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. IPR2018-00211
U.S. Patent No. 9,393,256

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 1-4 of United States Patent No. 9,393,256 to Ray et al. ("the '256 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 '256 patent issued on July 19, 2016, and is currently assigned to Gilead Pharmasset LLC ("Patent Owner"). This petition demonstrates that claims 1-4 are unpatentable.

The '256 patent claims methods that were anticipated by and obvious in light of the prior art. Specifically, the '256 claims methods of treating hepatitis C virus ("HCV") infection with a combination of two compounds, but both compounds were known as a result of being previously published and combining the two compounds was also known as a preferred method for treating HCV.

Thus, claims 1-4 of the '256 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))

U.S. Patent Application No. 15/400,088 is pending and claims priority to the application that issued as the ‘256 patent. 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 ’256 patent is available for *inter partes* review and that Petitioner is not barred or estopped from requesting the *inter partes* review

sought herein. The required fee is being paid through the Patent Trial and Appeal Board End to End System. The Office is authorized to charge fee deficiencies and credit overpayments to Deposit Account No. 601986.

B. Identification of Challenge

Petitioner respectfully requests cancellation of claims 1 – 4 of the ’256 patent based on the following ground:

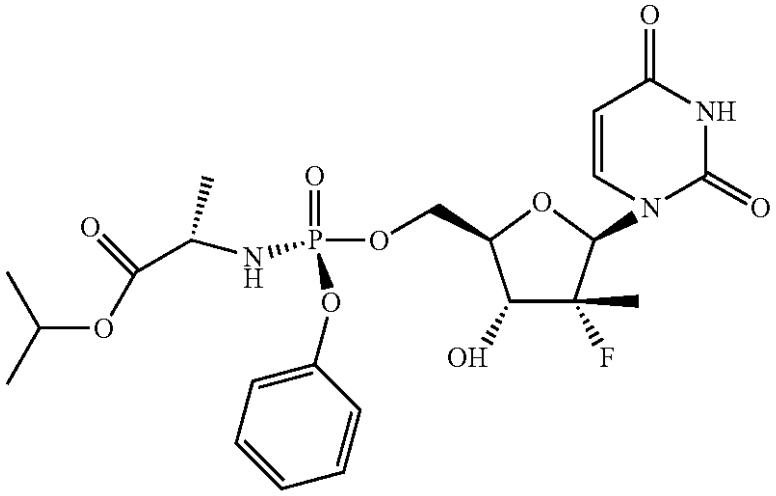
#	Claims	35 U.S.C. §	Prior Art
1	1 – 4	102 and 103	Legrand- Abravanel
2	1 – 4	102	Delaney
3	1 – 4	103	Sofia ‘634 and Guo

This Petition is supported by the declaration of Joseph M. Fortunak, Ph.D. EX1012. 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.

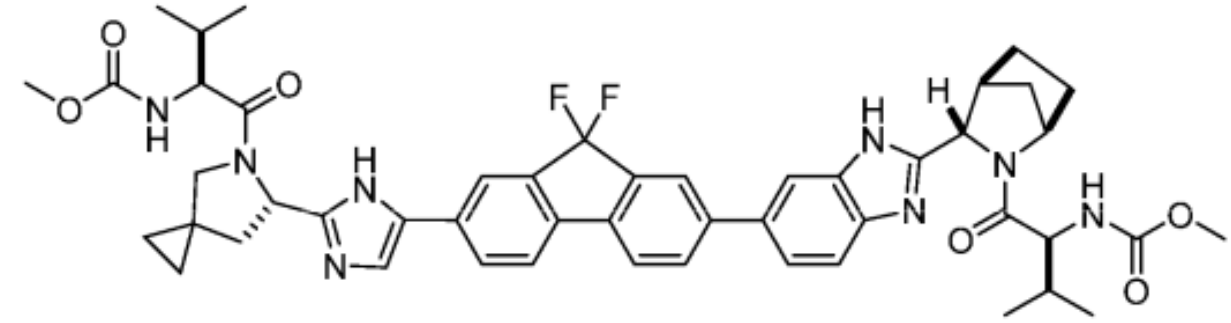
The Petition and its supporting materials, which are listed in the Appendix, establish a reasonable likelihood that Petitioner will prevail with respect to cancellation of the challenged claims. See 35 U.S.C. § 314(a).

IV. OVERVIEW OF THE ’256 PATENT

The ’256 patent relates to compositions and therapeutic methods that are useful for treating hepatitis C virus (HCV) infection. Various compositions comprising two or more compounds are disclosed in ’256. Specifically the ’256 patent claims a method of treating HCV by administering the following compounds to a human, either with or without ribavirin, but not including an interferon:



Compound 10



Compound 6

EX1001 at 79 (139:12-26) and 95.

The following chart describes the ’256 patent’s 4 claims:

Claim(s)	Recite
1, 2	A method of treating an HCV infection comprising administering orally to a human Compound 10 and Compound 6, wherein the method does not include administering interferon.
3, 4	The method of claim 1 wherein ribavirin either is or is not administered.

V. FILE HISTORY OF THE ’256 PATENT

U.S. Patent Application No. 13/875,252 (“the ’252 application”), filed on May 1, 2013, issued as the ’256 patent on July 19, 2016. EX1001 at 1. The ’252 application is a continuation of international application PCT/US2012/055621 filed on September 14, 2012, which claimed the benefit of two provisional applications, Provisional Application No. 61/535,885 filed on September 16, 2011, and Provisional Application No. 61/561,753 filed on November, 18, 2011. *Id.*

During prosecution of the ’252 application, the Examiner allowed the currently granted claims without making any substantive prior-art based rejections. EX1012 ¶27.

VI. PERSON OF ORDINARY SKILL IN THE ART

Because the ’256 patent pertains to compounds (namely a nucleos(t)ide NS5B polymerase inhibitor and an NS5A inhibitor) useful for treating viral infections such as HCV, 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. EX1012 ¶34.

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 ’256 patent provides definitions for certain claim terms, but these definitions are conventional. EX1012 ¶36. Thus, there is no reason to give any of the terms of the claims of the ’256 a meaning other than their ordinary and accustomed meaning. EX1012 ¶36.

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 September 16, 2011.

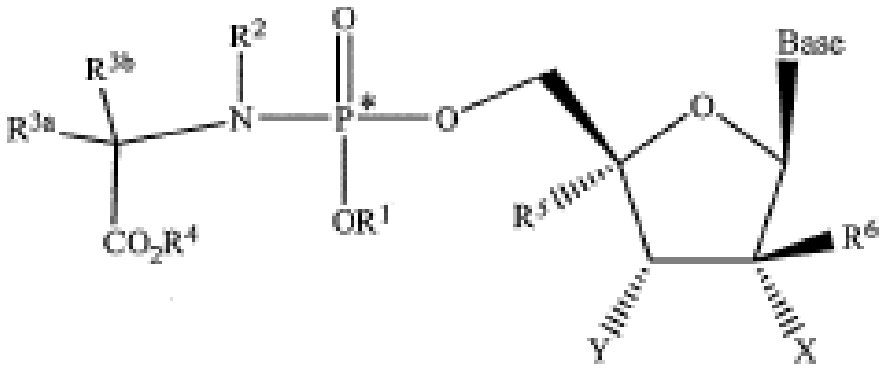
A. Nucleos(t)ide NS5B Polymerase Inhibitors PSI-7851 and PSI-7977 (Compound 10 in ’256) for Treating HCV Were Known

WO 2005/003147 to Clark (“Clark”; EX1002) taught modified fluorinated nucleoside analogs. EX1012 ¶38. More specifically, Clark taught (2’R)-2’-deoxy-

2’-fluoro-2’-C-methyl nucleosides, their pharmaceutically acceptable salt forms and prodrugs. *Id*.; EX1002 at 18:3-17. Clark taught that these compounds could be used to treat *Flaviviridae* viruses, including HCV infections. *Id.*; EX1002 at 1 (Abstract).

It was well known that, to interact with HCV NS5B polymerase, anti-viral nucleosides must generally first be converted into their triphosphate form. EX1012 ¶39. 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”; EX1003), 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.” *Id.*; EX1003 at 2.

WO 2008/121634 to Sofia et al. (“Sofia ‘634”; EX1004) disclosed specific phosphoramidate prodrugs of nucleoside derivatives claimed in Clark, which are useful for the treatment of viral infections, including HCV. EX1012 ¶40. The phosphoramidate prodrugs disclosed in Sofia ‘634 also included their stereoisomers, salts (acid or basic addition salts), hydrates, solvates or crystalline forms as represented by the following structure:



I

Id.; EX1004 at 10.

While Sofia ‘634 disclosed and claimed many compounds within the formula, it specifically disclosed Compound 10 as claimed in the ’256 patent. EX1012 ¶41. In particular, Sofia ’634 disclosed and claimed the molecule shown in Table IX-25 as compound IX-25-2. *Id.*; EX1004 at 255. This molecule was further disclosed as having been prepared and characterized, as example compound 25. EX1012 ¶41; EX1004 at 684. Compound 25 is further disclosed as one of 19 compounds for which antiviral testing results are revealed. EX1012 ¶41; EX1004 at 696. This compound is further disclosed in claim 2. EX1012 ¶41; EX1004 at 703:48-50. This compound is also known as PSI-7851 and “(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”, also known as PSI-7977 or GS-7977. EX1012 ¶41. Indeed, this is confirmed in the ’256 patent where U.S Patent No.7,964,580 (which

corresponds to Sofia ’634) is incorporated by reference. EX1001 at 13 (8:42); EX1012 ¶41.

B. Nucleos(t)ide NS5B Polymerase Inhibitors Were Combined With Other Antiviral Agents, Including NS5A Inhibitors, To Treat HCV

It was widely known that monotherapy with a direct acting antiviral polymerase inhibitors such as a nucleos(t)ide NS5B polymerase inhibitor was limited because of resistance mutations of HCV to nucleos(t)ide analogs. EX1012 ¶42; Legrand-Abravanel et al. “*New NS5B Polymerase Inhibitors for Hepatitis C,* Expert Opinion on Investigational Drugs,” 2010, 19(8): 963-75 (“Legrand-Abravanel”; EX1005) at 7. Therefore, it was recognized in the field that combination therapy with small molecule inhibitors such as NS5A inhibitors without interferon was the optimal standard of care. EX1012 ¶42; EX1005 at 9.

Clark taught that its nucleoside NS5B polymerase inhibitors 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. EX1012 ¶43. For example, Clark taught:

> *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.

EX1002 at 62:7 – 63:26 (emphasis added); EX1012 ¶43.

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. EX1003 at 1; EX1012 ¶44.

Sofia et al, "*β-D-2'-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 2007"; EX1006) 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. EX1012 ¶45.

Sofia '634 taught that the nucleotide NS5B polymerase inhibitors disclosed and claimed therein, including PSI-7851 and PSI-7977 (Compound 10 in the '256 patent) could be directed to a method of treatment in combination with another antiviral agent, wherein the administration is concurrent or alternative. EX1012 ¶46. Sofia '634 further suggested examples of "another antiviral agent" to include NS5A inhibitors. *Id*. Sofia '634 also provided:

> It is contemplated that another antiviral agent includes, but is not limited to interferon-α, interferon-β, pegylated interferon-α, ribavirin, levovirin, viramidine, another nucleoside HCV polymerase inhibitor, a HCV non-nucleoside polymerase inhibitor, a HCV protease inhibitor, a HCV helicase inhibitor or a HCV fusion inhibitor. *When the active compound or its derivative or salt are administered in combination with another antiviral agent the activity may be increased over the parent compound*. When the

> treatment is combination therapy, such administration may be concurrent or sequential with respect to the nucleoside derivatives. *"Concurrent administration" as used herein thus includes administration of the agents at the same time or different times. Administration of two or more agents at the same time can be achieved by a single formulation containing two or more active ingredients* or by substantially simultaneous administration of two or more dosage forms with a single active agent.

EX1004 at 668:24 – 669:8 (emphasis added); EX1012 ¶46.

U.S. Pub. No. 2006/0276511 to Serrano-Wu et al. ("Serrano-Wu"; EX1007) taught some of the early NS5A inhibitor compounds designed to inhibit the function of HCV NS5A protein. EX1012 ¶47. 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 Compound 10 in '256. EX1007 at 3 (¶0026); EX1012 ¶47.

WO2006/100310 to Simmen et al. ("Simmen"; EX1008) taught the NS5A inhibitors disclosed therein could be co-administered in combination with small molecule antagonists such as NS5B polymerase antagonists to treat HCV infections. EX1008 at 28:1-28; EX1012 ¶48.

Pockros *"New Direct-Acting Antivirals in the Development for Hepatitis C Virus Infection"*, Therapeutic Advances in Gastroenterology, May 2010, 3(3) 191-202 ("Pockros"; EX1009), taught that the compound BMS-790052 (daclatasvir), a first-in-class potent HCV NS5A inhibitor, was additive/synergistic with protease

and polymerase inhibitors (*i.e. nucleos(t)ide NS5B polymerase inhibitors*) in the replicon model and which may eventually be used in combination with protease and/or polymerase inhibitors. EX1009 at 8; EX1012 ¶49.

IX. SCOPE AND CONTENT OF THE PRIOR ART

The following prior art references, alone or in combination with each other, teach or suggest the methods recited in claims 1-4 of the '256 patent. EX1012 ¶50.

A. Legrand-Abravanel et al. *New NS5B Polymerase Inhibitors for Hepatitis C*, Expert Opinion on Investigational Drugs, 2010, 19(8): 963-75 ("Legrand-Abravanel"; EX1005)

Legrand-Abravanel was published online on July 15, 2010. See http://www.tandfonline.com/doi/full/10.1517/13543784.2010.500285. Therefore, it is prior art to the '256 patent under 35 U.S.C. § 102(b) because it was published more than one year before the filing of the earliest application to which the '256 patent claims priority.

Legrand-Abravanel taught that NS5B polymerase inhibitors will form an integral part of more effective anti-HCV therapy, in combination with interferon *or* with other directly acting antiviral agents. EX1005 at 1; EX1012 ¶52.

Legrand-Abravanel also highlighted that nucleos(t)ide inhibitors PS-7851 and PSI-7977 (Compound 10 in the '256 patent) had been selected for further clinical development. EX1005 at 4-5; EX1012 ¶53.

However, due to the resistant mutations of HCV to nucleos(tide) analogues,

Legrand-Abravanel taught that combination therapy with small molecule inhibitors and without IFN (interferon) was the ultimate goal and should be studied early with innovative drug development approaches. EX1012 ¶54. Legrand-Abravanel further suggested that several new antiviral compounds were in development and could be associated with polymerase inhibitors, including NS5A inhibitors. EX1005 at 9; EX1012 ¶54.

B. US Pub No. 2011/0306541 to Delaney ("Delaney"; EX1010)

Delaney is a U.S. Patent Application Publication of an application that was filed on June 10, 2011, and that claims priority to a provisional application filed on June 10, 2010. EX1010 at 1. Therefore, it is prior art to the '256 patent under 35 U.S.C. § 102(e) because it is a published patent application that was filed before the earliest application to which the '256 patent claims priority.

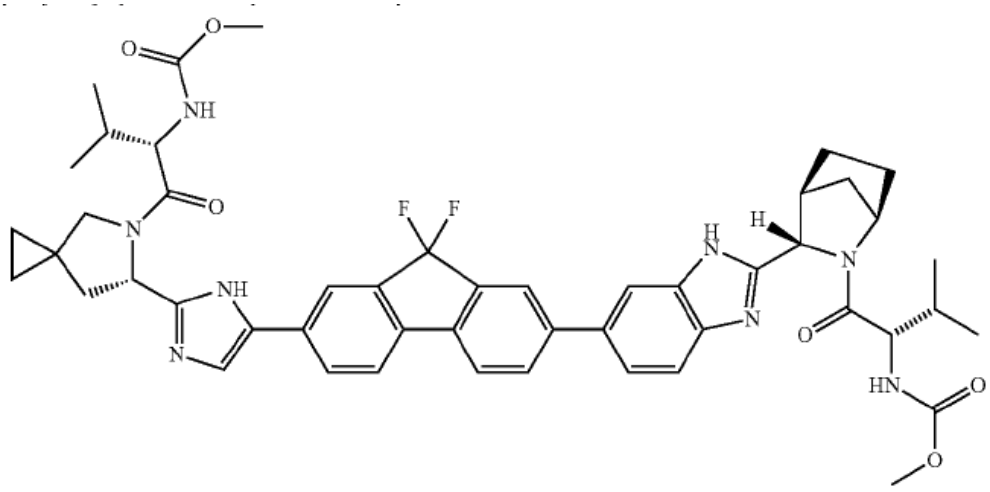
Delaney taught a dosing regimen for the treatment of HCV comprising the administering of one or more anti-HCV compounds or a pharmaceutically acceptable salts thereof and ribavirin, but not one or more interferon. EX1010 at 3 (¶0012); EX1012 ¶56.

Delaney also taught pharmaceutical formulations and routes of administration for the described dosing regimens, including oral administration. EX1010 at 6 – 8 (¶¶ 0044 – 0073); EX1012 ¶57.

Delaney further taught non-limited examples of suitable combinations

included combinations of one or more compounds with one or more additional therapeutic [sic] for HCV treatment including nucleos(t)ide inhibitors of HCV NS5B polymerase and NS5A inhibitors. EX1012 ¶58. Delaney specifically taught that one or more of its compounds may be combined with one or more compounds selected from a group including the nucleos(t)ide inhibitors of HCV NS5B polymerase, PSI-7851 and PSI-7977 (Compound 10 in the ’256 patent). EX1010 at 8 – 9 (¶¶ 0074-75); EX1012 ¶58.

Notably one of the compounds taught in Delaney that could be combined with PSI-7851 or PSI-7977 is GS-5885 (now known as ledispasvir), Example 16, Compound 16 as shown below.



(1-{3-[6-(9,9-Difluoro-7-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-9H-fluoren-2-yl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

EX1010 at 47 – 49 (¶218) and 55 (Table 1); EX1012 ¶59. Indeed, Compound 16 in Delaney is the same compound as Compound 6 claimed in claim 1 of the ’256 patent. EX1012 ¶59.

C. WO 2008/121634 to Sofia ("Sofia '634"; EX1004)

Sofia '634 was published on October 9, 2008. Therefore, it is prior art to the '256 patent under 35 U.S.C. 102(b) because it was published more than year before the filing of the earliest application to which the '256 patent claims priority.

Sofia '634 taught that the nucleotide NS5B polymerase inhibitors disclosed and claimed therein, including PSI-7851 and PSI-7977 (Compound 10 in the '256 patent) could be directed to a method of treatment in combination with another antiviral agent, wherein the administration is concurrent or alternative. EX1012 ¶61. Sofia '634 further suggested examples of "another antiviral agents" to include NS5A inhibitors. EX1004 at 667:8 – 669:8; EX1012 ¶61.

Sofia '634 further taught that when the active compound or its derivative or salt are administered in combination with another antiviral agent the activity may be increased over the parent compound. EX1012 ¶62. Sofia '634 also taught that when the treatment is combination therapy, it included administration of the agents at the same time and which could be achieved by a single formulation containing two or more ingredients. EX1004 at 667:8-669:8; EX1012 ¶62.

D. WO 2010/132601 to Guo ("Guo"; EX1011)

Guo was published on November 18, 2010. Therefore, it is prior art to the '256 patent because it was published before the filing of the earliest application to which the '256 patent claims priority.

Guo taught NS5A inhibitor compounds, including GS-5885 (now called ledipasvir), which is Compound 6 as claimed in the ’256 patent. EX1011 at 673 and 984; EX1012 ¶64.

Guo also taught that compounds of the invention, including GS-5885 (ledipasvir) could be combined with nucleos(t)ide inhibitors of HCV NS5B polymerase such as PSI-6130, a compound taught in Clark, as well as interferons and ribavirin. EX1011 at 31; EX1012 ¶65.

X. CLAIMS 1-4 ARE UNPATENTABLE

Each and every feature of claims 1-4 of the ’256 patent can be found in the prior art references identified below. EX1012 ¶66. In addition, a POSA would have been motivated to modify the references as discussed below and had a reasonable expectation of success of arriving at the claims of the ’256 patent. *Id*.

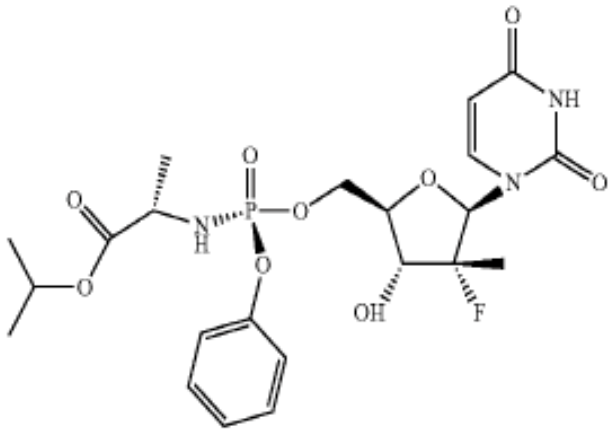
Each of claims 1-4 is presented below, followed by an analysis of the claims. The analysis below identifies exemplary disclosure of the cited references respective to the corresponding claim elements, and is not meant to be exhaustive.

A. Ground 1: Claims 1-4 Were Anticipated By And Obvious Over Legrand-Abravanel

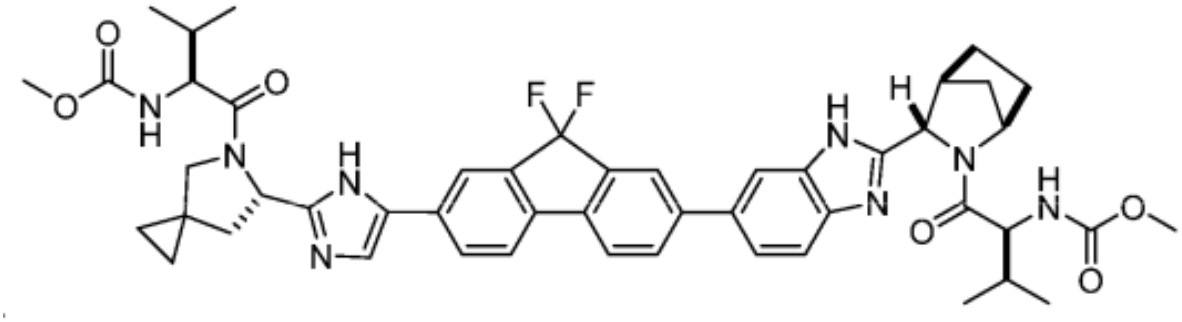
All of the claims of the ’256 patent were anticipated by Legrand-Abravanel. EX1012 ¶68. Claims 1-4 were also obvious over Legrand-Abravanel because a POSA would have been motivated to take the teachings in Legrand-Abravanel and arrive at the combination of anti-viral agents for treating HCV claimed in the ’256

patent. *Id*.

Claim 1 of the ‘256 patent recites “[a] method of treating an HCV infection in a human, comprising administering to the human: 1) compound 10 having the structure:



or a pharmaceutically acceptable salt thereof and 2) compound 6 having the structure:



or a pharmaceutically acceptable salt thereof, wherein the method does not include administering interferon.” EX1001 at 79 and 95.

Claims 2, 3 and 4 cover the method of claim 1, “wherein compound 10 and

compound 6 are administered orally" (claim 2); "wherein ribavirin is not administered to the human" (claim 3); and "further comprising administering ribavirin to the human" (claim 4). EX1001 at 79 and 95.

As set out in the background knowledge above, Compound 10, a nucleotide inhibitor of NS5B polymerase was already known. EX1012 ¶71. Indeed, the '256 patent states U.S Patent No.7,964,580 (which corresponds to Sofia '634) is incorporated by reference. EX1001 at 13 (8:42-46). Legrand-Abravanel also discloses Compound 10 when referring to the compound names PSI-7851 and PSI-7977. EX1005 at 3-5; EX1012 ¶71. Ribavirin and interferon were also known and formed part of the combination therapy for treating HCV at the time the parent applications to the '256 patent was filed. EX1012 ¶71. Furthermore, NS5A inhibitors (the class of compound which Compound 6 falls within) were also known to be useful for treating HCV in combination with other antiviral agents such as nucleotide inhibitors of NS5B polymerase. See Serrano-Wu (EX1007), Simmen (EX1008) and Pockros (EX1009); EX1012 ¶71.

Legrand-Abravanel taught that NS5B polymerase inhibitors will form an integral part of more effective anti-HCV therapy, in combination with interferon *or* with other directly acting antiviral agents. EX1005 at 1; EX1012 ¶72.

Legrand-Abravanel also highlighted that nucleos(t)ide inhibitors PS-7851 and PSI-7977 (Compound 10 in the '256 patent) had been selected for further

clinical development. EX1005 at 4-5; EX1012 ¶73.

However, due to the resistant mutations of HCV to nucleos(tide) analogues, Legrand-Abravanel taught that combination therapy with small molecule inhibitors and without IFN (interferon) was the ultimate goal and should be studied early with innovative drug development approaches. EX1012 ¶74. Legrand-Abravanel further suggested that several new antiviral compounds were in development and could be associated with polymerase inhibitors, including NS5A inhibitors. EX1005 at 9; EX1012 ¶74.

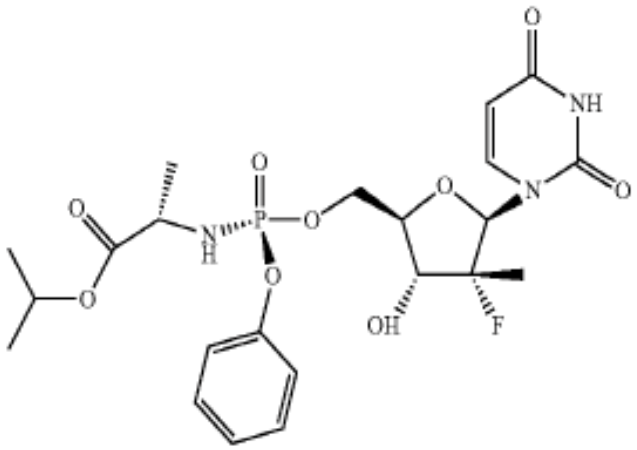
Taking into account the background knowledge in the art and the teachings of Legrand-Abravanel, claims 1-4 of ’256 were anticipated and obvious. EX1012 ¶75. In particular, Legrand-Abravanel taught, or at least suggested, combination therapies to treat HCV without administering interferon, and which may or may not include ribavirin. *Id*. Moreover, Legrand-Abravanel inherently taught the combination of NS5A inhibitors, such as Compound 6, with polymerase inhibitors such as Compound 10. *Id*. Legrand-Abravanel, therefore, anticipated claims 1-4 of the ’256 patent, or at minimum rendered them obvious. *Id*.

B. Ground 2: Claims 1-4 Were Anticipated By Delaney

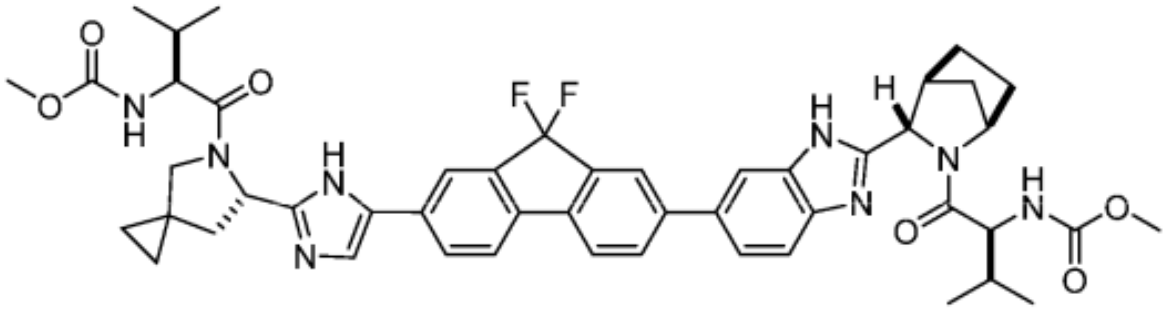
All of the claims of the ’256 patent were anticipated by Delaney. EX1012 ¶76.

Claim 1 of the ‘256 patent recites “[a] method of treating an HCV infection

in a human, comprising administering to the human: 1) compound 10 having the structure:



or a pharmaceutically acceptable salt thereof and 2) compound 6 having the structure:



or a pharmaceutically acceptable salt thereof, wherein the method does not include administering interferon." EX1001 at 79 and 95.

Claims 2, 3 and 4 cover the method of claim 1, "wherein compound 10 and compound 6 are administered orally" (claim 2); "wherein ribavirin is not administered to the human" (claim 3); and "further comprising administering

ribavirin to the human" (claim 4). EX1001 at 79 and 95.

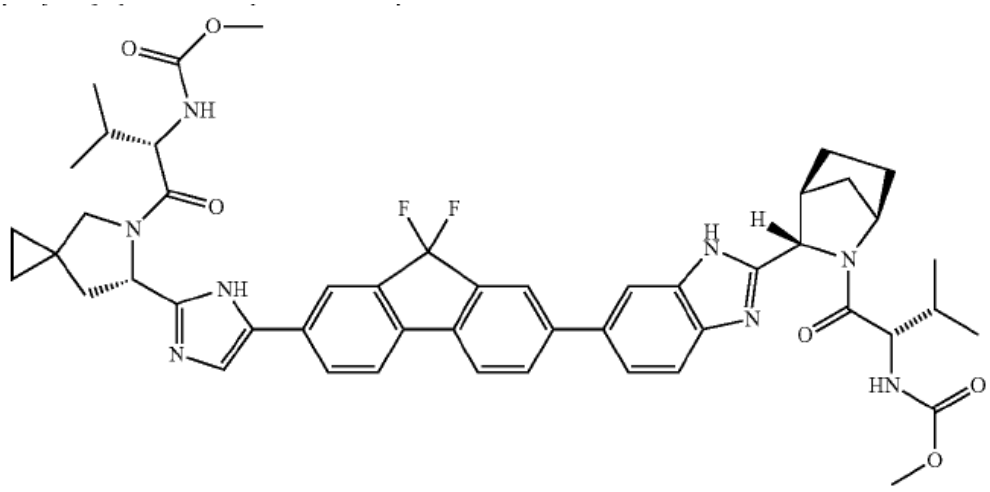
As set out in the background knowledge above, Compound 10, a nucleotide inhibitor of NS5B polymerase was already known. EX1012 ¶71. Indeed, the '256 patent states U.S Patent No.7,964,580 (which corresponds to Sofia '634) is incorporated by reference. EX1001 at 13 (8:42-46). Legrand-Abravanel also discloses Compound 10 when referring to the compound names PSI-7851 and PSI-7977. EX1005 at 3-5; EX1012 ¶79. Ribavirin and interferon were also known and formed part of the combination therapy for treating HCV at the time the parent applications to the '256 patent was filed. EX1012 ¶79. Furthermore, NS5A inhibitors (the class of compound which Compound 6 falls within) were also known to be useful for treating HCV in combination with other antiviral agents such as nucleotide inhibitors of NS5B polymerase. See Serrano-Wu (EX1007), Simmen (EX1008) and Pockros (EX1009); EX1012 ¶79.

Delaney taught a dosing regimen for the treatment of HCV comprising the administering of one or more anti-HCV compounds or a pharmaceutically acceptable salt thereof and ribavirin, but not one or more interferon. EX1010 at 3 (¶0012); EX1012 ¶80.

Delaney also taught pharmaceutical formulations and routes of administration for the described dosing regimens, including oral administration. EX1010 at 6 – 8 (¶¶ 0044 – 0073); EX1012 ¶81.

Delaney further taught non-limited examples of suitable combinations included combinations of one or more compounds with one or more additional therapeutic [sic] for HCV treatment including nucleos(t)ide inhibitors of HCV NS5B polymerase and NS5A inhibitors. EX1012 ¶82. Delaney specifically taught that one or more of its compounds may be combined with one or more compounds selected from a group including the nucleos(t)ide inhibitors of HCV NS5B polymerase, PSI-7851 and PSI-7977 (Compound 10 in '256). EX1010 at 8 – 9 (¶¶ 0074-75); EX1012 ¶82.

Notably one of the compounds taught in Delaney that could be combined with PSI-7851 or PSI-7977 is GS-5885 (now known as ledispasvir), Example 16, Compound 16 as shown below.



(1-{3-[6-(9,9-Difluoro-7-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-9H-fluoren-2-yl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

EX1010 at 47 – 49 (¶218) and 55 (Table 1); EX1012 ¶83. Indeed, Compound 16 in Delaney is the same compound as Compound 6 claimed in claim 1 of the '256

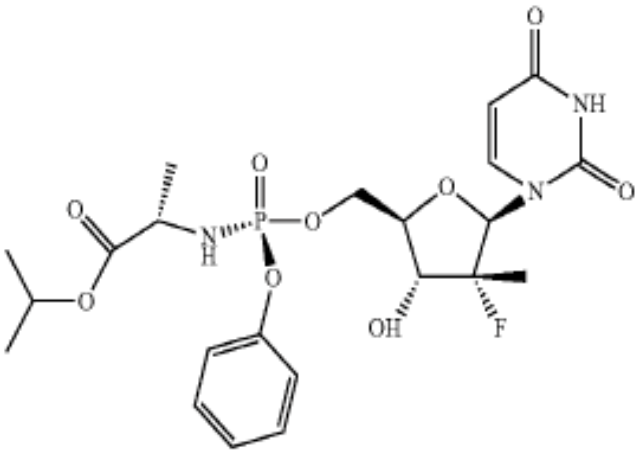
patent. EX1012 ¶83.

Delaney thus taught the combination of Compound 10 with Compound 6 wherein the dosage regimen for the method of treatment of HCV did not include interferon, but could include the administration of ribavirin. EX1012 ¶84. Delaney further taught non-limited examples of suitable combinations included combinations of one or more compounds with one or more additional therapeutic [agents] for HCV treatment including nucleos(t)ide inhibitors of HCV NS5B polymerase and NS5A inhibitors, but which implicitly could exclude ribavirin. *Id*. Therefore, Delaney anticipated claims 1-4 of the ’256 patent. *Id*.

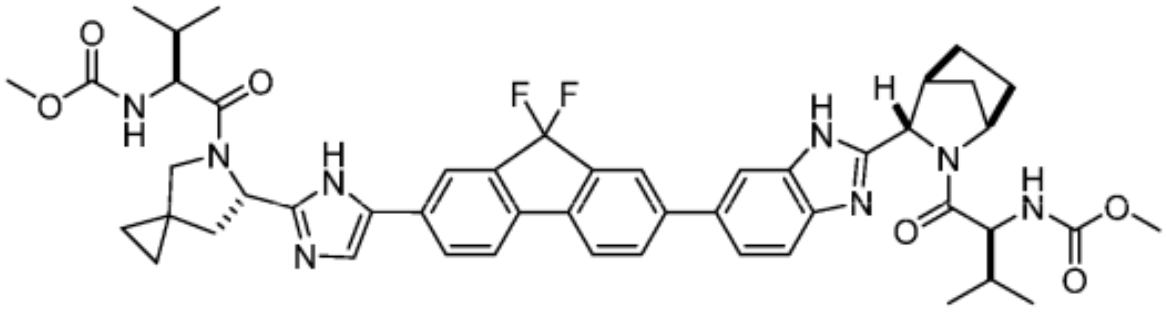
C. Ground 3: Claims 1-4 Were Obvious Over Sofia ‘634 and Guo

All of the claims of the ’256 patent were obvious over Sofia ‘634 and Guo. EX1012 ¶85. One of ordinary skill in the art would have been motivated by the background knowledge in the art to combine their teachings because they covered nucleos(t)ide inhibitors of HCV NS5B polymerase and NS5A inhibitors useful for treating HCV. *Id*.

Claim 1 of the ‘256 patent recites “[a] method of treating an HCV infection in a human, comprising administering to the human: 1) compound 10 having the structure:



or a pharmaceutically acceptable salt thereof and 2) compound 6 having the structure:



or a pharmaceutically acceptable salt thereof, wherein the method does not include administering interferon." EX1001 at 79 and 95.

Claims 2, 3 and 4 cover the method of claim 1, "wherein compound 10 and compound 6 are administered orally" (claim 2); "wherein ribavirin is not administered to the human" (claim 3); and "further comprising administering ribavirin to the human" (claim 4). EX1001 at 79 and 95.

As set out in the background knowledge above, Compound 10, a nucleotide

inhibitor of NS5B polymerase was already known. EX1012 ¶88. Indeed, the ’256 patent states U.S Patent No.7,964,580 (which corresponds to Sofia ’634) is incorporated by reference. EX1001 at 13 (8:42-46). Legrand-Abravanel also discloses Compound 10 when referring to the compound names PSI-7851 and PSI-7977. EX1005 at 3-5; EX1012 ¶88. Ribavirin and interferon were also known and formed part of the combination therapy for treating HCV at the time the parent applications to the ’256 patent was filed. EX1012 ¶88. Furthermore, NS5A inhibitors (the class of compound which Compound 6 falls within) were also known to be useful for treating HCV in combination with other antiviral agents such as nucleotide inhibitors of NS5B polymerase. See Serrano-Wu (EX1007), Simmen (EX1008) and Pockros (EX1009); EX1012 ¶88.

Sofia ’634 taught that the nucleotide NS5B polymerase inhibitors disclosed and claimed therein, including PSI-7851 and PSI-7977 (Compound 10 in the ’256 patent) could be directed to a method of treatment in combination with another antiviral agent, wherein the administration is concurrent or alternative. EX1012 ¶89. Sofia ’634 further suggested examples of “another antiviral agents” to include NS5A inhibitors. EX1004 at 667:8 – 669:8; EX1012 ¶89.

Sofia ’634 further taught that when the active compound or its derivative or salt are administered in combination with another antiviral agent the activity may be increased over the parent compound. EX1012 ¶90. Sofia ’634 also taught that

when the treatment is combination therapy, it included administration of the agents at the same time and which could be achieved by a single formulation containing two or more ingredients. EX1004 at 667:8-669:8; EX1012 ¶90.

Guo taught NS5A inhibitor compounds, including GS-5885 (now called ledipasvir), which is Compound 6 as claimed in the ’256 patent. EX1011 at 673 and 984; EX1012 ¶91.

Guo also taught that compounds of the invention, including GS-5885 (ledipasvir) could be combined with nucleos(t)ide inhibitors of HCV NS5B polymerase such as PSI-6130, a compound taught in Clark, as well as interferons and ribavirin. EX1011 at 31; EX1012 ¶92.

Both Sofia ‘634 and Guo taught pharmaceutical formulations of their respective claimed compounds and how they could be administered orally. EX1004 at 661 and EX1011 at 23-24; EX1012 ¶93.

A POSA would have been motivated by the teachings of Sofia ’634 and Guo, along with the existing background knowledge in the art, to combine the respective compounds claimed therein for treating HCV. EX1012 ¶94. A POSA would have also been motivated to test such compound combinations with or without an interferon and ribavirin for the purpose of assessing antiviral effectiveness and any viral resistance. *Id*. Accordingly, given the extensive knowledge in the art around direct-acting antiviral compounds for treating HCV,

and the teachings of Sofia ’634 and Guo, it would have been obvious to a POSA to arrive at claims 1-4 of the ’256 patent. *Id*. Therefore, Sofia ’634 and Guo rendered claims 1-4 of the ’256 patent obvious. *Id*.

XI. CONCLUSION

For these reasons, claims 1 – 4 of the ’256 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: December 6, 2017

/Daniel B. Ravicher/

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Counsel for Petitioner

XII. APPENDIX – LIST OF EXHIBITS

Exhibit No.	Description
1001	U.S Patent No. 9,393,256
1002	Clark
1003	Ma
1004	Sofia ’634
1005	Legrand-Abravanel
1006	Sofia 2007
1007	Serrano-Wu
1008	Simmen
1009	Pockros
1010	Delaney
1011	Guo
1012	Declaration of Joseph M. Fortunak, Ph.D.

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 4,980 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a).

Respectfully,

Dated: December 6, 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 1001-1012 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: December 6, 2017

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