

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

GILEAD PHARMASSET LLC  
Patent Owner

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Case No. IPR2018-00390  
U.S. Patent No. 8,889,159

**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 1-37 of United States Patent No. 8,889,159 to Cleary et al. (“the ‘159 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 ‘159 patent issued on November 18, 2014, and is currently assigned to Gilead Pharmasset LLC (“Patent Owner”). This petition demonstrates that claims 1-37 are unpatentable.

The ‘159 patent claims a composition and unit dosage forms for the treatment of hepatitis C virus (“HCV”) infection that were anticipated by and obvious in light of the prior art. Specifically, the ‘159 claims compositions and unit dosage forms comprising GS-7977, a known crystalline form of a known anti-HCV drug, and at least one excipient, but such compositions and unit dosage forms were known as a result of the previous disclosure of the crystalline form of the drug. Thus, claims 1-37 of the ‘159 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. 15/410,438 is pending and claims priority to an application that claims priority to the '159 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 '159 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 1–37 of the '159 patent on the following grounds:

#	Claims	35 U.S.C. §	Prior Art
1	1 – 37	102	Ross '645
2	1 – 37	103	Ross '645
3	1 – 37	102	Ross '237
4	1 – 37	103	Ross '237

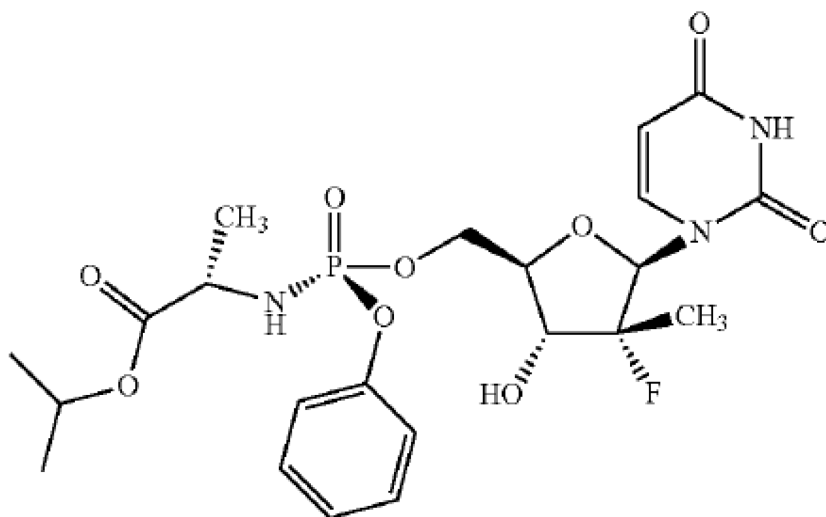
This Petition is supported by the declaration of Joseph M. Fortunak, Ph.D. EX1014. Dr. Fortunak is well qualified as an expert, possessing the necessary scientific, technical, and other specialized knowledge and training to assist in an understanding of the evidence presented herein, as well as possessing 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 '159 PATENT

The '159 patent relates to a composition and unit dosage form for the treatment of hepatitis C virus (HCV) infection comprising GS-7977 and at least one pharmaceutically acceptable excipient. The '159 patent also covers methods for making the composition and unit dosage form disclosed therein and a method of treatment comprising administering to (preferably) a human subject an effective amount of GS-7977 and an effective amount of ribavirin for a period of time. One aspect of the method of treatment covered in the '159 patent is an interferon-free treatment regimen. EX1001 at 1:14-28.

More specifically, the '159 patent relates to a composition comprising a crystalline form of the compound GS-7977 (also known as PSI-7977), which has the following molecular structure:



EX1001 at 46:37-52. The crystalline form covered by the '159 patent has X-ray



powder diffraction (XRPD) 2θ-reflections at about 6.1 and 12.7 (°). EX1001 at 46:56. The patent also discloses that the crystalline form of GS-7977 possesses a more complete set of 2θ-reflections at about: 6.1, 8.2, 10.4, 12.7, 17.2, 17.7, 18.0, 18.8, 19.4, 19.8, 20.1, 20.8, 21.8, and 23.3 (°). EX1001 at 46:57-60.

The pharmaceutical composition claimed by the '159 patent contains about 25%-35% by weight of crystalline GS-7977. EX1001 at 46:36-37. The pharmaceutical composition also contains at least one pharmaceutically acceptable excipient that is a diluent, disintegrant, glidant, or lubricant. EX1001 at 46:61-63. The patent further claims several choices of each type of excipient, and various amounts of each excipient contained in the pharmaceutical composition. EX1001 at 46:64-48:61.

The '159 patent also discloses a unit dosage form containing about 400 mg of crystalline GS-7977. EX1001 at 47:51-52.

The following chart describes the '159 patent's 37 claims:

Claim(s)	Recite
1-2	A pharmaceutical composition comprising about 25%-35% by weight of crystalline GS-7977 and at least one excipient.
3-12	The composition of claim 1 where at least one pharmaceutical excipient comprises a diluent, a disintegrant, a glidant and a lubricant, including various excipient options for selection.
13-15	The composition of claim 1 wherein the at least one excipient comprises various weight percentages for each excipient.
16-17	A unit dosage form containing about 400 mg of crystalline GS-7977

	and at least one excipient
18-27	The composition of claim 17 where at least one pharmaceutical excipient comprises a diluent, a disintegrant, a glidant and a lubricant, including various excipient options for selection.
28-29	The composition of claim 17 wherein the at least one excipient comprises a weight range for each excipient.
30	The unit dosage form of claim 17 comprising a capsule or tablet.
31-32	A process for preparing a tablet composition comprising the unit dosage form of claim 28.
33-37	A method of treating HCV in a human by administering the composition of claim 1, including in combination with ribavirin as part of an interferon-free regimen.

## V. FILE HISTORY OF THE '159 PATENT

U.S. Patent Application No. 13/686,664 (“the ’664 application”), filed on November 27, 2012, issued as the ’159 patent on November 18, 2014. The ’664 application claimed priority as a continuation-in-part of application No. PCT/US2012/055621, filed on Sep. 14, 2012, and as a continuation-in-part of U.S. Patent Application No. 13/661,509 (“the ’509 application”), filed on Oct. 26, 2012. The ’664 application also claimed the benefit of Provisional Applications Nos. 61/564,500 (“the ’500 provisional application”), filed on Nov. 29, 2011, and 61/707,459 (“the ’459 provisional application”), filed on Sep. 28, 2012.

During prosecution of the ’664 application, the Examiner made only one prior art based rejection of the pending claims, for being obvious over U.S. Patent Application Publication No. US 2010/0298257 to Ross (“Ross ’257”) in view of

US Patent Application Publication No. US 2011/0020272 to Schubert (“Schubert”) and World Health Organization, “Pharmaceutical excipients - an overview including considerations for paediatric dosing” (“WHO”). EX1002 at 85.

In response to the Examiner's obviousness rejection, Patent Owner amended the claims to recite polymorphic Form 6 of GS-7977 specifically and argued, “the claims, as currently amended, render the outstanding rejection moot for at least the reason that none of the cited references teaches or suggests Form 6 of GS-7977.” EX1002 at 108.

The Examiner withdrew the rejection, “because the claimed polymorph appears to be free of art.” EX1002 at 114. In the Notice of Allowability, the Examiner stated:

The prior art including the applied references does not disclose or suggest the claimed polymorph: the crystalline GS-7977 has XRPD 2θ -reflections (°) at about: 6.1 and 12.7 as recited in claim 8. For example, while the closest prior art of Ross (US publication application no. 2010/0298257) does teach crystalline GS-7977 has XRPD 2θ -reflections (°) at about: 5.0, 7.3, 9.4 and 18.1, it requires different polymorph.

EX1002 at 141.

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

As the '159 patent pertains to a composition and unit dosage form of a crystalline form of the nucleos(t)ide compound GS-7977, which can be used to

treat a subject infected with HCV, a POSA with respect to the '159 patent would (1) have a Ph.D. in chemistry or a closely related field with some experience in an academic or industrial laboratory focusing on drug discovery and/or development, including formulations, 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, including formulations, for the treatment of viral diseases. EX1014 at ¶39.

## **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 '159 patent provides definitions for certain claim terms, but these definitions are conventional. EX1014 at ¶41. Thus, there is no reason to give any of the terms of the claims of the '159 a meaning other than their ordinary and accustomed meaning. EX1014 at ¶41.

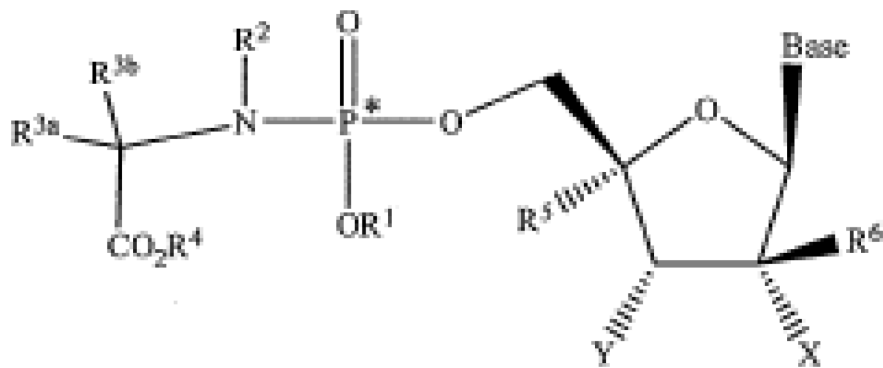
## VIII. BACKGROUND KNOWLEDGE IN THE ART

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 November 29, 2011.

### **A. GS-7977 Was A Known and Promising Antiviral Agent for Treating HCV**

WO 2008/121634 to Sofia et al. (“Sofia ’634”; EX1003) disclosed specific phosphoramidate prodrugs of nucleoside derivatives, which are useful for the treatment of viral infections, including HCV. EX1014 at ¶43. 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

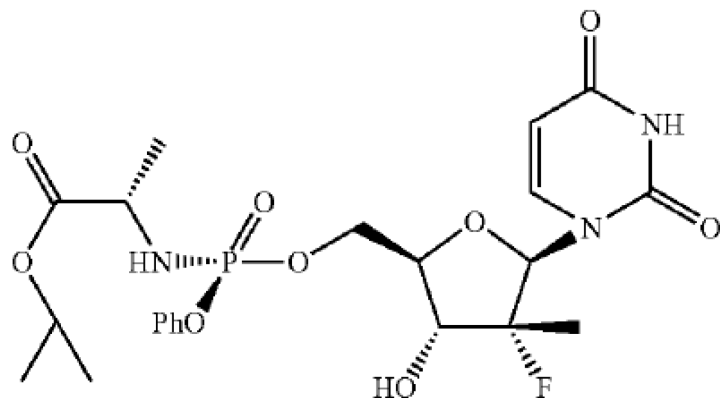
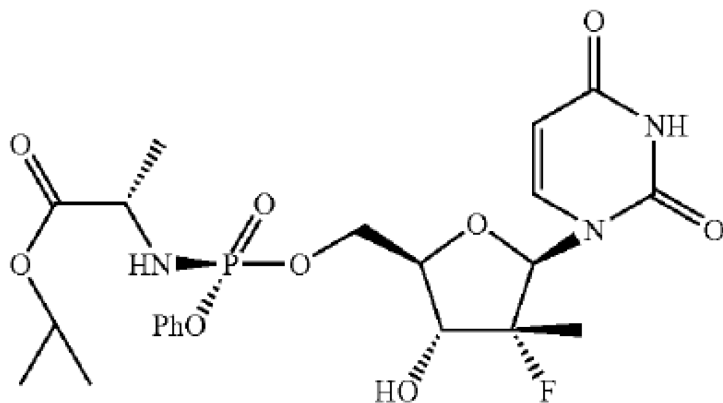
EX1003 at 699.

While Sofia '634 disclosed and claimed many compounds within the formula, it specifically covered the compound (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydrofuran-2-ylmethoxy]-phenoxy-phosphorylamino]-propionic acid isopropyl ester, also known as GS-7977 (or PSI-7977). EX1003 at 703:48-50. Indeed, the '159 confirms this. EX1001 at 8:3 (citing U.S Patent No.7,964,580, which corresponds to Sofia '634).

### B. Crystalline Forms of GS-7977 Were Known

Multiple crystalline forms of GS-7977 were already known in the art. EX1014 at ¶45. Sofia et al. "*Discovery of β-D-2' Deoxy-2'-α-fluoro-2'-β-C-methyluridine Nucleotide Prodrug (PSI-7977) for the Treatment of Hepatitis Virus*", September 16, 2010, 53, 7202-7218 ("Sofia 2010"; EX1004) disclosed a dichloromethane solvate crystalline form of GS-7977. EX1004 at 8.

U.S. Publication No. 2010/0298257 to Ross et al. ("Ross '257"; EX1005), which is identified as prior art by the '159 patent, EX1001 at 8:3-47, disclosed the following compounds  $R_p$ -4 and  $S_p$ -4, also known as GS-7977:



EX1005 at ¶¶0080-0109.

Ross '257 also taught solvates, hydrates, or mixed solvate-hydrate forms of  $S_p$ -4.  $S_p$ -4 was also disclosed to possibly exist as a mixed solvate-hydrate form with additional adsorbed water. EX1005 at ¶0081. The compound represented by  $S_p$ -4

was also disclosed as having solid state properties of being crystalline, crystal-like, or amorphous. EX1005 at ¶0092.

Furthermore, Ross '257 taught multiple crystalline forms of  $S_p$ -4. EX1014 at ¶48. Specifically, Ross '257 disclosed XRPD patterns and 2 $\theta$ -reflection angles for six distinct crystalline forms of  $S_p$ -4. EX1005 at ¶¶0098-0106. Ross '257 also taught a substantially pure crystalline  $S_p$ -4. EX1014 at ¶48. This disclosure of the substantially pure crystalline  $S_p$ -4 therefore teaches that a genus of crystalline forms of  $S_p$ -4 existed including any additional crystalline forms. EX1005 at ¶¶0107-0108; EX1014 at ¶48.

Indeed, selecting a single crystalline form of a compound possessing the preferred combination of optimal properties including (*e.g.*, stability, dissolution, and bioavailability) is a necessary and routine step in ensuring optimal drug performance. EX1014 at ¶49.

The ICH Q6A Guideline “*Specifications: Test Procedures and Acceptance Criteria For New Drug Substances and New Drug Products: Chemical Substances*” (“ICH”; EX1006) provides in Section 3.3.1 New Drug Substances:

c) Polymorphic forms: Some new drug substances exist in different crystalline forms, which differ in their physical properties. Polymorphism may also include solvation or hydration products (also known as pseudopolymorphs) and amorphous forms. Differences in these forms could, in some cases, affect the quality or performance of



the new drug products. *In cases where differences exist which have been shown to affect drug product performance, bioavailability or stability, then the appropriate solid state should be specified.*

EX1006 at 12. ICH taught a set of three Decision Trees for guidance about the need to set acceptance criteria for polymorphism in drug substances and drug products: “Decision trees #4(1) through 4(3) provide additional guidance on when, and how, polymorphic forms should be monitored and controlled.” EX1006 at 13, 28.

It was also known that the selection of a single most-preferred solid-state form was a matter of concern for drug regulatory agencies. EX1014 at ¶51. Routine approaches (including decision trees) to guide the evaluation and selection of an optimal crystalline form of a new drug substance for development are available in many relevant publications, including Byrn et al., “*Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations*,” *Pharmaceutical Research*, 12(7), 1995, 945-954 (“Byrn”; EX1007).

WO2011/123645 to Ross (“Ross ’645”; EX1008) also taught both GS-7977 compounds  $R_p$ -4 and  $S_p$ -4. EX1008 at 8:1-5. Ross ’645 specifically disclosed multiple crystalline forms of  $S_p$ -4. EX1014 at ¶52. In particular, Ross ’645 disclosed the specific crystalline form of compound  $S_p$ -4 as claimed in the pharmaceutical composition of the ’159 patent. EX1008 at 20:16-18. Indeed, the ’159 patent concedes this. EX1001 at 8:3 (citing US 2011/0251152, which relates

to Ross'645).

### **C. Tablet And Capsule Formulation Comprising Pharmaceutical Excipients Were Known**

Tablet formulations were well known and routine for use in the pharmaceutical industry for drug delivery. EX1014 at ¶53. Several textbooks and guides existed setting out general principles of tablet design, excipient selection, and tablet manufacture, all of which are commonly practiced in the field. EX1014 at ¶53. Examples of such principles are explained in, Lieberman, Lachman and Schwartz, *“Pharmaceutical Dosage Forms: Tablets”*, Volume 1, Chapter 3, 1989 by Marcel Dekker (“Lieberman”; EX1009), U.S Pharmacopeia 24 (NF19), *“Pharmaceutical Dosage Forms”*, General Information 1151-1161, 2117-2118, 2000 (“USP”; EX1010), and Remington, *“The Science and Practice of Pharmacy”*, 19<sup>th</sup> Edition, 1995 (“Remington”; EX1011).

Both Ross '257 and Ross '645 incorporate Remington by reference in relation to describing suitable formulations and pharmaceutical carriers, diluents and excipients. EX1005 at ¶0119; EX1008 at 23:13-16.

The '159 patent itself states that its embodiments may be modified using the materials and methods taught by Remington. EX1001 at 17:54-58.

Rowe et al., *“Handbook of Pharmaceutical Excipients”*, Fourth Edition, 2003 (“Rowe”; EX1012) provided a more thorough review of the excipients approved for use by the U.S Food and Drug Administration. Rowe taught a

compendium of monographs for excipients used in pharmaceutical compositions. EX1014 at ¶56. The monographs for each excipient provide information on the functional category, application in formulations, description, specifications, typical properties, incompatibilities, method of manufacture, and regulatory status of each excipient listed, as well as published references to such excipients. *See, e.g.*, EX1012 at 12, 28, and 33. The monographs also provide information on typical quantities of excipients used in various types of formulations. EX1014 at ¶56. The '159 patent cites an earlier version of Rowe from 1994 as teaching 'Tablet Preparation'. EX1001 at 15:21-17:67

**D. Tablet And Capsule Formulations Comprising Crystalline GS-7977 And Pharmaceutical Excipients Were Known**

Sofia '634 taught that the compounds disclosed therein, including GS-7977, could be directed to a composition comprising a pharmaceutically acceptable medium selected from among an excipient, carrier, diluent, and equivalent medium and a compound, that is intended to include its salts (acid or basic addition salts), hydrates, solvates and crystalline forms. EX1003 at 661:1-12.

Sofia '634 also taught that compounds of the invention therein, including GS-7977, could be formulated in a wide variety of oral administration dosage forms and carriers, including tablets. EX1003 at 661:13-16. Compound or compounds of the invention taught in Sofia'634 could be placed into the form of pharmaceutical compositions and unit dosages with one or more conventional

excipients, carriers or diluents. EX1003 at 661:22-25.

Sofia'634 further taught that the pharmaceutical compositions and unit dosage forms may be comprised of conventional ingredients in conventional proportions, with or without additional active compounds and the unit dosage form may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. EX1003 at 661:25-29. In particular, Sofia'634 taught that a typical preparation will contain from about 5% to about 95% active compound or compounds (w/w). EX1003 at 662:2-3. Furthermore, Sofia '634 disclosed that the compounds therein will generally be administered in admixture with one or more suitable pharmaceutical excipients, diluents or carriers selected with regard to the intended route of administration and standard pharmaceutical practice. EX1003 at 661:11-15.

Sofia '634 also provided a non-exhaustive list of suitable carriers for tablets, including starch, sugar, talc, methylcellulose, sodium carboxymethylcellulose, magnesium stearate and lactose. EX1003 at 663:7-20.

Ross '257 taught dosage, administration and use, providing:

An aspect of this embodiment is directed to a composition for the treatment of any of the viral agents disclosed herein said composition comprising a pharmaceutically acceptable medium selected from among an excipient, carrier, diluent and equivalent medium and any of the compounds **4**, Rp-**4**, or Sp-**4**, that is intended

to include its hydrates, solvates, and any crystalline forms of any of the compounds 4, Rp-4, or Sp-4 or its hydrates and solvates thereof.

EX1005 at ¶0111.

Ross '257 also taught that compounds 4, Rp-4, or Sp-4 (GS-7977), could be used for oral administration in the form of tablets. EX1005 at ¶0112. Ross '257 further taught the use of compounds 4, Rp-4, or Sp-4 (GS-7977) with one or more pharmaceutical excipients where the typical preparation would contain from about 5% to about 95% active compound or compounds (w/w). EX1005 at ¶0113. Suitable carriers for tablets were also taught in Ross '257 to have activity as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. EX1005 at ¶0113. Suitable carriers for tablets were also taught in Ross '257 as including but not limited to magnesium stearate starch, sugar, talc, methylcellulose, sodium carboxymethylcellulose and lactose. EX1005 at ¶0115.

Ross '645 also taught dosage, administration and use as described in Ross '257, albeit in relation to additional crystalline forms including the specific crystalline form of compound Sp-4 as claimed in the pharmaceutical composition of the '159 patent. EX1008 at 21-23.

**E. GS-7977 Was Known To Be In Clinical Trials at a 400mg Daily Dose**

Sofia 2010 disclosed that PSI-7977 (GS-7977) was in phase II clinical

development for the treatment of HCV infection. EX1004 at 9.

Lawitz et al., “*High Rapid Virologic Response (RVR) with PSI-7977 Daily Dosing Plus PEG-IFN/RBV in a 28-day Phase 2a Trial*” 61th Annual Meeting of the American Association for the Study of Liver Diseases, October 30- November 3, 2010 (“Lawitz”; EX1013) disclosed that the 200 mg and 400 mg daily doses of PSI-7977 (GS-7977) with PEG-IFN (pegylated interferon) and RBV (ribavirin) provided a more durable virological response than the 100 mg daily dose of PSI-7977. EX1013 at 1. Thus, a POSA would know that a 400 mg QD dose was one of two preferred doses for sustained virologic response when dosed with PEG-IFN and RBV. EX1014 at ¶65.

Ross ’257 taught a therapeutically effective amount of the compounds 4, Rp-4, or Sp-4 (GS-7977) for oral administration for a daily dosage to be between 0.001 and about 10g, including all values in between, such as 0.001-9.5g per day. In particular, Ross ’257 taught a daily dosage to be between 0.01 and 1g per day, including all incremental values of 0.01g (*i.e.*, 10mg) in between. EX1005 at ¶0126.

Ross ’645 also taught the same therapeutically effective amount for compounds 4, Rp-4, or Sp-4 (GS-7977) for oral administration for a daily dosage. EX1008 at 24:26-25:14.

**F. Method of Treating HCV Using A Tablet or Capsule Comprising Crystalline GS-7977 And A Pharmaceutical Excipient Was Known**

Sofia '634 taught that the nucleotide NS5B polymerase inhibitors disclosed and claimed therein, including GS-7977, could be directed to a method of treatment alone or in combination with another antiviral agent, wherein the administration is concurrent or alternative. EX1003 at 8-12. Sofia '634 further suggested examples of "another antiviral agent" to include ribavirin. EX1003 at 668:26-27. Furthermore, Sofia'634 disclosed that administration of two or more agents at the same time could 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. EX1003 at 669:5-8

Ross '257 taught that compounds 4, Rp-4, or Sp-4 (GS-7977) could be administered in a therapeutically effective amount to the subject. EX1005 at ¶00123. Ross '257 also taught that the said compounds could be alongside another antiviral agent, including ribavirin. EX1005 at ¶¶0128-0129. As taught in 'Sofia '634, Ross'257 disclosed that administration of two or more agents at the same time could 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. EX1005 at ¶0128-¶0129.

As disclosed in Ross '257, Ross '645 also taught that compounds 4, Rp-4, or

Sp-4 (GS-7977) could be administered in a therapeutically effective amount to the subject. EX1008 at 25:24-31. Further, Ross '645 disclosed that the said compounds could be alongside another antiviral agent, including ribavirin. EX1008 at 26:20.

## **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 the claims of the '159 patent. EX1014 at ¶50.

### **A. WO 2011/123645 to Ross (“Ross '645”; EX1008)**

Ross '645 was published on October 6, 2011, before the filing of the earliest application to which the '159 patent claims priority. Therefore, Ross '645 is prior art to the '159 patent under 35 U.S.C. § 102(a).

Ross '645 taught both GS-7977 compounds 4,  $R_p$ -4 and  $S_p$ -4. EX1008 at 8:1-5. Ross '645 specifically disclosed multiple crystalline forms of  $S_p$ -4. EX1014 at ¶72. In particular, Ross '645 disclosed the following identical crystalline form of compound  $S_p$ -4 as in claims 1, 2, 16 and 17 of the '159 patent:

An eleventh aspect of the third embodiment is directed to crystalline of  $S_p$ -4 having XRPD  $2\theta$  reflections ( $^\circ$ ) at about **6.1**, 8.2, 10.4, **12.7**, 17.2, 17.7, 18.0, 18.8, 19.4, 19.8, 20.1, 20.8, 21.8 and 23.3. EX1008 at 20:16-18 and 116:17-18.

Ross '645 also taught a composition using any of the compounds 4,  $R_p$ -4, or  $S_p$ -4 for oral administration for treatment, including in the form of tablets:



*An aspect of this embodiment is directed to a composition for the treatment of any of the viral agents disclosed herein said composition comprising a pharmaceutically acceptable medium selected from among an excipient, carrier, diluent, and equivalent medium and any of the compounds 4, R<sub>p</sub>-4, or S<sub>p</sub>-4, that is intended to include its hydrates, solvates, and any crystalline forms of any of compounds 4, R<sub>p</sub>-4, or S<sub>p</sub>-4 or its hydrates and solvates thereof.*

The compounds 4, R<sub>p</sub>-4, or S<sub>p</sub>-4 may be independently formulated in a wide variety of oral administration dosage forms and carriers. *Oral administration can be in the form of tablets, coated tablets, hard and soft gelatin capsules, solutions, emulsions, syrups or suspensions.*

EX1008 at 21:8-17 (emphasis added).

In addition, Ross '645 taught pharmaceutical compositions and unit dosages comprising compounds 4, R<sub>p</sub>-4, or S<sub>p</sub>-4 with one or more excipients, carriers, diluents where a typical preparation would contain from about 5% to about 95% active compound or compounds (w/w). EX1008 at 21:22-33.

Ross '645 further taught that the compounds 4, R<sub>p</sub>-4, or S<sub>p</sub>-4 would generally be administered in admixture with one or more suitable pharmaceutical excipients, diluents, or carriers selected with regard to the intended route of administration and standard pharmaceutical practice. EX1008 at 22:1-4. Furthermore, Ross '645 provided that solid form preparations included tablets. EX1008 at 22:5-9.

It was also known from Ross '645 that, in tablets, the active component generally is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired. EX1008 at 10-12. Ross '645 also provided a non-limited list of suitable carriers including, magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting cocoa butter and the like. EX1008 at 12-15. Ross '645 also includes a list of 24 patents with examples of solid formulations, said patents were incorporated by reference. EX1008 at 21:18-24.

Also disclosed in Ross '645 were suitable formulations along with pharmaceutical carriers, diluents and excipients as described in Remington, which was incorporated by reference. EX1008 at 23:13-16. Ross '645 stated that, “[a] skilled formulation scientist may modify the formulations within the teachings of the specification to provide numerous formulations for a particular mode of administration without rendering compositions containing the compounds contemplated herein unstable or compromising their therapeutic activity.” EX1008 at 23:16-20.

Ross '645 also taught a dosage range for oral administration to be between 0.01 and 1g per day, including all incremental values of 0.01g (*i.e.*, 10mg) in-between. EX1008 at 24:26-25:14

A further disclosure in Ross '645 was that compounds **4**,  $R_p$ -**4**, or  $S_p$ -**4** (GS-7977) could be administered in a therapeutically effective amount to the subject. EX1008 at 25:24-31. Further, Ross '645 disclosed that the said compounds could be administered alongside another antiviral agent, including ribavirin. EX1008 at 26:20. Ross '654 disclosed that administration of two or more agents at the same time could 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. EX1008 at 26:24-32.

**B. U.S Pub No. 2010/0298257 to Ross (“Ross '257”; EX1005)**

Ross '257 was published on November 25, 2010, more than a year before the filing of the earliest application to which the '159 patent claims priority. Therefore, Ross '257 is prior art to the '159 patent under 35 U.S.C. § 102(b).

Ross '257 taught both GS-7977 compounds  $R_p$ -**4** and  $S_p$ -**4**. EX1005 at ¶¶0080-0106. Ross '257 specifically disclosed six crystalline forms of  $S_p$ -**4**. EX1005 at ¶¶0098-0106. Ross '257 also taught a substantially pure crystalline  $S_p$ -**4**. EX1014 at ¶80. This disclosure of the substantially pure crystalline  $S_p$ -**4** therefore teaches that a genus of crystalline forms of  $S_p$ -**4** existed including any additional crystalline forms. EX1005 at ¶¶0106-0108.

Ross '257 also taught a composition using any of the compounds **4**,  $R_p$ -**4**, or  $S_p$ -**4** for oral administration for treatment, including in the form of tablets:

*An aspect of this embodiment is directed to a composition for the treatment of any of the viral agents disclosed herein said composition comprising a pharmaceutically acceptable medium selected from among an excipient, carrier, diluent, and equivalent medium and any of the compounds 4, R<sub>p</sub>-4, or S<sub>p</sub>-4, that is intended to include its hydrates, solvates, and any crystalline forms of any of compounds 4, R<sub>p</sub>-4, or S<sub>p</sub>-4 or its hydrates and solvates thereof.*

The compounds 4, R<sub>p</sub>-4, or S<sub>p</sub>-4 may be independently formulated in a wide variety of oral administration dosage forms and carriers. *Oral administration can be in the form of tablets, coated tablets, hard and soft gelatin capsules, solutions, emulsions, syrups or suspensions.*

EX1005 at ¶¶0111-0112 (emphasis added).

In addition, Ross '257 taught pharmaceutical compositions and unit dosages comprising compounds 4, R<sub>p</sub>-4, or S<sub>p</sub>-4 with one or more excipients, carriers, diluents where a typical preparation would contain from about 5% to about 95% active compound or compounds (w/w). EX1005 at ¶0113.

Ross '257 further taught that the compounds 4, R<sub>p</sub>-4, or S<sub>p</sub>-4 would generally be administered in admixture with one or more suitable pharmaceutical excipients, diluents, or carriers selected with regard to the intended route of administration and standard pharmaceutical practice. EX1005 at ¶0114. Furthermore, Ross'257 provided that solid form preparations included tablets. EX1005 at ¶0115.

It was also known from Ross '257 that, in tablets, the active component generally is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired. EX1005 at ¶0115. Ross'257 also provided a non-limited list of suitable carriers including, magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting cocoa butter and the like. EX1005 at ¶0115.

Also disclosed in Ross '257, was that suitable formulations along with pharmaceutical carriers, diluents and excipients are described in Remington, which was incorporated by reference. EX1005 at ¶0119. Ross '257 stated that a skilled formulation scientist may modify the formulations within the teachings of the specification to provide numerous formulations for a particular mode of administration without rendering compositions containing the compounds contemplated herein unstable or compromising their therapeutic activity. EX1005 at ¶0119.

Ross '257 also taught a dosage range for oral administration to be between 0.01 and 1g per day, including all incremental values of 0.01g (*i.e.*, 10mg) in between. EX1005 at ¶0126.

A further disclosure in Ross '257 was that compounds 4, Rp-4, or Sp-4 could be administered in a therapeutically effective amount to the subject. EX1005

at ¶0123. Ross '257 also disclosed that the said compounds could be administered alongside another antiviral agent, including ribavirin. EX1005 at ¶0129. Ross'257 disclosed that administration of two or more agents at the same time could 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. EX1005 at ¶¶0128-0129.

#### **X. EACH CLAIM OF THE '159 PATENT IS UNPATENTABLE**

Each and every feature of claims 1-37 of the '159 patent can be found in the prior art references identified below. EX1014 at ¶88. 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 '159 patent. *Id.* at 89 and 162.

Each of claims 1-37 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.

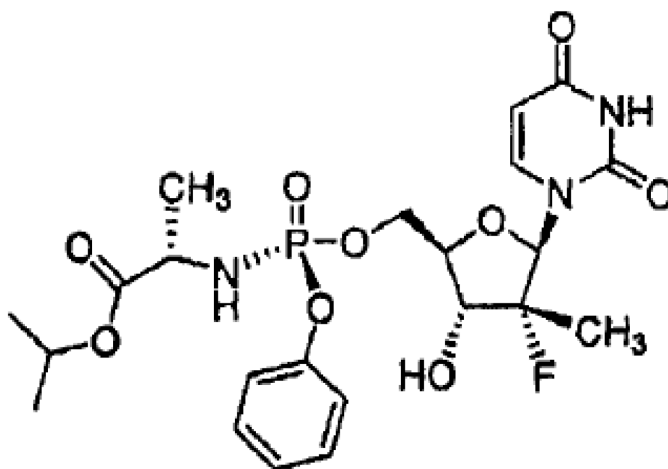
##### **A. Grounds 1 and 2: Claims 1-37 Were Anticipated By And Obvious Over Ross '645**

All of the claims of the '159 patent were anticipated by Ross '645. EX1014 at ¶89. They were also obvious over Ross '645. EX1014 at ¶89. In light of the teachings of Ross '645 and the background art, a POSA would have been motivated to, and had an expectation of success in, arrive at the pharmaceutical

compositions and unit dosage forms claimed in the '159 patent. EX1014 at ¶89.

**1. Claims 1 and 2 (composition comprising compound and excipient)**

Claim 1 of the '159 patent recites a pharmaceutical composition comprising about 25% to about 35% w/w of crystalline GS-7977 having the structure:



and at least one pharmaceutically acceptable excipient, wherein the crystalline GS-7977 has XRPD 2 $\theta$ -reflections ( $^{\circ}$ ) at about 6.1 and 12.7.

EX1001 at 46:36-56.

Claim 2 recites the composition according to claim 1 wherein the crystalline GS-7977 has XRPD 2 $\theta$ -reflections ( $^{\circ}$ ) at about 6.1, 8.2, 10.4, 12.7, 17.2, 17.7, 18.0, 18.8, 19.4, 19.8, 20.1, 20.8, 21.8 and 23.3. EX1001 at 46:57-60.

As set out in the background knowledge above, compound GS-7977 was already known. EX1014 at ¶92. Indeed, the '159 patent admitted this, including by citing U.S. Patent No. 7,964,580, which corresponds to Sofia '634. EX1014 at ¶92.

Pharmaceutical excipients were commonly used in compositions, such as tablets and unit dosage forms. EX1014 at ¶92. Examples of publications setting out the general principles of tablet design, excipient selection and tablet manufacture are explained in, Lieberman (EX1009), USP (EX1010) and Remington (EX1011). EX1014 at ¶92.

Rowe (EX1012) provided a more thorough review of excipients approved for use by the U.S Food and Drug Administration. EX1014 at ¶93. Rowe taught a compendium of monographs for excipients used in pharmaceutical compositions, including most of those used in the patent '159. EX1014 at ¶93. The monographs for each excipient provide information on the functional category, application in formulations, description, specifications, typical properties, incompatibilities, method of manufacture, and regulatory status of each excipient listed, as well as published references to such excipients. EX1014 at ¶93. The monographs also provide information on typical quantities of excipients used in various types of formulations. EX1014 at ¶93. The '159 patent also states that the embodiments in the patent may be modified by one of ordinary skill without straying from the expressed intent using materials and methods described in Remington. EX1001 at 17:54-58.

Ross '645 taught both GS-7977 compounds 4,  $R_p$ -4 and  $S_p$ -4. EX1008 at 8:1-5. Ross '645 specifically disclosed multiple crystalline forms of  $S_p$ -4. EX1014 at



¶94. In particular, Ross '645 disclosed the following identical crystalline form of compound *S<sub>p</sub>-4* as covered in claims 1 and 2 of the '159 patent:

An eleventh aspect of the third embodiment is directed to crystalline *S<sub>p</sub>-4* having XRPD 2θ reflections (°) at about **6.1**, 8.2, 10.4, **12.7**, 17.2, 17.7, 18.0, 18.8, 19.4, 19.8, 20.1, 20.8, 21.8 and 23.3.

EX1008 at 20:16-18 and 116:17-18.

Ross '645 also taught a composition using any of the compounds **4**, *R<sub>p</sub>-4*, or *S<sub>p</sub>-4* for oral administration for treatment, including in the form of tablets:

*An aspect of this embodiment is directed to a composition for the treatment of any of the viral agents disclosed herein said composition comprising a pharmaceutically acceptable medium selected from among an excipient, carrier, diluent, and equivalent medium and any of the compounds **4**, *R<sub>p</sub>-4*, or *S<sub>p</sub>-4*, that is intended to include its hydrates, solvates, and any crystalline forms of any of compounds **4**, *R<sub>p</sub>-4*, or *S<sub>p</sub>-4* or its hydrates and solvates thereof.*

EX1008 at 21:8-13 (emphasis added).

In addition, Ross '645 taught:

*The compounds **4**, *R<sub>p</sub>-4*, or *S<sub>p</sub>-4* together with one or more conventional excipients, carriers, or diluents, may be placed into the form of pharmaceutical compositions and unit dosages. The pharmaceutical compositions and unit dosage forms may be comprised of conventional ingredients in conventional proportions, with or without additional active compounds and the unit dosage*

*forms may contain any suitable effective amount of the active commensurate with the intended daily dosage range to be employed. The pharmaceutical compositions may be employed as solids, such as tablets or filled capsules, semisolids, powders, sustained release formulations, or liquids such as suspensions, emulsions or filled capsules for oral use; or in the form of suppositories for rectal or vaginal administration. A typical preparation will contain from about 5% to about 95% active compound or compounds (w/w).*

EX1008 at 21:22-33 (emphasis added).

From these embodiments a POSA would have known that Ross '645 disclosed the following:

- An identical crystalline form of GS-7977 as '159;
- pharmaceutical compositions containing an excipient;
- pharmaceutical compositions containing conventional ingredients in conventional amounts;
- pharmaceutical compositions containing any amount of active ingredient commensurate with the intended daily dosage range;
- pharmaceutical compositions comprising a tablet form;
- Typical preparations (e.g., tablets) containing from about 5% to about 95% active compound.

EX1014 at ¶97.

Accordingly, based on the disclosure of Ross '645, claims 1 and 2 of the

'159 patent were anticipated, as the claimed range of about 25% to about 35% w/w falls within the range taught by Ross '645 of about 5% to about 95% and there are no surprising or unexpected results from the narrower claimed range. EX1014 at ¶98. Ross '645 also rendered claims 1 and 2 obvious, as a POSA would have been motivated to prepare a suitable pharmaceutical composition with the known HCV agent. EX1014 at ¶98.

**2. Claims 3-12 (pharmaceutical composition comprising at least one pharmaceutically acceptable excipient)**

Claim 3 recites the composition according to claim 1, wherein the at least one pharmaceutically acceptable excipient comprises at least one diluent, a disintegrant, a glidant and a lubricant. EX1001 at 46:61-63.

Claim 4 recites the composition according to claim 3 wherein the at least one excipient comprises a diluent selected from a group consisting of dicalcium phosphate, cellulose, compressible sugars, dibasic calcium phosphate, hydrate, lactose, mannitol, microcrystalline cellulose, starch, tribasic calcium phosphate, and combinations thereof. EX1001 at 46:64 – 47:3.

Claim 5 recites the composition according to claim 4, wherein the diluent is selected from the group consisting of mannitol, microcrystalline cellulose, and combinations thereof. EX1001 at 47:4-6.

Claim 6 recites the composition according to claim 3, wherein the at least one pharmaceutically acceptable excipient comprises a disintegrant selected from

the group consisting of croscarmellose sodium, crospovidone, microcrystalline cellulose, modified corn starch, povidone, pregelatinized starch, sodium starch glycolat, and combinations thereof. EX1001 at 47:7-12.

Claim 7 recites to the composition according to claim 6, wherein the disintegrant is croscarmellose sodium. EX1001 at 47:13-14.

Claim 8 recites to the composition according to claim 3 wherein the at least one pharmaceutical excipient comprises a glidant selected from the group consisting of colloidal silicon dioxide, talc, starch, starch derivatives and combinations thereof. EX1001 at 47:15-19.

Claim 9 recites to the composition according to claim 8, wherein the glidant is colloidal silicon dioxide. EX1001 at 47:20-21.

Claim 10 recites to the composition according to claim 3 wherein the at least one pharmaceutically acceptable excipient comprises a lubricant selected from the group consisting of calcium stearate, magnesium stearate, polyethylene glycol, sodium stearyl fumarate, stearic acid, talc and combinations thereof. EX1001 at 47:22-26.

Claim 11 recites to the composition according to claim 10, wherein the lubricant is magnesium stearate. EX1001 at 47:27-28.

Claim 12 recites to the composition according to claim 1 further comprising a coating agent. EX1001 at 47:29-30.

As set out in the background knowledge above, pharmaceutical excipients were commonly used in compositions, such as tablets and unit dosage forms. EX1014 at ¶109. Examples of publications setting out the general principles of tablet design, excipient selection and tablet manufacture are explained in, Lieberman (EX1009), USP (EX1010) and Remington (EX1011). Rowe (EX1012) provided a more thorough review of the excipients approved for use by the U.S Food and Drug Administration. EX1014 at ¶109.

The '159 patent in fact states that the embodiments in the patent may be modified by one of ordinary skill without straying from the expressed intent using materials and methods described in Remington. EX1001 at 17:54-58.

Relevant to claim 3 of '159, Ross '645 taught the use of excipients including a pharmaceutically acceptable diluent, disintegrant, and lubricant:

Solid form preparations include, for example, powders, tablets, pills, capsules, suppositories, and dispersible granules. A solid carrier may be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

EX1008 at 21:5-9 (emphasis added).

Relevant to claims 4 and 5 of '159, Ross '645 taught a non-limited list of suitable carriers, including sugar, methylcellulose, carboxymethylcellulose, lactose, and magnesium stearate. EX1008 at 22:12-15. Various diluents for

pharmaceutical formulations, including microcrystalline cellulose and mannitol, were also common knowledge. *See, e.g.*, EX1012 at 3 and 28.

Relevant to claims 6 and 7 of '159, Ross '645 taught that a solid carrier may be one or more substances which may act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents or encapsulating material. EX1008 at 22:5-9. A number of the disintegrants claimed in the '159 patent were also common knowledge, including croscarmellose sodium (EX1012 at 44), crospovidone (EX1012 at 42), microcrystalline cellulose (EX1012 at 3), starch (EX1012 at 33), povidone (EX1012 at 47), pregelatinized starch (EX1012 at 39) and sodium starch glycolate (EX1012 at 53). EX1014 at ¶113.

Relevant to claims 8 and 9, Ross '645 taught suitable carriers included but were not limited to magnesium carbonate, magnesium stearate, *talc*, sugar, lactose, pectin, dextrin, *starch*, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting cocoa butter and the like. EX1008 at 22:12-15. The various glidants claimed in the '159 patent were also common knowledge, including colloidal silicon dioxide (EX1012 at 60), talc (EX1012 at 57) and starch (EX1012 at 33). EX1014 at ¶114.

Relevant to claims 10 and 11, Ross'645 taught that a solid carrier may be one or more substances which may act as diluents, flavoring agents, solubilizers,

*lubricants*, suspending agents, binders, preservatives, tablet disintegrating agents or encapsulating material. EX1008 at 22:5-9. The various lubricants claimed were also common knowledge, including calcium stearate (EX1012 at 63), magnesium stearate (EX1012 at 67), polyethylene glycol (EX1012 at 71), sodium stearyl fumarate (EX1012 at 77), stearic acid (EX1012 at 80) and talc (EX1012 at 57). EX1014 at ¶115.

In relation to claim 12, Ross '645 taught that oral administration can be in the form of tablets, *coated tablets*, hard and soft gelatin capsules, solutions emulsions, syrups, or suspensions. EX1008 at 21:15-17.

In addition to the above teachings, the '159 patent admits the general knowledge on pharmaceutical carriers, diluents and excipients, such as described in Remington, etc. Therefore, in view of Ross '645 and the common knowledge around pharmaceutical excipients for the purpose of formulating a compound, claims 3-12 were anticipated and obvious. EX1014 at ¶117.

**3. Claims 13-15 (composition comprising at least one pharmaceutically acceptable excipient by specific weight)**

Claims 13-15 of the '159 patent recite a composition according to claim 1 wherein at least one pharmaceutically acceptable excipient comprises particular weight of a diluent, disintegrant, glidant and a lubricant. Claims 14 and 15 further specify the excipients as mannitol, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate in particular weights.

EX1001 at 47:31-50.

Ross '645 taught the use of compounds 4, Rp-4, or Sp-4 (GS-7977) with one or more pharmaceutical excipients where the typical preparation would contain from about 5% to about 95% active compound or compounds (w/w), thereby encompassing the range claimed in the '159 patent. EX1008 at 21:32-33.

As discussed above, the various excipients (diluent, disintegrant, glidant and lubricant) claimed in the '159 patent are expressly disclosed in Ross '645 patent or were common knowledge as evidenced by Rowe (EX1012) and Remington (EX1011). EX1014 at ¶120.

Ross '645 further provided that the pharmaceutical compositions and unit dosage forms may be comprised of conventional ingredients in *conventional proportions*, with or without additional active compounds and the unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. EX1008 at 21:24-28.

With respect to the excipients specifically claimed in claims 13-15, it was common knowledge that mannitol is commonly used as a diluent and is usually 10-90% w/w in tablet formulations (EX1012 at 28); crosscarmellose sodium is commonly used as a disintegrant and may be used at concentrations up to 5% w/w (EX1012 at 44); and magnesium stearate is primarily used as a lubricant in capsule



and tablet manufacture at concentrations between 0.25% and 5.0% (EX1012 at 67). EX1014 at ¶122.

Ross '645 along with the common knowledge around pharmaceutical excipients as exemplified by Rowe and Remington, (which are both referenced by the '159 patent) anticipated claims 13-15, or at least rendered them obvious. EX1014 at ¶123.

**4. Claims 16-17 (unit dosage form comprising 400mg of crystalline GS-7977)**

Claims 16-17 recite to a unit dosage form comprising 400mg of crystalline GS-7977, wherein the crystalline GS-7977 has XRPD 2 $\theta$ -reflections ( $^{\circ}$ ) at about 6.1 and 12.7 and at about 6.1, 8.2, 10.4, 12.7, 17.2, 17.7, 18.0, 18.8, 19.4, 19.8, 20.1, 20.8, 21.8 and 23.3, and at least one pharmaceutically acceptable excipient. EX1001 at 47:51-48:9.

Ross '645 taught both GS-7977 compounds 4,  $R_p$ -4 and  $S_p$ -4. EX1008 at 8:1-5. Ross '645 specifically disclosed multiple crystalline forms of  $S_p$ -4. In particular, Ross '645 disclosed the following identical crystalline form of compound  $S_p$ -4 as covered in claims 16 and 17 of the '159 patent:

An eleventh aspect of the third embodiment is directed to crystalline of  $S_p$ -4 having XRPD 2 $\theta$  reflections ( $^{\circ}$ ) at about **6.1**, 8.2, 10.4, **12.7**, 17.2, 17.7, 18.0, 18.8, 19.4, 19.8, 20.1, 20.8, 21.8 and 23.3. EX1008 at 19:16-18 and 115:17-18.

Ross '645 also taught that the compounds 4, R<sub>p</sub>-4, or S<sub>p</sub>-4 (GS-7977) and the crystalline forms disclosed therein, together with one or more conventional *excipients*, carriers, or *diluents*, may be placed into the form of pharmaceutical compositions and *unit dosages*. EX1008 at 21:22-24.

Further, Ross '645 taught a dosage range for oral administration to be between 0.01 and 1g per day, including all incremental values of 0.01g (*i.e.*, 10mg) in between. EX1008 at 24:26-25:14. A POSA would have known that a 400 mg daily dose was within the dose range contemplated by Ross '645. EX1014 at ¶127.

Also, as mentioned in the background art, it was common knowledge that the 200 mg and 400 mg daily doses of PSI-7977 (GS-7977) with PEG-IFN (pegylated interferon) and RBV (ribavirin) provided a more durable virological response than the 100 mg daily dose of PSI-7977. EX1013 at 1; EX1014 at ¶128.

Ross '645, along with what was already common knowledge, such as that disclosed by Lawitz, anticipated claims 16 and 17 of the '159 patent, or at least rendered them obvious. EX1014 at ¶129.

**5. Claims 18-27 (unit dosage form comprising at least one pharmaceutical excipient)**

Claim 18 recites the unit dosage form according to claim 16, wherein the at least one pharmaceutically acceptable excipient comprises at least one diluent, a disintegrant, a glidant and a lubricant. EX1001 at 48:10-13.

Claim 19 recites the unit dosage form according to claim 18 wherein the at

least one excipient comprises a diluent selected from a group consisting of dicalcium phosphate, cellulose, compressible sugars, dibasic calcium phosphate, dehydrate, lactose, mannitol, microcrystalline cellulose, starch, tribasic calcium phosphate, and combinations thereof. EX1001 at 48:14-20.

Claim 20 recites the unit dosage form according to claim 19, wherein the diluent is selected from the group consisting of mannitol, microcrystalline cellulose, and combinations thereof. EX1001 at 48:21-22.

Claim 21 recites the unit dosage form according to claim 18, wherein the at least one pharmaceutically acceptable excipient comprises a disintegrant selected from the group consisting of croscarmellose sodium, crospovidone, microcrystalline cellulose, modified corn starch, povidone, pregelatinized starch, sodium starch glycolate, and combinations thereof. EX1001 at 48:23-28.

Claim 22 recites to the unit dosage form according to claim 21, wherein the disintegrant is croscarmellose sodium. EX1001 at 48:29-30.

Claim 23 recites to the unit dosage form according to claim 18 wherein the at least one pharmaceutical excipient comprises a glidant selected from the group consisting of colloidal silicon dioxide, talc, starch, starch derivatives and combinations thereof. EX1001 at 48:31-35.

Claim 24 recites to the unit dosage form according to claim 23, wherein the glidant is colloidal silicon dioxide. EX1001 at 48:36-37.

Claim 25 recites to the unit dosage form according to claim 18 wherein the at least one pharmaceutically acceptable excipient comprises a lubricant selected from the group consisting of calcium stearate, magnesium stearate, polyethylene glycol, sodium stearyl fumarate, stearic acid, talc and combinations thereof. EX1001 at 48:38-42.

Claim 26 recites to the unit dosage form according to claim 25, wherein the lubricant is magnesium stearate. EX1001 at 48:43-44.

Claim 27 recites to the unit dosage form according to claim 16 further comprising a coating agent. EX1001 at 48:45-46.

Ross '645 taught that the compounds 4, R<sub>p</sub>-4, or S<sub>p</sub>-4 (GS-7977) and the crystalline forms disclosed therein, together with one or more conventional *excipients*, carriers, or *diluents*, may be placed into the form of pharmaceutical compositions and *unit dosages*. EX1008 at 21:22-24.

With respect to claims 18-26 and the excipients claimed therein, reference is made back to the discussion of claims 3-12 above.

In relation to claim 27, Ross '645 taught that oral administration can be in the form of tablets, *coated tablets*, hard and soft gelatin capsules, solutions emulsions, syrups, or suspensions. EX1008 at 21:15-17.

In addition to the above teachings, the '159 patent admits the general knowledge on pharmaceutical carriers, diluents and excipients, such as described in

Remington, etc. EX1014 at ¶143. Therefore, in view of Ross '645 and the common knowledge around pharmaceutical excipients for the purpose of formulating a compound, claims 18-27 of the '159 patent were anticipated and obvious. EX1014 at ¶143.

**6. Claims 28-29 (unit dosage form comprising at least one pharmaceutically acceptable excipient by specific weight)**

Claim 28 of the '159 patent recites a composition according to claim 16 wherein at least one pharmaceutically acceptable excipient comprises particular weight of a diluent, disintegrant, glidant and a lubricant. Claim 29 further specifies the excipients as mannitol, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate in particular dosage and weight ranges. EX1001 at 48:47-61.

Ross '645 taught that the compounds 4, R<sub>p</sub>-4, or S<sub>p</sub>-4 (GS-7977) and the crystalline forms disclosed therein, together with one or more conventional *excipients*, carriers, or *diluents*, may be placed into the form of pharmaceutical compositions and *unit dosages*. EX1008 at 21:22-24.

Ross '645 further provided that the pharmaceutical compositions and unit dosage forms may be comprised of conventional ingredients in *conventional proportions*, with or without additional active compounds and the unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. EX1008 at

21:24-28.

Further, Ross '645 taught a dosage range for oral administration to be between 0.01 and 1g per day, including all incremental values of 0.01g (*i.e.*, 10mg) in between. EX1008 at 24:26-25:14. A POSA would know that a 400 mg daily dose was within the dose range contemplated by Ross '645. EX1014 at ¶147.

Also, as mentioned in the background art, it was common knowledge that the 200 mg and 400 mg daily doses of PSI-7977 (GS-7977) with PEG-IFN (pegylated interferon) and RBV (ribavirin) provided a more durable virological response than the 100 mg daily dose of PSI-7977. EX1013 at 1; EX1014 at ¶148..

With respect to the various weights of excipients set out in claims 28 and 29, Ross'645 along with the common knowledge around pharmaceutical excipients as exemplified by Rowe and Remington (which are both referenced by the '159 patent) anticipated claims 28 and 29, or at least rendered them obvious. EX1014 at ¶149.

**7. Claim 30 (unit dosage form comprising a capsule or tablet)**

Claim 30 recites a unit dosage form according to claim 16, wherein the unit dosage form comprises a capsule or a tablet. EX1001 at 48:62-63.

Ross '645 taught that solid form preparations include, for example, powders, *tablets*, pills, *capsules*, suppositories, and dispersible granules. A solid carrier may be one or more substances, which may also act as diluents, flavoring agents,

solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. EX1008 at 22:5-9.

Ross '645 thus anticipated claim 30, or at least rendered it obvious. EX1014 at ¶152.

**8. Claims 31-32 (process for preparing a tablet composition comprising the unit dosage form where GS-7977 is 400mg)**

Claim 31 recites a process for preparing a tablet composition comprising GS-7977 and various excipients. EX1001 at 48:64-49:12. Claim 32 recites a tablet composition comprising 400mg of GS-7977 made according to the process of claim 31. EX1001 at 49:13-14.

Ross '645 incorporates by reference Remington, which taught various formulation techniques that were also commonly known to a POSA. The process claimed in claim 31 would have been considered routine in light of the teachings of Ross'645 and Remington. EX1014 at ¶154.

With respect to claim 32, Ross '645 taught a dosage range for oral administration to be between 0.01 and 1g per day, including all incremental values of 0.01g (*i.e.*, 10mg) in between. EX1008 at 24:26-25:14. A POSA would know that a 400 mg daily dose was within the dose range contemplated by Ross '645. EX1014 at ¶155.

Also, as mentioned in the background art, it was common knowledge that the 200 mg and 400 mg daily doses of PSI-7977 (GS-7977) with PEG-IFN

(pegylated interferon) and RBV (ribavirin) provided a more durable virological response than the 100 mg daily dose of PSI-7977. EX1013 at 1; EX1014 at ¶156.

Therefore, Ross'645 anticipated claim 31-32, or at least rendered them obvious. EX1014 at ¶157.

**9. Claims 33-37 (method of treatment comprising administering the composition)**

Claim 33 recites treating a human infected with HCV comprising administering to the human the composition according to claim 1. EX1001 at 49:15-17. Claim 34 recites the method according to claim 33, wherein the composition is administered in combination with ribavirin. EX1001 at 49:18-20. Claim 35 recites treating a human infected with HCV comprising administering to the human the unit dosage form according to claim 16. EX1001 at 49:21-23. Claim 36 recites the method according to claim 35, wherein the unit dosage form is administered in combination with ribavirin. EX1001 at 49:24-26. Claim 37 recites a method according to claim 36, wherein the unit dosage form is administered in combination with ribavirin as part of an interferon-free treatment regimen. EX1001 at 49:26-29.

As discussed above, Ross '645 taught compositions and unit dosage forms comprising a specific crystalline form of GS-7977 at 400mg with a pharmaceutical excipient. EX1014 at ¶159.

Ross '645 also taught that compounds **4**, Rp-**4**, or Sp-**4** (GS-7977) could be



administered in a therapeutically effective amount to the subject. EX1008 at 24:12-14. Ross '645 further taught that the said compounds could be alongside “another antiviral agent”, including ribavirin. EX1008 at 26:20. Ross'645 disclosed that administration of two or more agents at the same time could 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. EX1008 at 24:24-25:24.

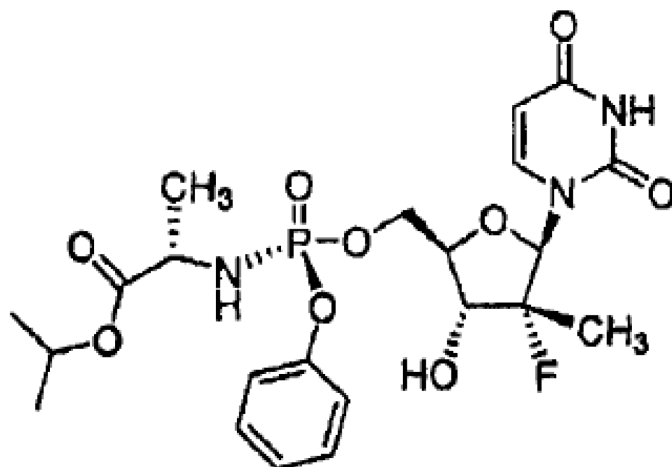
Accordingly, Ross '645 anticipated claims 33-37, or at least rendered them obvious. EX1014 at ¶161.

**B. Grounds 3 and 4: Claims 1-37 Were Anticipated By And Obvious Over Ross '257**

All of the claims of the '159 patent were anticipated by Ross '257. EX1014 at ¶162. They were also obvious over Ross '257. EX1014 at ¶162. In light of the teachings of Ross '257 and the background art, a POSA would have been motivated to, and had an expectation of success in, arrive at the pharmaceutical compositions and unit dosage forms claimed in the '159 patent. EX1014 at ¶162.

**1. Claims 1 and 2 (composition comprising compound and excipient)**

Claim 1 of the '159 patent recites a pharmaceutical composition comprising about 25% to about 35% w/w of crystalline GS-7977 having the structure:



and at least one pharmaceutically acceptable excipient, wherein the crystalline GS-7977 has XRPD 2 $\theta$ -reflections ( $^{\circ}$ ) at about 6.1 and 12.7. EX1001 at 46:36-56.

Claim 2 recites the composition according to claim 1 wherein the crystalline GS-7977 has XRPD 2 $\theta$ -reflections ( $^{\circ}$ ) at about 6.1, 8.2, 10.4, 12.7, 17.2, 17.7, 18.0, 18.8, 19.4, 19.8, 20.1, 20.8, 21.8 and 23.3. EX1001 at 46:57-60.

As set out in the background knowledge above, compound GS-7977 was already known. EX1014 at ¶165. Indeed, the '159 patent admitted this, including by citing U.S. Patent No. 7,964,580, which corresponds to Sofia '634. Pharmaceutical excipients were commonly used in compositions, such as tablets and unit dosage forms. EX1014 at ¶165. Examples of publications setting out the general principles of tablet design, excipient selection and tablet manufacture are explained in, Lieberman (EX1009), USP (EX1010) and Remington (EX1011). EX1014 at ¶165.

Rowe (EX1012) provided a more thorough review of excipients approved

for use by the U.S Food and Drug Administration. EX1014 at ¶166. Rowe taught a compendium of monographs for excipients used in pharmaceutical compositions, including most of those used in the patent '159. EX1014 at ¶166. The monographs for each excipient provide information on the functional category, application in formulations, description, specifications, typical properties, incompatibilities, method of manufacture, and regulatory status of each excipient listed, as well as published references to such excipients. EX1014 at ¶166. The monographs also provide information on typical quantities of excipients used in various types of formulations. EX1014 at ¶166. The '159 patent also states that the embodiments in the patent may be modified by one of ordinary skill without straying from the expressed intent using materials and methods described in Remington. EX1001 at 17:54-58.

Ross '257 taught both GS-7977 compounds  $R_p$ -4 and  $S_p$ -4. EX1005 at ¶¶0080-0106. Ross '257 specifically disclosed six crystalline forms of  $S_p$ -4. EX1005 at ¶¶0098-0106. Ross '257 also taught a substantially pure crystalline  $S_p$ -4. EX1014 at ¶167. This disclosure of the substantially pure crystalline  $S_p$ -4 therefore teaches that a genus of crystalline forms of  $S_p$ -4 existed including any additional crystalline forms. EX1005 at ¶¶0107-0108; EX1014 at ¶167.

Ross '257 also taught a composition using any of the compounds 4,  $R_p$ -4, or  $S_p$ -4 for oral administration for treatment, including in the form of tablets:

*An aspect of this embodiment is directed to a composition for the treatment of any of the viral agents disclosed herein said composition comprising a pharmaceutically acceptable medium selected from among an excipient, carrier, diluent, and equivalent medium and any of the compounds 4, R<sub>p</sub>-4, or S<sub>p</sub>-4, that is intended to include its hydrates, solvates, and any crystalline forms of any of compounds 4, R<sub>p</sub>-4, or S<sub>p</sub>-4 or its hydrates and solvates thereof. The compounds 4, R<sub>p</sub>-4, or S<sub>p</sub>-4 may be independently formulated in a wide variety of oral administration dosage forms and carriers. Oral administration can be in the form of tablets, coated tablets, hard and soft gelatin capsules, solutions, emulsions, syrups or suspensions.*

EX1005 at ¶0111 (emphasis added).

In addition, Ross '257 taught:

The compounds 4, R<sub>p</sub>-4, or S<sub>p</sub>-4 together with one or more conventional excipients, carriers, or diluents, may be placed into the form of pharmaceutical compositions and unit dosages. The pharmaceutical compositions and unit dosage forms may be comprised of conventional ingredients in conventional proportions, with or without additional active compounds and the unit dosage forms may contain any suitable effective amount of the active commensurate with the intended daily dosage range to be employed.

The pharmaceutical compositions may be employed as solids, such as tablets or filled capsules, semisolids, powders, sustained release formulations, or liquids such as suspensions, emulsions or filled capsules for oral use; or in the form of suppositories for rectal or

vaginal administration. A typical preparation will contain from about 5% to about 95% active compound or compounds (w/w).

EX1005 at ¶00113.

From these embodiments a POSA would have known that Ross '257 disclosed the following:

- A genus of crystalline forms of GS-7977 that include the specific crystalline form of claims 1 and 2 in the '159 patent;
- pharmaceutical compositions containing an excipient;
- pharmaceutical compositions containing conventional ingredients in conventional amounts;
- pharmaceutical compositions containing any amount of active ingredient commensurate with the intended daily dosage range;
- pharmaceutical compositions comprising a tablet form;
- Typical preparations (*e.g.*, tablets) containing from about 5% to about 95% active compound.

EX1014 at ¶170.

Accordingly, in light of the common knowledge relating to obtaining crystalline forms and pharmaceutically acceptable excipients discussed above, Ross '257 anticipated claims 1 and 2, or at least rendered them obvious. EX1014 at ¶171.

**2. Claims 3-12 (pharmaceutical composition comprising at least one pharmaceutically acceptable excipient)**

Claim 3 recites the composition according to claim 1, wherein the at least one pharmaceutically acceptable excipient comprises at least one diluent, a disintegrant, a glidant and a lubricant. EX1001 at 46:61-63.

Claim 4 recites the composition according to claim 3 wherein the at least one excipient comprises a diluent selected from a group consisting of dicalcium phosphate, cellulose, compressible sugars, dibasic calcium phosphate, dehydrate, lactose, mannitol, microcrystalline cellulose, starch, tribasic calcium phosphate, and combinations thereof. EX1001 at 46:64 – 47:3.

Claim 5 recites the composition according to claim 4, wherein the diluent is selected from the group consisting of mannitol, microcrystalline cellulose, and combinations thereof. EX1001 at 47:4-6.

Claims 6 recites the composition according to claim 3, wherein the at least one pharmaceutically acceptable excipient comprises a disintegrant selected from the group consisting of croscarmellose sodium, crospovidone, microcrystalline cellulose, modified corn starch, povidone, pregelatinized starch, sodium starch glycolat, and combinations thereof. EX1001 at 47:7-12.

Claim 7 recites to the composition according to claim 6, wherein the disintegrant is croscarmellose sodium. EX1001 at 47:13-14.

Claim 8 recites to the composition according to claim 3 wherein the at least

one pharmaceutical excipient comprises a glidant selected from the group consisting of colloidal silicon dioxide, talc, starch, starch derivatives and combinations thereof. EX1001 at 47:15-19.

Claim 9 recites to the composition according to claim 8, wherein the glidant is colloidal silicon dioxide. EX1001 at 47:20-21.

Claim 10 recites to the composition according to claim 3 wherein the at least one pharmaceutically acceptable excipient comprises a lubricant selected from the group consisting of calcium stearate, magnesium stearate, polyethylene glycol, sodium stearyl fumarate, stearic acid, talc and combinations thereof. EX1001 at 47:22-26.

Claim 11 recites to the composition according to claim 10, wherein the lubricant is magnesium stearate. EX1001 at 47:27-28.

Claim 12 recites to the composition according to claim 1 further comprising a coating agent. EX1001 at 47:29-30.

As set out in the background knowledge above, pharmaceutical excipients were commonly used in compositions, such as tablets and unit dosage forms. EX1014 at ¶182. Examples of publications setting out the general principles of tablet design, excipient selection and tablet manufacture are explained in, Lieberman (EX1009), USP (EX1010) and Remington (EX1011). EX1014 at ¶182. Rowe (EX1012) provided a more thorough review of the excipients approved for

use by the U.S Food and Drug Administration. EX1014 at ¶182.

The '159 patent in fact states that the embodiments in the patent may be modified by one of ordinary skill without straying from the expressed intent using materials and methods described in Remington. EX1001 at 17:54-58.

Relevant to claim 3 of '159, Ross '257 taught that the compounds **4**, R<sub>p</sub>-**4**, or S<sub>p</sub>-**4** would generally be administered in admixture with one or more suitable pharmaceutical excipients, diluents, or carriers selected with regard to the intended route of administration and standard pharmaceutical practice. EX1014 at ¶184. Ross '257 further taught the use of excipients including a pharmaceutically acceptable diluent, disintegrant, and lubricant:

Solid form preparations include, for example, powders, *tablets*, pills, capsules, suppositories, and dispersible granules. A solid carrier may be one or more substances which may also act as *diluents*, flavoring agents, solubilizers, *lubricants*, suspending agents, binders, preservatives, *tablet disintegrating agents*, or an encapsulating material.

EX1005 at ¶0114-0115 (emphasis added).

Relevant to claims 4 and 5 of '159, Ross '257 taught a non-limited list of suitable carriers, including sugar, methylcellulose, carboxymethylcellulose, lactose, and magnesium stearate. EX1005 at ¶0115. Various diluents for pharmaceutical formulations, including microcrystalline cellulose and mannitol, were also common knowledge. *See, e.g.*, EX1012 at 3 and 28.



Relevant to claims 6 and 7 of '159, Ross '257 taught that a solid carrier may be one or more substances which may act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents or encapsulating material. EX1005 at ¶0115. A number of the disintegrants claimed in the '159 patent were also common knowledge, including croscarmellose sodium (EX1012 at 44), crospovidone (EX1012 at 42), microcrystalline cellulose (EX1012 at 3), starch (EX1012 at 33), povidone (EX1012 at 47), pregelatinized starch (EX1012 at 39) and sodium starch glycolate (EX1012 at 53). EX1014 at ¶186.

Relevant to claims 8 and 9, Ross '257 taught suitable carriers included but were not limited to magnesium carbonate, magnesium stearate, *talc*, sugar, lactose, pectin, dextrin, *starch*, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting cocoa butter and the like. EX1005 at ¶0115. The various glidants claimed in the '159 patent were also common knowledge, including colloidal silicon dioxide (EX1012 at 60), talc (EX1012 at 57) and starch (EX1012 at 33). EX1014 at ¶187.

Relevant to claims 10 and 11, Ross '257 taught that a solid carrier may be one or more substances which may act as diluents, flavoring agents, solubilizers, *lubricants*, suspending agents, binders, preservatives, tablet disintegrating agents or encapsulating material. EX1005 at ¶0115. The various lubricants claimed were

also common knowledge, including calcium stearate (EX1012 at 63), magnesium stearate (EX1012 at 67), polyethylene glycol (EX1012 at 71), sodium stearyl fumarate (EX1012 at 77), stearic acid (EX1012 at 80) and talc (EX1012 at 57). EX1014 at ¶188.

In relation to claim 12, Ross '257 taught that oral administration can be in the form of tablets, *coated tablets*, hard and soft gelatin capsules, solutions emulsions, syrups, or suspensions. EX1005 at ¶0112.

In addition to the above teachings, the '159 patent admits the general knowledge on pharmaceutical carriers, diluents and excipients, such as described in Remington, etc.. EX1014 at ¶190. Therefore, in view of Ross '257 and the common knowledge around pharmaceutical excipients for the purpose of formulating a compound, claims 3-12 were anticipated and obvious. EX1014 at ¶190.

**3. Claims 13-15 (composition comprising at least one pharmaceutically acceptable excipient by specific weight)**

Claims 13-15 of the '159 patent recite a composition according to claim 1 wherein at least one pharmaceutically acceptable excipient comprises particular weight of a diluent, disintegrant, glidant and a lubricant. Claims 14 and 15 further specify the excipients as mannitol, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate in particular weights. EX1001 at 47:31-50.

Ross '257 taught the use of compounds 4, Rp-4, or Sp-4 (GS-7977) with one or more pharmaceutical excipients where the typical preparation would contain from about 5% to about 95% active compound or compounds (w/w), thereby encompassing the range claimed in the '159 patent. EX1005 ¶¶0113.

As discussed above, the various excipients (diluent, disintegrant, glidant and lubricant) claimed in the '159 patent are expressly disclosed in Ross '257 patent or were common knowledge as evidenced by Rowe (EX1012) and Remington (EX1011). EX1014 at ¶193.

Ross '257 further provided that the pharmaceutical compositions and unit dosage forms may be comprised of conventional ingredients in *conventional proportions*, with or without additional active compounds and the unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. EX1005 at ¶0113.

With respect to the excipients specifically claimed in claims 13-15, it was common knowledge that mannitol is commonly used as a diluent and is usually 10-90% w/w in tablet formulations (EX1012 at 28); crosscarmellose sodium is commonly used as a disintegrant and may be used at concentrations up to 5% w/w (EX1012 at 44); and magnesium stearate is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% (EX1012 at 67).

EX1014 at ¶195.

Ross '257 along with the common knowledge around pharmaceutical excipients as exemplified by Rowe and Remington, (which are both referenced by the '159 patent) anticipated claims 13-15, or at least rendered them obvious. EX1014 at ¶196.

**4. Claims 16-17 (unit dosage form comprising 400mg of crystalline GS-7977)**

Claims 16-17 recite to a unit dosage form comprising 400 mg of crystalline GS-7977, wherein the crystalline GS-7977 has XRPD 2 $\theta$ -reflections ( $^{\circ}$ ) at about 6.1 and 12.7 and at about 6.1, 8.2, 10.4, 12.7, 17.2, 17.7, 18.0, 18.8, 19.4, 19.8, 20.1, 20.8, 21.8 and 23.3, and at least one pharmaceutically acceptable excipient. EX1001 at 47:51-48:9.

Ross '257 taught both GS-7977 compounds  $R_p$ -4 and  $S_p$ -4. EX1008 at 7:1-5. Ross '257 specifically disclosed six crystalline forms of  $S_p$ -4. EX1005 at ¶¶0098-0104. Ross '257 also taught a substantially pure crystalline  $S_p$ -4. EX1014 at ¶198. This disclosure of the substantially pure crystalline  $S_p$ -4 therefore teaches that a genus of crystalline forms of  $S_p$ -4 existed including any additional crystalline forms. EX1005 at ¶¶0107-0108; EX1014 at ¶198.

Ross '257 also taught that the compounds 4,  $R_p$ -4, or  $S_p$ -4 (GS-7977) and the crystalline forms disclosed therein, together with one or more conventional *excipients*, carriers, or *diluents*, may be placed into the form of pharmaceutical

compositions and *unit dosages*. EX1005 at ¶0113.

Further, Ross '257 taught a dosage range for oral administration to be between 0.01 and 1g per day, including all incremental values of 0.01g (*i.e.*, 10mg) in between. EX1005 at ¶0126. A POSA would know that a 400 mg daily dose was within the dose range contemplated by Ross '257. EX1014 at ¶200.

Also, as mentioned in the background art, it was common knowledge that the 200 mg and 400 mg daily doses of PSI-7977 (GS-7977) with PEG-IFN (pegylated interferon) and RBV (ribavirin) provided a more durable virological response than the 100 mg daily dose of PSI-7977. EX1013 at 1; EX1014 at ¶201.

Ross '257, along with what was already common knowledge, such as that disclosed by Lawitz, anticipated claims 16 and 17 of the '159 patent, or at least rendered them obvious. EX1014 at ¶202.

**5. Claims 18-27 (unit dosage form comprising at least one pharmaceutical excipient)**

Claim 18 recites the unit dosage form according to claim 16, wherein the at least one pharmaceutically acceptable excipient comprises at least one diluent, a disintegrant, a glidant and a lubricant. EX1001 at 48:10-13.

Claim 19 recites the unit dosage form according to claim 18 wherein the at least one excipient comprises a diluent selected from a group consisting of dicalcium phosphate, cellulose, compressible sugars, dibasic calcium phosphate, dehydrate, lactose, mannitol, microcrystalline cellulose, starch, tribasic calcium

phosphate, and combinations thereof. EX1001 at 48:14-20.

Claim 20 recites the unit dosage form according to claim 19, wherein the diluent is selected from the group consisting of mannitol, microcrystalline cellulose, and combinations thereof. EX1001 at 48:21-22.

Claim 21 recites the unit dosage form according to claim 18, wherein the at least one pharmaceutically acceptable excipient comprises a disintegrant selected from the group consisting of croscarmellose sodium, crospovidone, microcrystalline cellulose, modified corn starch, povidone, pregelatinized starch, sodium starch glycolat, and combinations thereof. EX1001 at 48:23-28.

Claim 22 recites to the unit dosage form according to claim 21, wherein the disintegrant is croscarmellose sodium. EX1001 at 48:29-30.

Claim 23 recites to the unit dosage form according to claim 18 wherein the at least one pharmaceutical excipient comprises a glidant selected from the group consisting of colloidal silicon dioxide, talc, starch, starch derivatives and combinations thereof. EX1001 at 48:31-35.

Claim 24 recites to the unit dosage form according to claim 23, wherein the glidant is colloidal silicon dioxide. EX1001 at 48:36-37.

Claim 25 recites to the unit dosage form according to claim 18 wherein the at least one pharmaceutically acceptable excipient comprises a lubricant selected from the group consisting of calcium stearate, magnesium stearate, polyethylene

glycol, sodium stearyl fumarate, stearic acid, talc and combinations thereof. EX1001 at 48:38-42.

Claim 26 recites to the unit dosage form according to claim 25, wherein the lubricant is magnesium stearate. EX1001 at 48:43-44.

Claim 27 recites to the unit dosage form according to claim 16 further comprising a coating agent. EX1001 at 48:45.

Ross '257 taught that the compounds 4, R<sub>p</sub>-4, or S<sub>p</sub>-4 (GS-7977) and the genus of crystalline forms disclosed therein, together with one or more conventional *excipients*, carriers, or *diluents*, may be placed into the form of pharmaceutical compositions and *unit dosages*. EX1005 at ¶0113.

With respect to claims 18-26 and the excipients claimed therein, reference is made back to the discussion of claims 3-12 above.

In relation to claim 27, Ross '257 taught that oral administration can be in the form of tablets, *coated tablets*, hard and soft gelatin capsules, solutions emulsions, syrups, or suspensions. EX1005 at ¶0112.

In addition to the above teachings, the '159 patent admits the general knowledge on pharmaceutical carriers, diluents and excipients, such as described in Remington, etc. EX1014 at ¶216. Therefore, in view of Ross '257 and the common knowledge around pharmaceutical excipients for the purpose of formulating a compound, claims 18-27 of the '159 patent were anticipated and obvious. EX1014

at ¶216.

**6. Claims 28-29 (unit dosage form comprising at least one pharmaceutically acceptable excipient by specific weight)**

Claim 28 of the '159 patent recites a composition according to claim 16 wherein at least one pharmaceutically acceptable excipient comprises particular weight of a diluent, disintegrant, glidant and a lubricant. Claim 29 further specifies the excipients as mannitol, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate in particular dosage and weight ranges. EX1001 at 48:47-61.

Ross '257 taught that the compounds 4, R<sub>p</sub>-4, or S<sub>p</sub>-4 (GS-7977) and the genus crystalline forms disclosed therein, together with one or more conventional *excipients*, carriers, or *diluents*, may be placed into the form of pharmaceutical compositions and *unit dosages*. EX1005 at ¶00113.

Ross '257 further provided that the pharmaceutical compositions and unit dosage forms may be comprised of conventional ingredients in *conventional proportions*, with or without additional active compounds and the unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. EX1005 at ¶00113.

Further, Ross '257 taught a dosage range for oral administration to be between 0.01 and 1g per day, including all incremental values of 0.01g (*i.e.*, 10mg)



in between. EX1005 at ¶0126. A POSA would know that a 400 mg daily dose was within the dose range contemplated by Ross '257. EX1014 at ¶220.

Also, as mentioned in the background art, it was common knowledge that the 200 mg and 400 mg daily doses of PSI-7977 (GS-7977) with PEG-IFN (pegylated interferon) and RBV (ribavirin) provided a more durable virological response than the 100 mg daily dose of PSI-7977. EX1013 at 1; EX1014 at ¶221.

With respect to the various weights of excipients set out in claims 28 and 29, Ross '257 along with the common knowledge of pharmaceutical excipients as exemplified by Rowe and Remington (which are both referenced by the '159 patent) anticipated claims 28 and 29, or at least rendered them obvious. EX1014 at ¶222.

**7. Claim 30 (unit dosage form comprising a capsule or tablet)**

Claim 30 recites a unit dosage form according to claim 16, wherein the unit dosage form comprises a capsule or a tablet. EX1001 at 48:62-63.

Ross '257 taught that solid form preparations include, for example, powders, *tablets*, pills, *capsules*, suppositories, and dispersible granules. A solid carrier may be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. EX1005 at ¶00115.

Ross '257 thus anticipated claim 30, or at least rendered it obvious. EX1014

at ¶225.

**8. Claims 31-32 (process for preparing a tablet composition comprising the unit dosage form where GS-7977 is 400mg)**

Claim 31 recites a process for preparing a tablet composition comprising GS-7977 and various excipients. EX1001 at 48:64-49:12. Claim 32 recites a tablet composition comprising 400mg of GS-7977 made according to the process of claim 31. EX1001 at 49:13-14.

Ross '257 incorporates by reference Remington, which taught various formulation techniques that were also commonly known to a POSA. The process claimed in claim 31 would have been considered routine in light of the teachings of Ross'257 and Remington. EX1014 at ¶227.

With respect to claim 32, Ross '257 taught a dosage range for oral administration to be between 0.01 and 1g per day, including all incremental values of 0.01g (*i.e.*, 10mg) in between. EX1005 at ¶0126. A POSA would know that a 400 mg daily dose was within the dose range contemplated by Ross '257 and was within the range contemplated as "most preferably" by the inventors of '257. EX1014 at ¶228.

Also, as mentioned in the background art, it was common knowledge that the 200 mg and 400 mg daily doses of PSI-7977 (GS-7977) with PEG-IFN (pegylated interferon) and RBV (ribavirin) provided a more durable virological response than the 100 mg daily dose of PSI-7977. EX1013 at 1; EX1014 at ¶229.

Therefore, Ross'257 anticipated claims 31-32, or at least rendered them obvious. EX1014 at ¶230.

**9. Claims 33-37 (method of treatment comprising administering the composition)**

Claim 33 recites treating a human infected with HCV comprising administering to the human the composition according to claim 1. EX1001 at 49:15-17. Claim 34 recites the method according to claim 33, wherein the composition is administered in combination with ribavirin. EX1001 at 49:18-20. Claim 35 recites treating a human infected with HCV comprising administering to the human the unit dosage form according to claim 16. EX1001 at 49:21-23. Claim 36 recites the method according to claim 35, wherein the unit dosage form is administered in combination with ribavirin. EX1001 at 49:24-26. Claim 37 recites a method according to claim 36, wherein the unit dosage form is administered in combination with ribavirin as part of an interferon-free treatment regimen. EX1001 at 49:26-29.

As discussed above, Ross '257 taught compositions and unit dosage forms comprising a specific crystalline form of GS-7977 at 400 mg with a pharmaceutical excipient. EX1014 at ¶232.

Ross '257 also taught that compounds **4**, Rp-**4**, or Sp-**4** (GS-7977) could be administered in a therapeutically effective amount to the subject. EX1005 at ¶0123. Ross '257 further taught that the said compounds could be alongside “another

antiviral agent”, including ribavirin EX1005 at ¶¶0129. Ross ’257 disclosed that administration of two or more agents at the same time could 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. EX1005 at ¶¶0128-¶¶0129.

Accordingly, Ross ’257 anticipated claims 33-37, or at least rendered them obvious. EX1014 at ¶234.

## **XI. CONCLUSION**

For these reasons, claims 1-37 of the ’159 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 26, 2017

/Daniel B. Ravicher/

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## XII. APPENDIX – LIST OF EXHIBITS

<b>Exhibit No.</b>	<b>Description</b>
1001	U.S Patent No. 8,889,159
1002	File History Excerpts
1003	Sofia 634
1004	Sofia 2010
1005	Ross 257
1006	ICH
1007	Byrn
1008	Ross 645
1009	Lieberman
1010	USP
1011	Remington
1012	Rowe
1013	Lawitz
1014	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 12,809 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a).

Respectfully,

Dated: December 26, 2017

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

#### **XIV. CERTIFICATE OF SERVICE**

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105, I certify that I caused to be served a true and correct copy of the foregoing PETITION FOR *INTER PARTES* REVIEW and supporting materials (Exhibits 1001-1014 and Power of Attorney) by Priority Mail Express® or by means at least as fast and reliable as Priority Mail Express®, on the date below on the Patent Owner at the correspondence address of the Patent Owner as follows:

GILEAD PHARMASSET LLC  
333 LAKESIDE DRIVE  
FOSTER CITY, CALIFORNIA 94404

Respectfully,

Dated: December 26, 2017

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