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

_____

Case No. IPR2018-00126
U.S. Patent No. 9,284,342

_____

PETITION FOR *INTER PARTES* REVIEW

TABLE OF CONTENTS

I. INTRODUCTION

Initiative for Medicines, Access & Knowledge (I-MAK), Inc. ("Petitioner") requests *inter partes* review ("IPR") of claims 1-4 of United States Patent No. 9,284,342 to Ross et al. ("the '342 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 '342 patent issued on March 15, 2016, and is currently assigned to Gilead Pharmasset LLC ("Patent Owner"). This petition demonstrates that claims 1-4 of the '342 patent are unpatentable.

The '342 patent claims a pharmaceutical compound, composition and methods that were obvious in light of the prior art. Specifically, the '342 claims a particular crystalline 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 crystalline forms of a nucleoside compound to determine if one is more active was entirely conventional and expected. Identifying a specific crystalline form of a known nucleoside is not inventive, but obvious.

Thus, claims 1-4 of the '342 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 recently filed a petition for *Inter Partes* Review of U.S. Patent No. 8,633,309, which relates to the '342 patent. Case No. IPR2018-00125. 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 ’342 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 1-4 of the ’342 patent based on the following grounds:

#	Claims	35 U.S.C. §	Prior Art
1	1-4	103(a)	Sofia ‘634 and Sofia 2010
2	1-4	103(a)	Sofia ‘634 and Ma
3	1-4	103(a)	Clark ‘147 and Ma

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.

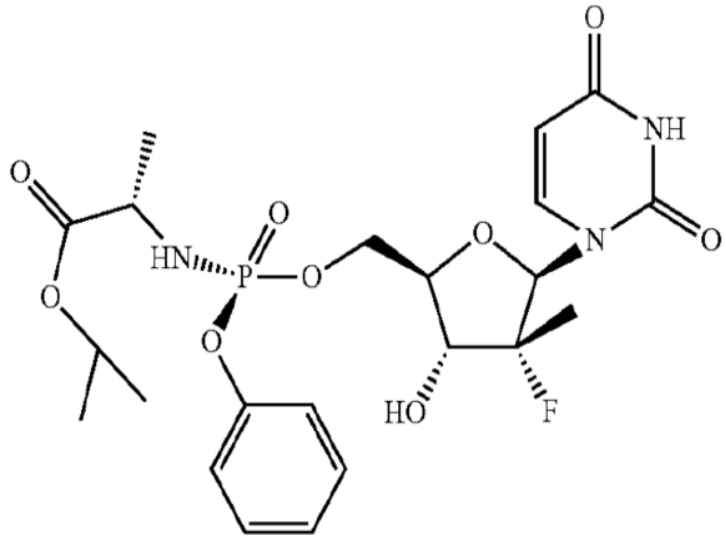
The Petition and its supporting materials, which are listed in the Appendix,

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 '342 PATENT

The '342 patent claims a crystalline compound represented by the following formula:

S_P-4



EX1001 at 89:42-58.

In describing the claimed invention, the '342 patent states:

> Disclosed herein are nucleoside phosphoramidates and their use as agents for treating viral disease. These compounds are inhibitors of RNA-dependent RNA viral replication and are useful as inhibitors of HCV NS5B polymerase, as inhibitors of HCV replication and for treatment of hepatitis C infection in mammals.

EX1001 at 1 (Abstract).

The '342 patent discloses that form 6 of the S_P-4 compound is the form with

XRPD 2Θ-reflections (°) at about: 6.1 and 12.7. EX1001 at 76:9-42. The '342 patent also discloses that there are at least two ways that the crystalline form 6 of S_P-4 can be obtained from form 1 of the same compound: 1) suspension in water (at 5-50 mg/mL) at ambient temperature for a few hours; and 2) grinding followed by slow conversion to form 6 upon standing exposed to atmospheric humidity. EX1001 at 73:10-50.

The following chart describes claims 1-4 of the '342 patent:

Claim(s)	Recite
1	Crystalline compound represented by the formula above having XRPD 2Θ-reflections (°) at about: 6.1 and 12.7.
2	Pharmaceutical composition having the crystalline compound of claim 1 and a pharmaceutically acceptable medium.
3, 4	Method of treating a hepatitis C virus infection in a human by administering the compound of claim 1, alone or with another antiviral agent.

V. FILE HISTORY OF THE '342 PATENT

U.S. Patent Application No. 13/925,078 ("the '078 application) was filed on June 24, 2013, and issued as the '342 patent on March 15, 2016. The '078 application claimed priority as a continuation of U.S. Patent Application No. 13/076,552 ("the '552 application") filed on Mar. 31, 2011, which claimed priority as a continuation-in-part of U.S. Patent Application No. 12/783,680 ("the '680 application") filed on May 20, 2010. The '078 application also claimed priority to

U.S. Provisional Applications Nos. 61/319,513 and 61/319,548, both of which were filed on Mar. 31, 2010, and U.S. Provisional Application 61/179,923 filed on May 20, 2009.

During prosecution of the ‘078 application, the Examiner made a single substantive rejection of double patenting, which the Patent Owner overcame by submitting a terminal disclaimer. EX1004 at 175. The Examiner then issued a Notice of Allowance stating in part:

> The claimed invention is seen to be novel and non-obvious over the prior art. The prior art does not disclose a crystalline composition of the claimed compound having the claimed XRPD peaks. References to the claimed compound in the prior art (see for example Sofia et al. WO2008/121634, reference included with PTO-1449) do not disclose the specific crystal structure described in the claims, or a method of preparing a crystalline form of the compound that would have resulted in that particular crystal. Because of the unpredictability of crystalline polymorphs, one of ordinary skill in the art would not have been able to, based on the prior art disclosure, predict or make this particular crystal form.
>
> While the prior art reference US8916538 (cited in PTO-892) discloses a crystalline 2'-C-methyluridine-N-alanyl phosphoramidite having an x-ray powder diffraction pattern with peaks similar to those described in the claims, the compound is a thiophosphate, and additionally lacks the 2'-fluoro group of the claimed compound. One of ordinary skill in the art would have had no motivation to modify

> this compound by substituting these groups to produce the claimed compound.
>
> For these reasons the claims are seen to meet the requirements of 35 USC 102 and 103.

EX1004 at 183-184.

As discussed below, the Examiner's conclusion that the failure of the prior art to expressly disclose a crystalline composition having the claimed XRPD peaks rendered the claims not obvious was incorrect. EX1002 at ¶30. While that may be a basis to conclude the specific crystal structure claimed in the '342 patent was novel, it is not a basis to conclude it was also not obvious. *Id.*

During prosecution the Examiner expressly discussed priority of the '078 application, finding:

> The parent application 12/783680, and its provisional applications 61/319513, 61/319548, and 61/179923, fail to provide support for the claimed invention as they do not include a written description under 35 USC 112 of a crystalline compound having the claimed x-ray diffraction peaks. Therefore the effective filing date of the present application is the filing date of the parent application 13/076552, filed March 31, 2011.

EX1004 at 169. Patent Owner never took issue with these findings.

VI. PERSON OF ORDINARY SKILL IN THE ART

Because the '342 patent pertains to nucleoside compounds, a 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 ¶38

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 '342 patent provides definitions for certain claim terms, but these definitions are conventional. EX1002 at ¶40. Thus, there is no reason to give any of the terms of the claims of the '342 a meaning other than their ordinary and accustomed meaning. *Id*.

VIII. BACKGROUND KNOWLEDGE IN THE ART

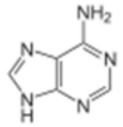
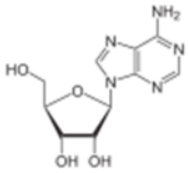
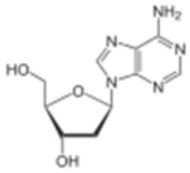
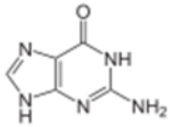
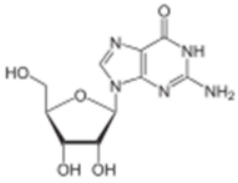
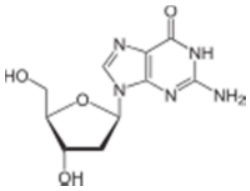
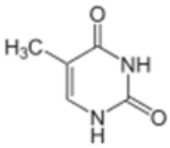
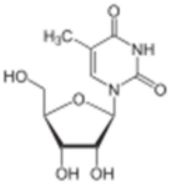
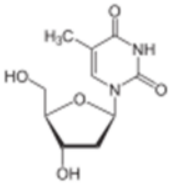
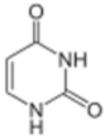
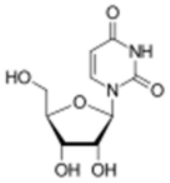
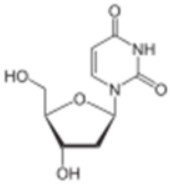
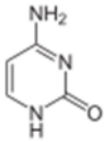
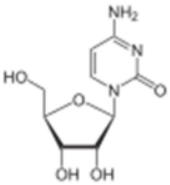
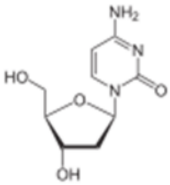
The background discussed below reflects knowledge skilled artisans would

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 March 31, 2011.

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 ¶42. 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. *Id*.

Nitrogenous Base	Ribose Derivative	Deoxyribose Derivative
 Adenine	 Adenosine (A)	 Deoxyadenosine (dA)
 Guanine	 Guanosine (G)	 Deoxyguanosine (dG)
 Thymine	 5-Methyluridine (m^5U)	 Thymidine (dT)
 Uracil	 Uridine (U)	 Deoxyuridine (dU)
 Cytosine	 Cytidine (C)	 Deoxycytidine (dC)

It was also well known that analogs of naturally-occurring nucleosides were

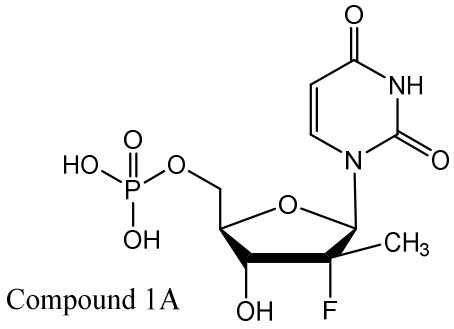
attractive targets for drug discovery and that such analogs were routinely used to treat diseases including viral infections and cancers. EX1002 at ¶43. Examples of such drugs included idoxuridine (antiviral) and gemcitabine for the treatment of cancer. *Id.* Additional examples of nucleoside drugs for 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 ¶44. 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™ phosphonamidate 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*.; 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). TDF and TAF are also used to treat hepatitis B viral infections. *Id*.

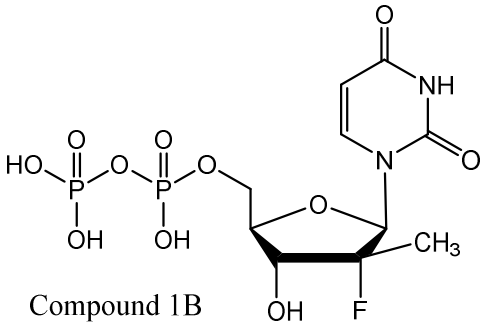
Nucleosides, however, were also well-known to be therapeutically-useful

only after intracellular, enzymatic conversion into the corresponding 5'-phosphorylated analogs; generally, these are the triphosphates. EX1002 at ¶45. 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 by-pass thymidine kinase,"* FEBS Letters, 1994, 351, 11-14 ("McGuigan 1994"; EX1009).

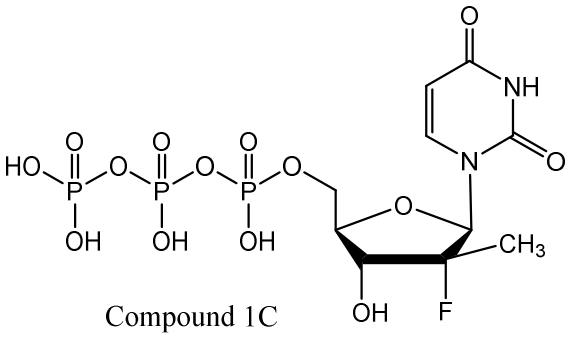
The mono-, di-, and triphosphate forms of the C2'-deoxy-C2'-methyl(up)-C2'-fluoro(down) uridine nucleoside are shown below. EX1002 at ¶46.



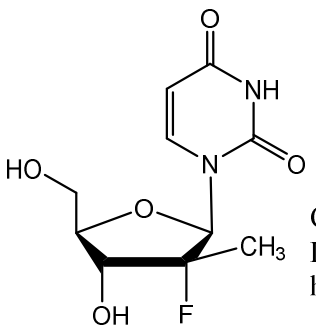
Compound 1A



Compound 1B



Compound 1C
Very active against hepatitis C virus



Compound 1D
Inactive against hepatitis C virus

Compounds 1A, 1B and 1C are phosphorylated analogs of an S_P-4 compound (the compound of '342 claim 1), 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 ¶47; Ma *et al.* *"Characterization of the Metabolic Activation of Hepatitis C Virus Nucleoside Inhibitor □-D-2'-Deoxy-2-Fluro-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 ¶47; 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 ¶48. Many nucleoside drugs – in particular, thymidines and uridines – were also known to be poor substrates for conversion into their monophosphate forms. *Id.*; EX1009 (McGuigan 1994) at 1-2; 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.

This was also known to be more common for virally-infected cells, which are often kinase-deficient. EX1002 at ¶49. 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 ¶50. Clark 2005 indicated that compound 1D – the unmodified nucleoside - had no activity in the HCV Replicon assay. 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 ¶51; 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 ¶52.

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.

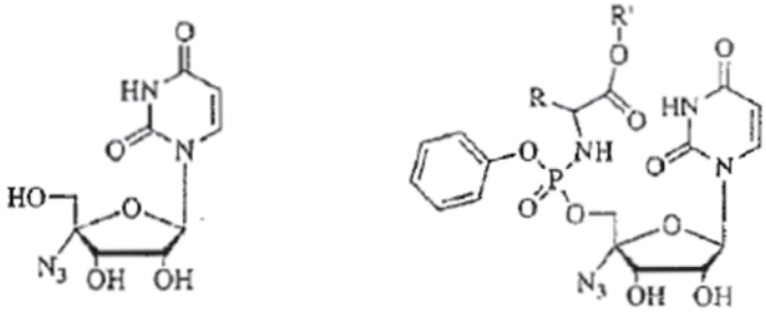
EX1002 at ¶53; EX1009 (McGuigan 1994) at 2-3. These analogs were well-known to provide advantages over unmodified nucleoside drugs in terms of physicochemical properties, cellular absorption, improved half-life, and very importantly, in terms of overcoming the problem of lack of biological activity due to poor intracellular phosphorylation. EX1002 at ¶53. The ProTide approach had been applied to activate nucleosides through kinase bypass for hepatitis C antiviral compounds as in Perrone. EX1002 at ¶53; EX1012 at 1. Thus, the ProTide approach was an obvious potential solution for overcoming the problem of poor intracellular phosphorylation of compound 1D. EX1002 at ¶53.

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 ¶54; EX1009 (McGuigan 1994) at 2-4; EX1012 (Perrone) at 2.

Perrone, in particular, had shown 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 ¶55; EX1012. 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. EX1002 at ¶55. It was also known that the limitation of poor phosphorylation

could be overcome in many cases by the application of ProTide prodrug technology. *Id*.

As an example, Perrone taught the following:



AZU (1) 2

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) at 1, and for phosphoramidate prodrugs of nucleosides. EX1002 at ¶57; Congiatu et al., "*Novel potential anticancer naphthyl phosphoramidates of BVdU: separation of diastereoisomers and assignment of the absolute configuration of the phosphorus cente*r," Journal of Medicinal Chemistry, 2006, 49, 452-455 ("Congiatu"; EX1006) at 1.

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. 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. EX1010 at 1 and 8.

As an example, the triphosphate of 1D possessed an intracellular half-life of 38 hours. EX1002 at ¶60; EX1010. This compared 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.

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

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 subsequent 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 above. EX1002 at ¶63; 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. EX1005 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.

G. Pharmaceutical Solids Were Well-Known to Exist in Multiple Solid-State and Crystalline Forms

A POSA was readily aware that S_P-4 could potentially exist in multiple solid-state forms. EX1002 at ¶66; Byrn S., "*Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations*," Pharmaceutical Research, 1995, 12(7), 945-954 ("Byrn"; EX1013); Hilfiker R., POLYMORPHISM IN THE PHARMACEUTICAL INDUSTRY, Wiley-VCH (2006), "*Relevance of Solid State Properties for Pharmaceutical Products*," Chapter 1, 1-19 ("Hilfiker Chapter 1"; EX1015). These forms might variously be amorphous, crystalline, hydrates, or solvates. *Id*. A POSA would also recognize that any crystalline form might exist in multiple molecular packing arrangements. *Id*. These different crystalline packing arrangements of a solid form are known as polymorphs. *Id*.

A POSA also knew that this difference in crystalline packing was a potential source of variability in properties, such as melting point, stability, aqueous solubility, formulation characteristics, bioavailability, bioequivalence, that are critical for understanding and controlling drug performance. EX1002 at ¶67.

It was routine and obligatory practice in the pharmaceutical industry to conduct solid-state and polymorph screening for new drug candidates. EX1002 at ¶ 68. "[I]n fact the whole existence of a drug is affected by the properties of the solid form, and the final goal of solid form development is to find and select the solid with the optimal characteristics for its intended use." EX1015 at 3.

Most active pharmaceutical ingredients (APIs) are produced by crystallization. EX1002 at ¶69. This is done to (among other things) assure the purity and consistency of APIs. *Id.*; EX1013 at 1-2. The ability of an API to exist in multiple crystalline forms (polymorphs) was therefore well-known to be important. EX1002 at ¶69.

A POSA knew that all new drug candidates that were solids would undergo a polymorph screen to assess the potential for multiple crystalline forms to exist, and their relative stability. EX1002 at ¶70; EX1013.

A POSA also knew that, while screening for polymorphs required significant labor, it was a conventional and routine exercise – and indeed, a required exercise for the pharmaceutical industry - with many publications describing the general approach for identification and characterization of polymorphs, hydrates, and solvates. EX1002 at ¶71; EX1013; Alvarez *"Polymorph Screening: Comparing an Automated Approach with a High Throughput Method"*, Crystal Growth and Design, 2009, 9(9), 4181-4188 ("Alvarez"; EX1016).

H. A Solid-State and Polymorph Screen for New Drug Candidates Would Always Evaluate the Impact of Water

The interactions of water with a pharmaceutical solid are critically important to evaluate for every new drug candidate. EX1002 at ¶72; Hilfiker R., POLYMORPHISM IN THE PHARMACEUTICAL INDUSTRY, Wiley-VCH (2006), *"Physical Characterization of Hygroscopicity in Pharmaceutical Solids,"* Chapter

9, 235-256 (“Hilfiker Chapter 9”; EX1017). A POSA thus knew that the interactions of a compound with water either by vapor sorption/desorption or by suspension/dissolution in aqueous solution were thoroughly investigated as part of routine evaluation for any new drug candidate in the pharmaceutical industry. EX1002 at ¶72.

Moisture can affect the stability of an API and its formulations. EX1002 at ¶73. The adsorption or absorption of water molecules into a drug or its formulation(s) can often induce hydrolytic instability. *Id.*; Yoshioka et al., *“Rational Storage Conditions for Accelerated Testing of Stability of Solid Pharmaceuticals,”* 79:10, 943-944 (1990) (“Yoshioka”; EX1018).

Other important properties such as crystal structure, powder flow, dissolution rate, lubricity, and compaction can be critically affected by moisture adsorption. EX1002 at ¶74; Ahlneck et al., *“The molecular basis of moisture effects on the physical and chemical stability of drugs in the solid state,”* Intl. J. Phar., 62:2-3, 87-95 (1990) (“Ahlneck”; EX1019).

A POSA also knew that the most common case of solvation for pharmaceutical solids is by incorporation of water molecules. EX1002 at ¶75; Gibson, *“Pharmaceutical Preformulation and Formulation, A Practical Guide from Candidate Drug Selection to Commercial Dosage Form,”* IHS Health Group, Chapter 3, 43- 44 (2004) (“Gibson”; EX1020). A POSA knew, therefore, that

evaluating the impact of water on a pharmaceutical solid would include characterization of the crystalline form obtained (i.e., polymorphic form and stability). EX1002 at ¶75.

Thus, the methods described for the preparation of S_P-4, form 6 in the '342 patent, EX1001 at 73:10-50, were well within the routine and customary tests performed on all new drug candidates to evaluate the stability of crystalline forms. EX1002 at ¶76. Indeed, such tests were an obligatory part of early drug development and are routinely reported to regulatory agencies. *Id*.; EX1013; Ex 1015; EX1017.

IX. SCOPE AND CONTENT OF THE PRIOR ART

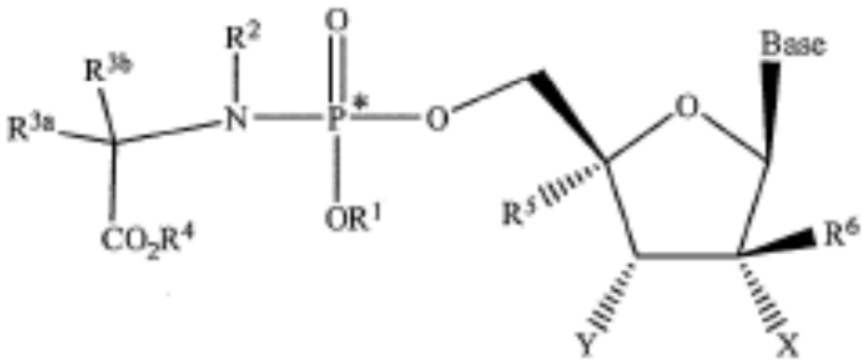
The following references taught or suggested the compounds, compositions and methods recited in claims 1-4 of the '342 patent. EX1002 at ¶77.

A. WO 2008/121634 to Sofia ("Sofia '634"; EX1005)

Sofia '634 is prior art under 35 U.S.C. § 102(b) to the '342 patent because it was published on October 9, 2008, more than year before the March 31, 2011, priority date to which the '342 patent is entitled to claim priority. EX1004 at 169. Even if the '342 patent is entitled to claim priority to its earliest filed provisional application, which was filed on May 20, 2009, Sofia '634 would still be prior art under 35 U.S.C. § 102(a).

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-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid isopropyl ester.” EX1005 at 703:48-50 (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 were 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 724:43-728:19 (claim 7).

Sofia ‘634 contained a substantial series of tables of “contemplated species” within the structure of formula I. *Id*. at 101-659. Notably, Sofia ‘634 highlighted a

very small number of examples, including Example 25, which is the compound claimed by the '342 patent, except that it does not indicate the stereochemistry at the 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. Notably, Example 81 of Sofia '634 taught the separation of isomers at phosphorous into their individual diastereomers. *Id*. 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. *Id*. 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*.

This teaching of the wide variability in activity of Sofia '634's phosphorous diastereomers would have motivated a POSA to investigate them. EX1002 at ¶82. Sofia '634's teaching would have given a POSA a reasonable expectation of success in isolating and testing the stereoisomers of its compounds. *Id*.

This motivation and expectation of success would also have been supported by the general knowledge that the stereochemistry at phosphorous of ProTide phosphoramidates had an influence on the rate of enzymatic cleavage. EX1002 at ¶83; Siccardi D., *"Stereospecific chemical and enzymatic stability of*

phosphoramidate triester prodrugs of d4T in vitro," Eur. J. Pharm. Sci., 2004, 22, 25-31 ("Siccaradi"; EX1021).

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. EX1005 at 665:19-23 and 667:8-668:13.

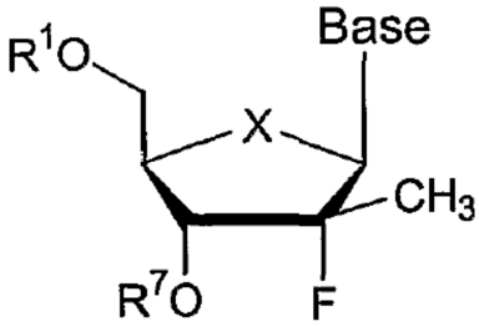
B. WO 2005/003147 to Clark ("Clark 147"; EX1007)

Clark '147 is prior art under 35 U.S.C. § 102(b) to the '342 patent because it was published on January 31, 2005, more than a year before the May 20, 2009, filing date of the earliest application to which the '342 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 (β-D or β-L) or its pharmaceutically acceptable salt or prodrug thereof of the structure:



wherein Base is a purine or pyrimidine base;

X is 0, S, CH2, Se, NH, N-alkyl, CHW *(R*, S, or racemic), C(W)z,

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 21:9-28.

C. Sofia et. al., "Discovery of a □-D-2'-Deoxy-2'-a-fluoro-2'□□-C-methyluridine Nucleotide Prodrug (PSI-7977) for the Treatment of Hepatitis C Virus," J. Med. Chem., 2010, 53:7202-7218 ("Sofia 2010"; EX1014)

Sofia 2010 is prior art under 35 U.S.C. § 102(a) to the '342 patent because it was published on September 16, 2010, before the March 31, 2011, priority date to which the '342 patent is entitled to claim priority. EX1004 at 169.

Sofia 2010 taught the identification of the triphosphate form of compound 1D above as a potent inhibitor of hepatitis C virus using antiviral assays. EX1014 at 2. Sofia 2010 described the recognized need for a prodrug form of the mono-phosphate of compound 1D as a means of biological conversion to the very potent and long-lasting triphosphate form. *Id*.

Sofia 2010 also taught the logic of selecting a ProTide phosphoramidate prodrug. *Id*. at 2-5. Sofia 2010 further taught the synthesis, isolation, and crystallization of its nucleoside prodrug, referred to as PSI-7977. *Id*. at 3.

Sofia 2010 provided results of assays used to determine the more active diastereomer of the ProTide prodrug (S_P-4 or R_P-4). *Id*. at 8. Sofia 2010 taught the recrystallization of PSI-7977 to obtain the purified S_P diastereomer (compound S_P-4 of the '342 patent) and that the crystallization of S_P-4 from dichloromethane resulted in the dichloromethane solvate of S_P-4, which was characterized by XRPD and single-crystal x-ray. *Id*.

Sofia 2010 therefore taught the S_P-4 diastereomer of PSI-7977. Sofia 2010 also taught the crystallization of this compound, and the dichloromethane solvate crystalline form of PSI-7977. EX1014 at 8 and 13.

A POSA would have been motivated by this teaching to investigate additional crystalline forms of PSI-7977 using techniques that were routine in the art. EX1002 at ¶93.

A POSA would also have known that dichloromethane is a "class II" solvent whose exposure to a patient should be limited due to inherent toxicity. EX1002 at ¶ *94; "Specifications: Test Procedures and Acceptance Criteria For New Drug Substances and New Drug Products: Chemical Substances,"* ICH Harmonised Tripartite Guideline, October 6, 21999 ("ICH"; EX1022).

Because the amount of residual dichloromethane in a standard dose of PSI-7977 as the dichloromethane solvate, known as of 2010 to be either 200 or 400 mg/day of active drug, EX1023, was several times greater than the Permissible Daily Exposure limit of 6 mg[1], a POSA would have been compelled to create

[1] The dichloromethane solvate of PSI-7977 contains approximately 13.8% of dichloromethane by weight. Thus a 200mg daily dose of active PSI-7977 would contain 32mg of dichloromethane – several times the acceptable limit for daily exposure.

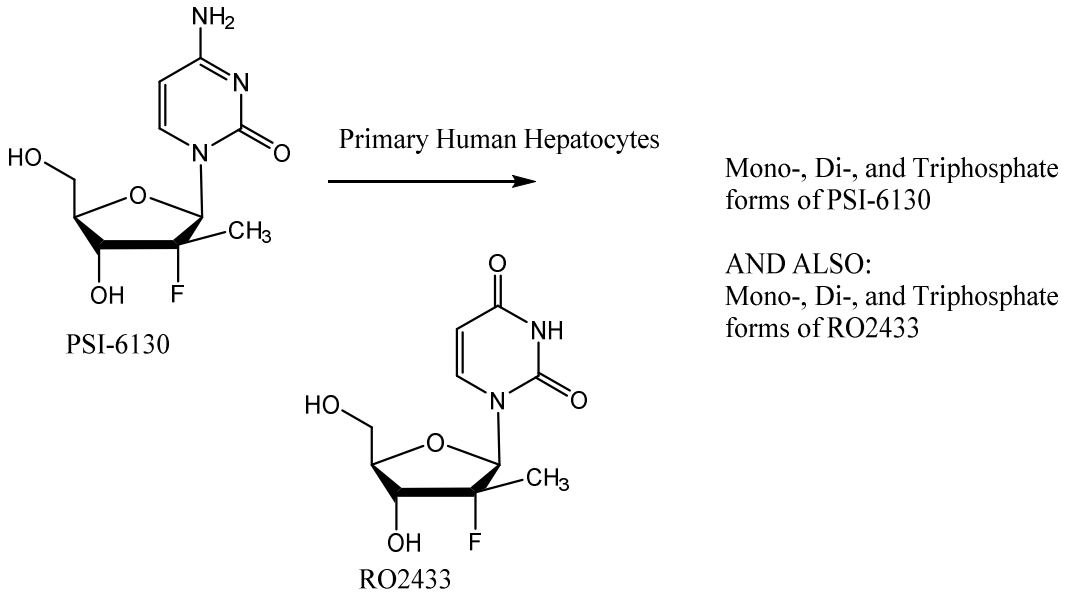
alternative crystalline forms of PSI-7977 for human use. EX1002 at ¶95.

It was also well-known in the art that the aqueous solubility, impact of water on stability (both to degradation and to crystalline form), and the water absorption/adsorption properties of a new drug candidate must be evaluated early in drug development. EX1002 at ¶96; EX1017 (Hilfiker Chapter 9). Thus, one of skill in the art would naturally have investigated these properties and would have expected to be able to isolate the S_P-4 crystalline form of a nucleoside. EX1002 at ¶96.

D. Ma et. al., *"Characterization of the metabolic activation of hepatitis C virus Nucleoside Inhibitor a □-D-2'-Deoxy-2'-fluoro-2'□□-C-methycytidine (PSI-6130) and Identification of a Novel Active 5'-Triphosphate Species,"* J. Biol. Chem., 2007, 282(41), 29812-29820 ("Ma"; EX1010)

Ma is prior art under 35 U.S.C. § 102(b) to the '342 patent because it was published on October 12, 2007, more than a year before the May 20, 2009, filing date of the earliest application to which the '342 patent claims priority.

Ma taught intracellular conversion of PSI-6130 (a cytidine nucleoside) into its phosphorylated derivatives as a part of activating the nucleoside for inhibition of hepatitis C virus in primary human hepatocytes. EX1010 at 1. Ma also taught the conversion of PSI-6130 into the uridine analog RO2433 (compound 1D above) and its phosphorylated derivatives under the same conditions. *Id.* This conversion taught by Ma is represented by the following:



EX1002 at ¶97.

It was known that the triphosphate form of PSI-6130 was a very potent inhibitor of hepatitis C virus. EX1010 at 1. Thus, Ma taught: 1) the triphosphate form of RO2433 was also a very potent inhibitor of hepatitis C virus; 2) the free nucleoside RO2433 (compound 1D) was inactive as an inhibitor of hepatitis C virus; 3) the monophosphate form of RO2433 was active against hepatitis C virus; and, 4) the triphosphate form of RO2433 had a much longer intracellular half-life than the triphosphate form of PSI-6130 (38 hours vs. 4.7 hours for PSI-6130 triphosphate). *Id.*

The exceptionally long intracellular half-life of the RO2433 triphosphate was presented as follows:

> The longer intracellular half-life of RO2433-TP (i.e., triphosphate) may have pharmacologic relevance for maintaining more constant

concentrations of the antiviral triphosphate over the dosing period in clinical studies.

EX1010 at 8.

Taken together, these results taught that a monophosphate prodrug form of compound 1D/RO2433 was a very attractive drug candidate for the treatment of hepatitis C viral infections. EX1002 at ¶100.

X. CLAIMS 1-4 ARE UNPATENTABLE

Each and every feature of claims 1-4 of the '342 patent can be found in or is suggested by the prior art, including specifically the references identified below. 101. Each of claims 1-4 is presented below followed by an analysis of the claims. The analysis below identifies exemplary disclosure of the cited references with respective to the corresponding claim elements, and is not meant to be exhaustive.

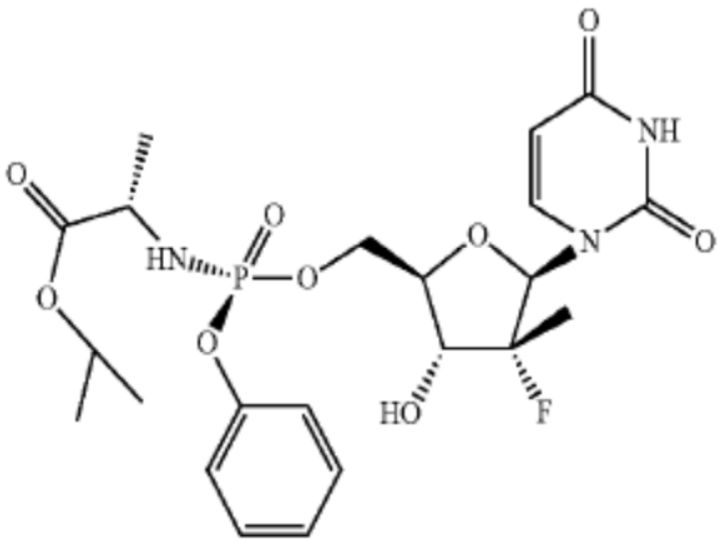
A. Ground 1: Claims 1-4 Were Obvious Over Sofia '634 and Sofia 2010

A POSA would have combined the teachings of Sofia '634 and Sofia 2010 because they both related to nucleoside prodrugs for the treatment of hepatitis C virus, and in particular □-D-2'-Deoxy-2'-α-fluoro-2'□□-C-methyluridine prodrugs. EX1002 at ¶102.

Claim 1 of the '342 patent recites:

A crystalline compound represented by the formula (S_P-4):

Sp-4



having XRPD 2Θ-reflections (°) at about: 6.1 and 12.7.

EX1001 at 89:43-60. Claim 2 is dependent upon claim 1 and recites, "A pharmaceutical composition comprising the crystalline compound according to claim 1 and a pharmaceutically acceptable medium." *Id*. at 90:1-3. Claim 3 is also dependent from claim 1 and recites, "A method of treating a hepatitis C virus infection in a human comprising administering to the human an effective amount of the crystalline compound according to claim 1." *Id*. at 90:4-6. Claim 4 depends from claim 3 and recites, "The method according to claim 3 further comprising administering to the human another antiviral agent." *Id*. at 90:7-8.

Sofia '634 taught phosphoramidate prodrugs of nucleoside derivatives for the treatment of viral infections in mammals, and in particular HCV. EX1005 at

2:15-21. Sofia ‘634 also taught: 1) stereoisomer, salt (acid or basic addition salt), hydrate, solvate, or crystalline forms of its compounds, 2) methods of treatment, uses, and processes for preparing each of which utilize its compounds, and 3) compositions comprising a “pharmaceutically acceptable medium” that includes crystalline forms of its compounds and a pharmaceutically acceptable medium. EX1005 at 661:1-7.

A discussed above, while Sofia 2010 disclosed many compounds, it focused on uridine analogs because they were among the most active. EX1014. Sofia 2010 also specifically highlighted phosphoramidates of □-D-2’-Deoxy-2’-α-fluoro-2’□□-C-methyluridine. *Id*. at 2. Thus, Sofia 2010 focused on phosphoramidates of the known uridine taught in Sofia ‘634. EX1002 at ¶105.

Regarding claim 1, Sofia ‘634 taught phosphoramidate prodrugs (ProTide) of its base nucleosides, providing potent antiviral compounds for treating hepatitis C viral infection in humans. EX1005 at 699. Sophia ‘634 also taught in Example 25 S_P-4 and R_P-4. *Id*. at 696. Sofia ‘634 further taught that the compound of Example 25 possesses potent activity against hepatitis C virus, *Id*., and the separation of diastereomers at phosphorous into individual S_P- and R_P-diastereomers. *Id*. at 693-694 (Example 81).

Sofia ‘634 taught that the individual diastereomers of phosphoramidate ProTide prodrugs may have different activities against hepatitis C virus. *Id*. at 693-

694 (Example 81). Thus, a POSA would select them as lead compounds to pursue in developing drug candidates. EX1002 at ¶107. Sofia '634 also taught crystalline forms and polymorphs, which a POSA would have already known were excellent candidates to form a drug compound. EX1002 at ¶107; EX1005 at 699 (claim 1).

Sofia 2010 taught the compound S_P-4 as a single diastereomer and its advantages. EX1014 at 1. Sofia 2010 also taught the crystalline dichloromethane solvate of S_P-4 including its XRPD and single-crystal x-ray structure. *Id*. at 8. Thus, Sofia 2010 and general knowledge in the art would have motivated one of skill in the art to investigate other crystalline forms of S_P-4 with an expectation that some would have superior characteristics. EX1002 at ¶108.

A POSA would also have expected that the specific phosphoramidate disclosed in Sofia 2010 was one of a small number of preferred phosphoramidate moieties for Sophia '634's crystalline prodrugs. EX1002 at ¶109. A POSA would expect that the specific phosphoramidate prodrug S_P-4 taught by Sofia 2010 would be a good drug candidate for the Sofia '634 compounds. *Id*.

A POSA would further know from Sofia 2010 that crystalline forms of the S_P-4 existed, and that an example of such crystalline forms was the dichloromethane solvate. EX1002 at ¶110; EX1014 at 8. A POSA would also have known, however, that a dichloromethane solvate of a drug would be disadvantageous because of the requisite human exposure to a toxic solvent upon

dosing. EX1002 at ¶110.

Therefore, a POSA would have been motivated to combine the teachings of Sofia ‘634 and Sofia 2010 to pursue isolation and testing of the disasteromers of the compounds taught in Sofia ‘634, as well as to search for alternative crystalline forms. EX1002 at ¶111. These crystalline forms would be structurally and functionally identical to the form claimed in claim 1 of the ‘342 patent. *Id.*

The only difference between claim 1 of the ‘342 patent and the crystalline forms of Sophia ‘634 that a POSA would have isolated, tested and determined had superior properties - as taught by Sophia 2010 - is the recitation of certain XRPD 2Θ-reflections, such reflections having no utility in themselves. EX1002 at ¶112.

However, the XRPD 2Θ-reflections recited in claim 1 do not provide the stereoisomer any of its properties or any functionality. EX1002 at ¶113. A crystalline form’s XRPD 2Θ-reflections are of no scientific or technical significance. *Id*. They are merely descriptive of some non-functional aspects of the XRPD 2Θ-reflections. *Id*. Although a POSA would not have been able to predict this exact recitation of 2 XRPD 2Θ-reflections, a POSA would be able to prepare the S_P-4 compound with such 2Θ-reflections and such properties merely by the application of processes and techniques which were both routine and obligatory to a POSA in the early stages of drug development. *Id*.

Thus, based on the stereoisomers of Sofia '634 and the crystalline form

represented in Sofia 2010, a POSA would have been motivated to search for alternative crystalline forms of S_P-4 to arrive at alternative crystalline forms with preferred properties. EX1002 at ¶114. The fact that some crystalline forms would have preferred properties over others was expected and unsurprising. *Id*.

The specific XRPD 2Θ-reflections recited in claim 1 of the '342 patent are obvious over the prior art because they are merely an incomplete recitation of a measured characteristic of the crystalline form that is dependent upon the packing arrangement of S_P-4 and the toxic solvent dichloromethane in a crystalline solid. EX1002 at ¶115. These factors result from the crystallization process and are expected, even if one cannot, in advance, know what the XRPD 2Θ-reflections of a particular crystalline form will be. *Id*.

Indeed, crystallization techniques were common knowledge to a POSA. EX1002 at ¶116. These techniques were discussed in many publications, including those cited above regarding common knowledge in the art. *Id*. Crystal and polymorph screening for new drug candidates was also a common and universally-practiced technique as part of the selection process for new drug candidates in the pharmaceutical industry. *Id*.

A POSA would also know that the methods described for the preparation of S_P-4, form 6 in the '342 patent, EX1001 at 73:10-50, were well within the routine and customary tests performed on all new drug candidates to evaluate the stability

of crystalline forms. EX1002 at ¶117. Indeed, such tests were an obligatory part of early drug development and are routinely reported to regulatory agencies. *Id*.; EX1013; EX 1015; EX1017.

Therefore, although Sofia '634 does not disclose the polymorph claimed in claim 1 exactly (i.e., such polymorph/crystalline solvate of S_P-4), it would have been obvious for a POSA to combine the teachings of Sofia '634 with Sofia 2010 and common knowledge in the art to arrive at multiple crystalline forms of its compounds. EX1002 at ¶118.

Lastly, as discussed above, solubility studies and crystallization from water and vapor sorption studies on new APIs are required as part of drug candidate selection for a number of very important reasons. EX1002 at ¶119. Thus, a POSA would have been motivated to screen the limited number of crystalline forms possible of promising drug candidates like those highlighted in Sofia '634. *Id*. Had a POSA performed this screening for the highlighted compounds in Sofia '634, they would have achieved the same crystalline form claimed in claim 1 of the '342 patent. *Id*. This result would not have been surprising or unexpected. *Id*.

Regarding claim 2, Sofia '634 taught compositions that include its crystalline compound and a pharmaceutically acceptable medium. EX1005 at 661:1-7.

Regarding claim 3, Sofia '634 taught methods of treatment and/or

prophylaxis by administering a therapeutically effective amount of its crystalline compound to a patient. EX1005 at 665:15-18.

Regarding claim 4, Sofia ‘634 taught methods of treatment by administering a therapeutically effective amount of the compound represented by formula I to a patient, in combination with another antiviral agent. EX1005 at 667:8 – 668:4.

Thus, each of claims 1-4 were obvious over Sofia ‘634 and Sofia 2010. EX1002 at ¶123.

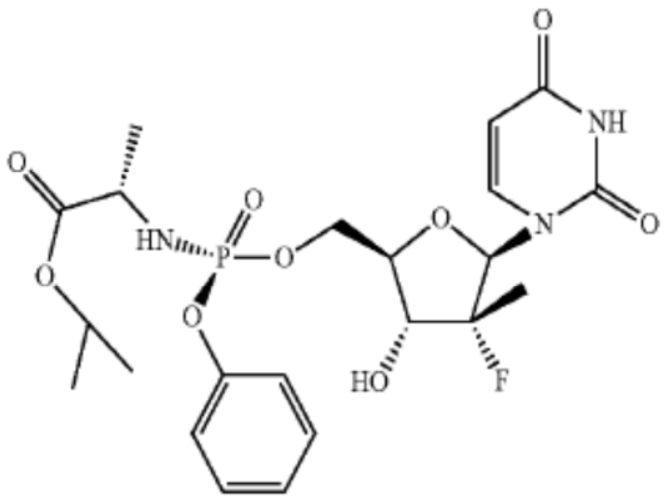
B. Ground 2: Claims 1-4 Were Obvious Over Sofia ‘634 and Ma

A POSA would have combined the teachings of Sophia ‘634 and Ma because they both related to nucleoside compounds for the treatment of hepatitis C virus. EX1002 at ¶124.

Claim 1 of the ‘342 patent recites:

A crystalline compound represented by the formula (S_P-4):

S_P-4



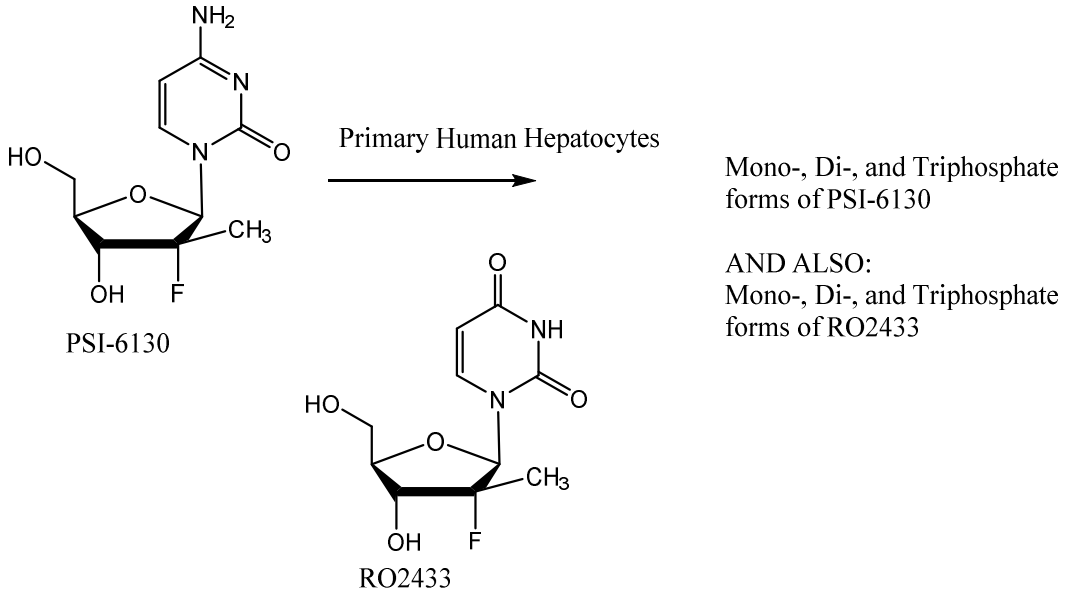
having XRPD 2Θ-reflections (°) at about: 6.1 and 12.7.

EX1001 at 89:43-60. Claim 2 is dependent upon claim 1 and recites, "A pharmaceutical composition comprising the crystalline compound according to claim 1 and a pharmaceutically acceptable medium." *Id*. at 90:1-3. Claim 3 is also dependent from claim 1 and recites, "A method of treating a hepatitis C virus infection in a human comprising administering to the human an effective amount of the crystalline compound according to claim 1." *Id*. at 90:4-6. Claim 4 depends from claim 3 and recites, "The method according to claim 3 further comprising administering to the human another antiviral agent." *Id*. at 90:7-8.

Sofia '634 taught phosphoramidate prodrugs of nucleoside derivatives for the treatment of viral infections in mammals, and in particular HCV. EX1005 2:15-21. Sofia '634 also taught: 1) stereoisomer, salt (acid or basic addition salt), hydrate, solvate, or crystalline forms of its compounds, 2) methods of treatment, uses, and processes for preparing each of which utilize its compounds, and 3) compositions comprising a "pharmaceutically acceptable medium" that includes crystalline forms of its compounds and a pharmaceutically acceptable medium. EX1005 at 661:1-7.

A discussed above, Ma taught intracellular conversion of PSI-6130 (a cytidine nucleoside) into its phosphorylated derivatives as a part of activating the

nucleoside for inhibition of hepatitis C virus in primary human hepatocytes. EX1010 at 1. Ma also taught the conversion of PSI-6130 into the uridine analog RO2433 (compound 1D above) and its phosphorylated derivatives under the same conditions. *Id.* This conversion taught by Ma is represented by the following:



EX1002 at ¶127.

It was known that the triphosphate form of PSI-6130 was a very potent inhibitor of hepatitis C virus. EX1010 at 1. Thus, Ma taught: 1) the triphosphate form of RO2433 was also a very potent inhibitor of hepatitis C virus; 2) the free nucleoside RO2433 (compound 1D) was inactive as an inhibitor of hepatitis C virus; 3) the monophosphate form of RO2433 was active against hepatitis C virus; and, 4) the triphosphate form of RO2433 had a much longer intracellular half-life than the triphosphate form of PSI-6130 (38 hours vs. 4.7 hours for PSI-6130

triphosphate). EX1002 at ¶128.

The exceptionally long intracellular half-life of the RO2433 triphosphate was presented as follows:

> The longer intracellular half-life of RO2433-TP (i.e., triphosphate) may have pharmacologic relevance for maintaining more constant concentrations of the antiviral triphosphate over the dosing period in clinical studies.

EX1010 at 8.

Taken together, these results indicate that a monophosphate prodrug form of compound 1D/RO2433 was a very attractive drug candidate for the treatment of hepatitis C viral infections. EX1002 at ¶130.

The only difference between claim 1 of the '342 patent and the crystalline forms of Sophia '634 compounds and Ma's identification of the specific RO2433 compound as being a preferred lead candidate to pursue for drug development, is the recitation of certain XRPD 2Θ-reflections. EX1002 at ¶131.

However, the XRPD 2Θ-reflections recited in claim 1 do not provide the stereoisomer any of its properties or any functionality. EX1002 at ¶132. A crystalline form's XRPD 2Θ-reflections are of no scientific or technical significance. *Id*. They are merely descriptive of some non-functional aspects of the XRPD 2Θ-reflections. *Id*.

Thus, based on the stereoisomeric teaching of Sofia '634 and Ma's

identification of the specific compound to pursue, a POSA would have been motivated to search for crystalline forms of RO2433 with preferred properties. EX1002 at ¶133. The fact that some crystalline forms would have preferred properties over others was expected and unsurprising. *Id*.

The specific XRPD 2Θ-reflections recited in claim 1 of the '342 patent are obvious over the prior art because they are merely a characterization of a measured characteristic of the crystalline form that is dependent upon the packing arrangement of S_P-4 and the toxic solvent dichloromethane in a crystalline solid. EX1002 at ¶134. These factors result from the crystallization process and are expected, even if one cannot, in advance, know what the XRPD 2Θ-reflections of a particular crystalline form will be. *Id*.

Indeed, crystallization techniques were common knowledge to a POSA. EX1002 at ¶135. These techniques were discussed in many publications, including those cited above regarding common knowledge in the art. *Id*. Crystal and polymorph screening for new drug candidates was also a common and universally-practiced technique as part of the selection process for new drug candidates in the pharmaceutical industry. *Id*.

A POSA would also have known that the methods described for the preparation of S_P-4, form 6 in the ‘342 patent, EX1001 at 73:10-50, were well within the routine and customary tests performed on all new drug candidates to

evaluate the stability of crystalline forms. EX1002 at ¶136. Indeed, such tests were an obligatory part of early drug development and are routinely reported to regulatory agencies. *Id*.; EX1013; EX 1015; EX1017.

Therefore, although Sofia '634 did not disclose the polymorph claimed in claim 1 of the '342 exactly (i.e., S_P-4), Ma highlighted RO2433 as a lead compound to pursue, and it would have been obvious for a POSA to take RO2433 and create stereoisomers as taught by Sofia '634 to arrive at multiple crystalline forms of its compounds. EX1002 at ¶137.

Lastly, as discussed above, solubility studies and crystallization from water and vapor sorption studies on new APIs are required as part of drug candidate selection for a number of very important reasons. EX1002 at ¶138. Thus, a POSA would have been motivated to screen the limited number of crystalline forms possible of promising drug candidates like those highlighted in Sofia '634. *Id*. Had a POSA performed this screening for the highlighted compounds in Sofia '634 and Ma, they would have achieved the same crystalline form claimed in claim 1 of the '342 patent. *Id*. This result would not have been surprising or unexpected. *Id*.

Regarding claim 2, Sofia '634 taught compositions that include its crystalline compound and a pharmaceutically acceptable medium. EX1005 at 661:1-7.

Regarding claim 3, Sofia '634 taught methods of treatment and/or

prophylaxis by administering a therapeutically effective amount of its crystalline compound to a patient. EX1005 at 665:15-18.

Regarding claim 4, Sofia '634 taught methods of treatment by administering a therapeutically effective amount of the compound represented by formula I to a patient, in combination with another antiviral agent. EX1005 at 667:8 – 668:4.

Thus, each of claims 1-4 were obvious over Sofia '634 and Ma. EX1002 at ¶142.

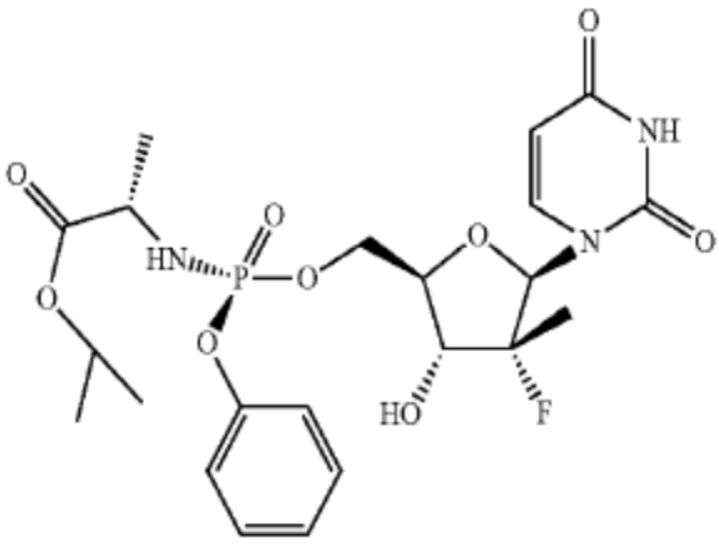
C. Ground 3: Claims 1-4 Were Obvious Over Clark 147 and Ma

A POSA would have combined the teachings of Clark '147 and Ma because they both related to nucleoside compounds for the treatment of hepatitis C virus. EX1002 at ¶143.

Claim 1 of the '342 patent recites:

A crystalline compound represented by the formula (S_P-4):

S_P-4



having XRPD 2Θ-reflections (^{o}) at about: 6.1 and 12.7.

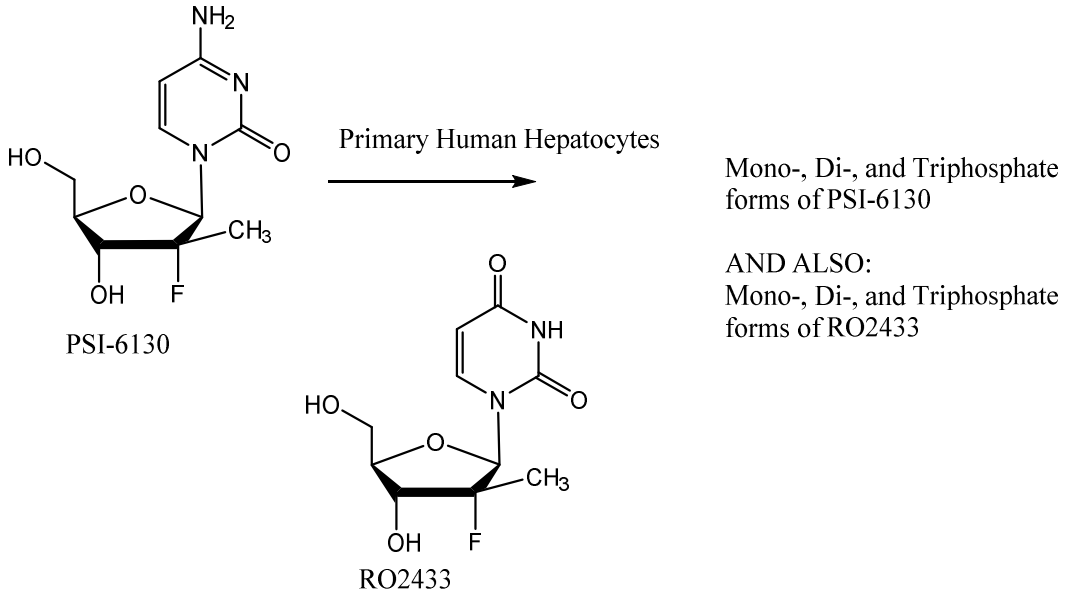
EX1001 at 89:43-60. Claim 2 is dependent upon claim 1 and recites, "A pharmaceutical composition comprising the crystalline compound according to claim 1 and a pharmaceutically acceptable medium." *Id*. at 90:1-3. Claim 3 is also dependent from claim 1 and recites, "A method of treating a hepatitis C virus infection in a human comprising administering to the human an effective amount of the crystalline compound according to claim 1." *Id*. at 90:4-6. Claim 4 depends from claim 3 and recites, "The method according to claim 3 further comprising administering to the human another antiviral agent." *Id*. at 90:7-8.

Clark '147 taught modified fluorinated nucleoside analogs. EX1007 at 96 (claim 1). More specifically, Clark '147 taught (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleosides, their pharmaceutically acceptable salt forms, and prodrugs. *Id*. Clark taught that these compounds could be used to treat *Flaviviridae* viruses, including hepatitis C viral infections. *Id*. at 1 (abstract).

Clark '147 also taught a variety of techniques used for the isolation and crystallization of isomers and polymorphs, i.e., "IV. Stereoisomerism and Polymorphism." EX1007 at 52:21 – 56:2. This disclosure included a discussion of methods for separating diastereomers, chiral chromatography, and purification by various forms of crystallization. *Id*.

These disclosures in Clark, combined with common knowledge in the art regarding polymorphs, polymorph screening, and crystallization of crystalline forms, would have motivated a POSA to pursue crystalline forms as drug candidates. EX1002 at ¶147.

Ma taught intracellular conversion of PSI-6130 (a cytidine nucleoside) into its phosphorylated derivatives as a part of activating the nucleoside for inhibition of hepatitis C virus in primary human hepatocytes. EX1010 at 1. Ma also taught the conversion of PSI-6130 into the uridine analog RO2433 (compound 1D above) and its phosphorylated derivatives under the same conditions. *Id.* This conversion taught by Ma is represented by the following:



EX1002 at ¶148.

It was known that the triphosphate form of PSI-6130 was a very potent

inhibitor of hepatitis C virus. EX1010 at 1. Thus, Ma taught: 1) the triphosphate form of RO2433 was also a very potent inhibitor of hepatitis C virus; 2) the free nucleoside RO2433 (compound 1D) was inactive as an inhibitor of hepatitis C virus; 3) the monophosphate form of RO2433 was active against hepatitis C virus; and, 4) the triphosphate form of RO2433 had a much longer intracellular half-life than the triphosphate form of PSI-6130 (38 hours vs. 4.7 hours for PSI-6130 triphosphate). *Id.*

The exceptionally long intracellular half-life of the RO2433 triphosphate was presented as follows:

> The longer intracellular half-life of RO2433-TP (i.e., triphosphate) may have pharmacologic relevance for maintaining more constant concentrations of the antiviral triphosphate over the dosing period in clinical studies.

EX1010 at 8.

Taken together, these results indicated that a monophosphate prodrug form of compound 1D/RO2433 was a very attractive drug candidate for the treatment of hepatitis C viral infections. EX1002 at ¶151.

Thus, one of skill would have been motivated to combine the teachings of Clark ‘147 and Ma and to pursue isolation and testing of crystalline forms of RO2433. EX1002 at ¶152. The only difference, then, between claim 1 of the ‘342 patent and the stereoisomers that one would have isolated, tested and determined

had superior properties is the recitation of certain XRPD 2Θ-reflections. *Id*.

However, the XRPD 2Θ-reflections recited in claim 1 do not provide the stereoisomer any of its properties or any functionality. EX1002 at ¶153. A crystalline form's XRPD 2Θ-reflections are of no scientific or technical significance. *Id*. They are merely descriptive of some non-functional aspects of the XRPD 2Θ-reflections. *Id*.

Thus, based on the stereoisomeric teaching of Clark '147 and Ma's identification of the specific compound to pursue, a POSA would have been motivated to search for crystalline forms of RO2433 with preferred properties. EX1002 at ¶154. The fact that some crystalline forms would have preferred properties over others was expected and unsurprising. *Id*.

The specific XRPD 2Θ-reflections recited in claim 1 of the '342 patent are obvious over the prior art because they are merely a characterization of a measured property of the crystalline form that is dependent upon the packing arrangement of S_P-4 and the toxic solvent dichloromethane in a crystalline solid. EX1002 at ¶155. These factors result from the crystallization process and are expected, even if one cannot, in advance, know what the XRPD 2Θ-reflections of a particular crystalline form will be. *Id*.

Indeed, crystallization techniques were common knowledge to a POSA. EX1002 at ¶156. These techniques were discussed in many publications, including

those cited above regarding common knowledge in the art. *Id*. Crystal and polymorph screening for new drug candidates was also a common and universally-practiced technique as part of the selection process for new drug candidates in the pharmaceutical industry. *Id*.

A POSA would also have known that the methods described for the preparation of S_P-4, form 6 in the '342 patent, EX1001 at 73:10-50, were well within the routine and customary tests performed on all new drug candidates to evaluate the stability of crystalline forms. EX1002 at ¶157. Indeed, such tests were an obligatory part of early drug development and are routinely reported to regulatory agencies. *Id*.; EX1013; EX1015; EX1017.

Therefore, although Clark '147 did not disclose the polymorph claimed in claim 1 of the '342 exactly (i.e., S_P-4), Ma highlighted RO2433 as a lead compound to pursue, and it would have been obvious for a POSA to take RO2433 and create stereoisomers as taught by Clark '147 to arrive at multiple crystalline forms of its compounds. EX1002 at ¶158.

Lastly, as discussed above, solubility studies and crystallization from water and vapor sorption studies on new APIs are required as part of drug candidate selection for a number of very important reasons. EX1002 at ¶159. Thus, a POSA would be motivated to screen the limited number of crystalline forms possible of promising drug candidates like those highlighted in Clark '147 and Ma. *Id*. Had a

POSA performed this screening for the highlighted compounds in Clark '147 and Ma, they would have achieved the same crystalline form claimed in claim 1 of the '342 patent. *Id*. This result would not have been surprising or unexpected. *Id*.

Regarding claims 2-4, Clark '147 taught:

> The present invention also provides methods for the treatment or prophylaxis of a hepatitis C virus infection … in a host comprising administering an effective amount of a (2'R)-2'-deoxy-2'-fluoro-2'-C-methylnucleosides (b-D or b-L) disclosed herein, or its pharmaceutically acceptable salt or prodrug thereof, in combination or alternation with one or more other effective antiviral agent(s), optionally in a pharmaceutically carrier or diluent thereof, as described herein.

(emphasis added) EX1007 at 21:5-14. The highlighted portions teach all of the additional limitations in claims 2-4. Thus, they were obvious over Clark '147 and Ma. EX1002 at ¶160.

XI. CONCLUSION

For these reasons, claims 1-4 of the '342 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: November 2, 2017

/Daniel B. Ravicher/

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Counsel for Petitioner

XII. APPENDIX – LIST OF EXHIBITS

Exhibit No.	Description
1001	U.S. Patent No. 9,284,342
1002	Declaration of Joseph M. Fortunak, Ph.D.
1003	*Curriculum Vitae* 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
1014	Sofia 2010
1015	Hilfiker Chapter 1
1016	Alvarez
1017	Hilfiker Chapter 9
1018	Yoshioka
1019	Ahlneck

1020	Gibson
1021	Siccardi
1022	ICH
1023	ClinicalTrials.gov

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 9,485 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a).

Respectfully,

Dated: November 2, 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 1001-1023 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: November 2, 2017

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