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. IPR2018-00123
U.S. Patent No. 8,735,372

PETITION FOR *INTER PARTES* REVIEW

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I. INTRODUCTION

Initiative for Medicines, Access & Knowledge (I-MAK), Inc. ("Petitioner") requests *inter partes* review ("IPR") of claims 1 and 2 of United States Patent No. 8,735,372 to Du et al. ("the '372 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 '372 patent issued on May 27, 2014, and is currently assigned to Gilead Pharmasset LLC ("Patent Owner"). This petition demonstrates that claims 1 and 2 are unpatentable.

The '372 patent claims methods that were obvious in light of the prior art. Specifically, the '372 claims a method of treating hepatitis C virus ("HCV") with a combination of two nucleoside compounds, but both nucleoside compounds were known as a result of being previously published and combining the two classes of compounds was also known as a preferred method for treating HCV.

Thus, claims 1 and 2 of the '372 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 two petitions for *Inter Partes* Review of U.S. Patent No. 7,964,580 and two petitions for *Inter Partes* Review of U.S. Patent No. 8,333,270, both of which relate to the '372 patent. Case Nos. IPR2018-00119, -00120, -00121 and -00122. 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 ’372 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 and 2 of the ’372 patent based on the following ground:

#	Claims	35 U.S.C. §	Prior Art
1	1 and 2	103(a)	Sofia, Congiatu and Serrano-Wu

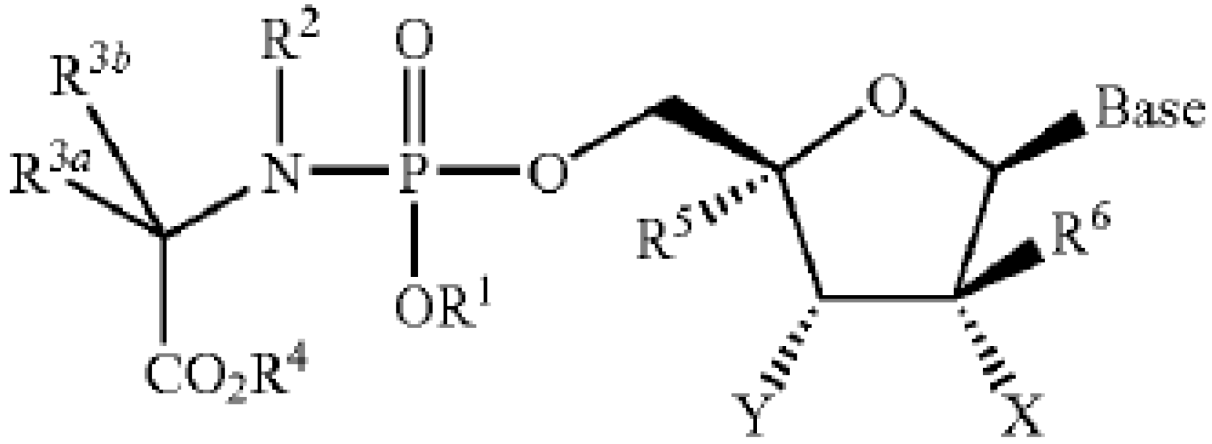
This Petition is supported by the declaration of Joseph M. Fortunak, Ph.D. EX1002. Dr. Fortunak is well qualified as an expert, possessing the necessary scientific, technical, and other specialized knowledge and training to assist in an understanding of the evidence presented herein, as well as possessing 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 '372 PATENT

The '372 patent relates to phosphoramidate prodrugs of nucleoside derivatives for the treatment of viral infections of the following general formula:



EX1001 at 5:4 – 7:45. In defining the structure's various components, the '372 patent states that the Base is "a naturally occurring or modified purine or pyrimidine base." EX1001 at 6:36 – 7:10. The '372 patent further provides a long list of substituents for each of R^1, R^2, R^{3a}, R^{3b}, R^4, R^5, R^6, X and Y. EX1001 at 5:15 – 6:37.

The following chart describes the '372 patent's 2 claims:

Claim(s)	Recite
1, 2	Methods of treating hepatitis C virus by administering an NS5a inhibitor and a compound within the general formula.

V. FILE HISTORY OF THE '580 PATENT

U.S. Patent Application No. 14/057,675 ("the '675 application"), filed on October 18, 2013, issued as the '372 patent on May 27, 2014. The '675 application claimed the benefit of U.S. Patent Application No. 13/609,614 ("the '614 application"), filed on September 11, 2012, U.S. Patent Application No. 13/099,671 ("the '671 application"), filed on May 3, 2011, 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 '675 application, the Examiner allowed the claims without making any substantive prior-art based rejections. EX1002 ¶27.

VI. PERSON OF ORDINARY SKILL IN THE ART

Because the '372 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 ¶33.

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 '372 patent provides definitions for certain claim terms, but these definitions are conventional. EX1002 ¶35. Thus, there is no reason to give any of the terms of the claims of the '372 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

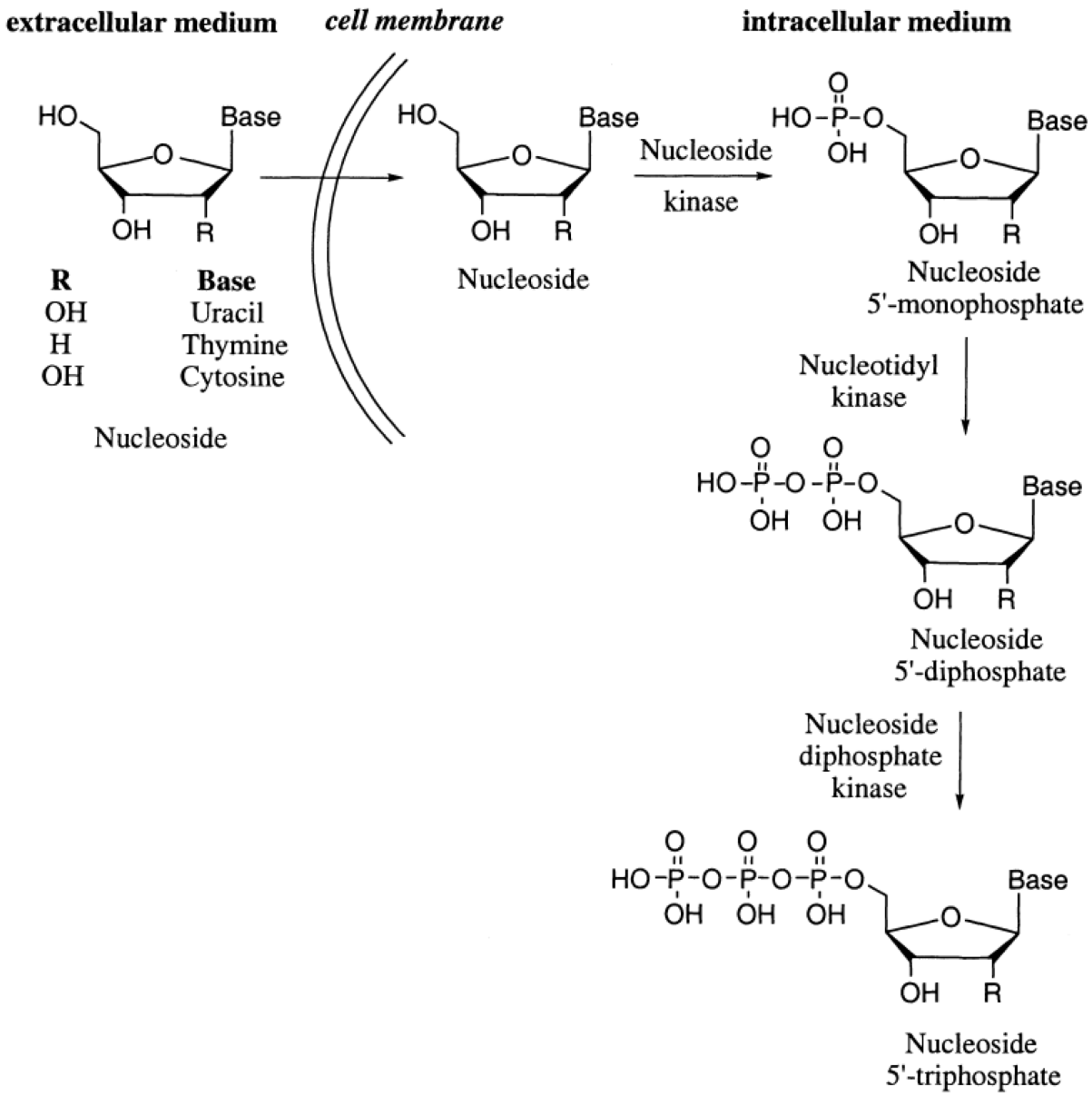
public knowledge that must be consulted when considering whether a claimed invention would have been obvious. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007); *Randall Mfg. v. Rea*, 733 F.3d 1355, 1362-63 (Fed. Cir. 2013).

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 March 21, 2008.

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. EX1002 ¶37. RNA viruses and reverse-transcribing (RT) viruses rely on their special DNA/RNA polymerases to synthesize viral DNA/RNA chains in the host cell, while DNA viruses use host-cell DNA polymerases to synthesize their viral DNA chains. *Id*.

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 ¶38. Nucleoside (N), after entering the cell, is converted into its 5'-monophosphate (NMP) by intracellular host or viral nucleoside kinases. *Id*. 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 ¶39. 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 inhibit viral DNA/RNA replication. *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) for incorporation into the viral DNA/RNA chain being synthesized. EX1002 ¶40. 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. EX1002 ¶41. First, Wagner et al. *"Pronucleotides: Toward the In Vivo Delivery of Antiviral and Anticancer Nucleotides,"* Medical Research Reviews, 2000, 20(6), 417-451 ("Wagner"; EX1003), described the use of nucleoside analogs for inhibition of various viruses. *Id*. Second, WO 2005/003147 to Clark ("Clark '147"; EX1004) described research and results about use of various nucleoside analogs for treatment of *Flaviviridae* infections from 1994 to 2004. *Id*.; EX1004 at 12:11 – 13:4.

The first commercially available antiviral nucleoside was the anti-herpes virus uridine analog Idoxuridine. EX1002 ¶42; Prusoff, WH, "Synthesis and

biological activities of iododeoxyuridine, an analog of thymidine," *Biochim Biophys Acta*. 32(1):295-6 (1959) ("Prusoff"; EX1005).

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. EX1002 ¶43.

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

Thus, it was generally known that nucleoside analogs suppress viral replication, particularly by incorporation into viral DNA/RNA chains. EX1002 ¶44.

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 – in Particular Phosphoramidates - Enabled Nucleosides To Overcome This Limitation

It was well known that, to interact with HCV NS5B polymerase, anti-viral nucleosides must generally first be converted into their triphosphate form. EX1002

¶45. 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-Fluro-2'-C -Methylcytidine (PSI-6130) and Identification of a Novel Active 5'-Triphosphate Species,"* J. Biol. Chem., 2007, 282(41), 29812-29820 ("Ma"; EX1006), 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 ¶45; EX1006 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"; EX1007) 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 ¶46; EX1007 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'→NMP) is generally the rate-limiting step in the course of its trisphosphorylation. EX1002 ¶47. 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." EX1007 at 1. Second, Wagner recited that ddNs' activation is hindered at the first phosphorylation step. EX1003 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"; EX1008), recognized that, "in most cases the first phosphorylation to the 5'-monophosphate is the rate-limiting step." EX1008 at 1.

Perrone (EX1007), Wagner (EX1003), and McGuigan 2006 (EX1008) 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 ¶49.

Several other references recognized this general knowledge. EX1002 ¶50. 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"; EX1009), recognized that nucleoside analogs have limitations because they depend on kinase-mediated activation to generate the bioactive (tri)phosphate forms. EX1009 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 known where nucleoside analogs are inactive, but the corresponding triphosphates are inhibitors at their enzyme target. EX1008 at 1.

To address this widely known issue, it was contemplated in the art to use the 5'-phosphate of nucleoside analogs as prodrugs to "bypass" the kinase-mediated monophosphorylation step of generating the active triphosphate form. EX1002 ¶52. 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. EX1009 (McGuigan 1994). 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 ¶52.

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 bioavailability of

nucleosides or phosphorylated nucleosides. EX1002 ¶53; EX1003 at 3 and 8. 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"; EX1010) recognized that aryloxy phosphoramidate triesters are an effective pro-tide motif for the intracellular delivery of (otherwise) charged antiviral nucleoside monophosphates and that the phenyl alanyl phosphoramidate approach was successful on a range of nucleosides by many research groups. EX1002 ¶54; EX1010 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 ¶55; EX1007 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 ¶56. 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 ¶57; EX1009 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 ¶58; EX1010 at 2-3 (Fig. 1).

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 ¶59; EX1008 at 1. McGuigan 2006 also recognized that several aryloxy phosphoramidate prodrugs achieve an anti-HIV activity (IC50) at the concentration of about 10 nM. EX1002 ¶59; EX1008 at 4 (Table 1).

Congiatu *et al*., *"Novel Potential Anticancer Naphthyl Phosphoramidates of BVdU: Separation of Diastereomers and Assignment of the Absolute Configuration of the Phosphorous Center,"* J. Med Chem. 2006, 49(2), 452-455 ("Congiatu"; EX1011) illustrated the well-known fact that the phosphorous atom of ProTide prodrugs constitutes a center of chirality. EX1002 ¶60; EX1011 at 2-3. Thus, a

phosphoramidate prodrug may exist as a mixture of stereochemical centers at the phosphorous. EX1002 ¶60. In the case of molecules with multiple centers of chirality (as is the case with nucleosides), these phosphorous stereoisomers are referred to as "diastereomers." *Id*. Congiatu also taught that the individual diastereomers at the phosphorous might likely possess different biological activity. *Id*. Congiatu further taught that separation of the phosphorous diastereomers gave rise to an approximately 15:1 difference in biological activity between such diastereomers. *Id*. Thus, Congiatu taught a POSA that the ProTide strategy must include testing of the individual phosphorous diastereomers to understand their differences in biologic activity. *Id*.

Therefore, the "Pronucleotide" or "ProTide" strategy, including the testing of the individual phosphorous diastereomers therein, had been a conventional technical means in the art. EX1002 ¶61.

In summary, it was generally known that, for antiviral 5'-phosphate prodrugs, the antiviral activity lies in the nucleoside itself. EX1002 ¶62. It was also generally known that the intracellular delivery (cell membrane permeation) could be improved because of the lipophilicity rendered by the modified phosphate group. *Id*. It was also generally known that intracellular hydrolysis of nucleoside monophosphate prodrugs 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*. It was also known that the ProTide monophosphate prodrugs were capable of overcoming the need for kinases in the first phosphorylation step of nucleosides. *Id*. It was further known that the phosphorous diastereomers of ProTide prodrugs likely exhibited different biologic activity with one diastereomer being very significantly more active than the other. *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. EX1002 ¶63; EX1009 (McGuigan 1994) at 1-3. The means existed to assess the cellular uptake and subsequent phosphorylation of nucleosides. EX1002 ¶63; EX1006 (Ma) at 4-8. Thus, it was generally known that the identification of nucleoside analogs whose activity was kinase-dependent was readily available. EX1002 ¶63.

D. Narrowing The Selections For The Phosphoramidate Prodrug

Phosphoramidate prodrugs have substitutions to be selected at the: 1) amino acid; 2) ester group on the amino acid; 3) ester group on phosphorous; and 4) optional substitution on nitrogen of the amino acid. EX1002 ¶64. Of these possibilities, the range of realistic options is reasonably limited. EX1002 ¶64. Perrone and Congiatu demonstrated 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, ethyl, isopropyl, butyl, or benzyl. EX1002 ¶64; EX1007; EX1011. The useful ester groups on phosphorous are aryl (typically phenyl but occasionally naphthyl). EX1002 ¶64. 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 ¶64; EX1007 at 3.

It was 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 ¶65. 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*.

More specifically, Perrone taught the activity of a series of 22 phosphoramidate nucleoside ProTide derivatives of 4'-azidouridine for antiviral hepatitis C activity, the choice of 1) alanine for the amino acid; 2) 2-butyl, benzyl, and isopropyl for the amino acid ester; 3) phenoxy for the ester on phosphorous; and 4) no substitution (i.e., a free N-H) on the amino acid nitrogen provided a very short list of three (Table 1 below) very active compounds. EX1002 ¶66.

Table 1. Anti HCV Activity and Cytotoxicity Data for (1) and Phenyl Phosphoramidate Nucleotide Analogues

compound	amino acid	ester	EC_{50} (μM)	CC_{50} (μM)
11	L-Ala	Me	3.1	> 100
12	L-Ala	Et	1.3	> 100
13	L-Ala	Bu	1.2	> 100
14	L-Ala	2-Bu	0.63	> 100
15	L-Ala	iPr	0.77	> 100
16	L-Ala	tBu	5.1	> 100
17	L-Ala	Bn	0.61	> 100
18	Me_2Gly	Et	10.3	> 100
19	Me_2Gly	Bn	3.4	> 100
20	cPntGly	Et	> 100	> 100
21	cPntGly	Bn	< 100	> 100
22	Phe	Et	1.37	> 100
23	Phe	Bn	< 100	> 100
24	Val	Bn	< 100	> 100
25	Gly	Bn	1.6	> 100
26	D-Ala	Bn	1.2	> 100
27	Leu	Et	2.3	> 100
28	Pro	Et	6.0	> 100
29	Met	Et	14	> 100
30	N-MeGly	Et	> 100	> 100
31	EtGlu	Et	> 100	> 100
32	β-Ala	Et	> 100	> 100
4'-azidouridine (1)	—	—	> 100	> 100

EX1007 at 4.

Perrone concluded that, although quite a number of active ProTide derivatives could readily be synthesized, a distinctive Structure-Activity-Relationship (SAR) was observed. EX1002 ¶67. Specifically, Perrone taught:

> In conclusion, ester variation was widely tolerated except for the *tert*-butyl, which gave a slight reduction in potency in the L-alanine series (16) and the benzyl in the case of the L-phenylalanine derivative (23). L-Alanine remained the most effective amino acid,

with glycine and D-alanine showing only slightly reduced potency. Dimethylglycine, L-leucine, and L-proline also provided compounds with antiviral potencies in a low micromolar range. It therefore appears that the amino acid core could be considerably varied to give antiviral agents with potencies within a 10-fold range in replicon cells. Importantly, potency optimization requires consideration of both amino acid and ester moieties as most clearly shown for the ethyl and benzyl esters of the L-phenylalanine analogues. Moreover, quite distinct SARs emerged from this family versus HCV as compared to our prior studies in other families. (emphasis added)

We also explored the possibility to replace the phenyl substituent on the phosphate with a more hydrophobic moiety, 1-naphthyl. Previously, we noted an increase in the in vitro potency of 1-naphthyl phosphoramidates compared to the corresponding phenyl phosphoramidates when investigating BVdU phosphoramidates in an anticancer assay.

EX1007 at 4.

Perrone also indicated (as shown in Table 3, reproduced below) that the 1-naphthyl(oxy) phosphate ester diastereomers displayed little or no difference in anti-HCV activity. EX1002 ¶68.

Table 3. Anti HCV Activity and Cytotoxicity Data for (1) and 1-Naphthyl Nucleotide Analogues

compound	phosphorus configuration	amino acid	ester	EC_{50} (μM)	CC_{50} (μM)
33	*S/R*	L-Ala	Bn	0.22	>100
34	R	L-Ala	Bn	0.39	>100
35	S	L-Ala	Bn	0.43	>100
17 (Phenyl ProTide)	*S/R*	L-Ala	Bn	0.61	>100
4'-azidouridine (1)				>100	>100

EX1007 at 4. These diastereomers were separated and displayed modestly better potency than the mixture of diastereomers for the direct phenoxy ester analog. EX1002 ¶68. While Perrone did not separate the diastereomers of the phenoxy ProTides, Congiatu taught that these diastereomers very often showed a marked difference in anti-HCV activity. EX1002 ¶68; EX1011.

Thus, Perrone taught that many phosphoramidate analogs can provide excellent activation of nucleosides for antiviral activity against HCV. EX1002 ¶69. Perrone also taught that the range of amino acids that were useful (out of 13 examined) was limited, with L-alanine being the best option. EX1002 ¶69.

Only 6 highly active phosphoramidate groups were particularly identified in Perrone (*i.e.* No.14, 15, 17, and 33-35) with compounds 34-35 being two separate diastereomers of compound 33. EX1002 ¶70; EX1007 at 4 (Tables 1 and 3). A POSA would have been motivated to try to attach each to the 5'-position of (2'R)-2'-deoxy-2'-fluoro-2'-C-methyluridine resulting in compounds within claims 1 and 2 of '372. EX1002 ¶70. This would have required synthesizing only 4 different

ProTide phosphoramidates. *Id*. Given that Congiatu found significant difference between the activity of phosphorous diastereomers, EX1011 at 2-3, a POSA would then have separated and tested the diastereomers of each of these 4 referred analogs. EX1002 ¶70.

Perrone described a uridine analog (4'-azidouridne), which like PSI-6206, was inactive in the HCV replicon assay although its triphosphate form (4'-azidouridine-TP) was a potent inhibitor of HCV NS5B polymerase. EX1007 at 1, 2-3, 5. Thus, Perrone described exactly the same problem as '372 and suggested the same solution to the problem. EX1002 ¶71.

Perrone provided a POSA with the relevant knowledge to prepare the corresponding L-alanine derivatives shown in Table 1 to exhibit low or sub-micromolar activity with a reasonable expectation of success in achieving the same outcome. EX1007 at 4. Specifically, a POSA would have prepared the derivatives of PSI-6206 that correspond to compounds (14), (15) and (17) in Perrone because they were described in Perrone as having "exceptional" antiviral activity. EX1002 ¶72. In addition, the "*(phenyl)(isopropyl-L-alaninyl)phosphate*" group (No.15) disclosed in Perrone boosted the inactive parent nucleoside to an activity of EC_{50} = 0.77 μM, while '372 used very similar phosphoramidate groups 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 ¶72; compare

EX1001 at 622 1:13 to EX1007 at 4.

In considering the similarity of Perrone and ’372, a POSA would not have focused on the structural differences between the parent nucleosides, PSI-6206 and 4'-azidouridine. EX1002 ¶73. A POSA would have selected the nucleoside in Sofia (EX1012) as a lead compound due to its superior properties and then sought to modify its structure by incorporating the specific phosphoramidate substituents from Perrone that were taught to provide an optimal solution for delivering an active HCV nucleoside to target cells. EX1002 ¶73; EX1007 at 4.

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 ¶74. This limitation was known to be overcome by the incorporation of phosphoramidate ProTide technology. EX1002 ¶74; EX1011 at 1-4. Such phosphoramidates were known to be precursors of active triphosphates and to inhibit viral replication in infected whole cells. EX1002 ¶74.

Phosphoramidates were also known to improve physicochemical properties of nucleosides, resulting in dramatic increases in intracellular concentrations of nucleoside analogs. EX1002 ¶75; EX1009 (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 ¶75.

F. The '372 Patent Acknowledges This Common Knowledge

The '372 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 ¶76. In particular, the '372 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 4:25-61.

The '372 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 ¶77. The '372 patent further acknowledges (claim 1) that the selection of nucleoside modifications is limited to the positions designated as R7 and R8 shown in claim 1 (*cf*. Paragraph 88). EX1002 ¶77.

For example, the '372 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 4:13 – 4:61 (emphasis added).

G. Nucleoside NS5B Inhibitors Were Combined With Other Antiviral Agents, Including NS5A Inhibitors, To Treat HCV

It was widely known that the standard of care for HCV treatment involved combination therapy, and in particular combination of nucleoside NS5B inhibitors with NS5A inhibitors. EX1002 ¶79.

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). EX1004 at 18.

Clark '147 also taught that its nucleosides could be administered as a nucleotide prodrug in combination or in alternation with one or more other

effective therapeutic agents i.e. another antiviral agent. For example, the '147 patent states:

> *In another embodiment for the treatment, inhibition, prevention and/or prophylaxis of any viral infection described herein, the active compound, derivative or salt can be administered in combination or alternation with another anitiviral agent. In general, in combination therapy, effective dosages of two or more agents are administered together, whereas during alternation therapy, an effective dosage of each agent is administered serially.* The dosage will depend on absorption, inactivation and excretion rates of the drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens and schedules should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions.
>
> *It has been recognized that drug-resistant variants of flaviviruses, pestiviruses or HCV can emerge after prolonged treatment with an antiviral agent. Drug resistance most typically occurs by mutation of a gene that encodes for an enzyme used in viral replication.* The efficacy of a drug against the viral infection can be prolonged, augmented or restored by administering the compound in combination or alternation with a second, and perhaps a third, antiviral compound that induces a different mutation from that caused by the principle drug. Alternatively, the pharmacokinetics, biodistribution or other

parameter of the drug can be altered by such combination or alternation therapy. *In general, combination therapy is typically preferred over alternation therapy because it induces multiple simultaneous stresses on the virus.*

For example, one skilled in the art will recognize that any antiviral drug or therapy can be used in combination or alternation with any nucleoside of the present invention. Any of the viral treatments described in the Background of the Invention can be used in combination or alternation with the compounds described in this specification. Nonlimiting examples of the types of antiviral agents or their prodrugs that can be used in combination with the compounds disclosed herein include: interferon, including interferon alpha 2a, interferon alpha 2b, a pegylated interferon, interferon beta, interferon gamma, interferon tau, and interferon omega, an interleukin, including interleukin 10 and interleukin 12, ribavirin; interferon alpha, or pegylated interferon alpha in combination with ribavirin or levovirin; levovirin; a protease inhibitor, including an NS3 inhibitor, a NS3-4A inhibitor; a helicase inhibitor; polymerase inhibitor including HCV RNA polymerase and NS5B polymerase inhibitor, gliotoxin; an IRES inhibitor; and antisense oligonucleotide, a thiazolidone derivative; a benzanilide, a ribozyme; another nucleoside, nucleoside prodrug or nucleoside derivative; a 1-amino-alkylcyclohexane; an antioxidant including vitamin E; squalene; amantadine; a bile acid; N-(phosphonoacetyl)-L-aspartic acid; a benzenedicarboxamide; a polyadenylic acid; a benzimidazoles; thymosin; a beta tubulin inhibitor; a prophylactic vaccine; an immune modulator, an IMPDH inhibitor, silybin-phosphatidylcholine phytosome; and

mycophenolate.

EX1004 at 62:7-63:26 (emphasis added).

Ma taught β-D-2'-deoxy-2'-fluoro-2'-C-methyluridine (RO2433, PSI-6026), a deaminated derivative of β-D-2'-deoxy-2'-fluoro-2'-C-methylcytidine (PSI-6130) and how antiviral agents targeting essential processes of HCV replication as part of optimized combination regimens could achieve increased clinical efficacy and potentially improved adverse event profiles as well as shortened treatment duration as compared to the current standard of care. EX1006.

Sofia, "β-D2′-Deoxy-2′-C-methyluridine Phosphoramidates: Potent and Selective Inhibitors of HCV RNA Replication", Poster #P-259, presented at the 14th International Symposium on Hepatitis C Virus and Related Viruses, Glasgow, Scotland, UK, Sep. 9-13, 2007. ("Sofia"; EX1012) taught a prodrug of β-D-2'-deoxy-2'-fluoro-2'-C-methylcytidine (PSI-6130) for the treatment of chronic HCV and the need for direct acting antivirals for use in combination with the standard of care.

U.S. Pub. No. 2006/0276511 to Serrano-Wu et al. ("Serrano-Wu"; EX1013) taught some of the early NS5A inhibitor compounds designed to inhibit the function of HCV NS5A protein. Serrano-Wu suggested how the NS5A compounds disclosed therein could be used in combination therapy with other antiviral agents, including compounds that inhibit NS5B protein such as those claimed in '372.

EX1013 at 3 (¶0026).

IX. SCOPE AND CONTENT OF THE PRIOR ART

The ‘315 and ‘309 provisional applications discuss broad genera of compounds, but do not discuss the specific compounds and stereochemistry around the phosphorous atom claimed in the ‘372 patent. EX1002 ¶85. They also do not describe combining the specific compound claimed in ‘372 with an NS5A inhibitor to treat a human infected by HCV. *Id*. For these reasons, the ‘372 patent’s claims are not entitled to claim priority to those provisional applications. The earliest application to which the ‘372 patent’s claims could make a valid claim priority is the ‘015 application filed on March 21, 2008.

The following prior art references in combination teach and suggest the specific NS5B compounds claimed by the ‘372 patent as well as combining those compounds with a NS5A inhibitor to treat a human infected with HCV. EX1002 ¶86.

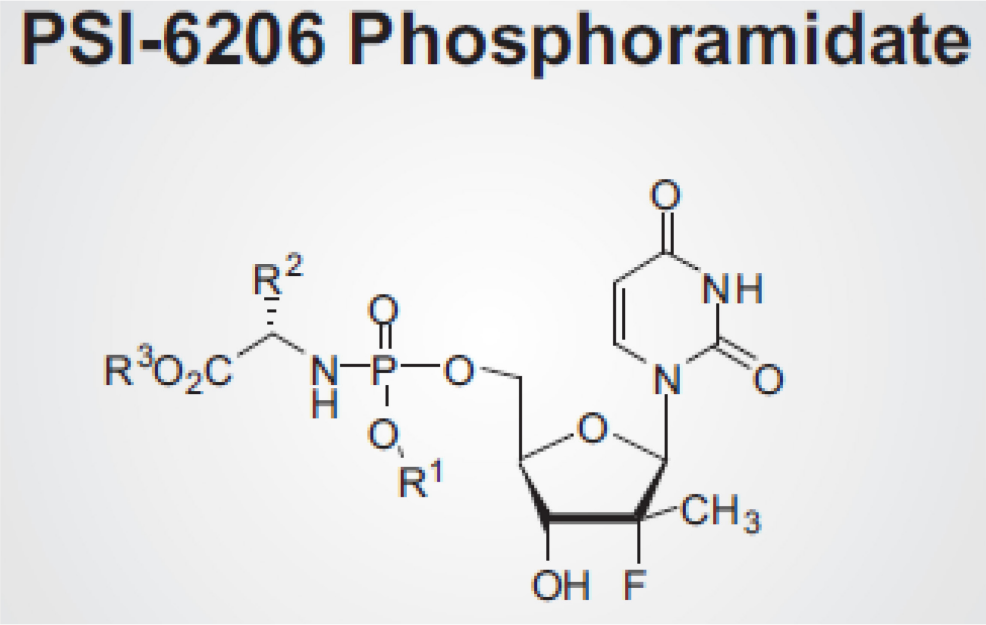
A. Sofia et al., "β-D2′-Deoxy-2′-C-methyluridine Phosphoramidates: Potent and Selective Inhibitors of HCV RNA Replication", Poster #P-259, presented at the 14th International Symposium on Hepatitis C Virus and Related Viruses, Glasgow, Scotland, UK, Sep. 9-13, 2007. (“Sofia”; EX1012)

Sofia is prior art under 35 U.S.C. § 102(a) to the ‘372 patent because it was published by September 13, 2007, before the March 21, 2008, filing date of the ‘015 application to which the ‘372 patent claims priority. While the ‘372 patent

also claims priority to the '315 and '309 provisional applications, as discussed above, the claims of the '372 patent are only entitled to the March 21, 2008, priority date, not the May 30, 2007, or October 24, 2007, priority dates. As such, the September 2007 publication of Sofia makes it prior art under 102(a).

Sofia taught a prodrug of β-D-2'-deoxy-2'-fluoro-2'-C-methylcytidine (PSI-6130) for the treatment of chronic hepatitis C. EX1012 at 1. In particular, Sofia taught that the triphosphate of PSI-6130 was a potent inhibitor of the HCV NS5B polymerase. *Id*.

Sofia also taught that PSI-6130 was converted to its uridine metabolite (PSI-6206) via cytidine deaminase and that, "phosphoramidates of PSI-6206 [were] as much as 100X more potent than the cytidine analog PSI-6130." *Id*. at n. 2. The structure of PSI-6206 phosphoramidate taught by Sofia is presented below. *Id*. at 1.



Sofia additionally taught that while PSI-6206 was not an inhibitor of HCV in the replicon assay and was not metabolized to its monophosphate derivative, its triphosphate was a potent inhibitor of the HCV NS5B polymerase. *Id*. at 1. Sofia further taught that metabolism studies showed the monophosphate of PSI-6130 was partially metabolized to the uridine monophosphate (PSI-6206), which could be converted to the triphosphate derivative. *Id*.

Sofia taught that investigating the potential for utilizing PSI-6206 as an inhibitor of HCV replication required bypassing the first phosphorylation step, which could be accomplished by the preparation of phosphoramidate derivatives at the 5'-position. *Id*. Sofia taught that such a strategy produced potent and safe inhibitors of HCV. *Id*. In Table 4, Sofia expressly taught that the uracil base compound (PSI-7672) had significantly more antiviral activity (15-fold) than the cytosine base compound. *Id*.

B. Congiatu et al., "Novel potential anticancer naphthyl phosphoramidates of BVdU: separation of diastereoisomers and assignment of the absolute configuration of the phosphorus center," J Med Chem vol. 49, pp. 452-455 (2006) ("Congiatu"; EX1011)

Congiatu is prior art under 35 U.S.C. § 102(b) to the '372 patent because it was published on December 17, 2005, more than a year before even the May 30, 2007, filing date of the earliest application to which the '372 patent claims priority.

Congiatu taught that nucleosides are useful for the treatment of cancer and

viral infections. EX1011 at 1. Congiatu also taught that the "phosphoramidate approach" (ProTide prodrugs of nucleoside mono-phosphates) was introduced by McGuigan *et al*. in 1992 to improve cellular penetration of nucleosides and to bypass the first step of kinase-mediated activation of nucleosides. *Id*. Congiatu taught that this was one of the most successful approaches for the delivery of nucleoside monophosphates inside cells. *Id*.

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

In addition, Congiatu taught that the phosphorous diastereomers of phosphoramidate nucleoside prodrugs may be separated and that it would not be unexpected for there to be a very substantial (in this case approximately 15-fold) difference in biological activity of such diastereomers. EX1011 at 2. Thus, Congiatu taught that the separate diastereomers of phosphoramidate prodrugs must be tested to determine which diastereomer is preferred as a drug candidate. EX1002 ¶93.

Further, Congiatu taught that nucleoside phosphoramidates are readily

obtained as mixtures of diastereomers at phosphorous. EX1011 at 1-2. Congiatu also taught that the R_P and S_P diastereomers at phosphorous may be separated by chromatography and that the stereochemistry at phosphorous may be assigned by spectroscopic methods. *Id*. at 2-3.

C. U.S. Pub. No. 2006/0276511 to Serrano-Wu ("Serrano-Wu"; EX1013)

Serrano-Wu is prior art under 35 U.S.C. § 102(b) to the '372 patent because it was published on December 7, 2006, more than a year before the March 21, 2008, filing date of the '015 application to which the '372 patent claims priority. While the '372 patent also claims priority to the '315 and '309 provisional applications, as discussed above, the claims of the '372 patent are only entitled to the March 21, 2008, priority date, not the May 30, 2007, or October 24, 2007, priority dates. As such, the December 2006 publication of Serrano-Wu makes it prior art under 102(b).

Even if the '372 patent's claims are entitled to the May 30, 2007, filing date of the earliest application to which the '372 patent claims priority, Serrano-Wu would still be prior art under § 102(a) because it was published before that date.

Serrano-Wu taught NS5A inhibitor compounds designed to inhibit the function of HCV NS5A protein. Serrano-Wu taught using NS5A compounds in combination therapy with other antiviral agents, including compounds that inhibit NS5B protein. EX1013 at 3 (¶0026).

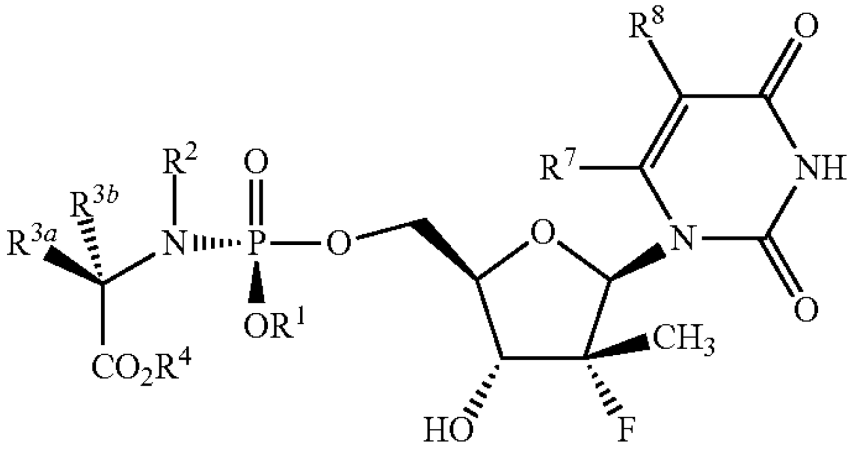
X. CLAIMS 1 AND 2 ARE UNPATENTABLE

Claims 1 and 2 are presented below followed by an analysis of why they are obvious in light of the cited references. The analysis below identifies exemplary disclosure of the cited references with respective to the corresponding claim elements, and is not meant to be exhaustive.

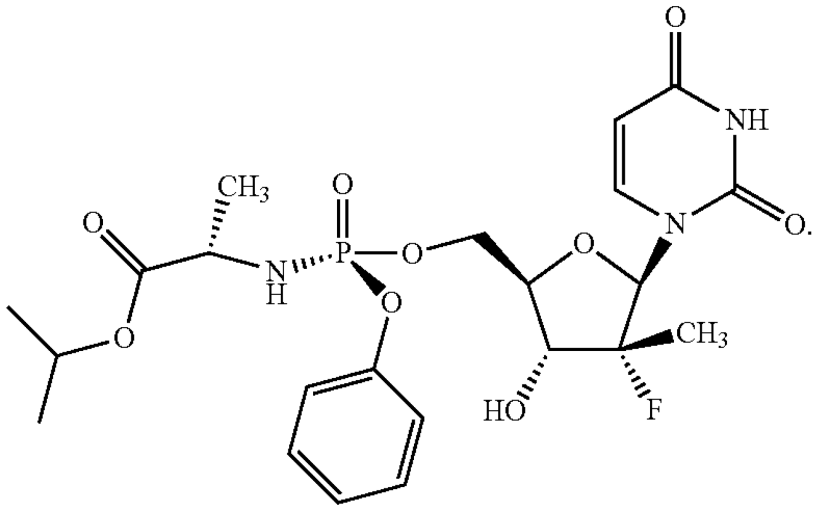
A. Ground 1: Claims 1-2 Were Obvious Over Sofia, Congiatu and Serrano-Wu

Claims 1 and 2 were obvious over Sofia, Congiatu and Serrano-Wu. EX1002 ¶97. A POSA would have been motivated to combine their teachings because they related to phosphoramidates of anti-viral nucleosides and NS5A inhibitors for the purpose of treating HCV. *Id*. The '372 patent also cites Serrano-Wu as a reference and several other references by the same authors as Sofia and Congiatu. EX1001 at 595:10.

Claims 1 recites, "[a] method of treating a human infected by hepatitis C virus, comprising administering to the subject an effective amount of a NS5a inhibitor and an effective amount of the compounds represented by the following formula:"



EX1001 at 629:63 – 632:4. Claim 2 depends from Claim 1 and recites, "wherein the compound is":



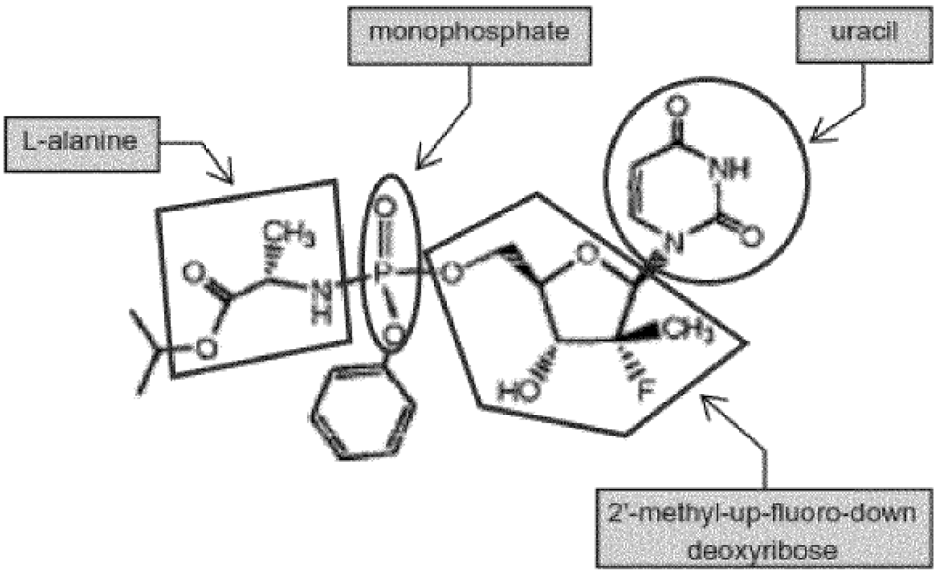
EX1001 at 632:4-21.

The compound formulas of claims 1 and 2 are 5'-phosphate (phosphoramidate) prodrugs of the uridine analog "(2'R)-2'-deoxy-2'-fluoro-2'-*C*-

methyluridine." EX1002 ¶99. In claim 1, a wide variety of phosphoramidate prodrugs are recited in the claimed method. *Id*. For claim 2, the 5'-phosphate (phosphoramidate) prodrug is specifically (phenyl)(isopropyl-L-alaninyl)phosphate. *Id*.

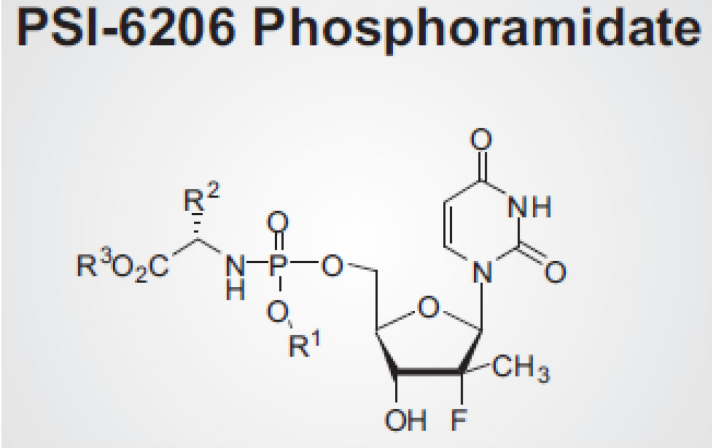
The compound of claim 2 is what was taught by Perrone as a ProTide to activate an inactive nucleoside analog against HCV. EX1002 ¶100; EX1007 at 1. Both claims 1 and 2 specify the use of a single diastereomer at phosphorous of the compounds in the claimed methods. EX1002 ¶100.

As can be seen from the formulas, the compounds of claim 1 and 2 are composed of a deoxyribose sugar, a base, and a masked phosphate group. EX1002 ¶101. 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 nitrogenous base at the conventional position via a glycoside bond. *Id*. The base is uracil. *Id*. The diagram does not specify the stereochemistry at phosphorous as a temporary convenience. This aspect of the compounds of the methods claimed is discussed further below.

Sofia taught a prodrug of β-D-2'-deoxy-2'-fluoro-2'-C-methylcytidine (PSI-6130) for the treatment of chronic hepatitis C. EX10012 at 1. In particular, Sofia taught that the triphosphate of PSI-6130 was a potent inhibitor of the HCV NS5B polymerase. *Id*. Sofia also taught that PSI-6130 was converted to its uridine metabolite (PSI-6206) via cytidine deaminase and that, "phosphoramidates of PSI-6206 [were] as much as 100X more potent than the cytidine nucleoside PSI-6130." *Id*. at n. 2. The structure of PSI-6206 phosphoramidate taught by Sofia is presented below. *Id*. at 1.



Sofia additionally taught that while PSI-6206 was not an inhibitor of HCV in the replicon assay and was not metabolized inside the cell to its monophosphate derivative, its triphosphate was a potent inhibitor of the HCV NS5B polymerase. *Id*. at 1. Sofia further taught that the monophosphate of PSI-6130 was partially metabolized to the uridine monophosphate PSI-6206, which could be converted to its triphosphate derivative. *Id*.

Sofia taught that investigating the potential for utilizing PSI-6206 as an inhibitor of HCV replication required bypassing the first phosphorylation step, which could be accomplished by the preparation of phosphoramidate derivatives at the 5'-position. *Id*. Sofia taught that such a strategy produced potent and safe inhibitors of HCV. *Id*. In Table 4, Sofia expressly taught that the uracil ProTide compound (PSI-7672) had significantly more antiviral activity (15x) than the cytosine ProTide. *Id*.

A POSA, reading Sofia, would immediately envisage the selection of both

the '372 general substituents of claim 1 and the specific substituents of claim 2 for R^1, R^2 and R^3 because of the general knowledge that phosphoramidate derivatives were useful for kinase by-pass. EX1002 ¶105. Typically, R^1 is aryl, and in particular a phenyl or para-substituted phenyl group bearing halogen or methoxy. *Id*. The substituent R^2 merely dictates the structure of the naturally occurring amino acid and R^3 is a simple alkyl group. *Id*. Indeed, the variability of R^2 in the prior art was much narrower than the full range of naturally-occurring amino acids, largely being restricted to glycine, alanine, valine, and phenylalanine (i.e., R^2 = H, CH_3, isopropyl, and benzyl). *Id*. R^3 was most often methyl, isopropyl, butyl, or benzyl in the prior art. *Id*. Thus, the variability at R^1, R^2 and R^3, when viewed through the eyes of a POSA would have been very limited. *Id*.

Moreover, a POSA would have known that certain specific combinations of R^1, R^2 and R^3 do actually exist that provide potent and safe inhibitors of HCV replication. EX1002 ¶106. While synthesizing and testing the range of compounds discussed in Sofia may take some labor, it would require only a routine amount of effort given the technology and resources available to a POSA. *Id*. A POSA would also know that this strategy was not limited by finding an inherently active nucleoside drug, but rather by finding one of potentially many acceptable combinations of R^1, R^2 and R^3 that would result in efficient intracellular delivery of the nucleoside prodrug. *Id*.

A POSA would thus know that the purpose of the phosphoramidate prodrug was to confer adequate stability and lipophilicity to deliver the nucleoside prodrug safely into the cell. EX1002 ¶107. After this delivery, the prodrug moieties were removed by known intracellular enzymes to yield the monophosphate. *Id*. Given this knowledge, the range of possible combinations for R^1, R^2, and R^3 would be further limited. *Id*.

In addition to Sofia, Congiatu taught a phosphoramidate "ProTide" approach to confer greatly enhanced potency by activating nucleosides. EX1011. Specifically, Congiatu taught that the addition of an aryloxy phosphoramidate group at the 5'-position of a nucleoside (in this case a thymidine) can confer greatly enhanced activity for a compound that otherwise had very poor anticancer activity. EX1011 at 1-3.

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

Congiatu employed the well-known ProTide strategy to prepare 13 stable phosphate-based prodrugs of the nucleoside. *Id*. at 1-2 (Scheme 1, Table 1). These

prodrugs were hydrolyzed into 5'-monophosphorylated derivatives of the nucleoside inside the cell, thereby bypassing the need for kinase-mediated monophosphorylation. *Id*.

A POSA would have been motivated to apply this phosphoramidate ProTide approach to Sofia's HCV nucleoside PSI-6206 and had a reasonable expectation of success in doing so because of both the general knowledge that nucleosides needed to be phosphorylated to be active in inhibiting HCV replication. EX1002 ¶111. As already explained in the background art, the fact that Perrone provided several examples of comparable nucleosides being triphosphorylated by its ProTide approach, this approach would have been common knowledge and the obvious approach to try. *Id*.

Congiatu further taught that nucleoside phosphoramidates are readily obtained as mixtures of diastereomers at phosphorous. EX1011 at 1-2. Congiatu also taught that the R_P and S_P diastereomers at phosphorous may be separated by chromatography and that the stereochemistry at phosphorous may be assigned by spectroscopic methods. *Id.* at 2-3

Congiatu taught in addition separation of diastereomers of nucleoside phosphoramidates. *Id*. And Congiatu taught that diastereomers of the publication had an approximately 15-fold difference in activity (0.5 micromolar vs. 7.4 micromolar). *Id*. Congiatu thus taught that the phosphorous diastereomers of

nucleoside phosphoramidates could be separated and that it would be expected they might have significantly different biologic activity. EX1002 ¶113. Thus, Congiatu taught that the separate diastereomers of phosphoramidate prodrugs must be tested to determine which diastereomer is preferred as a drug candidate. *Id*.

More specifically, Congiatu taught that a single diastereomer of a stable modified 5'-phosphate group would serve the function of increasing the activity, bioavailability and stability of a nucleoside analog, with the same mechanism and purpose of promoting intracellular delivery of a nucleoside analog and bypassing the kinase-mediated 5'-monophosphorylation. EX1011 at 2-3.

A POSA reading Sofia and Congiatu would be motivated to develop an active prodrug and would have envisaged applying the aryloxy phosphoramidate group to the (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl uridine taught in Sofia. EX1002 ¶115; EX10012 at 1; EX10011 at 1. Specifically, a POSA would envisage applying the specific, limited range of aryloxy phosphoramidate groups already know in the art as demonstrated by Perrone to activate an unactivated nucleoside for antiviral activity against hepatitis C virus. EX1002 ¶115.

The compound of claims 1 and 2 did not produce any unexpected results and the recitation of a single (presumably more active) diastereomer for such compound(s) is unsurprising. EX1002 ¶116. First, Congiatu provided the technical teaching that separation and testing of diastereomers of ProTide phosphoramidates

was important to understand their different antiviral potencies. *Id*. Second, a POSA would already know from the common knowledge that existed in the art that Perrone had identified the "*(phenyl)(isopropyl-L-alaninyl)phosphate*" group (No.15) as one of four particularly potent ProTide groups in a series of anti-HCV nucleoside analogs. *Id*.

Therefore, because Congiatu and the '372 patent employed the same theory and process, Congiatu identified the separation and testing of diastereomers at the phosphorous as necessary to understand the pattern of anti-HCV activity of a specific ProTide. EX1002 ¶117. The fact that the particular phosphoramidate group of claim 2 was already common knowledge in the art as shown by Perrone, any activity improvement achieved by the claimed compound using the same modified 5'-phosphate group would have been expected. *Id*. Indeed, that this was proven common knowledge is also proven by McGuigan 2006, whereby the 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 ¶117; EX1008 at 1, 4 (abstract and Table 1).

Therefore, even if (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl uridine is inactive, the '372 patent's claimed prodrug form does not produce unexpected results. EX1002 ¶118. Applying the well-known ProTide approach and the separation and

testing of individual diastereomers to Sofia's promising nucleoside would result in the compound claimed in claims 1 and 2. *Id*. Thus, Sofia and Congiatu, along with the common knowledge that was known in the art (*i.e.* Perrone and McGuigan 2006) render the specific compound formulas of claims 1 and 2 obvious. *Id*.

Claims 1 and 2 also include the added subject matter of combining the claimed compounds with an effective amount of an NS5A inhibitor to treat HCV.

As discussed in the background knowledge of the prior art, combining NS5B inhibiting compounds with NS5A inhibitors to treat a human infected with hepatitis C was known. EX1002 ¶120.

Not only did Sofia suggest a prodrug of β-D-2'-deoxy-2'-fluoro-2'-C-methylcytidine (PSI-6130) for the treatment of chronic HCV and the need for direct acting antivirals for use in combination with the standard of care, EX1012, Serrano-Wu taught its NS5A compounds used in combination therapy with other antiviral agents, including specifically NS5B protein. EX1013 at 3 (¶0026). Serrano-Wu also motivated such combinations therapy by teaching "improved drugs" would comprise its NS5A inhibitor compounds with HCV NS5B protein inhibitors. *Id*. at 3 (¶0026) and 14 (¶0212).

Accordingly, Sofia, Congiatu and Serrano-Wu rendered claims 1 and 2 as obvious**.** EX1002 ¶123.

XI. CONCLUSION

For these reasons, claims 1 and 2 of the ’372 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 9, 2017

/Daniel B. Ravicher/

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XII. APPENDIX – LIST OF EXHIBITS

Exhibit No.	Description
1001	U.S. Patent No. 8,735,372
1002	Declaration of Joseph M. Fortunak, Ph.D.
1003	Wagner
1004	Clark ‘147
1005	Prusoff
1006	Ma
1007	Perrone
1008	McGuigan 2006
1009	McGuigan 1994
1010	Cahard
1011	Congiatu
1012	Sofia
1013	Serrano-Wu

XIII. CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. §42.24(d), the undersigned certifies that this Petition complies with the type-volume limitation of 37 C.F.R. §42.24(a). The word count application of the word processing program used to prepare this Petition indicates that the Petition contains 8,488 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a).

Respectfully,

Dated: November 9, 2017

/Daniel B. Ravicher/
Daniel B. Ravicher, Lead Counsel
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XIV. CERTIFICATE OF SERVICE

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

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

Respectfully,

Dated: November 9, 2017

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