BEFORE THE CONTROLLER OF PATENTS, THE PATENT OFFICE, 
CHENNAI

IN THE MATTER OF A PRE-GRANT OPPOSITION UNDER SECTION 25 (1) 
AND RULE 55 OF THE PATENTS ACT, 1970

And

IN THE MATTER OF PATENT APPLICATION NO. 9149/CHENP/2012 DATED 
OCTOBER 10, 2012 IN THE NAME OF GILEAD PHARMASSET, LLC. 333 
LAKESIDE DRIVE, POSTER CITY, CALIFORNIA, 94404, U.S.A.

....APPLICANT/RESPONDENT

And

IN THE MATTER OF REPRESENTATION BY WAY OF NOTICE OF OPPOSITION 
FILED BY THE DELHI NETWORK OF POSITIVE PEOPLE (DNP+)

AND

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

......OPPONENTS/PETITIONERS

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STATEMENT OF CASE OF THE OPPONENTS

1. The Opponents are the Delhi Network of Positive People (DNP+), a community based non-profit organisation representing the needs of people living with HIV/AIDS (“PLHAs”) and Hepatitis C (HCV), registered as a Trust under Registration No. 8525, Additional Book No. 1423/1-23 IV Sub Registrar, New Delhi, with its registered address
2. **ANALYSIS OF THE APPLICANT’S SPECIFICATIONS**


2.2 Based on the information available on the Indian Patent Office’s online database inPASS, ‘9149 is currently under examination. Accordingly, under Section 25(1) of the Act and Rule 55(1), any person may file a representation by way of opposition at the appropriate office (Chennai) before the grant of a patent in ‘9194. The Opponents submit the present opposition and supporting evidence to ‘9149 based on the grounds set out below. The Opponents, as permitted under Section 25(1) of the Act and Rule 55(1), also request a hearing before this matter is finally decided.

**3. BACKGROUND TO ‘9149**

3.1 The Hepatitis C virus (HCV) presents a serious global health problem. The virus is transmitted through direct contact with an infected persons’ blood. Persons with needle-
stick injury, health care workers with exposure to blood/blood products, transfusion/blood product recipients, organ transplant recipients and intravenous drug users are some of the demographics who are at risk from HCV. According to the World Health Organization, over 80 million people have chronic HCV infection and are likely to develop liver cancer and/or cirrhosis. The best estimates available show India alone has an estimated 6 million people who are chronically infected with HCV, with 96,000 deaths annually due to the infection. India is also home to 2.1 million people living with HIV (PLHIV) and applying the global co-infection rate of 2.4% implies that approximately 50,400 people in this community may be co-infected with HCV.

3.2 Given the public health crisis around HCV, in India and elsewhere it is imperative that people living with HCV are able to access the latest and most effective treatments without unmerited patents standing in the way. Patents, such as ‘9149, afford the Applicant unmerited exclusive rights. ‘9149 would allow the Applicant to extend its monopoly period while continuing to price the medicine beyond the reach of not only Indian patients, but also many in need in other developing and even developed countries. The Applicant also strategically uses such unmerited patents in its licensing programme in India in order to manage the generic competition and further delay legitimate open competition. By managing the competition the Applicant is able to control the market in India but also in other countries where competitors may otherwise have been able to sell the medicine at more affordable prices.

3.3 ‘9149 claims an invention for a crystalline (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-yl) methoxy)(phenoxy)phosphoryl)amino)propanoate of formula S₈p₄ having XRPD 2θ reflections (±0.2°) at 6.1 and 12.7 and pharmaceutical compositions thereof, either alone or in combination with another antiviral agent.

3.4 According to documents made available on the Patent Office website, inPASS, the initial filing of ‘9149 on October 26, 2012 comprised 70 Claims relating to a crystalline form of (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2 l)methoxy)(phenoxy)phosphoryl)amino)propanoate, pharmaceutical compositions and their processes thereof, either alone or in combination with another antiviral agent.
Thereafter, on March 12, 2013, the Applicant amended certain pages of the complete specification and Claims, thereby reducing the numbers of Claims to 62 Claims.

3.5 On March 07, 2016, the Applicant submitted a more specific set of Claims reducing the number of Claims to 11. These Claims are attached as **Exhibit 2**. The Opponents believe that this is the set of Claims that the Applicant wishes to be examined. Accordingly, the Opponents set out their grounds of opposition against these amended Claims. However, should the Applicant amend any of its Claims during examination, the Opponents reserve their right to modify the present Opposition accordingly at that stage and/or file a supplementary Opposition.

3.6 The current set of Claims for ‘9149 as set out in **Exhibit 2** may be summarised as follows:

1. Claim 1 covers crystalline (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate represented by the formula Sp-4:

   ![Sp-4](image)

   having XRPD 2θ-reflections (±0.2°) at 6.1 and 12.7.

2. Claim 2 is dependent on claim 1 and covers crystalline (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate of claim 1 further having: XRPD 2θ-reflections (±0.2°) at about: 8.2, 10.4, 17.2, 17.7, 18.0, 18.8, 19.4, 19.8, 20.1, 20.8, 21.8, and 23.3.
3. Claim 3 is dependent on Claims 1 or 2 and covers a pharmaceutical composition comprising crystalline (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate of Claims 1 or 2 and a pharmaceutically acceptable medium.

4. Claim 4 is dependent on Claim 3 and covers a pharmaceutical composition according to claim 3, further comprising another antiviral agent.

5. Claim 5 is dependent on Claim 4 and covers a pharmaceutical composition according to claim 4, wherein the another antiviral agent is a HCV NS3 protease inhibitor.

6. Claim 6 is dependent on Claim 4 and covers a pharmaceutical composition according to claim 4, wherein the another antiviral agent is a HCV NS5A inhibitor.

7. Claim 7 is dependent on claim 4 and covers a pharmaceutical composition according to claim 4, wherein the another antiviral agent is a HCV NS3 protease inhibitor and a HCV NS5A inhibitor.

8. Claim 8 is dependent on Claims 1 or 2 and covers tablet comprising the crystalline Sp-4 of claims 1 or 2.

9. Claim 9 covers a tablet comprising Sp-4:

![Chemical Structure](image)

wherein at least 70% of the Sp-4 is the crystalline Sp-4 of Claims 1 or 2.
10. Claim 10 is dependent on claim 9 and covers the tablet of claim 9, wherein at least 80% of the Sp-4 is the crystalline Sp-4 of Claims 1 or 2.

11. Claim 11 is dependent on claim 9 and covers the tablet of claim 9, wherein at least 90% of the Sp-4 is the crystalline Sp-4 of Claims 1 or 2.

4. GROUNDS OF OPPOSITION

4.1 As described in the Background above, the invention claimed in ‘9149 relates to a crystalline (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2 yl) methoxy)(phenoxy)phosphoryl)amino)propanoate of formula Sp-4 having XRPD 2θ-reflections (±0.2°) at 6.1 and 12.7 and pharmaceutical compositions thereof, either alone or in combination with another antiviral agent. The Opponents believe that Claims 1 to 11 are not patentable on account of the following grounds under Section 25(1) of the Act:

a. Section 25(1)(e): Obviousness/Lack of inventive step
That the invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step having regard to the matter published as mentioned in clause (b) or having regard to what was used in India before the priority date of the applicant’s claim.

b. Section 25(1)(f) –Not an invention/Not Patentable
That the subject of any claim of the complete specification is not an invention within the meaning of this Act, or is not patentable under this Act, in particular under Sections 3(d) and (e).

c. Section 25(1)(h) –Not complied with the requirements of Section 8
That the Applicant has failed to disclose to the Controller the information required by Section 8 or has furnished the information that in any material particular was false to his knowledge.
5. **Invalid Priority Claim**

5.1 Before setting out the grounds of this opposition, the Opponents would like to put forward arguments relating to the invalid priority claims made in relation to ‘9149. These arguments are important for determining the relevant date for the purpose of prior publications (prior art) and how they support the Opponents’ grounds.

5.2 ‘9149 is a national phase application stemming from PCT Application No. PCT/US2011/030725 (published as WO 2011/123645), which was filed on March 31, 2011. Form 1 submitted by the Applicant for ‘9149 (attached as Exhibit 3) shows that ‘9149 claims priority from following three United States patent applications:

   (i) US 61/319,548 filed on March 31, 2010 (attached as Exhibit 4);
   (ii) US 61/319,513 filed on March 31, 2010 (attached as Exhibit 5); and
   (iii) US 12/783,680 filed on May 20, 2010 (attached as Exhibit 6).

5.3 ‘9149 is not entitled to the priority dates of March 31, 2010 or May 20, 2010 from the aforesaid US applications because the currently amended claims of ‘9149 are directed to a specific crystal line form with 2 specific XRD readings that are not supported by any of the US priority documents. In fact, no individual compound with a corresponding XRD 2θ peaks even within the 0.2 ± limitation is found within the priority documents. None of the US priority applications provide support for a crystalline (S)-isopropyl 2-(((S)-((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2yl) methoxy)(phenoxy)phosphoryl)amino)propanoate of formula Sp-4 having XRPD 20-reflections (±0.2°) at 6.1 and 12.7.

5.4 The Opponents submit that in US 61/319,548 (Exhibit 4) there are only broad synthesis examples provided with a generic crystallization step. Priority Applications US 61/319,513 (Exhibit 5) at page 17 and US 12/783,680 (Exhibit 6) at page 19 provide only a general disclosure on crystalline forms but there is no specific support for the form with XRD 20 peaks at 6.1 and 12.7.

5.5 Therefore, the currently amended Claims of ‘9149 are not entitled to claim priority from any of the listed priority applications US 61/319,548, US 61/319,513 and US
The first patent that supports crystalline (S)-isopropyl 2-(((S)-((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2y1 methoxy) (phenoxy)phosphoryl)amino)propanoate of formula Sp-4 having XRPD 2θ-reflections (±0.2°) at 6.1 and 12.7 is PCT/US2011/030725 filed on March 31, 2011, from which this application derives. Hence, any publications before the filing date of March 31, 2011 should be considered relevant prior art for judging the novelty and inventive step of ‘9194.

5.6 To substantiate the above arguments, the Opponents refer to prosecution proceedings at the European Patent Office (EPO) for European Application No. 11714465.9 (published as EP 2552930), which is the application corresponding with ‘9149. In the said EPO proceedings, the Applicant expressly admitted that there is a lack of support in the priority applications for the specific crystalline form claimed therein.

5.7 In response to the EPO’s International Search Authority report, the Applicant made a detailed submission dated May 02, 2013 (attached as Exhibit 7) in order to overcome the inventive step objection against the cited prior art WO2010135569 (WO ‘569) attached as D1 to the present opposition. D1 has a publication date of November 25, 2010, which is after the priority dates claimed for the European application in question (and ‘9149), namely March 31, 2010 and May 20, 2010. The Applicant goes to great lengths to submit comparative testing data for the claimed compounds against the cited prior art D1 compounds.

5.8 In a subsequent EPO office action dated August 13, 2013 (attached as Exhibit 8), the EPO examiner again raised the objection of the priority date and held that the crystalline Form 6 is not disclosed in any of the priority documents. Hence, the effective priority date for Claims 1 to 8 of the corresponding EPO application is the filing date March 31, 2011.

The relevant paragraph from the office action dated August 13, 2013, is reproduced below:

**Priority**
“Present claims 1-8 disclose crystalline form 6 of Sp-4 of claim 1 (see example 21-5 on pages 95-96 of the present published application).

Crystalline form 6 is not disclosed in any of the priority documents, hence the effective date of claims 1-8 is the filing date (31-03-2011).

Documents D3-D4 cited as XP-documents in the International Search Report do not disclose crystalline form 6. They are not relevant to the novelty of the present claims. However, since they have both a publication date prior to the filing date of the present application (the effective date of current claims 1-8), they can be used for the assessment of inventive step”.

5.9 As a result, the EPO maintained D1 as prior art and instructed the Applicant that it should be be added to the background description:

The relevant paragraph from the office action dated August 13, 2013, is reproduced below:

**Final remarks**

“To meet the requirements of Rule 42(1)(b) EPC, document D3 should be identified in the description and the relevant background art disclosed therein should be briefly discussed”.

5.10 In a response to the office action, the Applicant filed a reply to the EPO Examining Division on November 28, 2013 herewith filed as Exhibit 9, and proceeded to distinguish the specific form claimed in its application (Form 6) from the closest prior art, D1 (Forms 1-5). In its submissions, the Applicant again failed to rebut the lack of support in the priority documents. This failure to address the EPO’s refusal to recognise priority should, therefore, be taken as an admission that the filing date of March 31, 2011 is the effective date for the Claims of ‘9149.
5.11 In a subsequent office action dated April 08, 2014 (attached as Exhibit 10), the EPO again maintained the objection related to the priority claim. The relevant paragraph from the office action dated August 13, 2013, is reproduced below:

**Priority**

“Present claims 1-8 disclose crystalline form 6 of Sp-4 of claim 1 (see example 21-5 on pages 95-96 of the present published application).

Crystalline form 6 is not disclosed in any of the priority documents, hence the effective date of claims 1-8 is the filing date (31-03-2011).

Documents D3-D4 cited as XP-documents in the International Search Report do not disclose crystalline form 6. They are not relevant to the novelty of the present claims. However, since they have both a publication date prior to the filing date of the present application (the effective date of current claims 1-8), they can be used for the assessment of inventive step.”

5.12 Further, the Examining Division maintained the objection that D1 should be identified in the background description.

The relevant paragraph from the office action is reproduced below:

**Final remarks**

“To meet the requirements of Rule 42(1)(b) EPC, document D3 should be identified in the description and the relevant background art disclosed therein should be briefly discussed”.

5.13 In response to the subsequent office action dated April 08, 2014, the Applicant filed a reply to the EPO Examining Division on August 18, 2014 (attached as Exhibit 11) submitting amended claims and acknowledging D1 in the specification.
The relevant admission is reproduced below:

**Final Remarks:**

“Document D3 has been acknowledged in the description”.

5.14 As set out above, the Opponents submit that the priority Claims of ‘9149 do not meet the requirements of Section 11 of the Act, which requires that the claims of the complete specification must be contained in the document from which priority is claimed. As such, none of the US priority applications provide support for the crystalline (S)-isopropyl \(2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2yl)methoxy)(phenoxy)phosphoryl)amino)propanoate\) of formula Sp-4 having XRPD 20-reflections (±0.2°) at 6.1 and 12.7.

Moreover, as stated by Section 137 of the Act, given the Claims set out in’9149 were first disclosed in the parent PCT Application No. PCT/US2011/030725, the priority date of such claims should be the international filing date i.e. March 31, 2011. As such, publications prior to March 31, 2011 should be accepted for the purpose of determining whether the subject matter claimed in ‘9149 amounts to a new invention.

6. DETAILED GROUNDS

6.1 GROUND 1

Claims 1 to 11 are obvious, do not involve a technical advance and lack inventive step as defined under Section 2 (1) (ja) and, therefore, should be rejected under Sections 25(1)(e), 2(1)(j) and 2(1) (ja) of the Act.

6.1.1. Section 2(1) (j) defines an “invention” as a new product or process involving an **inventive step** and capable of industrial application. Therefore, all alleged inventions, in order to qualify for a patent, must satisfy the criteria of inventive step. Section 2(1) (ja) of the Patents Act defines an inventive step as “a feature of an invention that involves technical advance as compared to the existing knowledge or having economic significance or both and that makes the invention not obvious to a person skilled in the
art. The requirement of inventive step, as defined in Section 2(1) (ja) sets out two requirements:

- first, the feature involved in the alleged invention ought to involve a technical advance as compared to the existing knowledge; and
- second the feature should not be obvious to the person skilled in the art.

The above requirements are laid down to ensure that patents, which result in a monopoly, are granted only for genuine inventions.

6.1.2 The alleged invention is directed to the crystalline (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)oxy)(phenoxy)phosphoryl)amino)propanoate of formula Sp-4 having XRPD 2θ-reflections (±0.2°) at 6.1 and 12.7 and pharmaceutical compositions thereof, either alone or in combination with another antiviral agent. The Opponents submit that for a person skilled in the art, it would be obvious that the compound in the alleged invention can exist in a crystalline form and the finding of such form would be only a matter of routine experimentation.

It is submitted that Claims 1 to 11 of ‘9149 do not involve a technical advance as compared to the existing knowledge and are obvious to a person skilled in the art in light of the prior disclosures in the art. Therefore, Claims 1 to 11 of ‘9149 ought to be rejected under Section 25 (1) (e).

6.1.3 The Opponents rely on the following documents to establish the grounds of obviousness and lack of inventive step.


b. Article titled “Discovery of a β-D-20-Deoxy-20-r-fluoro-20-β-C-methyluridine Nucleotide Prodrug (PSI-7977) for the Treatment of Hepatitis C Virus”, by Sofia

c. Pharmasset Announces Results of a 28-day Phase 2a Study with PSI-7977 for the Treatment of Chronic Hepatitis C Infection, Pharmasset Inc, published May 4, 2010 marked as D3.


(a) As illustrated in the previous paragraphs, ‘9149 makes an invalid priority claim and is not entitled to priority from US 61/319,548, US 61/319,513 or US 12/783,680. The first patent that claims the crystalline (S)-isopropyl 2-(((S)-((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino) propanoate of formula Sp-4 having XRPD 20-reflections (±0.2°) at 6.1 and 12.7 is PCT/US2011/030725 filed on March 31, 2011 from which this application derives. Hence, any publication before the filing date of March 31, 2011 should be considered relevant prior art. The arguments in this section are premised on the priority claims for ‘9149 being invalid, and the priority date being established as the filing date of March, 31 2011.

(b) The Opponents submit that Claims 1 to 11 of ‘9149 lack inventive step and are obvious under Section 25(1)(e) in view of WO’569, when read alone or in combination with any of the references stated above. The Opponents would first like to draw the Controller’s attention to WO ‘569 published on November 25, 2010, attached as D1. WO
'569 discloses five polymorphic forms (Forms 1 - 5) of (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate. The compounds disclosed in WO ‘569 are inhibitors of RNA-dependent 5 RNA viral replication and are useful as inhibitors of HCV NS5B polymerase, as inhibitors of HCV replication and for treatment of hepatitis C infection.

(c) ‘9149 claims a crystalline form of (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate represented by formula Sp-4, having XRPD 2θ-reflections (±0.2°) at 6.1 and 12.7. Given that WO ‘569 already discloses five polymorphic forms (Form 1-5) of (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate, the presence of an additional crystalline form as claimed in ‘9149 is inherently known in the prior art and, therefore, is a known compound. The formation of crystalline forms and the additional properties associated with such crystalline forms was common knowledge and routine experimentation for a person skilled in the art as of the priority date of ‘9149. The Opponents submit that obtaining a crystalline form of a known compound does not involve an inventive step and is, therefore, unpatentable.

(d) As such, Claims 1 to 11 of ‘9149 do not involve a technical advance as compared to the existing knowledge and are obvious to a person skilled in the art in light of the disclosures in WO ‘569. The comparison of the Claims of ‘9149 with the claims claimed in WO ‘569 is provided in Table 1 below for the sake of clarity and convenience.

(c) **Table 1:** A comparison of independent claim 1 (as amended on 7th March 2016) with the disclosure in D1 is provided below:

<table>
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<th>Independent claim 1 of ‘9149 (as amended on 7 March 2016)</th>
<th>WO ‘569 (D1)</th>
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having XRPD 2θ-reflections (±0.2°) at 6.1 and 12.7

2. Claim 38 provides that the compound of Claim 35 is amorphous, crystal-like, crystalline, or combination thereof and Claim 39 narrows this down to crystalline.

3. WO ‘569, on page 7 provides brief description of the drawings and figures to related XRD diffractograms of Sp-4 Forms 1 to 5 and the amorphous form.

4. On pages 17 and 18, a further description of Sp-4 crystalline forms is provided, for example:

Page 18, line 3 onwards, WO’569 discloses:

A seventh aspect of the third embodiment is directed to a crystalline Sp-4 having XRPD 2θ-reflections (°) at about: 5.0, 7.3, 9.4, and 18.1.

An eighth aspect of the third embodiment is directed to a crystalline Sp-4 having XRPD
A ninth aspect of the third embodiment is directed to a crystalline Sp-4 having XRPD $2\theta$-reflections (°) at about: 4.9, 6.9, 9.8, 19.8, 20.6, 24.7, and 26.1.

A ninth aspect of the third embodiment is directed to a crystalline Sp-4 having XRPD $2\theta$-reflections (°) at about: 6.9, 9.8, 19.7, 20.6, and 24.6.

A ninth aspect of the third embodiment is directed to a crystalline Sp-4 having XRPD $2\theta$-reflections (°) at about: 5.0, 6.8, 19.9, 20.6, 20.9, and 24.9.

A tenth aspect of the third embodiment is directed to a crystalline Sp-4 having XRPD $2\theta$-reflections (°) at about: 5.2, 6.6, 7.1, 15.7, 19.1, and 25.0.

An eleventh aspect of the third embodiment is directed to crystalline Sp-4 having an XRPD diffraction pattern substantially as that shown in any one of Fig. 3, Fig. 4, Fig. 5, Fig. 6, Fig. 7, and Fig. 8.

A fourteenth aspect of the third embodiment is directed to substantially pure Sp-4.

A fifteenth aspect of the third embodiment is directed to substantially pure crystalline Sp-4.

Table 1 reveals that WO ‘569 already provided many crystalline forms of the specific Sp-4 structure and information related to the XRD diffraction pattern. The only...
difference between claim 1 of ‘9149 and WO ‘569 is that ‘9149 claims an alternative crystalline form.

(f) Hence, the crystalline form of (S)-isopropyl 2-(((S)-((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate of formula Sp-4 having XRPD 2θ-reflections (±0.2°) at 6.1 and 12.7 as claimed in ‘9149 is nothing but another crystalline form which inherently exists in a known compound. The Opponents submit that there is no inventive step in claiming a crystalline form of a known compound. It is further submitted that being the first person to prepare the alternative crystalline compound of a known compound does not fulfill the requirement of inventive step under the Indian Patents Act. Hence ‘9149 lacks inventive step and should be rejected on this ground alone in view of WO’ 569.


(a) Sofia et al relates to the synthesis, isolation and crystallization of the diastereomer of sofosbuvir (PSI-7977) and its potency in HCV assays. The article discusses the preparation and crystallization of diastereomer 51 (PSI-7977) using methylene chloride as a solvent and further establishes the configuration of the phosphorous center as Sp. This article further identifies the crystallization and X-ray structure determination of a phosphoramidate nucleotide prodrug and confirms the compound where stereochemistry at the phosphorus can be correlated unequivocally to the nucleotide phosphoramidate activity. Sofia et al also suggests that on the basis of its superior potency and ability to produce higher intracellular triphosphate levels, diastereomer 51 was selected for further study and subsequently crystallization techniques were used to selectively crystallize the most active diastereomer 51 from the diastereomeric mixture.

(b) The Opponents submit that at the time of priority of the present application ‘9149, it was common general knowledge that diastereomer 51 had the potential to possess superior potency and activity. Therefore, it would have been obvious to the person skilled
in the art to prepare an alternative crystalline form of (S)-isopropyl 2-(((S)-((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2yl)methoxy)(phenoxy)phosphoryl)amino)propanoate of formula Sp-4 having XRPD 2θ reflections (±0.2°) at 6.1 and 12.7 as claimed in ‘9149. Hence in view of the above, Claims 1 to 11 of ‘9149 are obvious and lack inventive step. Accordingly, Claims 1 to 11 should be rejected.

6.1.6 Pharmasset Announces Results of a 28-day Phase 2a Study with PSI-7977 for the Treatment of Chronic Hepatitis C Infection, Pharmasset Inc, published 4 May 2010 marked as D3.

High Rapid Virologic Response (RVR) with PSI-7977 Daily Dosing plus PEG-IFN/RBV in a 28-day Phase 2a Trial, AASLD 61th Annual Meeting for the Study of liver Diseases, published 1 November 2010, marked as D4.

(a) D3 relates to the results of a 28-day phase 2a study with PSI-7977 for the treatment of chronic Hepatitis C infection. It employed crystalline sofosbuvir (PSI-7977) for clinical testing in human volunteers.

D4 assesses the safety, tolerability, pharmacokinetics and antiviral activity of PSI-7977 for 28 days in combination with standard of care in treatment -naïve, HCV genotype 1 infected patients. Both D3 and D4 were published before March 31,2011.

(b) The timelines set out below indicate that Pharmasset planned and performed Phase 2 trials using a crystalline form of sofosbuvir before the filing date of March 2011.

- **January 2010** - Pharmasset initiated a 28-day Phase IIa study on PSI-7977. The study enrolled 63 chronic HCV infected patients. It focused on evaluating different doses of PSI-7977 in combination with Pegasys (peginterferon alfa 2a) and Copegus (ribavirin). The primary efficacy endpoint of the trial was to find the proportion of patients achieving rapid virologic response (RVR) within 28 days of treatment.

- **May 2010** - Phase II preliminary safety and efficacy results of the drug were announced. The study found that the HCV reached undetectable levels in 93% of the
patients. The drug administered with Pegasys and Copegus once daily, proved to be safe and well tolerated.

- August 2010- Pharmasset initiated Phase IIb clinical trials in the US, with 125 HCV-infected patients not treated previously. The primary endpoint of the study was to assess the safety and tolerability of PSI-7977 in combination with the current standard of care (SOC). The 12-week trial was designed to assess PSI-7977 200mg QD and 400mg QD in combination with pegylated interferon alfa 2a and ribavirin, the SOC in HCV patients.

(c) In light of the above, the main difference between ‘9149 and D1 - D4 is that the current application provides an alternative crystalline form. However, as explained in more detail below, testing, developing, optimising and selecting specific polymorphs of a drug product are routine experimental steps that form part of any pre-formulation study during drug development.

(d) One of the pertinent questions to be asked in assessing whether the invention claimed in ‘9149 has inventive step is whether the crystallization or identification of additional polymorphs over existing crystalline forms of a medicament for improving its physical and physicochemical properties was already known in the art?

(e) The common general knowledge in this field includes the basics of crystallization of a drug substance and a basic understanding of routine pre-formulation studies. Pharmaceutical solids – indeed any solid moleculars – may exist in either or both amorphous (powder) and crystalline forms. Amorphous forms of a solid lack a regular, long-range order in the packing arrangement of molecules relative to each other. Crystalline solids do possess long-range order in their molecular packing arrangement. By virtue of this property, crystalline solids will diffract X-rays and will display a regular pattern of peaks that denote the 2Ө angles of diffraction for the specific crystalline lattice.

(f) A compound is said to exist in polymorphic form if it crystallizes into more than one arrangement in the crystal lattice. Some compounds form crystals into which, in addition to the compound itself, a fixed proportion of solvent is incorporated as well. These are known as solvates or hydrates if the solvent is water. If one molecule of water is included per molecule of the compound, the resulting product is called a monohydrate;
if two molecules of water are included then the product is dihydrate and so on. Solvates and hydrates are sometimes referred to as pseudopolymorphs or pseudomorphs, to distinguish them from true polymorphs, which are solvent-free forms. It was well known and accepted that different crystal forms of the same compound (whether true polymorphs or solvates or hydrates) can have different physicochemical properties. These properties include solubility, dissolution rate, stability and processing characteristics.

(g) As a consequence the stability of the drug can be dependent on the crystal form as well. According to the Applicant the crystalline forms taught in D1 presented some problems in stability. However, it is important not to attach too much weight to these stability issues. This is because clear evidence exists to show that if a cogent rationale existed for performing crystallization experiments, a skilled team of pharmaceutical chemists would not be deterred from conducting them, especially in the quest for additional polymorphs with improved stability. In an empirical field, if the skilled person thought it relevant or worthwhile to consider alternative crystal forms and was sufficiently motivated to do so, he or she would be far more likely to conduct a crystallization experiment than to decline to do so based on a review of existing prior crystalline compounds.

(h) Yet another pertinent question is whether there was any motivation for solving the problem in the same way as that adopted by the Applicant?

(i) A polymorph screen is a routine pre-formulation step, which involves crystallizing an active pharmaceutical ingredient (API) from a variety of solvents and solvent mixtures and characterizing the resulting crystals for evidence of polymorphism or pseudopolymorphism. It was common general knowledge at the time ‘9149 was filed that it was recommended, and to an extent mandatory, to carry out a polymorph screen in respect of an API which one intended to market. Well before the filing of ‘9149, standard formulation textbooks were teaching with varying degrees of emphasis that, in the pre-formulation stage of pharmaceutical development, one should actively look for polymorphs.

(j) In addition to the prior art D1-D4, the Opponents would like to rely on the following prior arts, which set out the prior common knowledge and proven steps that
existed in the field with respect to looking for polymorphs and which would have made the subject matter claimed in ‘9149 routine and obvious:


*Lachman et al* discusses the standard formulation and techniques that are needed in the pre-formulation stage of pharmaceutical development. This publication focuses on the physiochemical properties of a new compound that could affect drug performance and development of dosage form. It also teaches that during pre-formulation, it is important to identify the polymorph that is stable at room temperature and to determine whether polymorphic transitions are possible within the temperature range used for stability studies and during processing (drying, milling, etc.). Lachman reaffirms that to screen for additional polymorphic forms of a particular drug, bridging solvents, supersaturated solutions, super-cooled melts and sublimination have proven useful.

The Opponents submit that from the teaching of *Lachman*, it is well established in the pharmaceutical industry that a solid form of an organic compound may exist in crystalline and/or amorphous forms. Amorphous forms are solids with random un-oriented molecules while crystalline forms are molecules arranged in a fixed geometric pattern or lattice. In a crystalline form, a molecule may exist in one of seven different crystal states and the particular crystal state that a molecule assumes depends upon the choice of the solvent that is used for recrystallization and/or the choice of the solvent used for precipitation. Experimental recrystallization with a wide range of solvents is common knowledge for a person ordinarily skilled in the art. Such recrystallization techniques have been reported extensively in chemistry textbooks, journals and periodicals.

Therefore, as of the priority date of ‘9149 and in view of the above reference, it would have been obvious to one skilled in the art, to combine the teachings of the WO’569 (D1) with known techniques of recrystallization in order to produce the claimed crystalline form of crystalline (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2yl)methoxy)(phenoxy)phosphoryl)amino)propanoate of formula Sp-4 having XRPD 2θ-
reflections (±0.2°) at 6.1 and 12.7. Hence, Claims 1 to 11 of ‘9149 are obvious to a person skilled in the art. They do not involve any technical advance over the existing knowledge. The mere fact that routine tests and experiments would have to be conducted in order to prepare the crystalline forms of a known compound does not confer an inventive step to the alleged invention described in the present application. Therefore, Claims 1 to 11 of ‘9149 should be rejected under Section 25(1)(e) of Patents Act.


(a) Aulton discusses the various physical and chemical properties of the drug molecule that needs to be determined during pre-formulation studies of the pharmaceutical compounds. This publication also teaches that during drug development stage, it is essential to determine certain fundamental physico-chemical properties of the drug molecule and other derived properties of the drug powder. This information will dictate many of the subsequent events and possible approaches in formulation development. Furthermore, Aulton also discusses about existence of polymorphism in pharmaceutical formulation and the use of the different types of solvents employed in recrystallization.

(b) The Opponents submit that the D6 suggests various standard formulation teaching that needs to be undertaken during the pre-formulation stage of pharmaceutical compound. It also discloses that the phenomenon of polymorphism is remarkably common and important, and one should actively look for various polymorphic form which show maximum therapeutic activity.

(c) The Opponents submit that once a product or chemical substance is known, crystallization of the substance merely involves routine trial and error to achieve different types of polymorphs. D6 provides teaching that most polymorphs are obtained by solvent manipulation and others can be produced without the presence of solvent by thermal techniques, notably sublimation and recrystallization from the melt. To a person skilled in the art, the above document lays a foundation to understand the technology and reaction conditions involved in preparation of polymorphs.
(d) The Opponents submit that recrystallization techniques are common knowledge for those skilled in art and have been disclosed in various publications including those discussed above. Hence, it would have been obvious to one skilled in the art, as of the priority date of ‘9149, to combine the teachings of the D1 with known techniques of recrystallization to produce the claimed compound of ‘9149.

(e) The Opponents state that in light of the above, the subject matter claimed in ‘9149 as a whole is prima facie obvious to a skilled person in the art and thus lacking inventive merit.


(a) *Borka et al* discusses the phenomenon of polymorphism among various pharmaceutical compounds and methods used to detect polymorphism in drugs. The article also reviews the polymorphism data that needs to be submitted by various pharmaceutical companies during drug registration process. This publication also highlights the fact that the presence of polymorphism plays an important role in biological activity between two forms of the same drug. Furthermore, this reference emphasises the importance of polymorphism in the active pharmaceutical substances and their effect on the biological activity.

(b) The *Borka* reference is important for the purpose of showing that the objective in looking for alternative crystal forms is not research conducted solely or even primarily to find an improved form i.e. a form with better stability. The objective is to establish that when a manufacturer intends to make and sell the product, it is required to systematically look for the different polymorphs for a drug in order to know that it is not going to change into something different.

(c) The Opponents submit that in view of the teachings of D7 there is sufficient motivation and teaching to do further developments of an existing compound. On reviewing D1 and D7 a person skilled in the art would be motivated to try for various polymorphic forms of the base compound in expectation of better physio-chemical properties like stability, solubility and biological activity. Thus, well before the priority
date for ‘9149, it was known that polymorphism plays an important role in the biological activity of the compound. The Opponents submit that experimental crystallization with a wide range of solvents is common knowledge for a person skilled in the art and such recrystallization techniques have been reported extensively in various chemistry books and journals. As a result, preparation of the polymorph of a known compound is not inventive in view of the above cited prior art. A person skilled in the art on reading D1 and D7 would be motivated to obtain the polymorph of (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate with reasonable expectation of success for the purpose of obtaining more advantageous properties.

6.1.10 **Chemistry of Active Substances, Directive 75/318/EEC, published October 1987 marked as D8.**

(a) The Opponents submit that most regulatory authorities have issued guidelines on the information needed for registration of pharmaceuticals. For example Volume III of “The Rules Governing Medicinal Products in the European Community” contains detailed guidelines on the quality, safety and efficacy of medicinal products for human use. As early as in the 1987 edition, there is a section providing guidance on the type of information required for the control of new active ingredients. D8 specifically teaches that during drug research and development programmes, it is important to submit data related to the chemistry of active substances and where applicable, unequivocal proof of structure, configuration, conformation and potential isomerism. The Guideline also discusses that the presence and absence of polymorphic forms, and the method of detection for the same should be provided.

(b) The Opponents submit that for a person skilled in the art, the above document lays a foundation to understand the technology and reaction conditions involved in the preparation of polymorphs. It was common general knowledge at the time ‘9149 was filed to carry out polymorph screening in respect of an active pharmaceutical substance. The Opponents submit that in view of D8 the subject matter claimed in ‘9149 is obvious and, therefore, lacks inventive step.

(a) The present guidance document by the Food and Drug Administration (FDA) provides recommendations about the selection of test procedures and the acceptance criteria for new chemical drug substances and new drug products. D9 discusses polymorphism in drug substances and teaches that new drug substances exist in different crystalline forms, which result in different physical properties. The guidance document also provides how differences in the polymorphic forms can affect the quality and or performance of new drug products. D9 also discusses the various procedures, such as melting point (including hot-stage microscopy), solid state IR, X-ray powder diffraction, thermal analysis procedures (like DSC (differential scanning calorimetry), TGA (thermogravimetric analysis) and DTA (differential thermal analysis)), Raman spectroscopy, optical microscopy, and solid state NMR (nuclear magnetic resonance) spectroscopy, that are used for the detection of the different polymorphic compounds.

(b) The guidance document also discusses that the preparation of polymorphs is an important approach to modify the physical and chemical properties of the concerned product. Therefore, D9 provides the necessary guidance to a person skilled in the art to obtain polymorphic forms as claimed in '9149. As a result, Claims 1 to 11 of '9149 are obvious to a person skilled in the art and do not involve any technical advance over the existing knowledge.


(a) D10 provides recommendations on the CMC for drugs substances that should be submitted to support the approval of original new drug applications (NDAs) and abbreviated new animal drug applications (ANADAs). This reference also discloses the information that needs to be submitted to ensure drug product quality. The Draft Guidance also emphasises that an applicant or drug substance manufacturer should
investigate whether a drug substance is capable of existing in different solid state forms. Moreover, guidance is given with respect to the fact that screening with a variety of solvents that have different polarities and hydrogen bonding properties can be valuable for early detection of other polymorphs.

(b) For a person skilled in the art the preparation of polymorphs is a routine exercise especially when an individual is aware of the method of the preparation of the different types of polymorphs. The Opponents submit that to a person skilled in the art, the above document lays a foundation to understand the technology and conditions involved in preparation of polymorphs. This guidance document establishes that when a manufacturer intends to make and sell the product, it is required to systematically look for the different polymorphic form of a drug that shows the maximum therapeutic activity.

(c) As clearly demonstrated in the prior art, obtaining crystalline forms of a given compound is standard procedure using routine experiments. Therefore, Claims 1 to 11 of ‘9149 are obvious and lack any inventive step which is a prerequisite for patentability.


(a) Bryn *et al* discusses the importance of controlling the crystalline form of drug substances in the New Drug Application (NDA) and Investigational New Drug (IND) process. D11 outlines the investigations and analytical tests available for identifying various polymorphic forms and controls needed to ensure the integrity of drug substance containing either a single morphic form or a mixture. This publication also suggests various solvents that are commonly used in recrystallization, including water methanol, ethanol, propanol, isopropanol, acetone, acetonitrile, ethyl acetate, hexanes and mixtures if appropriate.

(b) The Opponents submit that once a product or chemical substance is known, crystallization of the substance merely involves routine trial and error to achieve different
polymorphs, solvates, hydrates etc. A common general process for purifying and crystallizing an organic compound involves first dissolving the crude compound in a suitable solvent or a mixture of solvents, filtering the hot solution, allowing the hot solution to cool, which causes the dissolved compound to crystallize out and separating the crystals further while drying. The examples that are disclosed in ‘9149 describing the preparation of crystalline (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate follow such known techniques as described in D11.

6.1.14 As set out clearly above in D5 to D11, every new compound that is entered into human clinical trials in the US or Europe undergoes a fairly routine series of experiments (Polymorph Screen) before an original INDA (Investigational New Drug Application) is filed with a strict regulatory authority. This includes allowing the slow evaporation of solutions of the drug substance from many different solvents and/or solvent mixtures of differing properties (e.g., polarity, dielectric constant, boiling point) to encourage the crystallization of different polymorphs, solvates, or hydrates.

Another type of experimentation is hot-stage microscopy, and the heating of solid forms of the drug substance in suspensions of different solvents. This encourages the re-arrangement of solid forms to more stable crystalline polymorphs or pseudomorphs. It is also a given that vapor sorption-desorption studies will be conducted to discover the potential for different hydrates forms of the API.

These studies are part of the preclinical development program for API characterization and pre-formulation. Regulatory Authorities require a demonstration of consistency or “similarity” in the batch-to-batch performance of APIs and formulations as part of beginning human clinical trials. Stability, dissolution, absorption, and bioequivalence are dependent upon this consistency in physicochemical properties. For this reason, all new drug candidates in the E.U and the U.S undergo such screening as a routine exercise before first-in-human studies.

The Opponents submit that a person skilled in the art has a clear understanding of polymorphism given the extensive disclosures in the cited publications D1 to D11.
Therefore, Claims 1 to 11 of ‘9194 are devoid of any inventive features and should be rejected.

If the priority date is considered to be 31 March 2010, Claims 1 to 11 of ‘9149 are not patentable under Sections 25(1)(e), 2(1)(j) and 2(1)(ja) of the Act over D12, D13 or D14 supported by one or more or all of D5 - D11.

Without prejudice to the paragraphs above, the arguments in this section are based on the assumption that the priority date for the Claims of ‘9149 is March 31, 2010.


(a) In addition to the prior art discussed above, the subject matter of ‘9149 does not involve any inventive step and lacks any technical advance in view of WO‘634. WO ‘634 discloses phosphoramidate prodrugs of nucleoside derivatives for the treatment of viral infections in mammals and its stereoisomer, salt (acid or basic addition salt), hydrate, solvate, or crystalline form thereof, represented by the following structure.

(b) The compounds are known to be inhibitors of RNA dependent RNA viral replication and are useful. The phosphoramide pro-drug compound as discussed in WO ‘634 is known as sofosbuvir.

(c) The Opponents submit that recrystallization techniques are common knowledge for those skilled in art. These techniques have been disclosed in various publications, including those discussed above. Hence, although the polymorphic forms of sofosbuvir, namely form 6, are not explicitly discussed in the WO ‘634 patent, it would have been obvious to one skilled in the art to combine the teachings of WO ‘634 with the known techniques of recrystallization to produce crystalline forms of sofosbuvir. Experimental recrystallization with a wide range of solvents is common knowledge for a person.
ordinarily skilled in the art. Such recrystallization techniques have been reported extensively in chemistry textbooks, journals and periodicals.

(d) It is apparent that the only ‘alleged’ difference in the disclosures of the WO ‘634 patent application when compared with ‘9149 is that the latter specifically claims the crystalline crystalline Form 6 in claim 1.

(e) A comparison of the sole independent claim 1 (as amended on 7th March 2016) and dependent claim 2 with D5 is as provided below:

<table>
<thead>
<tr>
<th>Claims 1 and 2 of ‘9149 (as amended on 7th March 2016)</th>
<th>WO ‘634 (D12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Crystalline (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate represented by the formula Sp-4:</td>
<td></td>
</tr>
<tr>
<td>D12 Abstract provides:</td>
<td></td>
</tr>
<tr>
<td>Disclosed herein are phosphoramidate prodrugs of nucleoside derivatives for the treatment of viral infections in mammals, which is a compound, its stereoisomer, salt (acid or basic addition salt), hydrate, solvate, or crystalline form thereof, represented by the following structure.</td>
<td></td>
</tr>
<tr>
<td>having XRPD 20-reflections (±0.2°) at 6.1 and 12.7</td>
<td></td>
</tr>
<tr>
<td>2. Crystalline (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)</td>
<td></td>
</tr>
<tr>
<td>Under the heading “Summary of the Invention” on Page 9, D12 provides:</td>
<td></td>
</tr>
<tr>
<td>The present invention is directed toward novel phosphoramidate prodrugs of nucleoside derivatives for the treatment of viral infections in mammals, which is a</td>
<td></td>
</tr>
</tbody>
</table>
propanoate of claim 1 further having: XRPD 20-reflections (±0.2°) at about: 8.2, 10.4, 17.2, 17.7, 18.0, 18.8, 19.4, 19.8, 20.1, 20.8, 21.8, and 23.3.

Under the heading “Detailed Description of the Invention” on page 20, D12 provides:

An aspect of the invention is directed to a compound, its stereoisomers, salts (acid or basic addition salts), hydrates, solvates, or crystalline forms thereof, represented by the following structure:

Under the heading “Detailed Description of the Invention” on page 20, D12 provides:

An aspect of the invention is directed to a compound, its salts, hydrates, solvates, crystalline forms, and the like represented by formula I:

(f) Therefore, as is evident from the above, D12 already provided many options for crystalline forms in relation to the generic compounds encompassing the Sp-4 structure. The only difference between ‘9149 and D12 is the current application provides an alternative crystalline form. As such, Claims 1 and 2 of ‘9149 would have been obvious in light of D12.

(g) Screening and isolation of alternative crystalline forms as claimed in ‘9149 is obvious in view of D12 and the common general knowledge demonstrated in D5 to D11. Moreover, ‘9149 does not present any comparison between the various polymorphs. The Applicant has failed to provide sufficient comparative data to show any technical advance and inventive step over the prior art. Even though the Applicant has suggested that Form 6 has, for example, improved stability over Form 1, this fails to meet the level of a
patentable invention both in terms of selection versus the prior art as a whole. The Opponents submit that Claims 1 to 11 clearly lack any inventive step and, therefore, does not involve any technical advance over the existing knowledge.

(h) Claims 1 to 11 of ‘9149 are not patentable under sections 25(1)(e), 2(1)(j) and 2(1)(ja) of the Act over D13 supported by one or more or all of D5 to D11

6.1.16 **WO2006/063149 (WO ‘149) titled “Nucleosides with antiviral and anticancer activity”, published on 15 June 2006, Reagents of the University of Minnesota, marked as D13.**

(a) WO ‘149 discusses various nucleosides with antiviral and anticancer activity. Sofosbuvir is covered by the generic claims of D13 when:

X=O or oxy group,
R1=uracil

**Uracil structure:**

![Uracil structure](attachment:image)

R6=R7=H
R2=F
R3=OH
R4=Aryl group; C3-6 cycloalkyl (benzene)

(b) Furthermore, on page 9, lines 4-15 of WO ‘149, the matter of polymorphism and stereoisomerism in pharmaceutical compounds is discussed. WO’149 also discloses racemic, optically-active, polymorphic, or stereo-isomeric form, or mixtures thereof, of the compound of the invention. D13 also suggests how to prepare optically active forms (for example, resolution of the racemic form through recrystallization techniques; synthesis from optically-active starting materials; chiral synthesis; or chromatographic separation using a chiral stationary phase) and how to determine antiviral activity using the standard tests which are well known in the art.
(c) Hence Claims 1 to 11 of ‘9149 differ from D13 in the selection of a specific crystalline form.

(d) With respect to the selection of specific polymorphic forms, as shown by D5 to D11, such practice is part of routine experimentation and, therefore, does not involve any technical advance and inventive step. It is submitted that the sofosbuvir compound can be subjected to any number of recrystallizations using known isolation/recrystallization techniques to get the desired polymorph. Hence, in light of the above, there was sufficient motivation for the person skilled in the art to prepare the crystalline form of sofosbuvir.


(a) WO ‘147 relates to an invention for “(2’R)-2’deoxy-2’fluoro-2’-C-methyl nucleoside (β-D-β-L) or its pharmaceutically salt or prodrug thereof, and the use of such compounds for the treatment of a host infected with a virus belonging to the flaviviridae family, including HCV. More specifically, claim 6 of WO ‘147 covers the structure of the base compound for sofosbuvir, including its monophosphate, diphosphate, triphosphate or a stabilised phosphate prodrug. Therefore, claim 6 generically covers the pro-drug form of sofosbuvir.

(b) On page 51-54, ‘147 also discusses various techniques used for isolation of isomers and polymorphs. The Opponents submit that there is ample teaching in WO ‘147 on how to prepare the crystalline form of sofosbuvir. The Opponents submit the crystalline form claimed in ‘9149 is merely a routine exercise in light of D14 and the common general teachings with respect to testing for and obtaining polymorphic forms. Hence, Claims 1 to 11 of ‘9149 are obvious and lack inventive step.

6.2 GROUND III
Claims 1 to 11 are not an invention within the meaning of this Act and should be rejected under Section 25 (1) (f) of the Patents Act read with Section 3(d).

6.2.1 The Hon’ble Supreme Court of India in Novartis AG vs Union of India & Ors. (AIR 2013 SC 1311) (hereinafter the “Glivec case”) observed, “[T]he amended portion of section 3(d) clearly sets up a second tier of qualifying standards for chemical substances/ pharmaceutical products in order to leave the door open for true and genuine inventions but, at the same time, to check any attempt at repetitive patenting or extension of the patent term on spurious grounds”.

[See page 56, para 103].

The Supreme Court interpreted "efficacy" as "therapeutic efficacy” stating that the “therapeutic efficacy” of a medicine must be judged strictly and narrowly.

[See page 90, para 180].

The Court also stated that:

“...the physico-chemical properties of beta crystalline form of Imatinib Mesylate, namely (i) more beneficial flow properties, (ii) better thermodynamic stability, and (iii) lower hygroscopicity, may be otherwise beneficial but these properties cannot even be taken into account for the purpose of the test of section 3(d) of the Act, since these properties have nothing to do with therapeutic efficacy”

[See Glivec case, page 94, para 187]

6.2.2 It is submitted that in pharmacology, intrinsic activity or efficacy refers to the ability of a drug to induce a biological response in its molecular target. Efficacy is defined as “the generation of a response from the drug receptor complex”. Efficacy is that property intrinsic to a particular drug that determines how good an agonist the drug is.


6.2.3 Another useful and more detailed definition of efficacy is that provided in Tripathi K.D, “Essentials of Medical Pharmacology, 5th edition, Jaypee Brothers Medical
Publishers Ltd, Page 37, lines 10-13 (hereinafter Tripathi et al.), (filed herewith as D16) which broadly defines efficacy as “ability of the drug to activate (induce a conformational change in) the receptor consequent to receptor occupation.”

Both of the above definitions establish that a mere physical variant of an existing pharmaceutical product lacks the necessary quality of therapeutic efficacy which is a condition precedent to a known substance being considered patentable under the Act. It is also an established position of law that the term “efficacy” in Section 3(d) means therapeutic efficacy for pharmaceutical products.

6.2.4 The Opponents submit that the claimed subject matter falls under Section 3(d) as it is merely a new form of a known substance. The known substance having been disclosed in D1, D2, D12, D13 and D14. It is, therefore, incumbent upon the Applicant to show the Claims of ‘9149 result in the enhancement of therapeutic efficacy over the known forms discussed above. The Applicant has failed to meet this obligation as no data is provided in the application demonstrating any enhancement in the therapeutic efficacy of crystalline form of sofosbuvir exhibiting XRD peaks at 6.1 and 12.7 over other known crystalline forms of sofosbuvir. The only claim the Applicant makes is that the claimed invention in ‘9149 provides improved stability. However, as has been confirmed in Novartis AG v. Union of India 2013 (54) PTC 1 (SC), physical stability or storage stability is not sufficient to fulfil the requirement of therapeutic efficacy as mandated by Section 3(d).

6.2.5 The Opponents submit that the improved stability of the compound claimed cannot be equated with enhanced efficacy. It is immaterial for the purpose of efficacy as to how quickly or slowly the substance has dissolved. Different physical forms of the product may have different physical properties giving different degree of stability, solubility and bioavailability does not effect the properties of the drug.

A proper comparison of efficacy would have been a comparative therapeutic profile of the claimed compound with the known form of the compound. In such a comparative study efficacy could be claimed if the prepared crystalline form showed a therapeutic profile that is higher compared to the known compound. Accordingly, it is stated that there is no enhancement of efficacy in the crystalline form of crystalline (S)-isopropyl 2-
(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate of formula Sp-4 compared to the known compound. Therefore, both are to be construed as the same substance according to Section 3(d).

6.2.6 The Opponents contend that the Applicant is unable to show that the claimed subject matter in ‘9149 can meet the therapeutic efficacy requirements of Sections 3(d). Indeed, The US FDA correspondence ID Reference Number 3354896 dated August 20, 2013 (attached as Exhibit 12) clearly indicates that human clinical trials of sofosbuvir were conducted using both Form I and Form II. Form II is the crystalline form of the API that is marketed for human use. Form II is also the same crystalline Form referred to as Form 6 in ‘9149. Gilead Sciences purported to the US FDA that Form I and Form II (i.e. Form 6 of ‘9149) are bioequivalent. This is conclusive proof in itself that there is no enhancement of efficacy between these two different crystalline forms of Sp-4 (now commonly known as sofosbuvir). Gilead Sciences conducted early clinical trials in human patients suffering from Hepatitis C infection using doses of 200 mg and 400 mg/day of sofosbuvir. The final adult dose of 400 mg/day was selected for Phase III clinical trials. The human doses used in clinical trials were identical, whether as Form I or Form II (i.e. Form 6 in ‘9149). As such, the Applicant cannot justifiably claim on the one hand to the US FDA that two crystalline forms (including Form 6 as claimed in ‘9149) of sofosbuvir are equivalent, and on the other hand claim to the Indian Patent Office that these two Forms are not equivalent and that Form II (Form 6 as claimed in ‘9149) provides superior efficacy. The doses of drug used with either crystalline form are the same, and the Applicant has made no claims, nor can they claim, that the resultant switch from Form I to Form II (i.e. Form 6 as claimed in ‘9149) provides any improvement in clinical outcomes of human dosing (efficacy), particularly when the opposite is claimed to a Strict Regulatory Authority (US FDA).

In view of the above, the subject matter claimed in Claims 1-11 of ‘9149 does not amount to an invention under Section 3(d) and is, therefore, unpatentable.

6.2.7 Claims 4 to 7 of ‘9149 are not patentable under Section 3(e) of the Act.
Claims 4 to 7 of ‘9149 are directed to the combination with other anti-viral agents (either or both NS3 and NS5A inhibitors), are mere admixtures. It is submitted that the composition claimed in Claims 4 to 7 is not an invention within the meaning of Section 3(e) as the composition does not demonstrate any synergistic effect. The composition is a mere admixture of known substances, which results only in aggregation of the properties of the individual components. A composition demonstrating mere aggregation of properties is not patentable under Section 3(e).

Therefore, based on the aforesaid facts and submissions, Claims 4 to 7 of ‘9149 ought to be rejected.

6.3 GROUND IV

The Patent Applicant has not complied with the requirements of Section 8. Therefore, the Claims 1 to 11 are not patentable under Sections 25(1)(h) of the Act.

6.3.1 Section 25 (1) (h) of the Patents Act provides a ground for opposition if the Applicant has not furnished information required under Section 8 of the Patents Act, within the time prescribed by law.

Without prejudice to the others grounds raised above, ‘9149 should be rejected because the Applicant has not complied with the mandatory requirements of Section 8 of the Act.

6.3.2 Section 8 read with Rule 12(1) requires the Applicant, who is prosecuting patent application, either alone or jointly with any other person to file a statement at the Indian Patent office at regular time intervals stating whether he/she has made any application for a patent for the same or substantially same invention in any foreign country or countries and to furnish particulars of any such applications - especially objections raised and the amendments to the specifications.

Failure to disclose this information is a ground to oppose the grant of a patent under Section 25(1) (h) of the Act. Therefore, the burden is on the Applicant to furnish any and all foreign search reports from “any country outside India” in its possession at the time of filing its reply to the Indian Patent Office.
6.3.3 According to records available on the Indian Patent Office website, the Opponents would like to bring to the Indian Patent Office’s attention that the Applicant has failed to keep it informed of related prosecutions in other countries, in particular the following:

- Third party observations as filed against the corresponding application at the European Patent Office;
- The refusal of corresponding application no. UA201212444 in Ukraine.
- The refusal of corresponding application no. CN201180017181.3 (published as CN102858790) in China.

The Applicant is under an obligation to furnish the Patent Office with the status of the examination of the above and other related applications that are currently being prosecuted. The prosecution history for the ‘9149, available on inPASS shows that the Applicant had not furnished the information required under Section 8 of the Act, within the time prescribed. Thus *prima facie*, the Applicant has not complied with the requirements of Section 8. Given the Applicant’s failure to do so in light of the requirements under Sections 8, ‘9149 should be refused in its entirety.

**RELIEF SOUGHT:**

In light of the grounds stated and evidence presented above, the Opponents pray:

a) That Indian Patent Application No. 9149/CHENP/2012 in the name of Gilead Pharmasset LLC be rejected under Section 25(1) of the Patents (Amendment) Act, 2005;

And in doing so -

b) The Opponents be permitted to make further submissions in the event the Applicant makes any amendments to its claims;

c) The copy of the reply statement and evidence filed by the Applicant in response to this objection be made available to the Opponents;
d) That the Opponents be permitted to file further documents as evidence if necessary to support its case;

e) That the Opponents be granted an opportunity of being heard in the matter before any final order is passed.

Any other relief in the facts and circumstances of this case may be granted in favour of the Opponents in the interest of justice.

Dated 10 day of February, 2017

Fidus Law Chambers
Attorneys for the Opponents

For and behalf of the Delhi Network of Positive People
For and behalf of the Initiative for Medicines, Access & Knowledge (I-MAK), Inc
The address for service in connection with these proceedings is: -

Fidus Law Chambers,
Flat No. 021,
Mahagun Maestro, Plot F21 A, Sector 50,
Noida,
Uttar Pradesh

To:
The Controller of Patents,
The Patent Office Branch,
Chennai.