

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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INITIATIVE FOR MEDICINES, ACCESS & KNOWLEDGE (I-MAK), INC.  
Petitioner

v.

GILEAD PHARMASSET LLC  
Patent Owner

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Case No. IPR2018-00125  
U.S. Patent No. 8,633,309

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**PETITION FOR *INTER PARTES* REVIEW**

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## **I. INTRODUCTION**

Initiative for Medicines, Access & Knowledge (I-MAK), Inc. (“Petitioner”) requests *inter partes* review (“IPR”) of claims 1-12 of United States Patent No. 8,633,309 to Ross et al. (“the ‘309 patent”; EX1001) under the provisions of 35 U.S.C. § 311, § 6 of the Leahy-Smith America Invents Act (“AIA”), and 37 C.F.R. § 42.100 et seq. The ‘309 patent issued on January 21, 2014, and is currently assigned to Gilead Pharmasset LLC (“Patent Owner”). This petition demonstrates that claims 1-12 of the ‘309 patent are unpatentable.

The ‘309 patent claims pharmaceutical compounds, compositions and methods that were already known and obvious in light of the prior art. Specifically, the ‘309 claims a specific diastereomeric form of a specific nucleoside compound that was already known because it was the subject of a previous patent application by Patent Owner. In addition, investigating diastereomeric forms of a nucleoside compound and finding one was more active was entirely conventional and expected. Identifying a diastereomeric form that is more active than others is not inventive, but obvious.

Thus, claims 1-12 of the ‘309 patent are unpatentable and should be cancelled.

## **II. MANDATORY NOTICES**

### **A. Real Parties-in-Interest (37 C.F.R. § 42.8(b)(1))**

The real parties-in-interest for this petition are Initiative for Medicines, Access & Knowledge (I-MAK), Inc., and the Laura and John Arnold Foundation.

### **B. Related Matters (37 C.F.R. § 42.8(b)(2))**

Petitioner expects to be filing shortly hereafter a petition for *Inter Partes* Review of U.S. Patent No. 9,284,342, which relates to the '309 patent. Case No. IPR2018-00126. Petitioner is not aware of any other matter that would affect, or be affected by, a decision in this proceeding.

### **C. Lead and Back-Up Counsel (37 C.F.R. § 42.8(b)(3))**

Petitioner designates Daniel B. Ravicher (Reg. No. 47,015) as lead counsel. Petitioner is a not-for-profit public charity of limited resources and has been unable to retain back-up counsel. Petitioner respectfully requests that the Board exercise its authority under 37 C.F.R. § 42.5(b) to waive or suspend the requirement under 37 C.F.R. § 42.10 that Petitioner designate at least one back-up counsel.

### **D. Service Information (37 C.F.R. § 42.8(b)(4))**

Papers concerning this matter should be served on the following:

Address: Daniel B. Ravicher  
Ravicher Law Firm PLLC  
2000 Ponce De Leon Blvd Ste 600  
Coral Gables, FL 33134  
Email: dan@ravicher.com  
Telephone: 786-505-1205

Petitioner consents to service by email to dan@ravicher.com.

### **III. REQUIREMENTS FOR REVIEW**

#### **A. Grounds for Standing**

Petitioner certifies that the '309 patent is available for *inter partes* review and that Petitioner is not barred or estopped from requesting the *inter partes* review sought herein. The required fee is being paid through the Patent Trial and Appeal Board End to End System. The Office is authorized to charge fee deficiencies and credit overpayments to Deposit Account No. 601986.

#### **B. Identification of challenge**

Petitioner respectfully requests cancellation of claims 1-12 of the '309 patent based on the following grounds:

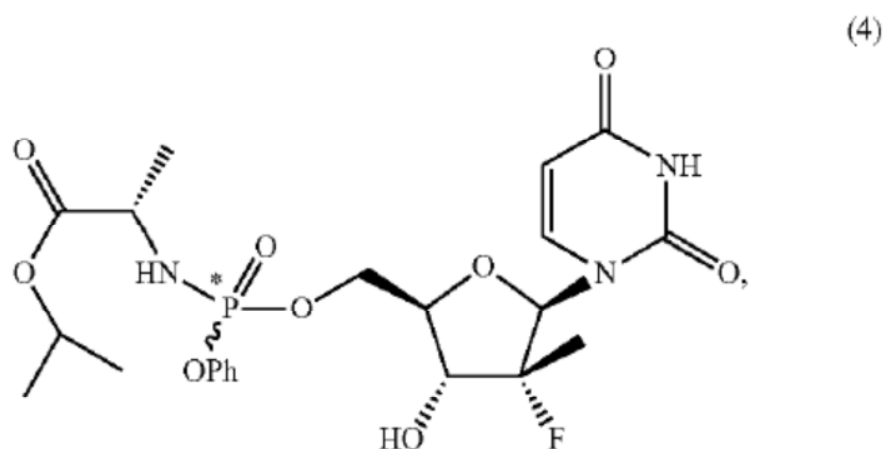
<b>#</b>	<b>Claims</b>	<b>35 U.S.C. §</b>	<b>Prior Art</b>
1	1-12	102(a)	Sofia '634
2	1-12	103(a)	Sofia '634 and Congiatu
3	1-12	103(a)	Clark '147 and Congiatu

This Petition is supported by the declaration of Joseph M. Fortunak, Ph.D. (EX1002). Dr. Fortunak is well qualified as an expert, possessing the necessary scientific, technical, and other specialized knowledge and training to assist in an understanding of the evidence presented herein, as well as possessing the expertise necessary to determine and explain the level of ordinary skill in the art as of the relevant timeframe.

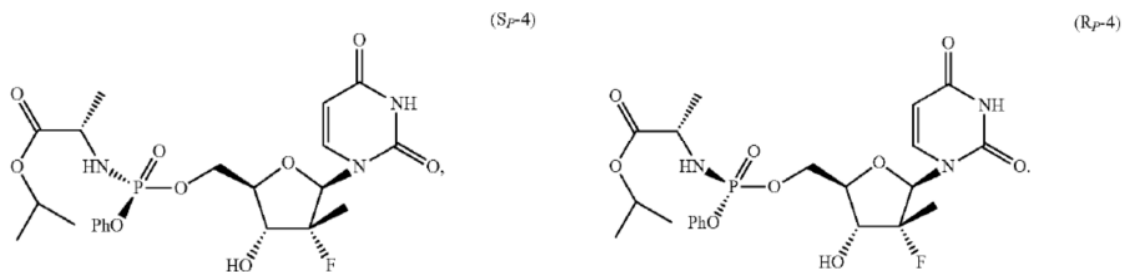
The Petition and its supporting materials, which are listed in the Appendix, establish a reasonable likelihood that Petitioner will prevail with respect to cancellation of the challenged claims. See 35 U.S.C. § 314(a).

#### IV. OVERVIEW OF THE '309 PATENT

The '309 patent claims a compound of the following "formula 4":



EX1001 at 76:2-15. The designation "P\*" represents a chiral phosphorous atom wherein the compound is at least 97% of the  $S_P$  stereoisomer represented by the formula  $S_P$ -4, and not more than 3% of the  $R_P$  stereoisomer." EX1001 at 76:16-48.



The patent's dependent claims further recite higher levels of chiral purity at



the phosphorous atom (98% and 99%), pharmaceutical compositions containing the  $S_p$ -4 diastereomer, methods of treatment of hepatitis C viral infection using  $S_p$ -4 and using  $S_p$ -4 in combination with another antiviral agent. Id. at 76:49 – 77:12.

The following chart describes the ‘309 patent’s 12 claims:

Claim(s)	Recite
1-3	The compound of formula 4 in which the compound is at least 97%, 98% or 99% of the $S_p$ stereoisomer.
4-6	Pharmaceutical compositions of claims 1 through 3 and a “pharmaceutically acceptable medium.”
7-12	Methods of treating hepatitis C viral infection by administering the compounds of claims 1, 2 and 3 with or without another antiviral agent.

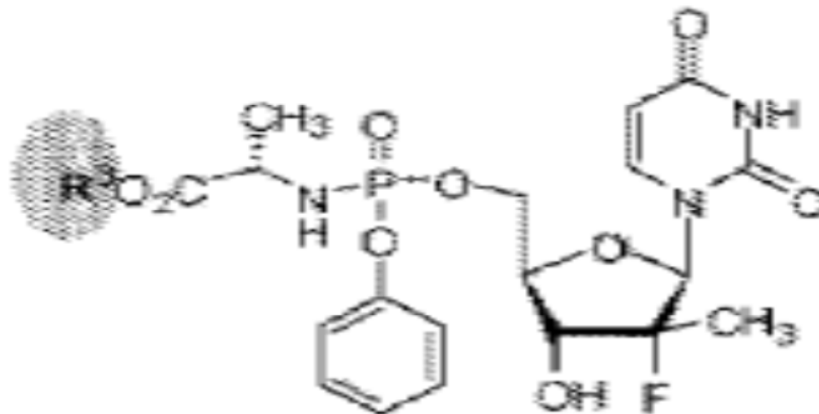
## V. FILE HISTORY OF THE ‘572 PATENT

U.S. Patent Application No. 13/738,425 (“the ‘425 application”), filed on January 10, 2013, issued as the ‘309 patent on January 21, 2014. The ‘425 application claimed priority as a divisional of U.S. Patent Application No. 12/783,680 (“the ‘680 application”), filed on May 20, 2010. The ‘425 application also claimed the benefit of Provisional Applications Nos. 61/319,513 (“the ‘513 provisional application”), filed on March 31, 2010, and 61/179,923 (“the ‘923 provisional application”), filed on May 20, 2009.

During prosecution of the ‘425 application, the Examiner rejected the pending claims for being obvious over a 2007 publication by Sofia and provided

the following analysis:

Sofia [2nd International Workshop on HCV-Resistance and New Compounds, October 31, 2007] teaches a phosphoramidate prodrug of formula:



wherein R3 is isopropyl group (page 8), which is a mixture of Sp and Rp stereoisomers. The disclosed phosphoramidate prodrug is a potent therapeutic agents for treating HCV infection (pages 1-13).

Sofia does not expressly teach wherein the Sp stereoisomer is at least 97%, 98% or 99% and Rp stereoisomer is not more than 3%, 2%, or 1%. Sofia does not expressly teach that the compound is in a pharmaceutical composition form.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to separate the mixture of Sp and Rp stereoisomers and formulate it into a pharmaceutical composition for treating HCV infection.

One having ordinary skill in the art at the time the invention was made would have been motivated to separate the mixture of Sp and Rp stereoisomers and formulate it into a pharmaceutical composition for treating HCV infection because the disclosed

phosphoramidate prodrug containing a mixture of Sp and Rp isomers is known to have potential therapeutic effect and usefulness in treating HCV infection, and separation the two isomers of a known therapeutic drug and identifying the therapeutic potency of each isomer are well known in the art. One of ordinary skill in the art would have reasonably expected the success because separating the isomers of the known therapeutic agents and identifying the potency of each isomer and formulate into a pharmaceutical composition is well within the ordinary and routine level of one skilled in the art.

Thus, the claimed invention as a whole is *prima facie* obvious over Sofia.

EX1004 at 12-13.

Patent Owner responded by arguing that the Office failed to establish a *prima facie* case of obviousness because (i) the Sofia article taught away from selecting an isopropyl group for R<sup>3</sup>, (ii) neither the Sofia article nor any other cited reference supported the assertion that one skilled in the art would have been motivated to separate the R<sub>P</sub> and S<sub>P</sub> stereoisomers and obtain compounds of at least 97%, 98% and 99% of the S<sub>P</sub> stereoisomer, and (iii) one skilled in the art could not have predicted the anti-hepatitis C virus activity of either the S<sub>P</sub> or R<sub>P</sub> stereoisomer.

EX1004 at 21-34.

Patent Owner also argued that non-obviousness of the claimed invention was supported by unexpected results, namely that the S<sub>P</sub> stereoisomer was more potent than the mixture of the two phosphorous-based stereoisomers and >20 times more

potent than the corresponding R<sub>P</sub> stereoisomer. EX1004 at 24.

The Examiner responded to Patent Owner's arguments by withdrawing the rejection because of the argument relating to unexpected results, not the arguments relating to the *prima facie* case of obviousness. EX1004 at 39.

Specifically, the Examiner said:

Applicant's arguments, submitted May 21, 2013, with respect to the rejection of instant claims 82-93 under 35 USC 103(a) for being obvious over Sofia et al., have been fully considered and found to be persuasive to remove the rejection as Applicant has demonstrated that the enantiomer Sp-4 is unexpectedly more potent in inhibiting HCV replication than the Rp-4 enantiomer, thereby overcoming the *prima facie* case of obviousness.

*Id.*

Similarly, in his Reasons for Allowance, the Examiner said:

While it is known in the art to make phosphoramidate compounds such as the instantly claimed ones, for example as described in US patent 7964580 (of record in previous action) and furthermore to resolve chiral compounds into individual enantiomers, Applicant has discovered that the Sp enantiomer of the claimed compound is unexpectedly more potent in inhibiting HCV replication as disclosed on p. 97 of the specification as originally filed. Therefore any *prima facie* case of obviousness is overcome by this finding of unexpected results. For these reasons the claims meet the requirements of 35 USC 102 and 103.

*Id.* at 56.

Again, the Examiner noted that it was the issue of purported unexpected results that overcame the pending rejections, not Patent Owner's arguments with respect to the *prima facie* case of obviousness.

## **VI. PERSON OF ORDINARY SKILL IN THE ART**

Because the '309 patent pertains to nucleoside compounds, a person of ordinary skill in the art ("POSA") would have either (1) a Ph.D. in chemistry or a closely related field with some experience in an academic or industrial laboratory focusing on drug discovery or development, and would also have some familiarity with antiviral drugs and their design and mechanism of action, or (2) a Bachelor's or Master's degree in chemistry or a closely related field with significant experience in an academic or industrial laboratory focusing on drug discovery and/or development for the treatment of viral diseases. EX1002 at ¶41.

## **VII. CLAIM CONSTRUCTION**

In an *inter partes* review, a claim in an unexpired patent is given its broadest reasonable construction in light of the specification. 37 C.F.R. § 42.100(b). Claim terms are also "generally given their ordinary and customary meaning," which is the meaning that the term would have to a person of ordinary skill in the art at the time of the invention in view of the specification. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Under either standard, there is a reasonable

likelihood that Petitioner will prevail with respect to the challenged claims.

The '309 patent provides definitions for certain claim terms, but these definitions are conventional. EX1002 at ¶42. Thus, there is no reason to give any of the terms of the claims of the '309 a meaning other than their ordinary and accustomed meaning. *Id.*

### **VIII. BACKGROUND KNOWLEDGE IN THE ART**

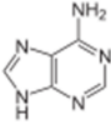
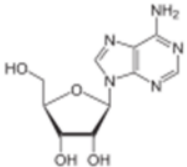
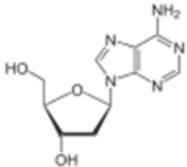
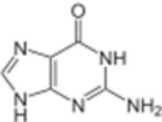
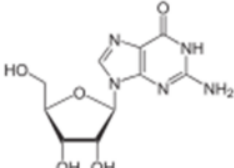
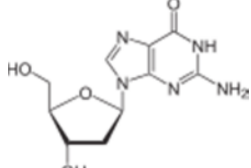
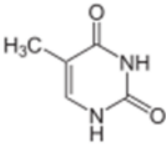
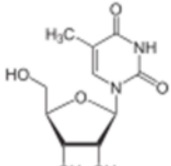
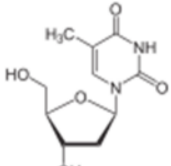
The background discussed below reflects knowledge skilled artisans would bring to bear in reading the prior art at the time of the invention and thereby assists in understanding how one would have inherently understood the references and why one would have been motivated to combine the references as asserted in this Petition. *Ariosa Diagnostics v. Verinata Health, Inc.*, No. 15-1215, slip op. 1, 11-12 (Fed. Cir. 2015). This knowledge of a skilled artisan is part of the store of public knowledge that must be consulted when considering whether a claimed invention would have been obvious. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007); *Randall Mfg. v. Rea*, 733 F.3d 1355, 1362-63 (Fed. Cir. 2013).

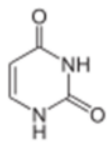
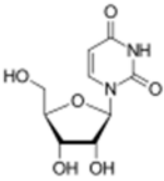
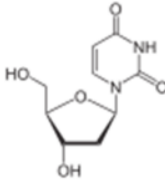
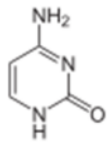
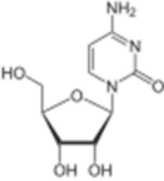
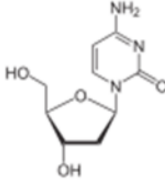
Below is a description of some of the relevant aspects of what was generally known in the art as of May 20, 2009.

#### **A. Nucleoside Analog Drugs Inhibited Viral Diseases**

Nucleosides were well-known to be found as structural components in deoxy-ribonucleic acids (DNA) or ribonucleic acids (RNA). EX1002 at ¶44.

Nucleosides are glycosylamines composed of a five-carbon sugar linked to what is known as a nitrogenous base. *Id.* Adenine, cytosine, guanine, thymine, and uracil are naturally-occurring nitrogenous bases. *Id.* Naturally-occurring, five-carbon sugar rings include ribose and deoxyribose. *Id.* The following table shows structures for these nitrogenous bases as well as the respective products of linking these bases to ribose and deoxyribose sugar rings.

<u>Nitrogenous Base</u>	<u>Ribose Derivative</u>	<u>Deoxyribose Derivative</u>
 <p>Adenine</p>	 <p>Adenosine (A)</p>	 <p>Deoxyadenosine (dA)</p>
 <p>Guanine</p>	 <p>Guanosine (G)</p>	 <p>Deoxyguanosine (dG)</p>
 <p>Thymine</p>	 <p>5-Methyluridine (m<sup>5</sup>U)</p>	 <p>Thymidine (dT)</p>

 <p>Uracil</p>	 <p>Uridine (U)</p>	 <p>Deoxyuridine (dU)</p>
 <p>Cytosine</p>	 <p>Cytidine (C)</p>	 <p>Deoxycytidine (dC)</p>

*Id.*

It was also well known that analogs of naturally-occurring nucleosides were attractive targets for drug discovery and that such analogs were routinely used to treat diseases including viral infections and cancers. EX1002 at ¶46. Examples of such drugs included idoxuridine (antiviral) and gemcitabine for the treatment of cancer. *Id.* Additional examples of nucleoside drugs for the treatment of viral diseases included azidothymidine (AZT), stavudine (d4T), and lamivudine (3TC) for the treatment of viral infections and particularly HIV. *Id.* Ribavirin is another nucleoside analog used for the treatment of viral diseases including hepatitis C viral infections. *Id.*

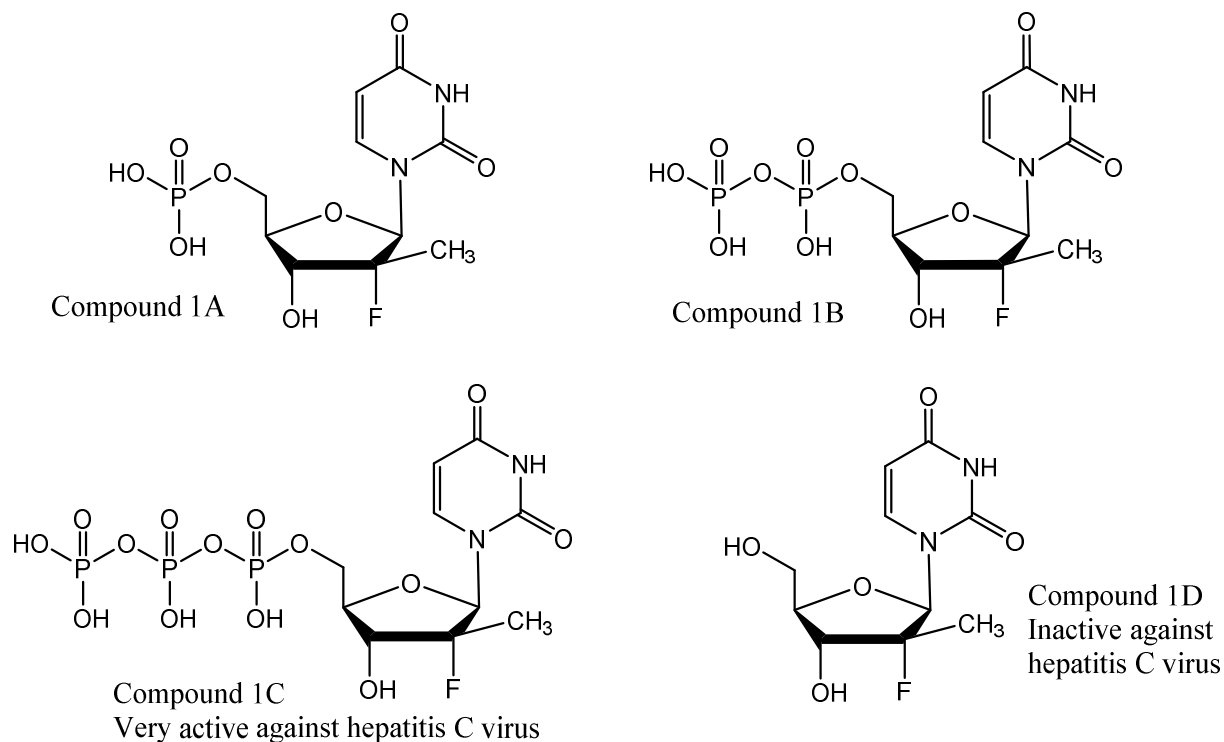
Acyclic nucleoside analogs were also known for the treatment of viral diseases. EX1002 at ¶46. Such drugs included aciclovir, tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide fumarate (TAF) for the treatment of



HIV and hepatitis B viral infections. *Id.* Both TDF and TAF are prodrugs of the nucleotide analog tenofovir/PMPA. *Id.* TAF is a ProTide™ phosphoramidate prodrug of PMPA. *Id.* The phosphorous diastereomers of TAF were known as of 2001 to possess approximately a 10-fold difference in antiviral activity against HIV. *Id.* TDF and TAF are also used to treat hepatitis B viral infections. *Id.*; Chapman, “Practical synthesis, separation, and stereochemical assignment of the PMPA pro-drug GS-7340” *Nucleosides Nucleotides and Nucleic Acids*, 2001, 20(4-7), 621-628 (“Chapman”; EX1008).

Nucleosides, however, were also well-known to be therapeutically-useful only after intracellular, enzymatic conversion into the corresponding triphosphate analogs. EX1002 at ¶47. This conversion into the triphosphates was known to happen in a stepwise fashion, with the first step being conversion to the corresponding monophosphate. *Id.*; McGuigan et al. “Certain phosphoramidate derivatives of dideoxy uridine (ddU) are active against HIV and successfully bypass thymidine kinase” *FEBS Letters*, 1994, 351, 11-14 (“McGuigan 1994”; EX1009).

The mono-, di-, and triphosphate forms of the C2'-deoxy-C2'-methyl(up)-C2'-fluoro(down) uridine nucleoside are shown below.



EX1002 at ¶48. Compounds 1A, 1B and 1C are phosphorylated analogs of a  $S_{P-4}$  compound, while compound 1D is un-phosphorylated. *Id.*

It was well-known that compound 1C was a preferred compound for the treatment of human hepatitis C viral infections. EX1002 at ¶49; Ma *et al.*

“*Characterization of the Metabolic Activation of Hepatitis C Virus Nucleoside Inhibitor  $\beta$ -D-2'-Deoxy-2-Fluoro-2'-C-Methylcytidine (PSI-6130) and Identification of a Novel Active 5'-Triphosphate Species*” J. Biol. Chem., 2007, 282(41), 29812-29820 (“Ma”; EX1010). For instance, it was known that the triphosphate compound 1C had a much longer intracellular half-life than its cytidine analog (38 hours vs. 4.7 hours) resulting in a much longer duration of action. EX1002 at ¶49;

EX1010 at 1 and 8.

**B. Some Nucleoside Drugs Were Poor Substrates for Phosphorylation**

A problem presented itself, however, in the identification of compound 1C as a promising antiviral drug. EX1002 at ¶50. Many nucleoside drugs – in particular, uridines – were also known to be poor substrates for conversion into their monophosphate forms. EX1002 at ¶50; EX1009 (McGuigan 1994) at 1-2. This was also known to be more common for virally-infected cells, which are often kinase-deficient. EX1002 at ¶50. Such knowledge was very important because drugs that would otherwise be very potent for disease treatment would be inactive if they did not undergo this phosphorylation process inside an infected cell. *Id.*

**C. Compound 1D Was a Superior Agent Against HCV, But a Poor Substrate for Phosphorylation**

Compound 1D had been disclosed in WO 2005/003147 to Clark (“Clark ‘147”; EX1007) and in Clark, J., "*Design, Synthesis, and Antiviral Activity of 2'-Deoxy-2'-fluoro-2'-C-methylcytidine, a Potent Inhibitor of Hepatitis C Virus Replication*," *Journal of Medicinal Chemistry*, 2005, 48(17), 5504-5508 (“Clark 2005”; EX1011). EX1002 at ¶51. Clark 2005 indicated that compound 1D – the unmodified nucleoside - had no activity in the HCV Replicon assay. EX1002 at ¶51; EX1011 at 3.

Ma showed, however, that the triphosphate form of 1D (compound 1C) was

a superior agent against hepatitis C virus, with excellent potency and a long intracellular half-life. EX1002 at ¶52; EX1010 at 1 and 8.

These publications established that - although compound 1C was an excellent antiviral agent - compound 1D was inactive because it could not be efficiently phosphorylated inside virally-infected cells to be converted to 1C. EX1002 at ¶53.

**D. ProTide Prodrugs of Nucleosides Were Well-Known to Overcome the Problem of Poor Phosphorylation**

ProTide prodrugs of nucleosides were first described in the early 1990s. EX1002 at ¶54; EX1009 (McGuigan 1994) at 2-3. These analogs were well-known to provide advantages over base nucleoside drugs in terms of physicochemical properties, cellular absorption, improved half-life, and very importantly, in terms of overcoming the problem of lack of biological activity due to poor intracellular phosphorylation. EX1002 at ¶54. The ProTide approach had been applied to activate nucleosides through kinase bypass for hepatitis C antiviral compounds as in Perrone P., "*Application of the Phosphoramidate ProTide Approach to 4'-Azidouridine Sub-micromolar Potency versus Hepatitis C Virus on an Inactive Nucleoside*," *Journal of Medicinal Chemistry*, 2007, 50(8), 1840-1843 ("Perrone"; EX1012 at 1). EX1002 at ¶54. Thus, the ProTide approach was an obvious potential solution for overcoming the problem of poor intracellular phosphorylation of compound 1D. *Id.*

Prior publications had disclosed that nucleoside compounds that were inefficiently phosphorylated inside a virally-infected cell could be converted into very active prodrugs for the treatment of viral diseases and cancer. EX1002 at ¶55; EX1012 (Perrone) at 2; EX1009 (McGuigan 1994) at 2-4.

Perrone, in particular, showed that conversion into a ProTide nucleoside analog completely overcame the lack of antiviral activity in the HCV Replicon Assay for the compound AZU (1), resulting in a very potent compound (2) against the hepatitis C virus. EX1002 at ¶56. Thus, it was known that an important component of nucleoside drug discovery was the assessment of whether a nucleoside drug could be efficiently phosphorylated inside a virally-infected cell. *Id.* It was also known that the limitation of poor phosphorylation could be overcome in many cases by the application of ProTide prodrug technology.

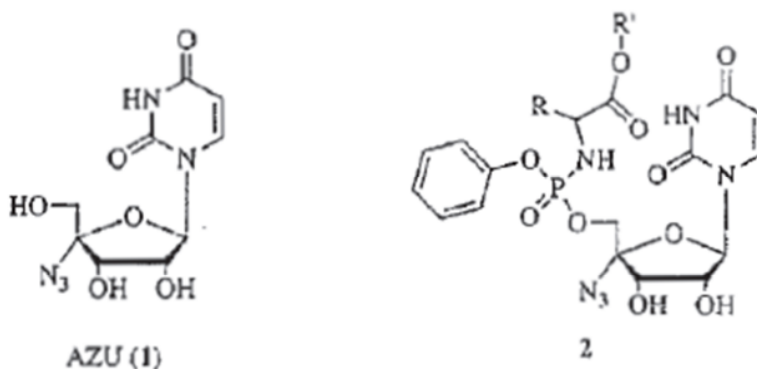


Figure 1. Structure of AZU and its corresponding phenyl-phosphoramidate ProTide.

EX1012 (Perrone) at 2.

**E. ProTide Prodrugs Were Diastereomeric at Phosphorous and Such Diastereomers Could Possess Different Biological Activity**

ProTide prodrugs have incorporated a phosphorous atom that is chiral.

EX1002 at ¶57. This was illustrated for both the phosphonic acid ProTide prodrugs of tenofovir, EX1008 (Chapman 2001) at 1, and for phosphoramidate prodrugs of nucleosides. Congiatu et al., “*Novel potential anticancer naphthyl phosphoramidates of BVdU: separation of diastereoisomers and assignment of the absolute configuration of the phosphorus center,*” J Med Chem 2006, 49, 452-455 (“Congiatu”; EX1006) at 1. EX1002 at ¶57.

Such isomeric compounds differ in the configuration of this single chiral center. EX1002 at ¶58. This difference in chirality at a single chiral center (with multiple chiral centers present) means that these compounds are diastereomeric; i.e., they can exist as a mixture of two diastereomers. *Id.*

**F. ProTide Analogs of Compound 1D Were Active Against HCV**

As discussed above, compound 1D was known, but reported to have no activity in the HCV Replicon assay. EX1002 at ¶59; EX1011 (Clark 2005) at 3. Ma showed that the tri-phosphorylated analog of 1D (i.e., compound 1C) was a superior agent against hepatitis C virus, with a long intracellular half-life and excellent antiviral activity. EX1002 at ¶59; EX1010 at 1 and 8.

As an example, the triphosphate of 1D possesses an intracellular half-life of 38 hours. EX1002 at ¶60; EX1010 at 1 and 8. This compares to the intracellular

half-life of only 4.7 hours for the analogous cytidine, which was previously shown to be very promising for the treatment of hepatitis C viral infection. *Id.*

Indeed, WO 2008/121634 to Sofia (“Sofia ‘634”; EX1005) disclosed that such ProTide prodrug moieties were effective for activating compound 1D, transforming 1D from a compound with no antiviral activity into a series of very potent compounds for the treatment of hepatitis C viral infections. EX1002 at ¶61; EX1005 at 695:15-698:3. Thus, a compound that lacked antiviral activity was readily transformed into a substantial number of ProTide analogs that possessed excellent activity against hepatitis C viral infection. EX1002 at ¶61.

The compounds of Sofia ‘634 were also known to exist as different diastereomers at phosphorous. EX1002 at ¶62; EX1005 at 693-694. Sofia ‘634 Example 81 taught:

Certain exemplified compounds were obtained as mixture of diastereomers because of chirality at phosphorous. The diastereomers were separated on a ChiralPak-AS-H (2 X 25 cm) column under Supercritical Fluid Chromatography (SFC) conditions using 20% methanol in carbon dioxide as solvent. The absolute stereochemistry of the P-chiral center of the diastereomers were not determined. However chromatographic resolution of these two diastereomers provides for isomers that are characterized as fast eluting and slow eluting isomers. Some examples are shown below.

EX1005 at 693-694.

Compounds whose diastereomers at phosphorous were separated and tested separately for hepatitis C antiviral activity were identified in Sofia '634 as compounds 15, 39, and 49. EX1005 at 693-694. Thus, Sofia '634 also illustrated separation of the phosphorous diastereomers of ProTide analogs of 1D. EX1002 at ¶63. Upon separation and separate testing in the HCV Replicon Assay, a substantial difference was seen in biological activity between the respective diastereomers of examples 15, 39, and 49 of Sofia '634, as shown in the table below.

<b>Compound</b>	<b>EC90 (uM)</b>
<b>Example 15 (Diastereomeric mixture)</b>	0.86
Fast Moving isomer of <b>Example 15</b>	1.35
Slow Moving isomer of <b>Example 15</b>	0.26
<b>Example 39 (Diastereomeric mixture)</b>	0.47
Fast Moving isomer of <b>Example 39</b>	0.78
Slow Moving isomer of <b>Example 39</b>	0.02
<b>Example 49 (Diastereomeric mixture)</b>	0.126
Fast Moving isomer of <b>Example 49</b>	0.03
Slow Moving isomer of <b>Example 49</b>	5.78

*Id.*; EX1005 at 694.

Thus, a POSA would readily know that the chiral phosphorous atom of



phosphoramidate nucleoside prodrugs would exist in separate diastereomeric forms and that these different diastereomers would likely have different antiviral activity. EX1002 at ¶64. Specifically, Sofia ‘634’s example isomers showed a difference of activity on the order of 5-fold, 39-fold and 190-fold. *Id.* at 693-694. Thus, a POSA would expect that isomers of Sofia ‘634’s compounds could have difference in activity of several orders of magnitude. EX1002 at ¶64.

In light of Sofia ‘634’s examples, it would have been entirely expected that isomers of its compounds could have much more than 20 times difference in activity. EX1002 at ¶65.

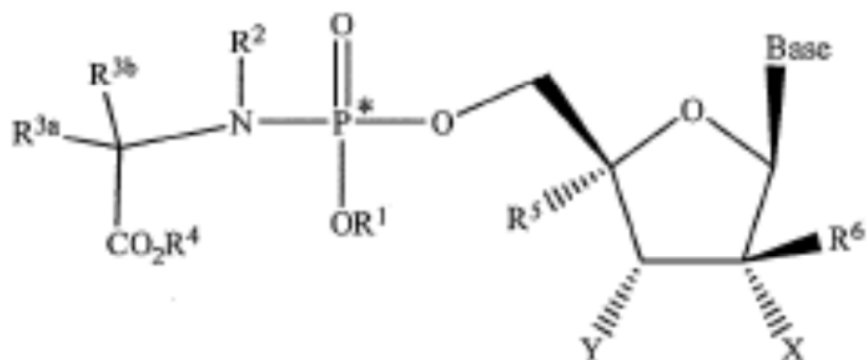
## **IX. SCOPE AND CONTENT OF THE PRIOR ART**

The following references taught or suggested the compounds, compositions and methods recited in claims 1-12 of the ‘309 patent. EX1002 at ¶66.

### **A. WO 2008/121634 to Sofia (“Sofia ‘634”, EX1005)**

Sofia ‘634 is prior art under 35 U.S.C. § 102(a) to the ‘309 patent because it was published on October 9, 2008, before the May 29, 2009, filing date of the earliest application to which the ‘309 patent claims priority.

Sofia ‘634 taught nucleoside phosphoramidate prodrugs of the following Formula I:



I

EX1005 at 1. While Sofia ‘634 taught many compounds within the formula, it highlighted some specific compounds, including “(S)-2-{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydrofuran-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid isopropyl ester.” EX1005 at 702:48-50 (claim 2).

Sofia ‘634 also taught a composition for treatment of viral diseases using any of the viral agents disclosed. *Id.* at 707:23-709:26 (claim 3). Such compositions are also taught to comprise a pharmaceutically acceptable medium *Id.* at 710:1-6 (claim 4). Further, Sofia ‘634 taught a method of treatment which comprises administering a therapeutically effective amount of a compound of formula I to a subject. *Id.* at 723:43-727:36 (claim 7).

Sofia ‘634 contained a substantial series of tables of “contemplated species” within the structure of formula I. *Id.* at 101-660. Notably, Example 25, is identical to formula 4 claimed by the ‘309 patent, even though it does not indicate the

diastereomeric composition at phosphorous to be  $S_P-4$ ,  $R_P-4$ , or a mixture of both. EX1005 at 684.

Sofia '634 further taught the separation of such mixtures of diastereomers into their respective individual diastereomers. *Id.* at 693-694, Example 81. Notably, Example 81 of Sofia '634 taught the separation of isomers at phosphorous into their individual diastereomers. Sofia '634 further taught that these diastereomers displayed differences in antiviral activity in three respective examples of: 1) 5-fold; 2) 39-fold; and 3) 190-fold. Thus Sofia '634 taught that the different diastereomers of its compounds, including compound 25, could be separated, and that these diastereomers would be expected to have substantially different antiviral activity. *Id.*; EX1002 at ¶70.

This teaching of the wide variability in activity of Sofia '634's phosphorous diastereomers would have motivated a POSA to investigate them. EX1002 at ¶71. Sofia '634's teaching would have given a POSA a reasonable expectation of success in isolating and testing the stereoisomers of its compounds. *Id.*

Sofia '634 further taught the use of such compounds and pharmaceutical compositions in combination with other antiviral agents for the treatment of hepatitis C viral infections. *Id.* at 665:19-23, and 667:8-668:13.

**B. Congiatu et al., “Novel potential anticancer naphthyl phosphoramidates of BVdU: separation of diastereoisomers and assignment of the absolute configuration of the phosphorus center,” J Med Chem vol. 49, pp. 452-455 (2006) (“Congiatu”; EX1006)**

Congiatu is prior art under 35 U.S.C. § 102(b) to the ‘309 patent because it was published on December 17, 2005, more than a year before the May 29, 2009, filing date of the earliest application to which the ‘309 patent claims priority.

Congiatu taught that nucleosides are useful for the treatment of cancer and viral infections. EX1006 at 1. Congiatu also taught that the “phosphoramidate approach” (ProTide prodrugs of nucleoside mono-phosphates) was introduced by McGuigan et al. in 1992 to improve cellular penetration of nucleosides and to bypass the first step of kinase-mediated activation of nucleosides. *Id.* Congiatu taught that this was one of the most successful approaches for the delivery of nucleoside monophosphates inside cells. *Id.*

Congiatu further taught separation of diastereomers of nucleoside phosphoramidates. *Id.* at 2-3. Congiatu further taught that diastereomers of the publication had an approximately 15-fold difference in activity (0.5 micromolar vs. 7.4 micromolar). *Id.* Congiatu thus taught that the phosphorous diastereomers of nucleoside phosphoramidates could be separated and that it would be expected they might have significantly different biologic activity. EX1002 at ¶74.

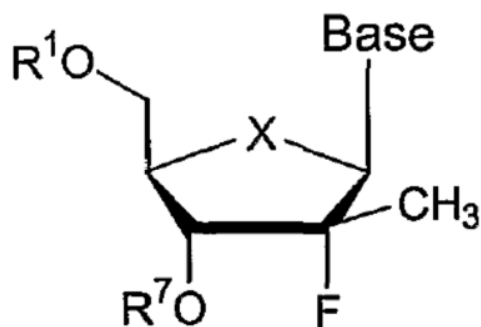
**C. WO 2005/003147 to Clark (“Clark ‘147”); EX1007)**

Clark ‘147 is prior art under 35 U.S.C. § 102(b) to the ‘309 patent because it was published on January 31, 2005, more than a year before the May 29, 2009, filing date of the earliest application to which the ‘309 patent claims priority.

Clark ‘147 taught modified fluorinated nucleoside analogs. EX1007. More specifically, Clark ‘147 taught (2’R)-2’-deoxy-2’-fluoro-2’-C-methyl nucleosides, their pharmaceutically acceptable salt forms, and prodrugs. *Id.* at 18:3-17. Clark ‘147 taught that these compounds could be used to treat *Flaviviridae* viruses, including hepatitis C viral infections. *Id.* at 1 (Abstract).

Specifically, Clark ‘147 taught and claimed:

A (2’R)-2’-deoxy-2’-fluoro-2’-C-methyl nucleoside ( $\beta$ -D or  $\beta$ -L) or its pharmaceutically acceptable salt or prodrug thereof of the structure:



wherein Base is a purine or pyrimidine base;

X is O, S, CH<sub>2</sub>, Se, NH, N-alkyl, CHW (*R*, *S*, or racemic), C(W)<sub>Z</sub>,

wherein W is F, Cl, Br, or I; and,

*Id.* at 96:1-97:23 (claim1). This teaching covers the base structure, including

mono-, di-, and triphosphate forms. It also covers prodrugs of such structure. *Id.* at 46:23- 48:20 and 57:3-62:4.

Clark '147 also taught a variety of techniques used for the isolation and crystallization of isomers and polymorphs, i.e., "IV. Stereoisomerism and Polymorphism." EX1006 at 52:21-55:22. This disclosure included a discussion of methods for separating diastereomers, chiral chromatography, and purification by various forms of crystallization. *Id.*

Clark '147 taught that its compounds could be used to treat hepatitis C viral infections. EX1007 at 1 (abstract). Clark '147 further taught that its compounds could be used in "more effective combination therapies," and specifically, "in combination or alternation with one or more other effective antiviral agent(s), optionally in a pharmaceutically acceptable carrier or diluent thereof, as described herein." EX1007 at 21:5-13.

## **X. CLAIMS 1-12 ARE UNPATENTABLE**

Each and every feature of claims 1-12 of the '309 patent can be found in or is suggested by the prior art, including specifically the references identified below. EX1002 at ¶79. Each of claims 1-12 is presented below followed by an analysis of the claims. The analysis below identifies exemplary disclosure of the cited references with respect to the corresponding claim elements, and is not meant to be exhaustive.

## A. Ground 1: Claims 1-12 Were Anticipated by Sofia

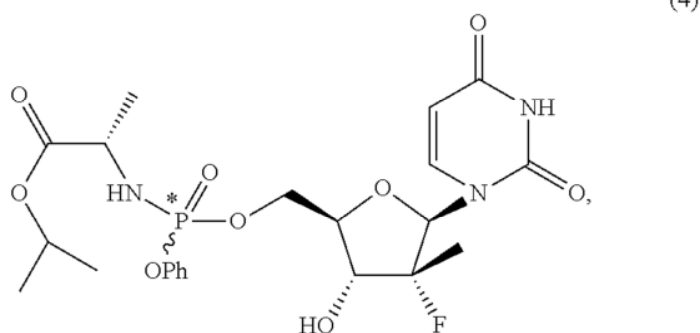
Sofia '634 taught, either expressly or inherently, each and every feature of claims 1-12. EX1002 at ¶80. It, thus, anticipates every claim of the '309 patent.

Below is a comparison of claims 1-12 to exemplary, but not exhaustive, disclosure in Sofia '634 that taught the corresponding claim elements.

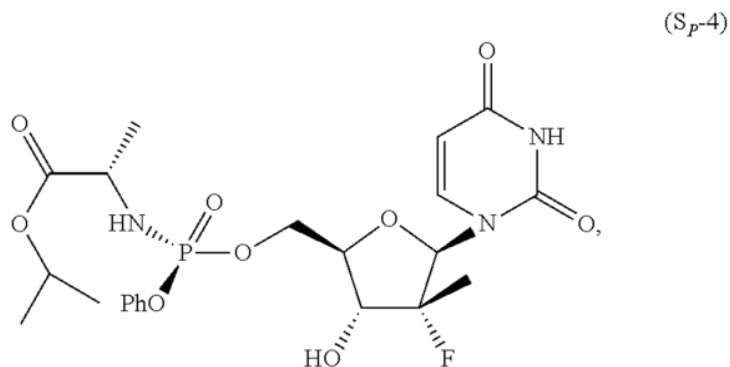
### 1. Claims 1-3 (compounds)

Claim 1 of the '309 patent recites:

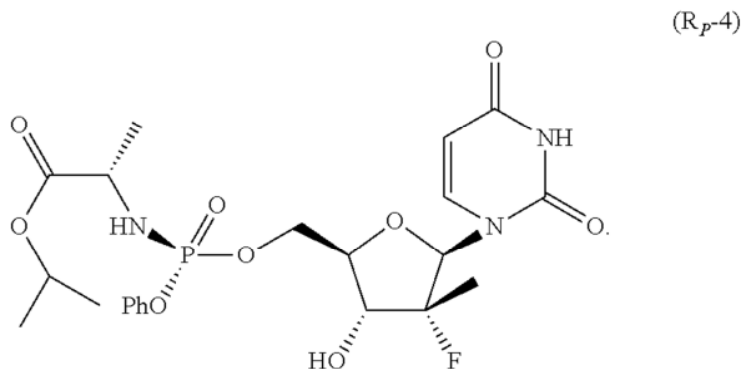
A compound represented by the formula (4):



wherein P\* represents a chiral phosphorus atom and wherein the compound is at least 97% of the  $S_P$  stereoisomer represented by the formula ( $S_P$ -4):



and not more than 3% of the  $R_P$  stereoisomer represented by the formula ( $R_P$ -4):



EX1001 at 76:1-47.

Claim 2 recites, “The compound according to claim 1, wherein the compound is at least 98% of the  $S_P$  stereoisomer represented by the formula ( $S_P$ -4) and not more than 2% of the  $R_P$  stereoisomer represented by the formula ( $R_P$ -4).”

*Id.* at 76:48-51. Claim 3 recites, “The compound according to claim 1, wherein the compound is at least 99% of the  $S_P$  stereoisomer represented by the formula ( $S_P$ -4) and not more than 1% of the  $R_P$  stereoisomer represented by the formula ( $R_P$ -4).”

*Id.* at 76:52-55.

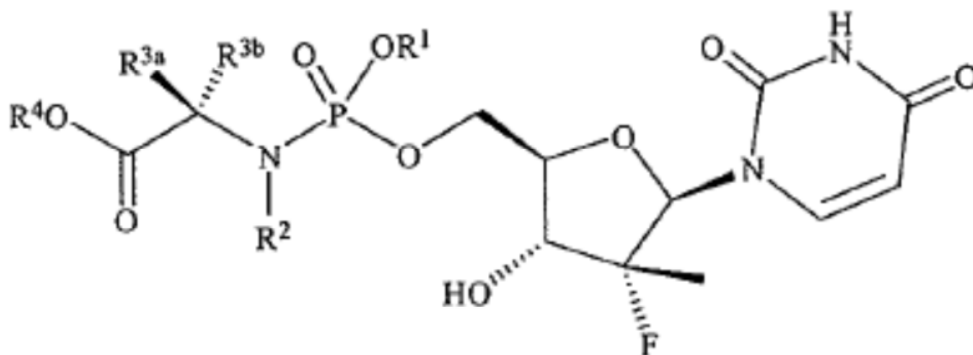
Sofia ‘634 taught phosphoramidate derivatives of nucleosides for the inhibition of hepatitis C viral replication and the treatment of hepatitis C viral infections. EX1005 at 2:15-21. Sofia ‘634 further taught the separation of phosphorous diastereomers of phosphoramidate nucleosides, and their differential antiviral activity against hepatitis C. *Id.* at 693-694, Example 81. Sofia ‘634 also



taught pharmaceutical compositions and methods of treatment using nucleoside phosphoramidates alone or in combination with other agents. *Id.* at 660:22-668:3.

While Sofia '634 provided a long list of tables illustrating contemplated compounds as examples of such phosphoramidate drugs, Sofia '634 identified a much shorter list of specific examples of phosphoramidate nucleoside compounds that were actually prepared. EX1005 at 676:13 – 682:20 Sofia '634 described the preparation of 7 examples and provided a Table titled "Examples" that listed an additional 53 compounds. EX1005 at 676:13 – 682:20 and 683:1 – 688:2.

Of these 60 specific compounds highlighted by Sofia '634, 57 are uridine phosphoramidate structures of the type shown:



EX1005 at 683:4. The stereochemistry at phosphorous is not indicated for these phosphoramidates. EX1002 at ¶85. Sofia '634 subsequently recites 14 additional examples of purine-based nucleotide phosphoramidates. *Id.*

Example 25 in Sofia '634 is the same compound as that represented by formula (4) in claim 1 of the '309 patent, because it has the following substitution

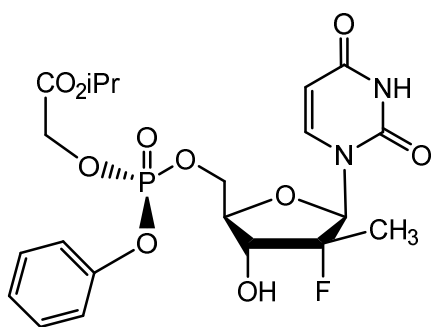
pattern: 1)  $R^1 = \text{phenyl}$ ; 2)  $R^2 = \text{H}$ ; 3)  $R^{3a} = \text{H}$ ; 4)  $R^{3b} = -\text{CH}_3$ ; 5)  $R^4 = \text{isopropyl}$ , except that Sophia's Example 25 is a mixture of diastereomers at phosphorous. EX1002 at ¶86; EX1005 at 684 (compound **25**); EX1001 at 76:1-47.

Sofia '634 taught that diastereomers may exist at phosphorous, and that such diastereomers may have different biological activity. EX1002 at ¶87. In Example 81, Sofia '634 taught some examples of separation and testing of compounds that are single diastereomers at phosphorous. EX1005 at 693-694. The results from this testing showed that in the compounds of Examples 15, 39, and 49, the separate diastereomers at phosphorous had very different EC90 ( $\mu\text{M}$  concentration) values as a measure of biological activity. *Id.*

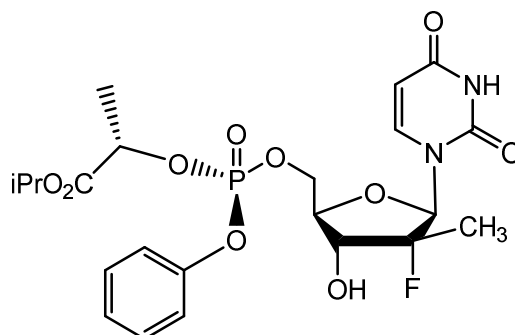
These differences were, respectively, 5-fold (Example 15); 39-fold (Example 39); and approximately 190-fold (Example 49). EX1002 at ¶88. Thus, a POSA would know from this disclosure that the phosphorous diastereomers of any phosphoramidate nucleoside drug candidate must be separated and tested individually to determine which diastereomer provide the predominate antiviral activity. EX1002 at ¶88.

A POSA would also expect that the specific disclosures of Examples 15, 39, and 49 would apply to Example 25. EX1002 at ¶89. As shown in the figure below, each of these compounds is a slightly different phosphoramidate prodrug analog versus the compound claimed in the '309 patent and each is a close structural

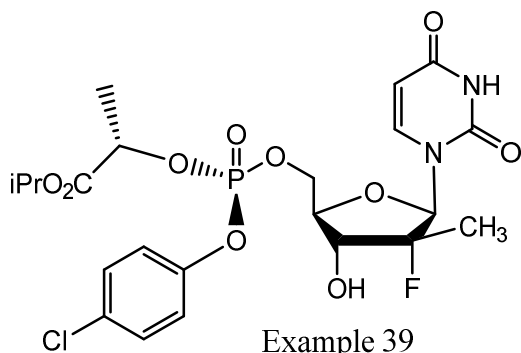
analog of Example 25. EX1002 at ¶89.



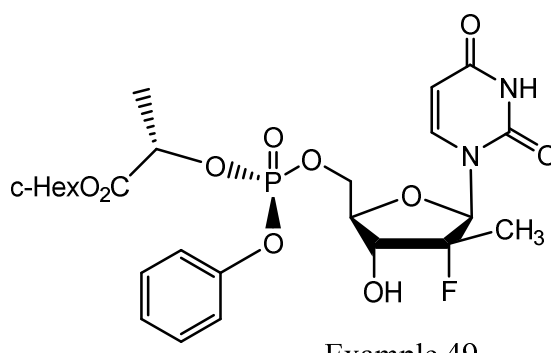
Example 15



'309 patent



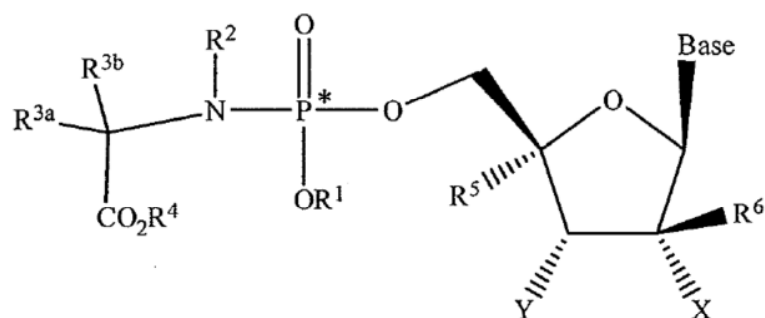
Example 39



Example 49

These figures compare the single phosphorous diastereomers of Examples 15, 39, and 49 from Sofia '634 to compound 4 claimed in the '309 patent. EX1002 at ¶90.

As is shown in the figures, Sofia '634 taught in its Example 25 a structure identical to compound 4. EX1005 at 684. Sofia '634 also taught that the Example 25 and Example 81 compounds were obtained as a mixture of diastereomers. EX1005 at 683, 693-694 and 702. Sofia '634 further taught, "A compound, *its stereoisomer*, salt, hydrate, solvate, or crystalline form thereof, represented by formula I:



I

EX1005 at 699:1-5 (claim 1; emphasis added). Such stereoisomers must, therefore, included stereoisomers (i.e., diastereomers) at phosphorous.

Sofia '634 taught that its example compounds, including compound 25, which is the nucleoside phosphoramidate claimed in the '309 patent, were a mixture of diastereomers at phosphorous. EX1005 at 693-694 (Example 81). This disclosure also taught the separation of diastereomers by chromatography on a Chiralpak-AS-H (2 x 25 cm) column under Supercritical Fluid Chromatography (SFC) conditions. *Id.* The chromatographic separation of diastereomers of compounds 15, 39, and 49 are provided as representative, non-limiting examples. EX1002 at ¶92. Sofia '634 taught the chromatographic separation of diastereomers of all its compounds especially its example compounds, including compound 25. *Id.*

A POSA would expect one diastereomer to be much more active than the other and known that it would be preferred to produce a compound of as much of

the more active diastereomer as possible. EX1002 at ¶93. It was generally known that such compounds could have, and indeed should have, as high a percent as possible of the preferred diastereomer. *Id.* Thus, Sofia '634's teaching of diastereomers of the compound claimed in the '309 patent inherently taught compounds of 97-99% of the preferred diastereomer. *Id.*

The recitation of diastereomeric purities of 97%, 98%, and 99% are merely arbitrary examples of limits of the bounds of claim 1. EX1002 at ¶94. As such, these arbitrary limits are inherently taught by Sofia '634, which expressly teaches both a mixture of diastereomers at phosphorous and individual stereoisomers at phosphorous. *Id.* The arbitrary limits set by the percentage recitations in the claims of the '309 patent are not meaningful from a standpoint of antiviral activity, since such differences (e.g., IC<sub>90</sub> values) would be within the range of experimental error of such assays. *Id.*

Further, a POSA's perspective would be on drug approvals for human dosing, and in that case, these arbitrary percentage recitations are irrelevant because the specifications for diastereomeric impurities in drug substances are negotiated with regulatory agencies on an individual basis and are justified based on the separate activity and toxicity of individual isomers. EX1002 at ¶95; Byrn S., "*Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations*," *Pharmaceutical Research*, 1995, 12(7), 945-954 (EX1013; "Byrn").

Thus, even though Sofia '634 did not expressly teach its diastereomer compounds had 97%, 98% or 99% of the more active stereoisomer, Sofia '634 nonetheless inherently taught a POSA all of the limitations of claims 1-3. EX1002 at ¶96. As such, Sofia '634 anticipated claims 1-3.

**2. Claims 4-6 (pharmaceutical compositions)**

Claims 4-6 claim pharmaceutical compositions comprising the compounds of claims 1-3, respectively, and a pharmaceutically acceptable medium. EX1001 at 76:56-64.

Sofia '634 taught compositions comprising its compounds and a pharmaceutically acceptable medium. EX1005 at 711:1-6 (claim 4). Thus, Sofia '634 taught the additional limitations of claims 4-6. EX1002 at ¶98. Therefore, Sofia '634 anticipated claims 4-6.

**3. Claims 7-12 (methods of treating hepatitis C)**

Claims 7, 9 and 11 claim methods of treating a hepatitis C virus infection in a human comprising administering to the human an effective amount of the compounds of claims 1-3, respectively. EX1001 at 76:65-77:10. Claims 8, 10 and 12 claim the methods of claims 7, 9 and 11, further comprising administering to the human another antiviral agent. *Id.* at 77:1-12.

Sofia '634 taught that its compounds were useful, "as inhibitors of HCV replication and for treatment of hepatitis C infection in mammals." EX1005 at

2:15-21 ("Field of Invention"). Sofia '634 also taught, "administering a therapeutically effective of at least two or more different compounds falling within the scope of the compound represented by formula I to the subject." *Id.* at 668:19-23. Thus, Sofia '634 taught the additional limitations of claims 7-12. EX1002 at ¶100. Therefore, Sofia anticipated claims 7-12.

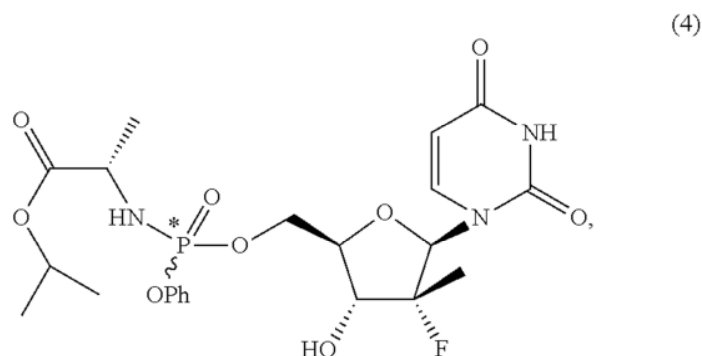
**B. Ground 2: Claims 1-12 Were Obvious Over Sofia '634 and Congiatu**

A POSA would have been motivated to combine the teachings of Sofia '634 and Congiatu because they both related to nucleoside phosphoramidate prodrugs. EX1002 at ¶101. The combined teaching of Sofia '634 and Congiatu render claims 1-12 of the '309 patent obvious. *Id.*

**1. Claims 1-3 (compounds)**

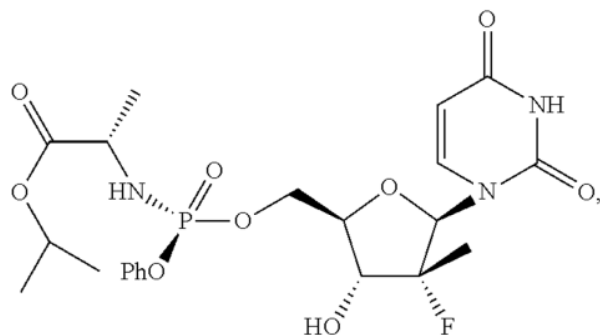
Claim 1 of the '309 patent recites:

A compound represented by the formula (4):

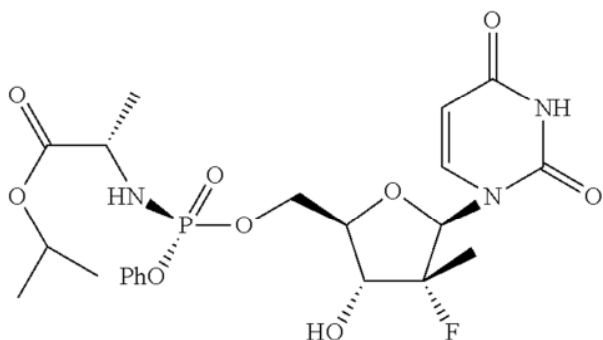


wherein P\* represents a chiral phosphorus atom and wherein the compound is at least 97% of the  $S_P$  stereoisomer represented by the

formula (S<sub>P</sub>-4):



and not more than 3% of the R<sub>P</sub> stereoisomer represented by the  
formula (R<sub>P</sub>-4):



EX1001 at 76:1-47.

Claim 2 recites, “The compound according to claim 1, wherein the compound is at least 98% of the S<sub>P</sub> stereoisomer represented by the formula (S<sub>P</sub>-4) and not more than 2% of the R<sub>P</sub> stereoisomer represented by the formula (R<sub>P</sub>-4).”

*Id.* at 76:48-51. Claim 3 recites, “The compound according to claim 1, wherein the compound is at least 99% of the S<sub>P</sub> stereoisomer represented by the formula (S<sub>P</sub>-4) and not more than 1% of the R<sub>P</sub> stereoisomer represented by the formula (R<sub>P</sub>-4).”

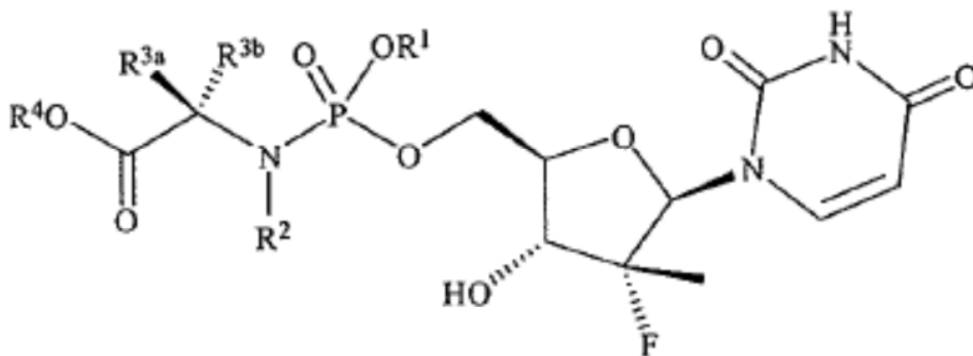


*Id.* at 52-55.

Sofia '634 taught phosphoramidate derivatives of nucleosides for the inhibition of hepatitis C viral replication and the treatment of hepatitis C viral infections. EX1005 at 2:15-21. Sofia '634 further taught the separation of phosphorous diastereomers of phosphoramidate nucleosides, and their differential antiviral activity against hepatitis C. *Id.* at 693-694, Example 81. Sofia '634 also taught pharmaceutical compositions and methods of treatment using nucleoside phosphoramidates alone or in combination with other agents. *Id.* at 711:1-716:4

While Sofia '634 provided a long list of tables illustrating contemplated compounds as examples of such phosphoramidate drugs, Sofia '634 identified a much shorter list of specific examples of phosphoramidate nucleoside compounds that were actually prepared. EX1005 at 676:13 – 682:20 (7 phosphoramidates). The Table titled “Examples” lists an additional 53 compounds for a total of 60. EX1005 at 683:1 – 688:2.

Of these 60 specific compounds highlighted by Sofia '634, 57 are uridine phosphoramidate structures of the type shown:



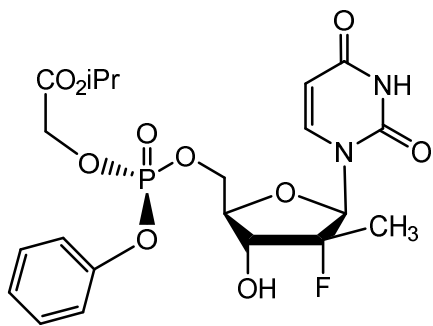
EX1005 at 683:4. The stereochemistry at phosphorous is not indicated for these phosphoramidates. EX1002 at ¶106. Sofia '634 subsequently recites 14 additional examples of purine-based nucleotide phosphoramidates. *Id.*

Example 25 in Sofia '634 is the same compound as that represented by formula (4) in claim 1 of the '309 patent, because it has the following substitution pattern: 1) R<sup>1</sup> = phenyl; 2) R<sup>2</sup> = H; 3) R<sup>3a</sup> = H; 4) R<sup>3b</sup> = -CH<sub>3</sub>; 5) R<sup>4</sup> = isopropyl, except that Sophia's Example 25 is a mixture of diastereomers at phosphorous. EX1002 at ¶107; EX1005 at 684 (compound 25); EX1001 at 76:1-47.

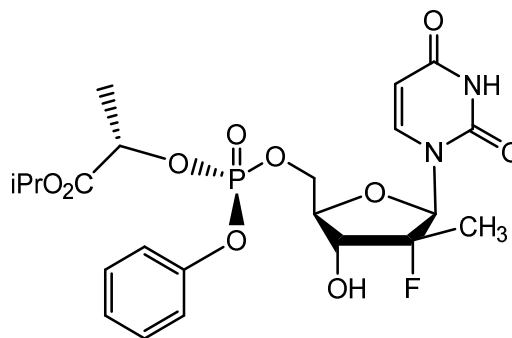
Sofia '634 taught that diastereomers may exist at phosphorous, and that such diastereomers may have different biological activity. EX1002 at ¶108. In Example 81, Sofia '634 taught some examples of separation and testing of compounds that are single diastereomers at phosphorous. EX1005 at 693-694 (Example 81). The results from this testing showed that in the compounds of Examples 15, 39, and 49, the separate diastereomers at phosphorous had very different EC<sub>90</sub> (μM concentration) values as a measure of biological activity. *Id.*

These differences were, respectively, 5-fold (Example 15); 39-fold (Example 39); and approximately 190-fold (Example 49). Thus, a POSA would know from this disclosure that the phosphorous diastereomers of any phosphoramidate nucleoside drug candidate must be separated and tested individually to determine which diastereomer provide the predominate antiviral activity. EX1002 at ¶109.

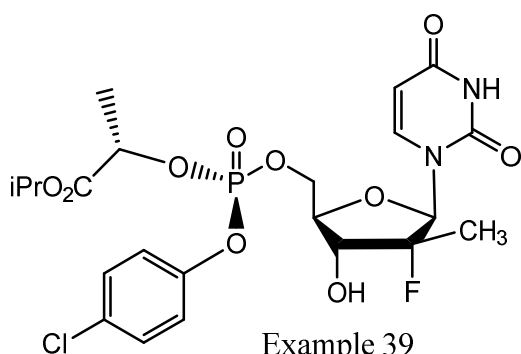
A POSA would also expect that the specific disclosures of Examples 15, 39, and 49 would apply to Example 25. EX1002 at ¶110. As shown in the figure below, each of these compounds is a slightly different phosphoramidate prodrug analog of the compound claimed in the '309 patent and each is a close structural analog of Example 25.



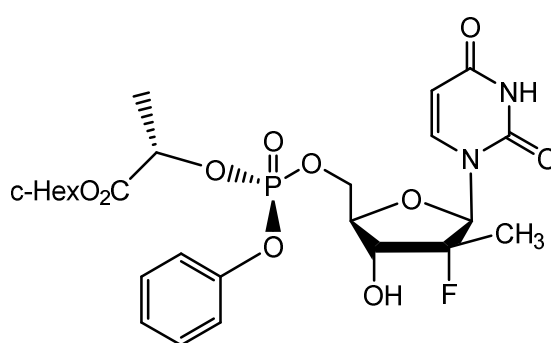
Example 15



'309 patent



Example 39

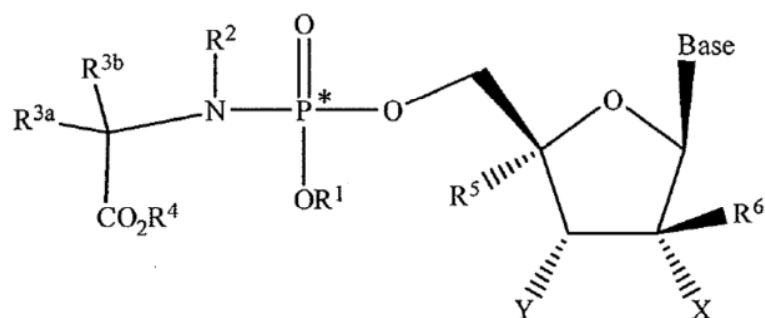


Example 49

EX1002 at ¶110.

These figures compare the single phosphorous diastereomers of Examples 15, 39, and 49 from Sofia '634 to compound 4 claimed in the '309 patent. EX1002 at ¶111.

As is shown in the figures, Sofia '634 taught in its Example 25 a structure identical to compound 4. EX1005 at 684. Sofia '634 also taught that the Example 25 and Example 81 compounds were obtained as a mixture of diastereomers. EX1005 at 684, and 693-694. Sofia '634 further taught, "A compound, *its stereoisomer*, salt, hydrate, solvate, or crystalline form thereof, represented by formula I:



I

EX1005 at 699:1-5 (claim 1; emphasis added). Such stereoisomers must, therefore, include stereoisomers (i.e., diastereomers) at the phosphorous. EX1002 at ¶112.

Sofia '634 taught that its example compounds, including compound 25, which is the nucleoside phosphoramidate claimed in the '309 patent, were a mixture of diastereomers. EX1005 at 693-694. This disclosure also taught the separation of diastereomers by chromatography on a Chiralpak-AS-H (2 x 25 cm) column under Supercritical Fluid Chromatography (SFC) conditions. EX1005 at 693-694 (Example 81)). The chromatographic separation of diastereomers of compounds 15, 39, and 49 are provided as representative, non-limiting examples. EX1002 at ¶113. Sofia '634 taught the chromatographic separation of diastereomers of all its compounds especially its example compounds, including compound 25. *Id.*

A POSA would expect one diastereomer to be much more active than the other and known that it would be preferred to produce a compound of as much of

the more active diastereomer as possible. EX1002 at ¶114. It was generally known that such compounds could have, and indeed should have, as high a percent as possible of the preferred diastereomer. *Id.* Thus, Sofia '634 teaching of diastereomers of the compound claimed in the '309 patent inherently taught compounds of 97-99% of the preferred diastereomer. *Id.*

The recitation of diastereomeric purities of 97%, 98%, and 99% are merely arbitrary examples of limits of the bounds of claim 1. EX1002 at ¶115. As such, these arbitrary limits are inherently taught by Sofia '634, which expressly teaches both a mixture of diastereomers at phosphorous and individual stereoisomers at phosphorous. *Id.* The arbitrary limits set by the percentage recitations in the claims of the '309 patent are not meaningful from a standpoint of antiviral activity, since such differences (e.g., IC<sub>90</sub> values) would be within the range of experimental error of such assays. *Id.*

Further, a POSA's perspective would be on drug approvals for human dosing, and in that case, these arbitrary percentage recitations are irrelevant because the specifications for diastereomeric impurities in drug substances are negotiated with regulatory agencies on an individual basis and are justified based on the separate activity and toxicity of individual isomers. EX1002 at ¶116; EX1013 at 1-10.

Thus, even though Sofia '634 did not expressly teach its diastereomer

compounds had 97%, 98% or 99% of the more active stereoisomer, to a POSA, Sofia '634 nonetheless inherently taught all of the limitations of claims 1-3. EX1002 at ¶117.

In addition, Congiatu taught that the phosphorous diastereomers of phosphoramidate nucleoside prodrugs may be separated and that it would not be unexpected for there to be a very substantial (in this case approximately 15-fold) difference in biological activity of phosphorous diastereomers. EX1006 at 2. Thus, Congiatu taught that the separate diastereomers of phosphoramidate prodrugs must be tested to determine which diastereomer is preferred as a drug candidate. EX1002 at ¶118.

Further, Congiatu taught that nucleoside phosphoramidates are readily obtained as mixtures of diastereomers at phosphorous. EX1006 at 1-2. Congiatu also taught that the  $R_p$  and  $S_p$  diastereomers at phosphorous may be separated by chromatography and that the stereochemistry at phosphorous may be assigned by spectroscopic methods. *Id.* at 2-3.

A POSA would have expected to be successful in applying Congiatu's teaching regarding the obtaining of mixtures of diastereomers to the Sofia '634 teaching of hepatitis C virus inhibiting nucleoside phosphoramidates, and specifically Sofia '634 compound 25, which is the same exact compound as that claimed by the '309 patent. EX1002 at ¶120.

Thus, Sofia '634 and Congiatu rendered claims 1-3 obvious to one of ordinary skill in art. EX1002 at ¶121.

During prosecution, the Examiner made a similar obviousness rejection of the '309 patent's claims. EX1004 at 12-13. Patent Owner was only able to overcome the obviousness rejection by arguing the claimed invention had purported unexpected results. EX1004 at 24.

Specifically, Patent Owner argued that it was unexpected that the  $S_P$  stereoisomer would be more potent than the mixture of the two phosphorous-based stereoisomers and >20 times more potent than the corresponding  $R_P$  stereoisomer. *Id.* (citing 1001 at 97).

However, the claimed invention did not have unexpected results, as it would have been entirely expected that one of the two diastereomers would be highly more potent than the other. EX1002 at ¶124. As discussed above, a POSA would have been motivated to separate a compound into its diastereomers and test their separate potencies. *Id.* A POSA would also expect that one diastereomer might be much more potent than the other since many such examples existed, and would be highly motivated to perform this test. *Id.* Thus, Patent Owner did not show during prosecution of the '309 patent that its claims had unexpected results. *Id.*

## **2. Claims 4-6 (pharmaceutical compositions)**

Claims 4-6 claim pharmaceutical compositions comprising the compounds



of claims 1-3, respectively, and a pharmaceutically acceptable medium. EX1001 at 76:56-64.

Sofia '634 taught compositions comprising its compounds and a pharmaceutically acceptable medium. EX1005 at 711:1-716:4. Thus, Sofia '634 and Congiatu rendered claims 4-6 obvious to one of ordinary skill in art. EX1002 at ¶126.

### **3. Claims 7-12 (methods of treating hepatitis C)**

Claims 7, 9 and 11 claim methods of treating a hepatitis C virus infection in a human comprising administering to the human an effective amount of the compounds of claims 1-3, respectively. EX1001 at 76:65-77:10. Claims 8, 10 and 12 claim the methods of claims 7, 9 and 11, further comprising administering to the human another antiviral agent. *Id.* at 77:1-12.

Sofia '634 taught that its compounds were useful, "as inhibitors of HCV replication and for treatment of hepatitis C infection in mammals." EX1005 at 2:15-21 (Field of Invention). Sofia '634 also taught, "administering a therapeutically effective of at least two or more different compounds falling within the scope of the compound represented by formula I to the subject." *Id.* at 665:19-23. Thus, Sofia '634 and Congiatu rendered claims 7-12 obvious to one of ordinary skill in art. EX1002 at ¶128.

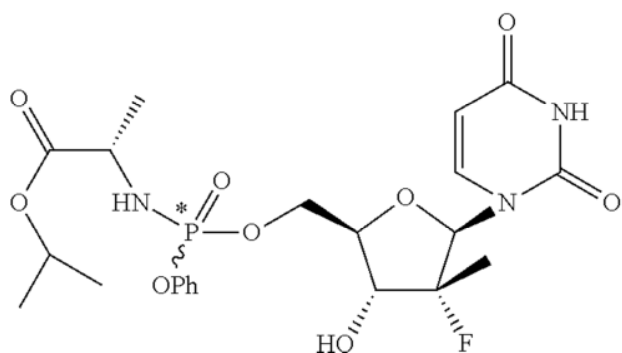
**C. Ground 3: Claims 1-12 Were Obvious Over Clark '147 and Congiatu**

A POSA would have been motivated to combine the teachings of Clark '147 and Congiatu because they both related to nucleoside phosphoramidate prodrugs. EX1002 at ¶129. The combined teaching of Clark '147 and Congiatu make claims 1-12 of the '309 patent obvious. *Id.*

**1. Claims 1-3 (compounds)**

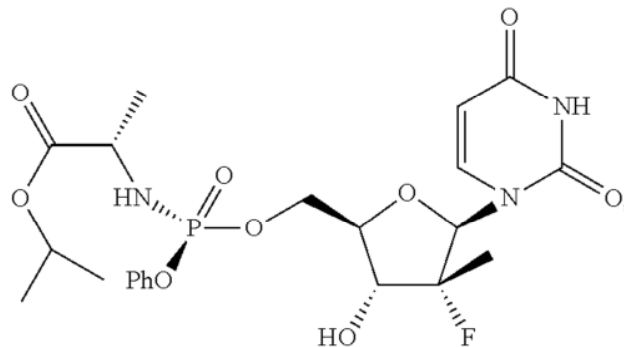
Claim 1 of the '309 patent recites:

A compound represented by the formula (4):



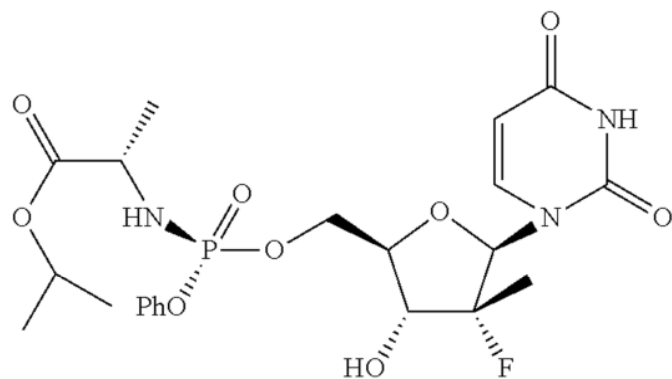
wherein P\* represents a chiral phosphorus atom and wherein the compound is at least 97% of the  $S_P$  stereoisomer represented by the formula ( $S_P$ -4):

(S<sub>P</sub>-4)



and not more than 3% of the R<sub>P</sub> stereoisomer represented by the formula (R<sub>P</sub>-4):

(R<sub>P</sub>-4)



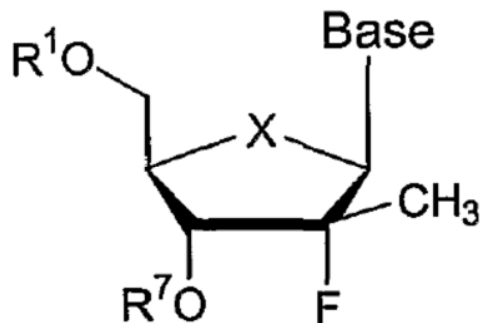
EX1001 at 76:1-47. Claim 2 recites, “The compound according to claim 1, wherein the compound is at least 98% of the S<sub>P</sub> stereoisomer represented by the formula (S<sub>P</sub>-4) and not more than 2% of the R<sub>P</sub> stereoisomer represented by the formula (R<sub>P</sub>-4).” *Id.* at 76:48-51. Claim 3 recites, “The compound according to claim 1, wherein the compound is at least 99% of the S<sub>P</sub> stereoisomer represented by the formula (S<sub>P</sub>-4) and not more than 1% of the R<sub>P</sub> stereoisomer represented by the formula (R<sub>P</sub>-4).” *Id.* At 76:52-55.

Clark ‘147 taught modified fluorinated nucleoside analogs. EX1007. More

specifically, Clark '147 taught (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleosides, their pharmaceutically acceptable salt forms, and prodrugs. *Id.* at 18:3-17. Clark '147 taught that these compounds could be used to treat *Flaviviridae* viruses, including hepatitis C viral infections. *Id.* at 1 (Abstract).

Specifically, Clark '147 taught and claimed:

A (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside ( $\beta$ -D or  $\beta$ -L) or its pharmaceutically acceptable salt or prodrug thereof of the structure:



wherein Base is a purine or pyrimidine base;

X is O, S, CH<sub>2</sub>, Se, NH, N-alkyl, CHW (*R*, *S*, or racemic), C(W)<sub>z</sub>,

wherein W is F, Cl, Br, or I; and,

*Id.* at 96:1-97:23 (claim1). This teaching covers the base structure, including mono-, di-, and triphosphate forms. It also covers prodrugs of such structure. *Id.* at 46:23- 48:20 and 57:3-62:4.

Clark '147 also taught a variety of techniques used for the isolation and crystallization of isomers and polymorphs, i.e., "IV. Stereoisomerism and Polymorphism." EX1006 at 52:21-55:22. This disclosure included a discussion of

methods for separating diastereomers, chiral chromatography, and purification by various forms of crystallization. *Id.*

A POSA would expect one diastereomer to be much more active than the other and known that it would be preferred to produce a compound of as much of the more active diastereomer as possible. EX1002 at ¶134. It was generally known that such compounds could have, and indeed should have, as high a percent as possible of the preferred diastereomer. *Id.* Thus, Clark '147's teaching of diastereomers inherently taught compounds of 97-99% of the preferred diastereomer. *Id.*

The recitation of diastereomeric purities of 97%, 98%, and 99% are merely arbitrary examples of limits of the bounds of claim 1. As such, these arbitrary limits are inherently taught by Clark '147. EX1002 at ¶135. The arbitrary limits set by the percentage recitations in the claims of the '309 patent are not meaningful from a standpoint of antiviral activity, since such differences (e.g., IC<sub>90</sub> values) would be within the range of experimental error of such assays. *Id.*

Further, a POSA's perspective would be on drug approvals for human dosing, and in that case, these arbitrary percentage recitations are irrelevant because the specifications for diastereomeric impurities in drug substances are negotiated with regulatory agencies on an individual basis and are justified based on the separate activity and toxicity of individual isomers. EX1002 at ¶136;

EX1013 at 1-10.

Congiatu taught that the phosphorous diastereomers of phosphoramidate nucleoside prodrugs may be separated and that it would not be unexpected for there to be a very substantial (in this case approximately 15-fold) difference in biological activity of phosphorous diastereomers. EX1006 at 2-3. Thus, Congiatu taught that the separate diastereomers of phosphoramidate prodrugs must be tested to determine which diastereomer is preferred as a drug candidate. EX1002 at ¶137.

Further, Congiatu taught that nucleoside phosphoramidates are readily obtained as mixtures of diastereomers at phosphorous. EX1006 at 1-2. Congiatu also taught that the  $R_P$  and  $S_P$  diastereomers at phosphorous may be separated by chromatography and that the stereochemistry at phosphorous may be assigned by spectroscopic methods. EX1006 at 2-3.

A POSA would have expected to be successful in applying Congiatu's teaching regarding the obtaining of mixtures of diastereomers to Clark '147's teaching of hepatitis C virus inhibiting nucleoside phosphoramidates. EX1002 at ¶139.

Thus, Clark '147 and Congiatu rendered claims 1-3 obvious to one of ordinary skill in art. EX1002 at ¶140.

During prosecution, in response to an obviousness rejection made by the Examiner, Patent Owner argued that it was unexpected that the  $S_P$  stereoisomer

would be more potent than the mixture of the two phosphorous-based stereoisomers and >20 times more potent than the corresponding R<sub>P</sub> stereoisomer. EX1004 at 24.

However, the claimed invention did not have unexpected results, as it would have been entirely expected that one of the two diastereomers would be highly more potent than the other. EX1002 at ¶142. As discussed above, a POSA would have been motivated to separate a compound into its diastereomers and test their separate potencies. *Id.* A POSA would also expect that one diastereomer might be much more potent than the other since many such examples existed, and would be highly motivated to perform this test. *Id.* Thus, Patent Owner did not show during prosecution of the '309 patent that its claims had unexpected results. *Id.*

## **2. Claims 4-6 (pharmaceutical compositions)**

Claims 4-6 claim pharmaceutical compositions comprising the compounds of claims 1-3, respectively, and a pharmaceutically acceptable medium. EX1001 at 76:56-64.

Clark '147 taught that its compounds for use as pharmaceuticals. EX1007 at 1 (Abstract). Inherent in this teaching are compositions comprising such compounds and a pharmaceutically acceptable medium. EX1002 at ¶144. Thus, Clark '147 and Congiatu rendered claims 4-6 obvious to one of ordinary skill in art. *Id.*

### **3. Claims 7-12 (methods of treating hepatitis C)**

Claims 7, 9 and 11 of the '309 patent claim methods of treating a hepatitis C virus infection in a human comprising administering to the human an effective amount of the compounds of claims 1, 2 and 3. EX1001 at 76:65-77:10. Claims 8, 10 and 12 of the '309 patent claim the methods of claims 7, 9 and 11 further comprising administering to the human another antiviral agent. EX1001 at 77:1-12.

Clark '147 taught that its compounds could be used to treat hepatitis C viral infections. EX1007 at 1 (Abstract). Clark '147 further taught that its compounds could be used in “more effective combination therapies,” and specifically, “in combination or alternation with one or more other effective antiviral agent(s), optionally in a pharmaceutically acceptable carrier or diluent thereof, as described herein.” EX1007 at 21:13-15. Thus, Clark '147 and Congiatu rendered claims 7-12 obvious to one of ordinary skill in art. EX1002 at ¶146.

## **XI. CONCLUSION**

For these reasons, claims 1-12 of the '309 patent are unpatentable over the asserted prior art. Petitioner therefore respectfully requests that an *inter partes* review be instituted and that they be found unpatentable and canceled.



Respectfully submitted,

Dated: October 30, 2017

/Daniel B. Ravicher/

Daniel B. Ravicher, Lead Counsel

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*Counsel for Petitioner*

## XII. APPENDIX – LIST OF EXHIBITS

Exhibit No.	Description
1001	U.S. Patent No. 8,633,309
1002	Declaration of Joseph M. Fortunak, Ph.D.
1003	<i>Curriculum Vitae</i> of Joseph M. Fortunak, Ph.D.
1004	File History Excerpts
1005	Sofia '634
1006	Congiatu
1007	Clark '147
1008	Chapman
1009	McGuigan 1994
1010	Ma
1011	Clark 2005
1012	Perrone
1013	Byrn

### **XIII. CERTIFICATE OF COMPLIANCE**

Pursuant to 37 C.F.R. §42.24(d), the undersigned certifies that this Petition complies with the type-volume limitation of 37 C.F.R. §42.24(a). The word count application of the word processing program used to prepare this Petition indicates that the Petition contains 8,780 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a).

Respectfully,

Dated: October 30, 2017

/Daniel B. Ravicher/  
Daniel B. Ravicher, Lead Counsel  
Reg. No. 47,015

**XIV. CERTIFICATE OF SERVICE**

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), I certify that I caused to be served a true and correct copy of the foregoing PETITION FOR *INTER PARTES* REVIEW and supporting materials (Exhibits 1001-1013 and Power of Attorney) by overnight courier (Federal Express or UPS), on the date below on the Patent Owner at the correspondence address of the Patent Owner as follows:

GILEAD PHARMASSET LLC  
C/O GILEAD SCIENCES, INC.  
333 LAKESIDE DRIVE  
FOSTER CITY, CALIFORNIA 94404

Respectfully,

Dated: October 30, 2017

/Daniel B. Ravicher/  
Daniel B. Ravicher, Lead Counsel  
Reg. No. 47,015