygiene Annual Conference
- 11/2021 Session Chair, Parasite Immunology, 70th Annual American Society of Tropical Medicine and Hygiene Annual Conference
- 11/2021 “Malaria driven expansion of mature, short-lived functional CD56neg NK cells correlates with clinical immunity to malaria.” 70th Annual American Society of Tropical Medicine and Hygiene Annual Conference.
- 05/2021 “Immunologic profiles defining clinical states in malaria”. Human Immunology Project Consortium Annual Meeting. Bethesda, Md.
- 10/2020 Session Chair, Malaria Laboratory Studies, 69th Annual American Society of Tropical Medicine and Hygiene Annual Conference
- 11/2018 Symposium Chair, “Naturally Acquired Immunity – Updates from the Field,” 67th Annual American Society of Tropical Medicine and Hygiene Annual Conference, New Orleans, LA
- 11/2018 “Immunologic consequences of antimalarial chemoprevention.” Speaker. 67th Annual American Society of Tropical Medicine and Hygiene Annual Conference. New Orleans, LA.
- 12/2018 “Health and Well-being in Persons Living with HIV and AIDS.” Invited speaker, The Medical Management of HIV/AIDS and Hepatitis, San Francisco, CA.
- 12/2017 “Longevity, Health, and Well-being in our Patients.” Invited speaker, UCSF Continuing Medical Education Series, The Medical Management of HIV/AIDS and Hepatitis, San Francisco, CA.

C. International Meetings

- 05/2024 “Immunological consequences of early life malaria exposure in children.” Invited Speaker, Asia-Pacific Vaccine and Immunotherapy Conference, Melbourne, Australia.
- 12/2023 “New insights into protective immunity following repeated malaria in children.” Invited Speaker, 18th International Congress of Immunology, Cape Town, South Africa.
- 05/2023 “Immunologic consequences of early life malaria exposure.” Invited Speaker, Gordon Malaria Research Conference, Barcelona, Spain.
- 03/2023 “Immune regulatory mechanisms underlying naturally acquired immunity to malaria.” Speaker and Co-Chair, Bill and Melinda Gates Foundation Convening on “Naturally Acquired Immunity to Malaria under Chemoprevention”, London, UK.
- 07/2019 Session Chair and Invited Mentor, Gordon Research Seminar and Gordon Research Conference on Malaria, Les Diablerets, Switzerland
- 04/2016 “Cardiotoxicity of antimalarials: DHA-PQ intermittent preventative therapy.” Invited participant, World Health Organization Evidence Review Group on Antimalarials

XIII. TEACHING AND TRAINEES

A. Formal Courses (since 2017)

Academic Yr	Course No. & Title	Teaching Contribution
2023-2024	Stanford University, Immunology Research Seminars for Medical Students (Immunol 210) Autumn, Winter, Spring Quarters	Course Director
2023-2024	Stanford University, Translational Immunology (Immunol 208/Immunol 209) Winter, Spring Quarters	Course Director
2023-2024	Stanford University, Cellular and Molecular Immunology, and Introductory Course: (Imm 200, BIO 230, MI 200)	Course Director
2022-2023	Stanford University, Immunology Research Seminars for Medical Students (Immunol 210) Autumn, Winter, Spring Quarters	Course Director
2022-2023	Stanford University, Translational Immunology (Immunol 208/Immunol 209) Winter, Spring Quarters	Course Director
2022-2023	Stanford University, Cellular and Molecular Immunology, and Introductory Course: (Imm 200, BIO 230, MI 200)	Course Instructor
2021-2022	Stanford University, Immunology Research Seminars for Medical Students (Immunol 210) Autumn, Winter, Spring Quarters	Course Director
2021-2022	Stanford University, Translational Immunology (Immunol 208/Immunol 209) Winter, Spring Quarters	Course Director
2021-2022	Stanford University, Cellular and Molecular Immunology, and Introductory Course: (Imm 200, BIO 230, MI 200)	Course Instructor
2020-2021	Stanford University, Immunology Research Seminars for Medical Students (Immunol 210) Autumn, Winter, Spring Quarters	Course Director
2020-2021	Stanford University, COVID-19 Pandemic: Lessons Learned (BIOS 297, Fall, Spring Quarters)	Course Director
2020-2021	Stanford University, Translational Immunology (Immunol 208/Immunol 209), Winter, Spring Quarters	Course Director
2019-2020	Stanford University, Translational Immunology (Immunol 208/Immunol 209) Winter, Spring Quarters	Course Director
2019-2020	Stanford University, Epidemiology	Lecturer
2018-2019	Stanford University, Global Medical Issues in Women (FemGen 206)	Lecturer
2018-2019	Stanford University Translational Immunology, Immunol 209	Lecturer

B. Trainees

I. Graduate Students

a. Primary Supervised and Co-mentored Graduate Students (since 2017)

Dates	Name	Program	Project	Honors/Awards	Current Position (if graduated)
2023-present	Kenneth Musinguzi (primary)	Makerere University Immunology Program (PhD)	Impact of early life malaria exposure on vaccine immunogenicity	NIH/NIAID Fogarty International Center Trainee	n/a
2023-present	Anna Nguyen (co-mentor; primary: Jade Benjamin-Chung)	Stanford Epidemiology and Biostatistics (PhD)	Evaluating the causal effects of anti-malarial chemoprevention in pregnancy and childhood on growth outcomes	- 2024 NIH/NIAID F31 recipient	n/a
2022-present	Savannah Lewis	Stanford Microbiology and Immunology (PhD)	Mechanisms of NK cell adaptation in malaria	- 2023 Blatvinik Fellow - 2023 Stanford Immunology Annual	n/a

				Scientific Conference Most Outstanding Presentation	
2022-2023	Zachary Renfro	Stanford Medical School (M.D., MedScholars)	Toll like receptor responses following malaria infection in children		n/a
2021-present	Alea Delmastro	Stanford Immunology Program (PhD) (Co-Advisor, Mike Angelo)	Gravidity-dependent myeloid cell adaptation in malaria-endemic settings		n/a
2021-2024	Jordan John Lee	Stanford Epidemiology and Biostatistics (MPh) (Co-Advisor, Jade Benjamin-Chung)	Impact of IPTp on non-malarial causes of fever	- 2023 Invited speaker, Stanford Global Health Convening	Los Angeles County Department of Public Health
2020-2022	Daniel Ruiz-Betancourt	Stanford Medical School (M.D., MedScholars)	Toll like receptor responses following COVID-19 in adults		Medical Student, Stanford University
2020-present	Jason Nideffer	Stanford Immunology Program (PhD) (Co-Advisor, Maria Grazia Roncarolo)	Mechanisms underlying disease tolerance to malaria in young children	- 2023 Chem-H Stanford Graduate Interdisciplinary Fellowship - 2023 Invited speaker, Gordon Research Seminar on Malaria - 2022 Invited speaker, EMBL Innate Immunity conference	n/a
2020-2023	Adam Kiro Singh	Stanford Microbiology and Immunology (PhD)	Role of Tr1 cells in gravidity-dependent protection from malaria in pregnancy		*Successfully Defended Thesis Sep '23
2018-2020	Margaret Murray	Stanford Epidemiology and Biostatistics (MPh)	Biologic Sex and Malaria Risk		Consultant
2018-2021	Kate Naluwu	Makerere University Immunology (MPh)	HLA-G and infant malaria risk		Research Technician, IDRC Uganda
2017-2022	Nicholas Zehner	Stanford Medical School (M.D., MedScholars)	Sickle cell trait and malaria risk in young infants		Internal Medicine Resident, Stanford University

b. Graduate Rotation Students (since 2017)

2024 (Win) Soyeon Kim (Stanford Immunology PhD Program)
 2023 (Spr) Xariana Carmen Valles Torres (Stanford Immunology PhD Program)
 2022 (Spr) Chloe Kashigawa (Stanford Immunology PhD Program)
 2022 (Spr) Potchara Boonrat (Stanford Immunology PhD Program)
 2022 (Win) Savannah Lewis (Stanford Microbiology and Immunology PhD Program)
 2021 (Fall) Alea Delmastro (Stanford Immunology PhD Program)
 2020 (Fall) Jason Nideffer (Stanford Immunology PhD Program)
 2018 (Fall) Yeeun Kim (Stanford Immunology PhD Program)

c. PhD Thesis Advisory Committee (since 2017)

2023- Evan Maestri (Stanford Immunology PhD Program)
 2023- Potchara Boonrat (Stanford Immunology PhD Program)
 2023- Maddie Lee (Stanford Immunology PhD Program)
 2023 Hunter Martinez (Stanford Immunology PhD Program)
 2023- Candace Liu (Stanford Immunology PhD Program)
 2018-2021 Nicole Marie Davis (Stanford Microbiology and Immunology PhD Program)
 2018 Marta Andres-Terres (Stanford Immunology PhD Program)
 2017-2021 Aditya Rao (Stanford Immunology PhD Program)

d. PhD Thesis Examiner (since 2017)

2020 Megan Soon (Queensland Institute for Medical Research, Queensland, Australia)
 2018 Marzeh Jabbarzare (University of Melbourne, Melbourne Australia)

II. Postdoctoral Fellows Mentored (since 2017)

Dates	Name	Position	Project	Honors/Awards	Current Position (if graduated)
2023-present	Muhammad Abdelbasset Ahmad, PhD	Post-doctoral fellow, Stanford University	Impact of in utero malaria exposure on infant immunity		
2022-present	Florian Bach, PhD	Post-doctoral fellow, Stanford University	Impact of antimalarial chemoprevention in infancy on immune competence	2023-2026 Stanford University Berry Postdoctoral Fellowship	
2021-present	Stephen Tukwasibwe	Post-doctoral fellow, Infectious Diseases Research Collaboration, Uganda	Impact of prior malaria exposure on NK cell antibody-dependent cellular cytotoxicity		
2020-2023	Kattria van der Ploeg, PhD	Post-doctoral fellow, Stanford University	SARS-CoV-2 specific T cells following natural infection		Research Scientist, Stanford University
2020-2023	Karen Jacobson, MD	Post-doctoral fellow, Stanford University	1) SARS-CoV-2 pathogenesis 2) Impact of in utero SARS-CoV-2 infection on infant growth and neurodevelopment	-2023 ASTMH/Burroughs Wellcome Postdoctoral Fellowship - 2023 Thrasher Award 2023 NIAID K23 2023: Impact Score 11	Research Scientist, Kaiser Permanente Northern California Division of Research

2018 – 2021	Maureen Ty, PhD	Post-doctoral fellow, Stanford University	CD56 negative NK cells in malaria		Laboratory Leadership Services Fellow, Centers for Disease Control
2017 - present	Kathleen Dantzler, PhD	Post-doctoral fellow, Stanford University	Mechanisms underlying malaria-induced $\gamma\delta$ T cell dysfunction	2020-2023 AP Giannini Postdoctoral fellowship 2021-2022 ASTMH Centennial Award 2021 Thrasher Award 2019-2020 Stanford MCHRI Postdoctoral Fellowship	

I. Undergraduate Students Mentored (since 2017)

Dates	Name	Position	Project	Honors/Awards	Current Position (if graduated)
2023-2024	Nora Ming-Min Yang	Honors Thesis Advisor, Stanford University	Epigenetic Mechanisms of Trained Immunity in Monocytes During Natural Malaria Infection in Humans	2023- Stanford Merigan Student Fellowship in Infectious Diseases 2024- Honors in Human Biology 2024- Joshua Lederberg Award for Academic Excellence in Human Biology	
2019-2020	Heman Gill	Honors Thesis Advisor, Stanford University	Assessing Relationships Between Antibody-Dependent Cellular Cytotoxicity and Innate Cell Phenotypes in Children from Tororo, Uganda	Honors in Human Biology, Stanford University	Health Team Manager, the Primary school

XIV. CLINICAL SERVICE

01/21	Attending Physician, COVID-19 Consult Service, Stanford University Medical Center	2 weeks attending
08/17 –	Attending Physician, Infectious Diseases Consultation Service, Stanford University Medical Center	2 weeks attending/year
07/12 – 12/16	Attending Physician, Joint Infectious Diseases/HIV Consultation Service, Zuckerberg San Francisco General Hospital	1 month attending/year
07/10 – 12/16	Attending Physician, Positive Health Program/Ward 86 HIV Primary Care, Zuckerberg San Francisco General Hospital	1/2 day clinic/week
07/10 – 06/14	ER Attending Physician, San Francisco Veteran's Administration	1-2 weekend shifts/month

Appendix B

APPENDIX B

**Elements of Challenged Claims with Exemplary Disclosures from
WO '323, WO '351, and US '079**

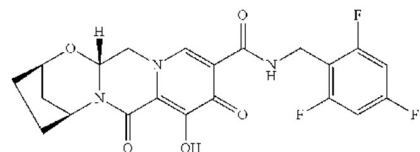
Claim 1			
Claims	<u>WO '323 (EX-1005)</u>	<u>WO '351 (EX-1006)</u>	<u>US '079 (EX-1007)</u>
Claim 1: 1[pre] - A tablet	<i>See Declaration, Section VIII.A.</i> WO '323 discloses a pharmaceutical composition comprising therapeutically effective amounts of a “[Formula I] compound disclosed herein” and one or more “additional therapeutic agents,” e.g., anti-HIV agents, including <i>solid unitary dosage forms for simultaneous oral administration</i>. WO '323 (EX-1005), 37:7–21; 12:18–20; <i>see also id.</i> at 5:14–22 (using a “pharmaceutical composition described	<i>See Declaration, Section VIII.B.</i> WO '351 discloses a “<i>pharmaceutical combination</i> comprising (a) dolutegravir [(DTG)], (b) emtricitabine [(FTC)] and (c) tenofovir or a prodrug thereof” and its use for the treatment of HIV infection. WO '351 (EX-1006), Abstract, 1:3–7 (emphasis added), 3:15–16, 3:23–26 (amounts of compounds when taken together are effective to treat HIV infection in a human); <i>see also id.</i> at 4:1–15 (DTG	<i>See Declaration, Section VIII.E.</i> US '079 refers to “large size <i>tablets</i>” which may result in esophageal damage ..., which ultimately leads to poor patient compliance. US '079 (EX-1007), [0019]. It further states that “[t]he combination of antiretroviral drugs administered in a <i>single unit dosage form</i> may result in increased patient compliance as the pill burden is reduced and dosing schedules are simplified.” <i>Id.</i> at [0022].

	hereinabove for the treatment of HIV infection in a human being having or at risk of having the infection”) (treating the “proliferation of the HIV virus” and “treating AIDS” in “e.g. a human”). WO ’323 states that “[p]harmaceutical compositions of the invention are formulated so as to allow the active ingredients contained therein to be bioavailable upon administration of the composition to a patient[,] ... and take the form of one or more dosage units, <i>where for example, a tablet may be a single dosage unit.</i>” <i>Id.</i> at 36:11–23 (emphasis added) (also stating that “[a]ctual methods of preparing such dosage forms are known, or will be	identified as an INSTI); 6:24–32 (FTC identified as an NRTI), 9 (tenofovir identified as an NtRTI). WO ’351 discloses that “the combination of the present invention is administered once daily” and is “preferably a <i>solid oral dosage form ... in particular a tablet.</i>” <i>Id.</i> at 17:27–28, 23:6–8 (emphasis added).	US ’079 discloses pharmaceutical compositions “comprising at least one INSTI and at least one anti-HIV or anti-retroviral agent optionally with pharmaceutically acceptable excipients.” <i>Id.</i> at [0036]. The term “pharmaceutical composition” is said to include <i>tablets</i>, and the pharmaceutical composition may be administered orally through <i>unit dosage forms including tablets.</i> <i>Id.</i> at [0036], [0071] (emphasis added). US ’079 states that “[a] <i>tablet formulation is the preferred solid dosage form</i> due to its greater stability, less risk of chemical interaction between different medicaments, smaller bulk, accurate dosage, and ease of production.” <i>Id.</i> at [0078]
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	apparent, to those skilled in this art”). WO ’323 also claims pharmaceutical compositions, such as “pharmaceutical composition comprising a compound of any of claims 1–32 ... or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.” 240–41 (claim 33 depending from claim 32). It also claims methods treatment, such as a “method of treating HIV infection in a human by administering to the human having or at risk of having the infection by administering ... a therapeutically effective amount of ... a pharmaceutical composition claim 33.”). <i>Id.</i> at 241 (claim 37).		(emphasis added); <i>see also id.</i> at [0079] (“[s]olid unit dosage forms are <i>preferably in the form of tablets</i> either single or bilayered or multilayered tablets”). US ’079 exemplifies a <i>tablet</i> containing DTG (50 mg), TDF (300 mg), FTC (200 mg), and excipients having a uncoated weight of 1030 mg and coated weight of 1055 mg. <i>Id.</i> at [0129]–[0130].
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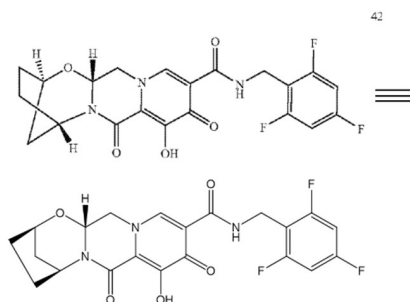
	WO '323 discloses and claims methods for treating or preventing HIV with a combination therapy comprising therapeutically effective amounts of a “compound disclosed herein” and one or more “additional therapeutic agents,” e.g., anti-HIV agents, including by oral administration of a <i>solid unitary dosage form</i>, where “a compound disclosed herein is combined with one or more additional therapeutic agents.” <i>Id.</i> at 37:7–21; <i>see also id.</i> at 40:18–20 (disclosing similar multi-agent “unitary dosage form for simultaneous administration to a patient, for example as a <i>solid dosage form for oral administration.</i>”) (emphasis added); 39:25–27 (“In certain embodiments, a compound disclosed herein, or a pharmaceutically		
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	acceptable salt thereof, is combined with two additional therapeutic agents.”); 241 (claims 34–36 - composition of claim 33 further comprising anti-HIV agents selected from <i>inter alia</i> “HIV nucleoside inhibitors of reverse transcriptase, [and] HIV nucleotide inhibitors of reverse transcriptase [N(t)RTIs]”); 241–42 (claims 37–40 - method of treating HIV infection in a human by administering a therapeutically effective amount of a pharmaceutical composition claim 33, including a method further comprising administering to a human a therapeutically effective amount of one or more anti-HIV agents selected from <i>inter alia</i> N(t)RTIs.)).		
1[a] - 50 mg of the compound of Formula I:	See Declaration, Section VIII.A, and 1[pre].	See Declaration, Section VIII.B, and 1[pre].	See Declaration, Section VIII.E, and 1[pre].



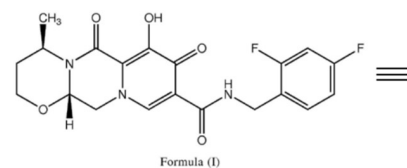
or a pharmaceutically acceptable salt thereof

WO '323 discloses specific compounds of Formula (I) and methods for their synthesis, including a **Compound 42** (below). See generally WO '323 (EX-1005), 44–212; see also *id.* at 99:8–101:25 (Example 42). These compounds are said to be INSTIs. *Id.* at 6:7–8.



Compound 42 corresponds to **Formula (I) in 1[a]** in a slightly different orientation. EX-1004, ¶ 74. **Compound 42** is claimed as part of small Markush group of seven compounds. *Id.* at 240–41 (claim 32).

WO '351 discloses dolutegravir (DTG) (see Formula (I) (below), in combination with FTC and a tenofovir prodrug, preferably as a tablet.



WO '351 (EX-1006), Abstract, 2:15–16, 4:1–25, 23:6–8; see also EX-1004, ¶ 61 (structure reoriented to match Formula (I) orientation). DTG is preferably in “the form of a **pharmaceutically acceptable salt**,” and “especially the mono-sodium salt.” WO '351 (EX-1006) at 5:22–27 (emphasis added).

US '079 refers to the term “integrase inhibitor(s)” as including their **pharmaceutically acceptable salts** and pharmaceutically acceptable prodrugs. US '079 (EX-1007), [0041].

US '079 exemplifies a tablet containing DTG (**50 mg**), TDF (300 mg), FTC (200 mg), and excipients having a uncoated weight of 1030 mg and coated weight of 1055 mg. *Id.* at [0129]–[0130].

	WO '323 also discloses <i>pharmaceutically acceptable salts</i> of INSTI compounds, e.g., compound 42. <i>Id.</i> at 5:23–25, 5:26–6:6; <i>see also id.</i> at 14:16–15:20 (defining “pharmaceutically acceptable salt” and disclosing salts derived from an alkali metal (for example, sodium)). WO '323 discloses and claims pharmaceutical compositions, e.g., tablets, containing a “<i>therapeutically effective amount</i>” of an INSTI of Formula (I), e.g., compound 42, or a <i>pharmaceutically acceptable salt thereof</i>, including with other anti-HIV agents. <i>Id.</i> at 35:8–17, 36:12–15, 36:18–21, 37:7–19; <i>see also id.</i> at 241–42 (claims 33 (depending from claim 32), 34–36), (claims	WO '351 prefers pharmaceutical combinations providing “in particular <i>40 to 60 mg</i>” DTG per day. WO '351 (EX-1006), 19:3–12 (emphasis added). It identifies combinations having <i>about 50 mg</i> DTG, about 200 mg of FTC, and about 25 mg of TAF. <i>Id.</i> at 19:30–20:2 (emphasis added).	
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	37 (depending from claim 32 or 33), 38–40) (treating HIV with therapeutically effective amount of claim 33 composition). WO '323 discloses pharmaceutical compositions where a Formula (I) compound, e.g., Compound 42, is present in the composition in “an amount which is effective to treat a particular disease or condition of interest.” <i>Id.</i> at 35:11–17. This includes compositions containing “about 25 to about 500 mg” of a Formula (I) compound and also “about 25 mg, 50 mg, 100 mg, ...” of a Formula (I) compound, e.g., Compound 42. <i>Id.</i> at 35:17–23 (emphasis added).		
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1[b] - 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and	See Declaration, Section VIII.A, and 1[pre] and 1[a]. WO '323 discloses combination therapy comprising a therapeutically effective amount of an INSTI of Formula (I) compound (or a salt thereof), and therapeutically effective amounts of, e.g., an NTRI, an NtRTI, and combinations thereof. WO '323 (EX-1005), 37:7–12, 38:13–21; <i>see also id.</i> at 241 (claims 33–36), 241–42 (claims 37–40); 16:8–21 (“therapeutically effective amount routinely determined by [POSA]”). This includes in solid unitary dosage forms for simultaneous oral administration, e.g., tablets. <i>Id.</i> at 37:7–21, 40:18–22, 12:18–20.	See Declaration, Section VIII.B, and 1[pre] and 1[a]. WO '351 discloses a “particularly preferred embodiment” where the prodrug of tenofovir is [TAF], also known as GS-7340” WO '351 (EX-1006), 12:21–13:13 (emphasis added). In a particularly preferred embodiment “[TAF] is present in the form of its hemifumarate or fumarate.” <i>Id.</i> at 13:16–18 (emphasis added). WO '351 prefers pharmaceutical combination providing “in particular 5 to 42 mg” TAF per day. <i>Id.</i> at 19:3–12 (emphasis added); <i>see also id.</i> 19:30–20:6 (describing pharmaceutical combinations with about 25 mg of TAF). It identifies	See Declaration, Section VIII.E, and 1[pre] and 1[a]. US '079 refers to the term “anti-HIV agent” as including pharmaceutically acceptable salts and pharmaceutically acceptable prodrugs. <i>Id.</i> at [0041] (emphasis added). It then discloses NRTIs/NtRTIs as anti-HIV agents, and prefers “tenofovir, emtricitabine, lamivudine or zidovudine” US '079 (EX-1007), [0047], [0051] (emphasis added). US '079 prefers that “the pharmaceutical composition comprises dolutegravir, tenofovir and emtricitabine/lamivudine optionally with one or more pharmaceutically acceptable
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	Specific NtRTIs include “tenofovir” and its prodrug salts “[TDF] and <i>[TAF] fumarate</i> .” <i>Id.</i> at 38:18–21 (emphasis added).	combinations having about 50 mg DTG, about 200 mg of FTC, and <i>about 25 mg of TAF</i> . <i>Id.</i> at 19:30–20:2.	excipients. <i>Id.</i> at [0055] (emphasis added). US ’079 exemplifies a tablet containing DTG (50 mg), TDF (300 mg), FTC (200 mg), and excipients having a uncoated weight of 1030 mg and coated weight of 1055 mg. <i>Id.</i> at [0129]–[0130].
1[c] - 200 mg emtricitabine or a pharmaceutically acceptable salt thereof.	See Declaration, Section VIII.A, and 1[pre], 1[a], and 1[b]. WO ’323 discloses combination therapy comprising a therapeutically effective amount of an INSTI of Formula (I) compound (or a salt thereof), e.g., compound 42 , and <i>therapeutically effective amounts of, e.g., an NRTI</i> , an NtRTI, and combinations thereof. WO ’323 (EX-1005), 37:7–12, 38:13–21 (emphasis added).	See Declaration, Section VIII.B, and 1[pre], 1[a], and 1[b]. WO ’351 discloses pharmaceutical combinations, e.g., tablets containing <i>FTC</i> . WO ’351 (EX-1006), Abstract, 6:24–32 (emphasis added). In a preferred embodiment “[<i>FTC</i>] is present in the form of its <i>free base</i> .” <i>Id.</i> at 8:10–11 (emphasis added).	See Declaration, Section VIII.E, and 1[pre], 1[a], and 1[b]. US ’079 refers to the term “anti-HIV agent” as including <i>pharmaceutically acceptable salts</i> and pharmaceutically acceptable prodrugs. US ’079 (EX-1007), [0041] (emphasis added). It then discloses NRTIs/NtRTIs as anti-HIV agents, and prefers “tenofovir, <i>emtricitabine</i> , lamivudine or zidovudine....” <i>Id.</i> at

	This includes in solid unitary dosage forms for simultaneous oral administration, e.g., tablets. <i>Id.</i> at 37:7–21, 40:18–22, 12:18–20. Specific NRTIs include “<i>emtricitabine [FTC]</i>” <i>Id.</i> at 38:14–17 (emphasis added).	WO ’351 prefers that the pharmaceutical combination comprise “in particular 150 to 250 mg” FTC per day. <i>Id.</i> at 19:3–12 (emphasis added); <i>see also id.</i> (describing pharmaceutical combinations with about 200 mg of FTC). It identifies combinations having about 50 mg DTG, about 200 mg of FTC, and about 25 mg of TAF. <i>Id.</i> at 19:30–20:2.	[0047], [0051] (emphasis added). US ’079 prefers that “the pharmaceutical composition comprises dolutegravir, tenofovir and emtricitabine/lamivudine optionally with one or more pharmaceutically acceptable excipients. <i>Id.</i> at [0055] (emphasis added). US ’079 exemplifies a tablet containing DTG (50 mg), TDF (300 mg), FTC (200 mg), and excipients having a uncoated weight of 1030 mg and coated weight of 1055 mg. <i>Id.</i> at [0129]–[0130].
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Elements of Challenged Claims with Exemplary Disclosures from WO '323, WO '351, and US '709

Claims 2-8

Claims	<u>WO '323</u>	<u>WO '351</u>	<u>US '709</u>
Claim 2			
The tablet of claim 1,	See Declaration, Section VIII.A, and Claim 1.	See Declaration, Section VIII.B, and Claim 1.	See Declaration, Section VIII.E, and Claim 1.
wherein the tablet comprises 50 mg of the compound of Formula I as a pharmaceutically acceptable salt thereof.	<i>See 1[a]</i> above WO '323 discloses <i>pharmaceutically acceptable salts</i> of INSTI compounds, e.g., compound 42. WO '323 (EX-1005), 5:23–25, 5:26–6:6 (emphasis added); <i>see also id.</i> at 14:16–15:20 (defining “pharmaceutically acceptable salt” and disclosing salts derived from an alkali metal (for example, sodium)); <i>see also id.</i> at 15:17–19 (referring to salts containing Na⁺).	<i>See 1[a]</i> above WO '323 states that “the term ‘dolutegravir’ comprises all the <i>pharmaceutically acceptable salts</i>, hydrates and/or solvates thereof[,]” and that DTG is preferably in “the form of a <i>pharmaceutically acceptable salt</i>,” and “especially the mono-sodium salt.” WO '351 (EX-1006), 5:22–27 (emphasis added).	<i>See 1[a]</i> above US '079 refers to the term “integrase inhibitor(s)” as including their <i>pharmaceutically acceptable salts</i> and pharmaceutically acceptable prodrugs. US '079 (EX-1007), [0041] (emphasis added).

	WO '323 discloses and claims pharmaceutical compositions, e.g., tablets, containing a “therapeutically effective amount” of an INSTI of Formula (I), e.g., compound 42, or a <i>pharmaceutically acceptable salt thereof</i>, including with other anti-HIV agents. <i>Id.</i> at 35:8–17, 36:12–15, 36:18–21, 37:7–19; <i>see also id.</i> at 241–42 (claims 33–40).		
Claim 3			
The tablet of claim 1,	<i>See Declaration, Section VIII.A, and Claim 1.</i>	<i>See Declaration, Section VIII.B, and Claim 1.</i>	<i>See Declaration, Section VIII.E, and Claim 1.</i>
wherein the tablet comprises 25 mg tenofovir	<i>See 1[b]</i>	<i>See 1[b]</i>	<i>See 1[b]</i>

alafenamide as a pharmaceutically acceptable salt thereof.	WO '353 discloses NtRTIs that include “tenofovir” and its prodrug salts “[TDF] and <i>[TAF] fumarate</i> .” WO '323 (EX-1005), 38:18–21 (emphasis added).	WO '323 states that “the term ‘tenofovir alafenamide’ comprises all the <i>pharmaceutically acceptable salts</i> , hydrates and/or solvates thereof[,]” and that TAF is particularly preferred in the “form of its hemifumarate or fumarate, especially its hemifumarate.” WO '351 (EX-1006), 13:11–18.	US '079 refers to the term “anti-HIV agent” as including <i>pharmaceutically acceptable salts</i> and <i>pharmaceutically acceptable prodrugs</i> . US '079 (EX-1007), [0041] (emphasis added). It then discloses NRTIs/NtRTIs as anti-HIV agents, and prefers “ <i>tenofovir</i> , emtricitabine, lamivudine or zidovudine” <i>Id.</i> at [0047], [0051] (emphasis added).
Claim 4			
The tablet of claim 1,	<i>See Declaration, Section VIII.A, and Claim 1.</i>	<i>See Declaration, Section VIII.B, and Claim 1.</i>	<i>See Declaration, Section VIII.E, and Claim 1.</i>
wherein the tablet comprises 50 mg of the compound of Formula I as a pharmaceutically acceptable salt thereof,	<i>See 1[a] and claim 2</i> WO '323 also discloses <i>pharmaceutically acceptable salts</i> of INSTI compounds, e.g., compound	<i>See 1[a] and claim 2</i> WO '351 states that DTG is preferably in “the form of a <i>pharmaceutically acceptable salt</i> ,” and	<i>See 1[a] and claim 2</i> US '079 refers to the term “integrase inhibitor(s)” as including their <i>pharmaceutically</i>

	42. WO '323 (EX-1005), 5:23–25, 5:26–6:6 (emphasis added); <i>see also id.</i> at 14:16–15:20 (defining “pharmaceutically acceptable salt” and disclosing salts derived from an alkali metal (for example, sodium)); <i>see also id.</i> at 15:17–19 (referring to salts containing Na⁺). WO '323 discloses and claims pharmaceutical compositions, e.g., tablets, containing a “therapeutically effective amount” of an INSTI of Formula (I), e.g., compound 42, or a <i>pharmaceutically acceptable salt thereof</i>, including with other anti-HIV agents. <i>Id.</i> at 35:8–17, 36:12–15, 36:18–21, 37:7–19 (emphasis added); <i>see also id.</i> at 241–42 (claims 33–40).	“especially the mono-sodium salt.” WO '351 (EX-1006), 5:22–27 (emphasis added).	<i>acceptable salts</i> and pharmaceutically acceptable prodrugs. US '079 (EX-1007), [0041] (emphasis added).
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25 mg tenofovir alafenamide as a pharmaceutically acceptable salt thereof,	<i>See 1[b] and claim 3</i> WO '353 discloses NtRTIs that include “tenofovir” and its prodrug salts “[TDF] and [TAF] fumarate.” WO '323 (EX-1005), 38:18–21 (emphasis added).	<i>See 1[b] and claim 3</i> WO '323 states that “the term ‘tenofovir alafenamide’ comprises all the pharmaceutically acceptable salts, hydrates and/or solvates thereof[,]” and that TAF is particularly preferred in the “form of its hemifumarate or fumarate, especially its hemifumarate.” WO '351 (EX-1006), 13:11–18.	<i>See 1[b] and claim 3</i> US '079 refers to the term “anti-HIV agent” as including pharmaceutically acceptable salts and pharmaceutically acceptable prodrugs. <i>Id.</i> at [0041] (emphasis added). It then discloses NRTIs/NtRTIs as anti-HIV agents, and prefers “tenofovir, emtricitabine, lamivudine or zidovudine” US '079 (EX-1007), [0047], [0051] (emphasis added).
and 200 mg emtricitabine.	<i>See 1[c].</i> Specific NRTIs include “emtricitabine [FTC].” WO '323 (EX-1005), 38:15–17 (emphasis added).	<i>See 1[c].</i> WO '351 states that “[i]n a preferred embodiment emtricitabine is present in the form of its free base, i.e. not in the form of an acid	<i>See 1[c].</i> US '079 discloses NRTIs/NtRTIs as anti-HIV agents, and prefers “tenofovir, emtricitabine, lamivudine or zidovudine”

		addition salt.” WO ’351 (EX-1006), 8:10–11.	US ’079 (EX-1007), [0047], [0051] (emphasis added).
Claim 5			
The tablet of claim 1,	See Declaration, Section VIII.A, and Claim 1.	See Declaration, Section VIII.B, and Claim 1.	See Declaration, Section VIII.E, and Claim 1.
wherein the tablet comprises 52 mg of the sodium salt of the compound of Formula I.	<i>See 1[a] and claims 2, 4</i> WO ’323 discloses that examples of “pharmaceutically acceptable salts” include salts derived from an appropriate base, such as an alkali metal (<i>for example, sodium</i>)” WO ’323 (EX-1005), 14:16–15:20 (emphasis added); <i>see also id.</i> at 15:17–19 (referring to salts containing Na⁺). WO ’323 discloses and claims pharmaceutical compositions, e.g., tablets, containing a “therapeutically effective	<i>See 1[a] and claims 2, 4</i> WO ’351 prefers that DTG is especially in the form of “the <i>mono-sodium salt.</i>” WO ’351 (EX-1006), 5:22–27 (emphasis added); <i>see also id.</i> at 6:8–10 (numbers referring to weight (mg) are based on the weight of DTG in its free form).	<i>See 1[a] and claims 2, 4</i> US ’079 refers to the term “integrase inhibitor(s)” as including their <i>pharmaceutically acceptable salts</i> and pharmaceutically acceptable prodrugs. US ’079 (EX-1007), [0041] (emphasis added).

	amount” of an INSTI of Formula (I), e.g., compound 42 , or a <i>pharmaceutically acceptable salt thereof</i> , including with other anti-HIV agents. <i>Id.</i> at 35:8–17, 36:12–15, 36:18–21, 37:7–19 (emphasis added); <i>see also id.</i> at 241–42 (claims 33–40).		
Claim 6			
The tablet of claim 1,	See Declaration, Section VIII.A, and Claim 1.	See Declaration, Section VIII.B, and Claim 1.	See Declaration, Section VIII.E, and Claim 1.
wherein the tablet comprises 25 mg tenofovir alafenamide as tenofovir alafenamide fumarate.	WO ’353 discloses NtRTIs that include “tenofovir” and its prodrug salts “[TDF] and <i>[TAF] fumarate</i> .” WO ’323 (EX-1005), 38:18–21 (emphasis added).	WO ’351 prefers that TAF “is present in form of its hemifumarate or <i>fumarate</i> .” WO ’351 (EX-1006), 13:16–18 (emphasis added).	US ’079 refers to the term “anti-HIV agent” as including <i>pharmaceutically acceptable salts</i> and <i>pharmaceutically acceptable prodrugs</i> and prefers “ <i>tenofovir</i> , emtricitabine, lamivudine or

			zidovudine” US ’079 (EX-1007), [0047], [0051] (emphasis added).
Claim 7			
The tablet of claim 1,	See Declaration, Section VIII.A, and Claim 1.	See Declaration, Section VIII.B, and Claim 1.	See Declaration, Section VIII.E, and Claim 1.
wherein the tablet comprises 28 mg tenofovir alafenamide hemifumarate.	<i>See 1[b] and claims 3–4</i> WO ’323 discloses NtRTIs that include “tenofovir” and its prodrug salts “[TDF] and <i>[TAF] fumarate</i> .” WO ’323 (EX-1005), 38:18–21 (emphasis added).	<i>See 1[b] and claims 3–4</i> WO ’351 especially prefers that TAF as its <i>hemifumarate</i> .” WO ’351 (EX-1006), 13:16–18; <i>see also id.</i> at 13:20–22 (numbers referring to weight (mg) are based on the weight of TAF as free base).	<i>See 1[b] and claims 3–4</i> US ’079 refers to the term “anti-HIV agent” as including <i>pharmaceutically acceptable salts</i> and <i>pharmaceutically acceptable prodrugs</i> and prefers “ <i>tenofovir</i> , emtricitabine, lamivudine or zidovudine” US ’079 (EX-1007), [0047], [0051] (emphasis added).
Claim 8			
The tablet of claim 1,	See Declaration, Section VIII.A, and Claim 1.	See Declaration, Section VIII.B, and Claim 1.	See Declaration, Section VIII.E, and Claim 1.

wherein the tablet comprises 52 mg of the sodium salt of the compound of Formula I,	See 1[a] and claim 5 WO '323 discloses that examples of “pharmaceutically acceptable salts” include salts derived from an appropriate base, such as an alkali metal (<i>for example, sodium</i>). WO '323 (EX-1005), 14:16–15:20 (emphasis added); <i>see also id.</i> at 15:17–19 (referring to salts containing Na⁺). WO '323 discloses and claims pharmaceutical compositions, e.g., tablets, containing a “therapeutically effective amount” of an INSTI of Formula (I), e.g., compound 42, or a <i>pharmaceutically acceptable salt thereof</i>, including with other anti-HIV agents. <i>Id.</i> at 35:8–17, 36:12–15, 36:18–21, 37:7–19 (emphasis added); <i>see</i>	See 1[a] and claim 5 WO '351 prefers that DTG is especially in the form of “the <i>mono-sodium salt</i>.” WO '351 (EX-1006), 5:22–27 (emphasis added); <i>see also id.</i> at 6:8–10 (numbers referring to weight (mg) are based on the weight of DTG in its free form).	See 1[a] and claim 5 US '079 refers to the term “integrase inhibitor(s)” as including their <i>pharmaceutically acceptable salts</i> and pharmaceutically acceptable prodrugs. US '079 (EX-1007), [0041] (emphasis added).
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	<i>also id.</i> at 241–42 (claims 33–40).		
28 mg tenofovir alafenamide hemifumarate,	<i>See 1[b] and claim 7</i> WO '353 discloses NtRTIs that include “tenofovir” and its prodrug salts “[TDF] and [TAF] fumarate.” WO '353 (EX-1005), 38:18–21 (emphasis added).	<i>See 1[b] and claim 7</i> WO '351 especially prefers that TAF as its hemifumarate.” WO '351 (EX-1005), 13:16–18; <i>see also id.</i> at 13:20–22 (numbers referring to weight (mg) are based on the weight of TAF as free base).	<i>See 1[b] and claim 7</i> US '079 refers to the term “anti-HIV agent” as including pharmaceutically acceptable salts and pharmaceutically acceptable prodrugs and prefers “tenofovir, emtricitabine, lamivudine or zidovudine” US '079 (EX-1007), [0047], [0051] (emphasis added).
and 200 mg emtricitabine	<i>See 1[c] and claim 4</i> Specific NRTIs include “emtricitabine [FTC]” <i>Id.</i> at 38:14–17 (emphasis added).	<i>See 1[c] and claim 4</i> WO '351 states that “[i]n a preferred embodiment emtricitabine is present in the form of its free base, i.e. not in the form of an acid addition salt.” WO '351 (EX-1005), 8:10–11.	<i>See 1[c] and claim 4</i> US '079 discloses NRTIs/NtRTIs as anti-HIV agents, and prefers “tenofovir, emtricitabine, lamivudine or zidovudine....” US '079

		(EX-1007), [0047], [0051] (emphasis added).
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<u>Elements of Challenged Claims with Exemplary Disclosures from WO '323, WO '351, and US '709</u>			
<u>Claims 9-13</u>			
Claims	<u>WO '323</u>	<u>WO '351</u>	<u>US '709</u>
Claim 9			
The tablet of claim 1,	<i>See Declaration, Section VIII.A, and Claim 1.</i>	<i>See Declaration, Section VIII.B, and Claim 1.</i>	<i>See Declaration, Section VIII.E, and Claim 1.</i>
wherein the tablet has a total weight of less than 1000 mg.	<i>See 1[pre]</i> WO '323 refers to a “pharmaceutical composition,” e.g., tablet, as “a formulation of a compound of the invention and a medium generally accepted in the art for the delivery of the biologically active compound to mammals, e.g., humans. Such a	<i>See 1[pre]</i> WO '351 discloses pharmaceutical compositions, e.g., tablets, with pharmaceutical excipients where the <i>total amount</i> of dolutegravir, emtricitabine and tenofovir alafenamide is particularly <i>192 to 326 mg per day</i> with the remainder excipients. WO '351 (EX-1006),	<i>See 1[pre]</i> US '079 exemplifies a tablet containing DTG (50 mg), TDF (300 mg), FTC (200 mg), and specific excipients, having a uncoated weight of 1030 mg and coated weight of 1055 mg. US '079 (EX-1007), [0129]–[0130] (emphasis added).

	medium includes all pharmaceutically acceptable carriers, diluents or excipients therefor.” WO ’323 (EX-1005), 16:4–7. <i>See also</i> 37:13–16 (“In one embodiment, pharmaceutical compositions comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof in combination with one or more additional therapeutic agents, and a pharmaceutically acceptable carrier, diluent or excipient are provided”).	17:15–18; <i>see also id.</i> at 19:30–20:2 (pharmaceutical composition comprising 50 mg dolutegravir, 200 mg emtricitabine, and 25 mg of tenofovir alafenamide for a <i>total amount of 275 mg with the remainder excipients</i>) (emphasis added). WO ’351 states that “in a preferred embodiment the pharmaceutical composition can preferably comprise one or more pharmaceutical excipient(s)” where “suitable pharmaceutical excipients are glidants (d), fillers (e), disintegrants (f), binders (g), lubricants (h) and surfactants (j). <i>Id.</i> at 20:23–30. Glidants are present “in particular [in] 0.2 to 1.5 wt% based on the total	
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		weight of the oral dosage form.” <i>Id.</i> at 21:3–5. Fillers are present “still more preferably [in] 10 to 15 wt% of the total weight of the dosage form.” <i>Id.</i> at 21:20–22. Disintegrants are present “still more preferably [in] 3 to 6 wt% based on the total weight of the dosage form.” <i>Id.</i> at 22:1–3. Binders are present “still more preferably [in] 2.5 to 4.5 wt% based on the total weight of the dosage form.” <i>Id.</i> at 22:8–10. Lubricants are present “in particular [in] 0.2 to 2 wt% based on the total weight of the dosage form.” <i>Id.</i> at 22:17–19. Surfactants are present “in particular [in] 1 to 3 wt%	
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		based on the total weight of the dosage form.” <i>Id.</i> at 22:23–25.	
Claim 10			
The tablet of claim 1,	<i>See Declaration, Section VIII.A, and Claim 1.</i>	<i>See Declaration, Section VIII.B, and Claim 1.</i>	<i>See Declaration, Section VIII.E, and Claim 1.</i>
wherein the tablet has a total weight of less than 800 mg.	<i>See 1[pre] and claim 9</i>	<i>See 1[pre] and claim 9</i>	<i>See 1[pre] and claim 9</i>
Claim 11			
The tablet of claim 1,	<i>See Declaration, Section VIII.A, and Claim 1.</i>	<i>See Declaration, Section VIII.B, and Claim 1.</i>	<i>See Declaration, Section VIII.E, and Claim 1.</i>
wherein the tablet has a total weight of less than 730 mg.	<i>See 1[pre] and claim 9</i>	<i>See 1[pre] and claim 9</i>	<i>See 1[pre] and claim 9</i>

Claim 12			
The tablet of claim 1,	<i>See Declaration, Section VIII.A, and Claim 1.</i>	<i>See Declaration, Section VIII.B, and Claim 1.</i>	<i>See Declaration, Section VIII.E, and Claim 1.</i>
wherein the tablet contains less than about 15% of the compound of Formula I or a pharmaceutically acceptable salt thereof.	<i>See 1[pre]</i>	<i>See 1[pre]</i> WO '351 discloses a pharmaceutical composition comprising 50 mg dolutegravir, 200 mg emtricitabine, and 25 mg of tenofovir alafenamide for a total amount of 275 mg <i>with the remainder excipients</i> . WO '351 (EX-1006), 19:30–20:2 (emphasis added).	<i>See 1[pre]</i> US '079 exemplifies a tablet containing DTG (50 mg), TDF (300 mg), FTC (200 mg), and specific excipients, having a uncoated weight of 1030 mg and coated weight of 1055 mg. US '079 (EX-1007), [0129]–[0130]. The coated tablet contains DTG is an <i>amount of ~5% of the total weight of the coated tablet (50 mg / 1055 mg)</i> .
Claim 13			
The tablet of claim 1,	<i>See Declaration, Section VIII.A, and Claim 1.</i>	<i>See Declaration, Section VIII.B, and Claim 1.</i>	<i>See Declaration, Section VIII.E, and Claim 1.</i> US '079 exemplifies a tablet containing DTG (50 mg),

			TDF (300 mg), FTC (200 mg), and specific excipients, having a uncoated weight of 1030 mg and coated weight of 1055 mg. US '079 (EX-1007), [0129]–[0130]. The coated tablet contains DTG is an <i>amount of ~5% of the total weight of the coated tablet (50 mg ÷ 1055 mg)</i> .
wherein the tablet contains less than about 11% of the compound of Formula I or a pharmaceutically acceptable salt thereof.	<i>See 1[pre]</i>	<i>See 1[pre]</i> WO '351 discloses a pharmaceutical composition comprising 50 mg dolutegravir, 200 mg emtricitabine, and 25 mg of tenofovir alafenamide for a total amount of 275 mg <i>with the remainder excipients</i>. WO '351 (EX-1006), 19:30–20:2 (emphasis added).	<i>See 1[pre]</i> US '079 exemplifies a tablet containing DTG (50 mg), TDF (300 mg), FTC (200 mg), and specific excipients, having a uncoated weight of 1030 mg and coated weight of 1055 mg. US '079 (EX-1007), [0129]–[0130]. The coated tablet contains DTG is an <i>amount of ~5% of the total weight of the coated tablet (50 mg ÷ 1055 mg)</i>.