

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

GILEAD PHARMASSET LLC
Patent Owner

Case No. IPR2018-00122
U.S. Patent No. 8,334,270

PETITION FOR *INTER PARTES* REVIEW

TABLE OF CONTENTS

I.	INTRODUCTION	1
II.	MANDATORY NOTICES.....	2
A.	Real Parties-in-Interest (37 C.F.R. § 42.8(b)(1))	2
B.	Related Matters (37 C.F.R. § 42.8(b)(2))	2
C.	Lead and Back-Up Counsel (37 C.F.R. § 42.8(b)(3))	2
D.	Service Information (37 C.F.R. § 42.8(b)(4)).....	2
III.	REQUIREMENTS FOR REVIEW.....	3
A.	Grounds For Standing.....	3
B.	Identification of Challenge.....	3
IV.	OVERVIEW OF THE ‘270 PATENT	4
V.	FILE HISTORY OF THE ‘270 PATENT	5
VI.	PERSON OF ORDINARY SKILL IN THE ART.....	5
VII.	CLAIM CONSTRUCTION.....	6
VIII.	BACKGROUND KNOWLEDGE IN THE ART.....	6
A.	The Use of Nucleoside Analogs As Antiviral Agents And Their Mechanism of Action Were Known.....	7
B.	Anti-Viral Nucleosides Must Be Converted Into Their Triphosphates To Be Active, Monophosphorylation Was The Rate-Limiting Step In Such Conversion, and 5’-Phosphate Prodrugs Enabled Nucleosides To Overcome This Limitation	12
C.	The Means Were Available to Determine Which Nucleosides Were Kinase Dependent.....	17

D.	Narrowing The Selection Of Options For The Phosphoramidate Prodrug	18
E.	Phosphoramidates Improved Nucleosides	18
F.	The ‘270 Patent Acknowledges This Common Knowledge	19
IX.	SCOPE AND CONTENT OF THE PRIOR ART	21
A.	Clark ‘147	22
B.	Clark 2005	23
C.	Perrone	25
D.	McGuigan ‘327	26
X.	CLAIMS 1, 2, 10-18 AND 20-25 ARE UNPATENTABLE	27
A.	Ground 1: Claims 1, 2, 10-18 and 20-25 Were Obvious Over Clark ‘147, Clark 2005 and Perrone	28
1.	Claims 1, 2, 16-18 (compound).....	28
2.	Claims 10-12 and 20-22 (compositions comprising compound).....	43
3.	Claims 13-15 and 23-25 (methods of treating viral infections).....	44
B.	Ground 2: Claims 1, 2, 10-18, 20-25 Were Obvious Over Clark ‘147, Clark 2005 and McGuigan ‘327	45
1.	Claims 1, 2, 16-18 (compound).....	45
2.	Claims 10-12 and 20-22 (compositions comprising compound).....	57
3.	Claims 13-15 and 23-25 (methods of treating viral infections).....	57
XI.	CONCLUSION	58
XII.	APPENDIX – LIST OF EXHIBITS.....	60
XIII.	CERTIFICATE OF COMPLIANCE	61

XIV. CERTIFICATE OF SERVICE.....62

I. INTRODUCTION

Initiative for Medicines, Access & Knowledge (I-MAK), Inc. (“Petitioner”) requests *inter partes* review (“IPR”) of claims 1, 2, 10-18 and 20-25 of United States Patent No. 8,334,270 to Sofia et al. (“the ‘270 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 ‘270 patent issued on December 18, 2012, and is currently assigned to Gilead Pharmasset LLC (“Patent Owner”). This petition demonstrates that claims 1, 2, 10-18 and 20-25 of the ‘270 patent are unpatentable.

The ‘270 patent claims pharmaceutical compounds, compositions and methods that were obvious in light of the prior art. Specifically, the ‘270 claims a specific prodrug form of a specific nucleoside compound, but the prodrug technique used by Patent Owner was entirely conventional and the nucleoside compound to which Patent Owner applied the prodrug technique had been previously disclosed (and patented) by Patent Owner years before. Taking a known prodrug approach and applying it to a known nucleoside is not an invention. It’s obvious.

Thus, claims 1, 2, 10-18 and 20-25 of the ‘270 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 is filing concurrently herewith another petition for *Inter Partes* Review of the '270 patent, Case. No. IPR2018-00121, in order to comply with the word count limit for a single petition. Petitioner previously filed two petitions for *Inter Partes* Review of U.S. Patent No. 7,964,580, which relates to the '270 patent. Case Nos. IPR2018-00119 and -00120. 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 '270 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, 2, 10-18 and 20-25 of the '270 patent based on the following grounds:

#	Claims	35 U.S.C. §	Prior Art
1	1, 2, 10-18, 20-25	103(a)	Clark '147, Clark 2005 and Perrone
2	1, 2, 10-18, 20-25	103(a)	Clark '147, Clark 2005 and McGuigan '327

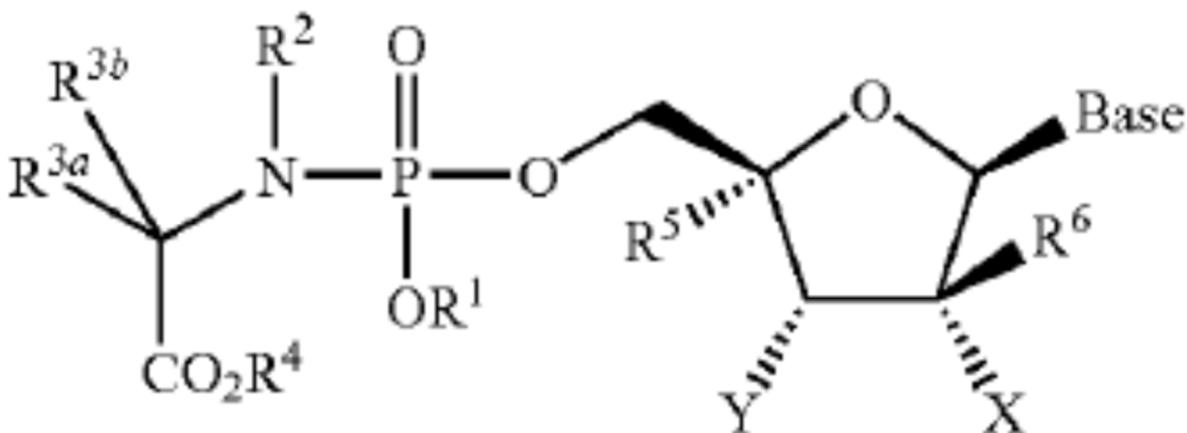
This Petition is supported by the declaration of Joseph M. Fortunak, Ph.D. (EX1002). Dr. Fortunak is well qualified as an expert, possessing the necessary scientific, technical, and other specialized knowledge and training to assist in an understanding of the evidence presented herein, as well as possessing 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 '270 PATENT

The '270 patent relates to phosphoramidate prodrugs of nucleoside derivatives of the following general formula:



EX1001 at 4:47 - 7:17. In defining the structure's various components, the '270 patent states that the Base is "a naturally occurring or modified purine or pyrimidine base." EX1001 at 6:12-14. The '270 patent further provides a long list of substituents for each of R¹, R², R^{3a}, R^{3b}, R⁴, R⁵, R⁶, X and Y. EX1001 at 4:66 – 6:11.

The following chart describes claims 1, 2, 10-18 and 20-25 of the '270 patent:

Claim(s)	Recite
1, 2, 16, 17, 18	Specific compounds (including the individual diastereomers) within the general formula.
10 - 12, 20 - 22	Pharmaceutical compositions having the compound of claim 1 or 16, including to treat hepatitis C virus infection
13 - 15, 23 - 25	Methods of treating a subject infected by hepatitis C virus by administering an effective amount of the compound of claim 1 or 16, including co-administering another antiviral agent.

V. FILE HISTORY OF THE '270 PATENT

U.S. Patent Application No. 13/099,671 (“the ‘671 application”), filed on May 3, 2011, issued as the ‘270 patent on December 18, 2012. The ‘270 patent claims the benefit of U.S. Patent Application No. 12/053,015 (“the ‘015 application”), filed on March 21, 2008, and two provisional applications, Provisional Application No. 60/909,315 filed on March 30, 2007 (“the ‘315 provisional application”), and Provisional Application No. 60/982,309 filed on October 24, 2007 (“the ‘309 provisional application”).

During prosecution of the ‘671 application, the Examiner allowed the claims without making any substantive prior-art based rejections. EX1002 at ¶27.

VI. PERSON OF ORDINARY SKILL IN THE ART

Because the ‘270 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 ¶35.

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 '270 patent provides definitions for certain claim terms, but these definitions are conventional. EX1002 at ¶37 Thus, there is no reason to give any of the terms of the claims of the '270 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).

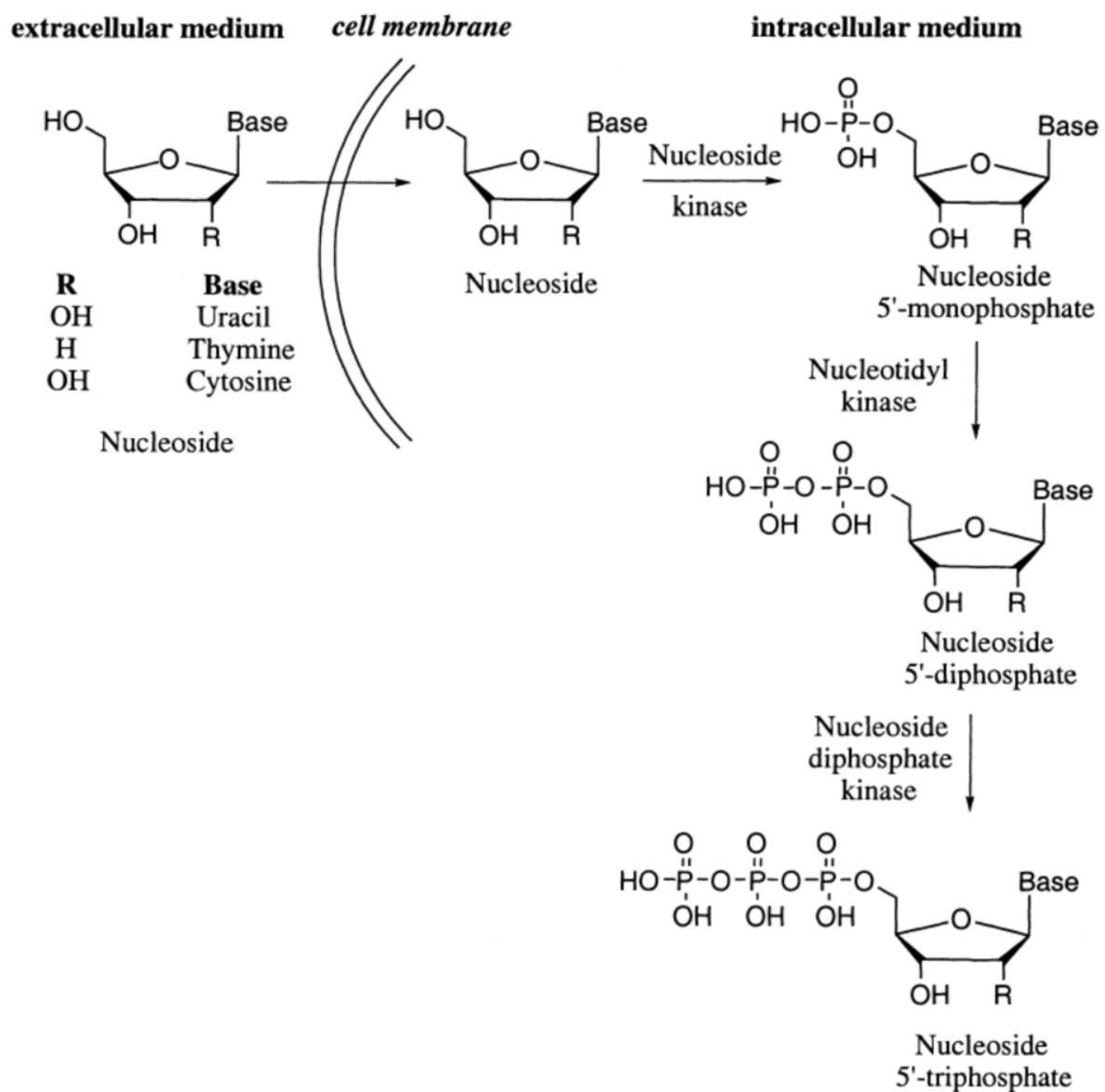
Below is a description of some of the relevant aspects of what was generally known in the art as of either March 30, 2007, or October 24, 2007.

A. The Use of Nucleoside Analogs As Antiviral Agents And Their Mechanism of Action Were Known

It was generally known to persons skilled in the art that viruses replicate their genetic materials in their host cell through one of two mechanisms. RNA viruses and reverse-transcribing (RT) viruses rely on their special DNA/RNA polymerase to synthesize viral DNA/RNA chains in the host cell, while DNA viruses use host-cell DNA polymerases to synthesize their viral DNA chains. EX1002 at ¶39.

The basic building blocks that DNA/RNA polymerases recognize and use to synthesize viral DNA/RNA are 5'-triphosphate nucleosides (NTP, where N=A, U/T, G, C). EX1002 at ¶40. Nucleoside (N), after entering the cell, is converted into its 5'-monophosphate (NMP) by the intracellular host or viral nucleoside

kinase. NMP is then further converted into the 5'-triphosphate form (NTP), and finally NTP is recognized by host or viral RNA/DNA polymerases and added to the tail of the viral DNA/RNA chain being synthesized. *Id.* The below figure exemplifies the known mechanism for phosphorylation of nucleosides for incorporation into RNA.



Id.

The incorporation of modified nucleosides, however, into lengthening RNA chains can result in viral inhibition, when the modified nucleoside will inhibit further incorporation of subsequent nucleoside units. EX1002 at ¶41. This inhibition is known as “chain termination.” *Id.* Based on this mechanism, people in the art have long used nucleoside analogs (N’) that are recognizable by viral DNA/RNA polymerases or viral nucleoside kinases to subsequently inhibit the chain extension of viral DNA/RNA. *Id.*

Specifically, such nucleoside analogs (N’) are recognized by host or viral nucleoside kinases and converted sequentially into their 5’-triphosphate (NTP), which is then recognized by a corresponding host or viral DNA/RNA polymerase in the cell so as to compete with natural 5’-triphosphate nucleosides (NTP) and finally added to the tail of the viral DNA/RNA chain being synthesized. EX1002 at ¶42. The extension of the viral DNA/RNA chain is terminated because of the difference between the analog and natural nucleosides, which results in suppression of viral replication. *Id.*

Several references recognized this general knowledge. First, Wagner et al. “Pronucleotides: Toward the *In Vivo* Delivery of Antiviral and Anticancer Nucleotides” *Medical Research Reviews*, 2000, 20(6), 417-451 (“Wagner”; EX1010), described the use of nucleoside analogs for inhibition of various viruses.

EX1002 at ¶43. Second, WO 2005/003147 to Clark (“Clark ‘147”); EX1006) described research and results about use of various nucleoside analogs for treatment of *Flaviviridae* infections from 1994 to 2004. EX1002 at ¶43; EX1006 at 12:11 – 13:4.

The first commercially available antiviral nucleoside was the anti-herpes virus uridine analog Iododeoxuridine, which was synthesized in the 1950s.

EX1002 at ¶44; Prusoff et al. “Synthesis and biological activities of iododeoxyuridine, an analog of thymidine” *Biochim Biophys Acta.*, 1959, 32(1), 295-6 (“Prusoff”; EX1011).

Since then many nucleoside analogs have been discovered and used as inhibitors of viral enzymes involved in viral DNA/RNA synthesis, including those listed in the table below.

Anti-viral nucleoside analog	Target for inhibition	Analogous to	Publication time
9-β-D-arabinofuranosyladenine (Vidarabine)	DNA polymerase of multiple viruses	adenosine	1964
Acycloguanosine (ACV, Aciclovir)	herpes simplex virus thymidine kinase; varicella herpes zoster virus thymidine kinase	guanosine	1970s
Ribavirin	Hepatitis C virus (HCV) RNA polymerase	guanosine /adenosine	1972

2',3'-dideoxy-3'-thiacytidine (3TC, Lamivudine)	Hepatitis B virus (HBV) reverse transcriptase; HIV reverse transcriptase	cytidine	1980s
Stavudine (d4T)	HIV reverse transcriptase	thymidine	1980s
Azidothymidine (AZT, Zidovudine)	HTLV-III/LAV reverse transcriptase	thymidine	1985
	HIV reverse transcriptase	thymidine	1986
2',3'-dideoxyinosine (ddI, Didanosine)	HIV reverse transcriptase	adenosine	1988
2',3'-dideoxycytidine (ddC, Zalcitabine)	HIV reverse transcriptase	cytidine	1988
dideoxy uridine (ddU) 5'-phosphates	HIV reverse transcriptase	uridine	1994
Emtricitabine (FTC)	HIV reverse transcriptase	cytidine	1996
Abacavir (ABC)	HIV reverse transcriptase	guanosine	Before 1998
DHPG (Ganciclovir)	Cytomegalovirus guanosine kinase	guanosine	1998
Entecavir (ETV)	HBV reverse transcriptase	guanosine	1990s
(2'R)-2'-dO-2'-F-2'-C-methyluridine 5'-phosphate	HCV RNA polymerase	uridine	2005
Telbivudine	HBV reverse transcriptase	thymidine	2005
4'-azido-uridine 5'-phosphoramidate	HCV RNA polymerase	uridine	Feb 2007

EX1002 at ¶45.

Thus, as of March 2007, it was generally known that nucleoside analogs suppress viral replication by incorporation into viral DNA/RNA chains. EX1002 at ¶46.

B. Anti-Viral Nucleosides Must Be Converted Into Their Triphosphates To Be Active, Monophosphorylation Was The Rate-Limiting Step In Such Conversion, and 5'-Phosphate Prodrugs Enabled Nucleosides To Overcome This Limitation

It was well known that, to interact with HCV NS5B polymerase, anti-viral nucleosides must first be converted into their triphosphate form. EX1002 at ¶47. This was described, for example, in Ma et al. “Characterization of the Metabolic Activation of Hepatitis C Virus Nucleoside Inhibitor β -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”; EX1005), which recognized this general knowledge, saying, “[c]onversion to the active 5'-triphosphate form by cellular kinases is an important part of the mechanism of action for nucleoside analogs.” EX1002 at ¶47; EX1005 at 2.

Perrone et al. “Application of the Phosphoramidate ProTide Approach to 4'-Azidouridine Confers Sub-micromolar Potency versus Hepatitis C Virus on an Inactive Nucleoside” J. Med. Chem. 2007, 50(8), 1840-1849 (“Perrone”; EX1008) also recognized this general knowledge, saying, “[a]ll antiviral agents acting via a nucleoside analogue mode of action need to be phosphorylated, most of them to their corresponding 5'-triphosphates.” EX1002 at ¶48; EX1008 at 1.

It was also well known that, for incorporation of a nucleoside analog into the viral DNA/RNA chain, kinase-mediated 5'-monophosphorylation of the nucleoside analog ($N' \rightarrow N'MP$) is generally the rate-limiting step in the course of its triphosphorylation. EX1002 at ¶49. Several references recognized this general knowledge. *Id.*

First, Perrone recognized that, “the first phosphorylation step to produce the 5'-monophosphate has often been found to be the rate-limiting step in the pathway to intracellular nucleotide triphosphate formation.” EX1002 at ¶50; EX1008 at 1 (“The first phosphorylation step to produce the 5'-monophosphate has often been found to be the rate-limiting step in the pathway to intracellular nucleotide triphosphate formation”). Second, Wagner recited that ddNs' activation is hindered at the first phosphorylation step. EX1002 at ¶50; EX1010 at 2. Third, McGuigan, et al. “Application of Phosphoramidate ProTide Technology Significantly Improves Antiviral Potency of Carbocyclic Adenosine Derivatives” *J. Med. Chem.*, 2006, 49, 7215-7726 (“McGuigan 2006”; EX1012), recognized that, “in most cases the first phosphorylation to the 5'-monophosphate is the rate-limiting step.” EX1002 at ¶50; EX1012 at 1.

Perrone (EX1008), Wagner (EX1010), and McGuigan 2006 (EX1012) also evinced the general knowledge that, although 5'-triphosphates of some nucleoside analogs (NTP) are potent viral inhibitors, these nucleoside analogs (N') themselves

showed little or no activity in inhibition assays, generally because of the host cell's lack of corresponding kinase activity which renders the 5'-monophosphorylation of these analogs extremely slow. EX1002 at ¶51.

Several other references recognized this general knowledge. EX1002 at ¶52. First, 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"; EX1013), recognized that nucleoside analogs have limitations because they depend on kinase-mediated activation to generate the bioactive (tri)phosphate forms. EX1002 at ¶52; EX1013 at 1. McGuigan 1994 also recognized that dideoxythymidine and 3'-O-methylthymidine are nucleoside analogs which are inactive against HIV, while their triphosphates are exceptionally potent inhibitors of HIV reverse transcriptase, and the inactivity of these nucleoside analogs is attributed to poor phosphorylation by host cells. *Id.*

McGuigan 2006 also recognized that poor phosphorylation can be a major cause of poor activity, with several examples now known where nucleoside analogs are inactive but the corresponding triphosphates are inhibitors at their enzyme target. EX1002 at ¶53; EX1012 at 1.

To address this widely known issue, it was contemplated in the art to use the 5'-phosphate of nucleoside analogs as a prodrug to "bypass" the kinase-mediated

monophosphorylation so that it can be quickly converted into the active triphosphate form. EX1002 at ¶54. Since 1990 or earlier, stable 5'-phosphate-based prodrugs of nucleoside analogs have been designed and employed to improve the intracellular delivery and activation of the nucleoside analogs, and such prodrugs could readily be hydrolyzed into 5'-monophosphates of the nucleoside analogs (NMP) by enzymes inside the cell. EX1002 at ¶54; McGuigan 1994, EX 1013. The 5'-monophosphate is then rapidly converted into the triphosphate form to be fully activated. Such a technique has been called "Pronucleotide" or simply "ProTide". EX1002 at ¶54.

First, Wagner, recognized that various prodrug or "pronucleotide" approaches have been devised and investigated, with the general goal of promoting passive diffusion through cell membranes and increasing the bio-availability of nucleosides or phosphorylated nucleosides. EX1002 at ¶55; EX1010 at 3 and n8. This approach of derivatization had been applied using various protecting groups for the phosphate moiety. *Id.*

Second, Cahard et al. "Aryloxy phosphoramidate triesters as pro-tides" 2004, 4(4), 371-81 ("Cahard"; EX1014) recognized that aryloxy phosphoramidate triesters are an effective pro-tide motif for the intracellular delivery of charged antiviral nucleoside monophosphates and that the phenyl alanyl phosphoramidate approach was successful on a range of nucleosides by many research groups.

EX1002 at ¶56; EX1014 at 1, 4.

Third, Perrone recognized that unmodified nucleoside monophosphates are unstable in biological media and also show poor membrane permeation because of the associated negative charges at physiological pH. EX1002 at ¶57; EX1008 at 1. Perrone also recognized that the known aryloxy phosphoramidate ProTide approach allows bypass of the initial kinase dependence by intracellular delivery of the mono-phosphorylated nucleoside analog as a membrane-permeable ProTide form. *Id.* The technology greatly increased the lipophilicity of the nucleoside monophosphate analog with a consequent increase of membrane permeation and intracellular availability. *Id.*

The “ProTide” technology was known to show great success in the intracellular delivery and activation of many nucleoside analogs. EX1002 at ¶58. A large number of thus-modified nucleosides showed a boost in the inhibition activity on virus replication by tens, hundreds, or even thousands of times, in comparison with the parent nucleoside analogs. *Id.*

McGuigan 1994 recognized that the aryloxy phosphoramidate (3c) of a ddU increases its potency by approximately 50 times. EX1002 at ¶59; EX1013 at 3 (Fig. 1).

Cahard recognized that the aryloxy phosphoramidate prodrug (21) for d4A boosts the activity of the parent nucleoside analog d4A by 1000 – 4000 fold and

the aryloxy phosphoramidate prodrug (22) for ddA boosts the activity of the parent nucleoside analog ddA by >100 fold. EX1002 at ¶60; EX1014 at 2 (Fig. 1) and 3.

McGuigan 2006 recognized that the ProTide approach was highly successful when applied to L-Cd4A with potency improvements in vitro as high as 9000-fold against HIV. EX1002 at ¶61; EX1012 at 1. McGuigan 2006 also recognized that several aryloxy phosphoramidate prodrugs achieve an anti-HIV activity at the level of about 10 nM. EX1002 at ¶61; EX1012 at 4 (Table 1).

Therefore, the “Pronucleotide” or “ProTide” strategy had been a conventional technical means in the art. EX1002 at ¶62.

In summary, it was generally known that, for antiviral 5'-phosphate prodrugs, the antiviral activity lies in the nucleoside itself. EX1002 at ¶63. It was also generally known that the intracellular delivery (cell membrane permeation) relies on the lipophilicity rendered by the modified phosphate group and that their intracellular hydrolysis into the monophosphate form is mainly attributed to the structural nature of the modified phosphate group and the corresponding enzymes in the host cell. *Id.*

C. The Means Were Available to Determine Which Nucleosides Were Kinase Dependent

The general knowledge that many nucleosides were kinase-dependent in activation to their triphosphates was reflected in an early reference in the field by McGuigan 1994. EX1002 at ¶64; EX 1013 at 1-3. The means existed to assess the

cellular uptake and subsequent phosphorylation of nucleosides. EX1002 at ¶64; EX1005 (Ma) at 4-8. Thus, it was generally known that the identification of nucleoside analogs whose activity was kinase-dependent was readily available. EX1002 at ¶64.

D. Narrowing The Selection Of Options For The Phosphoramidate Prodrug

Phosphoramidate prodrugs have optional substitution to be selected at the: 1) amino acid moiety; 2) ester group on the amino acid; 3) ester group on phosphorous; and 4) optional substitution on nitrogen of the amino acid. EX1002 at ¶65. Of these possibilities, the range of realistic options is reasonably limited. *Id.* Perrone demonstrates how the amino acid moiety is most often glycine, alanine or valine, and how the ester group on the amino acid is most often methyl, isopropyl, or benzyl. EX1002 at ¶65; EX1008. The useful ester groups on phosphorous are aryl (typically phenyl). EX1002 at ¶65.

It would be readily known to a POSA that designing an appropriate ProTide involves a selection process that is limited in scope and adaptable to a nucleoside that is the promising drug candidate. EX1002 at ¶66. As such, the selection of a phosphoramidate prodrug moiety would require labor, but with a limited selection of options and a high degree of probable success. *Id.*

E. Phosphoramidates Improved Nucleosides

It was well-known in the art, *e.g.* McGuigan 1994, that the biological

activity of nucleosides could be hampered due to poor phosphorylation by one or more of the kinases needed for conversion to the active triphosphate form. EX1002 at ¶67. This limitation was known to be overcome by the incorporation of phosphoramidate ProTide technology. EX1002 at ¶67; EX1012 (McGuigan 2006) Such phosphoramidates were known to be precursors of active triphosphates and to inhibit viral replication in infected whole cells. EX1002 at ¶67.

Phosphoramidates were also known to improve physicochemical properties of nucleosides, resulting in dramatic increases in intracellular concentrations of nucleoside analogs. EX1002 at ¶68; EX1013 (McGuigan 1994). Enzyme-mediated hydrolysis of the phosphoramidates resulted in the nucleoside monophosphate being released, thus bypassing the need for the slow, first-step monophosphorylation. EX1002 at ¶68.

F. The '270 Patent Acknowledges This Common Knowledge

The '270 patent acknowledged that the antiviral principle of nucleoside analogs and the use of 5'-phosphate-based prodrugs of nucleoside analogs to bypass the rate-limiting mono-phosphorylation and promote intracellular delivery was generally known. EX1002 at ¶69. In particular, the '270 patent uses the term "pronucleotides" to refer to exactly the conventional knowledge described above that had been repeatedly published for more than a decade. EX1001 at 4:30; EX1002 at ¶69.

The '270 patent acknowledges that its purported invention is merely selecting a specific nucleoside analog and modified 5'-phosphate groups based on the well-known "ProTide" approach. EX1002 at ¶70.

For example, the '270 patent states in its Background that:

Nucleoside inhibitors of NS5B polymerase can act either as a non-natural substrate that results in chain termination or as a competitive inhibitor which competes with nucleotide binding to the polymerase. To function as a chain terminator the nucleoside analog must be taken up by the cell and converted in vivo to a triphosphate to compete for the polymerase nucleotide binding site. This conversion to the triphosphate is commonly mediated by cellular kinases which imparts additional structural requirements on a potential nucleoside polymerase inhibitor. Unfortunately, this limits the direct evaluation of nucleosides as inhibitors of HCV replication to cell-based assays capable of in situ phosphorylation.

In some cases, the biological activity of a nucleoside is hampered by its poor substrate characteristics for one or more of the kinases needed to convert it to the active triphosphate form. Formation of the monophosphate by a nucleoside kinase is generally viewed as the rate limiting step of the three phosphorylation events. To circumvent the need for the initial phosphorylation step in the metabolism of a nucleoside to the active triphosphate analog, the preparation of stable phosphate prodrugs has been reported. Nucleoside phosphoramidate prodrugs have been shown to be precursors of the active nucleoside triphosphate and to inhibit viral

replication when administered to viral infected whole cells (McGuigan, C, et al., *J. Med. Chem.*, 1996, 39, 1748- 1753; Valette, G., et al., *J. Med. Chem.*, 1996, 39, 1981-1990; Balzarini, J., et al., *Proc. National Acad Sci USA*, 1996, 93, 7295-7299; Siddiqui, A. Q., et al., *J. Med. Chem.*, 1999, 42, 4122-4128; Eisenberg, E. J., et al., *Nucleosides, Nucleotides and Nucleic Acids*, 2001, 20, 1091-1098; Lee, W.A., et al., *Antimicrobial Agents and Chemotherapy*, 2005, 49, 1898); US 2006/0241064; and WO 2007/095269.

Also limiting the utility of nucleosides as viable therapeutic agents is their sometimes poor physicochemical and pharmacokinetic properties. These poor properties can limit the intestinal absorption of an agent and limit uptake into the target tissue or cell. To improve on their properties prodrugs of nucleosides have been employed. It has been demonstrated that preparation of nucleoside phosphoramidates improves the systemic absorption of a nucleoside and furthermore, the phosphoramidate moiety of these "pronucleotides" is masked with neutral lipophilic groups to obtain a suitable partition coefficient to optimize uptake and transport into the cell dramatically enhancing the intracellular concentration of the nucleoside monophosphate analog relative to administering the parent nucleoside alone. Enzyme-mediated hydrolysis of the phosphate ester moiety produces a nucleoside monophosphate wherein the rate limiting initial phosphorylation is unnecessary.

EX1001 at 3:64 – 4:46 (emphasis added).

IX. SCOPE AND CONTENT OF THE PRIOR ART

The '315 provisional application does not include a description of the

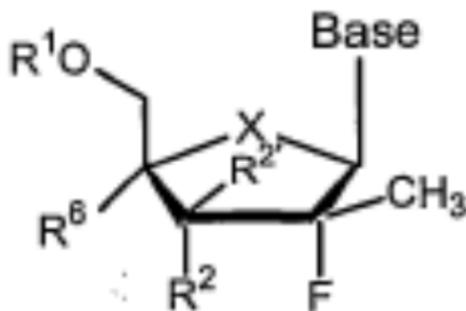
specific compounds claimed by the '270 patent. EX1002 at ¶72. While the '315 provisional discusses broad genera of compounds, it does not discuss the specific compounds and stereochemistry around the phosphorous atom claimed in the '270 patent. *Id.* Therefore, the claims of the '270 patent are not entitled to claim priority to the March 30, 2007, filing date of the '315 provisional application. At most, they are entitled to claim priority to the '309 provisional application filed on October 2, 2007.

The following references taught or suggested the compounds, compositions and methods recited in claims 1, 2, 10-18 and 20-25 of the '270 patent. EX1002 at ¶73.

A. WO 2005/003147 to Clark (“Clark ‘147”); EX1006)

Clark '147 is prior art under 35 U.S.C. § 102(b) to the '270 patent because it was published on January 13, 2005, more than a year before even the May 30, 2007, filing date of the earliest application to which the '270 patent claims priority.

Clark '147 taught (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleosides or prodrugs thereof having the natural β -D configuration and their use for treating hepatitis C virus (HCV). EX1002 at ¶80; EX1006 at 18. Specifically, Clark '147 taught nucleosides of the following formula:



Id. Clark '147 taught the base could be a purine or pyrimidine and defined pyrimidine to include uracil. *Id.*

Clark '147 also taught that its nucleosides could be administered as a nucleotide prodrug to increase activity, bioavailability, stability or otherwise alter the properties of the nucleoside. EX1002 at ¶81; EX1006 at 45:24-47:20.

Clark '147 taught that a number of nucleotide prodrug ligands were known and that, in general, alkylation, acylation or other lipophilic modification of the mono, di or triphosphate of the nucleoside will increase the stability of the nucleotide. EX1002 at ¶82; EX1006 at 45:24-47:20.

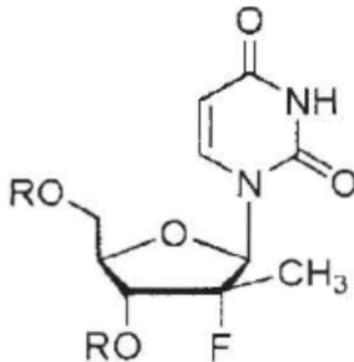
B. Clark, J., "Design, Synthesis, and Antiviral Activity of 2'-Deoxy-2'-fluoro-2'-C-methylcytidine, a Potent Inhibitor of Hepatitis C Virus Replication," Journal of Medicinal Chemistry, vol. 48, No. 17, pp. 5504-5508 (2005). ("Clark 2005"; EX1007)

Clark 2005 is prior art under 35 U.S.C. § 102(b) to the '270 patent because it was published on July 26, 2005, more than a year before even the May 30, 2007, filing date of the earliest application to which the '270 patent claims priority.

Clark 2005 taught 2'-C-methyl nucleosides were potent for HCV inhibition.

EX1002 at ¶83; EX1007 at 1. Clark 2005 further taught that, “[t]he degradation enzymes cytidine deaminase (CDA) and deoxycytidine monophosphate deaminase (dCMPDA) are responsible for the in vivo metabolic conversion of cytidine or cytidine monophosphate to uridine.” EX1002 at ¶83; EX1007 at 3.

Clark 2005 then prepared and tested the 2'-deoxy-2'-fluoro-2'-C-methyluridine, the structure of which is below, for anti-HCV activity.



EX1002 at ¶84; EX1007 at 3 (Scheme 3).

Table 2 of Clark 2005, copied below, showed that the cytidine and uridine forms of the nucleoside (compounds 1 and 9, respectively) had an identical lack of toxicity, but that the uridine form also demonstrated no activity as compared to the cytidine. EX1002 at ¶85; EX1007 at 3.

Table 2. Anti-HCV Activity and Cellular Toxicity of Compounds **1**, **9**, 2'-C-Methylcytidine (2'-C-MeCyd), and 2'-Deoxy-2'-fluorocytidine (2'-FdCyd)

compound	cpBVDV ^a (MDBK cells)		HCV replicon ^b	
	EC ₉₀ (μM) ^b	CC ₅₀ (μM)	EC ₉₀ (μM)	CC ₅₀ ^c (μM)
1	>100	>100	5.40 ± 2.6	>100
9	>100	>100	>100	>100
2-C-MeCyd	2.30 ± 0.1	>100	19.0 ± 5.7	>100
2-FdCyd	>100	>100	6.50 ± 1.6	>100

^a cpBVDV = cytopathic BVDV. ^b 96 h, average of at least four experiments. ^c MTS CC₅₀ was determined in a 4-day assay using the Celltiter 96 nonradioactive cell proliferation assay from Promega (Madison, WI).

EX1007 at 3.

C. Perrone et al. “Application of the Phosphoramidate ProTide Approach to 4’-Azidouridine Confers Sub-micromolar Potency versus Hepatitis C Virus on an Inactive Nucleoside” J. Med. Chem. 2007, 50(8), 1840-1849 (“Perrone”; EX1008)

Perrone is prior art under 35 U.S.C. § 102(a) to the ‘270 patent because it was published on March 17, 2007, before even the May 30, 2007, filing date of the earliest application to which the ‘270 patent claims priority.

Perrone taught a phosphoramidate “ProTide” approach to confer potency against hepatitis C virus by activating otherwise inactive nucleosides. EX1002 at ¶86; EX1008. Specifically, Perrone taught that the addition of an aryloxy phosphoramidate group at the 5’-position of a uridine nucleoside can confer antiviral activity inhibitory activity in the HCV replicon assay for a compound that was otherwise inactive against hepatitis C virus. EX1002 at ¶86; EX1008 at 2.

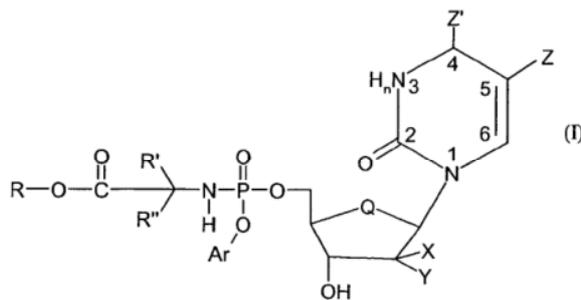
Perrone also taught that a potent HCV inhibitor nucleoside did not show inhibitory activity in the HCV replicon assay because of the extremely slow intracellular 5'-monophosphorylation of the nucleoside. EX1002 at ¶87; EX1008 at 2-4. In addition, Perrone taught that the triphosphate nucleoside analogue showed potent inhibition of HCV in the NS5B Polymerase assay as a means of identifying nucleosides which were inefficiently phosphorylated. EX1002 at ¶87; EX1008 at 1.

Perrone employed the well-known ProTide strategy to prepare about 20 stable phosphate-based prodrugs of the nucleoside. EX1002 at ¶88; EX1008 at 4 (Table 1). These prodrugs were hydrolyzed into 5'-monophosphorylated derivatives of the nucleoside inside the cell, thereby bypassing the need for kinase-mediated monophosphorylation. EX1002 at ¶88; EX1008 at 1-2. Among these aryloxy phosphoramidate prodrugs, Perrone particularly taught that, "the isopropyl ester (15) showed high potency and represented one of the most active phosphoramidates prepared." EX1002 at ¶88; EX1008 at 3.

D. WO 2005/012327 to McGuigan ("McGuigan '327"; EX1009)

McGuigan '327 is prior art under 35 U.S.C. § 102(b) to the '270 patent because it was published on February 10, 2005, more than a year before even the May 30, 2007, filing date of the earliest application to which the '270 patent claims priority.

McGuigan '327 taught phosphoramidate nucleosides and methods of preparation thereof. EX1002 at ¶89; EX1009. McGuigan '327 specifically taught compounds of formula (I) and pharmaceutically acceptable derivatives or metabolites thereof:



EX1009 at 5.

McGuigan '327 taught a synthesis method in which a phosphate-based prodrug of nucleoside analogs is synthesized from an aryloxy phosphoramidate with a leaving group C-1 and a uridine nucleoside analog. EX1002 at ¶90; EX1009.

McGuigan '327 taught that, in its formula (I), "X and Y are independently selected from the group comprising H, F, Cl, Br, I, OH and methyl (-CH₃)."

EX1002 at ¶91; EX1009 at 5:22-23.

X. CLAIMS 1, 2, 10-18 AND 20-25 ARE UNPATENTABLE

A POSA would have been motivated to combine the references as discussed below and had a reasonable expectation of success of arriving at the subject matter of each of claims 1, 2, 10-18 and 20-25. *Id.*

Each of claims 1, 2, 10-18 and 20-25 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, 2, 10-18 and 20-25 Were Obvious Over Clark '147, Clark 2005 and Perrone

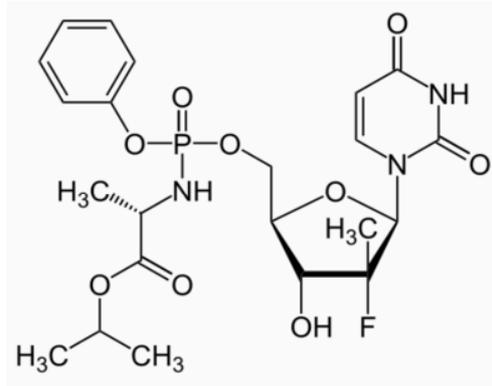
The combination of Clark '147, Clark 2005 and Perrone rendered claims 1, 2, 10-18 and 20-15 obvious. EX1002 at ¶158. One of ordinary skill in the art would have been motivated to combine their teachings because they each related to phosphoramidates of anti-viral nucleosides, and in particular anti-HCV. EX1002 at ¶158. The '270 patent also cites each as references. EX1001 at 3 and 5.

1. Claims 1, 2, 16-18 (compound)

Claims 1 and 2 recite Markush Groups of compounds that include, "(S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate." EX1001 at 605:35 – 606:63. Claims 16-18 recite Markush Groups of compounds that include, "(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." EX1001 at 607:57 – 616:23.

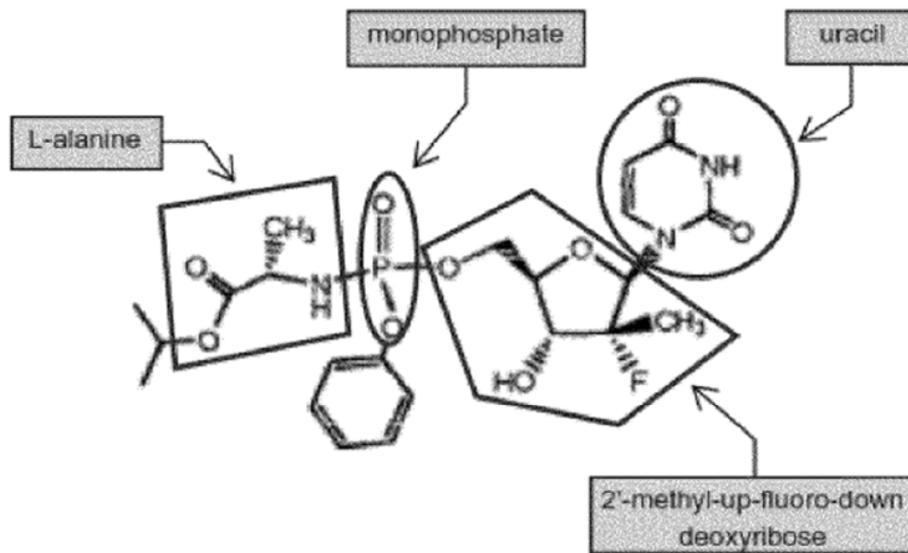
The compounds claimed in claims 1, 2, 16-18 are 5'-phosphate (phosphoramidate) prodrugs of the uridine analog "(2'R)-2'-deoxy-2'-fluoro-2'-C-

methyluridine”, wherein the 5’-phosphate group is the “(phenyl)(isopropyl-L-alaninyl)phosphate” group. EX1001 at 493:42-46; EX1002 at ¶160. Included within these claims is a specific compound that has the formula:



Id.

As can be seen from the formula, the compound of claim 1 is composed of a deoxyribose sugar, a base and a masked phosphate group. EX1002 at ¶161. An annotated version of this compound is set out in the following diagram that shows the compound has a deoxyribose sugar ring, which is substituted at the 2'-position with a methyl group in the "up" configuration and a fluoro radical in the "down" position. *Id.* The deoxyribose sugar is substituted with a base at the conventional position. *Id.* The base is uracil. *Id.*

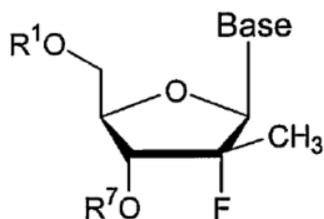


EX1002 at ¶161.

Clark '147 taught a set of nucleoside analogs or their prodrugs as HCV inhibitors with the core structure being 2'-deoxy-2'-fluoro-2'-C-methyl nucleoside and its 5'-modified prodrugs. EX1002 at ¶162; EX1006 at 2. Specifically, Clark '147 taught an HCV RNA polymerase inhibitor and its use in treating HCV.

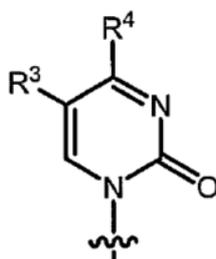
EX1002 at ¶162. See, for example, claim 40, which recited:

Use of an anti-virally effective amount of a (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β -D or β -L) of the following formula or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of hepatitis C infection in a host:



wherein

Base is



R¹ and R⁷ are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate..., acyl..., alkyl..., sulfonate ester..., a lipid..., an L or D-amino acid, a carbohydrate, a peptide, a cholesterol, or other pharmaceutically-acceptable leaving group which when administered in vivo is capable of providing a compound wherein R¹ or R⁷ is independently H or phosphate; R¹ and R⁷ can also be linked with cyclic phosphate group;

R³ and R⁴ are independently H, halogen..., OH, OR', SH, SR', NH₂,

....”

EX1006 at 137-138.

A POSA would immediately contemplate R^3 as H and R^4 as OH because those are two of the first three substituents listed for those positions. EX1002 at ¶163. In doing so, a POSA would also recognize that this would result in the base being uridine. *Id.* Further, a POSA would select R^1 to be phosphate and R^7 to be H, again because those are the first two substituents listed, and this would result in the 5'-phosphate of "(2'R)-2'-deoxy-2'-fluoro-2'-C-methyl uridine," which is the same nucleotide moiety as the compound of claims 1, 2 and 16-18. EX1002 at ¶163.

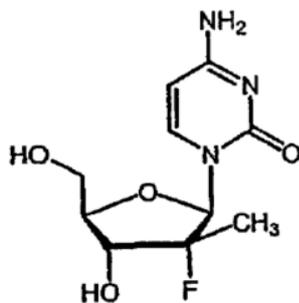
A POSA would readily recognize that these substituents are essentially obligatory for R^1 and R^7 in terms of resulting in a nucleoside which is capable of being activated (i.e., phosphorylated) at the C5' position and which also results in the natural C3' substitution of -OH. EX1002 at ¶164.

In terms of R^4 , a POSA would naturally pick this group = OH or NH_2 as these would result in cytidine or uridine base substitution on the sugar rings. EX1002 at ¶165. The R^3 substitution would naturally first be chosen as an -H (hydrogen atom) because this results in incorporation of the natural cytosine and uracil rings into the nucleoside. *Id.*

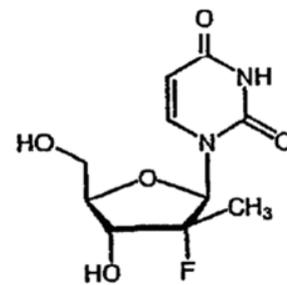
These would not necessarily be the only substitutions that a POSA would infer from Clark '147, but they are the simplest, and they would be considered as obligatory from the perspective of a medicinal chemist. EX1002 at ¶166.

Incorporating the natural cytidine and uridine rings into the structure would be a necessary first step in establishing a natural understanding of the structure-activity relationships of a C2'-substituted nucleoside. *Id.* Thus, Clark '147 taught that a 5'-phosphate of "(2'R)-2'-deoxy-2'-fluoro-2'-C-methyl uridine" is an HCV inhibitor. *Id.*

In addition, Example 5 of Clark '147 experimentally validated the HCV inhibition effect of (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine (formula below), which proved that the 5'-triphosphate of (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine (i.e. C'TP) (an example compound of Claim 40, where R¹=triphosphate, R⁷=H, R³=H, and R⁴=NH₂) was an active and potent HCV inhibitor. EX1002 at ¶167; EX1006 at 88.



(2'R)-2'-deoxy-2'-F-2'-C-Me cytidine



(2'R)-2'-deoxy-2'-F-2'-C-Me uridine

Because Clark '147 taught that its Base was preferably a purine or pyrimidine and also defined that pyrimidine includes uracil, EX1006 at 137 (claim 40), and because it was common knowledge that uracil is one of the four bases in RNA, a POSA would have been motivated to replace the cytidine in the active

(2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine 5'-triphosphate with a uridine (R⁴=OH) and had an expectation that this would produce a likewise active and potent HCV inhibitor. EX1002 at ¶168.

Therefore, Clark '147 not only taught that 5'-phosphates of (2'R)-2'-deoxy-2'-fluoro-2'-C-methyluridine are HCV inhibitors, it also motivated a POSA to choose it as an active agent. EX1002 at ¶169. In other words, based on the experimental results of Example 5 of Clark '147 and the common knowledge in the art, a POSA would have been fully motivated to specifically choose, from the various compounds encompassed by Claim 40, the 5'-phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug) of (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl uridine as a practicable HCV inhibitor. *Id.*

Moreover, Claim 40 of Clark '147 also taught that the 5'-phosphate can be a “stabilized phosphate prodrug,” EX1006 at 137, which when administered *in vivo* is capable of providing a compound wherein R¹ or R⁷ is independently H or phosphate. EX1002 at ¶170. This taught that the 5'-phosphate can be further modified to stabilize the prodrug, and the stabilized phosphate prodrug will turn into the 5'-monophosphate form (R¹=phosphate, and R⁷=H) to be activated. *Id.*

Specifically, Clark '147 taught:

Any of the nucleosides described herein can be administered as a nucleotide prodrug to increase the activity, bioavailability, stability or

otherwise alter the properties of the nucleoside. A number of nucleotide prodrug ligands are known. In general, alkylation, acylation or other lipophilic modification of the mono, di or triphosphate of the nucleoside will increase the stability of the nucleotide. Examples of substituent groups that can replace one or more hydrogens on the phosphate moiety are alkyl, aryl, steroids, carbohydrates, including sugars, 1, 2-diacylglycerol and alcohols. Many are described in R. Jones and N. Bischofberger, Antiviral Research, 27 (1995) 1-17. Any of these can be used in combination with the disclosed nucleosides to achieve a desired effect.

EX1006 at 47:16-25 (emphasis added).

Further, Clark '147 taught:

The nucleosides described herein can be administered as a nucleotide prodrug to increase the activity, bioavailability, stability or otherwise alter the properties of the nucleoside. A number of nucleotide prodrug ligands are known. In general, alkylation, acylation or other lipophilic modification of the mono-, di-or triphosphate of the nucleoside reduces polarity and allows passage into cells. Examples of substituent groups that can replace one or more hydrogens on the phosphate moiety are ailcyl, (sic) aryl, steroids, carbohydrates,

including sugars, 1,2- diacylglycerol and alcohols. Many are described in R. Jones and N. Bisehoferger, *Antiviral Research*, 1995, 27: 1-17. Any of these can be used in combination with the disclosed nucleosides to achieve a desired effect.”

EX1006 at 15-24 (emphasis added).

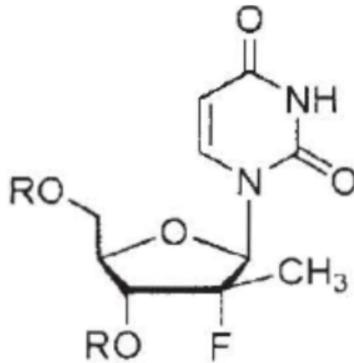
Therefore, Clark ‘147 explicitly taught that alkylation, acylation, arylation, or other lipophilic modification can be made to the phosphate group in the 5’-phosphate of (2’R)-2’-deoxy-2’-fluoro-2’-C-methyluridine to increase its activity, bioavailability and stability, and that the modified prodrug will convert into the 5’-monophosphate form (U’MP) after its entry into the cell. EX1002 at ¶173.

Therefore, claims 1, 2, and 16-18 are different from Clark ‘147 only in that the stable 5’-phosphate group on the nucleoside analog in claims 1, 2, and 16-18 is the “(phenyl)(isopropyl-L-alaninyl)phosphate” group. EX1002 at ¶174.

Clark 2005 taught, “The degradation enzymes cytidine deaminase (CDA) and deoxycytidine monophosphate deaminase (dCMPDA) are responsible for the *in vivo* metabolic conversion of cytidine or cytidine monophosphate to uridine.” EX1007 at 3. Thus, Clark 2005 taught that the cytidine form of the Clark ‘147 nucleoside could metabolically convert *in vivo* to the uridine form. EX1002 at ¶174; EX1007 at 3.

Clark 2005 tested both 2’-deoxy-2’-fluoro-2’-C-methylcytidine and 2’-deoxy-

2'-fluoro- 2'-C-methyluridine, the structure of which is below, for anti-HCV activity. EX1002 at ¶176.



EX1007 at 3 (Scheme 3).

Clark 2005 showed in Table 2 that the cytidine and uridine forms of the nucleoside had an identical lack of toxicity. EX1002 at ¶177; EX1007 at 3. Clark 2005 also showed in Table 2 that the uridine form demonstrated no activity as compared to the cytidine. *Id.*

The Clark 2005 results would have motivated a POSA to understand the lack of activity of the uridine form and to pursue methods to activate the uridine if the lack of activity were due to inefficient phosphorylation. EX1002 at ¶178.

General knowledge in the art as described above would have motivated a person skilled in the art to use the well-known strategy to select a suitable stable 5'-phosphate group for (2'R)-2'-deoxy-2'-fluoro-2'-C-methyluridine of the Clark '147 and Clark 2005, in order to increase its activity. EX1002 at ¶179.

One would have been specifically motivated to refer to Perrone, which

taught a phosphoramidate “ProTide” approach to confer potency against hepatitis C virus by activating otherwise inactive nucleosides. EX1002 at ¶180; EX1008. Specifically, Perrone taught use of an aryloxy phosphoramidate group as the 5'-group of a uridine analog can significantly boost the inhibitory activity against the HCV RNA polymerase. EX1002 at ¶180; EX1008 at 1. Perrone also taught that a potent HCV inhibitor nucleoside did not show inhibitory activity in the inhibition assay against RNA replication of HCV because of the extremely slow intracellular 5'-monophosphorylation of the nucleoside. *Id.*

To address this issue, Perrone employed the well-known conventional ProTide strategy and prepared about 20 stable phosphate-based prodrugs of the nucleoside, wherein the aryl group on the phosphate group renders the prodrugs strongly lipophilic so that the prodrugs can readily permeate the cell membrane. EX1002 at ¶181; EX1008 at 4. These prodrugs are hydrolyzed into 5'-monophosphate derivatives of the nucleoside in the cell to bypass the kinase-mediated monophosphorylation. EX1002 at ¶181; EX1008 at 1-2. Among these aryloxy phosphoramidate prodrugs, Perrone particularly taught that, “the isopropyl ester (15) showed high potency and represented one of the most active phosphoramidates prepared.” *Id.* at 3.

A POSA would have been motivated to apply the phosphoramidate ProTide approach of Perrone to the known HCV nucleosides of Clark '147 and had a

reasonable expectation of success in doing so because of the general knowledge that nucleosides needed to be phosphorylated to active in HCV replication and the fact that Perrone provided several examples of comparable nucleosides being triphosphorylated by its ProTide approach. EX1002 at ¶182. Applying Perrone's ProTide approach to Clark '147 and Clark 2005's promising nucleoside would result in the compound claimed in claims 1, 2, and 16-18. *Id.* Thus, Clark '147, Clark 2005 and Perrone render claims 1, 2, and 16-18 obvious. *Id.*

More specifically, Perrone taught that a stable modified 5'-phosphate group suitable for nucleoside analog 5'-phosphates is the “(phenyl)(isopropyl-L-alaninyl)phosphate” group, which has the same function in Perrone as in Clark '147 and Clark 2005, i.e., a function of increasing the activity, bioavailability and stability of an anti-HCV uridine analog, with the same mechanism and purpose of promoting intracellular delivery of a uridine analog and bypassing the kinase-mediated 5'-monophosphorylation. EX1002 at ¶183. Such stable modified 5'-phosphate group could also activate the inactive uridine nucleoside of Clark '147 and Clark 2005, which a POSA would be motivated to achieve. *Id.*

A POSA reading Clark '147, Clark 2005 and Perrone would have been motivated to develop an active prodrug and would have envisaged applying the aryloxy phosphoramidate group identified to be highly active in Perrone to the (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl uridine taught in Clark '147 and Clark 2005.

EX1002 at ¶184.

The nucleosides taught in Perrone and the (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl uridine taught in Clark '147 and Clark 2005 are both uridine analogs used to inhibit HCV through the same mechanism. EX1002 at ¶185. The structural difference between these two uridine analogs themselves would not have dissuaded a POSA who wanted to obtain a more active and potent prodrug by applying Perrone's phosphoramidate group to the 5'-position of Clark '147 and Clark 2005's (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl uridine. *Id.*

In addition, there are only 6 highly active phosphoramidate groups particularly identified in Perrone (*i.e.* No.14, 15, 17, and 33-35). EX1008 at 4. A POSA would have been motivated to try to attach each to the 5'-position of Clark '147 and Clark 2005's (2'R)-2'-deoxy-2'-fluoro-2'-C-methyluridine resulting in the compounds of claims 1, 2, 16-18. EX1002 at ¶186.

Perrone describes a uridine analog (4'-azidouridine) which, like PSI-6206, is inactive in the HCV replicon assay although its triphosphate form (4'-azidouridine-TP) is a potent inhibitor of HCV NS5B polymerase. EX1008 at 1. Thus, Perrone described exactly the same problem as Clark '147, Clark 2005 and suggested the same solution to the problem. EX1002 at ¶187. As Clark '147, Clark 2005 and Perrone lie in precisely the same technical field, and each describe exactly the same problem and propose the same general solution, a POSA would have been

motivated to combine their teachings. *Id.*

Specifically, a POSA would have been motivated to prepare the corresponding L-alanine derivatives shown in Table 1 of Perrone to exhibit low or sub-micromolar activity and had a reasonable expectation of success in achieving the same outcome as Perrone. EX1002 at ¶188; EX1008 at 4. A POSA would in particular prepare the derivatives of PSI-6206 that correspond to compounds 14, 15 and 17 in Perrone because they are described as having “exceptional” antiviral activity. EX1002 at ¶188; EX1008 at 3-4.

In considering the similarity of Clark ‘147, Clark 2005 and Perrone, a POSA would not focus on the structural differences between the parent nucleosides, 2'-deoxy-2'-fluoro-2'-C-methyluridine and 4'-azidouridine. EX1002 at ¶189. A POSA would investigate the 2'-deoxy-2'-fluoro-2'-C-methyluridine nucleoside in Clark 2005 as a lead compound and incorporate the specific phosphoramidate substituents from Perrone because they were taught to provide an optimal solution for delivering an active HCV nucleoside to target cells. *Id.*

Thus, the compound of claims 1, 2, 16-18 would have been obvious to a POSA based on the teachings of Clark ‘147, Clark 2005 and Perrone. EX1002 at ¶190.

The compounds of claims 1, 2, 16-18 did not produce any unexpected results. EX1002 at ¶191. First, Perrone provided the technical teaching that use of

the “(phenyl)(isopropyl-L-alaninyl)phosphate” group (No.15) significantly boosts the activity of anti-HCV nucleoside analogs. EX1008 at 4. Therefore, because Perrone and the ‘270 patent employed the same mechanism and theory, any activity improvement achieved by the claimed compound using the same modified 5’-phosphate group would have been expected. EX1002 at ¶191.

Second, the “(phenyl)(isopropyl-L-alaninyl)phosphate” group (No.15) disclosed in Perrone boosts the inactive parent nucleoside to an activity of $EC_{50} = 0.77 \mu\text{M}$, while the target application uses the same phosphoramidate group to boost the inactive parent nucleoside (2’R)-2’-deoxy-2’-fluoro-2’-C-methyl uridine to an activity of the same magnitude of that achieved in Perrone. EX1002 at ¶192; compare EX1001 at 300 to EX1008 at 4. Therefore, even if (2’R)-2’-deoxy-2’-fluoro-2’-C-methyl uridine is inactive, the ‘270 patent’s claimed prodrug form does not produce unexpected results. EX1002 at ¶192.

Third, in the prior art, use of phosphoramidate prodrugs (ProTide) achieved increases in antiviral activity of as high as thousands of times the activity of the unmodified parent nucleoside, even to an activity/potency of several nM. EX1002 at ¶193; EX1012 (McGuigan 2006) at 1, 4 (abstract and Table 1).

With regards to HCV, phosphoramidate prodrugs (ProTide) achieved an increase in anti-HCV activity of more than 450-fold, to an activity of $EC_{50} = 0.22 \mu\text{M}$. EX1008 at 4 (Table 3). EX1002 at ¶194.

2. Claims 10-12 and 20-22 (compositions comprising compound)

Claim 10 recites, “A pharmaceutical composition comprising the compound according to claim 1.” EX1001 at 607:39-40. Claim 11 recites, “The pharmaceutical composition according to claim 10 further comprising a pharmaceutically acceptable medium.” EX1001 at 41-42. Claim 12 recites, “The pharmaceutical composition according to claim 11 comprising an effective amount of the compound according to claim 1 to treat a hepatitis C virus infection.” EX1001 at 43-45. Claims 20-22 are identical to claims 10-12 except that they depend from claim 16.

Clark ‘147 and Clark 2005 taught that their compounds were potent and safe inhibitors of HCV replication. EX1006 at 2; EX1007 at 1. Inherent in this teaching are compositions comprising such compounds and a pharmaceutically acceptable medium and that such compositions are for treating hepatitis C. EX1002 at ¶196.

Further, Perrone also taught that applying its phosphoramidate ProTide approach to nucleosides could activate them as HCV inhibitors for use in treating people. EX1008 1. Inherent in this teaching are compositions comprising such compounds and a pharmaceutically acceptable medium and that such compositions are for treating hepatitis C. EX1002 at ¶197. Thus, Clark ‘147, Clark 2005 and Perrone rendered claims 10-12 and 20-22 obvious. *Id.*

3. Claims 13-15 and 23-25 (methods of treating viral infections)

Claim 13 recites, “A method of treating a subject infected by a virus selected from among hepatitis C virus ..., which comprises administering to the subject an effective amount of the compound according to claim 1.” EX1001 at 607:46-52.

Claim 14 recites, “The method of claim 13 wherein the virus is hepatitis C virus.” EX1001 at 607:53-54. Claim 15 recites, “The method of claim 14, which further comprises administering to the subject an effective amount of another antiviral agent.” EX1001 at 607:55-57. Claims 23-25 are identical to claims 13-15 except that they depend from claim 16.

Clark ‘147 and Clark 2005 taught that their compounds were potent and safe inhibitors of HCV replication. EX1006 at 2; EX1007 at 1. Further, Perrone also taught that applying its phosphoramidate ProTide approach to nucleosides could activate them as HCV inhibitors for use in treating people. EX1008 at 1. Thus, Clark ‘147, Clark 2005 and Perrone rendered claims 13, 14, 23 and 24 obvious. EX1002 at ¶199.

Clark ‘147 further taught that its compounds could be used in “more effective combination therapies,” and specifically, “in combination ... with another effective antiviral agent.” EX1006 at 17. Thus, Clark ‘147, Clark 2005 and Perrone rendered claims 15 and 25 obvious. EX1002 at ¶200.

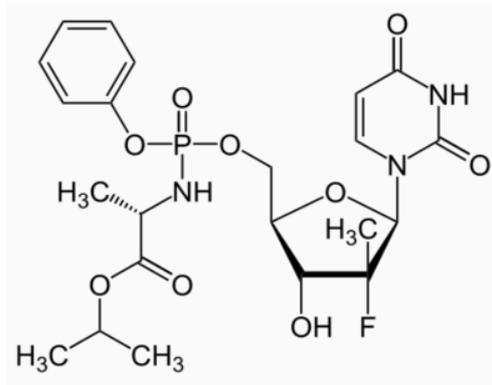
B. Ground 2: Claims 1, 2, 10-18, 20-25 Were Obvious Over Clark '147, Clark 2005 and McGuigan '327

The combination of Clark '147, Clark 2005 and McGuigan '327 rendered the claims 1, 2, 10-18 and 20-15 obvious. EX1002 at ¶201. One of ordinary skill in the art would have been motivated to combine their teachings because they each related to phosphoramidates of anti-viral nucleosides. *Id.* The '270 patent also cites each as references. EX1001 at 3 and 5.

1. Claims 1, 2, 16-18 (compound)

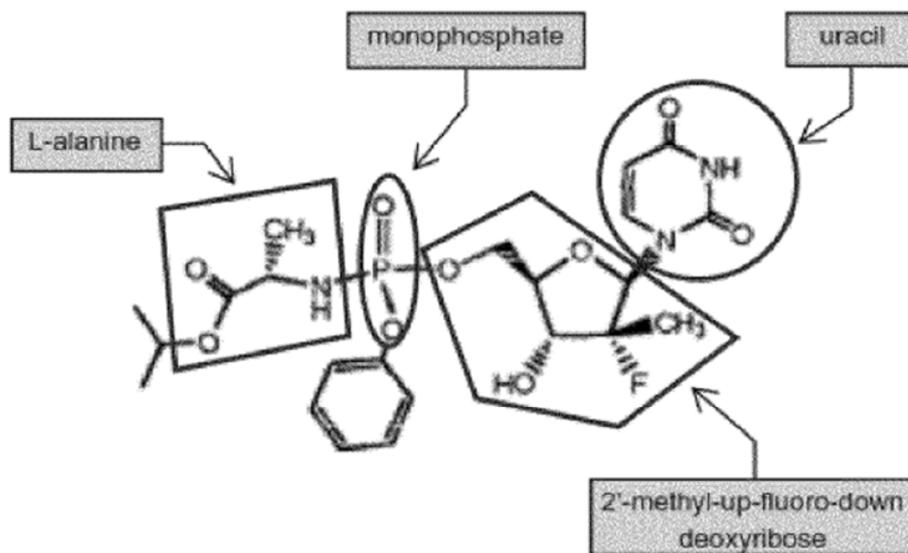
Claims 1 and 2 recite Markush Groups of compounds that include, “(S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate.” EX1001 at 605:35 – 606:63. Claims 16-18 recite Markush Groups of compounds that include, “(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.” EX1001 at 607:57 – 616:23.

The compounds claimed in claims 1, 2, 16-18 are 5'-phosphate (phosphoramidate) prodrugs of the uridine analog “(2'R)-2'-deoxy-2'-fluoro-2'-C-methyluridine”, wherein the 5'-phosphate group is the “(phenyl)(isopropyl-L-alaninyl)phosphate” group. EX1001 at 493:42-46; EX1002 at ¶203. Included within these claims is a specific compound that has the formula:



Id.

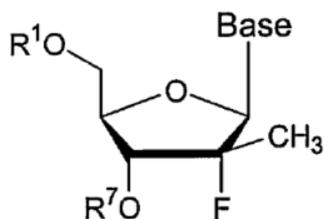
As can be seen from the formula, the compound of claim 1 is composed of a deoxyribose sugar, a base and a masked phosphate group. EX1002 at ¶204. An annotated version of this compound is set out in the following diagram that shows the compound has a deoxyribose sugar ring, which is substituted at the 2'-position with a methyl group in the "up" configuration and a fluoro radical in the "down" position. *Id.* The deoxyribose sugar is substituted with a base at the conventional position via a glycosidic bond. *Id.* The base is uracil. *Id.*



EX1002 at ¶

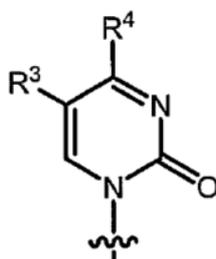
Clark '147 taught a set of nucleoside analogs or their prodrugs as HCV inhibitors with the core structure being 2'-deoxy-2'-fluoro-2'-C-methyl nucleoside and its 5'-modified prodrugs. EX1006 at 2. Specifically, Clark '147 taught an HCV RNA polymerase inhibitor and its use in treating HCV. See, for example, claim 40, which recited:

Use of an anti-virally effective amount of a (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β -D or β -L) of the following formula or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of hepatitis C infection in a host:



wherein

Base is



R¹ and R⁷ are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate..., acyl..., alkyl..., sulfonate ester..., a lipid..., an L or D-amino acid, a carbohydrate, a peptide, a cholesterol, or other pharmaceutically-acceptable leaving group which when administered in vivo is capable of providing a compound wherein R¹ or R⁷ is independently H or phosphate; R¹ and R⁷ can also be linked with cyclic phosphate group;

R³ and R⁴ are independently H, halogen..., OH, OR', SH, SR', NH₂,

....”

EX1006 at 137-138.

A POSA would immediately contemplate R³ as H and R⁴ as OH because those are two of the first three substituents listed for those positions. EX1002 at ¶206. In doing so, a POSA would also recognize that this would result in the base being uridine. *Id.* Further, a POSA would select R¹ to be phosphate and R⁷ to be H, again because those are the first two substituents listed, and this would result in the 5'-phosphate of "(2'R)-2'-deoxy-2'-fluoro-2'-C-methyl uridine," which is the same nucleotide moiety as the compound of claims 1, 2 and 16-18. *Id.*

A POSA would readily recognize that these substituents are essentially obligatory for R¹ and R⁷ in terms of resulting in a nucleoside which is capable of being activated (i.e., phosphorylated) at the C5' position and which also results in the natural C3' substitution of -OH. EX1002 at ¶207.

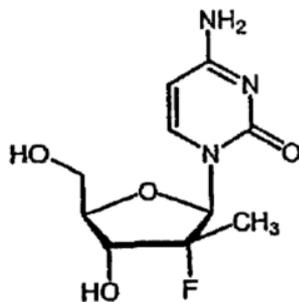
In terms of R⁴, a POSA would naturally pick this group = OH or NH₂ as these would result in cytidine or uridine base substitution on the sugar rings. EX1002 at ¶208. The R³ substitution would naturally first be chosen as an -H (hydrogen atom) because this results in incorporation of the natural cytosine and uracil rings into the nucleoside. *Id.*

These would not necessarily be the only substitutions that a POSA would infer from Clark '147, but they are the simplest, and they would be considered as obligatory from the perspective of a medicinal chemist. EX1002 at ¶209.

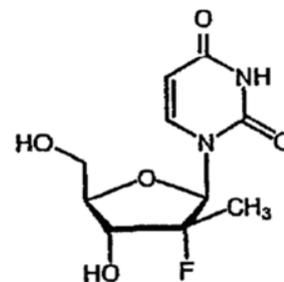
Incorporating the natural cytidine and uridine rings into the structure would be a

necessary first step in establishing a natural understanding of the structure-activity relationships of a C2'-substituted nucleoside. *Id.* Thus, Clark '147 taught that a 5'-phosphate of "(2'R)-2'-deoxy-2'-fluoro-2'-C-methyl uridine" is an HCV inhibitor. *Id.*

Furthermore, Example 5 of Clark '147 experimentally validated the HCV inhibition effect of (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine (formula below), which proved that the 5'-triphosphate of (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl cytidine (i.e. C'TP) (an example compound of Claim 40, where R¹=triphosphate, R⁷=H, R³=H, and R⁴=NH₂) was an active and potent HCV inhibitor. EX1006 at 137.



(2'R)-2'-deoxy-2'-F-2'-C-Me cytidine



(2'R)-2'-deoxy-2'-F-2'-C-Me uridine

Because Clark '147 taught that its Base was preferably a purine or pyrimidine and also defined that pyrimidine includes uracil, EX1006 at 137 (claim 40), and because it was common knowledge that uracil is one of the four bases in RNA, a POSA would have been motivated to replace the cytidine in the active (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine 5'-triphosphate with a uridine

(R⁴=OH) and had an expectation that this would produce a likewise active and potent HCV inhibitor. EX1002 at ¶211.

Therefore, Clark '147 not only taught that 5'-phosphates of (2'R)-2'-deoxy-2'-fluoro-2'-C-methyluridine are HCV inhibitors, it also motivated a POSA to choose it as an active agent. EX1002 at ¶212. In other words, based on the experimental results of Example 5 of Clark '147 and the common knowledge in the art, a POSA would have been fully motivated to specifically choose, from the various compounds encompassed by Claim 40, the 5'-phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug) of (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl uridine as a practicable HCV inhibitor. *Id.*

Moreover, Claim 40 of Clark '147 also taught that the 5'-phosphate can be a "stabilized phosphate prodrug," EX1006 at 137:16, which when administered *in vivo* is capable of providing a compound wherein R¹ or R⁷ is independently H or phosphate. EX1002 at ¶213. This taught that the 5'-phosphate can be further modified to stabilize the prodrug, and the stabilized phosphate prodrug will turn into the 5'-monophosphate form (R¹=phosphate, and R⁷=H) to be activated. *Id.*

Specifically, Clark '147 taught:

Any of the nucleosides described herein can be administered as a nucleotide prodrug to increase the activity, bioavailability, stability or otherwise alter the properties of the nucleoside. A number of

nucleotide prodrug ligands are known. In general, alkylation, acylation or other lipophilic modification of the mono, di or triphosphate of the nucleoside will increase the stability of the nucleotide. Examples of substituent groups that can replace one or more hydrogens on the phosphate moiety are alkyl, aryl, steroids, carbohydrates, including sugars, 1, 2-diacylglycerol and alcohols. Many are described in R. Jones and N. Bischofberger, Antiviral Research, 27 (1995) 1-17. Any of these can be used in combination with the disclosed nucleosides to achieve a desired effect.

EX1006 at 47:16-25 (emphasis added).

Further, Clark '147 taught:

The nucleosides described herein can be administered as a nucleotide prodrug to increase the activity, bioavailability, stability or otherwise alter the properties of the nucleoside. A number of nucleotide prodrug ligands are known. In general, alkylation, acylation or other lipophilic modification of the mono-, di-or triphosphate of the nucleoside reduces polarity and allows passage into cells. Examples of substituent groups that can replace one or more hydrogens on the phosphate moiety are ailcyl, (sic) aryl, steroids, carbohydrates, including sugars, 1,2- diacylglycerol and alcohols. Many are

described in R. Jones and N. Bisehoferger, *Antiviral Research*, 1995, 27: 1-17. Any of these can be used in combination with the disclosed nucleosides to achieve a desired effect.”

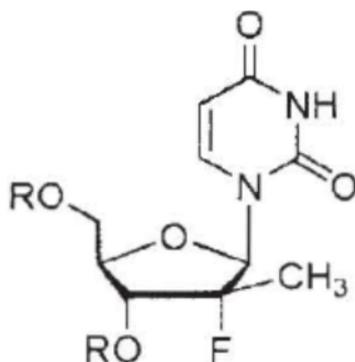
EX1006 at 15-24 (emphasis added).

Therefore, Clark ‘147 explicitly taught that alkylation, acylation, arylation, or other lipophilic modification can be made to the phosphate group in the 5’-phosphate of (2’R)-2’-deoxy-2’-fluoro-2’-C-methyluridine to increase its activity, bioavailability and stability, and that the modified prodrug will convert into the 5’-monophosphate form (U’MP) after its entry into the cell. EX1002 at ¶216.

Therefore, claims 1, 2, and 16-18 are different from Clark ‘147 only in that the stable 5’-phosphate group on the nucleoside analog in claims 1, 2, and 16-18 is the “(phenyl)(isopropyl-L-alaninyl)phosphate” group. EX1002 at ¶217.

Clark 2005 taught, “The degradation enzymes cytidine deaminase (CDA) and deoxycytidine monophosphate deaminase (dCMPDA) are responsible for the *in vivo* metabolic conversion of cytidine or cytidine monophosphate to uridine.” Thus, Clark 2005 taught that the cytidine form of the Clark ‘147 nucleoside could metabolically convert *in vivo* to the uridine form. EX1002 at ¶218; EX1007 at 3.

Clark 2005 tested both 2’-deoxy-2’-fluoro-2’-C-methylcytidine and 2’-deoxy-2’-fluoro- 2’-C-methyluridine, the structure of which is below, for anti-HCV activity. EX1002 at ¶219.



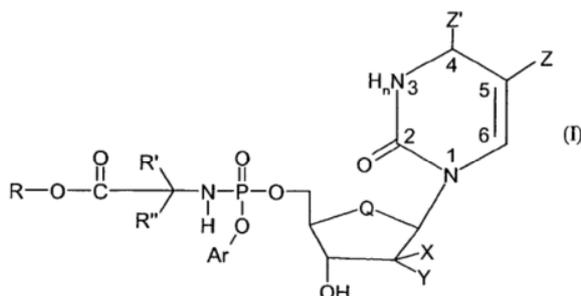
EX1007 at 3 (Scheme 3).

Clark 2005 showed in Table 2 that the cytidine and uridine forms of the nucleoside had an identical lack of toxicity. *Id.* Clark 2005 also showed in Table 2 that the uridine form demonstrated no activity as compared to the cytidine. *Id.*

The Clark 2005 results would have motivated a POSA to understand the lack of activity of the uridine form and to pursue methods to activate the uridine if the lack of activity were due to inefficient phosphorylation. EX1002 at ¶221.

General knowledge in the art as described above would have motivated a person skilled in the art to use the well-known strategy to select a suitable stable 5'-phosphate group for (2'R)-2'-deoxy-2'-fluoro-2'-C-methyluridine of the Clark '147 and Clark 2005, in order to increase its activity. EX1002 at ¶222.

One would have been specifically motivated to refer to McGuigan '327's teaching of compounds of formula (I):



wherein:

R is selected from the group comprising alkyl, aryl and alkylaryl;

R' and R'' are, independently, selected from the group comprising H, alkyl and alkylaryl, or R' and R'' together form an alkylene chain so as to provide, together with the C atom to which they are attached, a cyclic system;

Q is selected from the group comprising -O- and -CH₂-;

X and Y are independently selected from the group comprising H, F, Cl, Br, I, OH and methyl (-CH₃);

Ar is a monocyclic aromatic ring moiety or a fused bicyclic aromatic ring moiety, either of which ring moieties is carbocyclic or heterocyclic and is optionally substituted;

Z is selected from the group comprising H, alkyl and halogen; and

n is 0 or 1, wherein when n is 0, Z' is -NH₂ and a double bond exists

between position 3 and position 4, and when n is 1, Z' is =O;

with the proviso that when n is 1, X and Y are both H, R is methyl (-CH₃), one of R' and R" is H and one of R' and R" is methyl (-CH₃), then Ar is not phenyl (-C₆H₅).

EX1002 at ¶223; EX1009 at 5-6.

McGuigan '327 taught that, in its formula (I), "X and Y are independently selected from the group comprising H, F, Cl, Br, I, OH and methyl (-CH₃)," and specifically highlighted that, "[p]referably, R is methyl, ethyl, *n*- or *i*-propyl," *Id.* at 9:20, "preferred compounds include those where R' and R" are both methyl, one of R' and R" is H and one of R' and R" is methyl," *Id.* at 10:5-6, "preferably Q is Q," *Id.* at 11:14, and "More preferably, Ar is selected from the group comprising: Ph-," *Id.* at 13:1-2.

Therefore, a POSA would have been encouraged by McGuigan '327 to select Q=O, n=1, Z'=O, Z=H, X=-CH₃, Y=F, Ar=phenyl, R=isopropyl, R'=H, and R"=-CH₃ in the compound of formula (I) of McGuigan '327 which would be identical to the compound of claims 1, 2, 16-18. EX1002 at ¶225. A POSA would have been motivated to select these substituents because they were indicated by McGuigan '327 to be preferred and Clark '147 and Clark 2005 taught the same exact sugar ring and base structure. EX1002 at ¶225.

Thus, it would have been obvious to a person skilled in the art to obtain the

compound of claims 1, 2 and 16-18 based on Clark '147, Clark 2005 and McGuigan '327 in combination with the general knowledge in the art at the time. EX1002 at ¶226.

2. Claims 10-12 and 20-22 (compositions comprising compound)

Claim 10 recites, “A pharmaceutical composition comprising the compound according to claim 1.” EX1001 at 607:39-40. Claim 11 recites, “The pharmaceutical composition according to claim 10 further comprising a pharmaceutically acceptable medium.” EX1001 at 41-42. Claim 12 recites, “The pharmaceutical composition according to claim 11 comprising an effective amount of the compound according to claim 1 to treat a hepatitis C virus infection.” EX1001 at 43-45. Claims 20-22 are identical to claims 10-12 except that they depend from claim 16.

Clark '147 and Clark 2005 taught that its compounds were potent and safe inhibitors of HCV replication. EX1006 at 2; EX1007 at 1. Inherent in this teaching are compositions comprising such compounds and a pharmaceutically acceptable medium and that such compositions are for treating hepatitis C. EX1002 at ¶228. Thus, Clark '147, Clark 2005 and McGuigan '327 rendered claims 10-12 and 20-22 obvious. *Id.*

3. Claims 13-15 and 23-25 (methods of treating viral infections)

Claim 13 recites, “A method of treating a subject infected by a virus selected

from among hepatitis C virus ..., which comprises administering to the subject an effective amount of the compound according to claim 1.” EX1001 at 607:46-52. Claim 14 recites, “The method of claim 13 wherein the virus is hepatitis C virus.” EX1001 at 607:53-54. Claim 15 recites, “The method of claim 14, which further comprises administering to the subject an effective amount of another antiviral agent.” EX1001 at 607:55-57. Claims 23-25 are identical to claims 13-15 except that they depend from claim 16.

Clark ‘147 and Clark 2005 taught that its compounds were potent and safe inhibitors of HCV replication. EX1006 at 2; EX1007 at 1. Further, McGuigan ‘327 also taught that applying its phosphoramidate ProTide approach to nucleosides could activate them as antivirals for use in treating people. EX1009 at 3. Thus, Clark ‘147, Clark 2005 and McGuigan ‘327 rendered claims 13, 14, 23 and 24 obvious. EX1002 at ¶230.

Clark ‘147 further taught that its compounds could be used in “more effective combination therapies,” and specifically, “in combination ... with another effective antiviral agent.” EX1006 at 17. Thus, Clark ‘147, Clark 2005 and McGuigan ‘327 rendered claims 15 and 25 obvious. EX1002 at ¶231.

XI. CONCLUSION

For these reasons, claims 1, 2, 10-18 and 20-25 of the ’270 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 26, 2017

/Daniel B. Ravicher/

Daniel B. Ravicher, Lead Counsel

Reg. No. 47,015

Ravicher Law Firm, PLLC

2000 Ponce De Leon Blvd Ste 600

Coral Gables, FL 33134

Tel: (786) 505-1205

Email: dan@ravicher.com

Counsel for Petitioner

XII. APPENDIX – LIST OF EXHIBITS

Exhibit No.	Description
1001	U.S. Patent No. 8,334,270
1004	Sofia
1005	Ma
1006	Clark '147
1007	Clark 2005
1008	Perrone
1009	McGuigan '327
1010	Wagner
1011	Prusoff
1012	McGuigan 2006
1013	McGuigan 1994
1014	Cahard

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 10,455 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a).

Respectfully,

Dated: October 26, 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 1001-1014 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 26, 2017

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