BEFORE THE CONTROLLER OF PATENT
PATENT OFFICE, KOLKATA

THE PATENTS ACT, 1970 (AS AMENDED)
Section 25(1)

In the matter of
AND
In the matter of
Pre-grant oppositions to the grant of patent under Section 25(1)

1. Gilead Pharmasset, LLC - The Applicant
   Sankalp Rehabilitation Trust,
   Hepatitis Coalition of Nagaland - The Opponent
Present in the hearing held on 30/10/2018
Sudhir Chandra Agarwal, Senior Advocate
Sanjeev Tiwari, Amrish Tiwari,
Jyoti Ramani of K&S Partners - For the Applicant
Anand Grover, Senior Advocate
Priyam Lizmary Cherian - For the Opponent

AND

2. Gilead Pharmasset, LLC - The Applicant
   Initiative for Medicines, Access
   & Knowledge, Inc. (IMAK) - The Opponent
Present in the hearing held on 31/10/2018
Sanjeev Tiwari, Amrish Tiwari,
Jyoti Ramani of K&S Partners - For the Applicant
Shwetasree Majumdar of Fidus
Law Chambers - For the Opponent

AND
3. Gilead Pharmasset, LLC - The Applicant
   Optimus Pharma Limited & India Cares - The Opponents
   
   **Present in the hearing held on 05/02/2019**
   Sanjeev Tiwari, Amrish Tiwari,
   Jyoti Ramani of K&S Partners - For the Applicant
   Rajeshwari Hariharan of
   Rajeshwari & Associates - For the Opponents

   **AND**

   4. Gilead Pharmasset, LLC - The Applicant
      Ramesh Ganapathy - The Opponent
      
      **Present in the hearing held on 07/06/2019**
      Sanjeev Tiwari, Amrish Tiwari,
      Jyoti Ramani of K&S Partners - For the Applicant
      Bency Varghese - For the Opponent

   **AND**

   5. Gilead Pharmasset, LLC - The Applicant
      Nagendra Kumar Lagisetty - The Opponent
      
      **Present in the hearing held on 21/10/2019**
      Sanjeev Tiwari, Amrish Tiwari,
      Jyoti Ramani of K&S Partners - For the Applicant
      Soumen Mukherjee of Synergy IPR - For the Opponent

   **AND**

   6. Gilead Pharmasset, LLC - The Applicant
      P. Guruvaiah - The Opponent
      
      **Present in the virtual hearing held on 29/09/2020**
      Sanjeev Tiwari, Amrish Tiwari,
      Jyoti Ramani of K&S Partners - For the Applicant
      Suresh Gupta - For the Opponent

   **AND**

   7. Gilead Pharmasset, LLC - The Applicant
      Dhaval Dayabhai Diyora - The Opponent
DECISION

1. An application for patent with application number 3658/KOLNP/2009 was filed on 20/10/2009 by the Applicant for the invention titled “Nucleoside phosphoramidate prodrugs”. It is derived from PCT international application no. PCT/US2008/058183 having international filing date 26/03/2008 and claiming earlier priority from three USA patent applications having number 60/909,315 dated 30/03/2007, 60/982,309 dated 24/10/2007 and 12/053,015 dated 21/03/2008. A request for examination of the said application was filed by their agent on 21/03/2011. The application was published under section 11(A) of the Patents Act, 1970 as amended in 2005 (hereinafter referred as ‘Act’) in the Patent Office Journal on 19/03/2010.

2. The timeline and sequence of various actions that have taken place during the processing of the instant patent application and the pre-grant oppositions filed therein are as follows-
<table>
<thead>
<tr>
<th>S. No.</th>
<th>Action</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Indian Patent Application No. 3658/KOLNP/2009 was filed as a national phase patent application.</td>
<td>20/10/2009</td>
</tr>
<tr>
<td>2</td>
<td>Application was published under Section 11A</td>
<td>19/03/2010</td>
</tr>
<tr>
<td>3</td>
<td>Request for Examination filed</td>
<td>21/03/2011</td>
</tr>
<tr>
<td>4</td>
<td>Amended claims filed</td>
<td>12/12/2011</td>
</tr>
<tr>
<td>5</td>
<td>IMAK filed pre-grant opposition</td>
<td>21/11/2013</td>
</tr>
<tr>
<td>6</td>
<td>Indian Pharmaceutical Alliance filed pre-grant opposition</td>
<td>03/01/2014</td>
</tr>
<tr>
<td>7</td>
<td>Natco Pharma filed pre-grant opposition</td>
<td>27/02/2014</td>
</tr>
<tr>
<td>8</td>
<td>Sankalp Rehabilitation Trust filed pre-grant opposition</td>
<td>10/09/2014</td>
</tr>
<tr>
<td>9</td>
<td>First Examination Report issued</td>
<td>29/01/2015</td>
</tr>
<tr>
<td>10</td>
<td>Indian Pharmaceutical Alliance withdrew pre-grant opposition</td>
<td>09/02/2015</td>
</tr>
<tr>
<td>11</td>
<td>Optimus Pharma Ltd. filed pre-grant opposition</td>
<td>20/02/2015</td>
</tr>
<tr>
<td>12</td>
<td>Notice for pre-grant opposition of IPA issued</td>
<td>17/02/2015</td>
</tr>
<tr>
<td>13</td>
<td>Notice for Pre-grant opposition to IMAK Opposition was issued</td>
<td>25/02/2015</td>
</tr>
<tr>
<td>14</td>
<td>Natco Pharma withdrew pre-grant opposition</td>
<td>07/03/2015</td>
</tr>
<tr>
<td>15</td>
<td>Notice for Optimus Pharma opposition issued</td>
<td>24/04/2015</td>
</tr>
<tr>
<td>16</td>
<td>Reply to IMAK and IPA Pre-grant Opposition filed</td>
<td>07/05/2015</td>
</tr>
<tr>
<td>17</td>
<td>Virupaksha Organic filed pre-grant opposition</td>
<td>27/05/2015</td>
</tr>
<tr>
<td></td>
<td>Event Description</td>
<td>Date</td>
</tr>
<tr>
<td>---</td>
<td>----------------------------------------------------------------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>18</td>
<td>Reply to Optimus Pharma Opposition filed</td>
<td>21/07/2015</td>
</tr>
<tr>
<td>19</td>
<td>Notice for Virupaksha Organic opposition issued</td>
<td>21/09/2015</td>
</tr>
<tr>
<td>20</td>
<td>India Cares filed pre-grant opposition</td>
<td>23/10/2015</td>
</tr>
<tr>
<td>21</td>
<td>Form 13 along with five (5) amended claims filed</td>
<td>05/11/2015</td>
</tr>
<tr>
<td>22</td>
<td>Detailed response to FER filed</td>
<td>24/11/2015</td>
</tr>
<tr>
<td>23</td>
<td>Reply to Virupaksha Organic Opposition filed</td>
<td>11/12/2015</td>
</tr>
<tr>
<td>24</td>
<td>Notice for India Care pre-grant opposition issued</td>
<td>09/05/2016</td>
</tr>
<tr>
<td>25</td>
<td>Notice for Sankalp Pre-grant opposition was issued</td>
<td>17/05/2016</td>
</tr>
<tr>
<td>26</td>
<td>Reply to India care pre-grant opposition was filed</td>
<td>05/08/2016</td>
</tr>
<tr>
<td>27</td>
<td>Reply to Sankalp Pre-grant opposition filed</td>
<td>12/08/2016</td>
</tr>
<tr>
<td>28</td>
<td>Declaration of Dr. Wnuk filed by Applicant against Optimus Pharma and India Care oppositions</td>
<td>22/08/2016</td>
</tr>
<tr>
<td>29</td>
<td>Declaration of Dr. Wnuk filed by Applicant against Virupaksha Organic, Sankalp and IMAK opposition</td>
<td>08/11/2016</td>
</tr>
<tr>
<td>30</td>
<td>Vector Biosciences filed pre-grant opposition</td>
<td>06/07/2017</td>
</tr>
<tr>
<td>31</td>
<td>Notice for Vector Bioscience pre-grant opposition issued</td>
<td>20/07/2017</td>
</tr>
<tr>
<td>32</td>
<td>Reply along with Declaration of Dr. Wnuk to Vector Bioscience pre-grant opposition filed</td>
<td>16/10/2017</td>
</tr>
<tr>
<td>33</td>
<td>IMAK filed supplementary pre-grant opposition</td>
<td>17/04/2018</td>
</tr>
<tr>
<td>34</td>
<td>Reply to IMAK supplementary pre-grant opposition filed</td>
<td>05/09/2018</td>
</tr>
<tr>
<td>35</td>
<td>Hearing in Virupaksha Organic &amp; Vector Opposition scheduled. Vide controller’s email</td>
<td>08/10/2018</td>
</tr>
<tr>
<td>No.</td>
<td>Event Description</td>
<td>Date</td>
</tr>
<tr>
<td>-----</td>
<td>-----------------------------------------------------------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>36</td>
<td>Hearing of Sankalp Opposition</td>
<td>30/10/2018</td>
</tr>
<tr>
<td>37</td>
<td>Hearing of IMAK Opposition took place</td>
<td>31/10/2018</td>
</tr>
<tr>
<td>38</td>
<td>Sankalp filed Written Submissions</td>
<td>14/11/2018</td>
</tr>
<tr>
<td>39</td>
<td>Applicant filed written submissions against IMAK &amp; Sankalp Oppositions</td>
<td>14/12/2018</td>
</tr>
<tr>
<td>40</td>
<td>IMAK filed written submissions</td>
<td>17/12/2018</td>
</tr>
<tr>
<td>41</td>
<td>Ramesh Ganapathy filed pre-grant opposition</td>
<td>02/01/2019</td>
</tr>
<tr>
<td>42</td>
<td>Combined hearing of India Care and Optimus Pharma oppositions was held</td>
<td>05/02/2019</td>
</tr>
<tr>
<td>43</td>
<td>Notice in Ramesh Ganapathy pre-grant opposition was issued</td>
<td>06/02/2019</td>
</tr>
<tr>
<td>44</td>
<td>Applicant filed Written Submissions in India Care and Optimus Pharma Oppositions</td>
<td>19/02/2019</td>
</tr>
<tr>
<td>45</td>
<td>Reply to Ramesh Ganapathy Opposition filed</td>
<td>20/02/2019</td>
</tr>
<tr>
<td>46</td>
<td>India Care and Optimus Pharma filed their Written Submissions</td>
<td>25/03/2019</td>
</tr>
<tr>
<td>47</td>
<td>Nagendra Kumar Lagisetty filed pre-grant opposition</td>
<td>06/06/2019</td>
</tr>
<tr>
<td>48</td>
<td>Hearing in Ramesh Ganapathy Opposition was held</td>
<td>07/06/2019</td>
</tr>
<tr>
<td>49</td>
<td>Notice in Nagendra Kumar Lagisetty opposition issued</td>
<td>07/06/2019</td>
</tr>
<tr>
<td>50</td>
<td>Applicant filed written submissions in Ramesh</td>
<td>20/06/2019</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>Ganapathy Opposition</td>
<td></td>
</tr>
<tr>
<td>51</td>
<td>Ramesh Ganapathy filed his written submissions</td>
<td>21/06/2019</td>
</tr>
<tr>
<td>52</td>
<td>Reply to Nagendra Kumar Lagisetty opposition filed</td>
<td>27/06/2010</td>
</tr>
<tr>
<td>53</td>
<td>Hearing in Nagendra Kumar Lagisetty held</td>
<td>21/10/2019</td>
</tr>
<tr>
<td>54</td>
<td>P Guruvaiah filed pre-grant opposition</td>
<td>28/10/2019</td>
</tr>
<tr>
<td>55</td>
<td>Nagendra Kumar Lagisetty filed written submissions</td>
<td>04/11/2019</td>
</tr>
<tr>
<td>56</td>
<td>Applicant filed written submissions in Nagendra Kumar Lagisetty opposition</td>
<td>05/11/2019</td>
</tr>
<tr>
<td>57</td>
<td>Reply to P. Guruvaiah Pre-grant opposition filed</td>
<td>07/11/2019</td>
</tr>
<tr>
<td>58</td>
<td>Hearing in P. Guruvaiah opposition held</td>
<td>29/09/2020</td>
</tr>
<tr>
<td>59</td>
<td>Dhaval Dayabhai Diyora filed pre-grant Opposition</td>
<td>07/10/2020</td>
</tr>
<tr>
<td>60</td>
<td>Applicant filed its written submissions in P. Guruvaiah opposition</td>
<td>13/10/2020</td>
</tr>
<tr>
<td>61</td>
<td>Notice in Dhaval Dayabhai Diyora opposition issued</td>
<td>14/10/2020</td>
</tr>
<tr>
<td>62</td>
<td>P. Guruvaiah filed written submission</td>
<td>17/10/2020</td>
</tr>
<tr>
<td>63</td>
<td>Reply to Dhaval Dayabhai Diyora Opposition filed</td>
<td>22/10/2020</td>
</tr>
<tr>
<td>64</td>
<td>Hearing in Dhaval Dayabhai Diyora held</td>
<td>28/09/2021</td>
</tr>
<tr>
<td>65</td>
<td>Dhaval Dayabhai Diyora filed his written submissions</td>
<td>12/10/2021</td>
</tr>
<tr>
<td>66</td>
<td>Applicant filed written submissions in Dhaval Dayabhai Diyora Opposition</td>
<td>12/10/2021</td>
</tr>
<tr>
<td>No.</td>
<td>Event Description</td>
<td>Date</td>
</tr>
<tr>
<td>-----</td>
<td>------------------------------------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>67</td>
<td>Prof. YLN Murthy filed pre-grant opposition</td>
<td>29/10/2021</td>
</tr>
<tr>
<td>68</td>
<td>Notice in Prof. YLN Murthy opposition issued</td>
<td>03/12/2021</td>
</tr>
<tr>
<td>69</td>
<td>Reply in Prof. YLN Murthy opposition filed</td>
<td>24/12/2021</td>
</tr>
<tr>
<td>70</td>
<td>Hearing in Prof. YLN Murthy opposition held</td>
<td>08/06/2022</td>
</tr>
<tr>
<td>71</td>
<td>Prof. YLN Murthy filed written submissions</td>
<td>20/06/2022</td>
</tr>
<tr>
<td>72</td>
<td>Applicant filed written submissions in Prof. YLN Murthy opposition</td>
<td>22/06/2022</td>
</tr>
</tbody>
</table>

It is to note that present patent application was allotted to the undersigned Controller on 22/09/2017.

**Pre-Grant [Section 25(1)] Proceedings**

3. Following is the list of opponents who have filed the representations for opposition to grant of patent for the patent application number 3658/KOLNP/2009 under section 25(1) of the Patent Act-

   **Opponent 1**- Initiative for Medicines Access & Knowledge (I-MAK) (hereafter referred as **O1**)
   
   **Opponent 2**- Indian Pharmaceutical Alliance (hereafter referred as **O2**)
   
   **Opponent 3**- Natco Pharma (hereafter referred as **O3**)
   
   **Opponent 4**- Sankalp Rehabilitation Trust, Hepatitis Coalition of Nagaland (HepCon) and Network of PLHIV living in the Asia Pacific region (APN+) (hereafter referred as **O4**)
   
   **Opponent 5**- Optimus Pharma Ltd. (hereafter referred as **O5**)
   
   **Opponent 6**- Virupaksha Organic (hereafter referred as **O6**)
   
   **Opponent 7**- India Cares (hereafter referred as **O7**)
   
   **Opponent 8**- Vector Biosciences (hereafter referred as **O8**)
   
   **Opponent 9**- Mr. Ramesh Ganapathy (hereafter referred as **O9**)


Opponent 10- Lagisetty Nagendra Kumar (hereafter referred as O10)

Opponent 11- Mr. P. Guruvaiah (hereafter referred as O11)

Opponent 12- Mr. Dhaval Dayabhai Diyora (hereafter referred as O12)

Opponent 13- Prof. Y. L. N. Murthy (hereafter referred as O13)

It may be noted that the opponents O2, O3, O6 and O8 have withdrawn their pre-grant oppositions at various stages of proceedings before the hearings and accordingly no hearings conducted for such oppositions. Said oppositions, as filed by O2, O3, O6 and O8, are thus considered to disposed therewith and are not discussed herein.

Grounds of opposition-

4. Following are the grounds of opposition which were taken by various opponents in their notice of opposition-

Ground I- Section 25(1) (b): The invention so far as claimed in any claim of the complete specification has been published before the priority date of the claim

- Said ground regarding lack of novelty was taken by the opponents O1, O4, O5, O7, O9, O10, O11 and O13.

Ground II- Section 25(1) (e): 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 before the priority date in India or elsewhere in any document.

- Said ground regarding lack of inventive step was taken by the all the opponents O1, O4, O5, O7, O9, O10, O11, O12 and O13.

Ground III- Section 25(1) (f): 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.

- Said ground was taken by all the opponents O1, O4, O5, O7, O9, O10, O11, O12 and O13.
**Ground IV- Section 25(1)(g):** The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.

- Said ground was taken by the opponents O1, O4, O5, O7, O9, O10, O11 and O12.

**Ground V- Section 25(1) (h):** The Applicant has failed to disclose to the Controller the information required under Section 8 or has furnished the information which in any material particular was false to his knowledge.

- Said ground was taken by the opponents O1, O4, O5, O7, O10 and O11.

It may be noted that during oral hearings some opponents have not argued all the grounds of oppositions filed by them and such grounds were also not referred by them in written hearing submissions, accordingly only those grounds of opposition which were argued/discussed during oral hearing or referred to in written hearing submissions has been discussed in the present decision.

**List of documents**

5. Following is the list of documents filed as exhibits/annexures by the opponents in the pre-grant representations under section 25(1) of the Patents Act -

   **A.** List of exhibits filed by Opponent 1-


   Exhibit 2 - Statement on a Nonproprietary Name Adopted by the USAN Council for Sofosbuvir

   Exhibit 3 - Valentino Stella, Prodrugs as Therapeutics, Opinion on Therapeutic Patents, March 2004, Vol 14 No.3

   Exhibit 4 - Amended claims for 3658/KOLNP/2009

   Exhibit 5 - WO 2005/003147

   Exhibit 6 - Plinio Perrone et al, Application of the Phosphoramidate ProTide Approach to 4 ’Azidouridine Confers Sub-micromolar potency
Exhibit 7- Christopher McGuigan, et al, Certain Phosphoramidate Derivatives of Dideoxy Uridine (ddU) are Active Against HIV and successfully By-pass Thymidine Kinase FEBS Letter 351, 1994
Exhibit 8 - Dominique Cahard et al, Aryloxy Phosphoramidate Triesters as Pro-Tides, Mini-Reviews in Medicinal Chemistry, 2004
Exhibit 10 - WO 2006/067606
Exhibit 11 - WO 2002/08241
Exhibit 12 - WO 2005/012327

B. List of exhibits filed by Opponent 4 -
Exhibit C- WO 01/092282 (published on 06.12.2001)
Exhibit D- WO 2006/012078 (published on 02.02.2006)
Exhibit E- WO 2007/020193 (published on 22.02.2007)
Exhibit I- Jisson Kim et al., “Direct measurement of nucleoside Monophosphate Delivery from a Phosphoramidate Pronucleotide by Stable
Isotope Labeling and LC-ESI-MS/MS" Mol Pharm. 2004 Mar-Apr; 1(2):102-11
Exhibit P- WO 2006/067606
Exhibit Q- WO 2002/08241

C. List of annexures filed by Opponent 5 -
Annexure A: WO20005/012327
Annexure B: WO 2001/92282
Annexure E: WO 2005/003147
Annexure I: Christopher McGuigan et al, "Aryl 763-768, Phosphoramidates of d4T have improved anti-HN efficacy in tissue culture and may act by the general of novel intracellular metabolite", Journal of Medicinal Chemistry, 1996, 39, 1748-1753
Annexure K: Jisook Kim et al, "Direct Measurement of Nucleoside Monophosphate Delivery from a Phosphoramidate Pronucleotide by stable isotope labelling and LC-ESI-MS/MS", MOLECULAR PHARMACEUTICS VOL. 1, NO.2, 102-111
Annexure N: Vidhya V. Iyer, et al "Synthesis, in vitro anti-breast cancer activity, and intracellular decomposition of amino add methyl ester and
Annexure Q: US 2003/0109697
Annexure R: US 6589941
Annexure S: W01999/037753
Annexure T: WO 1996/29336
Annexure U: WO 1999/43691
Annexure V: WO 2003/000713
- Affidavit of Dr. Dnyandev R Rane

**D. List of annexures filed by Opponent 7-**

Annexure 1: Copy of WO 2005/012327
Annexure 3: Copy of WO 2005/003147, titled "Modified fluorinated nucleoside analogues" published-on January 13, 2005
Annexure 4: Copy of article by Eisuke Murakaini et, al, titled, as "Mechanism of Activation of D-2'-Deoxy-2' -Fluoro-2 -c-Methy 1 cytidine and Inhibition of Hepatitis C virus NS5B RNA polymerase" Antimicrobial Agents and Chemotherapy, Feb. 2007, p. 503-509.
Annexure 5: Copy of article by Plinio Perrone titled "Application of the phosphoramidate Protide approach to 4'-Azidouridine confers sub-micromolar potency versus Hepatitis C virus on an inactive nucleoside", Journal of Medicinal Chemistry, 2007, 50, 1840-1849
Annexure 6: Copy of WO 2006/121820 titled “Phosphoramidate prodrugs for treatment of viral infection” published on, 16 November 2006
- Affidavit by Mr. Otto Orlean Yang MD

**E. List of annexures filed by Opponent 9**

Annexure A- WO 2005/012327
Annexure B- “Guidelines For Examination Of Patent Applications In The Field Of Pharmaceuticals”
Annexure C- WO 2001/92282
Annexure D- WO 2001/90121
Annexure F- The opposition division of the European patent office (order dated 31.10.2016)
Annexure H- Perrone et al., Journal of Medicinal Chemistry 2007, 50, pp. 1840-1849
Annexure I- WO 2004/002999
Annexure J- WO 2006/012440

**F. List of annexures filed by Opponent 10**

Annexure A1- WO 2008/121634 A2
Annexure A-2- Copy of amended the statement of claims filed on 26th December 2012 by introducing 14 claims.
Annexure A-3- U.S. provisional application 60/909,315 (First priority 30 March 2007)
Annexure A-4- U.S. provisional application 60/982,309 (Second priority, 24 October 2007),
Annexure A-5- U.S. patent application 12/053,015 (Third priority, 21 March 2008),
Annexure A6- Sofia et al; Poster presented at the 14th International Symposium on Hepatitis C Virus and Related Viruses, held in Glasgow (Scotland) on 9-13th September 2007
Annexure A8- Ma et al 2007, J.Biol.Chem. 282, pp 29812-29820
Annexure A10- WO2005/012327
Annexure A12- WO 2004/002999
Annexure A13- WO 2004/096286
Annexure A14- Murakami et al

G. List of annexures filed by Opponent 11 -
Annexure I: WO 2005/012327 A2
Annexure VI: WO 2001/92282
Annexure VII: WO2001/90121
Annexure VIII: WO2004/002999
Annexure IX: WO2006/012440
Annexure X: Post grant opposition filed in EPO for the corresponding NP application
H. List of annexures filed by Opponent 12 -
Annexure A1: The published claims of the WO 2008/121634 A2
Annexure A2: Amended claims filed by the applicant on 26/12/2011
Annexure A3: U.S. provisional application 60/909,315
Annexure A4: U.S. provisional application 60/982,309
Annexure A5: U.S. patent application 12/053,015
Annexure A6: Poster presented at the 14th International Symposium on Hepatitis C Virus and Related Viruses, held in Glasgow (Scotland) on 9-13 September 2007
Annexure A8: Ma et al 2007, J. Biol. Chem. 282, pp 29812-29820
Annexure A10: WO2005/012327
Annexure A12: WO 2004/002999
Annexure A13: WO 2004/096286

I. List of exhibits filed by Opponent 13 -
c) (D3) WO 2004/002999 of Idenix
d) (D4) WO 2001/90121 of Idenix
e) (D5) US 6348587 of Emory
f) (D6) US 60/309,315
g) (D7) US 60/982,309
h) (D8) Decision of the opposition division of the European patent office (order dated 31.10.2016)
Cited Prior Art Documents

6. Following is the list of all the documents cited by various opponents during pre-grant opposition hearings under section 25(1) of the Patents Act and filed in written hearing submissions as prior art documents–

1. WO2005/003147 A2, published on 13.01.2005 (hereafter referred as D1)
2. WO2005/012327, published on 10.02.2005 (hereafter referred as D2)
3. WO 01/092282, published on 06.12.2001 (hereafter referred as D3)
4. WO 2006/012078, published on 02.02.2006 (hereafter referred as D4)
5. WO 2007/020193, published on 22.02.2007 (hereafter referred as D5)


16. WO 2006/067606, published on 29.06.2006 (hereafter referred as D16)


20. US6348587, published on 19.02.2002 (hereafter referred as D20)


22. WO2001/90121, published on 29.11.2001(hereafter referred as D22)

23. Sofia et al., "β-D2’-Deoxy-2’-C-methyluridine Phosphoramidates: Potent
and selective inhibitors of HCV RNA replication", Poster#P259 presented at the 14th International Symposium on Hepatitis C Virus and Related Viruses, Glasgow, Scotland, UK, Sep. 9-13, 2007 (hereafter referred as D23)


26. WO2006/012440, published on 02.02.2006 (hereafter referred as D26)

27. WO2004096286. published on 11.11.2004 (hereafter referred as D27)


29. The thesis entitled "Design, Synthesis and Biological Evaluation of Novel Nucleotide Prodrugs as Potential Anti-Hepatitis C Virus Agents" was submitted by Plinio Perrone (D29)

It may be noted that all the documents and submissions filed during filing and proceedings of pre-grant representation are considered while deciding upon the present case. For the sake of brevity all the submissions and arguments are not being repeated here to the fullest extent, only the relevant parts of submissions provided by both the parties after hearing is reproduced herein and all the prior art documents cited during hearings and submitted in written submissions by the parties are discussed herewith.

7. The original claims were amended to five claims during reply to the First Examination Report in November 2015; the said amended claims which
were relied on during the reply to all oppositions and argued upon are as
under:

1. (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 having the following
structure:

\[
\begin{align*}
\text{Structure 1}
\end{align*}
\]

or a stereoisomer thereof.

2. The compound as claimed in claim 1 wherein the stereoisomer is
(S)-isopropyl-2-([(S)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrim-
idin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl]
methoxy][phenoxy]phosphoryl]amino)propanoate having following
structure:

\[
\begin{align*}
\text{Structure 2}
\end{align*}
\]

3. The compound as claimed in claim 1 wherein the stereoisomer is
(S)-isopropyl-2-([(R)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrim-
idin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl]
methoxy][phenoxy]phosphoryl]amino)propanoate having following
structure:

\[
\begin{align*}
\text{Structure 3}
\end{align*}
\]
4. A composition comprising the compound as claimed in any of the claims 1 to 3, and a pharmaceutically acceptable medium.

5. A process for preparing the compound or a stereoisomer thereof as claimed in claim 1, said process comprising:

   reacting a compound 4" with a nucleoside analog 5'

   \[ \text{wherein } X' \text{ is a leaving group.} \]

WRITTEN HEARING SUBMISSIONS ON GROUNDS OF OPPOSITION:

8. **Ground (I) : Section 25(1)(b)- that the invention so far as claimed in any claim of the complete specification has been published before the priority date of the claim.**

8(a) Hearing submission by the opponents on section 25(1)(b)-

(i) OPPONENT 1 (O1) -

O1 has relied on D1 (WO2005/003147 A2) for novelty and has submitted as follows-

D1 covers an invention for "(2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside(β-D or β-L), or its pharmaceutically acceptable 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 (page 16, lines 3-8)". Page 16 at lines 16- 24 of D1 adds that 2' substitutions of β-D or β-L nucleosides of the invention claimed impart greater specificity for HCV and include a method for treating various viruses included HCV, or its pharmaceutically acceptable salt or prodrug. More specifically, the compound set out in claim 6 of D1 covers the structure of the base compound for sofosbuvir, including its monophosphate, diphosphate, triphosphate or a stabilised phosphate prodrug. Under the heading "Definitions", on page 31, lines 7-22 of D1 the patent document states that "The term "pharmaceutically acceptable salt or
"prodrug" is used throughout the specification to describe any acceptable form. Page 46, lines 16-18 of D1 state: ‘Any of the nucleosides described herein can be administered as a nucleotide prodrug to increase the activity, bioavailability, stability or otherwise alter the properties of the nucleoside’.

Pages 47-48 disclose how pharmaceutical compositions based upon the -D or -L compound or its pharmaceutically acceptable salt or prodrug can be prepared in a therapeutically effective amount for treating a flaviviridae infection, including HCV. Page 59, lines 4-23 of D1, discusses similar phosphoramidates as claimed. Pages 51-54 of D1, under the heading ‘Stereoisomerism and Polymorphism’ discusses how the nucleoside compounds covered have several chiral centres and may exist in and be isolated in optically active and racemic forms, as do most amino acids which can exist as separate enantiomers. Pages 52-53 then set out commonly known techniques in the art for obtaining optically active materials. In the specification of D1, different types of prodrugs of sofosbuvir including phosphoramidate prodrugs are mentioned. It is not difficult for a person skilled in the art to reach the phosphoramidate prodrug claimed in impugned application.

(ii) OPPONENT 5 (O5) & OPPONENT 7 (O7) -
O5 & O7 have relied on D2 (WO 2005/012327) for novelty. As per their submission, in case of claims where several compounds are claimed within a single claim in the nature of Markush, each compound must be deemed to be disclosed. Also in a case where lack of novelty is alleged, the prior art must disclose the invention as claimed. In the present case, such a disclosure can be found by way of D2 which discloses various nucleoside derivatives. It teaches that nucleosides may be substituted as 5’ position. It also teaches addition of phosphoramidates moiety attached to the P atom, an aryl O-moïety, and alpha amino moiety. D2 discloses compounds with general formula I
R is selected from the group comprising alkyl, aryl and alkylaryl; R is alkyl (includes a branches alkyl group); R’ is Hydrogen; R” is alkyl; Further, when one of R’ and R” is H and one of R’ and R” is Me or PhCHs, the moiety corresponds to alanine or phenylalanine. Further, D2 discloses that the stereochemistry at the asymmetric centre – CR’ R” corresponds to an L-amino acid. The stereochemistry at the asymmetric centre – CR’R” can, however, correspond to a D-amino acid. Alternative, mixture of compounds can be employed having symmetric centres corresponding to L and D amino acids. Q is O; X is CH3; Y is F; Ar is monocyclic aromatic moiety (includes phenyl) Z is Hydrogen; N=1; Z’ is = O;

The Opponents submit that when the aforesaid substitutions are made, the resultant compound is nothing but the pro-drug or sofosbuvir which is claimed in the present application. It is submitted that the claims and subject matter of D2 is written in “Markush format” i.e. in the alternative or “OR”. Such form of disclosing compounds have received interpretation and now it is the settled position of law that Markush claims are to be read as disclosing individually, each compound embraced within the Markush. Further, the Patent Office manual clearly states that a species would be anticipated by a generic disclosure. Therefore, the disclosure in D2 written in the Markush format embraces the compound claimed by the impugned application. The argument of the Applicant that the coverage of compounds by D2 is subject to a proviso, is entirely ill-founded because:

a) It is not the case of the Opponent that the compounds claimed as Prodrug by the Applicant fall within the scope of the proviso and therefore are excluded.

b) The proviso only excludes certain compounds; however, the proviso does not mean that the aforesaid compounds as disclosed are not so disclosed; the proviso is like a saving clause or an exception that only excludes some
compounds from the scope. Therefore, in the light of the disclosures made in the D2, the compounds claimed in claim 1 to 8 are not novel and liable to be rejected on this ground alone.

(iii) OPPONENT 9 (O9) -
O9 has also relied on document D2 (WO 2005012327) and has submitted that the claims of the alleged invention lack novelty and are anticipated by the document D2 which was published on 10 February 2005. The D2 discloses a chemical compound having formula I

![Formula I](image)

wherein: R is selected from the group comprising alkyl, aryl and alkylaryl; R' and R" are, independently, selected from the group comprising H, alkyl and alkylaryl, or R' and R" together form an alkylene chain so as to provide, together with the C atom to which they are attached, a cyclic system; Q is selected from the group comprising -O- and -CH2-; X and Y are independently selected from the group comprising H, F, Cl, Br, I, OH and methyl (-CH3); Ar is a monocyclic aromatic ring moiety or a fused bicyclic aromatic ring moiety, either of which ring moieties is carbocyclic or heterocyclic and is optionally substituted; Z is selected from the group comprising H, alkyl and halogen; and n is 0 or 1. Wherein when n is 0, Z' is -NH2 and a double bond exists between position 3 and position 4, and when n is 1, Z' is =O; or a pharmaceutically acceptable derivative or metabolite of a compound of formula I; with the proviso that when n is 1, X and Y are both H, R is methyl (-CH3), one of R' and R" is H and one of R' and R" is methyl (-CH3), then Ar is not phenyl (-C6H5).

By "a pharmaceutically acceptable derivative" is meant any pharmaceutically acceptable salt, ester or salt of such ester or any other compound which upon administration to a recipient is capable of providing (directly or indirectly) a compound of formula (I).
Suitably, except where R is 2-Bu (−CH2−CH(CH3)2) and one of R’ and R” is H and one of R’ and R” is methyl (−CH3), when n is 1 and X and Y are both H, then Ar is not unsubstituted phenyl (−C6 H5). By "pharmaceutically acceptable metabolite" is meant a metabolite or residue of a compound of formula (I) which gives rise in use to a compound of formula (II).

\[
\text{(II)}
\]

The opponent submits that the Sofosbuvir as claimed in the present application is covered by D2. The present specification discloses and claims (S)-2- \((2R,3R,4R,5R)-5-(2,4\text{-dioxo}-3,4\text{-dihydro}-2H\text{-pyrimidin}-1\text{-yl})-4\text{-fluoro}-3\text{-hydroxy}-4\text{-methyl\text{-tetrahydrofuran\text{-2-ylmethoxy}}-\text{phenoxy}}\text{-phosphoryl amine})\text{-propionicacid isopropyl ester.}

The compound Sofosbuvir claimed in the present specification is explicitly disclosed in D2, where the substitutions of R, R’, R”, Q, X, Y, Ar and Z given therein as below; R is selected from a group comprising alkyl; R’ and R” are independently selected from the group comprising H, alkyl; Q is selected from the group comprising –O–; X and Y are independently selected from the group comprising F and methyl (−CH3); Ar is monocyclic aromatic ring moiety; Z is selected from when n is 1, Z’ is=O;

When the markush compound of D2 is substituted with above groups or substituents, (S)-2- \((2R,3R,4R,5R)-5-(2,4\text{-dioxo}-3,4\text{-dihydro}-2H\text{-pyrimidin}-1\text{-yl})-4\text{-fluoro}-3\text{-hydroxy}-4\text{-methyl\text{-tetrahydrofuran\text{-2-ylmethoxy}}-\text{phenoxy}}\text{-phosphoryl amino})\text{-propionicacid isopropyl ester is obtained. Hence the compound disclosed in the claim 1 of the present application is anticipated by D2. Hence claim 1 and its diastereomers of claims 2 & 3 are not novel and are anticipated by the disclosures of D2.

The present specification discloses the preparation of nucleoside phosphoramidate prodrugs by reacting an appropriately substituted phosphochloridate with a nucleoside containing a free 5’-hydroxyl moiety.
D2 exemplifies the process involving synthesis of phosphoramidate esters containing alanine as the amino acid, and unsubstituted phenyl, using a leaving group. Thus the process as disclosed in the present application (claim 5) is anticipated by the disclosure of D2. D2 discloses the above process for the preparation and use of the following prodrug moiety into the base compound.

Therefore the process as claimed in claim 5 is anticipated in light of above disclosures in D2 and hence such process is not novel. A pharmaceutical composition comprising the compounds disclosed in D2 and pharmaceutically acceptable excipients, carrier or diluent is also disclosed in D2 (page 14, lines 24 to 26). Thus the composition claimed in claim 4 lacks novelty over D2. Thus the given disclosures in D2 the present application stands anticipated. Hence all claims 1 to 5 of the present application are anticipated by disclosure in D2 and ought to be rejected on this ground alone.

In addition I would like to bring to your notice that, the “Guidelines For Examination Of Patent Applications In The Field Of Pharmaceuticals” in para 7.5 states that “Sometimes the prior art may inherently disclose the subject matter of an invention. In one case before the IPAB, it was held that “patent is invalid for anticipation if a single prior art reference discloses each and every limitation of the claimed invention. The prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating prior art. It is not necessary that inherent anticipation requires that a person skilled in the art at the time would have recognized the inherent disclosure. But it is necessary that the result is a necessary consequence of what was deliberately intended in the invention” [paragraph 58 of the decision of the IPAB in Enercon (India) Limited vs AloysWobben
ORA/6/2009/PT/CH,ORDER (No. 18 of 2013)]. On applying the above IPAB order to the present application it is very clear that the claims 1 to 5 of the present application are anticipated by the disclosure of D2 and ought to be rejected. Further the “Guidelines For Examination Of Patent Applications In The Field Of Pharmaceuticals” provides illustrative examples to analyze the markush claims as follows; based on the decision of the IPAB in Enercon (India) Limited vs AloysWobben ORA/6/2009/PT/CH,ORDER (No. 18 of 2013). On applying the analysis laid down by the “Guidelines For Examination Of Patent Applications In The Field Of Pharmaceuticals” based on decision of Enercon (India) Limited vs AloysWobben ORA/6/2009/PT/CH,ORA/6/2009/PT/CH,ORDER (No. 18 of 2013), the claims 1 to 5 of the present application is anticipated by the disclosure of D2 and ought to be rejected.

(iv) OPPONENT 11 (O11) –
O11 has also relied on document D2 and argued that D2 clearly discloses the compound claimed in claim 1 of the opposed patent application and hence the compound claimed in claim 1 lacks novelty. The compounds claimed in dependent claims 2 and 3 are also anticipated by the disclosures of D2 as the stereoisomers are disclosed in D2. The opponent herewith submitted that the combination of specific substituent’s is as directly and unambiguously derived from D2 as the combination of substituent’s yielding the compounds claimed in claims 2 and 3 of the present application. The composition claimed in claim 4 is also anticipated by the disclosures of D2. Therefore, the compounds and composition claimed in claims 1 to 4 are lacking novelty in view of the disclosures in D2.

Opponent also argued that D2 discloses the process involving synthesis of Phosphoramidate esters containing alanine as the amino acid, and unsubstituted phenyl using a leaving group. D2 discloses the process for the preparation and use of to the base compound.
Thus, the process as claimed in claim 5 of the present disclosures of D2. Additionally, the process claim does not provide any clarity on reaction conditions. Rather, it vaguely identifies reactants and says reacting the reactants. The claims 1 to 5 of the impugned patent application anticipated and lacks novelty in view of the disclosures in any of the prior art documents D2.

(v) OPPONENT 13 (O13) -
O13 relied on D23 (Sofia et al.) which is a poster presented by the inventors of the present Application. It is therefore submitted that the details of the compounds disclosed therein, the nature of the compounds and their activities including the compounds claimed in the Present Application, were known to the Applicant on a date before the priority date of the Present Application. D23 indicates that, “a prodrug of β-D-2’-deoxy-2’-fluoro-2’-C-methylcytidine, PSI-6130, for the treatment of chronic hepatitis C”, were under development. (LHS, ‘Introduction’, lines 5-6). It also discloses the PSI-6130 is converted into its uridine metabolite (PSI-6206) via cytidine deaminase. The poster goes on to disclose that the triphosphate derivative of this metabolite PSI-6206 is a potent inhibitor of the HCV NS5B monophosphate. (LHS, ‘Introduction’, lines 7-10)

![Chemical structures of PSI-6130 and PSI-6206](image)

It may be noted that the EC90 value for PSI-6130 has been disclosed as 4.6 ± 2.0 mM and the EC90 value for PSI-6206 has been disclosed as >100 mM. Further, D23 also discloses that to investigate potential of PSI-6206 as an inhibitor of HCV replicon, the first phosphorylation step was to be bypassed, and the same was accomplished by preparation of phosphoramidate derivatives at the 5’-position. This strategy is said to have resulted in potent and sage inhibitors of HCV replication. (LHS, ‘Introduction’, lines 18-21). Further, the PSI-6206 Phosphoramidate is disclosed as
Wherein: R1 is a phosphorus ester; R2 is an amino acid side chain; and R3 is an amino acid ester. A comparison of compound of claim 1 of the Present Application and PSI-6206 Phosphoramidate disclosed in D23 et al would clearly indicate that the claim 1 compound of the Present Application was already disclosed.

<table>
<thead>
<tr>
<th>Compound of Claim 1 of Present Application</th>
<th>PSI-6206 Phosphoramidate</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Compound Structure" /></td>
<td><img src="image2.png" alt="Phosphoramidate Structure" /></td>
</tr>
</tbody>
</table>

Therefore, the compound of claim 1 is not novel, and claims 2-5 dependent on claim 1 also lack novelty.

8(b) **Hearing submission by the applicant on section 25(1)(b)**

As the documents D1, D2 and D23 are relied upon by the opponents the applicant submission is provided in that reference.

(i) D1 was relied upon by the O1 to argue that the compounds disclosed therein are novelty destroying. It is submitted that D1 is not a novelty destroying document. It is admitted position in law that anticipatory prior art should have enabling disclosure. Neither the Opposition petition nor during the arguments it has been demonstrated by the Opponent that the claimed compounds are disclosed in D1, let alone enabled. It is submitted that the said patent document is not novelty destroying in view of the following reasons:

a. The compounds which the Opponent rely upon in petition are not disclosed, mentioned, listed or described in the cited prior art specification.
b. D1 discloses a (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside of the formula

![Nucleoside Structure Image]

c. It is clear from the definition of R1 that there is no specific disclosure or teaching of a phosphoramidate group for R1.
d. D1 refer to certain prodrugs generally, it does not specifically describe the phosphoramidate group claimed.
e. Not a single prodrug compound is synthesized in D1.
f. It does not describe specifically "phosphoramidate" as a prodrug. It does not disclose/teach the preparation of any prodrug let alone be the specific prodrug "phosphoramidate".
g. D1 describes/mentions many types of nucleoside prodrugs- 2', 3'-and/or 5'-phosphoether lipid; 2', 3'- and/or 5'-phosphoether lipid; Aryl esters; Cyclic and non-cyclic phosphonate esters; Cyclic phosphoramidate substituted 1',3'-propanyl cyclic phosphoramidate
h. D1 does not disclose a phosphoramidate moiety let alone the specific claimed phosphoramidate group itself.
i. D1 provides examples of some of the prodrug which are 3'-monoester or 3'- and 5'- diesters prodrugs (on page 61 of D1) or N-acyl prodrugs.
It is well established that a generic disclosure does not take away the novelty of any specific example falling within the terms of that disclosure.

D1 does not specifically mention or disclose the 5'-phosphoramidate prodrug of the 2-deoxy-2'-fluoro(down)-2'-methyl (up) nucleoside.

D1 provides no guidance to persons of ordinary skill in the art concerning the synthesis of phosphoramidate prodrug of (2R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside.

There is no actual HCV activity data for any prodrug compound. Thus, the claimed compounds are not anticipated by D1.

(ii) D2 is not a novelty destroying document for the present invention in view of the following reasons:

MARKUSH OF D2
a. The compounds which the Opponent rely upon in petition are not disclosed, mentioned, listed or described in the cited prior art specification.

b. 10 substituents for the compounds of formula (I) of D2 are to be selected to reach to the claimed compound i.e. R, R’, R‖, Ar, Q, X, Y, Z, Z’ & n.

c. Out of these ten substituents, 4 are fixed in accordance with standard procedure 5, where the nucleoside is fixed to 5-(2-bromovinyl)-2’-deoxyuridine.

d. D2 in the standard procedure 5 has fixed the nucleoside to be (E)-5-(2-bromovinyl)-2’-deoxyuridine (BVDU) wherein the base has been fixed to bromovinyluracil and sugar moiety has been fixed to 2’-deoxyuracil having no substitution at 2’-position.

e. D2 strongly prefers the base to be 2-bromovinyl-uracil in all the exemplified compounds except one which is a well-known anti-cancer drug “Gemcitabine”. Not a single compound is disclosed with an unsubstituted uracil base.

f. Therefore, synthetic procedure of D2 by following the standard procedure-5 described therein, a person skilled in art will always start with (E)-5-(2-bromovinyl)-2’-deoxyuridine and the resulting nucleoside analogue will always have (2-bromovinyl)-2’-deoxyuridine.

g. D2 does not disclose nucleoside moiety having the required, stereospecific substitution at the 2’-position, i.e. 2’-fluoro (down), 2’-methyl (up).
h. D2 fails to disclose the specific phosphoramidate moiety at 5’-position of sugar ring of the Gilead’s claimed compounds.

i. It provides preparation of 48 preferred or promising compounds on page 23 to 72 containing BVDU nucleoside and 3 examples of phosphoramidate derivatives of known drug Gemcitabine. Among the prepared exemplified compounds all the compounds have only hydrogen at 2’-position carbon i.e. 2’-position is unsubstituted except three compounds which are Phosphoramidates of Gemcitabine which has difluoro substitution on 2’-position. Not a single compound is prepared with unsubstituted uracil base attached to sugar and the unique substitution pattern of 2’-fluoro (down) and 2’-methyl (up) at 2’-position of sugar ring and phosphoramidate with isopropyl ester of alanine amino acid.

j. D2 provides activity data for ~98 compounds in table on page 106-109 which includes naturally as well as non-naturally occurring amino acids.

k. Activity has been reported for Breast cancer, colon cancer, prostate cancer.

l. Activity reported for ~98 compounds with all having 2-bromovinyluridine except 6 compounds.

m. Not a single compound has unsubstituted uracil base attached to sugar and the unique substitution pattern of 2’-fluoro (down) and 2’-methyl (up) at 2’-position of sugar ring and isopropyl ester of alanine amino acid.

n. There is no actual HCV activity which is reported qua the compounds which are sought to be identified by the Opponent.

o. Rather on page 3, D2 states that “however, based on our prior art, the phenyl methoxyalaninyl phosphoramidate (7) would be anticipated to be amongst the most optimal of structures.” “Surprisingly, it has now been found that other derivatives of oxyamino acid-phosphoramidate nucleoside analogues are significantly more potent in the treatment of cancer than the phenyl methoxyalaninyl phosphoramidate (7).” The support for the above statement has been provided on page 12 of D2
where it mentions surprising finding that the benzyl ester compound (8) is more potent against cancer cell lines than the methyl ester compound (7).

![Chemical structure of compound (7)](image1)

p. D2 states on page 13 that the simultaneous modification in the two regions i.e. amino acid and aryl moiety show high potency against a range of cancer cell types and significantly and surprising more potent that compound (7).

![Chemical structure of compound (8)](image2)

q. Very importantly, it can be noticed from the finding of the Inventors that the most optimal compound for the research in the field of cancer is compound (7) which has a Bromo Vinyl Deoxy Uracil base. Here, the Author/inventors considered the prior art from 1994 till date 2004. Further, the finding of authors of D2 concludes that the compounds incorporating modification at amino acid ester region and modification at aryloxy group attached to Phosphorus atom in compound (7), results into more potent compounds for the treatment of cancer.
(iii) The Applicant argued that averments made for lack of novelty or inventive step in respect of D23 are factually and legally incorrect, misleading and are liable to be rejected. As per the Opponent D23 can be considered as a valid prior art considering the Applicant has wrongly claimed the priority date of March 30, 2007 and effective date of priority should be October 24, 2007. Opponent alleges that date claimed from US 60/909,315 is not validly claimed for the entire set of claims in the Present Application and claim 1-5 are not entitled to claim priority from US provisional application No. 60/909,315. In this regard, Opponent relies on opposition proceeding of corresponding EP patent EP2203462.

The applicant submitted that D23 cannot be considered as a valid prior art as it is published after the priority date (March 30, 2007) of the present application i.e. September 2007. Without prejudice and even otherwise, the averments made regarding priority date of claims are factually and legally incorrect, misleading, and hence denied. Applicant submits that the present claim 1 is directed to a compound or a stereoisomer thereof, which is well supported in the priority document US 60/909,315.

The support for the same is as follows:

a. The compound of claim 1 has the support from the page 195 (compound IX-25-2) of the priority document US 60/909315.

b. On page 8-9 of the priority document there is disclosed a compound of formula (I)

\[ \text{in order for general formula (I) to include the compound of claim 1 the following matches must hold:} \]
R1 = phenyl; R2 = hydrogen; R3a = hydrogen; R3b = methyl; R4 = isopropyl; R5 = hydrogen; R6 = methyl; X = F; Y = OH
Base = Uracil, for that base has to be formula b with R7 and R8 being hydrogen.

From the definitions of various substituents on page 9 of the Priority document, it is clear that R1 is aryl which includes phenyl, (page 9, line 1-2); R2 is hydrogen, (page 9, line 7); R3a is H and R3b is independently selected from H, CH₃....(page 9, line 20), R4 is C₁₋₁₀ alkyl, (page 10, line 1) and the definition of Alkyl covers isopropyl (page 13 line 10), R5 is hydrogen (page 10 line 3); R6 is CH₃ (page 10 line 11); X is F (page 10 line 12); Y is OH (page 10 line 13), Base is formula b wherein R7 and R8 are independently hydrogen (page 11).

c. Further, on page 34 of priority document, the first aspect of the second embodiment is directed to a compound of formula (1-3) which also covers or supports the specific compound of claim 1.
d. Claim 1 of the US provisional priority document encompasses presently pending claims 1, 2 and 3. It reads as under:

“A compound, its stereoisomer, salt, hydrate, solvate, or crystalline form thereof, represented by formula (I):
For understanding of stereoisomers, the provisional priority document US 60/909,315 has below reference:

On page 63 of priority document contains enabling disclosure for the stereoisomers at the chiral centers. The relevant passage referred to in pages 63-64 reads:

*The following tables contain numeric identifiers associated with various substituent designators that should be viewed in light of the accompanying structure. These structures are contemplated species of the various aspects of the disclosed embodiments and are not intended to be limiting on full breadth of the contemplated compound represented by the structure of formula I. In each of the presented tables, the phosphoramidate substituent containing the substituents $R^{3a}$ and $R^{3b}$ are depicted without reference to stereochemical structure (ef. Structures I-1, I-3, and I-5 above). It is contemplated that the compounds recited below embody compounds in which $R^{3a}$ projects towards the viewer while $R^{3b}$ projects away from the viewer (ef. Structures I-2, I-4, and I-6). Moreover, it is contemplated that the compounds recited below also embody compounds in which $R^{3a}$ projects away from the viewer while $R^{3b}$ projects towards the viewer. Not meant to be limiting, however, the inventors of the present invention contemplate that preferred compound are those in which $R^{3a}$ projects towards the viewer and $R^{3b}$ projects away from the viewer such that the natural L-amino acid (S)-configuration is presented.*

Additionally, the inventors recognize that the phosphorus atom of the phosphoramidate moiety is another source of chirality. Although the structures below do not specifically depict chirality...
at phosphorus, the inventors recognize that stereochemical configurations are possible such that in a staggered (or zig-zag) line structure the oxo-substituent projects towards the viewer while the OR1 substituent projects away from the viewer, and vice versa. Therefore, the structures below include all possible stereochemical configurations possible for phosphorus.”

This is then followed by formula (II)

In case of IX-25-2 each of R2-R9 have been specified and should be read in combination with formula IX on page 187. The applicant considered that the passage on page 63-64 referring to the first orientation of R3a and R3b is a preferred variation as is further shown e.g. by example 13 on page 620 where all the tested compounds have this configuration. There is also no selection from lists involved because all the substituents in formula (II) are set out in a single line. this should be combined with the statement of all possible stereochemical configurations possible for phosphorus and IX-25-2 which is considered to be directly related to it, thereby directly individualizing the diastereomers of claim 2 and 3.

Thus, the presently pending claims 1, 2 and 3 are not only specifically claimed in the priority document but also were fully enabled and supported by the priority document.

Furthermore, on page 40-41 of priority document US 60/909,315, the fifth aspect of second embodiment clearly defines the stereochemistry around the chiral carbon atom. Further, if this structure (extracted below) is read with following sentences at page 63-64 of the priority document, chirality on
phosphorus atom is well defined and thus, clearly covering and supporting the compounds of claims 1, 2 & 3:

Additionally, the inventors recognize that the phosphorus atom of the phosphoramidate moiety is another source of chirality. Although the structures below do not specifically depict chirality at phosphorus, the inventors recognize that stereochemical configurations are possible such that in a staggered (or zig-zag) line structure the oxo-substituent projects towards the viewer while the OR1 substituent projects away from the viewer, and vice versa. Therefore, the structures below include all possible stereochemical configurations possible for phosphorus”.

It can be seen that chirality at carbon and phosphorus atom are fully enabled and supported even in the priority document. Accordingly, not only claim 1 but claims 2 and 3 are also fully enabled in the provisional priority document 60/909,315.

f. The Applicant also refers to page 609 “compounds and preparation” section along with example 5 on page 614 to example 8 on page 617 of the priority application US 60/909,315, which provides the preparation of compounds.

g. Further to this, the present compete specification 3658/KOLNP/2009 on page 684 mentions that “Example number 13-54 and 56-66 are prepared using similar procedures described for examples 5-8. The example number, compound identification, and NMR/MS details are shown below” the said table includes compound 25 on page 685.
h. The examples 5-8 of the complete specification are same as examples 5-8 of the priority application US 60/909,315 dated March 30, 2007. Thus, the priority application dated March 30, 2007 provides support for the claimed compounds and its stereoisomers as highlighted above.

i. The Applicant also refers back to page 18 of the complete specification, which reads "It is contemplated that compounds of formula I are racemic because the chirality at phosphorous. Applicant contemplates use of the racemate and/or the resolved enantiomers".

j. The priority document US 60/909,315 on page 612, under example 3 provides the process for the preparation of phosphoramidate compounds by condensation of nucleoside analog 5 with suitably substituted phosphochloridate compound 4.

k. A skilled person would reasonably and correctly understand that utilizing the same reaction conditions and the same process with the appropriate phosphorchloridate would, and in fact did, produce the compound of Example 25 of ‘3658.

l. The priority document teaches how to prepare the appropriate phosphorochloridate in Example 2 (id. at pages 611-612). The specification also teaches how to prepare the appropriate 2'-deoxy-2'-fluoro-2'-C-methyluridine in Example 4 (id. at pages 613-614).

m. Further, Applicant submits that following passages on page 63 of priority document indicate the disclosure for the two diastereomers. Formula IX-25-2 on page 195 of the priority document in combination with pages 63-64, and claims disclose example 25 of ‘3658 and its stereoisomer,

n. Therefore, compounds of claim 1 are well supported by the priority document 60/909,315 dated 30 March, 2007 and compounds of claim 2 and 3 are not just covered but also disclosed by the original disclosure of priority document
60/909,315 dated 30 March 2007. Therefore, Applicant submits that the compounds of claims 1, 2 and 3 are well supported by the original disclosure of priority application 60/909,315 dated 30 March 2007.

- Further, Opposition division of EPO in its decision dated 31.10.2016 has not considered D23 for the purpose of novelty analysis. Reference made to para 32.2 of decision by EPO Opposition division with respect to D23 (D8 of EPO opposition decision).

9. Ground (II) : 25(1)(e)- 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 before the priority date in India or elsewhere in any document

9(a) Hearing submission by the opponents on section 25(1)(e)

(i) Opponent 4 -
O4 submitted that the Applicant has in its reply to the opposition dealt with the prior art cited by the Opponents in isolation, as though they have been cited for contesting the novelty of the claimed compounds. It is submitted that while determining obviousness, the prior art documents are to be read together and not in isolation. The Delhi High Court in the matter of Glaverbell SA vs. Dave Rose and Ors. [MANU/DE/0205/2010] held “that mosaicking may not be relevant to undermine novelty in the circumstances of the case, but obviousness has to be seen while looking into the techniques and technologies of existing and pre-existing state of article discussions on prima facie case and balance of convenience”.

Further, it is pertinent to note that while determining obviousness it is to be appreciated that,

a. Any problem known in the field can provide a reason for combining the elements in the manner claimed;

b. Familiar items may have obvious uses beyond their primary purposes;

c. A person of ordinary skill often will be able to fit the teachings of multiple patents based on the known purposes of familiar items;
This was also recognized in *KSR International Co. vs. Telectum Inc.* 550 US 398 wherein the US Supreme Court noted, “The Circuit first erred in holding that courts and patent examiners should look only to the problem the patentee was trying to solve. Under the correct analysis, any need or problem known in the field and addressed by the patent can provide a reason for combining the elements in the manner claimed. Second, the appeals court erred in assuming that a person of ordinary skill in the art attempting to solve a problem will be led only to those prior art elements designed to solve the same problem...It is common sense that familiar items may have obvious uses beyond their primary purposes, and a person of ordinary skill often will be able to fit the teachings of multiple patents together like pieces of a puzzle...Third, the court erred in concluding that a patent claim cannot be proved obvious merely by showing that the combination of elements was obvious to try. When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp...” (See Pages 15-18).

Further, the Applicant has in its reply argued that the prior art documents do not suggest or motivate development of Sofosbuvir (compound of claim 1) as claimed in the Present Application. It is submitted that the Applicant has applied the law on obviousness incorrectly as the test of obviousness does not require absolute predictability of success. The US Supreme Court in the matter of *KSR International Co.* also took note that absolute predictability of success is not a requirement in determining obviousness and cited *In Re O’Farrell* (853 F.2d 894 (Fed. Cir. 1988)), wherein it stated, “Obviousness does not require absolute predictability of success. Indeed, for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice. There is always at least a possibility of unexpected results that would then provide an objective basis for showing that the invention, although apparently obvious, was in law nonobvious...”

The UK Court of Appeals, in *Windsurfing International v Tabur Marine (Great Britain)* 1985 WL 310551 laid down the test for obviousness noting,
“We think there are four steps which require to be taken in answering the jury question.
The first is to identify the inventive concept embodied in the patent in suit. Thereafter, the court has to assume the mantle of the normally skilled but unimaginative addressee in the art at the priority date and to impute to him what was, at that date, common general knowledge in the art in question. The third step is to identify what, if any, differences exist between the matter cited as being "known or used" and the alleged invention. Finally, the court has to ask itself whether, viewed without any knowledge of the alleged invention, those differences constitute steps which would have been obvious to the skilled man or whether they require any degree of invention”.

It is the Opponents’ case that on the priority date of the Present Application, following features were known in the art:

a. 2’-deoxy-2’-fluorouridine was known an anti-HCV agent;
b. ProTide approach to activate an inactive nucleoside by phosphate prodrug formation was known;
c. L-alanine was a preferred amino acid in ProTide approach;
d. Isopropyl moiety in prodrug compounds were known to show better activity.

That is, the Applicant has put together these known features in the prior art to arrive at the claimed compound as below:

A. 2’-deoxy-2’-fluorouridine was known an anti-HCV agent

D2 (WO2005/012327) titled as, “Chemical Compounds” discloses Phosphoramidate derivative of nucleotide used in treatment of cancer..
Further, the publication indicates that base moiety such as deoxyuridine may be substituted at 5-position (see abstract). Further, the Phosphoramidate moiety has attached to the P atom, an aryl O-moiety and an α-amino acid moiety (See Vol. I, page 41, abstract).

D2 discloses a compound of the following formula:

Among the several substitutions disclosed for the above compound, one of the substitutions may also be thus:

R is alkyl (includes a branches alkyl group); R’ is Hydrogen ; R’’ alkyl;
Further, when one of R’ and R’’ is H and one of R’ and R’’ is Me or PhCH2, the moiety corresponds to alanine or phenylalanine. Further D2 discloses that the stereochemistry at the asymmetric centre –CR’R’” corresponds to an L-amino acid. The stereochemistry at the asymmetric centre –CR’R’” can, however, correspond to a D-amino acid. Alternatively, mixtures of compounds can be employed having symmetric centres corresponding to L and D amino acids.

Q is O; X is CH3; Y is F; Ar is monocyclic aromatic moiety (includes phenyl); Z is Hydrogen, n=1; Z’ is =O

The compound above disclosed also includes pharmaceutically acceptable derivative, i.e. any pharmaceutically acceptable salt, ester, or salt of such ester.

On making the above disclosed substitutions, a person reading D2 would arrive at the following compound:
Further, D2 discloses that changes to the ester derivative indicated significant changes in potency. For instance, D2 reported a ca 4-fold potency boost of phosphoramidate of d4T (10) over phosphoramidate of d4T (9):

Hence, D2 not only teaches uridine nucleosides but also teaches an aryl and monophosphate moiety attached to such nucleoside. Further, on reading D2 a person skilled in the art working on nucleosides with phosphoramidate substitution would be motivated to attempt different ester substitutions to analyse change in potency.

D1 (WO 2005/003147) titled, “Modified Fluorinated Nucleoside Analogues” discloses (2’-R)-2’-deoxy-2’ fluoro-2’-C-methyl nucleoside (β-D or β-L), its pharmaceutically acceptable salt or prodrug for treatment of Hepatitis C of the following formula:

Amongst the substitution disclosed therein, the following substitution also features as one of the embodiments:
Base naturally occurring pyrimidine base; R7: H; X: O; R1: monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug
Hence, a POSITA working on developing a nucleoside for treating Hepatitis C, on reading D1 would be taught that a fluorinated nucleoside, particularly, (2'-R)-2'-deoxy-2' fluoro-2'-C-methyl nucleoside may act as an anti-HCV agent.
The Opponent further relied on D3 (WO01/092282) titled, “Methods and Compositions For Treating Flaviviruses and Pestiviruses” and relates to treatment of flavivirus with 1',2', 3' modified nucleoside, its pharmaceutically acceptable salt or prodrug thereof. D3 discloses a prodrug of compound XVI reproduced below:

![Compound XVI](image)

(XVI)

Among the substitutions disclosed therein, a POSITA may also attempt the following substitution wherein-
Base is purine or pyrimidine; R6: hydrogen; R8: chlorine, bromine, iodine; R7: alkyl; X:O; R9: OH; R10: H; R1: monophosphate
Attention is also drawn to compound XI

![Compound XI](image)

(XI)
Several of the embodiments of Compound XI includes uracil as base. A POSITA reading D3 would look at the several embodiments with R1 as H, monophosphate; R2 as H, R7 as H, R6 as CH₃, X as O and Base as Uracil. Therefore, a POSITA working on a nucleoside to be used as anti-HCV agent, on reading D3 would be taught that uracil may also be used as a base in nucleosides for treating HCV.

B. ProTide approach to activate an inactive nucleoside by phosphate prodrug formation was known

The Opponent further relied on document D4 published on 02 February 2006, titled, “Nucleoside Aryl Phosphoramidates for the Treatment of RNA-Dependent RNA Viral Infection” discloses nucleoside aryl phosphoramidates to be useful for the treatment of Hepatitis C infection. D4 discloses compounds of formula:

Where Ar: unsubstituted phenyl; R₁: hydrogen; R₂ and R₃: hydrogen; R₇: hydrogen; R₁₁: methyl; R₈: C₁-6 alkyl, substituted by C₁-4 alkoxy

Further, D4 discloses that, “the aryl phosphoramidates of the present invention act as prodrugs of the corresponding nucleoside 5’-monophosphates. Endogenous kinase enzymes convert the 5’-monophosphate into their 5’-triphosphate derivatives which are the inhibitors of the RNA-dependent RA viral polymerase. Thus, the aryl phosphoramidates may provide for efficient target cell penetration than the nucleoside itself, may be less susceptible to metabolic degradation, and may have the ability to target a specific tissue, such as the liver, resulting in a wider therapeutic index allowing for lowering the overall dose of the antiviral agent”.

Further, the examples exemplified in D4 disclose compounds that are alanine phosphates. Therefore, a POSITA working on developing a
nucleoside to act as anti-HCV agent, on reading D4 would be motivated to work on nucleosides with aryl phosphoramidates substitution.

The Opponent relied on document D5 (WO 2007/020193), published on 22 February 2007, titled, “Antiviral Phosphoramidates” which discloses nucleoside compounds useful for treatment of Hepatitis C virus. It discloses Phosphoramidate derivatives of 4'-substituted nucleoside compounds with improved physiochemical and pharmacokinetic properties. D5 identifies several prior art documents and observes that pyrimidine and purine nucleoside derivatives were known were known for anti-HIV and anti-HCV activity. D5 notes that, “Although nucleoside derivatives have proven to be effective inhibitors of HCV polymerase, their practical utility is often limited by two factors. Firstly, suboptimal physical properties and poor pharmacokinetics frequently limit the intracellular concentration of the nucleoside derivative.” Further, D5 points out that, “if the prodrug successfully penetrates an infected cell and is converted to the parent nucleoside, the biologically activity of these compounds depend upon kinase-mediated phosphorylation to generate the nucleoside triphosphate...” D5 points out that the above-identifies problems can be overcome by aryloxy Phosphoramidate derivatives (7a). It discloses that, “The Phosphoramidate moiety is masked with neutral lipophilic groups to obtain a suitable partition coefficient to optimize uptake and transport into cells. Enzyme mediated hydrolysis of the ester produces a nucleoside monophosphate 7e wherein the rate limiting initial phosphorylation is unnecessary and the second and third phosphorylation are less sensitive to structural modification of the nucleoside moiety.” This has also been represented structurally in Scheme I, as reproduced below:
D5 discloses several compounds of the formula

\[
\text{I}
\]

Of which one of the R6 substituents is

\[
\text{A}
\]

D5 discloses several embodiments of this Formula I, including the following:

-(S)-2-\{(2R,3S,4R,5R)-2Azido-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-3,4-dihydroxy-tetrahydro-furan-2-ylmethoxy|-phenoxy-phosphorylamino|3-phenyl-propionic acid isopropyl ester

-2-\{(2R,3S,4R,5R)-2Azido-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-3,4-dihydroxy-tetrahydro-furan-2-ylmethoxy|-phenoxy-phosphorylamino|2-methyl-propionic acid isopropyl ester

-(S)-2-\{(2R,3S,4R,5R)-2Azido-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-3,4-dihydroxy-tetrahydro-furan-2-ylmethoxy|-phenoxy-phosphorylamino|propionic acid isopropyl ester
That is, many of the embodiments disclose phosphoramidates with propionic acid isopropyl esters.

Hence, a POSITA working on developing a nucleoside with anti-HCV activity on reading D5 with D4, D2, D1 and D3 would be motivated to work on phosphoramidates of (2'-R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside with purine or pyrimidine as base. Further, the POSITA would be motivated to work on their propionic acid isopropyl acid.

The Opponent relied on D6 which is a publication titled “Mechanism of Activation of β-D-2'-Deoxy-2'-c-methylcytidine and Inhibition of Hepatitis C virus NS5B RNA polymerase” Antimicrobial Agents and Chemotherapy, Feb, 2007, p.503-509 authored by Eisuke Murakami et al which discloses that β-D-2'-Deoxy-2'-c-methylcytidine (PSI-6130) is a potent specific inhibitor of hepatitis C virus. Further, it reports that, “PSI-6130 monophosphate (PSI-6130-MP) was efficiently phosphorylated to the diphosphate and subsequently to triphosphate by recombinant human UMO-CMP kinase and nucleoside diphosphate kinase, respectively.”

Further, D6 notes that “A 2'-C-Me- modification of 2'-deoxycytidine, 2'-FdC, and cytidine (2'-OH) significantly decreases the kcat/Km values (60- to 100-fold). Gemicitabine, which possess two fluorines at the 2’-position is a slightly better substrate than 2’-FdC. A fluoro or hydroxyl group at the 2’-arabinosyl (2’-up) position is proposed to form a hydrogen bond with the dCK active-site residue Arg 128, and the interaction could enhance the reaction rate.” This is also shown structurally as below.
D6 in the discussion notes that “PSI-6130 is worthy of further investigation as a treatment for HCV infection.” Therefore, a POSITA working on developing nucleosides as anti-HCV agents, on reading D6 with D2, D1, D3, D4 and D5 would be motivated to explore propionic acid isopropyl ester-phosphoramidates of PSI-6130.

The Opponent relied on document D7 (Landowski et al) which is a publication titled “Targeted delivery to PEPT1-overexpressing cells: Acidic, basic, and secondary floxuridine amino acid ester prodrugs”. While D7 recognize Floxuridine as the proven anticancer agent, they note that, “prodrug strategies may be necessary to improve its physiochemical properties and selectivity and to reduce undesirable toxic effects.”. The report shows the “feasibility of achieving enhances transport and selective antiproliferative action of amino acid ester prodrugs of floxuridine in cell systems overexpressing PEPT1.”

D7 also discuss that, “Prodrug strategies are generally adopted to improve the undesirable properties of therapeutic drugs to overcome barriers, such as poor oral absorption, chemical instability, and toxicity. The design of amino acid ester prodrugs offers a high degree of flexibility, because there are a large variety of amino acids available for optimization of prodrugs.”

After different amino acid prodrugs, D7 conclude that, “A carefully selected amino acid can also make a nucleoside analogue, such as floxuridine into a carrier-mediated substrate. Peptide transporter-mediated uptake of these prodrugs could potentially increase intestinal absorption if delivered orally or be used to target specific cancer cell types expressing these transporters. Further studies with more structurally diverse amino acids and nucleoside analogues could eventually lead to the development of a structure-activity and structure-transport relationship database that could facilitate optimal prodrug design.”

Hence a POSITA working on developing a nucleoside as an anti-HCV agent, on reading D7 along with D1, D2, D3, D4 and D5, D6 would be motivated to explore amino acid prodrugs, including propionic acid isopropyl ester-phosphoramidates of nucleosides such as PSI-6130.
The Opponent relied on document D8 which is a publication titled “Certain Phosphoramidate derivatives of dideoxy uridine(ddU) are active against HIV and successfully by-pass thymidine kinase” FEBS Letters 351 (1994) 11-14, authored by Christopher McGuigan et al. The authors noted that in their effort to deliver masked phosphates inside living cells they discovered “certain triester derivatives of the inactive nucleoside analogue, dideoxy uridine (ddU) are inhibitors of HIV replication at μM levels.” Further D8 found that certain Phosphoramidate derivative retaining their activity in thymidine kinase-deficient cells, indicate that they act by intracellular release of the free nucleotide, and that they successfully by-pass the nucleoside kinase.

D8 note that dideoxythymidine, and 3’-O-methylthymidine are nucleoside analogues which are inactive against HIV, whilst their triphosphates are exceptionally potent inhibitors of HIV RT. They note that the inactivity may be attributed to poor phosphorylation by host kinases. They suggest that if the masked phosphate strategy could deliver nucleotides intracellularly, the nucleoside kinase would be by-passed. This could also overcome the structural constraints imposed by host enzymes. The authors note that, they applied this approach successfully to nucleoside analogue dideoxy uridine (ddU) which is essentially inactive but was found to have selective antiviral effect on phosphorylation. Further, D8 report that Aryloxy Phosphoramidate (3c) was found to be a potent agent being about 50-time more active than parent nucleoside analogue. The structures of the parent nucleoside and the aryloxy Phosphoramidate (3c) is reproduced below for easy reference.

Hence, a POSITA working on a nucleoside to use as anti-HCV agent on reading D8 would be taught that the problem of poor membrane
penetration could be overcome by kinase bypass using arloxy Phosphoramide nucleosides. Hence a POSITA on reading D8 along with D1, D2, D3, D4, D5, D6 and D7, would be motivated to explore amino acid prodrugs, including propionic acid isopropyl ester- phosphoramideates or arloxy phosphoramidates of nucleosides such as PSI-6130.

The Opponent also relied D9 which is a publication titled “Direct Measurement of Nucleoside Monophosphate Delivery from a Phosphoramide Pronucleotide by Stable Isotope Labeling and LC-ESI-MS/MS” Mol Pharm. 2004 Mar-Apr;1(2):102-11, authored by Jisoon Kim et al. The authors in D9 noted that amino acid phosphoramidates of nucleosides are shown to be potent antiviral and anticancer agents with the potential to act as nucleoside monophosphate prodrugs. Therefore, the authors investigated their ability to deliver 3’-azido-3’-deoxythymidine (AZT) 5’-monophosphate to cells. The authors in D9 note that, “...the problem of inefficient cellular nucleoside phosphorylation could be overcome by the use of nucleoside monophosphates (NMPs). Unfortunately, NMPs are not metabolically stable in vivo, and they are incapable of crossing cellular membranes since they carry a charge of -2 at physiological pH. To address this challenge, several clever prodrug or “pronucleotide” approaches have been devised for the intracellular delivery of NMPs. Nucleoside amino acid phosphoramide monoesters have shown promise as a potential pronucleotide strategy. In particular, we have demonstrated that 3’-azido-3’-deoxythymidine (AZT) amino acid phosphoramideates are potent, nontoxic antiviral, and/or anticancer agents.” D9 investigated the below produce decomposition pathway for AZT amino acid Phosphoramide and found that direct intracellular nucleoside Phosphoramide 5’-monophosphate can proceed via P-N bond hydrolysis (Pathway A). (RHS, Conclusions, lines 1-5).
Hence, a POSITA working on a nucleoside as an anti-HCV agent, on reading D9 with D1, D2, D3, D4, D5, D6, D7 and D8 would be motivated to explore monophosphate prodrugs of nucleosides particularly amino acid prodrugs, including propionic acid isopropyl ester-phosphoramidates of nucleosides such as PSI-6130.

C. L-alanine was a preferred amino acid in ProTide approach

The Opponent also relied on document D10 which is a publication titled “Aryl Phosphoramidate Derivatives of d4T Have Improved Anti-HIV Efficacy in Tissue Culture and May Act by the Generation of a Novel Intracellular Metabolite” J. Med. Chem. 1996, 39, 1748-1753, authored by Christopher McGuigan and Dominique Cahard et al. D10 note that, “New phosphate derivatives of the anti-HIV nucleoside analogue d4T were prepared as potential membrane-soluble prodrugs of the bioactive free nucleotide...Moreover, the derivatives appear to bypass the dependence of the nucleoside on thymidine kinase-mediated activation, retaining full activity in thymidine kinase-deficient cells. This strongly suggests the successful intracellular delivery of free nucleotides by the masked phosphate triester prodrugs... Moreover, we herein report the generation of a new metabolite, a partially hydrolyzed phosphate diester, alaninyl d4T monophosphate. We suggest that at least part of the antiviral action of the prodrugs derives from the intracellular generation of such novel diesters.
which may add considerable weight to the suggested further preclinical development of the phosphate prodrugs.” (abstract)

That is D10 reported that hydrolyzed phosphate diester, alaninyl d4T monophosphate were partly responsible for antiviral action of the prodrugs. D10 noted, “...while AZT is inherently more potent than either d4T or the d4T phosphate in thymidine kinase competent CEM cells, the phosphoramidate derivative 4a is >1300 times more active than AZT in the kinasedeficient CEM cell line.

In terms of structure-activity relationships in operation, it is apparent that relatively small changes in the amino acid region lead to significant changes in activity. Thus, of the series 4a-f, the alanine compound 4a is the most potent...

Therefore, a POSITA on reading D10 would be taught that alaninyl d4T monophosphate showed good potency and therefore would be motivated to apply this teaching to the known teaching of D1, D2, D3, D4, D5, D6, D7, D8 and D9 to explore phosphoramidates of nucleosides such as PSI-6130.

The Opponent further relied on document D11 a publication titled “Aryl Phosphoramidate Derivatives of d4T Have Improved Anti-HIV Efficacy in Tissue Culture and May Act by the Generation of a Novel Intracellular Metabolite” Proc. Natl. Acad. Sci. USA Vol. 93, pp. 7295-7299, July 1996, authored by J. Balzarini et al. D11 analyse So324 which is a 2′,3′-dideoxy-2′,3′-didehydrothymidine- 5′-monophosphate (d4T-MP) prodrug containing at the phosphate moiety a phenyl group and the methylester of alanine linked to the phosphate through a Phosphoramidate linkage. So324 is
shown to have better has anti-HIV activity in human CEM, MT4, and monocyte/macrophage cells than d4T. They note that, “After uptake of So324 by intact human lymphocytes, d4T-MP is released and subsequently converted intracellularly to d4TTP. In addition, accumulation of substantial amounts of a novel d4T derivative has been found. This d4T metabolite has been characterized as alaninyl d4T-MP. The latter metabolite accumulates at 13- to 200-fold higher levels than d4T-TP depending the experimental conditions. Alaninyl d4T-MP should be considered as an intra- and/or extracellular depot form of d4T and/or d4T-MP. These findings may explain the superior anti-retroviral activity of So324 over d4T in cell culture.”

The structure of So324 is reproduced below for reference:

![So324](image)

The authors further note that, “The unexpected property of So324 to accumulate alaninyl d4T-MP into drug exposed cells opens an exciting new area for the development of novel, structurally related nucleotide prodrugs.” Hence, a POSITA working on developing nucleosides that act as anti-HCV agents, on reading D11 with D1, D2, D3, D4, D5, D6, D7, D8 and D9 would be motivated to develop monophosphate nucleoside prodrugs containing at phosphate moiety a phenyl group and the methylester of alanine linked to the phosphate through phosphoramidate linkage as seen in So324.

The Opponent further relied on document D12 which is a publication titled “Characterization of the Activation Pathway of Phosphoramidate Triester Prodrugs of Stavudine and Zidovudine” Molecular Pharmacology, 56:693–704 (1999), authored by Didier Saboulard et al. D12 note, “The phosphoramidate triester prodrugs of anti-human HIV 2',3’-
dideoxynucleoside analogs (ddN) represent a convenient approach to bypass the first phosphorylation to ddN 5’-monophosphate (ddNMP), resulting in an improved formation of ddN 5’-triphosphate and, hence, higher antiviral efficacy...” (abstract, lines 1-5)

D12 investigated the metabolism of triester prodrugs of d4T and AZT. The authors took note that The L-alaninyl-d4TMP phosphotriester can be considered the prototype compound of the phosphoramidate prodrug concept. The authors noted that, “For both the d4TMP and AZTMP phosphoramidate derivatives, L-alanine was shown to be the preferred amino acid.”

In fact, relatively small changes of the amino acids was found to have marked effect on the eventual antiviral activity, eg. L-alanine compound 2 is 40, >3000, and 80-fold more active than the corresponding D-alanine (5), β-alanine (12), or glycine (6) prodrugs. Stability in the human serum of L-alaninyl-containing Phosphoramidate of d4TMP proved to be highly dependent on the nature of the alkyl ester group, with for instance, an ethyl providing higher stability than the methyl group. The authors
particularly noted that, “From these data, it can be concluded that the antiviral activity of the Phosphoramidate prodrug derivatives is strongly dependent on the nature of the nucleoside moiety (d4T or AZT) and the amino acid substituent.” Hence, a POSITA working on developing a nucleoside as an anti-HCV agent on reading D12 along with D1, D2, D3, D4, D5, D6, D7, D8, D9 and D11 would be motivated to develop a L-alaninyl monophosphate nucleoside prodrugs containing at phosphate moiety a phenyl group and the methylester of alanine linked to the phosphate through phosphoramidate. Further, the POSITA would also be motivated to explore the impact of change in the alkyl ester group attached to the Phosphoramidate.

The Opponent further relied on document D13 which is a publication titled “Synthesis, in Vitro Anti-Breast Cancer Activity, and Intracellular Decomposition of Amino Acid Methyl Ester and Alkyl Amide Phosphoramidate Monoesters of 3'-Azido-3'-deoxythymidine (AZT)” J. Med. Chem. 2000, 43, 2266-2274 authored by Vidhya V. Iyer et al. D13 reported the synthesis and anticancer activity of a series of AZT phosphoramidate monoesters containing amino acid methyl ester (3a-11a) and N-alkyl amide (3b-11b, 9c-9f) moieties. They observed marked stereochemical preference for the L-amino acid stereochemistry in MCF-7 cells. While AZT and the two AZT aromatic amino acid methyl ester phosphoramidates 8a and 9a were found to be more cytotoxic toward MCF-7 cells than to CEM cells, the authors opined that the selective cytotoxicity could be associated with greater intracellular levels of phosphoramidate monoester and/or phosphorylated AZT. The structure of compounds identified are reproduced below
The authors pointed out that Lack of cytotoxicity of 3a and improved activity for 4a and 5a suggest that the presence of an α-substituent is necessary for the methyl ester derivatives. Further, L-leucyl amino acid moiety was inactive as both the methyl ester 6a and methyl amide 6b. Hence a POSITA working on an anti-HCV nucleoside, on reading D13 would be taught that for better activity L-amino acid esters would be preferred in phosphoramidate nucleosides. Iyer et al report Phosphoramidate ProTide technology approach to ribonucleotide analogue 4'-azidouridine to generate new antiviral agents for inhibition of HCV. They note that ProTide approach can be used to deliver monophosphate of ribonucleotide analogues. Further, Iyer et al report that 5'-triphosphate of 4'-azidocytidine was described as a competitive inhibitor of cytidylate incorporation by HCV polymerase and a potent inhibitor of native, membrane-associated HCV replicase in vitro but first phosphorylation step to produce the 5'-monophosphate was rate-limiting in pathway to intracellular nucleotide triphosphate formation. They further noted that as unmodified agents, nucleoside monophosphates are unstable in biological media and they also show poor membrane permeation because of associated negative charges at physiological pH, which could be overcome by the ProTide approach.

The Opponent further relied on document D14 which is a publication titled “Application of the Phosphoramidate ProTide Approach to 4’-Azidouridine Confers Sub-micromolar Potency versus Hepatitis C Virus on an Inactive Nucleoside” J. Med. Chem. 2007, 50, 1840-1849 authored by Plinnio Perrone et al. D14 in their investigation of applying ProTide technology to
ribonucleoside analogue 4'-azidouridine, found that isopropyl ester (compound 15) showed high potency and represented one of the most active phosphoramidates prepared.

The phosphoramidate approach increased potency in the replicon assay when compared to the inactive parent compound, corresponding to boost anti-HCV potency of >450-fold. All phosphoramidates tested were found to be non-toxic in the replicon assay (CC50 >100μM). Therefore, a POSITA working on developing an anti-HCV nucleoside, on reading D14 along with D1, D2, D3, D4, D5, D6, D7, D8, D9, D11 and D12 would be motivated to develop a L-alaninyl isopropyl monophosphate nucleoside prodrugs containing at phosphate moiety a phenyl group and the methylester of alanine linked to the phosphate through phosphoramidate.

The Opponent further relied on document D15 which is a publication titled “Aryloxy Phosphoramidate Triesters as Pro-Tides” Mini-Reviews in Medicinal Chemistry, 2004, 4, 371-381 authored by Dominique Cahard et al. The authors tested HIV related compounds and described the development of aryloxy phosphoramidate triesters as an effective protide motif. D15 found that one of the most remarkable demonstrations of effectiveness of the aryloxy phosphoramidate approach came from in dideoxydihydro purine d4A [compound 34].

It will be seen that in compound 34, isopropyl is one of the preferred substitutions. Further, D15 at all noted that Gilead (who is the Applicant in the Present Application) has been active in commercialising Acyclic
nucleoside phosphonates had reported that aryloxy phosphoramidates (compound 34) of PMPA (tenofovir) are highly active anti-retroviral. That is, before the date of priority, the Applicant was also using the ProTide technology and has found aryloxy phosphoramidates to have high antiviral activity. Attention is also drawn to the Figure depicted in D15

A POSITA reading D15 would be taught the following:
- the O Aryl at the phosphorus atom is “essential” as the leaving group;
- the α-amino acid is “strongly preferred”. In fact, alanine was found to be the most effective amino acid
- the esterification of the amino acid moiety is “essential”;
- Primary alkyl, secondary alkyl or benzyl groups are “preferred”.

The Opponent further relied on document D16 (WO 2006/067606), a PCT publication titled “Uridine Derivatives as antiviral drugs against a flaviviridae, especially HCV”. D16 discloses uridine derivative of the compound below, with R1 being H, and R4 being O-phosphate as well its possible tautomers, its possible pharmaceutically acceptable addition salts with an acid or base, and its N-oxide forms, for a drug having activity against flaviviridae including HCV.

Further, D16 teaches several substitutions including
R1 : monohalogenated alkynyl or dihalogenated alkenyl ; R2 : a halogen;
R3 : hydroxyl; R4 : O-phosphate as well as its possible tautomer, its possible pharmaceutically acceptable additions salts with an acid or a base, and its N-oxide forms and such other prodrugs include for instance, esters, such as amino acid esters, e.g. alanine esters. Hence, a POSITA working on developing an anti-HCV nucleoside, on reading D16 along with D1, D2, D3, D4, D5, D6, D7, D8, D9, D11, D12 and D14 would be motivated to develop phosphoramidate nucleoside prodrugs with alanine esters.

The Opponent further relied on document D17 (WO 02/08241) which is a PCT publication titled “Prodrugs of Phosphonate Nucleotide Analogues and Methods for Selecting and making same” published on 31 January, 2002. D17 screened prodrugs of methoxyphosphonate nucleotide analogues with antiviral or antitumor activity which led to identification of Novel ester amidate of PMPA (tenofovir isopropyl). D17 identified as GS 7340 as a preferred embodiment and also teaches the method of making it. The structure of GS 7340 is reproduced below:

Further, the stereoisomers of GS 7340 have also been are claimed in claims 20. D17 reported that GS-7340 showed ten-fold increase in antiviral activity as opposed to tenofovir disoproxil fumarate at table 1(Example 9). It may be noted that the GS-7340 is a prodrug containing at the phosphate moiety a phenyl group and the Isopropylester of alanine linked to the phosphate through a Phosphoramidate linkage. Therefore, a POSITA working on developing an anti-HCV nucleoside on reading D17, D1, D2, D3, D4, D5, D6, D7, D8, D9, D10, D11, D12, D13, D14, D15 and D16 would be motivated to develop a (2’-R)-2’-deoxy-2’ fluoro-2’-C-methyl nucleoside prodrug containing at the phosphate moiety a phenyl group.
and the Isopropylester of alanine linked to the phosphate through a Phosphoramidate linkage.

Therefore, the compound of claim 1 is obvious. Compounds of claims 2 and 3 which are dependent of claim 1 are also thereby rendered obvious. The teachings of prior art are represented in tabular form for easy reference:

<table>
<thead>
<tr>
<th>Teaching Prior art</th>
<th>2'-deoxy-2'-fluorocytidine is a potent anti-HCV agent and its in vivo uridine derivative is inactive</th>
<th>Arylester phosphoramides may be used for kinase bypass</th>
<th>ProTide approach can be used to activate an inactive nucleoside</th>
<th>L-alanine is a preferred amino acid in ProTide approach</th>
<th>Isopropylester of alanine linked to the phosphate</th>
<th>Chirality at Phosphate in a Phosphoramidate gives two stereoisomers</th>
</tr>
</thead>
<tbody>
<tr>
<td>WO '327 (Exhibit A)</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WO 2005/03147 (Exhibit B)</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WO 01-92282 (Exhibit C)</td>
<td></td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WO 2006/012078 (Exhibit D)</td>
<td></td>
<td></td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WO 2007/020193 (Exhibit E)</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Murakami et al (Exhibit F)</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Landsweissi et al (Exhibit G)</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>McGuigan et al (Exhibit H)</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Kim et al (Exhibit I)</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>McGuigan and Cahard et al (Exhibit J)</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Balzarini et al (Exhibit K)</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saboohi et al (Exhibit L)</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iyer et al (Exhibit M)</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perrone et al (Exhibit N)</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Cahard et al (Exhibit O)</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>

(ii) Arguments of opponent 1 (O1)-
D1 covers an invention for "(2'R)-2'-deoxy-2'-fluoro-2'C-methyl nucleoside (/3-D or /3-L), or its pharmaceutically acceptable 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 (page 16, lines 3-8). Page 16 at lines 16-24 of '147 - 2'substitutions of -D or -L nucleosides of the invention claimed impart greater specificity for HCV and include a method for treating viruses viruses included HCV, or its pharmaceutically acceptable salt or prodrug. Claim 6 of '147 covers the structure of the base compound for sofosbuvir, including its monophosphate, diphosphate, triphosphate or a stabilised phosphate prodrug. "Definitions", on page 31, lines 7-22 of '147: "The term "pharmaceutically acceptable salt or prodrug" is used throughout the specification to describe any acceptable form ... Page 46, lines 16-18 of '147 state: "Any of the nucleosides described herein can be administered as a nucleotide prodrug to increase the activity, bioavailability, stability or otherwise alter the properties of the nucleoside". Pages 47-48 disclose how pharmaceutical compositions based upon the -D or -L compound or its pharmaceutically acceptable salt or prodrug can be prepared in a therapeutically effective amount for treating a flaviviridae infection, including HCV. Page 59, lines 4-23 of '147, discusses similar phosphoramidates as claimed in the impugned patent '3658. Pages 51-54 of '147, under the heading 'Stereoisomerism and Polymorphism' discusses how the nucleoside compounds covered have several chiral centres and may exist in and be isolated in optically active and racemic forms, as do most amino acids which can exist as separate enantiomers. Pages 52-53 then set out commonly known techniques in the art for obtaining optically active materials. In the specification of 147 Patent different types of prodrugs of Sofosbuvir including phosphoramidate prodrugs are mentioned. It is not difficult for a person skilled in the art to reach the phosphoramidate prodrug claimed in the impugned application. The '147 specification also discloses a prior art Zon et al., Progress in Med. Chem. 19, 1205 (1982) (page 102). This prior art mentions "nucleoside prodrug" amongst a host of other prodrugs that can be used for Sofosbuvir. The alleged inventors of the impugned application continually refer to an absence of the actual, specific nucleoside compound in the prior art Thus, the alleged inventors do not attempt to answer the question of obviousness, but merely reiterate repeatedly that the
compound was novel. The mere absence of a compound from the prior art does not make it un-obvious.

D8 demonstrates the success of using the Pro Tide prodrug strategy to activate the intracellular presence of active triphosphates of an inactive HIV compound ddU. On page 279, column 2 of Exhibit 7, the authors cite the use of the aryloxy phosphoramidate prodrugs (the prodrug as used in 3658). The article discloses that phosphorylation of the drug (to create phosphoramidates of nucleosides) with a range of phosphates may act as a blocking agent and that a labile phosphate group is a prerequisite for creating a prodrug with exactly the same type of utility as claimed in 3658. (Page 279 column 1). The Applicant therefore specifically refuses to address the issue of obviousness and instead relies solely upon novelty as their reliance on patentability in this regard.

D10 (McGuigan (1996)) speaks about the common knowledge in the field of how to activate nucleosides by intracellular phosphorylation for drug activation and how the Pro Tide prodrug approach was known to be advantageous by providing the drug in a form that is already monophosphorylated. Page 296 column 1 para 4 mentions that the aryl region of phosphoramidate regulates activity of the drug. Column 2 last paragraph mentions mechanism of action is that the phosphorylation of the prodrug to produce the active drug in vivo. The article discloses that phosphoramidate prodrugs overcome the same basic problem to be solved in the 3658 application. It also discloses structurally the same phosphoramidate design as 3658. Thus, the impugned application is only applying prior knowledge to solve a problem to a different example of the same structural class of compounds (nucleosides) for which it was designed and successfully applied in the prior art. The article mentions that also the phosphoramidate derivative of d4T IS more advantageous than d4T itself. (Page 298. Para 2). This shows that the phosphoramidate group has been known to be used as a prodrug for nucleoside applications since 1998. There is no new teaching in the impugned application.

D17 (WO2002/08241) discloses the nearly identical prodrug and diastereomers
claimed by the applicant in '3658. Pages 30-33 of the patent provides for separation of the diastereoisomers. Page 357 line 10, mentions that the common general knowledge is that "In general, the phosphorus atom of the parent drug is the preferred site for prodrug modification, .... ". Therefore, the very basis of the impugned application considered is as common general knowledge in chemistry. Line 25 on Page 357 further mentions that the method of conversion by which the prodrug is converted to an active drug in vivo is not important, but the method by which the drug is stored in an inactive form is important. This document is not being relied on in support of our claims of lack of novelty but as an authority for the method of functioning of a prodrug in Chemistry. Once again, the Applicant refuses to acknowledge or address the issue of obviousness and instead relies upon a novelty argument as the sole reason for patentability.

D15 (Cahard et al.) under heading phosphates of AZT = mentions that the phosphoramidate pronucleotide has been researched since 1992. The figure on the right hand top corner of page 284 predicts similar structure the prodrug moiety (marked) page 285 mentions that the aryloxy phosphoramidate improves the potential of active drug which (otherwise) eventually loses its activity due to a shorter half-life. Importantly, this article further mentions that the Gilead group has been active in the commercialization of ANPs and have reported that aryloxy phosphoramidate of PMPA (tenovir) are highly active anti-retrovirals. (Page 286). Since this article is from 2004, it is clear that the subject matter of the impugned application was already known to persons in the pharmaceutical industry (drug manufacturers).

This article has noted a significant preference for L-alanine over D-alanine (5-60 fold), whereas Gilead observed a preference for one phosphonate diastereoisomer over the other. (Page 287 first para). As stated in our additional grounds of opposition, this has not been disclosed in the impugned application.

This article also clearly mentions that Gilead was using or working with phosphoramidate prodrugs. Clearly, this shows that Gilead’s research with respect to phosphoramidate prodrugs was in the public domain even in
2004, as this article refers to it time and again (Page 289 first paragraph last sentence) In its conclusion, the article provides a solution of activating the inactive nucleoside by phosphate prodrug formation. It further discusses pro-tide synthesis on a range of phosphoramidate nucleoside analogues. (Page 291, first column) This means that the solution provided by the impugned application was known and used before filing of the patent application.

D16 covers uridine nucleoside derivatives as antiviral drugs against flaviviridae, especially HCV. D16 discloses the acid esters e.g. alanine esters as potential prodrugs. It was well-known to a POSA that Flaviviridae virus and assays against such virus were used as a surrogate for HCV anti viral assay in drug discovery. The objections of the alleged inventors of the impugned application are being disingenuous as they well know this was the case.

D14 claims an aryloxy phosphoramidate ProTide Approach for a ribonucleoside 4’ azidouridine derivative (a uridine based nucleoside) was able to deliver the monophosphates to HCV replicon cells and unleash the antiviral potential of the triphosphates in a manner which lm proves antiviral activity over the parent compound. Moreover, the ProTide prodrugs tested by the authors included the alanine isopropyl ester as the phosphoramidate (Table 1, compound 15 on page 4), the exact same prodrug as claimed by the Applicant in '3658. Perrone makes no such sweeping claims and indeed Perrone makes it clear that ProTide nucleoside analogs are an excellent choice for intracellular activation of nucleoside drugs. Perrone also makes it clear that the prior art and the cited reference have defined conditions under which the ProTide approach is expected to work. Perrone also outlines a limited series of phosphoramidate structural variants that are observed to provide excellent intracellular activation of nucleosides. A person skilled in the art will easily be able to predict the prodrug and attached prodrug strategy underlying an active drug if the chemical structure of the said active drug is known. A person having common knowledge of chemistry will know which chemical entity IS to be used for keeping a drug in an inactive form to preserve its shelf life and to
enhance biological after administration. Perrone et al provides that 5’ monophosphate IS considered to be the prodrug (i.e., phosphoramidate) is a lipophilic prodrug of the corresponding 5’ monophosphate species. (Page 266 column 2, 3rd paragraph last line) Further, Perrone et al provides the possibility to apply a Pro Tide approach to the inactive 4’-azidouridine (1) in order to bypass the first phosphorylation step and thereby generate novel antiviral agents (2) with potent activity against HCV (Page 267 first paragraph). Perrone et al mentions the application of the phosphoramidate approach as a successful tool in overcoming the phosphorylation block of 1 and oonverting an inactive nucleoside analogue to a potent inhibitor of HCV replication. (Page 268 last paragraph) Isopropyl esters show high potency and represent one of the most active phosphoramidates prepared. (Page 268). The anti-HCV and Cytotoxicity data in Table 1 pertains to phosphoramidates, all of which demonstrate significant anti-HCV activity. The data in Table 1 constitute measurable yardsticks for a person skilled in the art to determine which compound to use. Using Perrone’s conclusions, a small set of phosphoramidate protides can be isolated and then a person skilled in the art can select which one s/he wants to investigate.

Conclusion: The ProTide method when applied, made no difference to the already significant anti-HCV activity of the 4’-azidocytidine compound that Perrone selected. Although Perrone observed that the 1-naphthylphosphorami date provided the best anti-HCV activity in a cellular assay, given that the naphthol group released intracellularly as a human metabolite is carcinogenic, a person skilled in the art intending to select an optimized drug for administration to humans would not opt for Perrone’s choice and would be able to predict the chemical structure of the ideal prodrug based on Perrone’s data without any undue experimentation. Once again rather than addressing the question of obviousness, the Applicant has elected to state only that the compound is novel, without answering the question of obviousness.

(iv) Arguments of the opponents 5 (O5) & 7 (O7)

It is submitted that the claims of the impugned application lack inventive step in view of various prior arts and the common general knowledge that
existed as of the priority date of March 30, 2007. It is admitted by the Applicant that nucleotides are known and the need for manufacture of such nucleotides is also spelt out in the prior art. The problem solved by the inventors is merely to provide further nucleotides. There is no technical advance in providing such nucleotides as it was following the steps already known in the prior art. As stated earlier, it was known in the art that full potential of nucleosides that are either inactive or that do not exhibit sufficient activity can be realized by using the ProTide approach i.e. by coupling the nucleoside with a phosphate moiety. Some of the key developments are as under:

(A) The ProTide approach was first developed and proposed by McGuigan in 1992-93. Such Protides are also repeated in the paper published in 1994 (FEBS Letters, 1994) (D8)

(i) In this paper, McGuigan reports the success of the ProTide strategy using dideoxy-uridine (ddu) and AZT, consistent with his previous approach, McGuigan has proposed aryloxyphosphoramidates.

(ii) The author also recognizes the need for masking the highly charged phosphate groups in order to facilitate intracellular release of nucleoside. Though the author prepared many phosphates, bis(2, 2, 2-trichloroethyl) phosphate groups were found successful in the kinase by activation of inactive nucleosides.

(iii) The author further found that certain phosphoramidate derivatives of AZT are patent and selective inhibitors of HIV. As against ethylmethoxyalaninylphosphochloridate, the author found aryloxyphosphoramidates are useful as masking agents for AZT, the phosphate nucleoside.

(B) Jones et al, 1995 (D18)

(i) By '95, it became established that for purine/pyramide based nucleotides that are inactive within a cell, preparation of nucleosides is the best approach. The same architecture of the phosphoramidate as proposed by earlier workers was maintained i.e. an amino ester phosphoramidates.

(ii) After conducting various studies, the author concludes that aryl esters and activated alkyl esters are capable of functioning s nucleoside prodrugs.
(C) McGuigan 96 (D10)
(i) This another paper reporting successful use of methyl esters as phosphoramidate architecture to activate nucleosides.
(ii) Here also, an aminyl group formed part of the ProTide architecture. Alkyl ester (methyl ester) prepared was found to undergo hydrolysis and cleave off the phosphate nucleoside (Figure 1).

(D) Balzarini, 1996 (D11)
(i) In this report, the authors find that 2’-3’-dideoxynucleoside (ddn) are potential inhibitors of HIV replication. However, their activity is limited by intracellular phosphorylation. To overcome this problem, the authors prepared phosphoramidates prodrug of d4T (stavudine, or type of ddn) called S0-324 which is a prodrug and is made of phenyl group with a methylester of alanine linked to the phosphate through a phosphoramidate linkage.
(ii) The approach is consistent with earlier approaches using methyl ester in the phosphoramidate – architecture.

(E) Didier et al, 1999 (D12)
(i) The authors of this paper had also worked on HIV reverse transcriptase inhibitors and followed the ProTide strategy to activate such nucleosides, especially ddn, AZT etc. Didier’s work proved that the preferred amino acid is L-alanine and amongst the esters, ethyl and methyl were most promising.

(F) Cahard et al, 2004 (D15)
In this review article, the authors, attempted to find out whether there was any general phosphoramidate motif that could be applied to all nucleosides. While no such motif was found, some general principles were established. A dependence of length of amino acid on anti-viral activity was found and alanine was found most efficacious. On the other hand, the alkyl side chain could be between 1-6 carbon atoms. Final reference was given to phenolmethoxyalaninyl group.

(G) PlinionPerrone et al. – 2007 (D14)
(i) In this paper, the author reports application of the phosphoramidateProTide technology to ribonucleoside analogues i.e. 4’azidouridine, which are antiviral agents for inhibition of Hepatitis C.
(ii) The authors reiterate that aryloxy-phosphoramidate are efficient, lipophilic prodrugs in which the masking groups are represented by amino ester and aryl moiety. In this study, the said approach was applied to 4AZT. The authors have previously found that L-alanine had shown best anti HIV activity for parent d4T parent molecule. Now, the authors compared the stereochemistry at amino position by preparing D-alanine benzyl ester phosphoramidates. The authors also prepared other esters including methyl ester, ethyl, butyl, 2butyl, isopropyl, terbutyl and benzyl ester.

(iii) As a result of the study, the authors found that isopropyl ester showed the highest potency and represented one of the most active phosphoramidates prepared. Thus, the author had prepared L-alanine isopropyl ester and found that it exhibited best anti HIV and cytotoxic activity for activation of nucleoside analogues. The results are reported in Table 1 where the EC 50 value of isopropyl ester of L-alanine is reported as 0.77.

(iv) The author also studies the correlation between amino acid and ester function and found that the HCV inhibition effect with isopropyl ester provides the best. The author concludes recommending this ProTide approach to successfully bypass the rate limiting phosphorylation of ribonucleoside analogue.

(v) Thus, by 2007, the following became clear and established:

(a) The general architecture of a phosphoramidate (part) of a prodrug includes an ester linked to amino acid and phosphate group;

(b) Perrone et al (2007) have found that alanine is the most preferred amino acid and isopropyl ester is the most preferred ester;

(c) Such combination was found to undergo hydrolysis and liberate the nucleoside in phosphate form (intra-cellularly).

(H) Prodrugs already prepared – Choice of Nucleoside

(i) Prior to March 2007, many workers in the art had experimented with various nucleosides and tried to activate the same using the phosphoramidate approach. The enzymes responsible for phosphorylating the nucleosides to their triphosphate form were known; the mechanism of action was also known.
(ii) Prior to 2005, various nucleosides were known, such as AZT, ddu etc which exhibited anti-viral activity. Some key developments are as under:
(a) WO 99/43691 (D19) discloses various nucleosides in which chlorine is in down position;
(b) WO 2005/003147 (D1) discloses family of fluoro-nucleoside analogues et 2’ position which have fluorine in down position and methyl in up position. Such alignment is said to find favour with intracellular enzyme action. Clark the inventor reports that the 2’substitutions on the nucleoside impacts greater specificity for hepatitis C virus.
(c) The disclosure includes formation of prodrugs using the nucleosides disclosed. The claims include prodrug.
(d) Clark et al, 2005 (D21): The said patent WO 2005/003147(D1) is to be read with Clark’s paper wherein 2’deoxy-cytidine as well as 2’deoxy uridine compounds were prepared. Compound 9 did not exhibit activity quite like other nucleosides reported by McGuigan (1994)(D8).
(e) Murakami et al.(D6): In this paper, the authors prepared various nucleosides.

(iii) Cytidine and uridine were found to act as more or less similar substrates as far as the enzyme UCK-1 was concerned. In this case, uridine, cytidine and other substrates acted as phosphate acceptors. Further, the findings were consistent with the earlier studies that UCK-1 which is the enzyme which acts on the nucleoside has a high specificity for 2 hydroxyl group. Therefore, presence of 2 hydroxyl group at 2’ position is necessary for the nucleoside to be available as an effective substrate in the intracellular kinase phosphorylation mechanism.
(iv) The authors conducted Structure Activity Relationship (SAR) for 2-modified nucleosides and found that addition of fluoro at the 2’ position caused decrease in kinetic parameters. In conclusion, the author proposes that nucleosides with methyl up fluoro down position such as in PSI-6130 which would find favour with the catalyzing enzyme and increase the reaction rate. At the 3’ position, studies of Murakami et al. showed preference for OH group, which is consistent with the finding of other authors previously.
(I) WO 2005/003147 (D1):

(i) This is a patent application filed by Clark et al. disclosing various modified fluorinated nucleoside analogues. The nucleoside analogues proposed in this application exhibit greater specificity for Hepatitis C virus on account of substitutions at 2’ position. In particular, the nucleosides have methyl up and fluorine down at 2’ position.

(ii) The inventors have found that the (2’R)-2’-deoxy-2’-fluoro-2’-C-methyl Beta-D- nucleoside have EC50 (effective concentration to achieve 50% inhibition) when tested in an appropriate cell-based assay, of less than 15 micromolar, and more particularly, less than 10 or 5 micromolar.

(iii) The application also proposes (2’R)-2’-deoxy-2’-fluoro-2’-C-methyl Beta-D- nucleoside including its pharmaceutically acceptable salt or a prodrug thereof.

(iv) Wherein in the base, R7 includes a stabilized phosphate prodrug having substituted alkyl or alkyl peptide derivatives including an L-D-amino acid or such living group which when administered in vivo is capable of providing a compound wherein R1 or R7 are independently phosphate. The invention contemplates that any phosphate nucleosides may include mono or di-ester derivative of 5’monophosphates.

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

74
(vi) The invention specifically states and proposes prodrugs and derivatives that may be administered in order to improve the antiviral activity of the compound. It is proposed that the prodrug may be modified and attached at the 5' position. The activity can be assessed by preparing prodrug, using known method and testing antiviral activity. It is also envisaged that phosphoramidates may be prepared using various substituents such as phenyl, methyl, trifluoromethyl, ethyl, propyl and isopropyl. The Application proposes that the prodrugs include moieties cleavable at 3’ or 5’ position the masking agent includes L-amino acid with an alkyl ester.

Thus, the prior art provides the following teachings prior to the priority date of March 2007:

- a) Native nucleosides are per se inactive and not suitable for direct administration to patient; hence, to overcome the limitation of nucleosides, ProTide approach was developed;

- b) Proposals for possible structures of various ProTides was proposed and experimented on various nucleosides such as AZT, D4T, ddU etc. and found to be successful; experimental prodrugs using various nucleosides were also prepared in the art and found to exhibit excellent antiviral activity;

- c) In particular, prodrug moiety comprising isopropyl ester with L-alanine amino acid was found to be most efficacious when combined with nucleosides to activate the concerned nucleoside (Plinio Perrone et al.);

- d) The Nucleoside which is to be activated may be selected from any nucleoside including those taught by D1. In fact, D1 itself recommends that prodrugs may be found in order to activate the nucleosides disclosed therein. The application clearly states that conventionally known prodrug moieties may be used, including alkyl ester moieties. Perrone et al. suggests the use of isopropyl alaninyl moiety.

- e) The process of formation of activated nucleoside or ProTide is also known and documented i.e. condensation of nucleoside with selected phosphate ester.

- f) The site at which the condensation is to occur, is also known and disclosed by D1 i.e. 5’ position.
g) There is sufficient motivation to prepare such prodrugs as prodrugs have been commonly prepared in case of all nucleosides that are inactive or poorly phosphorylated within a cell (e.g. Page 564);

Thus, during the period prior to March, 2007, a person skilled in the art was well aware that the manner of improving bioavailability of a nucleoside is to create a prodrug. The protecting groups or masking groups used in the prodrug were also well researched and the best protecting groups were suggested/reported. Thus, sufficient guidance was available in the art for preparing the prodrugs as claimed in the present application.

It is pertinent to note that around the period prior to March 2007, Sofosbuvir as a compound was already disclosed by WO’147 (D1). The said patent application also disclosed the manner in which prodrugs may be made. In fact, WO’147 itself recommends the preparation of prodrugs in order to active the nucleotides disclosed by the application. in order to prepare such nucleotides, there were narrow, limited and finite number of choices –isopropyl ester as protecting group with L-alanine amino acid, which was already demonstrated to be efficacious in activating nucleosides such as D4T.

It is notable that the Applicant as well as the expert, Dr. Stainslaw do not address the issue of obviousness. Both treat all references individually and say that the compound claimed is not disclosed.

However, the key question as to whether the compound would be obvious in view of collective reading of the prior art – this is not addressed at all despite being given time and opportunity.

An important aspect is that no toxicity was observed by a person skilled in the art either in the nucleosides proposed by Clark or by Perone et al.. The expert of the Applicant (Dr. Stainslaw) does not contend that there is any bar in the combination of Perone’s ProTide motif with the Clark nucleosides. In fact, the expert, Dr. Stainslaw does not deal with the issue of obviousness at all. The expert only deals with the issue of novelty. The expert also does not state that there is any in compatibility in making such a combination. It is a well known fact that by March 2007, there were many workers preparing ProTides and substantial encouragement is gained from WO’147
which specifically urges the reader to use the nucleosides disclosed by converting them into nucleotides by using the ProTide approach.

In view of the above, the compounds claimed in the impugned application are obvious and are liable to be rejected.

(iv) Arguments of Opponent 9 (O9)-

O9 states 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).

a). It is submitted that in general all antiviral compounds are used for a treatment of HIV infections, HCV infections. Prima facie it is submitted that the said compound for treatment of HIV and/or HCV infections are nothing but a mere extension of other HIV and HCV compounds already known and established in prior art.

D3 (WO 2001/92282) discloses a basic chemical structure encompassing several thousand compounds for treating viral infections caused by flavivirus and pestivirus. The basic structure of D3 is also drawn to a sugar attached to a nitrogenous base. Further D3 discloses various substituents which encompasses in its structure several possible nucleotides. From the substituents it is clear that it envisages and encompasses compounds similar the compounds of the present application. The compounds of D3 comprises a halo and an alkyl substitution in the sugar and the said compounds are presented as phosphate prodrugs. The phosphate prodrugs by definition include within its scope phosphoramidate compounds. Further these prodrugs also comprises of base such a uracil, thymidine etc., which may be found either as their substituted/unsubstituted form. It is submitted that the compound of the present application may be arrived by substitution of various substituent of D3. Various examples of D3 may be examined and found to fall within the scope of the present application and vice versa.

Comparison of structure of present application and D3 (WO 2001/92282)
b). In the alternate and without prejudice to the above, D22 (WO 2001/90121) discloses compounds for treating viral infections caused by hepatitis C virus. It is submitted that the compounds of present application are known and encompassed within the basic chemical structure of D22. The basic structure is drawn to a sugar attached to a nitrogenous base. Further it discloses various substituents which encompasses in its markush several possible nucleotides. The compounds of D22 comprises a halo and an alkyl substitution in the sugar and the said compounds are presented as phosphate prodrugs such as phosphoramidates. Further these prodrugs also comprises of base such as uracil, thymidine, etc., which may be found either in substituted/unsubstituted form. It is submitted that the compound of the present application may be arrived by substitution of various substituent of D22. Various examples of D22 may be examined and found to fall within the scope of the present application and vice versa. The compound claims and isomers of the present application fall within the scope of D22. D22 disclosed a method and composition for treating a host infected with hepatitis C virus comprising administering an effective hepatitis C treatment amount of a described 1', 2' or 3'-modified nucleoside or a pharmaceutically acceptable salt or prodrug thereof, is provided (Ref: Abstract). D22 discloses compound of formula (XI) or a pharmaceutically acceptable thereof. The chemical compound having formula XI (Ref: Claim 8)
Base is a purine or pyrimidine base as defined herein (Disclosed the term pyrimidine base includes, but is not limited to uracil); R₁ is phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); X is O; R₂ is H; R₆ is alkyl (including lower alkyl); R₇ is chlorine, bromine, iodine (absence of fluorine); (Ref: Claim 08)

D22 discloses a pharmaceutical composition for the treatment (or) prophylaxis of a Hepatitis C virus in a host, comprising an effective amount of a compound of formula XI. (Ref: Claim 34). It discloses a method for the treatment (or) prophylaxis of a Hepatitis C virus infection in a host, comprising administering an anti-virally effective amount of a compound of formula XI. (Ref: Claim 86)

D22 discloses a use of a compound of formulas XI or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the Hepatitis C virus. (Ref: Claim 137) Therefore, a person ordinary skilled in the art working on nucleoside to be used as anti HCV agent, on D22 taught that uracil may also be used as a base in nucleosides for treating HCV.

Comparison of structure of present application and WO 2001/90121
Building blocks to arrive at the molecules of present application is known, compounds similar in structure to the compounds as disclosed in the present application are known in the prior art, compounds similar to that of present application are known to exert antiviral activity and phosphate prodrugs for modification of physicochemical parameters are known. The stereoisomers fall within the scope of the compound.

c). D23 (Sofia et al., "β-D2′-Deoxy-2′-C-methyluridine Phosphoramidates: Potent and Selective Inhibitors of HCV RNA Replication", Poster #P-259, presented at the 14th International Symposium on Hepatitis C Virus and Related Viruses, Glasgow, Scotland, UK, Sep. 9-13, 2007 was published on September 9-13, 2007) before the effective filing date of IN ‘658. This Sofia can be considered as a valid prior art considering the Applicant has wrongly claimed the priority date of March 30, 2007 and the effective date of priority should be October 24, 2007. Sofia was filed by Phamasset.

Sofia was published on September 9-13, 2007. Sofia has earliest published over IN ‘658. i.e. October 24, 2007 (provisional application of US 60/982,309). While the IN ‘658 patent application claims priority to the US 60/309,315 provisional application filed on March 30, 2007, that application did not include a description of the specific compounds claimed by the IN ‘658. While it discusses broad generically of compound, it does not discuss the specific compounds and stereochemistry around the phosphorous atom claimed in the IN ‘658 patent application. Thus, the claims of the IN ‘658 patent only entitled to the October 24, 2007, priority date. Not May 30, 2007, priority date. As such, the September 2007 publication of Sofia makes it prior art. Sofia and present opposed patent application IN ‘658 of inventors same i.e. Sofia, Michael, J. and Jinfa, du. The Opponent would further like to rely on the Opposition proceeding against the corresponding patent number EP2203462 granted to the Applicant in European Union. The Opponent submits that while granting the Auxiliary request 1 in the opposition proceeding the said patent, The opposition division of the European patent office (order dated 31.10.2016) noted that the auxiliary request 1 was not entitled to priority form US ‘315.
Therefore, claim 1 of the present application cannot claim priority from US ‘315. Sofia taught a prodrug of β-D-2'-deoxy-2'-fluoro-2'-C-methylcytidine (PSI-6130) for the treatment of chronic hepatitis C. In particular, Sofia taught that the triphosphate of PSI6130 was a potent inhibitor of the HCV NS5B polymerase. Sofia also taught that PSI-6130 was converted to its uridine metabolite (PSI-6206) via cytidine deaminase and that, “phosphoramidates of PSI-6206 as much as 100X more potent than the cytidine analog PSI-6130.” The structure of PSI-6206 phosphoramidate taught by Sofia is presented below.

Sofia discloses compound PSI-6206 which is 2'-deoxy-2'-fluoro-2'-C-methyluridine and compound PSI-6130 which is its corresponding 2'-methylcytidine. PSI-6206 and PSI6130 are reproduced below:
Sofia further discloses that PSI-6130 is converted into PSI-6206 and that PSI-6130 is inactive in vitro, but its triphosphate counterpart is a potent inhibitor of the HCV NS5B polymerase. It also states that for investigation of the potential of PSI-6206 as an inhibitor of the HCV replication, the bypass of the first phosphorylation step is required. It further reports that in order to investigate the potential for utilizing PSI-6206 as an inhibitor of HCV replication required the first phosphorylation step to be bypassed.

Sofia disclosed radical R2 is a variable defining the amino acid residue (see title of table 1). It can be appreciated that the radical R2 of the amino acid side chain is projecting away from the viewer as is the case in compounds of claims 1-3 of the Present Application. Radical R3 is the amino acid ester radical and R1 is the phosphate ester (see title of table 3). No exact meanings/substitutions of radicals R1 to R3 are disclosed in the poster and each compound is identified by a code. Further, the EC90 values for the compounds disclosed in tables 1-3 are lower than the parent compound PSI-6206 thus confirming that they had better anti-HCV activity. Sofia teaches that 5’-phosphoramidate derivatives of PSI-6206 are potent inhibitors of HCV, that selected phosphoramidates of PSI-6206 are as much as 100x more potent than cytidine analogue PSI-6130, that β-D-2’-Deoxy-2’-fluoro-2’-C-methyluridine phosphoramidates have potential as therapeutic agents for treatment of HCV infection and that several PSI-6206 phosphoramidates have demonstrated stability profiles that are attractive for further development (see conclusions). It is submitted that starting from the teachings disclosed in Sofia, an alternative technical problem could be formulated, which is, providing an active form of PSI-6206 which is useful in the treatment of HCV. The structural variation seen in tables 3 and 5 (Sofia)
would have motivated a skilled person to carefully select the amino acid part, which is known to have a potential negative impact on cytotoxicity. The data in the Sofia et al therefore would lead a person skilled in the art to work out the groups at R1, R2, R3 with a reasonable expectation of success. Disclosed methods & results; scheme 1: preparation of phosphoramidates is depicted in a markush formula in the third box left hand column of the poster as follows:

![Scheme 1: Preparation of Phosphoramidates](image)

Anticipation of Claim 1 These same correlations presented application challenged claims by virtue of the identical nature of the prior art disclosures shown below:

<table>
<thead>
<tr>
<th>IN ‘658 of claim 1</th>
<th>Sofia</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="IN ‘658 of claim 1" /></td>
<td><img src="image" alt="Sofia" /></td>
</tr>
</tbody>
</table>

Opposed patent application admission of the use of the claimed compound (Sofosbuvir) is consistent with a Sofia published by Pharmasset.

Sofia is the closest prior art as it aims at the same purpose and has structurally the most features in common with the claim 1-3. More precisely, Sofia teaches that selected phosphoramidate are potent HCV inhibitors.
d. D24 (Ma et al., Journal of Biological Chemistry, Vol. 282, No. 41, pp. 29812–29820). Ma was published on October 12, 2007 before the effective filing date of IN ‘658. Ma published on October 12, 2007. This document can be considered as a valid prior art considering the Applicant has wrongly claimed the priority date of March 30, 2007 and the effective date of priority should be October 24, 2007.

Ma has disclosed in, β-D-2’-deoxy-2’-fluoro-2’-C-methylcytidine (PSI-6130) is a potent inhibitor of hepatitis C virus (HCV) replication in the subgenomic HCV replicon system, and its corresponding 5’-triphosphate is a potent inhibitor of the HCV RNA polymerase in vitro. In addition the deaminated derivative of PSI-6130, β-D-2’-deoxy-2’-fluoro-2’-Cmethyluridine (RO2433, PSI-6026) and its corresponding phosphorylated metabolites were identified in human hepatocytes after incubation with PSI-6130. The formation of the 5’-triphosphate (TP) of PSI-6130 (PSI-6130-TP) and RO2433 (RO2433-TP).

The structure of PSI-6130 is shown below fig. 1

![Fig. 1](image)

The structure of RO2433 is shown below fig. 2

![Fig. 2](image)

The structure of RO2433-TP is shown below fig. 3

![Fig. 3](image)
Ma has disclosed in 2′-Deoxy-2′-fluoro-2′-C-methylcytidine (PSI-6130) with human hepatocytes which results into formation of the phosphate of its uridine analogue, RO2433-TP.

Ma disclosed determined whether the PSI-6130-derived uridine analog RO2433 could inhibit HCV replication targeting NS5B polymerase. Huh7 cells containing a subgenomic genotype 1b Con1 strain HCV replicon were incubated with RO2433 or PSI-6130 for 72 h, and dose-dependent inhibition of luciferase reporter activity was determined. RO2433 did not inhibit the HCV replication in the HCV subgenomic replicon system at concentrations up to 100 μM, whereas PSI-6130 inhibited HCV replication with a mean IC50 of 0.6 μM under the same assay conditions. The lack of potency in the replicon could be related to inefficient compound phosphorylation. To address whether the triphosphate of RO2433 directly inhibits the HCV RNA polymerase, the RNA synthesis activity of the native membrane-associated HCV replication complexes isolated from the same replicon cells was tested in the presence of RO2433-TP. RO2433-TP inhibited the RNA synthesis activity of HCV replicase with a mean IC50 of 1.19 μM, whereas PSI6130-TP inhibited HCV replicase with a mean IC50 of 0.34 μM. RO2433-TP also inhibited the RNA synthesis activity of the recombinant HCV Con1 NS5B on a heteropolymericRNA template derived from the 3-end of the negative strand of the HCV genome with an IC50 of 0.52 μM and Ki of 0.141μM, as compared with an IC50 of 0.13 μM and Ki of 0.023 μM for PSI- 6130-TP under the same assay conditions. These results established that both RO2433-TP and PSI-6130-TP are intrinsically potent inhibitors of RNA synthesis by HCV polymerase.” (Page 29815, RHS column, para 1, lines 4-31). Ma also determined the half-life of PSI-6130 TP and RO 2433-TP. Here half-life is defined as the time needed for the triphosphates to be reduced to 50% that of the highest level of triphosphates after extra cellular parent compound removal (Page 29818, RHS column, table 4). The table is reproduced for reference below
Therefore, Ma concluded that “The longer intracellular half-life of RO2433-TP may have pharmacologic relevance for maintaining more constant concentrations of the antiviral triphosphate over the dosing period in clinical studies” (Page 29819, RHS column, para 3, lines 27-31). Ma further notes that “Despite the intrinsic potency of RO2433-TP against HCV polymerase, RO2433 was not active in the HCV replicon system at concentrations up to 100 μM. RO2433 was either not phosphorylated in the replicon cells or could not penetrate the cell membrane. However, RO2433, when formed intracellularly from radiolabeled PSI-6130, dissociated rapidly across the cell membrane with a half-life faster than 30 min. Therefore, RO2433 is most likely not efficiently phosphorylated to form RO2433-MP. Similarly, the uridine analog of the HCV replication inhibitor R1479 (4-azidocytidine) was inactive in the replicon system. However, when delivered as a monophosphate prodrug, 4-azidouridine could be converted into a potent inhibitor of HCV replication, demonstrating that a block of monophosphate formation resulted in lack of antiviral activity of 4-azidouridine. Assuming a likely block of RO2433 phosphorylation to its monophosphate, RO2433-MP in human hepatocytes was most likely formed through the deamination of PSI-6130-MP by the cellular dCMP deaminase and subsequently further phosphorylated to RO2433-DP and -TP by uridine/ cytidine monophosphate kinase and possibly nucleoside. Despite the intrinsic potency of RO2433-TP against HCV polymerase, RO2433 was not active in the HCV replicon system at concentrations up to 100 μM. RO2433 was either not phosphorylated in

### TABLE 4

<table>
<thead>
<tr>
<th></th>
<th>PSI-6130-TP</th>
<th>RO2433-TP</th>
</tr>
</thead>
<tbody>
<tr>
<td>t_{1/2} h</td>
<td>4.7 ± 0.6</td>
<td>38 ± 16</td>
</tr>
</tbody>
</table>

The half-life (t_{1/2}) values were calculated by nonlinear fitting of intracellular triphosphate concentrations to a single phase exponential decay equation. t_{1/2} was defined as the time needed for the triphosphates to be reduced to 50% of the highest level of the triphosphates after extracellular parent compound removal. Data shown are the mean ± S.D. of values of four independent experiments using hepatocytes from four donors.
the replicon cells or could not penetrate the cell membrane. However, RO2433, when formed intracellularly from radiolabeled PSI-6130, dissociated rapidly across the cell membrane with a half-life faster than 30 min. Therefore, RO2433 is most likely not efficiently phosphorylated to form RO2433-MP. Similarly, the uridine analog of the HCV replication inhibitor R1479 (4-azidocytidine) was inactive in the replicon system. However, when delivered as a monophosphate prodrug, 4-azidouridine could be converted into a potent inhibitor of HCV replication, demonstrating that a block of monophosphate formation resulted in lack of antiviral activity of 4-azidouridine. Assuming a likely block of RO2433 phosphorylation to its monophosphate, RO2433-MP in human hepatocytes was most likely formed through the deamination of PSI-6130-MP by the cellular dCMP deaminase and subsequently further phosphorylated to RO2433-DP and -TP by uridine/cytidine monophosphate kinase and possibly nucleoside diphosphate kinase. The proposed metabolic pathway for PSI-6130 is illustrated in Fig. 7. Using a primer-directed nucleotide incorporation assay mediated by HCV NS5B, we demonstrated that the incorporation of both PSI-6130-MP and RO2433-MP resulted in the complete blockage of the next nucleotide incorporation similar to that of the obligatory chain terminator 3-dCMP and 3-dUMP (Fig. 3, B and C). Therefore, the 2-C- methyl-2-Fluoro motif resulted in functional chain terminators on the respective uridine and cytidine analogs. It has been proposed that the chain termination activity of 2-Cmethyl nucleotide analogs is related to a steric clash of the 2-methyl group with the ribose of the next incoming nucleotide substrate based on modelling of the NS5B initiation complex from bacteriophage 6 RNA-dependent RNA polymerase and NS5B crystal structures. Similar steric hindrance could occur with PSI- 6130-TP and RO2433- TP after incorporation due to the presence of the 2-C-methyl group” (Page 29819 LHS column, para 3, lines 39-59 and RHS column, para 1 and 2, lines 1-18). The proposed metabolic pathway of PSI-6130 is reproduced below for reference.
Ma describes the corresponding phosphorylated metabolites of RO2433 and that the 5'-triphosphate (TP) of RO2433 (RO2433-TP) inhibited HCV RNA synthesis in HCV replicon cells and also inhibited the action of recombinant HCV polymerase NS5B with potencies comparable with those of the 5'-triphosphate of PSI-6130 (PSI-6130-TP). Further Ma note that that the uridine analog RO2433-TP had superior intracellular stability compared to the cytidine analog PSI-6103.

Ma describes a person skilled in the art to identify the phosphoramidate forms of both cytidine and uridine as having anti-viral activity and therefore possessing the realistic potential as anti-viral agents.

e). D14 (Perrone et al., Journal of Medicinal Chemistry 2007, 50, pp. 1840-1849 (2006)). Perrone was published on March 17, 2007 before the effective filing date of IN ‘658. Perrone discloses a phosphoramidate “ProTide” approach to confer potency against hepatitis C virus by activating otherwise inactive nucleosides. Specifically, Perrone taught that the addition of an arylxy phosphoramidate group at the 5'-position of a uridine nucleoside can confer antiviral activity inhibitory activity in the HCV replicon assay for a compound that was otherwise inactive against hepatitis C virus. Perrone also taught that a potent HCV inhibitor nucleoside did not show inhibitory activity in the HCV replicon assay because of the extremely slow intracellular 5'-monophosphorylation of the nucleoside. In addition, D3 taught that the triphosphate nucleoside analogue showed potent inhibition of HCV in the NS5B Polymerase assay as a means of identifying nucleosides which were inefficiently phosphorylated.

Perrone disclosed, 4'-azidocytidine was discovered as a potent inhibitor of HCV replication in cell culture. The corresponding 5'-triphosphate was
described as a competitive inhibitor of cytidylate incorporation by HCV polymerase and a potent inhibitor of native, membrane-associated HCV replicase in vitro...the first phosphorylation step to produce the 5'-monophosphate has often been found to be the rate-limiting step in the pathway to intracellular nucleotide triphosphate formation, suggesting that nucleoside monophosphate analogues could be useful antiviral agents...nucleoside monophosphate...also show poor membrane permeation” (Page 1840, LHS para 4 and RHS para 3, lines 9-15).

Perrone disclosed, aryloxy-phosphoramidates are considered to be efficient lipophilic prodrugs of the corresponding 5'-monophosphate species in which the two masking groups are represented by anamino acid ester and an aryl moiety. (Page 1840, RHS para 4).

Perrone disclosed compound 15 in the fig.1 below R is H, R1 is methyl and R2 is isopropyl.

Perrone disclosed, as shown in Table 1, L-alanine derivatives represented a series of active antiviral phosphoramidates (11-17). Low or sub-molecular activity was noted in marked contrast to the inactive nucleoside parent (1). The tert-butyl ester (16) was the least active of the series...The isopropyl ester (15) showed high potency and represented one of the most active phosphoramidates prepared. Similarly the 2-butyl ester (14) was highly active...in contrast to the previous observations with other nucleoside analogues. Together with benzyl analogue (17), these three esters provided the most potent compounds of the HCV replication inhibitors in the L-alanine series, all having μM inhibition of HCV. The antiviral activity of these three phosphoramidates was exceptional if compared to the parent compound 1. EC50 > 100μM), providing strong support for the notion of
Perrone employed the well-known ProTide strategy to prepare stable phosphate-based prodrugs of the nucleoside (Table 1). These prodrugs were hydrolyzed into 5'-monophosphorylated derivatives of the nucleoside inside the cell, thereby bypassing the need for kinase-mediated monophosphorylation. Among these aryloxy phosphoramidate prodrugs, Perrone is particularly taught that, “the isopropyl ester (15) showed high potency and represented one of the most active phosphoramidates prepared”. Compound 1, identified in this paragraph name as azidouridine. The relevant portions of table showing biological activity of the L-alanine phosphoramidates (compound 15) in the HCV replicon assay as reported in Perrone (Page no 1843 LHS, table 1) is reproduced below:

<table>
<thead>
<tr>
<th>compound</th>
<th>amino acid</th>
<th>ester</th>
<th>EC50 (µM)</th>
<th>CC50 (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>L-Ala</td>
<td>Me</td>
<td>3.1</td>
<td>&gt;100</td>
</tr>
<tr>
<td>12</td>
<td>L-Ala</td>
<td>Et</td>
<td>1.3</td>
<td>&gt;100</td>
</tr>
<tr>
<td>13</td>
<td>L-Ala</td>
<td>Bu</td>
<td>1.2</td>
<td>&gt;100</td>
</tr>
<tr>
<td>14</td>
<td>L-Ala</td>
<td>2-Bu</td>
<td>0.63</td>
<td>&gt;100</td>
</tr>
<tr>
<td>15</td>
<td>L-Ala</td>
<td>iPr</td>
<td>0.77</td>
<td>&gt;100</td>
</tr>
<tr>
<td>16</td>
<td>L-Ala</td>
<td>tBu</td>
<td>5.1</td>
<td>&gt;100</td>
</tr>
<tr>
<td>17</td>
<td>L-Ala</td>
<td>Bn</td>
<td>0.61</td>
<td>&gt;100</td>
</tr>
<tr>
<td>18</td>
<td>Me₂Gly</td>
<td>Et</td>
<td>10.3</td>
<td>&gt;100</td>
</tr>
<tr>
<td>19</td>
<td>Me₂Gly</td>
<td>Bn</td>
<td>3.4</td>
<td>&gt;100</td>
</tr>
<tr>
<td>20</td>
<td>cPitGly</td>
<td>Et</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>21</td>
<td>cPitGly</td>
<td>Bn</td>
<td>&lt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>22</td>
<td>Phe</td>
<td>Et</td>
<td>1.37</td>
<td>&gt;100</td>
</tr>
<tr>
<td>23</td>
<td>Phe</td>
<td>Bn</td>
<td>&lt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>24</td>
<td>Val</td>
<td>Bn</td>
<td>&lt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>25</td>
<td>Gly</td>
<td>Bn</td>
<td>1.6</td>
<td>&gt;100</td>
</tr>
<tr>
<td>26</td>
<td>d-Ala</td>
<td>Bn</td>
<td>1.2</td>
<td>&gt;100</td>
</tr>
<tr>
<td>27</td>
<td>Leu</td>
<td>Et</td>
<td>2.3</td>
<td>&gt;100</td>
</tr>
<tr>
<td>28</td>
<td>Pro</td>
<td>Et</td>
<td>6.0</td>
<td>&gt;100</td>
</tr>
<tr>
<td>29</td>
<td>Met</td>
<td>Et</td>
<td>14</td>
<td>&gt;100</td>
</tr>
<tr>
<td>30</td>
<td>N-Me₃Gly</td>
<td>Et</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>31</td>
<td>EtGlu</td>
<td>Et</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>32</td>
<td>β-Ala</td>
<td>Et</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>4'-azidouridine (1)</td>
<td>--</td>
<td>--</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>

Perrone disclosed, a series of phosphormaidateProTides of 4'-azidouridine were prepared and evaluated as inhibitors of HCV replication in vitro. The
phosphoramidate approach provided novel compounds with highly increased potency in the replicon assay when compared to the inactive parent compound, corresponding to boosts in anti-HCV potency of >450-fold. All phosphoramidates tested were non-toxic in the replicon assay (CC50 >100μM)...This report demonstrates the ability of ProTide approach to successfully bypass the rate limiting initial phosphorylation of a ribonucleoside analogue and thus confer significant antiviral activity on an inactive parent nucleoside. (Page 1844; conclusion)

Perrone describes a person skilled in the art to identify the phosphoramidate forms of uridine derivative as having potency versus hepatitis C virus. Further Perrone considers as the prior art and that the skilled person would have combined compound 15, the structurally closest phosphoramidate in Perrone, with the nucleoside in Sofia.

f). WO 2004/002999 was published on January 08, 2004 before the effective filing date of IN ‘658.WO 2004/002999 discloses compound of formula (IV) (or) prodrug (or) stereo isomeric or pharmaceutically acceptable salt for treating Flaviviridae. More specifically D3 discloses a chemical compound having formula IV (Ref: Page 19)

R1 is phosphate (including mono-, di- or triphosphate and a stabilized phosphate) or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein R1 is phosphate (including mono-, di- or triphosphate); wherein in one embodiment R2 and/or R3 is not phosphate (including mono-, di- or triphosphate or a stabilized phosphate prodrug). R2 is H; X is -0; R6 is methyl (-CH3); R7 is Fluoro (-F); Base is of the formula (F) (Ref: page 20)
W1 is N; W4 is CH; X2 is H; Y1 is OH;

The term "pharmaceutically acceptable salt or prodrug" is used throughout the specification to describe any pharmaceutically acceptable form (such as an ester, phosphate ester, salt of an ester or a related group) of a nucleoside compound (Ref: page no: 107).

The term amino acid is used, it is considered to be a specific and independent disclosure of each of the esters of α-alanine in the D and L-configuration (Ref: Page no. 106)

B. Nucleotide Prodrug Formulations The nucleosides described herein can be administered as a nucleotide prodrug to increase the activity, bioavailability, stability or otherwise alter the properties of the nucleoside. A number of nucleotide prodrug ligands are known. In general, alkylation, acylation or other lipophilic modification of the mono-, di- or triphosphate of the nucleoside reduces polarity and allows passage into cells. Examples of substituent groups that can replace one or more hydrogens on the phosphate moiety are alkyl, aryl, steroids, carbohydrates, including sugars, 1,2-diacylglycerol and alcohols. Many are described in R. Jones and N. Bischoferger, Antiviral Research, 1995, 27:1-17. Any of these can be used in combination with the disclosed nucleosides to achieve a desired effect. (Ref: Page no. 108)

2' and/or 3' prodrugs of 1', 2', 3' or 4'-branched nucleosides, and their pharmaceutically acceptable salts and derivatives are described. These prodrugs are useful in the prevention and treatment of Flaviviridae infections, including HCV infection, and other related conditions. Compounds and compositions of the prodrugs of the present invention are
described. Methods and uses are also provided that include the administration of an effective amount of the prodrugs of the present invention, or their pharmaceutically acceptable salts or derivatives. These drugs may optionally be administered in combination or alteration with further anti-viral agents to prevent or treat Flaviviridae infections and other related conditions. (Ref: Abstract).

Hence, a person of skilled in the art working on developing an HCV nucleoside. WO 2004/002999 would be taught that a fluorinated nucleoside, particularly, (2'-R)-2'-deoxy2'fluoro-2'-C-methyl nucleoside. (Ref: Page no 4)

WO 2006/012440 was published on February 02, 2006 before the effective filing date of IN ‘658. WO 2006/012440 discloses compound of formula (I)

Wherein X is halogen (F); R 2 is alkyl of C1-C3; R 3 is H; R 5 is H, alkyl; R 4 is OH; R 5 is H (Ref: Page no 4 and 5)

The term "alkyl," as used herein, unless otherwise specified, refers to a saturated straight or branched hydrocarbon chain of typically C1 to C10, and specifically includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl, cyclohexyl, cyclohexylmethyl, 3-methylpentyl, 2,2-dimethylbutyl, and 2,3-dimethylbutyl, and the like. The term includes both substituted and unsubstituted alkyl groups. Alkyl groups can be optionally substituted with one or more moieties selected from the group consisting of alkylamino, phosphonic acid, phosphate, or phosphonate (Ref: Page no. 7)
A method to prepare the anti-HCV nucleosides containing the 2'-deoxy-2'-fluoro2'-C-methyl-β-D-ribofuranosyl nucleosides from a preformed, preferably naturally occurring, nucleoside (Ref: field of the invention; Page no. 1) Therefore, a person ordinary skilled in the art working on nucleoside to be used as antiHCV agent, on WO 2006/012440 taught that uracil may also be used as a base in nucleosides for treating HCV.

The opposed patent application compound (Sofosbuvir) has two components, a phosphoramidate and a nucleoside as shown in this formula, which is teaches combination of elements was obvious i.e. Sofia and Perrone.

KSR Int'l Co. v. Teleflex Inc
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 wherein the US Supreme Court noted “The Circuit first erred in holding that courts and patent examiners should look only to the problem the patentee was trying to solve. Under the correct analysis, any need or problem known in the field and addressed by the patent can provide a reason for combining the elements in the manner claimed. Second, the appeals court erred in assuming that a person of ordinary skill in the art attempting to solve a problem will be led only to those prior art elements designed to solve the same problem...It is common sense that familiar items may have obvious uses beyond their primary purposes, and a person of ordinary skill often will be able to fit the teachings of multiple patents together like pieces of a puzzle...Third, the court erred in concluding that a patent claim cannot be
proved obvious merely by showing that the combination of elements was obvious to try. When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp...” The US Supreme Court in the matter of KSR International Co. also took note that absolute predictability of success is not a requirement in determining obviousness. Thus all claims of the present invention are obvious by a collective reading of prior art. The compounds of present invention are taught and motivated by disclosure in prior art. Hence all the claims of the present invention are ought to be rejected. In this regard the opponent craves leave to refer and rely on submission made in the previous ground and the same are not being reiterated for the sake of brevity.

(v) Arguments of opponent 10 (O10)-
The Opponent puts forward the following further argument/explanation regarding obviousness of claim 1 in view of D27 (WO 2004096286). This is to be considered in addition to the arguments mentioned in the written notice of opposition dated 6th June, 2019 which applies mutatis mutandis.

(A-13):
In response to the Applicant’s submission dated 27th June 2019, the Opponent respectfully disagrees with the Applicant for the following points:
Claim-1 belong to the same chemical category and have a similar mechanism of action against Hepatitis C Virus (HCV).
D27 is an invention of GILEAD SCIENCES, INC, i.e. predecessor in title of the present applicant. D27 discloses that present invention relates generally to the accumulation or retention of therapeutic compounds inside cells. More particularly, the invention relates to attaining high concentrations of active metabolite molecules in virally infected cells (e.g. cells infected with HCV or HIV). Such effective targeting may be applicable to a variety of therapeutic formulations and procedures (Ref: Summary of the invention/page No: 3)
It discloses a conjugate comprising an antiviral compound linked to one or more phosphonate groups; or a pharmaceutically acceptable salt or solvate thereof. (Ref: Claim 1)
It also discloses in claim 2: *The conjugate of claim 1*, or a pharmaceutically acceptable salt or solvate thereof, that is a compound of *any one of formulae 501-569 substituted* with one or more groups A0, wherein: A 0 is A1, A2 or W3 with the proviso that the conjugate includes at least one A1. It can be seen from the definition of the various substituents, as defined in claim 2, that

\[ A^1 \text{ is:} \]

wherein M12b may be 0; and wherein Y2 may independently be a bond; and wherein W 6 is W3 independently substituted with 1, 2, or 3 A3 groups.

Therefore, it is seen that according to the definition of markush, A0 or A1 can be same as ‘~ W3’

Claim 3 defines: *The conjugate of claim 2*, or a pharmaceutically acceptable salt or solvate thereof, which has the formula:

\[ [\text{DRUG}]-(A^0)^{nn} \]

Wherein DRUG is a compound of any one of formulae 501-561; and nn is 1, 2, or 3. Claim 4 defines: *The conjugate of claim 2* which has *any one of formulae 1-108*

wherein: A0 is A1 (Explained above- reference claim 2) X106 is O; X107 is uracil; X108 is F; X108 is OH; X109 is C1- C8 alkyl.

In another specific embodiment the invention provides a compound of any one of formulae 1-108 (Ref: Page no: 16) and compound of formula 104 (Ref: Page No: 28);
Therefore the nucleoside moiety of claim 1 of the present application is covered under D27.

Further according to claim 48: *The conjugate of any one of claims 2-27 wherein each A3 is of the formula:*

![Chemical structure](image)

R1 can be independently alkyl of 1 to 18 carbon atoms (Ref: claim 2)

From the above, it is clear that the phosphoramidate of claim 1 is clearly envisaged.

An anti-viral conjugate as described herein (Ref: claim 102)

A pharmaceutical composition comprising a pharmaceutically acceptable excipientents and a conjugate, or a pharmaceutically acceptable salt or solvate thereof, as described in any one of claims 1-89 and 91-102 or a compound as described in claim 103 or 104. (Ref: Claim 105)

A unit dosage form comprising a conjugate, or a pharmaceutically acceptable salt or solvate thereof, as described in any one of claims 1-89 and 91-102 or a compound as described in claim 103 or 104; and a pharmaceutically acceptable excipients (Ref: Claim 106)

A method for promoting an anti-viral effect in vitro or in vivo comprising contacting a sample in need of such treatment with a conjugate as described in any one of claims 1-89 and 91-102 or a compound as described in claim 103 or 104, or a pharmaceutically acceptable salt or solvate thereof. (Ref: Claim 107)

*The method of claim 107 wherein the contacting is in vivo.* (Ref: Claim 108)

A method of inhibiting a viral infection in an animal, comprising administering an effective amount of a conjugate as described in any one of claims 1-89 and 91-102 or a compound as described in claim 103 or 104, or a pharmaceutically acceptable salt or solvate thereof, to the animal. (Ref: Claim 109)

*The method of claim 109 wherein the conjugate or compound is formulated with a pharmaceutically acceptable carrier.* (Ref: Claim 110).
It is submitted that D27 relates to compound of formula 104 derivative possessing anti hepatitis C activity. The disclosed compound is said to have anti hepatitis C activity and the several compounds disclosed includes the compound 104, which may be expressed by a formula as set out hereunder, as explained from the general structure disclosed in claims of D27 as outlined above.

On the other hand, the structure of the compound as claimed in claim 2 in IN 3658/KOLNP/2009 is as under:-

It is submitted that if one would make a structural comparison, it can be said without doubt that the two structures are identical in nature barring the substituents to the extent that as –O-CH2- phosphate in 5’th position in A-13 is replaced with –CH2-O-phosphate in 5’th position in the Indian application.

In order to appreciate the relevant of the close resemblance of the structure of the said two compounds one has to look into them more closely. It has to be particularly seen whether there was any motivation or otherwise any teaching in the art that could have prompted the applicant (a person skilled in the art) to substitute –O-CH2- with –CH2-O- in 5’th position. It is evident that there is a clear teaching that –O-CH2- and –CH2-O- may be used interchangeably.

However, it is relevant to state that while they may be used interchangeably, there is evidence in the present patent application to show that there is no fixed pattern or one cannot lay down a hypothesis as to the superiority of one over the other as a matter of rule. In some cases –O-CH2- is found to be superior to –CH2-O- and in some cases vice versa.
It is submitted that there could not have been a guarantee to the inventor that the –CH2-O substitution would work but due to successful use of both –O-CH2- and –CH2-O- in an interchangeable manner in several chemical compounds, it was not at all surprising to substitute –O-CH2- with –CH2-O-. Therefore, in the Opponent’s opinion such substitution cannot be said to possess an *inventive step* particularly when the compound 104 was taught in D27 compound possessing anti-hepatitis C activity. Therefore, there is teaching, suggestion and motivation in D27 to arrive at the present claim 1, without being inventive. Comparison of present invention with D27 is summarized below table:

<table>
<thead>
<tr>
<th>IN 3658/KOLNP/2009</th>
<th>A-13 (WO2004095286)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Chemical Structure" /></td>
<td><img src="image2" alt="Chemical Structure" /></td>
</tr>
</tbody>
</table>

(Sofosbuvir)

In view of the above, the subject-matter of opposed claims 1 to 4 lacks an inventive step. Besides, it is generally recognized that in the field of pharmaceuticals, separating the various stereoisomers of a racemic mixture does not involve an inventive step. Therefore, the subject-matter of the opposed claims 2 and 3 also lack an inventive step. This is without prejudice to the fact that opposed claims 2 and 3 have not even been disclosed in the specification of the opposed application.

General procedures for nucleoside phosphoramidate Derivative example:
Comparison of present invention with D27 (A-13) is summarized below table:

<table>
<thead>
<tr>
<th>IN 3658/KOLNP/2009</th>
<th>A-13 (WO2004095286)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image3" alt="Example 3" /></td>
<td><img src="image4" alt="Example 3" /></td>
</tr>
</tbody>
</table>

A solution of the appropriate phosphoramide derivative (4.5 equivalents) in acetonitrile and water (1:1) was added to a mixture of sodium triacetoxyborohydride (3.0 equivalents) and (R)-1-(4-bromophenyl)-2,2-dimethylpropan-1-one (4.5 equivalents) in acetonitrile with vigorous stirring at room temperature. After stirring for 24 hours, the reaction mixture was filtered and washed with water. The filtrate was concentrated to give the crude product, which was purified by column chromatography to give the desired phosphoramidate derivative.
Above said table exemplified compound with such combination. Further points based in A-13 may also be noted. Page no. 525-587 of A-13; Example 259 discloses: *By way of example and not limitation*, embodiments of the invention are named below in tabular format (Table 100). These embodiments are of the general formula “MBF”:

![Diagram of MBF]

Each embodiment of MBF is depicted as a substituted nucleus (Sc). *Sc is described in formula 1-108* herein, wherein A 0 is the point of covalent attachment of Sc to Lg, as well as in Tables 1.1 to 1.5 below. For those embodiments described in Table 100, Sc is a nucleus designated by a number and each substituent is designated in order by letter or number. Tables 1.1 to 1.5 are a schedule of nuclei used in forming the embodiments of Table 100. Each nucleus (Sc) is given a number designation from Tables 1.1 to 1.5, and this designation appears first in each embodiment name. Similarly, Tables 10.1 to 10.19 and 20.1 to 20.36 list the selected linking groups (Lg) and prodrug (Pd1 and Pd2) substituents, again by letter or number designation, respectively. Accordingly, a compound of the formula MBF includes compounds having Sc groups based on formula 1-108 herein as well as compounds according to Table 100 below. In all cases, compounds of the formula MBF have groups Lg, Pd1 and Pd2 setforth in the Tables below. Accordingly, each named embodiment of Table 100 is depicted by a number designating the nucleus from Table 1.1-1.5, followed by a letter designating the linking group (Lg) from Table 10.1- 10.19, and two numbers designating the two prodrug groups (Pd 1 and Pd 2 ) from Table 20.1-20.36. In graphical tabular form, each embodiment of Table 100 appears as a name having the syntax: Sc. Lg. Pd1. Pd2

Each Sc group is shown having a 100ilde (“~”). The 100ilde is the point of covalent attachment of Sc to Lg. Q1 and Q2 of the linking groups (Lg), it should be understood, do not represent groups or atoms but are simply connectivity designations. Q 1 is the site of the covalent bond to the nucleus.
(Sc) and Q 2 is the site of the covalent bond to the phosphorous atom of formula MBF. Each prodrug group (Pd 1 and Pd 2 ) are covalently bonded to the phosphorous atom of MBF at the 10ilde symbol (“~”). Some embodiments of Tables 10.1-10.19 and 20.1-20.36 may be designated as a combination of letters and numbers (Table 10.1-10.19) or number and letter (Table 20.1-20.36). For example, there are Table 10 entries for B J1 and B J2. In any event, entries of Table 10.1-10.19 always begin with a letter and those of Table 20.1-20.36 always begin with a number. When a nucleus (Sc) is shown enclosed within square brackets (“[ ]”) and a covalent bond extends outside the brackets, the point of covalent attachment of Sc to Lg may be at any substitutable site on SC. Selection of the point of attachment is described herein. By way of example and not limitation, the point of attachment is selected from those depicted in the schemes and examples.

The nucleus from Table 1.1-1.5: Table 1.1:

![Diagram](image1.png)

Linking group (Lg) from Table 10.1-10.19: Table 10.1:

![Diagram](image2.png)

The two prodrug groups (Pd 1 and Pd 2 ) from Table 20.1-20.36:

Table 20.12:

![Diagram](image3.png)

Table 20.36:
compound of formula 104:

Comparison of present invention with A13 is summarized below table:

<table>
<thead>
<tr>
<th>IN 3658/KOLNP/2009</th>
<th>A-13 (WO2004096286)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Chemical Structure" /></td>
<td><img src="image2" alt="Chemical Structure" /></td>
</tr>
</tbody>
</table>

**Ref:** Page No: 28 and Example 259

**Ref:** Table I.1 with Example 259
On the basis of the above, one of ordinary skill in the art would have been motivated to use the teaching of D27 (i.e., Page No: 28 and Example 259/Table 1.1) of the patent to produce compounds of claim 1-3.

(vi) Arguments of Opponent 11 (O11) -

The subject matter of claims 1 to 5 lacks inventive step in view of the disclosures and teachings of any of the prior art documents D1 to D9 either alone or in combination with each other. Many prior art documents disclose the claimed features in the impugned patent application individually or in combination.

LACK OF INVENTIVE STEP IN VIEW OF DISCLOSURES IN WO 2005/012327 A2:
The subject matter claimed in claims 1 to 5 of alleged invention is not new and lacking novelty in view of the disclosures in ‘327 as discussed in above paragraph of Ground-I. Therefore, the claims 1 to 5 which are not new cannot involve any inventive step as required under section 2(1) (ja) of the Patents Act, 1970. Thus, the invention claimed in alleged claims 1 to 5 are lacking inventive step in view of the disclosures.

LACK OF INVENTIVE STEP IN VIEW OF DISCLOSURES IN Perrone et al. (2007)(D14) IN COMBINATION WITH Ma et al (D24): The prior art document [The priority of provisional application cannot be given to the present application claims 1 to 5 of present application application]the thesis entitled "Design, Synthesis and Biological Evaluation of Novel Nucleotide Prodrugs as Potential Anti-Hepatitis C Virus Agents"was submitted by Plinio Perrone on February 2007, i.e. before the earliest priority date claimed by the present application [The priority of provisional application cannot be given to the present application claims 1 to 5 of present application].

The thesis Chapter 1, in that Perrone first recalls that there is a variety of evidence that suggests the arylphosphoramidate approach is the key to increasing the anti-HCV activity of modified nucleosides and mentions (i) that the phosphoramidate of d4A has shown a 1000-fold boost inactivity in HIV-2 CEM cells compared to the parent nucleoside and (ii) that the same parent nucleoside is inactive against Hepatitis B virus while the
phosphoramidate is active at sub-11M levels (see paragraph 1.7.3. on pages 22-23).

The thesis Chapter 4, on page 78, Perrone reports that "4'-Azidouridine (24) was tested against HCV in the replicon assay and was found completely inactive, whereas the corresponding 5’-triphosphate had an activity at 0.22J1M against RdRp [i.e. HCVNS5Bj. The activity of 4’-Azido uridine triphosphate and the inactivity of the corresponding nucleoside might indicate that 4’-azidouridine (24) is poorly phosphorylated by the kinases (see Chapter One). One possibility to overcome this problem was the delivery in to the cell of corresponding 5’-monophosphate via phosphoramidate technology."

On page 86, Perrone reports that L-alanine phosphoramidates of 4’-azidouridine with different substituents were prepared to explore the SAR [Structure Activity Relationship] in the ester position. The biological activity of the L-alanine phosphoramidates in the HCV replicon assay are presented in Table 4.7:
It can be seen that when R=isopropyl (compound 150), a sub micromolar inhibitory effect (EC50) in the HCV replicon assay is obtained. Perrone notes that methyl, ethyl and isopropyl derivatives did not show a significant difference in potency (see page 87).

On page 83, Perrone shows the phosphorochloridates (see formula below) used to prepare the L-alaninephosphoramidates of 4'-azidouridine, among which there is compound 130 with R= L-alanine and R' =isopropyl.
Its objective is to solve the same general technical problem as the present application, namely providing nucleoside inhibitors of HCV NS5B and provides nucleoside phosphoramidates with a strong structural resemblance with the compounds claimed by the present application. Perrone may therefore qualify as a closest prior art document for the alleged invention.

The difference between compound 150 and the compound of claim 1 of the present application is that a N3 group and a hydroxyl group are respectively present in the C4' and C2' positions of the 4'-azidouridine part of compound 150 instead of a H in the C4' position and F/CH3 in the C2' position for the 13-O-2'-deoxy-2'-fluoro-2'-C-methyluridine part of the compound of present application claim 1.

Claim 1 of present application

Compound 150

Both compounds present similar sub micromolar inhibitory effects in the HCV replicon assay (EC50 at 0.9611M for the compound 150 of Perrone vs. EC90 at 0.39 for the compound of present application application claim 1).

Accordingly, no technical effect can be associated to the difference in structure and the objective technical problem can be formulated has providing alternative anti-HCV compounds to that of Perrone.
Ma et al. discloses that R02433-TP (the triphosphate from of 13-0-2'-deoxy-2'-fluoro-2'-Cethyluridine, see below) is a potent inhibitor of RNA synthesis by HCV polymerase while unphosphorylated R02433 is not active (see page 29815, right column).

It draws a parallel between R02433 and 4'-azidouridine, which is inactive against HCV, but which becomes a potent inhibitor of HCV replication when delivered as a monophosphate prodrug, demonstrating that a block of monophosphate formation resulted in lack of antiviral activity of 4'-azidouridine; 06 assumes a similar block of R02433 phosphorylation to its monophosphate R02433-MP(see page 29819, left column), which prevents the subsequent phosphorylation to R02433-0P and R02433-TP (see figure7, page 29819).

In addition, it notes that the longer intracellular half-life of R02433-TP as compared to PSI-6130-TP (the cytidine analogue of R02433-TP, the under going clinical development) (38h vs.4.7h) may have pharmacological relevance for maintaining more constant concentrations of the antiviral triphosphate over the dosing period in clinical studies.

The person skilled in the art who wish to solve the objective technical problem would have been prompted to replace 4'-azidouridine by 13-0-2'-deoxy-2'-fluoro-2'-C-methyluridine in the compound 150of D2,there by arriving at the compound of claim1, as he would have expected this would allow overcoming the block of phosphorylation of R02433, thereby inhibiting HCV replication and leading to the clinically advantageous R02433-TP.

Accordingly, the subject-matter of claim 1 and 5 lacks an inventive step in view of the disclosures in Perrone combined with Ma et al.

Besides, it is generally recognized that in the field of pharmaceuticals, separating the various stereoisomers of a racemic mixture s obvious to a person skilled in the art and does not involve an inventive step. Therefore, the subject matter of claims 2 and 3 also lack an inventive step in view of
the disclosures in D14 combined with D24. The composition claimed in claim 4 is also obvious to a person skilled in the art as the composition preparation by using the compound is obvious to a person skilled in the art and does not involve inventive step in view of the disclosures in D14(Perrone) combined with D24 (Ma et al.)

LACK OF INVENTIVE STEP IN VIEW OF DISCLOSURES IN D23 (Sofia) IN COMBINATION WITH Perrone et al.:

D23 is a poster presented at the 14th International Symposium on Hepatitis C Virus and Related Viruses which was held in Glasgow(Scotland) on 9-13 September 2007, i.e. between the first and second in validly claimed priority dates [The priority of provisional application cannot be given to the present application claims 1 to 5 of present application].

It discloses the \( \beta-D-2'-\text{deoxy-2'}-\text{fluoro-2'}-\text{C-methyluridine phophoramidate} \) compound PSI-6206 having the following formula:

![Formula](image)

It further discloses that \( \beta-D-2'-\text{deoxy-2'}-\text{fluoro-2'}-\text{C-methyluridine phophoramidates are potent inhibitors of HCV and that they have potential as therapeutics for the treatment of HCV.} \) It also shows that variants at the R1, R2 or R3 positions exhibit a strong inhibitory activity in the HCV replicon assay. Thus, person skilled in the art wish to solve the objective technical problem previously defined using Perrone as closest prior art, namely providing alternative anti-HCV compounds to that of D14, would have been in cited to replace the 4'-azidouridine part of compound 150 of D14 by the \( \beta-D-2'-\text{deoxy-2'}-\text{fluoro-2'}-\text{C-methyluridine part of PSI-6206, thereby arriving at the compound of claim 1, as he would have expected this compound to be an anti-HCV compound in view of D23 which discloses that} \)
phosphoramidates of β-D-2′-deoxy-2′-fluoro-2′-Cmethyluridine are potent inhibitors of HCV.

Besides, it is generally recognized that in the field of pharmaceuticals, separating the various stereoisomers of a racemic mixture is obvious to a person skilled in the art and does not involve an inventive step. Therefore the subject matter of claims 2 and 3 also lack an inventive step in view of the disclosures in D23 combined with D14. The composition claimed in claim 4 is also obvious to a person skilled in the art as the composition preparation by using the compound is obvious to a person skilled in the art and does not involve inventive step in view of the disclosures in D23 combined with D14.

LACK OF INVENTIVE STEP IN VIEW OF DISCLOSURES IN D21 (Clark et al.) IN COMBINATION WITH D14:

D21 aims at solving the same general technical problem as the present application, namely providing nucleoside inhibitors of HCV replication and provides a nucleoside identical to the nucleoside part of the compounds claimed by the present application. D5 may therefore qualify as a closest prior art document.

The difference between the compound of present application claim 1 and compound 9 of D21 (Clark et al.) lies in the presence of a phosphoramidate arm in the compound of present application claim 1. The effect of this difference is that the compound of claim 1 is active against HCV.

The objective technical problem can thus be formulated as modifying the compound 9 of D21 to make active against HCV.

D14 mentions that phosphoramidate modifications of inactive nucleoside analogs has made them active antiviral compounds (see paragraph 1.7.3. on pages 22-23). This is particularly the case of an anti-HCV uridine analog (see
Table 4.7 on page 86) which is rendered active by exactly the same phosphoramidate as that of the compound of present application claim 1 (compound 150 in Table 4.7).

Therefore, person skilled in the art wishing to solve the objective technical problem would have been prompted to modify compound 9 by adding a phosphoramidate moiety, in particular with the phosphoramidate moiety of compound 150 of D14, which is one of the most active anti-HCV derivative of the uridine analog tested in D14, thereby arriving at the compound of claim 1 of the present patent application.

Accordingly, the subject-matter of claim 1 and 5 lacks an inventive step in view of the disclosures in D21 combined with D14.

Besides, it is generally recognized that in the field of pharmaceuticals, separating the various stereoisomers of a racemic mixture is obvious to a person skilled in the art and does not involve an inventive step. Therefore the subject-matter of claims 2 and 3 also lack an inventive step in view of the disclosures in D21 combined with D14. The composition claimed in claim 4 is also obvious to a person skilled in the art as the composition preparation by using the compound is obvious to a person skilled in the art and does not involve inventive step in view of the disclosures in D21 combined with D14.

LACK OF INVENTIVE STEP IN VIEW OF DISCLOSURES IN D3, D22, D25, D26 EITHER ALONE OR IN COMBINATION THEREOF:

D3 (WO01/092282) discloses a basic chemical structure encompassing several thousand compounds for treating viral infections caused by flavivirus and pestivirus. The basic structure is also drawn to a sugar attached to a nitrogenous base. Further it discloses various substituent’s which encompasses in its structure several possible nucleotides. From the substituent’s it is clear that it envisages and encompasses compounds similar the compounds of the present application. The compounds of D3 comprises a halo and an alkyl substitution in the sugar and the said compounds are presented as phosphate prodrugs. The phosphate prodrugs by definition include within its scope phosphoramidate compounds. Further these prodrugs also comprises of base such as uracil, thymidine etc., which may be found either as their substituted / unsubstituted form. It is
submitted that the compound of the present application may be arrived by substitution of various substituent. Various examples of D3 may be examined and found to fall within the scope of the present application and vice versa. Thus, the disclosures and teachings makes the compounds claimed in claims 1 to 3 and composition claimed in claim 4 along with the process for preparation of compounds of claims 1 to 3 claimed in claim 5 of present application is obvious to a person skilled in the art and hence the claims 1 to 5 does not involve inventive step.

D22 (WO2001/90121) discloses compounds for treating viral infections caused by hepatitis C virus. It is submitted that the compounds of present application are known and encompassed within the basic chemical structure of D22. The basic structure is drawn to a sugar attached to a nitrogenous base. Further it discloses various substituents which encompasses in its Markush several possible nucleotides. The compounds of comprises a halo and an alkyl substitution in the sugar and the said compounds are presented as phosphate prodrugs such as phosphoramidates. Further these prodrugs also comprises of base such as uracil, thymidine, etc., which may be found either in substituted/unsubstituted form. It is submitted that the compound of the present application may be arrived by substitution of various substituent of D22. Various examples of D22 may be examined and found to fall within the scope of the present application and vice versa. The compound claims and isomers of the present application fall within the scope of D22.

D22 disclosed a method and composition for treating a host infected with hepatitis C virus comprising administering an effective hepatitis C treatment amount of a described1',2'or3'-modified nucleoside or a pharmaceutically acceptable salt or prodrug thereof, is provided (Ref: Abstract). It discloses compound of formula (XI) or a pharmaceutically acceptable thereof. The chemical compound having formula XI (Ref: Claim8)
Base is a purine or pyrimidine base as defined herein (Disclosed the term pyrimidine base includes, but is not limited to uracil); R1 is phosphate (including monophosphate, diphosphate, triphosphate, or astabilized phosphate prodrug); X is O; R2 is H; R6 is alkyl (including lower alkyl); R7 is chlorine, bromine, iodine (absence of fluorine); (Ref: Claim 08)

D22 discloses a pharmaceutical composition for the treatment (or) prophylaxis of a Hepatitis C virus in a host, comprising an effective amount of a compound of formula XI. (Ref: Claim 34). It discloses a method for the treatment (or) prophylaxis of a Hepatitis C virus infection in a host, comprising administering an anti-virally effective amount of a compound of formula XI. (Ref: Claim 86)

It discloses a use of a compound of formulas XI or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a host infected with the Hepatitis C virus. (Ref: Claim 137)

Therefore, a person ordinary skilled in the art working on nucleoside to be used as anti HCV agent, on D21 taught that Uracil may also be used as a base in nucleosides for treating HCV. Building blocks to arrive at the molecules of present application is known, compounds similar in structure to the compounds as disclosed in the present application are known in the prior art, compounds similar to that of present application are known to exert antiviral activity and phosphate prodrugs for modification of physicochemical parameters are known. The stereoisomers fall within the scope of the compounds as disclosed in prior art. Thus, the disclosures and teachings of D22 makes the compounds claimed in claims 1 to 3 and composition claimed in claim 4 along with the process for preparation of compounds of claims 1 to 3 claimed in claim 5 of present application application is obvious to a person skilled in the art and hence the claims 1 to 5 does not involve inventive step.

D25 (WO2004/002999) discloses compound of Formula (IV) (or) prodrug (or) stereoisomeric or pharmaceutically acceptable salt for treating Flaviviridae. More specifically it discloses a chemical compound having formula IV (Ref: Page19)
Wherein, R1 is phosphate (including mono-, di- or tri phosphate and a stabilized phosphate) or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein R1 is phosphate (including mono-, di- or tri phosphate); wherein in one embodiment R2 and/or R3 is not phosphate (including mono-, di- or triphosphate or a stabilized phosphate prodrug). R2 is H; X is 0; R6 is methyl(-CH3); R7 is Fluro(-F); Base is of the formula (F) (Ref: page20)

W is N; W4 is CH; X2 is H; Y1 is OH;

The term "pharmaceutically acceptable salt or prodrug" is used throughout the specification to describe any pharmaceutically acceptable form (such as an ester, phosphate ester, salt of an ester or a related group) of a nucleoside compound (Ref: page no: 107). The term amino acid is used, it is considered to be a specific and independent disclosure of each of the esters of α-alanine in the D and L-configuration (Ref: Page no.106). The nucleosides described herein can be administered as a nucleotide prodrug to increase the activity, bioavailability, stability or otherwise alter the properties of the nucleoside. A number of nucleotide prodrug ligands are known. In general, alkylation, acylation or other lipophilic modification of the mono-, di- or triphosphate of the nucleoside reduces polarity and allows passage into cells. Examples of substituent groups that can replace one or more hydrogen’s on the phosphate moiety are alkyl, aryl, steroids, carbohydrates, including sugars, 1,2-diacylglycerol and alcohols. Many are described in R. Jones and N. Bischoferger, Antiviral Research, 1995, 27:1-17. Any of these can be used in combination with the disclosed nucleosides to achieve a desired effect. (Ref: Page no.108) 2’ and/or 3’ prodrugs of 1’,2’,3’ or 4’-branched
nucleosides, and their pharmaceutically acceptable salts and derivatives are described. These prodrugs are useful in the prevention and treatment of Flaviviridae infections, including HCV infection, and other related conditions. Compound sand compositions of the prodrugs of the present invention are described. Methods and uses are also provided that include the administration of an effective amount of the prodrugs of the present invention, or their pharmaceutically acceptable salts or derivatives. These drugs may optionally be administered in combination or alteration with further anti-viral agents to prevent or treat Flaviviridae infections and other related conditions. (Ref: Abstract) Hence, a person skilled in the art working on developing an HCV nucleoside, D25 would be taught that a fluorinated nucleoside, particularly, 2'-R)-2'-deoxy-2'fluoro-2'-C-methylnucleoside. Thus, the disclosures and teachings of D25 makes the compounds claimed in claims 1 to 3 and composition claimed in claim 4 along with the process for preparation of compounds of claims 1 to 3 claimed in claim 5 of present application is obvious to a person skilled in the art and hence the claims 1 to 5 does not involve inventive step.

D26 (WO2006/012440) discloses compound of formula (I) (Ref: Page no 4)

Wherein X is halogen (F); R2is alkyl of C1-C3; R3 is H; R5 'is H, alky; R4is OH; R5is H (Ref: page no.4 and 5)

The term "alkyl," as used herein, unless otherwise specified, refers to a saturated straight or branched hydrocarbon chain of typically C1 to C10, and specifically includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl, cyclohexyl, cyclohexymethyl, 3-methylpentyl, 2,2-dimethyl butyl, and 2,3-dimethylbutyl, and the like. The term includes both substituted and unsubstituted alkyl groups. Alkyl groups can be optionally substituted with
one or more moieties selected from the group consisting of alkylamino, phosphonic acid, phosphate, or phosphonate (Ref: Pageno.7)

A method to prepare the anti-HCV nucleosides containing the 2'-deoxy-2'-fluoro-2'-Cmethyl-β-D-ribofuranosynucleosides from a preformed, preferably naturally occurring, nucleoside (Ref: field of the invention; Page no.1). Therefore, a person ordinary skilled in the art working on nucleoside to be used as anti-HCV agent and D26 taught that Uracil may also be used as a base in nucleosides for treating HCV. Thus, the disclosures and teachings of D26 makes the compounds claimed in claims 1 to 3 and composition claimed in claim 4 along with the process for preparation of compounds of claims 1 to 3 claimed in claim 5 of present application is obvious to a person skilled in the art and hence the claims 1 to 5 does not involve inventive step.

The technical problem defined in the impugned patent application providing anti-HCV compounds and obtaining its various stereoisomeric forms is routine and obvious to try by the person skilled in the art in view of the disclosures in cited prior art documents either alone or in combination with each other. Therefore, in view of the disclosures in the any of the cited prior art documents, the subject matter of claims 1 to 5 are clearly obvious to a person skilled in the art. Hence, it clearly establishes that the disclosures of cited prior art alone or in combination with each other makes the compounds claimed in alleged claims 1 to 3 and their composition claimed in claim 4 of instant invention along with their preparation process claimed in claim 5 is obvious to a person skilled in the art and clearly does not involve any inventive step as required under section 2(1)(ja) of the Patents Act, 1970.

Therefore, the alleged inventions claims 1 to 5 are liable for rejection/refusal on this ground alone.

(vii) Arguments of opponent 12 (O12) -
During hearing O12 stated that they rely on documents cited in pre-grant opposition filed by them and no oral arguments presented thereon. Further no submission on inventive step was provided by O12 in written hearing submissions.
Without prejudice to the ground of lack of novelty raised above, it is submitted that claims 1-5 of the present Application lack an inventive step.

D23 (Sofia et al.) discloses PSI-6206 and clearly teaches that
a. 5’-Phosphoramidate derivatives of PSI-6206 are potent inhibitors of HCV in the sub genomic replicon assay;
b. Selected phosphoramidates of PSI-6206 are as much as 100x more potent than the cytidine analog PSI-6130, Its derivatives show no cytotoxicity across several different cell lines;
c. PSI-6206 phosphoramidates showed good stability with the potential to be rapidly released at liver.
d. Several PSI-6206 phosphoramidates demonstrated stability profiles that are attractive for further development; and
e. β-D-2’-Deoxy-2’-fluoro-2’-C-methyluridine phosphoramidates have potential as therapeutic agents for the treatment of HCV infection.”

Therefore, D23 would motivate a person skilled in the art (POSITA) working on developing anti-HCV agents to explore the 5’-phosphoramidates of PSI6206.

D24 (Ma et al.) discloses that prodrug of nucleoside analogs has shown promise by noting that, “ribonucleoside analogs with 2-C-methyl, 2-O-methyl, or 4-azido substituents on the ribose moiety have been reported to be inhibitors of HCV replication...Prodrugs of two nucleoside analogs, 2-C-methylcytidine (NM107) and 4-azidocytidine (R1479), have...shown efficacy in HCVinfected patients.” D24 further discloses a proposed metabolic pathway for PSI-6130 and notes that, “PSI-6130 is a potent and highly selective nucleoside inhibitor of HCV replication targeting NS5B polymerase... PSI-6130-TP and its uridine analog RO2433-TP, in primary human hepatocytes...The longer intracellular half-life of RO2433-TP may have pharmacologic relevance for maintaining more constant concentrations of the antiviral triphosphate over the dosing period in clinical studies.” Therefore, a POSITA on reading 23 and D24 would be taught that
phosphorylated forms of the cytidine and uridine analogs have the potential anti-HCV activity. A POSITA thus, on reading D23 and D24 would be motivated to explore prodrugs of PSI-6130.

D25 (WO 2004/002999) discloses compound of formula (IV) and its prodrugs, stereoisomers or pharmaceutically acceptable salt for treating Flaviviridae.

![Chemical structure of (IV)](image)

wherein; R1 is phosphate (including mono-, di- or triphosphate and a stabilized phosphate); R2 is H; X is -0; R6 is methyl (-CH3); R7 is Fluoro (-F); Base is of the formula (F) (see D3, internal page 20)

![Chemical structure of (F)](image)

wherein; W1 is N; W4 is CH; X2 is H; Y1 is OH;

"pharmaceutically acceptable salt or prodrug" is any pharmaceutically acceptable form (such as an ester, phosphate ester, salt of an ester or a related group) of a nucleoside compound. Furthermore, the amino acid is considered to be a specific and independent disclosure of each of the esters of α- alanine. D25 also discloses Fluorine substitutions at the R7 position. It motivates to identify the compounds including prodrugs to explore compounds with anti-viral activities. Further, highlighted substitutions on the disclosed compound of D25, would provide a POSITA to arrive at compounds with anti-viral activity.

D22 (WO’121) discloses a method and composition for treating hepatitis C virus by administering an effective amount of a described 1’, 2’ or 3’-
modified nucleoside or a pharmaceutically acceptable salt or prodrug thereof of the disclosed compound of Formula XI.

Wherein; Base is a purine or pyrimidine (pyrimidine base includes, but is not limited to uracil); R1 is phosphate including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug; X is O; R2 is H; R6 is alkyl (including lower alkyl); R7 is chlorine, bromine, iodine. 31. The absence of Fluorine at the R2 position would motivate a POSITA to explore the impact of making such a substitution.

D20-US'587 discloses a family of 2'-fluoro nucleoside compounds useful for treating hepatitis C virus. The compound disclosed herein discloses substitution at 2' position:

Base is a purine or pyrimidine base; R1 is OH, H, OR3, N3, CN, halogen, including F, or CF3, lower alkyl, amino, loweralkylamino, di(lower)alkylamino, or alkoxy, and base refers to a purine or pyrimidine base; R2 is H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug.

D20 discloses, “...advantage of ....ability to access separately either the “natural” (1a) D or the “unnatural” (1b) L enantiomer of the nucleosides by appropriate choice of L- or D-glutamic acid Starting material, respectively.”
Therefore, a POSITA on reading cited prior art documents would be taught about the various uridine substituted prodrugs useful in treating hepatitis C and be able to arrive at the compound of claim 1 of the Present Application.

9(b) Hearing submission by the applicant on section 25(1)(b)-
D1 (WO 2005/003147)

D1 discloses a (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside. It is clear from the definition of R1 that there is no specific disclosure or teaching of a phosphoramidate group for R1. D1 does not disclose a phosphoramidate moiety let alone the specific claimed phosphoramidate group itself. It may refer to certain prodrugs generally, it does not specifically describe the phosphoramidate group claimed. It is well established that a generic disclosure does not take away the novelty of any specific example falling within the terms of that disclosure. It does not specifically mention or disclose the 5’-phosphoramidate prodrug of the 2-deoxy-2’-fluoro(down)-2’-methyl (up) nucleoside. It provides no guidance to persons of ordinary skill in the art concerning the synthesis phosphoramidate prodrug of (2R)-2’-deoxy-2’-fluoro-2’-C-methyl nucleoside. Hence no motivation to even pick this compound as of the date of filing of the instant application. In 2005, D1 reports nucleoside compounds for treatment of HCV. It does not disclose or describe any aryloxy phosphoramidate. D1 refers to certain prodrugs generally, it does not specifically describe the phosphoramidate group claimed. Prodrugs are generically disclosed along with pharmaceutically
acceptable salts, and compositions. Further, a number of categories of prodrugs have been speculated. The structure of prodrugs provided in the specification are either N-acyl prodrugs or amide ester prodrugs at 3'- or 3'- and 5'- amide ester prodrugs. The structure of these prodrugs are as follows:

**N-acyl prodrugs**

![N-acyl prodrugs diagram]

**Other prodrugs**

![Other prodrugs diagram]

**D2 (WO2005/012327)**

D2 provides a compound of formula (I)

![D2 compound diagram]

Thousands compounds possible as per the formula (I). It reports Activity for Breast cancer, colon cancer, prostate cancer. The compounds which the Opponent rely upon in petition are not disclosed, mentioned, listed or described in the cited prior art specification. 10 substituents for the compounds of formula (I) of WO’327 are to be selected to reach to the
claimed compound i.e. R, R’, R‖, Ar, Q, X, Y, Z, Z’ & n. Out of these ten substituents, 4 are fixed in accordance with standard procedure 5, where the nucleoside is fixed to 5-(2-bromovinyl)-2′-deoxyuridine. D2 in the standard procedure 5 has fixed the nucleoside to be (E)-5-(2-bromovinyl)-2′-deoxyuridine (BVDU) wherein the base has been fixed to bromovinyluracil and sugar moiety has been fixed to 2′-deoxyuracil having no substitution at 2′-position. D2 strongly prefers the base to be 2-bromovinyl-uracil in all the exemplified compounds except one which is a well-known anti-cancer drug “Gemcitabine”. Not a single compound is disclosed with an unsubstituted uracil base. Therefore, synthetic procedure of D2 by following the standard procedure-5 described therein, a person skilled in art will always start with (E)-5-(2-bromovinyl)-2′-deoxyuridine and the resulting nucleoside analogue will always have (2-bromovinyl)-2′-deoxyuridine. D2 does not disclose nucleoside moiety having the required, stereospecific substitution at the 2′-position, i.e. 2′-fluoro (down), 2′-methyl (up). D2 fails to disclose the specific phosphoramidate moiety at 5′-position of sugar ring of the Gilead’s claimed compounds. It provides preparation of 48 preferred or promising compounds on page 23 to 72 containing BVDU nucleoside and 3 examples of phosphoramidate derivatives of known drug Gemcitabine. Among the prepared exemplified compounds all the compounds have only hydrogen at 2′-position carbon i.e. 2′-position is unsubstituted except three compounds which are Phosphoramidates of Gemcitabine which has difluoro substitution on 2′-position. Not a single compound is prepared with unsubstituted uracil base attached to sugar and the unique substitution pattern of 2′-fluoro (down) and 2′-methyl (up) at 2′-position of sugar ring and phosphoramidate with isopropyl ester of alanine amino acid. D2 provides activity data for ~98 compounds in table on page 106-109 which includes naturally as well as non-naturally occurring amino acids. Activity reported for ~98 compounds with all having 2-bromovinyluridine except 6 compounds. Not a single compound has unsubstituted uracil base attached to sugar and the unique substitution pattern of 2′-fluoro (down) and 2′-methyl (up) at 2′-position of sugar ring and isopropyl ester of alanine amino acid. There is no actual HCV activity which is reported qua the compounds which are sought to be
identified by the Opponent. Rather on page 3, D2 states that “however, based on our prior art, the phenyl methoxyalaninyl phosphoramidate (7) would be anticipated to be amongst the most optimal of structures.” “Surprisingly, it has now been found that other derivatives of oxyamino acid-phosphoramidate nucleoside analogues are significantly more potent in the treatment of cancer than the phenyl methoxyalaninyl phosphoramidate (7).” The support for the above statement has been provided on page 12 of D2 where it mentions surprising finding that the benzyl ester compound (8) is more potent against cancer cell lines than the methyl ester compound (7).

D2 states on page 13 that the simultaneous modification in the two regions i.e. amino acid and aryl moiety show high potency against a range of cancer cell types and significantly and surprising more potent that compound (7).

Very importantly, it can be noticed from the finding of the Inventors that the most optimal compound for the research in the field of cancer is compound (7) which has a Bromo Vinyl Deoxy Uracil base. Here, the Author/inventors considered the prior art from 1994 till date 2004. Further, the finding of authors of D2 concludes that the compounds incorporating modification at amino acid ester region and modification at aryloxy group attached to Phosphorus atom in compound (7), results into more potent compounds for the treatment of cancer. In light of above disclosure, one skilled in the art would select to have a compound with benzyl group or other group
mentioned in D2 at alanine amino acid moiety and substituted phenyloxy group at phosphorus atom in compound (7).

D3 (WO 2001/92282)

D3 describes 18 Markush compound with generic formulae in which encompass millions of permutations of substituents at various positions. D3 reports activity for Flavivirus or Pestivirus infection. For formula (XI) of D3, the R7 substituent definition does not include fluorine. Among the many possible substituents, chlorine, bromine and iodine were the only halogens contemplated at this position, suggesting that fluorine was omitted purposefully. No other formula in D3 encompasses compounds with 2'-fluoro (down) – 2'-methyl (up) substitution, either. There is no generalized Scheme even to make the said class of compounds. No motivation to even pick this compound as of the date of filing of the instant application. D3 also does not teach use of a phosphoramidate at the 5′-carbon of the sugar moiety. R1 can be hydrogen or monophosphate or diphosphate or triphosphate or acetyl, it is not specifically disclosed as “phosphoramidate” prodrug. D3 does not indicate that a phosphoramidate would be a preferred substituent at the 5′ position, nor does it contain any examples with a 5′ phosphoramidate. D3 specification describes preparation of various compounds falling within the Markush compound (XI) in table format on page 137. It is important to note here that there is no example of a compound wherein R7 is an alkyl group let alone the specific alkyl be “methyl” and R6 is fluoro. Not a single compound synthesized actually. It states that the compounds are synthesized according to published procedure, no actual process for synthesis mentioned. 6 compounds are reported for the anti-viral activity, no specific Anti-HCV activity reported for these compounds. Applicant also argued that in 2001, D3 described the generic formulae which encompass millions of permutations of substituents at various positions. However, the present invention is specifically directed to 5′-phosphoramidate compounds with a 2′-fluoro (down) – 2′-methyl (up) substitution pattern on the sugar ring, which is not even encompassed, let alone disclosed or exemplified, by the formulae in D3. For example, for Formula (XI) of D3, the R7 substituent definition does not include fluorine.
Among the many possible substituents, chlorine, bromine and iodine were the only halogens contemplated at this position, suggesting that fluorine was omitted purposefully. No other formula in D3 encompasses compounds with 2’-fluoro (down) – 2’-methyl (up) substitution, either. D3 also does not teach use of a phosphoramidate at the 5’-carbon of the sugar moiety. For example, D3 does not indicate that a phosphoramidate would be a preferred substituent at the 5’ position, nor does it contain any examples with a 5’ phosphoramidate. Thus, D3 fails to provide any guidance or suggestion as to compounds having a phosphoramidate linkage with an alanine isopropyl ester at the 5’-position as required by the instant claims. The disclosure of D3 fails in both aspects. D3 does not disclose or suggest the claimed compounds. In particular, D3 does not disclose the phosphoramidate moieties required by the present claims, nor does it suggest combining those phosphoramidates with the required nucleoside.

D4 (WO 2006/012078)
In 2006, D4 reports phosphoramidate derivative of only purines bases with methyl (up) and hydroxy (down) substitution pattern at 2’-position. Total 5 compounds are synthesized and no actual activity reported for any of the compounds. It provides one Markush structure which can have multiple billions of compounds. D4 is restricted to phosphoramidate derivative of only purines bases. Further, D4 is restricted to phosphoramidate derivative of only purines bases with methyl (up) and hydroxy (down) substitution pattern at 2’-position. D4 relates to structurally very different nucleoside compounds. D4 does not provide any teaching or disclosure for the phosphoramidates with pyrimidine base. It does not give any teaching for the compounds having fluoro (down) and methyl (up) substitution pattern at 2’-position.

D5 (WO 2007/020193)
In 2007, D5 reports nucleoside compounds which are substituted at 5’-position with either azido or alkynyl or -(Z)-CH=CHCl group. It provides one Markush structure which can generate multiple billions of compounds. D5 relates to nucleoside compounds which are substituted at 5’-position with either azido or alkynyl or -(Z)-CH=CHCl group. D5 also differ significantly in
respect of substitution at 2’-position as the definitions of R9 and R10 does not include methyl and fluoro at all in compound of general formula (I). Total 77 compounds are synthesized and Luciferase activity IC50 is given for 5 compounds. D5 relates to structurally very different nucleoside compounds. It does not give any teaching for the compounds having fluoro (down) and methyl (up) substitution pattern at 2’-position.

D6 (Murakami et al. 2007)

D6 describes the mechanism of activation of a cytosine-based nucleoside, as indicated clearly in the title of the paper. Besides a minor mention of adenine-based compounds (see Table 1), the paper is limited to the cytosine-based nucleoside. D6 is also absolutely silent on the topic of prodrugs. D6 is limited to the study of a specific cytidine-based nucleoside; it does not make conclusions that could necessarily be applied more generally to all “β-D-2’-deoxy-2’fluoro-2’C-methyl nucleosides. D6 discusses studies intended to address questions regarding certain aspects of the metabolism and mechanism of activation of β-D-2’-deox y-2’-fluoro-2’-C-methylcytidine. D6 discusses enzymatic studies focused on understanding the conversion of β-D-2’-deoxy-2’-fluoro-2’-C-methylcytidine to its monophosphate, diphosphate, and then triphosphate forms. (Id.) These in vitro/ex-vivo studies were performed using cloned human enzymes. (Id., pp. 503-504). D6 comes to exactly the opposite conclusion as that of the Opponent. Murakami et al. suggest that “PSI-6130 is worth of further investigation.” (In the last sentence of the paper). It is important to note that PSI-6130 has a cytosine base, and none has a uracil base, as required by the Gilead’s Claimed compounds. Further, as PSI-6130 is not a prodrug, if anything this would have suggested to an artisan that prodrug formation was unnecessary. Applicant argued that D6 reports the enzymatic studies focused on understanding the conversion of β-D-2’-deoxy-2’-fluoro-2’-C-methylcytidine and concluded that “PSI-6130 is worth of further investigation. It is important to note that PSI-6130 has a cytosine base not the uracil base as in claimed compounds. Further, as PSI-6130 is not a prodrug.
D7 (Landowski et al 2005)
D7 relates to floxuridine amino acid ester prodrugs compounds synthesized using aspartic acid, lysine, and proline amino acids. It reports the compounds for anti-cancer activity. D7 describes amino acid ester prodrugs of floxuridine for targeted delivery to the PEPT1 transporter. It is important to be note that Floxuridine has been used in treatment of colon carcinoma and hepatic metastases. Compounds of D7 are floxuridine amino acid ester prodrugs, and therefore differ significantly in structure compared to the Gilead’s claimed compounds. There is no disclosure or suggestion of compounds having 2'-fluoro (down), 2'-methyl (up) substitution of the ribose ring. D7 relates to structurally very different nucleoside moieties, different phosphoramidate groups, and different activity and its teaching is in no way applicable to the Gilead’s claimed HCV-antiviral nucleoside compounds. Prodrugs are prepared always at 3'-, or 5'- or 3' and 5'- positions. Prodrugs are always amino ester prodrugs not related to phosphoramidate at all.

D8 (McGuigan et al 1994)
D8 relates to “the simple nucleoside analogue” dideoxy uridine (ddU), which is structurally very different from the nucleoside moiety of Gilead’s compounds. Activity of the compounds is reported for HIV. D8 are ddU derivatives and do not have any substitution at the 2’-C and 3’-C positions. Only for 4 compounds with all compounds being 2’,3’-dideoxy uridine. Relates to 2’,3’-dideoxy uridine (ddU), and do not have any substitution at the 2’-C and 3’-C positions. It does not disclose the same chemical groups and substitution patterns as those of the instant claims (neither in the nucleoside moiety nor in the phosphoramidate moiety), D8 studied the activity of compounds for HIV using T-cells. These cells are not the same as those used in HCV research, and have different enzymes and relative amounts of those enzymes that metabolize the administered compounds. Results in a cell line used to test anti-HIV activity cannot be assumed to carry over to other cell lines used to test anti-HCV activity. D8 fails to disclose the specific phosphoramidate group present in the Gilead’s compounds. It reports HIV activity for 4 compounds with all compounds being 2’,3’-dideoxy uridine.
D9 (Kim et al 2004)
D9 describes 3’-azido-3’-deoxythymidine (AZT) amino acid phosphoramidates as antiviral, and/or anticancer agents. Activity reported for HIV. The compounds of D9 are 3’-azido-3’-deoxythymidine, and secondly these compounds are amino acid phosphoramidates that lack an aryloxy group. The compounds disclosed in D9 are 3’-azido thymidine analogues and are unsubstituted at 2’-position i.e. do not have any substitution at 2’-position. D9 compounds i.e. AZT (3’-azido-3’-deoxythymidine) differs significantly in structure compared to the nucleoside moiety of the Gilead’s claimed compound D9 fails to disclose the specific phosphoramidate group present in the Gilead’s claimed compounds. D9 does not disclose the same chemical groups and substitution patterns as those of the Gilead’s claimed compounds.

D10 (McGuigan et al 1996)
D10 is concerned with aryl phosphoramidate derivatives of d4T as possible anti-HIV agents. d4T is a 2’,3’-didehydro-2’,3’-dideoxythymidine analogue. The compounds of the present application differ significantly, in that they are 2’-deoxyuridine analogues having 2’-fluoro (down) – 2’-methyl (up) substitution and a uracil base. Different nucleoside moieties, different phosphoramidate groups, and different activity. D10 fails to disclose the specific phosphoramidate group present in the compounds of the present claims. An aryl moiety is very important for antiviral activity as evident from the data for the methyl (6a) and ethyl (6b) phosphates showing very little antiviral activity (page 1749). Restricted to only thymidine phosphoramidate. It gives the preparative method only for the synthesis of phosphoramidate derivatives of 2’,3’-Dideoxy-2’,3’-didehydrothymidine. Thus, the compounds of D10 fall short of disclosing or suggesting the claimed compounds with respect to both the nucleoside and phosphoramidate portions. D10 relates to compounds with structurally very different nucleoside moieties, different phosphoramidate groups, and different anti-viral activity compared to the compounds of the present claims, and its teaching is in no way transferable to the HCV-antiviral nucleoside analogues of the present claims. Finally,
D10 investigates HIV-antiviral activity, and has no relevance to HCV-antiviral activity. The cells tested are not the same as those used in HCV research, and have different enzymes and relative amounts of those enzymes that metabolize the administered compounds. Results in a cell line used in HIV research cannot be assumed to carry over to other cell lines used in HCV research. In summary, D10 does not provide the basis for an inventive step rejection for at least these reasons, and, therefore, cannot be used to support a rejection on inventive step. In addition, Applicant argued that in 1996, D10 reports aryl phosphoramidate derivatives of d4T as possible anti-HIV agents and d4T is a 2’,3’-didehydro-2’,3’-dideoxythymidine analogue. D10 is restricted to only thymidine phosphoramidate. The compounds of D10 fall short of disclosing or suggesting the claimed compounds with respect to both the nucleoside and phosphoramidate portions. In summary, it relates to different nucleoside moieties, different phosphoramidate groups, and different activity.

D11 (Balzarini et al 1996)

D11 compound relates to the field of antiretroviral nucleotide prodrugs. D11 describes the prodrug of 2’,3’-dideoxy-2’,3’-didehydrothymidine-5’-monophosphate (d4T-MP) as an anti-HIV agents designated as So324. D11 studied the activity of compounds for HIV-1 and HIV-2, feline immunodeficiency virus (FIV), visna virus, and MSV using CEM TK+ cells. D11 studied the activity of compounds for HIV-1 and HIV-2, feline immunodeficiency virus (FIV), visna virus, and MSV using CEM TK+ cells. CEM TK+ cells are not the same as those used in HCV research, and have different enzymes and relative amounts of those enzymes that metabolize the administered compounds. D11 fails to disclose the specific phosphoramidate group present in the Gilead’s claimed compounds. D11 does not disclose the same chemical groups and substitution patterns as those of the Gilead’s claimed compounds. In addition, Applicant argued that in 1996, D11 describes the prodrug of 2’,3’-dideoxy-2’,3’-didehydrothymidine-5’-monophosphate (d4T-MP) as an anti-HIV agent designated as So324. D11 studied the activity of compounds for HIV-1 and HIV-2, feline immunodeficiency virus (FIV), visna virus, and MSV using CEM
TK+ cells. CEM TK+ cells are not the same as those used in HCV research, and have different enzymes and relative amounts of those enzymes that metabolize the administered compounds. D11 does not disclose the specific phosphoramidate group, the same chemical groups and substitution patterns present in the Gilead’s claimed compounds.

D12 (Saboulard et al 1999)-
D12 reports the activation pathway of a series of phosphoramidate prodrugs of d4TMP and AZTMP in different biological media. D12 reports anti-HIV activity of the 2’,3’-didehydro-2’,3’-dideoxythymidine(d4T) and 3’-azido-2’,3’-dideoxythymidine (AZT) triesters. D12 studied the activity of compounds for HIV using CEM TK+ cells. The cells used for HIV activity have different enzymes and relative amounts of the enzymes needed to metabolize the administered compounds. D12 fails to disclose the specific phosphoramidate group present in the Gilead’s claimed compounds. D12 does not disclose the same chemical groups and substitution patterns as those of the Gilead’s claimed compounds.

D13 (Iyer et al 2000)
D13 reports the synthesis and anticancer activity of a series of AZT phosphoramidate monoesters containing amino acid methyl ester (3a-11a) and N-alkyl amide (3b-11b, 9c-9f) moieties. Activity reported for cancer. AZT is a 3’-azido analogue which is unsubstituted in the 2’-position. As discussed in respect of other references, AZT (3’-azido-3’-deoxythymidine) differs significantly in structure compared to the nucleoside moiety of the Gilead’s claimed compound. D13 fails to disclose the specific phosphoramidate group present in the Gilead’s claimed compounds. D13 does not disclose the same chemical groups and substitution patterns as those of the Gilead’s claimed compounds. D13 reports that anti-cancer activity of amino acid phosphoramidate is enhanced by an aromatic amino acid side chain preferably L-indolyl methyl group [compound 9b, table-2].

D14 discloses 4’-azido, 2’-hydroxy pronucleotides compounds. Activity reported for 28 compounds with all being 4’-azidouridine compounds. D14
describes the particular compounds studied therein as having “a bulky azido group at the 4’-position”. D14 does not provide any disclosure or suggestion of compounds lacking a 4’-azido group. D14 provides no disclosure or suggestion of compounds having 2’-fluoro (down), 2’-methyl (up) substitution of the deoxyribose ring. D14 does not talk about any other phosphoramidate except that of 4’-azidouridine. D14 reported an increase of in vitro potency of a 1-naphthyl-phosphoramidate analogue compared to the corresponding phenyl derivative while investigating the anticancer activity of BVdU phosphoramidates. D14 have reported that unexpected correlation was found between amino acid and ester function and while the L-phenylalanine derivative was substantially inactive as a benzyl ester (23), the corresponding ethyl ester (22) showed a significantly increased antiviral activity. The most active compound prepared in the series was the 1-naphthyl L-alanine benzyl ester phosphoramidate with an EC50 of 0.22 μM in the replicon assay. Twenty-two phosphoramidates were prepared, including variations in the aryl, ester, and amino acid regions. Perrone only describes the synthesis of phosphoramidates of 4’-azidouridine. D14 clearly warn that “a separate ProTide motif optimization process is needed for each nucleoside analogue versus a given target” (at p. 1843, left column). D14 reports that “quite distinct SARs emerged from this family versus HCV as compared to our prior studies in other families” (at p. 1843, right column). D14 teaches that conclusions drawn from data on the disclosed 4’-azido, 2’-hydroxy pronucleotides cannot be applied to other systems with any expectation of success. Rather, D14 makes clear that ProTide systems are unpredictable and must be painstakingly researched and modified for each nucleoside analogue. Thus, the teaching of D14 is specific to the 4’-azido, 2’-hydroxy nucleosides disclosed, and cannot be applied to other systems with any expectation of success. In fact, at the time, no direct-acting antiviral NS5B inhibitors or prodrugs thereof were on the market for treating HCV and, in particular, no prodrugs of nucleoside/nucleotide analogue inhibitors of HCV NS5B. At the time the application was filed, there were no nucleotide analogs with a phosphoramidate moiety on the market as an antiviral, let alone as an anti-HCV therapeutic. In contrast, nucleoside
inhibitors having other types of prodrug groups were in clinical trials as potential anti-HCV therapeutics. For example, NM283, a prodrug of 2'-C-methyl cytidine having a valine ester 3’ prodrug moiety, was “so far the only inhibitor of the NS5B polymerase with demonstrated antiviral activity in the clinics” {De Francesco & Migliaccio, Nature, 436, 18 August 2005, 953-960 at 955}. Another compound, R1626, was reported in October 2006 to have promising results in a Phase IB clinical trial {Roberts et al., (2006) AASLD Abstracts, Hepatology 692A, LB2 }.

NM283

R1626

A person of ordinary skill in the art might have looked to these compounds as promising starting points for further research, but would not have looked to D14. For the sake of argument, even if a person of ordinary skill in the art would have looked to D14, he would clearly have recognized the limitations of its teachings as discussed above. Applicant also argued that in 2007, D14 reports 4'-azido, 2'-hydroxy pronucleotides compounds, and therefore differ significantly in structure compared to the compounds of the present invention. There is no disclosure or suggestion of compounds lacking a 4'-azido group, and no disclosure or suggestion of compounds having 2'-fluoro (down), 2'-methyl (up) substitution of the ribose ring. It is therefore clear that Perrone et al. cannot be said to disclose or suggest the compounds presently claimed. Further, D14 reports that 1-naphthyl phosphoramidate has increased potency as compared to corresponding phenyl phosphoramidate (in anti-cancer assay). The most active compound as reported in D14 was 1-naphthyl L-alanine benzyl ester phosphoramidate. D14 clearly warn that “a separate ProTide motif optimization process is needed for each nucleoside analogue versus a given target”. (at p. 1843, left column). A few paragraphs later, the authors point out again that “quite distinct SARs emerged from this family versus HCV as compared to our prior studies in other families” (at p. 1843, right column). In addition, D14
describe the particular compounds being studied as having “a bulky group (azido) at the 4'-position” (at 1841, left column), implying that this substituent could have steric properties important to the synthesis and biological behavior of this compound, and that removing it would likely result in significant changes in structure-property relationships. Thus, D14 teaches that conclusions drawn from data on the disclosed 4’-azido, 2’-hydroxy pronucleotides cannot be applied to other systems with any expectation of success. Rather, D14 makes clear that ProTide systems are unpredictable and must be painstakingly researched and modified for each nucleoside analogue. In other words, for all the aforementioned reasons, successfully applying a ProTide system to any given nucleoside analogue is far from obvious. Furthermore, at the time the instant application was filed, there was no basis to believe that the prodrug moieties disclosed in D14 would lead to a successful anti-HCV compound. In fact, at the time, no direct-acting antiviral NS5B inhibitors or prodrugs thereof were on the market for treating HCV and, in particular, no prodrugs of nucleoside/nucleotide analogue inhibitors of HCV NS5B. Furthermore, at the time the application was filed, there were no nucleotide analogs with a phosphoramidate moiety on the market as an antiviral, let alone as an anti-HCV therapeutic. In contrast, nucleoside inhibitors having other types of prodrug groups were in clinical trials as potential anti-HCV therapeutics. For example, NM283. For the sake of argument, even if a person of ordinary skill in the art would have looked to D14, he would clearly have recognized the limitations of its teachings. As noted above, the teaching of D14 is specific to the 4’-azido, 2’-hydroxy nucleosides disclosed, and cannot be applied to other systems with any expectation of success. Rather, as made clear in D14 itself, ProTide systems are unpredictable and must be painstakingly researched, modified and specifically adapted to each separate nucleoside analogue D14 does not provide the basis for an inventive step rejection for at least these reasons.

D15 (Cahard et al 2004)

D15 is a mini-review paper and primarily discusses nucleoside analogues AZT and d4T both of which are thymidine analogues and differ significantly
in structure compared to the nucleoside moiety of Gilead’s compounds. Activity is reported for HIV. d4T is a 2',3'-didehydro-2',3'-dideoxy analogue, while AZT is a 3'-azido analogue which is unsubstituted in the 2'-position. D15 investigates the activity of compounds for HIV using CEM TK+ cells (at page 376). These cells are not the same as those used in HCV research, and have different enzymes and relative amounts of those enzymes that metabolize the administered compounds. Thus, has no relevance to HCV-antiviral activity. D15 fails to disclose the specific phosphoramidate group present in the Gilead’s claimed compounds. It reports that Alanine remains a good choice of amino acid, although the achiral a,a-dimethylglycine is a good alternative. Concludes that an aryloxy phosphoramidate approach “works poorly for AZT” (page 380, first left column) but well for d4T, and investigates structure-activity relationships (SARs) for d4T. It concludes that phosphoramidates with 2-naphthyloxy and benzylxy esters are best in the case of d4T (at page 376). D15 does not disclose the same chemical groups and substitution patterns as those of the Gilead’s claimed compounds. Activity is highly dependent on the chemistry at the phosphoramidate and the nucleoside (e.g. the 2'-C and 3'-C positions of the sugar, as well as the base). Changes in activity of one system, such as the d4T system in D15, cannot be expected to translate to other nucleotide analogue systems such as those of the Gilead’s claimed compounds. This is clearly illustrated by the teaching of D15 itself, which concludes that the aryloxy phosphoramidate approach “works poorly for AZT” (at page 380, first column). D15 concludes that the aryloxy phosphoramidate approach “works poorly for AZT” (see page 380, first column) but well for d4T, and investigates SARs for d4T. It is concluded that 2-naphthyloxy and benzylxy phosphoramidates are best in the case of d4T (at page 376). Like D8, D15 investigates HIV-antiviral activity, and has no relevance to HCV-antiviral activity. D15 fails to disclose the specific phosphoramidate group present in the compounds of the present claims. Thus, the compounds of D15, similar to the compounds in the references discussed above, fall short on both portions of the compound—both the nucleoside portion and on the phosphoramidate portion. As has already been discussed by reference to
both Perrone et al. and McGuigan et al (1994), pronucleotidie systems are unpredictable and must be painstakingly researched, modified and specifically adapted to each separate nucleoside analogue. Activity is highly dependent on the chemistry at the phosphoramidate and the nucleoside (e.g. the 2'-C and 3'-C positions of the sugar, as well as the base). Changes in activity of one system, such as the d4T system in D8, cannot be expected to translate to other nucleotide analogue systems such as those of the instant claims. This is clearly illustrated by the teaching of D15 itself, which concludes that the aryloxy phosphoramidate approach “works poorly for AZT” (at page 380, first column).

D16 (WO 2006/067606)

D16 relates to nucleoside and nucleotide analogues incorporating a non-natural nucleobase i.e. a monohalogenated alkynyl or dihalogenated alkenyl substituted uracil. D16 nucleoside compounds are always monosubstituted at the 2’-position and cannot have the 2’-fluoro (down) – 2’-methyl (up) substitution pattern of the Gilead’s claimed compounds. Phosphoramidates are not contemplated or much less mentioned in D16. In particular, R4 does not include a phosphoramidate group; instead, R4 is selected only from among hydroxyl, -O-alkyl, -O-CO-alkyl, -O-phosphate, -O-diphosphate, -O-triphosphate and -O-phosphonate. Scope of D16 is restricted to only uridine derivative of formula (I) which does not have the unique substitution of 2’-methyl and 2’-fluoro. Example section provides the preparation of monohalogenated and dihalogenated uridine derivatives depicted in schemes of the application. Applicant also argued that in 2006, D16 reports nucleoside and nucleotide analogues incorporating a non-natural nucleobase i.e. a monohalogenated alkynyl or dihalogenated alkenyl substituted uracil which are monosubstituted at the 2’-position.

D17 (WO 02/08241)

D17 is concerned with a screening method for identifying a methoxyphosphonate nucleotide analogue prodrug conferring enhanced activity in a target tissue and the method is primarily concerned with screening for HIV-antiviral activity. Therefore no synthetic scheme or process is described. The identified and preferred compound of D17 is an
adenine (i.e. purine nucleobase) derivative; it does not even have a pentose ring let alone the specific substituted pentose ring of the Gilead’s Claimed compounds.

Further, it is a methoxyphosphonate, not a phosphoramidate compound. D17 also discloses compounds having the general formula (3)

\[
\begin{align*}
\text{B} \rightarrow \text{E} \rightarrow \text{O} \rightarrow \text{R}^1 \\
\text{R}^2
\end{align*}
\]

(3)

there is not a single preferred or exemplified compound for the general formula (3) wherein E represents a ribofuranose ring. Even if one substitutes E as

\[
\begin{align*}
\text{R}^7 \rightarrow \text{R}^7
\end{align*}
\]

2'-C can only ever be mono-substituted (and also cannot be a fluoro group), or has a double bond with 3'-C. D17 relates to compounds which are structurally remote from the Gilead’s claimed compounds. The in vitro anti-HIV-1 activity and cytotoxicity in MT-2 cells and stability inhuman plasma and MT-2 cell extracts of GS-7340 (freebase) and tenofovir disoproxil fumarate (TDF), are reported in example 9 (Table 1). D17 does not give any data or studies of a single compound of general formula (3) having phosphoramidate group as that of GS-7171 wherein E is a sugar moiety.

D18 (Jones et al 1995)

D18 is a review paper capturing different literatures known in the field of nucleotide prodrugs. D18 fails to provide any teaching for preparing a
prodrug containing the phosphoramidate moiety present in Gilead’s claimed compounds let alone in combination with the specific nucleoside moiety. Paras 1 & 2 of page 4 of D18 highlighted by the Opponent, are very general statements revealing the disadvantages of nucleotide and making nucleotide prodrugs. It discloses the following compounds:

![Chemical structures](image)

Applicant also argued Opponent relied upon figure-1, item 9 and figure-5 in D18. D18 is a mini review paper of 1995 capturing different literatures known in the field of nucleotide prodrugs. Para 1 on page 2 of D8 highlighted by the Opponent, are very general statements revealing the therapeutic potential of nucleoside and nucleotide analogues for treatment of viral diseases and cancer. The compound indicated by the Opponent reproduced herein below is structurally significantly different from the Gilead’s claimed compounds.
Further, other paras highlighted by the opponent are also general statements revealing rationale of making nucleotide prodrugs and its intracellular mechanism. D18 fails to provide any teaching for preparing a prodrug containing the phosphoramidate moiety present in Gilead’s claimed compounds let alone in combination with the specific nucleoside moiety D19 D20 (WO 99/43691 or US 6348587)

D19 provides 2'-fluoronucleosides of several general formulae.

There is no specific teaching or disclosure for a phosphoramidate group at R2, let alone the specific phosphoramidate moiety of the present invention. D19 does not disclose or suggest the particular nucleoside group with a 2'-fluoro (down) – 2'-methyl (up) substitution pattern. No exemplified compound with phosphoramidate group or specific phosphoramidate moiety D19 provides a general definition of R2 as “stabilized phosphate prodrug”. In addition, Applicant also argued that its PCT counterpart i.e., D19 has been cited in the other pre grant opposition proceedings filed by Natco Pharma and Optimus Pharma. D20 provides 2'-fluoronucleosides of several general formulae having following structure:
The compounds of the present invention have a 2'-fluoro (down) – 2'-methyl (up) substitution pattern. This substitution pattern is not disclosed in D20. Furthermore, there is no specific teaching or disclosure for a phosphoramidate group at R2, let alone the specific phosphoramidate moiety of the present invention. The disclosure of D20 thus fails in at least two respects. First, D20 does not describe the phosphoramidate group claimed. Second, D20 does not disclose or suggest the particular nucleoside group with a 2'-fluoro (down) – 2'-methyl (up) substitution pattern, let alone in combination with the claimed phosphoramidate moiety.

D21 Clark et al. 2005

D21 describes the synthesis and biological activity of 2'-deoxy-2'fluoro-2'fluoro-2'-C-methyl cytidine as a potent anti-HCV agent. D21 does not disclose a compound as presently claimed. It does not even mention phosphoramidates, let alone suggest the combination of the particular phosphoramidate group and the particular nucleoside group claimed. Inventors reported that the Compound “2'-deoxy-2'-fluoro-2'-C-methyluridine” (compound 9) demonstrated no activity or cytotoxicity in any assay. Inventors also reported that the Compound “2'-deoxy-2'-fluoro-2'-C-methylcytidine” (compound 1) demonstrated activity in HCV replicon assay. Applicant also argued that D21, describes the synthesis and biological activity of 2'-deoxy-2'fluoro-2'fluoro-2'-C-methyl cytidine as a potent anti-HCV agent. D21 does not disclose a compound as Gilead’s claimed compound. It reported that the Compound “2'-deoxy-2'-fluoro-2'-C-methyluridine” (compound 9) demonstrated no activity or cytotoxicity in any assay and the Compound “2'-deoxy-2'-fluoro-2'-C-methylcytidine”
(compound 1) demonstrated some activity in HCV replicon assay. Clark et al. does not teach or suggest any prodrug let alone the phosphoramidate prodrug claimed in present application.

**D22 (WO 2001/90121)**

D22 describes 18 Markush compound with generic formulae in which encompass millions of permutations of substituents at various positions. D22 reports activity for Flavivirus or Pestivirus infection. For formula (XI) of D22, the R7 substituent definition does not include fluorine. Among the many possible substituents, chlorine, bromine and iodine were the only halogens contemplated at this position, suggesting that fluorine was omitted purposefully. No other formula in D22 encompasses compounds with 2'-fluoro (down) – 2'-methyl (up) substitution, either. There is no generalized Scheme even to make the said class of compounds. No motivation to even pick this compound as of the date of filing of the instant application. It also does not teach use of a phosphoramidate at the 5'-carbon of the sugar moiety. R1 can be hydrogen or monophosphate or diphosphate or triphosphate or acetyl, it is not specifically disclosed as “phosphoramidate” prodrug. It does not indicate that a phosphoramidate would be a preferred substituent at the 5’ position, nor does it contain any examples with a 5’ phosphoramidate. D22 specification describes preparation of various compounds falling within the Markush compound (XI) in table format on page 141. It is important to note here that there is no example of a compound wherein R7 is an alkyl group let alone the specific alkyl be “methyl” and R6 is fluoro. Not a single compound synthesized actually. It states that the compounds are synthesized according to published procedure, no actual process for synthesis mentioned. Applicant also argued that in 2001, D22 described the generic formulae which encompass millions of permutations of substituents at various positions. However, the present invention is specifically directed to 5’-phosphoramidate compounds with a 2’-fluoro (down) – 2’-methyl (up) substitution pattern on the sugar ring, which is not even encompassed, let alone disclosed or exemplified, by the formulae in D22. For example, for Formula (XI) of D22 as highlighted by the Opponent, the R7 substituent definition does not include fluorine. Among
the many possible substituents, chlorine, bromine and iodine were the only halogens contemplated at this position, suggesting that fluorine was omitted purposefully. No other formula in D22 encompasses compounds with 2'-fluoro (down) – 2'-methyl (up) substitution, either. D22 also does not teach use of a phosphoramidate at the 5'-carbon of the sugar moiety. For example, it does not indicate that a phosphoramidate would be a preferred substituent at the 5’ position, nor does it contain any examples with a 5’ phosphoramidate. Thus, D22 fails to provide any guidance or suggestion as to compounds having a phosphoramidate linkage with an alanine isopropyl ester at the 5'-position as required by the instant claims. The disclosure of D22 fails in both aspects. D22 does not disclose or suggest the claimed compounds. In particular, D22 does not disclose the phosphoramidate moieties required by the present claims, nor does it suggest combining those phosphoramidates with the required nucleoside.

D23 Sofia et al 2007

As alleged by the Opponent, D23 can be referred to in order to substantiate its arguments relating to inventive step. D23 cannot be considered as a valid prior art as it is published after the priority date (March 30, 2007) of the present application i.e. September 2007. Without prejudice, it is submitted that a person skilled in the art could not have arrived at the claimed compounds with the relied teachings of D23. There is literally no possibility in D23 of determining critical substituents. The skilled person is obliged to determine the most likely possibilities of the undefined R1-R3 substituents. While D23 (the SAR results in table 1-4) indicates that structural variation occurs for R1-R3 there is no information at all as to which possibilities are encompassed and whether or not this includes alkyl or phenyl. Further, Applicant submits that every known variation of group corresponding to R1-R3 in D23 would lead the skilled person to believe that different moieties are the best candidates. Also, D23 made clear that modifications at R1-R3 may result in significant differences in activity and toxicity of the compounds. D23 shows that structural variation may lead to pronounced differences in activity, compounds indicated in table 3 as being more active may be more toxic according to table 5. Each of the moieties R1-R3 affects the potency
and toxicity to a different extent. The skilled person could not simply select a best possible combination of substituents as the tables in Sofia et al. refer to individual compounds and do not support or suggest any additional mixing or shuffling of substituents. It is not therefore possible to deduce from D23 which specific values of R1-R3 have which properties. Additionally, Applicant argued that D23 and D24 cannot be considered as a valid prior art documents as these are published after the priority date (March 30, 2007) of the present application i.e. September 2007 and October 12, 2007 respectively. Without prejudice, it is submitted that a person skilled in the art could not have arrived at the claimed compounds with the relied teachings of D23. There is literally no possibility in D23 of determining critical substituents. The skilled person is obliged to determine the most likely possibilities of the undefined R1-R3 substituents. While D23 (the SAR results in table 1-4) indicates that structural variation occurs for R1-R3 there is no information at all as to which possibilities are encompassed and whether or not this includes alkyl or phenyl. Further, Applicant submits that every known variation of group corresponding to R1-R3 in D23 would lead the skilled person to believe that different moieties are the best candidates. Also, D23 made clear that modifications at R1-R3 may result in significant differences in activity and toxicity of the compounds. D23 shows that structural variation may lead to pronounced differences in activity, compounds indicated in table 3 as being more active may be more toxic according to table 5. Each of the moieties R1-R3 affects the potency and toxicity to a different extent. The skilled person could not simply select a best possible combination of substituents as the tables in D23 refer to individual compounds and do not support or suggest any additional mixing or shuffling of substituents. It is not therefore possible to deduce from D23 which specific values of R1-R3 have which properties. Further, Applicant argued that Opposition division of EPO in its decision (Exhibit D8 submitted and relied upon by present opponent) has rejected D23 even for inventive step analysis. The learned Controller may refer to paras 33, 33.1, 33.2, 35.3 & 36 of decision by EPO Opposition division with respect to these documents.
D24 (Ma et al 2007)
As alleged by the Opponent, D24 can be referred to in order to substantiate its arguments relating to inventive step. D24 cannot be considered as a valid prior art as it is published after the priority date (March 30, 2007) of the present application i.e. October 12, 2007. Without prejudice, it is submitted that D24 does not disclose a compound as presently claimed. It does not even mention phosphoramidates, let alone suggest the combination of the particular phosphoramidate group and the particular nucleoside group claimed. In addition, Applicant argued that D24 cannot be considered as a valid prior art document as these are published after the priority date (March 30, 2007) of the present application i.e. September 2007 and October 12, 2007 respectively. Without prejudice, it is submitted that D24 does not disclose a compound as presently claimed. It does not even mention phosphoramidate, let alone suggest the combination of the particular phosphoramidate group and the particular nucleoside group claimed. Further, Applicant argued that even the European Patent Office has opined in its decision that presently claimed invention is non-obvious in light of D24 (D6 of EPO decision). The learned Controller may please refer to para 35.3 of the EPO decision in this regard.

D25 (WO 2004/002999)
Opponent refers to compound of formula (IV) of D25.

![Compound (IV)](image1)

**Base (F)**

wherein for Base (B), $W^4$ cannot be CH if $W^1$, $W^2$ and $W^3$ are N;

wherein for Base (E), (F), (K), (L), (W) and (X), $W^4$ cannot be CH if $W^1$ is N:
The allegations made in respect of D25 are totally incorrect, misleading and should be rejected. The generic formulae in D25 encompass millions of permutations of substituents at various positions. However, the present invention is specifically directed to 5'-phosphoramidate compounds with a 2'-fluoro (down) – 2'-methyl (up) substitution pattern on the sugar ring, which is not even encompassed, let alone disclosed or exemplified, by the formulae in D25. Particularly, in compound of formula (IV) (on page 19) alleged by opponent taking base as “(F)”, the definition of base running from page 20 to 26 does not encompass the uracil base as of the presently claimed compounds of Gilead. The definition of various substituents on said pages and also in claims in respect of formula (IV) in combination with base (F) does not cover or include uracil base. In this regard, please note the definition of W1 and W4 read with proviso on page 26 of D25. Further, D25 also does not teach use of a phosphoramidate at the 5'-carbon of the sugar moiety. R1 in the compound (IV) highlighted by the opponent can be selected from a laundry list of substituents. For example, R1 can be hydrogen or monophosphate or diphosphate or triphosphate or stabilized phosphate, it is not specifically disclosed as “phosphoramidate” prodrug. D25 also does not teach use of a phosphoramidate at the 5'-carbon of the sugar moiety. For example, D25 does not indicate that a phosphoramidate would be a preferred substituent at the 5' position, nor does it contain any examples with a 5' phosphoramidate. D25 does not disclose or suggest the claimed compounds. In particular, it does not disclose the phosphoramidate moieties required by the present claims, nor does it suggest combining those phosphoramidates with the required nucleoside. Thus, D25 fails to provide any guidance or suggestion as to compounds.
having a phosphoramidate linkage with an alanine isopropyl ester at the 5’-position as required by the instant claims. Applicant also argued in 2004, D25 disclosed various generic compounds which encompass millions of permutations of substituents at various positions. However, the present invention is specifically directed to 5’-phosphoramidate compounds with a 2’-fluoro (down) – 2’-methyl (up) substitution pattern on the sugar ring, which is not even encompassed, let alone disclosed or exemplified, by the formulae in D24. Particularly, in compound of formula (IV) (on page 19) alleged by opponent taking base as “(F)”, the definition of base running from page 20 to 26 does not encompass the uracil base as of the presently claimed compounds of Gilead. The definition of various substituents on said pages and also in claims in respect of formula (IV) in combination with base (F) does not cover or include uracil base. In this regard, Applicant would like to draw the Controller’s attention towards the definition of W1 and W4 read with proviso on page 26 of D25. Further, D25 also does not teach use of a phosphoramidate at the 5’-carbon of the sugar moiety. R1 in the compound (IV) highlighted by the opponent can be selected from a laundry list of substituents. For example, R1 can be hydrogen or monophosphate or diphosphate or triphosphate or stabilized phosphate, it is not specifically disclosed as “phosphoramidate” prodrug. D25 also does not teach use of a phosphoramidate at the 5’-carbon of the sugar moiety. For example, it does not indicate that a phosphoramidate would be a preferred substituent at the 5’ position, nor does it contain any examples with a 5’ phosphoramidate. An inventive step rejection of the present claims can be established only by showing cited references that give a person of ordinary skill in the art sufficient reason, motive and clear direction to combine (A) the particular phosphoramidate at the 5’-position and (B) the particular nucleoside of the instant application (that is, both the sugar group with the particular substituents thereon, and the particular base) and also by showing that the cited references enable the skilled artisan to make the combination. The disclosure of D25 fails in both aspects. D25 does not disclose or suggest the claimed compounds. In particular, D25 does not disclose the
phosphoramidate moieties required by the present claims, nor does it suggest combining those phosphoramidates with the required nucleoside.  

**D26 (WO2006/012440)**

In 2006, D26 provides a method for preparing the anti-HCV nucleosides containing the 2’-deoxy-2’-fluoro-2’-C-methyl-[β]-D-ribofuranosyl nucleosides from a preformed, preferably naturally-occurring, nucleoside.  

D26 also provides a process for preparing a 2-deoxy-2-fluoro-2-methyl-D-ribonolactone derivative and conversion of the lactone to nucleosides with potent anti-HCV activity, and their analogues.  

D26 does not disclose a compound as presently claimed. It does not even mention phosphoramidates, let alone suggest the combination of the particular phosphoramidate group and the particular nucleoside group claimed. It only provides the preparation of 2’-deoxy-2’-fluoro-2’-C-methyl-[β]-D-ribofuranosyl nucleosides.  

**D27 (WO 2004096286)**

D27 provides phosphonate analogs of antiviral compounds. D27 relates to a conjugate comprising an antiviral compound linked to one or more phosphonate groups or pharmaceutically acceptable salt or solvate thereof.  

D27 provides conjugates of compounds 1-108 provided from page 16 to 28 of specification. Opponent highlights the compound 104, the generic formulae of which encompass hundreds of permutations of substituents at various positions. For instance, Opponent has selected X106 as “O” out of 5 substituents, X107 as “uracil” out of 36 various substituents, X108 as “F” and “OH” out of 12 substituents, X109 as C1-8 alkyl out of 7 substituents.  

There is no exemplified compound with such combination of substituents as selected by the Opponent. D27 does not disclose even a single compound with 2’-fluoro (down) and 2’-methyl (up) substitution at deoxyribose sugar ring of nucleoside moiety containing uracil base. The present invention is specifically directed to 5’-phosphoramidate compounds with a 2’-fluoro (down) –2’-methyl (up) substitution pattern on the sugar ring, which is not disclosed or exemplified, by the formulae in D27. Further, the compound considered by the Opponent on page 21 of opposition petition for comparison purpose is not disclosed or enabled in D27, it is a hypothetical
compound. Even if the opponent’s hypothetical compound is compared with the claimed compound of present invention, the compound of the present invention is structurally different from the opponent’s hypothetical compound as shown above. As regards example 259, compound of formula MBF from page 525 of D27.

Essentially, entire argument of the Opponent was based on the premise that A0 can be A3. A0 is not equivalent to A3 and if the appropriate definition of A0 is to be considered then altogether different compound will emerge. D27 provides a compound of formulae 501-561 from page 3-11, which is substituted with one or more group A0. A0 is defined as A1, A2, and W3. The same is reiterated on page 14, 69, 90, 92, 95. Definition of “linker from page 47 of WO’286 states “linkers include portions of substituents A1 and A3, which include moieties such as: …………..and caproamide”. D27 on page 71-74 defines A1 of the following formula
A0 is never A3 and A0 can be A1. Further, A3 is part of A1 in all the formulae of A1 mentioned on page 71-74 of D27. It is submitted that A3 is always has to be read as connected to the structure of A1 not in isolation. Further, on page 90 D27 provides a compound of formula

\[ \text{[DRUG]} - (\text{A}^0)_{mn} \]

Wherein drug is a compound of formula 501-569 and A0 is A1, A2, and W3. Further, on page 92 D27 defines A0 is A1. Accordingly, A0 is never equivalent to A3, but A1, A2 and W3. Further, opponent is trying to project A1 as A3, which is not at all the case as per the disclosure of D27. Further, D27 mentions on page 141, that the linker can include all or a portions of the group A0, A1, A2, or W3. Further, it states on page 143 that the linking group or linker is attached to the phosphonate group through a carbon atom of the linker. There are numerous examples in each table for nucleus, linking group as well as prodrugs groups. Opponent has not indicated any specific group or compound but has referred to table 1.1 for nucleus and table 10.1 for linking group. Table 1.1 on page 527 discloses the following nucleus:
Table 1.1 of D27 does not disclose or teach a “nucleoside” containing natural nitrogenous base let alone the nucleoside with uracil base. As regards table 10.1 to 10.19 for linking moiety, it is submitted that there are 159 kinds of Markush structures for linking moieties described in table 10.1 to 10.19, opponent has not specifically alleged as to which Markush structure of linking moiety would lead to the presently claimed compound. Even though opponent creates a hypothetical compound by misreading the definitions mentioned in D27, opponent admitted that the linker as present in presently claimed compounds is missing in D27. As regards Pd1 and Pd2, Applicant submits that the Pd1 and Pd2 are to be read and are relevant only in conjunction with Markush formula MBF, nucleus and linking groups. The Markush formula MBF in connection with nucleus as mentioned on table 1.1 gives rise to altogether different compounds and further when combined with linking groups of 159 Markush structure from table 10.1, will generate totally different compounds. After all these arguments, opponent admitted that the compounds of the present invention differ in respect of linker as the linker in the compounds of D27 contains phosphorus-carbon bond (P-C) in
contrast to phosphorus-oxygen bond. As regards the compound 104, the generic formulae of which encompass hundreds of permutations of substituents at various positions. For instance, Opponent has selected X106 as “O” out of 5 substituents, X107 as “uracil” out of 36 various substituents, X108 as “F” and “OH” out of 12 substituents, X109 as C1-8 alkyl out of 7 substituents. There is no exemplified compound with such combination of substituents as selected by the Opponent. D27 does not disclose even a single compound with 2’-fluoro (down) and 2’-methyl (up) substitution at deoxyribose sugar ring of nucleoside moiety containing uracil base. The present invention is specifically directed to 5’-phosphoramidate compounds with a 2’-fluoro (down) –2’-methyl (up) substitution pattern on the sugar ring, which is not disclosed or exemplified, by the formulae in D27. Further, the compound considered by the Opponent on page 20 of opposition petition for comparison purpose is not disclosed or enabled in D27, it is a hypothetical compound. Even if the opponent’s hypothetical compound is compared with the claimed compound of present invention, the compound of the present invention is structurally different from the opponent’s hypothetical compound. Applicant also argued Opponent in their opposition petition alleged that D27 discloses conjugates of compounds of formula 1-108. Opponent has indicated particularly compound of formula 104 and referred to formula of A3 from page 81 of D27 for comparing the claimed compound of present invention i.e. sofosbuvir, vis-à-vis compound of A-13 which is a hypothetical compound not disclosed in D27. Opponent alleged that the compounds of D27 only differs in respect of linker. During the oral hearing, Opponent raised altogether new arguments with respect to D27. Opponent referred to example 259, compound of formula MBF from page 525 of D27.

\[
\begin{align*}
\text{MBF} & \\
\text{Sc} & \quad \text{Lg} \\
Pd & \quad \text{Pd}^2 \\
Pd & \quad \text{Pd}^1 \\
O & \\
\end{align*}
\]
Opponent referred to compounds of Table 1.1 for nucleus (Sc), table 10.1 for linking group (Lg), and table 20.12 & 20.36 for the prodrug groups (Pd1, Pd2). Opponent alleged that by the combined reading of the said referred embodiments of D27, one can arrive at compounds of present invention. Alternatively, opponent took a stand that if one extrapolates the teachings of D27, one can derive the presently claimed compounds. Further, Opponent alleged that D27 discloses similar structure and similar preparation can be made. In response, the Applicant respectfully disagrees with the Opponents’ characterization of the pending claims as well as the reference relied upon. The allegations made in respect of D27 are totally incorrect, misleading and should be rejected. Essentially, entire argument of the Opponent was based on the premise that A0 can be A3. As demonstrated during the oral hearing A0 is not equivalent to A3 and if the appropriate definition of A0 is to be considered then altogether different compound will emerge. Please refer the following analysis:

D27 provides a compound of formulae 501-561 from page 3-11, which is substituted with one or more group A0. A0 is defined as A1, A2, and W3. The same is reiterated on page 14, 69, 90, 92, 95. WO’286 provides conjugates of compounds 1-108 provided from page 16 to 28 of specification and defines A0 is A1 on page 28. Definition of “linker from page 47 of D27 states “linkers include portions of substituents A1 and A3, which include moieties such as: ...............and caproamide”. D27 on page 69 describes that conjugate is compound that is substituted with one or more phosphonate groups either directly or indirectly through a linker and that is optionally substituted with one or more groups A0. Page 71-74 of D27 defines A1. It is clear from the definitions and structures of A1 that A0 is never A3 and A0 can be A1. Further, A3 is part of A1 in all the formulae of A1 mentioned on page 71-74 of D27. It is submitted that A3 is always has to be read as connected to the structure of A1 not in isolation. Opponent erroneously refers to structure of A3 on page 81 without context or relevance and substitutes the structure of A3 from page 81 in compound of formula 104 at the place of A0 and creates a hypothetical compound and alleges that it is identical to the claimed compound except the linker. As submitted above, Opponent’s understanding
and allegations in respect of definitions of A0 and A1 is incorrect and misleading. Further, on page 90 D27 provides a compound of formula

$$[\text{DRUG}]-\langle A^0 \rangle_{nm}$$

Wherein drug is a compound of formula 501-569 and A0 is A1, A2, and W3. Further, on page 92 D27 defines A0 is A1. Accordingly, A0 is never equivalent to A3, but A1, A2 and W3. Further, opponent is trying to project A1 as A3, which is not at all the case as per the disclosure of D27. In this regard, Applicant has highlighted structures for A1 from pages 71-74 of D27 as above. Further, D27 mentions on page 141, that the linker can include all or a portions of the group A0, A1, A2, or W3. Further, it states on page 143 that the linking group or linker is attached to the phosphonate group through a carbon atom of the linker. In view of above, Applicant submits that A0 is never equal to A3 as presumed or projected by the Opponent. Therefore, Opponent’s allegation regarding the comparison table including hypothetical compound on page 21 of the Opposition petition are incorrect, misleading and should be rejected.

**D28 (Perrone thesis)**

Applicant argued that at the onset, it is submitted that there is no confirmation on the publication date of the thesis or date of availability of this document in public domain for this document to be considered as a prior art. From the second page of this document, it appears that this document has been published in year 2013. Even if it is considered, it relates to structurally different compounds that are namely 4’-azido cytidine, 4’-azido uridine, 4’-azido adenosine, b-2’-methyladenosine, and b-2’-methylguanosine. Perrone thesis cannot be considered as a valid prior art as the same is published after the priority date (March 30, 2007) of the present application i.e. 2013. Without prejudice, it relates to structurally very different compounds that are namely 4’-azido cytidine, 4’-azido uridine, 4’-azido adenosine, b-2’-methyladenosine, and b-2’-methylguanosine. This thesis concludes that the Perrone’s work mainly involved 4’-azido nucleosides which have very different 2’-position substitution. Additionally, Applicant also filed declaration from Dr. Wnuk in opposition proceedings of
Sankalp, IMAK and Optimus & India care to substantiate their arguments on inventive step.

10. **Ground (III) : Section 25(l)(f)-** 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

10 (a) **Hearing submission by the opponents on section 25(1)(f)-**

Opponents mainly argued Section 3(d) under this ground. Section 3(e) and (3(i) was also raised by some opponents but same was not argued during the hearings hence not considered and discussed upon in the present decision.

(i) **Arguments of the Opponent 1 (O1):**

O1 relied on scope of Section 3(d) and the Hon’ble Supreme Court judgement in *Novartis AG Vs. Union of India (UOJ) and Ors. AIR 2013 SC 1311* in paragraphs 171, 173, 180 and 187, which discusses what constitutes efficacy and therapeutic efficacy, and holds that the only test of efficacy is therapeutic efficacy. Also, relied on paragraph 192, it is held "However, in case of chemicals and especially pharmaceuticals if the product for which patent protection is claimed is a new form of a known substance with known efficacy, then the subject product must pass, in addition to Clauses (j) and (ja) of Section 2(1), the test of enhanced efficacy as provided in Section 3(d) read with its explanation."

IMAK argued that Claims 1, 2 and 3 of D2 is the "known substance" in the present case. The Opponent submits that the same "known substance" has been sought to be patented in present application. The disclosures in D2 with respect to the use of a phosphoramidate group to convert the active form of the drug as also in Zon et al., demonstrates that present application not only claims the prodrug of the same compound as in D2 but that even the prodrug was disclosed and claimed in D2.

Without prejudice to (b), given that the "nucleoside phosphoramidate prodrugs" claimed are designed to improve the pharmacokinetic properties of the base compound disclosed in D1, and once delivered intracellularly cleaves back to the known form without any additional therapeutic efficacy, it is at best a "new form" of a "known substance". Therefore, present application does not cross the patent eligibility threshold under Section 3(d).
The Hon’ble Division Bench of the Delhi High Court in *F. Hoffmann-La Roche Ltd. and Ors. v. Cipla Ltd. 2016(65) PTC l(Del) (Annexure II)* paragraphs 14-18,27-29 discusses that Section 3(d) is a patent eligibility threshold, the onus to cross which is on an Applicant. The Hon’ble Court in Para 31 specifically holds that prodrugs shall be considered as a "new form of a known substance" in the following words: "Thus Section 3(d) envisages a variety of derivatives of known substances, some illustrative types could be as under:--

A compound which is not active in itself but is metabolized in the body to form an active drug known as prodrug. For eg., chloramphenicol succinate ester is used as an intravenous prodrug of chloramphenicol, because pure chloramphenicol does not dissolve in water."

It is clear from the language of the Explanation to Section 3(d) that the examples cited there are merely illustrative and not conclusive. In the backdrop of the Hon’ble Division Bench specifically considering a prodrug to be a "new form of a known substance", the present invention falls foul of Section 3(d) and cannot be allowed to proceed to grant. It is not open to the Learned Patent Controller to disregard the aforesaid binding precedent or to create a carve out by way of an interpretation in favour of the Applicant.

Without prejudice to the foregoing, it is an established position that a new form of a known substance can be patented only if it enhances the known efficacy of the substance. In the present case, no comparative data has been filed by the Applicant showing enhanced efficacy between the subject matter of D2 and present application.

Without prejudice to the foregoing, it is submitted that present application can also be considered to be a new use of the known substance in D2, which discloses phosphoramidate derivatives of nucleotides for use in the treatment of cancer and claims the Markush structure of the formula claimed in the present invention.

According to the Applicant, the D2 does not disclose the compounds of the present invention. The D2 provides for BVU which is Bromo vinyl uridine and GemCyt which is Gemcytabine.
The Opponent submits that Claim I of the D2 covers a broad Markush structure which can be used to predict the present compound. The reference to the said structure may be found in Page 414 of the Opposition and is represented by the formulae below:

![Chemical Structures](image)

More specifically the compound in present application is similar to structure III (shown above) in D2 and is clearly known in the art. The present Applicant has merely selected one of the several potential chemical structures from structure III of D2 and hence no new substance is disclosed in the present application.

In chemistry it is well known that the presence of a particular chemical moiety makes a particular group of chemicals behave in a particular way. The presence of the nucleosides cytidine and uridine in the representative chemical entities of BVU and GemCyt can also be predicted to behave in the same manner as the drug represented by the impugned application because the same also has the nucleoside moiety uridine or cytidine present. The mere fact that D2 targets cancer and impugned application targets HCV is not material when the process of development of the subject matter of present application is the same as the drug in D2. It is therefore a clear example of a new use of a known substance.

(ii) Arguments of the Opponent 4 (O4):
Sankalp did not argue section 3(d) during the hearing. However, in written notes of arguments, Sankalp argued that claims 1-3 fall under section 3(d). They rely on the disclosure of (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine in D1. D1 states that, “In each example above, the first drawn structure is the
preferred form". Therefore the below reproduced structure which is first
drawn on page 221, is the most preferred structure:

where X is O; R1 is monophosphate, diphosphate, triphosphate, or a
stabilized phosphate prodrug, R6 is H and R2 is H.
Further, the activity of this compound (2'R)-2'-deoxy-2'-fluoro-2'-C-
methylcytidine in different anti-HCV replicon assays (Table 1 is reproduced
below for reference):

| Replicon       | (2'R)-2'-deoxy-2'-fluoro-2'-C-
methylcytidine |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV-WT 1b</td>
<td>4.6 ± 2.0</td>
</tr>
<tr>
<td>S282T mut. 1b</td>
<td>30.7 ± 11.7</td>
</tr>
<tr>
<td>9-13 (subgenomic)</td>
<td>4.6 ± 2.3</td>
</tr>
<tr>
<td>21-5 (full-length)</td>
<td>1.6 ± 0.7</td>
</tr>
</tbody>
</table>
* Values represent EC<sub>90</sub> (µM)

The Applicant has not shown any enhanced efficacy over the known
compound as disclosed above. It is submitted that the compound of claim 1
of the Present Application is merely an ester derivative of known
monophosphate of (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine. Therefore,
claims 1-3 fail the test of Section 3(d) and therefore must be rejected.
(iii) Arguments of the Opponent 5 (O5) and Opponent 7(O7):
Prodrugs as claimed are not patentable under Section 3(d) of the Patents
Act. It is submitted that prodrugs as such are inactive moieties. Prodrugs or
vehicles that enable a nucleoside to be delivered into the body. Prodrugs are
pharmacologically inactive chemical derivatives that could be used to alter
the physiochemical properties of drug in a temporary manner or to increase
their usefulness and to decrease associated toxicity. The role is limited to
delivery of the nucleoside \textit{in vivo} into the cell in activated form so that the process of viral strand formation may begin. In the instant application also, the Applicant clearly states that the claims are drawn to nucleotides i.e. prodrugs. In such a case where prodrugs are per se inactive, no activity can be shown and has been shown. Hence, on this ground alone, the application is liable to be rejected. The applicant in the application has not shown any therapeutic efficacy of the claimed prodrugs. The applicant has only demonstrated \textit{in vivo} activity and that too of the nucleoside i.e. the nucleoside after it is cleaved and enters the body. The prodrug therefore, is in the same status as a salt or an ester and is not patentable under Section 3(d) unless enhanced therapeutic efficacy can be demonstrated. In the present case, no such efficacy has been shown. The activity shown in the application is cytotoxicity data which only shows inhibition of HCV replication, which is nothing but the \textit{in vitro} activity of the nucleoside. The efficacy of the nucleotide, as claimed has not been demonstrated at all. The application is liable to be rejected on this ground alone.

(iv) Arguments of the Opponent 9 (O9)

a) Claims 1 to 5 are anticipated by D2 as proved in the previous ground under novelty. Therefore, the present application is the mere discovery of new property or new use of the known compound. Under this ground the claims 1 to 5 of the present application ought to be rejected. Because for the mere discovery of any new property or new use for a known compound, efficacy will not come into picture and no need to discuss about efficacy. Therefore, claims 1 to 5 of the present application ought to be rejected.

b) Claims 1 to 5 are anticipated by D23 (Sofia) as proved in the previous ground under obviousness. Sofia discloses the structure of PSI-6206 phosphoramidate. D23 discloses SAR studies and records EC90 clone A cells (μM) of different amino acid ester substitutions (R3) SAR (as disclosed in Table 3. In the amino acid ester (R3) position of PSI-6206 was known. The compound PSI-6206 is the closest prior art as it aims at the same purpose and has structurally the most features in common with the opposed patent application claim 1-3 of present application.
Therefore, the applicant must to have shown sufficiently enhanced efficacy of the compounds of claims 1-3 over any of the compounds in Table-3 in D23.

c) In the alternate and without prejudice to the above, under section 3(d) of the Patents Act a new form of a known substance is not an invention unless it results in enhancement of the known efficacy of the known substance. Section 3(d) was introduced to prevent patents on modifications of known substances and to stop the evergreening of patents.

Under the law each product claim that relates to a new form of a known substance has to satisfy section 3(d) of the Patents Act. Claims 1 to 5 of the present application fall under section 3(d) of the Act since they are new form of known compounds i.e, isomers and derivatives. The present application is derivatives of phosphoramidate.

Opponent argued that it is established in the law that the section 3(d) has to satisfied independently of section 2(1)(j) and 2(1)(ja). The burden is always on the applicant. In the Novartis AG Vs Union of India and others the Hon'ble Supreme Court of India held that the expression "efficacy" in the section 3(d) in case of pharmaceutical substances is to be understood as therapeutic efficacy. Further it is also an established position that the data relating to efficacy ought to be provided in the complete specification. In the present application claims 1 to 3 directed towards a product and they are derivatives of phosphoramidate and stereoisomers. In order to discharge the burden of section 3(d) the applicant ought to have compared therapeutic efficacy with the closest compounds. The applicant has failed to discharge this burden. Claim 5 is directed towards mere use of known process without new reactants and its end product is not a new compound. Hence these claims ought to be rejected for not satisfying the requirement under section 3(d).

(v) Arguments of the Opponent 10 (O10)

The Opponent argued that from the above discussion, it would be amply clear that on the effective priority date of claim of the present invention, the applicant was fully aware that they have already disclosed similar compounds in D27. This particular compound (whose chemical formula is
same) is not only described in the specification but also defined in the claims. Therefore, it was a clear intention of the applicant to protect similar nucleoside-phosphoramidate conjugates so as to exclude others from patentability.

The compound of formula 1 of the present application ought to be construed as at least a derivative of the compound of D27 outlined above. As indicated above the compounds are clearly disclosed to be effective anti-viral drug effective in the treatment of Hepatitis C virus. Therefore, it is incumbent on the applicant to show as to how the compound of claim 1 of the present invention has a marked improvement of efficacy over the above exemplified compound of D27.

In this context, it is noted that the applicant in paragraph 9.1-9.7 of its response has carefully tried to draw an analogy of efficacy of compound of claim 1 and Sofosbuvir (claim 2) and to this end its reasoning that the EC90 value of compound 25 of the present invention indicates a markedly improved efficacy is not only misleading but also an effort to divert the attention. It can be clearly seen that from the table on pages 694-697 of the present invention that in terms of EC90 value at least compounds 39, 49, 53, 55 with the same nucleoside are better or comparable antiviral compounds than compound 25. Even in compound 25 the stereospecificity of P centre has not been defined and the EC90 data of compound 25 (racemate) cannot be taken to be an indicator of the activity of the individual diastereoisomers as claimed in claim 2 or 3.

Further, it is not clear from the specification that the stated stereospecificity of Fluorine and Methyl in the sugar moiety has a specific role in terms of efficacy.

That Sovaldi® is a commercial successful product and the applicant’s contention that its efficacy is a support to present claim 1 against the 3(d) requirement is absolutely unacceptable. It is respectfully submitted that Sofosbuvir (claim 2) being a specific diastereoisomer of present claim 1, a corresponding claim has been introduced in the specification as a hindsight after its commercial success and upon realising the disclosure of the present invention does not support or protect such a claim/product in any way.
Therefore, in the humble submission of the opponent, claim 1 of the present invention ought to be refused under Section 3(d) of the Act as the applicant (Gilead) has failed to substantiate the improved efficacy vis-a-vis compound of D27 as outlined above.

This is in addition to the submission on obviousness and Section 3(d) specifically in view of D23 (Sofia et al).

(vi) Arguments of the Opponent 11 (O11)
Opponent argued that in light of the above arguments raised under different grounds it is evident that the Applicant is claiming new form of already known substances disclosed in documents D1 to D9. For instance, claims 2 and 3 merely claim stereoisomeric forms of a compound 1 which lack enhanced efficacy when compared to the parent compound disclosed in claim 1 and in documents D1 to D9. Additionally, the Applicant claims composition under claim 4 which is merely an admixture of all known compounds/ingredients and lack synergy. Therefore, claim 4 has to be rejected in view of section 3(e) of the Act.

(vii) Arguments of the Opponent 12 (O12)
Opponent relied on D21 (Clark et al.), to argue that it relates to the same subject-matter as claimed and disclosed in the impugned Application. Specifically, it discloses the utilization of exactly the same nucleoside (Compound 9) as claimed in the impugned Application. Clark et al., further discloses that the Compound 9 along with other compounds were tested for anti-HCV activity in a cell-based quantitative real-time RT-PCR assay, wherein it was found that compound 9 exhibits no activity or cyto-toxicity in the cell based assay. It is the contention of the Applicant that since compound 9 did not exhibit any activity in the cell based assay, the compounds as claimed in claims 1-3 do not fall within the ambit of S. 3(d), for the reason that there was no known activity for the compounds as claimed in claims 1-3. Opponents argued that usage of an assay that cannot elucidate/determine the efficacy of the active moiety due to following facts:

a. It was amply known to the skilled artisan, as of the earliest priority date of the impugned application, that cell based assay cannot determine the
efficacy of the active moiety (*i.e.* the nucleoside analog devoid of the phosphoramidate moiety), reliance being placed on the admission of inventors of the impugned application in the background section of the impugned application

b. The experimental data furnished in the impugned application, wherein activity varies with varying phosphoramidate moieties, also corroborates the fact the cell based assay used for testing activity of pro-drugs of the impugned application is not determinative of the efficacy of the active moiety/compound; rather, it is limited to assessment of activity of the pro-drugs. Reliance was placed on the experimental data provided at Pages 695-696 of the impugned application.

The aforesaid facts make it clear that – nucleoside alone cannot enter the cell and get converted into triphosphate to compete for the polymerase nucleotide binding site, which limits direct evaluation of nucleosides as inhibitors of HCV replication by cell-based assays capable of in situ phosphorylation. Simply put, it is not that Compound 9 of prior-art document A-11 is a non-active compound, it is the limitation associated with the cell based assay that the said assay cannot determine the activity of the compound 9.

Consequently, the key issue that arises is - can the Applicant circumvent the requirement of showing enhanced efficacy of the pro-drug by resorting to (or using) an assay that is not determinative of the actual efficacy of the active moiety?

It is submitted that merely by resorting to assay that is not determinative of the actual efficacy of the active moiety, the Applicant cannot circumvent the requirement of showing enhanced efficacy of the pro-drug. It is a matter of the record that active moiety (*i.e.* the nucleoside analog) is one and the same; and in-fact, the experimental data (wherein activity varies with varying phosphoramidate moieties) also corroborates the fact the cell based assay used for testing activity of pro-drugs of the impugned application is not determinative of the efficacy of the active moiety/compound but is limited to assessment of activity of the pro-drugs. Consequently, it does not lie in the mouth of the Applicant that the efficacy of the compound
(Compound 9) disclosed in prior-art document Clark et al. is not known and hence, there does not arise a question of the Applicant having to establish enhanced efficacy of the claimed compounds over the compound 9 of Clark et al.

Section 3(d) of Patent Act, 1970 is very clear on that the – New forms (i.e. pro-drugs as claimed in the impugned application) of an already known substance (i.e. Compound 9 of prior-art document A-11) may be considered to be the same substance, and such pro-drugs can only be deemed patentable if they differ significantly in properties with regard to “therapeutic efficacy”. Hence, section 3(d) clearly sets up a second tier of qualifying bar for new forms of known substances 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.

Based on detailed submission made supra, it is evidently clear that the invention as claimed in the impugned Application is merely directed towards a new form (pro-drug) of an already known substance (compound 9, disclosed in prior-art A-11), plainly and squarely falling within the ambit of Section 3(d) of the Patents Act, 1970, as stand amended, and hence, each of the claims 1-3 ought to be refused on this ground alone.

(viii) Arguments of the Opponent 13 (O13)

Opponent argued that even though anti-HCV activity of the compound of claim 1 has been disclosed at page 687 of the complete specification, the Applicant has failed to show how the said compound shows enhanced efficacy over the known compounds of D23. Therefore, the Applicant has failed to overcome the test of Section 3(d). Thus, claims 1-5 of the Present Application must be rejected.

10(b) Hearing submission by the applicant on section 25(1)(f)-

(i) Applicant’s arguments in reply to opposition by O4-

The Opponents had not argued Section 3(d) during the oral hearings. However, Opponent has relied on Section 3(d) in their opposition petition based on McGuigan et al (2000)-Exhibit R, and Iyer, JMC 2000-Exhibit M. As per the opponent, Applicant ought to have compared the therapeutic
efficacy of sofosbuvir with at least one aryl phosphoramidate ester prodrug of the prior art. Opponents did not identify any specific compound which according to them was the known substance of which the sofosbuvir were argued to be derivative. At the time of oral hearings, Opponent also indicated that WO’147 (D1) may be considered by the Controller for Section 3(d) without substantiating any pleadings on the said documents. Opponent has not pressed the arguments on Section 3(d) during the oral hearings. Without prejudice, it is submitted that the argument on Section 3(d) of the Opponent is completely baseless and not maintainable. In fact, Section 3(d) requires-

a. Identification of “..a..” known substance with the known efficacy;

b. If Section 3(d) applies, enhancement of efficacy was to be compared with “..a..” known substance with the known efficacy.

The provisions of Section 3(d) are extremely clear on the language employed both in the main part of the section and in the explanation, which use the word ‘substance’ in singular. The Applicant also submits that the words “other derivatives” ought to be interpreted *ejusdem generis* and every new compound cannot be treated as a derivative of any earlier compound. It is only new forms of compounds which are derived from the same known compound or the substance i.e. a new form of a known entity (Section 2(ta)) that would attract the rigors of Section 3(d). The relevant paragraph 77-79 from the opposition petition of O4 is set out herein below.

“77. Christopher Mcguigan et al, 'Phosphoramidate derivatives of stavudine as inhibitors of HIV: unnatural amino acids may substitute for alanine', published in or about April 2000, a copy of which is attached and marked herein as "Exhibit R" discloses that aryl substitution, carboxyl ester variation has little impact on the antiviral activity of. Aryl phosphoramidates. It therefore emerges that the L-alanine moiety is the key determinant of intracellular phosphate delivery.

78. There are numerous alternative amino acid moieties for a person skilled in the art to investigate. For instance, a variety of alternative
unnatural amino acid moieties including o.-n-alkylglycine, o.-phenylglycine or 0.,0.-sym-nalkyl-glycine are known [Exhibit R], L-valine, L-leucine, L-tyrosine, L-phenylalanine, L-tryptophan, D-phenylalanine, and D tryptophan [page 2267, column 1, plactum 24, Exhibit-M] etc.

79. In order to discharge the burden of Section 3(d), the Applicant ought to have compared therapeutic efficacy of at least one aryl phosphoramide ester prodrug containing other amino acid moieties which has high efficacy with the present prodrug containing L-alanine amino acid moiety. The Patent Applicant has failed to discharge this burden. The only evidence that has been supplied is the evidence of antiviral effect through an HCV replicon assay. This evidence cannot be considered to be evidence of improvement ill therapeutic efficacy over the phosphoramide esters containing other amino acid moieties.”

From the above, it is clear that though Section 3(d) is not applicable as the compounds of the present Invention constitute New Chemical Entities (NCEs). Further, Opponent has not identified “a” known substance with known efficacy for comparison of efficacy.

Without prejudice to this submission, the Applicant has given comparative efficacy data in Table on page 696 in the complete specification. This table include comparative activity and toxicity data against structurally close compounds which are prepared in accordance with present invention (compounds in table are not the part of prior art documents). The Controller may specifically refer to following compound no. 5, 6, 15, 27, 28 vis-a-vis Compound no. 25 (compound claimed in claim 1) for comparison of therapeutic efficacy.
Opponent in their written notes of arguments in Para 114-116 are now mentioning that D1 discloses the activity of (2'R)-2'-deoxy-2'fluoro-2'-C-methylcytidine; and has alleged that compound of claim 1 of the present application is merely an ester derivative of known monophosphate of (2'R)-2'-deoxy-2'fluoro-2'-C-methylcytidine.

Essentially, Opponent submission is that claimed compound sofosbuvir are ester derivatives of compounds disclosed in D1. This is mere an afterthought. There is no such submission in opposition petition nor the same has been demonstrated in the written notes of arguments.

Applicant submits that Claimed compounds are NCE and not mere derivatives. Further, the learned controller may refer to Judgement of **F. HOFFMANN-LA ROCHE LTD V CIPLA LTD** argued during the hearing w.r.t. issue of structural similarity and Section 3(d). In this case, the compound of suit patent differs from the compound of prior art in respect of one moiety i.e. methyl vs ethynyl, rest complete compound has exactly identical structure.

<table>
<thead>
<tr>
<th>The suit patent no. IN'774 “Erlotinib Hydrochloride”</th>
<th>Example 51 of EP'0566226 patent filed by Zeneca Ltd</th>
</tr>
</thead>
</table>
In the above matter, the Court held that section 3(d) is not applicable. Section 3(d) does not apply to every pharmaceutical case:

It is submitted that the provisions of Section 3(d) are not applicable to the present case as detailed under:

a) **New Form:** The compounds of the present invention are a new chemical entity, and are not related to any known substance in a way that would fall within Sec. 3(d).

b) **Mere Discovery:** The present invention cannot be held to be a “mere discovery” within the meaning of Sec. 3(d). In fact, the present invention relates to a new chemical entity.

c) **Known therapeutic efficacy:** Without prejudice, even if it is assumed that Sec. 3(d) is applicable in present case, the Opponent has failed to point out known efficacy of any other known substance against which any comparable data is to be submitted in the present case. There is no known substance over which the present invention can be deemed to be lacking in efficacy. In fact the efficacy of the compounds of the present invention is significantly enhanced and different over any other medicines for the treatment of HCV infection known as of the filing date. The reliance on section 3(d) is misplaced and untenable. The Opponent has completely failed to discharge its onus of proof in respect of Sec. 3(d).

It is humbly submitted that the reliance of *Novartis Vs. UOI* by the Opponent is also not maintainable in as much as the present case is completely different from the Novartis case. A table distinguishing the present case from the Novartis case which was part of replies set out by the Applicant is set out herein below:
<table>
<thead>
<tr>
<th>NOVARTIS PATENT CASE</th>
<th>PRESENT PATENT APPLICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patent application for beta crystalline form of a known substance, i.e., a second</td>
<td>The claims are not in respect of a form of a known substance, but rather to new substances</td>
</tr>
<tr>
<td>The Applicant claimed the patent on the basis of enhanced properties of the beta</td>
<td>The claimed compound has unexpectedly high levels of therapeutic efficacy against HCV</td>
</tr>
<tr>
<td>crystalline form over the free base compound, viz. increased bioavailability,</td>
<td>as compared to any other prior art compound being investigated to perform the same</td>
</tr>
<tr>
<td>thermodynamic stability, etc.</td>
<td>function. Efficacy of Sofosbuvir is undisputed. In fact, sofosbuvir is the first ever</td>
</tr>
<tr>
<td>Enhanced therapeutic efficacy was claimed over the already known free base of the</td>
<td>direct acting nucleoside approved for HCV.</td>
</tr>
<tr>
<td>compound, i.e. the ‘known substance’.</td>
<td>There exists no ‘known substance’ with “known efficacy” over which enhanced therapeutic</td>
</tr>
<tr>
<td>Compound was a derivative (polymorph) of a compound that was disclosed in a prior</td>
<td>efficacy could be claimed.</td>
</tr>
<tr>
<td>patent.</td>
<td>No previous patent discloses, implicitly or explicitly, the claimed compound of the</td>
</tr>
<tr>
<td>Inventive step was claimed to be</td>
<td>present patent.</td>
</tr>
<tr>
<td></td>
<td>The invention lies, <em>inter alia</em>, in</td>
</tr>
</tbody>
</table>
producing a beta crystalline form of salt derivative of Imatinib free base.

The Zimmermann patent specifically included in its scope the salt derivatives of the Imatinib free base.

The active ingredient and marketable form were already available on the basis of the previous patent.

The beta crystalline form of Imatinib Mesylate is a polymorph of Imatinib Mesylate, which in turn, is a salt form of Imatinib. Both the compounds are derivatives of Imatinib free base and, thus, qualify the Explanation to S. 3(d) and are not inventions within the meaning of the Act.

The claimed polymorph had known and obvious properties of the known base or its salt.

The unique and novel combination of specific nucleoside with specific phosphoramidate moiety for treatment of HCV.

The unique present compound have not been specifically disclosed in any previous patent.

No such compound was already known, let alone be available, in the pharmaceutical market.

The claimed compound is not a derivative of any known substance and, thus, not included within the scope of S. 3(d).

The compound has surprising, unexpected and unique properties.

Conclusion on Section 3(d):

a. The ground of Section 3(d) has no applicability;
b. Without prejudice to the same, the invention provides anti-HCV assay data for the claimed compounds and structurally similar compounds, and the said data is contained in the specification.

c. The present is a case of new chemical entities with unexpected potency against HCV.

Hence Section 3(d) has no applicability and the compounds are patentable.

(ii) Applicant's arguments in reply to opposition by O1-

The Applicant relied on the comparative efficacy data in table on page 696 in the complete specification. This table include comparative activity and toxicity data against structurally close compounds which are prepared in accordance with present invention (compounds in table are not the part of prior art documents). Specific reliance to compound no. 5, 6, 15, 27, 28 vis-a-vis Compound no. 25 (compound claimed in claim 1) for comparison of therapeutic efficacy was made.

During the hearing, Opponent submission was that claimed compound sofosbuvir is a derivative of compounds disclosed in WO’147 or a prodrug form of metabolites disclosed in WO’147. There is no such submission in opposition petition nor the same has been demonstrated in the written notes of arguments.

Applicant submits that Claimed compounds are NCE and not mere derivatives. Applicant submits that Explanation part of Section 3(d) only mentions “metabolite” but not “prodrug”, same is reproduced herein below:

“Explanation. —For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy”.

In other words, Metabolites of a known substance (example drug or prodrug being a known substance) shall be considered as same substance unless it shows enhanced efficacy over known substance and not vice versa. If a claimed compound/prodrug was known and we were claiming a “Metabolite” of said prodrug without showing any enhanced efficacy over said prodrug
then Section 3(d) would come into the play but not in present scenario wherein claimed compounds are novel and inventive per se. In fact, the efficacy of the claimed compounds, particularly sofosbuvir is undisputed, significantly enhanced and different over any other medicines for the treatment of HCV infection known as of the filing date. Accordingly, Section 3(d) is not applicable in the present case.

Further, Applicant relied on Judgement of **F. HOFFMANN-LA ROCHE LTD V CIPLA LTD** and **Novartis Vs. UOI** by arguing that the present case is completely different from the Novartis case. Applicant relied on the table showing difference between the present invention and Novartis case.

(iii) Applicant’s arguments in reply to opposition by O5 & O7-

The Applicant relied on the comparative efficacy data in table on page 696 in the complete specification. This table include comparative activity and toxicity data against structurally close compounds which are prepared in accordance with present invention (compounds in table are not the part of prior art documents). Specific reliance to the compound no. 5, 6, 15, 27, 28 vis-a-vis Compound no. 25 (compound claimed in claim 1) for comparison of therapeutic efficacy was made.

Without prejudice to the above, Applicant submits that the inventors of D1 (WO’147) disclose and claim (2’R)-2’-deoxy-2’-fluoro-2’-C-methyl nucleosides. In 2005, the inventors of this Application carried out research work directed towards design, synthesis and antiviral activity of 2’-deoxy-2’-fluoro-2’-C-methylcytidine and found that of 2’-deoxy-2’-fluoro-2’-C-methylcytidine and 2’-C-methylcytidine are potent inhibitors of HCV replication. During this research work, Clark et al. (D21) also reported that the compound “2’-deoxy-2’-fluoro-2’-C-methyluridine” was found to be inactive in HCV replicon assay. To show enhanced efficacy of the claimed compound of the present invention, it is evident that the activity of the phosphoramidate compound claimed in the present invention i.e. sofosbuvir is enhanced in comparison to compound of WO’147 i.e. “2’-deoxy-2’-fluoro-2’-C-methyluridine” in HCV replicon assay which is nil on records as on 2005. Accordingly, Applicant have met the requirement of Section 3(d) by showing enhanced therapeutic efficacy of sofosbuvir over inactive 2’-deoxy-
2’-fluoro-2’-C-methyluridine of Clark 2005 publication (which could be a structurally closest known nucleoside or metabolite) for purposes of section 3(d). Controller may refer to below chart for purposes of Section 3(d) and its non-applicability.

<table>
<thead>
<tr>
<th>Clark 2005 Publication (structurally closest known nucleoside/metabolite with no activity)</th>
<th>3658/KOLNP/2009 Present application (Sofosbuvir)</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Diagram of Clark 2005 Publication nucleoside]</td>
<td>![Diagram of 3658/KOLNP/2009 nucleoside]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prodrugs disclosed and exemplified in WO’147</th>
<th><strong>N-acyl prodrugs</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>![Diagram of N-acyl prodrugs]</td>
<td></td>
</tr>
</tbody>
</table>

170
It can be clearly noted that Sofosbuvir is structurally different from the prodrugs disclosed in WO’147. Sofosbuvir has enhanced therapeutic efficacy over 2'-deoxy-2'-fluoro-2'-C-methyluridine (structurally closest nucleoside/metabolite) of Clark 2005 publication since 2'-deoxy-2'-fluoro-2'-C-methyluridine has no activity reported. The description of the present invention provides the comparative activity and toxicity data against structurally closest compounds/nucleotides which are prepared in accordance with present invention (compounds that are not the part of any prior art documents). Accordingly, Section 3(d) is not applicable in the present case.

(iv) Applicant’s arguments in reply to opposition by O9-
Applicant submitted similar line of arguments on Section 3(d) as presented for the above 4 opponents. Applicant relied on the comparative efficacy data in table on page 696 in the complete specification.

As regards D2 (WO’327), the Applicant submits that WO’327 fails to disclose the compounds presently claimed, and so the Opponent’s arguments in relation to an alleged new property or new use of a known substance must necessarily fail. It does not disclose a compound as presently claimed. No nucleoside moiety having the required, stereospecific substitution at the 2’-position, i.e. 2’-fluoro (down), 2’-methyl (up) is disclosed or enabled, let alone bound to the required specific phosphoramide group. Accordingly, as already noted, WO’327 cannot form the basis for an argument that the
presently-claimed subject matter represents a new property or new use of a known substance.

As regards D23 (Sofia et al.), the Applicant respectfully disagrees with the Opponent’s assertions. Sofia et al cannot be considered as a valid prior art as it is published after the priority date (March 30, 2007) of the present application i.e. September 2007. Further, Applicant relied on Judgement of **F. HOFFMANN-LA ROCHE LTD V CIPLA LTD** and **Novartis Vs. UOI** by arguing that the present case is completely different from the Novartis case.

Applicant relied on the table showing difference between the present invention and Novartis case.

(v) Applicant’s arguments in reply to opposition by O10-

Applicant submitted similar line of arguments on Section 3(d) as presented for above 5 opponents. Applicant relied on the comparative efficacy data in table on page 696 in the complete specification. As regards D23 (Sofia et al.), the Applicant respectfully disagrees with the Opponent’s assertions. Sofia et al cannot be considered as a valid prior art as it is published after the priority date (March 30, 2007) of the present application i.e. September 2007. Further, as argued during the oral hearing, the instant opponent in fact acknowledges that the closest prior art compound *vis a vis* currently pending claim 1 could be from the document which is after the priority date of the present invention. In fact, this admission from the Opponent proves the fact that Section 3(d) is not applicable in the present matter as there were no structurally closest known compound available against sofosbuvir as on the priority date. Further, Applicant relied on Judgement of **Novartis Vs. UOI** by arguing that the present case is completely different from the Novartis case. Applicant relied on the table showing difference between the present invention and Novartis case.

(vi) Applicant’s arguments in reply to opposition by O11-

Applicant submitted similar line of arguments on Section 3(d) as presented for above 6 opponents. Applicant relied on the comparative efficacy data in table on page 696 in the complete specification. Further, Applicant relied on Judgement of **F. HOFFMANN-LA ROCHE LTD V CIPLA LTD** and **Novartis Vs. UOI** by arguing that the present case is completely different from the
Novartis case. Applicant relied on the table showing difference between the present invention and Novartis case.

(vii) Applicant’s arguments in in reply to opposition by O12-
Applicant submitted similar line of arguments on Section 3(d) as presented for above 7 opponents. Applicant relied on the comparative efficacy data in table on page 696 in the complete specification. For the purpose of section 3(d), Opponent relied upon D21 (Clark et al. 2005) during the oral hearing.

It describes the synthesis and biological activity of 2’-deoxy-2‘fluoro-2‘fluoro-2‘-C-methyl cytidine as a potent anti-HCV agent. It does not disclose a compound as Gilead’s claimed compound. It reported that the Compound “2’-deoxy-2‘-fluoro-2‘-C-methyluridine” (compound 9) demonstrated no activity or cytotoxicity in any assay and the Compound “2’-deoxy-2‘-fluoro-2‘-C-methylcytidine” (compound 1) demonstrated some activity in HCV replicon assay. It does not teach or suggest any prodrug let alone the phosphoramidate prodrug claimed in present application.

As per the Opponent, claimed compounds 1-3 are derivatives of compound 9 of Clark et al. The learned Controller may refer to below structures:
As can be seen from above structures, the claimed compound of the present invention cannot be said as derivative of compound 9 of D21. Phosphoramidate group present in claimed compound cannot be said to be derived from the Compound 9. The specific Phophoramidate group is phenoxy phosphoramidate of isopropyl ester of L-alanine amino acid moiety which has following unique constitution:

- attached to hydroxyl group of 5’-position of nucleoside
- has phenyl group attached to phosphorus
- has amide ester with L-alanine amino acid moiety
- has isopropyl ester at carboxyl of alanine amino acid.

Hence, Section 3(d) is not applicable to the present case.

Without prejudice, claimed compound of the present invention has enhanced therapeutic efficacy over compound 9 of Clark et al, which has no activity at all. Activity of Claimed compound is well supported in as filed specification in table on page 696. Further, person skilled in the art would not be motivated to choose “2’-deoxy-2’-fluoro-2’-C-methyluridine”, compound 9 for further research in order to arrive at anti-HCV compounds, rather will be guided to start with “2’-deoxy-2’-fluoro-2’-C-methylcytidine compound (Compound 1 of Clark et al) which demonstrated some activity. The learned Controller may refer to below structures of Compound 1 and Claimed compound herein below:
As can be seen from above structures, “2’-deoxy-2’-fluoro-2’-C-methylcytidine (compound 1) cannot be considered to be a known substance for the purpose of Section 3(d) as the same is structurally different from the Gilead’s claimed compound. Hence, section 3(d) is also not applicable in view of compound 1.

Further, Applicant relied on Judgement of **F. HOFFMANN-LA ROCHE LTD v CIPLA LTD.**

(viii) **Applicant’s arguments in reply to opposition by O13-**

Applicant submitted similar line of arguments on Section 3(d) as presented for above 8 opponents. Applicant relied on the comparative efficacy data in table on page 696 in the complete specification. As regards D23 (Sofia et al.), the Applicant disagrees with the Opponent’s assertions. Sofia et al cannot be considered as a valid prior art as it is published after the priority
date (March 30, 2007) of the present application i.e. September 2007. Further, as argued during the oral hearing, that Section 3(d) is not applicable in the present matter as there were no structurally closest known compound available against sofosbuvir as on the priority date. Sofia et al is document published by the same inventor of instant application after six months of the filing of the instant application. Sofia et al cannot be relied on the purpose of Section 3(d) as per the Indian Patents law. From the above, it is clear that Section 3(d) is not applicable as the compounds of the present Invention constitute New Chemical Entities (NCEs). Further, Opponent has not identified “a” known substance with known efficacy for comparison of efficacy.

11. **Ground (IV) : Section 25(1)(g)**-

11(a)- **Hearing submissions filed by the opponents on section 25(1)(g)**-

(i) Arguments of the opponent O1-

It is submitted that the claims are not clearly defined in the specification and go beyond the scope of disclosure of the specification. The compound of Claim 1 comprises a mixture of two diastereoisomers at the P-center of stereochemistry and is known as PSI-7581. Claim 2 and 3 are the individual diastereoisomers. Further the complete specification of the patent application does not disclose any stereospecific method of synthesis and of purification of compounds of Claims 2 and 3. There is no disclosure in the patent application as to how to obtain the compounds of Claim 1 or the compounds of Claims 2 and 3. It is submitted that Claims 2 and 3 go beyond the scope of claims of the complete specification as there is no disclosure in the application of any individual compound having the structure disclosed in the said claims, with the specific stereochemical configuration at the phosphorous atom. In particular, in Example 81, on pages 694-695 of the specification, the separation of a mixture of diastereomers into a "fast moving isomer" and a "slow moving isomer" in relation to their respective elution times is disclosed. It only provides the conditions of chromatographic resolution of the diastereomeric mixture of compounds 15, 39 and 49. This example not only leaves undetermined the
nature of the separated diastereomers, but also, none of the separated examples in Example 81 relates to the compounds of Claims 2 and 3. There is also no teaching as to how to modify the chromatographic resolution of Example 81 in order to achieve the chromatographic resolution of the diastereomers of the compound of Claim 1 and to obtain compounds of Claims 2 and 3. None of the compounds exemplified are the compound of Claims 1, 2 and 3. No chromatographic conditions, i.e. column, solvents to be used are provided for the separation of the enantiomers of compound 25, the compound of Claim 1, and nothing indicates that the disclosed separation method could be applied to this compound. Further, the absolute stereochemistry of the P-chiral centres of the diastereomers cannot be determined using this method. Accordingly, the person skilled in the art wishing to obtain the compounds of Claims 2 and 3 on the basis of the specification is left with the undue burden of having to devise stereospecific methods of synthesis and purification of these compounds by himself.

It is common knowledge that any compound produced as a result of a chemical reaction is expected to be obtained as a mixture of isomers. However, the impugned application fails to specifically mention whether an S or an R isomer is being prepared, and how these isomers can be distinguished. Example 81 of the impugned application (Page 694) states "certain exemplified compounds were obtained as mixture of diastereoisomers". Also, the Applicant in the impugned application has only mentioned the terms fast moving and slow-moving isomers without identifying which isomer falls under each category. The difference is due to the presence of same chemical group in different positions of the P-moiety. Further, Example 81 does not state why one isomer is preferable over another or why the mixture of isomers is not mentioned in the specification. The justification for having two separate claims claiming the two isomers is completely missing from the specification. The Opponent reiterates that in the corresponding European patent similar grounds of opposition has been raised. The opposition board in their decision accepted the arguments of the opponents and rejected the claims 2 and 3 and the dependent claims.
relating to the isomeric forms of the compositions comprising the compounds and pharmaceutically acceptable medium thereof.
Given that the specification mentions the difference of activity of the 2 isomers – anything which is not disclosed in the specification cannot be claimed. Hence, insufficiency is made out.

(ii) Arguments of the opponent O4-
Claims 1-5 must be rejected as the complete specification does not sufficiently describe the invention. Preparation of compound of claim 1 not sufficiently described. It is submitted that Compound IX-25-2 in Table IX on page 251 of complete specification is the closest compound to compound of claim 1 that has been disclosed in the specification. In absence of a specific method for preparation of this aspect of the embodiment, a person having ordinary skill in the art will be drawn to method used for preparing phosphoramidate as identified at example 3 (internal page 675 of the complete specification).
While example 4 (page 676, complete specification) provides the general preparation for compound of markush formula similar to claim 1, the exact process to make compound of claim 1 is not disclosed. Further the complete specification is silent on how to prepare compounds of example 3 and example 4 (page 675, complete specification) in order to would enable making compound at IX-25-2.
Similarly, even Examples 5-8 (pages 677-680 of the complete specification); examples 13-54 and 56-66 (pages 684-689, complete specification) provides only a general process and does not provide an exact process for making compound of claim 1.
Further, compound of claim 1 contains 6 stereogenic centres. The complete specification is silent on how to distinguish or arrive at the isomers of claims 2 and 3. Even Example 81 in the complete specification only provides a general process for arriving at mixture of stereoisomers exemplified in the complete specification. In fact, the complete specification does not identify the stereoisomers by their chirality at the Phosphorus atom (as claimed in claims 2 and 3) rather, it only identifies them as slow and fast moving isomers as provided on page 695 of the complete specification. The examples
of the mixtures of diastereomers exemplified in the complete specification is have only been exemplified vis-à-vis slow and fast moving isomers, and not the compounds of claims 2 and 3.

Further, the Applicant has failed to disclose the preference of particular stereoisomers of claims 2 and 3. Further, it is submitted that methods claimed in claims 4 and 5 have not been disclosed.

(iii) Arguments of the opponents O5 & O7-

The claims of the application are indefinite, broad and not supported by the specification:

(a) The claims of the application are drawn to various prodrug compounds including stereoisomers thereof. This is specifically in respect of claims 2 and 3 which claim stereoisomer at phosphorus atom. The specification on the other hand provides no description with regard to any such stereoisomer; the complete specification is entirely silent on how to arrive at any isomer including that of Claims 2 and 3. In fact, there is no description of any stereoisomer at all, much less the efficacy thereof.

(b) The exact process for preparation of compound of Claim 1 is not disclosed. The specification is entirely silent as to how the said compound is to be prepared. Example 4 provides general instructions for preparing compounds similar to that claimed in claim 1; however, the actual process of preparation of the compound of Claim 1 is not disclosed. Therefore, the requirement of Section 10(4) is not fulfilled.

(c) The specification generally provides a long list of various compounds. However, there is no guidance in the specification as to which compound is best suited for antiviral activity and which compound is most activated when the nucleotide approach is used. In other words, there is no preference for a specific compound.

(d) It is submitted that Claims 2 and 3 go beyond the scope of claims of the complete specification as there is no disclosure in the application of any individual compound having the structure disclosed in the said claims, with the specific stereochemical configuration at the phosphorous atom.

(e) In particular, in Example 81, on pages 694-695 of the specification, the separation of a mixture of diastereomers into a “fast moving isomer” and a
“slow moving isomer” in relation to their respective elution times is disclosed. It only provides the conditions of chromatographic resolution of the diasteriomic mixture of compounds 15, 39 and 49. This example not only leaves undetermined the nature of the separated diastereomers, but also, one of the separated examples in Example 81 relates to the compounds of Claims 2 and 3. There is also no teaching as to how to modify the chromatographic resolution of Example 81 in order to achieve the chromatographic resolution of the diastereomers of the compound of Claim 1 and to obtain compounds of Claims 2 and 3. None of the compounds exemplified are the compound of Claims 1, 2 and 3.

(f) No chromatographic conditions, i.e. column, solvents to be used are provided for the separation of the enantiomers of compound 25, the compound of Claim 1, and nothing indicates that the disclosed separation method could be applied to this compound. Further, the absolute stereochemistry of the P-chiral centres of the diastereomers cannot be determined using this method. Accordingly, the person skilled in the art wishing to obtain the compounds to Claims 2 and 3 on the basis of the specification is left with the undue burden of having to devise stereospecific methods of synthesis and purification of these compounds by himself.

(iv) Arguments of the opponent O9-
The complete specification does not sufficiently and clearly describe the invention for the method by which is to be performed. Further the claims are not appropriately supported by the specification of the alleged application. Hence, without prejudice to the grounds raised in this representation, the Opponent invokes Section 25(1) (g).

Preparation of compound of claim 1 has not been sufficiently described-
Opposed patent application applicant has failed to specifically describe the process for the preparation of compound of claim 1. Compound IX-25-2 (Generically) in Table IX on page 251 mentions all substituents of the compound claimed in claim 1 of the Present Application.

This table has to be read in combination with generically structure given on page 243 of the complete specification which does not mention the stereochemistry on “Phosphorus atom”.
In the absence of a specific method for preparation of this aspect of the embodiment, a person having ordinary skill in the art will be drawn to method used for preparing phosphoramidate as identified at example 3 (internal page 675 of the complete specification). The general preparation for making the nucleoside as in claim 1 has been given at example 4 (internal page 676 of the complete specification). However, no procedure to prepare the exact compound of claim 1 has been disclosed in the complete specification. Further, nothing in the complete specification indicates that the disclosed method for preparing example 3 and example 4 would enable making compound at IX25-2. Present application discloses examples 5-8 (on pages 677-680 of the complete specification); one finds that they only disclose a process for the preparation of methyl ester analog of the compound claimed in claim 1 of the Present Application. Also, the complete specification has provided that examples 13-54 and 56-66 on pages 684-689 may be prepared using similar procedures used for examples 5-8. It is submitted that example 25 covered in these pages (see particularly page 685 of the complete specification) covers the compound claimed in claim 1. It is submitted that the specification has only given a general method of preparation and does not enable the preparation of the compound of claim 1. The Opponent submits that the compound of claim 1 of the compound IX-25-2; Table IX on page 251 of the complete specification does not specify the stereochemistry of the asymmetric carbon linked to group R3b (methyl group i.e. –CH3). The specification of the alleged application has not provided any specific process for the preparation of stereoisomers. Further, the Applicant has also failed to show any activity and reason for choosing the diastereomers identified in claims 2 and 3. Preparation of stereoisomers claimed in claims 2 and 3 has not been sufficiently described
The Opponent submitted complete specification at page 19, the Applicant has stated that the term “P*” means that the phosphorus atom is chiral and the compounds of formula I (as given at page 8) are racemic because the chirality of phosphorus. It then states that ‘applicant contemplates use of the racemate and/or the resolved enantiomer’ (emphasis added). The use of
the term ‘the’ clearly indicates that the observation is in relation to the racemate of the compound reproduced below-

![Chemical structure diagram]

The passage at page 19 of the complete specification, then goes on to other cases mentioned in the complete specification, where the asterisk does not appear next to the phosphorus atom. It states that ‘in these instances, it is understood that the phosphorus atom is chiral and that one of the ordinary skill understands this to be so unless the substituents bound to the phosphorus exclude the possibility of chirality at the phosphorus.’ In other words, the skilled person would understand that a formula not showing P* but only P may still be chiral. It cannot be read from this passage that the patentee contemplates the use of resolved enantiomers of a compound of formula IX-25- 2, since such a compound is depicted in the patent application with a P and not P*, as well as because the observation of using resolved enantiomers is only made in connection with compound of Formula I. This passage cannot be read to be disclosing the pure resolved diastereoisomers claimed in claim 2 and 3. Even if one is to assume that separate stereoisomers can be arrived at, the complete specification does not disclose how to assign the phosphorus atom steric configuration of the two separated diastereoisomers of claim 2 and 3.

Further, the compounds claimed in claims 2 and 3 depict specifically different configurations at phosphorus atom ((S) and (R) respectively. However, neither these structures nor the IUPAC name of claims 2 and 3 are disclosed as such in the specification of the Present Application. The specification of the Present Application however, fails to disclose specific preparation of stereoisomer, except for the generic procedure in Example 81 which states that certain exemplified compounds were obtained as mixture of diastereomers because of the chirality at phosphorous. The diastereomers were separated on a Chiralpak-AS-H (2 X 25 cm) column under Supercritical Fluid Chromatography (SFC) conditions using 20% methanol in carbon dioxide as solvent. The absolute stereochemistry of the P-chiral
centre of the diastereomers was not determined. However, chromatographic resolution of these two diastereomers provides for isomers that are characterized as fast eluting and slow eluting isomers (see page 695 of the complete specification). The examples given are reproduced below:

<table>
<thead>
<tr>
<th>Compound</th>
<th>EC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example 15 (Diastereometric mixture)</td>
<td>0.86</td>
</tr>
<tr>
<td>Fast Moving isomer of Example 15</td>
<td>1.35</td>
</tr>
<tr>
<td>Slow Moving isomer of Example 15</td>
<td>0.26</td>
</tr>
<tr>
<td>Example 19 (Diastereometric mixture)</td>
<td>0.47</td>
</tr>
<tr>
<td>Fast Moving isomer of Example 19</td>
<td>0.78</td>
</tr>
<tr>
<td>Slow Moving isomer of Example 19</td>
<td>0.92</td>
</tr>
<tr>
<td>Example 49 (Diastereometric mixture)</td>
<td>0.126</td>
</tr>
<tr>
<td>Fast Moving isomer of Example 49</td>
<td>0.93</td>
</tr>
<tr>
<td>Slow Moving isomer of Example 49</td>
<td>5.78</td>
</tr>
</tbody>
</table>

The specification of the Present Application failed to specify (R) and (S) nomenclature to the fast moving and slow moving isomer, which means the applicant did not conclude whether fast moving isomer or the slow moving isomer is the (S)-isomer or vice versa. The Applicant appears to have left to the insight of the reader to find out the stereochemistry of the fast moving and slow moving isomers. If one would assume that the compound of claim 1 can be separated into a slow and fast eluting isomer by following the procedure in Example 81, even then it would be unknown how to determine which of the fast / slow eluting isomers is (R) isomer and (S) isomer. The person having of skilled in the art would have known that the synthesis of nucleosides is often complicated, as a result of the number of chiral centres in the sugar ring and the number of reactive functional groups attached to the sugar (which might give rise to unwanted reactions and which would therefore need masking with suitable protecting groups). Hence, it is difficult to a person skilled in the art to prepare subject matter claimed in claims 1 to 3 specifically claims 2 and 3 and their isolation as a specific diastereomers.

(iv) Arguments of the opponent O10-

At the outset, it is to be noted that the compounds of claims 2 and 3 have not even been mentioned anywhere in the application as filed. Present claim 2 and 3 define the PS and the PR diastereoisomer of the compound of claim 1. The two compounds are disclosed in claims 2 and 3 by means of
structural formulae. Those structural formulae are not disclosed as such in the application as filed. The issue is therefore whether said PS and the PR diastereoisomers are disclosed in the application as filed and can be claimed by means of the structural formulae of claims 2 and 3. The applicant states that the subject matter of claims 2 and 3 finds support in-

a) Compound IX-25-2 in the light of pages 99 and 100 of the application as filed; b) Example 25 in the light of the disclosure of Example 81 and pages 692 to 693 of the application as filed.

It is strongly submitted that none of the above mentioned passages provide a clear and unambiguous disclosure of the subject matter of claims 2 and 3. The subject matter of claims 2 and 3 finds no basis in the application as filed.

a) Compound IX-25-2 in the light of pages 99 and 100 and page 20

During the hearing the applicant’s agent insists that the definition of “P*” on page 20, lines 8 to 16 applies to the whole application. The Opponent disagrees. The disclosure of pages 99 and 100 replaces the disclosure of page 20 when compound IX-25-2 comes into question because pages 99 and 100 specifically refer to tables II to XXXII -including table IX- and contain the information as to the stereochemistry of the phosphorous.

The disclosure of page 20 cannot be combined with the disclosure of compound IX-25-2. On page 99 from line 28 to page 100, line 3 the information on the phosphorous stereochemistry of the compounds of the subsequent tables is provided. The disclosure of pages 99 and 100 simply recognizes that the phosphorous atom is chiral and its configurations S and R are assigned according to the CIP nomenclature. It is necessary to specify that the tetrahedral phosphorous atom is chiral because differently from carbon atoms, the phosphorous oxide compounds are generally less stable and can racemise via a bipyramidal intermediate without a bond cleavage. Hence, in some cases the chirality at the phosphorous atom cannot be detected. Therefore, the disclosure of pages 99 and 100 merely recognize that the compounds disclosed in the subsequent tables exist as phosphorous chiral compounds. However, this disclosure does not individualize the PR and the PS diastereoisomers as depicted and claimed in
claims 2 and 3. Hence, the subject matter of claims 2 and 3 and the structural formulae of claims 2 and 3 cannot be derived from the disclosure of compound IX-25-2 in the light of pages 99 and 100 of the application as filed.

b) Examples 25 and 81 & b1) Example 25 in combination with the disclosure of page 20

Example 25 discloses the mixture of the PS diastereoisomer and the PR diastereoisomer of the compound of claim 1. This mixture has been depicted with the structural formula 25 of page 695. According to applicant, the disclosure of the isolated PS diastereoisomer and the PR diastereoisomer of Example 25 would be easily understood by the skilled person in the light of the definition of page 20, lines 8 to 16. The Opponent strongly disagrees. The disclosure of page 20 refers to the meaning of “P*” and “P” in the structural Markush formulae depicted in the application. The structural formula 25 of page 695 is an exception, because this formula in the context of the application is meant to disclose the PS/PR mixture concretely obtained in Example 25. Therefore, the disclosures of page 20 and of Example 25 stand alone and cannot be combined to arrive at the compounds of claims 2 and 3. As the consequence, the subject matter of claims 2 and 3 and the structural formula of claims 2 and 3 cannot be derived from the structural formula 25 of page 695 in the light of the disclosure of page 20.

b2) Example 25 in the light of Example 81 and page 692 to 693

The applicant submits that the subject matter of claims 2 and 3 results from Example 25 in the light of Example 81. The opponent denies such contention of the applicant. Example 25 read in the light of Example 81 and pages 692-693 does not disclose the subject matter of claims 2 and 3. Example 81 discloses the separated diastereoisomers of the compounds of Examples 15, 39, and 49. Since Example 25 is not mentioned in Example 81, the two separated diastereoisomers of Example 25 are not disclosed as such. Example 81 further mentions that certain exemplified compounds of the instant opposed patent application were obtained as a mixture of diastereoisomers and that the diastereoisomers were separated. This
disclosure is a generalized disclosure of the separation of the
diastereoisomers of the exemplified compound. This generalized disclosure
does not individually disclose that the isomers of Example 25 were
separated.

In this context it is submitted that it is not relevant whether it is easy or not
to determine the stereochemistry of the phosphorous atom. What is relevant
is that each feature of a claim and each combination of features of a claim
must be clearly and unambiguously disclosed in the application as filed.
This is not the case for the stereochemistry R or S of the phosphorous atom
of the compounds of claims 2 and 3. In fact, the result of the allegedly
disclosed separation of compound 25 according to Example 81 does not
provide as a clearly and unambiguously disclosed information the separated
isomers of compound 25 having a determined stereochemistry S or R as
instead is required by claims 2 and 3. Claim 2 does not disclose the isolated
PS and PR diastereoisomers of compound 25. Hence, claim 2 as filed does
not disclose the subject matter of claims 2 and 3 as not defined in the
present application. The definition “its stereoisomer” defines all the possible
isomers of the compound 25 at any of the 6 stereocentres. Even when
assuming, only for the sake of the argument, that the skilled person reading
the application considers that the stereocenter 2R, 3R, 4R, 5R (on the sugar
moiety) do not vary for the purpose of the opposed patent, the skilled person
would understand that a stereoisomer of the compound 25 within the frame
of the opposed application is the R isomer of the chiral carbon atom of the
alanine moiety. He also understands that suitable isomers are the CRPS,
CRPR, CSPR, CPS isomers (C is the chiral carbon atom of the alanine
moiety and P is the chiral phosphorus atom). No preference to any of these
isomers is given in original claim 2. The combination of compound 25 with
the term “stereoisomer” hence refers to several different diastereoisomers of
the claimed compound. No one of these isomers is individualized by the
disclosure of claim 2 as filed, let alone the diastereoisomers of instant claims
2 and 3 of the opposed patent application. Hence, claim 2 as filed does not
disclose the subject matter of the present claims 2 and 3 and ought to be
disallowed.
The above argument holds equally good for the non-allowance of the amendment of the claims made by the applicant on 11th December, 2015 under the provision of section 59 of the Act as ‘……….. no amendment of a complete specification shall be allowed, the effect of which would be that the specification as amended would claim or describe matter not in substance disclosed or shown in the specification before the amendment, or that any claim of the specification as amended would not fall wholly within the scope of a claim of the specification before the amendment.’

It is further reiterated that the opposed patent application does not disclose in an enabling manner the separation of the two compounds of present claims 2 and 3 from the mixture of Example 25. Moreover, the Opponent maintains the position that it amounts to an undue burden for the skilled person to determine the stereochemistry of the phosphorous atom of the compounds claimed in present claims 2 and 3 with the technology and the knowledge available at the filing date of the opposed patent application. The opposed patent provides no examples on how to determine the stereochemistry of the phosphorous atom of phosphoramidates in general and of the claimed compounds in particular.

In the premises, present claims 2 and 3 of the instant application ought to be refused due to no support/ non-enablement and in violation of the provision of section 59 of the Act. Similarly claim 4 and 5, being claims defining a composition comprising ‘compounds as claimed in any of the claims 1 to 3’ and ‘a process for preparation of the compound of claim 1 or a stereoisomer thereof’ respectively ought to be refused in view of no support/non-enablement.

(v) Argumens of the opponent O11-

The compounds in claims 2 and 3 which represent the two possible stereo chemical configurations at the phosphorus of the compound as claimed in claim-1 and these structures are not described or depicted as such in any part of the complete specification as filed. In fact there is no specific compound having a specific stereo chemical configuration at the phosphorus atom is disclosed in the complete specification as filed. The examples described in the complete specification do not demonstrate clearly
the stereo isomeric form. There is no working examples described for the stereo isomeric form and its method of preparation.

The complete specification does not disclose any stereo specific method of synthesis and/or of purification of compounds claimed in claims 2 and 3. In particular, it should be noted that Example 81 on pages 692-693 which relates to the separation of a "fast moving isomer" and a "slow moving isomer" from mixtures of diastereoisomers at the P-chiral center is not applied to the compound of claim 1 (i.e. Example 25) and nothing indicates that it could be applied to this compound. Besides, the absolute stereochemistry of the P-chiral centers of the diastereoisomers cannot be determined using this method.

Accordingly, the one of skill in the art wishing to obtain the compounds claimed in claims 2 and 3 on the basis of the complete specification is left with the undue burden of having to devise stereospecific methods of synthesis and/or of purification of these compounds claimed in claim 2 and 3 by himself.

Thus, the subject-matter of claims 2 and 3 is not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. Therefore, the complete specification is not sufficiently describing the claimed compounds in claim 2 and 3 and the method by which these claimed compounds can be obtained.

The complete specification fails to describe the claimed pharmaceutical composition in claim 4 and process/method by which the claimed pharmaceutical composition prepared clearly by way of best mode of carrying out the invention. Claim 4 relate to compositions comprising the compounds of claims 1-3 and a pharmaceutically acceptable medium. As such, the subject-matter of the claim 4 is not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

There is no clarity on the pharmaceutically acceptable medium as claimed in claim 4. The description is not clearly describing the “pharmaceutically acceptable medium” and its contents.
In addition, inasmuch as claim-4 aims at protecting pharmaceutical composition comprising the compounds of claims 1 to 3 that is the first medical use of these compounds then their subject-matter is also insufficiently disclosed in this regard. There is no working example described for the process/method by which the claimed pharmaceutical composition with any of the compounds of claims 1 to 3 is prepared. Accordingly, the one of skill in the art wishing to obtain the pharmaceutical compositions on the basis of the complete specification is left with the undue burden of having to devise methods of preparation by himself. Thus, the subject-matter of claim 4 is not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. Therefore, the complete specification is not sufficiently describing the pharmaceutical composition and the method by which claimed compositions can be obtained.

Therefore, the alleged claims 2 to 4 of the invention do not meet the requirements of section 10 (4) (a) and (b) along with Section 10(5) of the Patents Act, 1970. Thus, the alleged invention claims 2 to 4 are liable for rejection/refusal on this ground alone.

(vi) Arguments of the opponent O12-

With regards the issue/ground of insufficiency of disclosure, kind attention of the Ld. Controller was invited towards the settled position in law that - the Applicant is casted with a duty to disclose the invention, for which the protection (or monopolistic rights) is being sought, so fully and particularly that a person skilled in the pertinent art can reasonably practice the invention without bearing any undue burden of experimentation. Further, a duty is casted unto the Applicant to disclose, in the as-filed complete specification, a best mode of carrying out (or practicing) the invention over which the protection is sought.

Reference was made to Section 10(4)(a) and 10(4)(b) of the Patents Act – “10(4) every complete specification shall –

(a) fully and particularly describe the invention and its operation or use and the method by which it is to be performed; and (b) disclose the best method of
performing the invention which is known to the applicant and for which he is entitled to claim protection”

Plain reading of provisions of S. 10(4)(b) indicates the mandatory nature of the requirement of disclosure of the best method of performing the invention that is being claimed in one or more claims of the patent application.

Further, provisions of S. 10(4)(b) makes it crystal clear that the Applicant cannot simply avoid his duty to disclose the best mode of practicing the claimed invention, by making bald statements that the application is directed towards a person skilled in the art, and he would or should have known how to practice the claimed invention.

Subject matter of claims over which protection is sought:

The currently pending claim 1 is drawn to a compound of the formula represented below or a stereoisomer thereof.

Claims 2 and 3 are directed to specific stereoisomers at the phosphorous atom, Sp and Rp respectively, of the compound of claim 1. Claim 4 is directed to compositions comprising the claimed compounds; and claim 5 is directed to a process of preparing the claimed compounds.

Non-disclosure of stereochemical structures of the compounds as claimed in pending claims 2 and 3, Attention of the Ld. Controller was drawn towards the fact that the compound disclosed in claims 2 and 3 of the impugned Application are diastereomers of the compound of claim 1 (example 25 highlighted below) i.e. define the PS and the PR diastereomers of the compound of claim 1. The opponent submitted that the impugned Application, albeit discloses plausible existence of diastereomers, owing to chirality at the phosphorous atom, it fails to disclose compounds as claimed in any of the claims 2 and 3 of the impugned Application. The closest compound disclosed in the impugned application is example IX-25-2 (highlighted herein-below); however, it fails to disclose the P stereochemistry
(PS and the PR diastereomers) of the phosphoramidate moiety. This can be seen by reference to the structure of formula IX (P.246) in combination with the parameters of compound IX-25-2 indicated in Table IX-25 (p.254). [Page 246 of impugned Application, WO'634A2]

Further disclosure of pages 99 and 100 of the impugned Application (content whereof are reproduced herein-below), simply recognizes that the phosphorous atom is chiral and its configurations are S and R. It is noteworthy that the phosphorous oxide compounds and their derivatives are generally less stable and can racemise via a bipyramidal intermediate without a bond cleavage. Hence, in several cases the chirality at the phosphorous atom cannot be detected. Therefore, the disclosure of pages 99 and 100 merely recognize that the compounds disclosed in the subsequent tables may exist as phosphorous chiral compounds. However, the disclosure fails to individualize the PR and the PS diastereoisomers as being claimed in claims 2 and 3 of the impugned Application. [Page 90 of impugned Application, WO'634A2]
The aforesaid facts makes it crystal clear that there is absolutely no disclosure with regards the structural formula of diastereomers as claimed in claim 2 and 3 of the impugned Application. Based on submission made supra, it is evident that the Applicant of the Applicant failed to fulfill the duty casted upon them to disclose the best mode of carrying out (or practicing) the claimed invention and hence, each of the claims 2 and 3 are liable to be refused on this ground alone.

Non-disclosure of best mode (method) for separating diastereomers and therapeutic activity of the compounds as claimed in pending claims 2 and 3.
With regards obtaining diastereomers as being claims in pending claims 2 and 3, attention of the Ld. Controller was invited towards the fact that the Applicant is placing reliance on Example 81 provided at Page 692 of the as-filed application to contest that the Example 81 provides a best mode of practicing the invention (method for obtaining the compounds) as claimed in pending claims 2 and 3, contents whereof are reproduced hereinbelow for ready reference:

[Example 81, Pages 692-693 of impugned Application, WO'634A2]

Following notable facts glean from bare perusal of Example 81 of the impugned application:

i. None of the examples (viz. Example 15, 39 or 49) corresponds to the compounds as claimed in any of the claims 2 and 3;

ii. It remains to be presumed that the method disclosed in Example 81 would be amenable to resolve the diastereomeric mixture and would allow one to obtain the compounds as being claimed in pending claims 2 and 3 of the impugned application;

iii. Based on the disclosure at Example 81, one cannot a priori predict, leave alone, ascertain, the compound/diastereomer being obtained as the “Fast moving isomer” and/or “Slow moving isomer”, even if one were to presume that the method as disclosed in Example 81 would be able to resolve the diastereomeric mixture of compound as claimed in claim 1;

iv. Undue burden of experimentation is to be borne by the skilled artisan intending to arrive at the compounds as claimed in any of the claims 2 and 3 by trying and testing the generic method disclosed at Example 81 and various modifications thereof;
v. Undue burden of experimentation is also to be borne by the skilled artisan intending to arrive at the compounds as claimed in any of the claims 2 and 3 by ascertaining the absolute stereochemistry of the compounds eluted as “Fast moving isomer” and “Slow moving isomer”;

vi. Undue burden of experimentation is also to be borne by the skilled artisan intending to use the compounds as claimed in any of the claims 2 and 3 by subjecting each of these compounds to rigorous testing and trials to understand if any of these compounds has the desired efficacy and/or if any of these compounds exhibits toxicity that would render them unsuitable for the purposes as laid down in the impugned application.

The aforesaid facts give rise to the following questions/issues –
(i) Can a mere disclosure of a speculative method, which has not been tried and/or tested for preparation and/or separation of the claimed compound(s), be construed to be the disclosure of best mode of practicing the claimed invention, as required u/S 10(4)(b)?

(ii) Can an Applicant simply avoid its duty of disclosure of best mode of practicing the claimed invention u/S 10(4)(b) by disclosing a generic method that imposes an undue burden of experimentation on the skilled artisan intending to practice the claimed invention?

Based on the aforesaid facts, it is clear that by no stretch of imagination, the impugned application be construed to be in consonance with the provisions of S. 10(4)(b), and for this reason alone, each of the claims 2 and 3 ought be refused u/S 25(1)(g).

Non-disclosure of best mode (method) for synthesizing the compounds as claimed in pending claims 1-3 and 5, and non-disclosure of best mode (method) for obtaining a composition as claimed in claim 4

Kind attention of the Ld. Controller was further drawn towards the fact that - it is an admitted position of the Applicant in the Statement and Evidence to the instant representation that the Application does not specifically disclose a method for synthesis of compound as claimed in pending claim 1; however, a generic method has been disclosed and a skilled artisan should be (or would be) able to synthesize the compound of claim 1 based on such disclosure. Particularly, the Applicant is placing reliance on the process
disclosed in Examples 5 to 8 of the specification, to contest that these generalized synthetic processes for preparation of compounds, which are similar to the claimed compounds, provides sufficient guidance to the skilled artisan on how to synthesize the claimed compounds. For ready reference, relevant portions from Statement and Evidence are reproduced herein:

[Page 27-28 of Statement of Evidence of Applicant to the instant representation]

18.3 The Example in the specification which is most relevant to the claimed subject matter is Example 25. That Example discloses the preparation of a compound according to claim 1, as a diastereomeric mixture (see page 683 of corresponding WO 2008/121634 A2). The specification explains that the compounds of Example 25 can be prepared “using similar procedures described for Examples 5-8” (see id. at page 682).

18.4 Examples 5 to 8 can be found at pages 675 to 678 of WO 2008/121634 A2. Each of Examples 5 to 8 exemplify the same general synthetic process. In each case the process described includes dissolving the appropriate phosphorochloridate (depending upon the particular phosphoramidate promoiety desired) in tetrahydrofuran (THF), adding that solution to a mixture of 2'-deoxy-2'-fluoro2'-C-methyluridine and N-methylimidazole with vigorous stirring at room temperature, and then stirring overnight. Examples 5 to 8 clearly demonstrate that regardless of the particular phosphorochloridate utilized as starting material, the reaction is carried out in the same manner under the same conditions and produces the corresponding prodrug.

18.5 Given this demonstration that varying the phosphorochloridate did not impact the reliability of the reaction, these Examples demonstrate that a skilled person would reasonably and correctly understand that utilizing the same reaction conditions and the same process with the appropriate phosphorochloridate would, and in fact did, produce the compound of Example 25.

18.6 It would be quite evident to a person skilled in the art that the corresponding reaction done in Example 25 of ‘3658 involved the addition of phenyl isopropyloxalaninyl phosphorochloridate dissolved in THF to a mixture of 2'-deoxy-2'-fluoro-2'-C-methyluridine and N-methylimidazole in the
same way as in Examples 5 to 8. The reaction scheme is shown below, and follows that in Examples 5 to 8.

It is noteworthy that, as established supra, when the impugned application fails to disclose the exact stereochemical structures of the compounds claimed in claims 1-3 of the impugned Application, there does not arise a question of disclosure of exact methods of preparation of compounds as claimed therein.

It is also noteworthy that the pending claim 5 is drawn towards a method for synthesis of compounds of claims 1-3. As established supra, when the impugned application fails to disclose the exact stereochemical structures of the compounds claimed in claims 1-3 of the impugned Application, there does not arise a question of the impugned application being in consonance with provisions of S. 10(4)(b) with regards pending claim 5, and hence, claim 5 ought to be refused.

Also noteworthy is the fact that pending claim 4 is drawn towards a composition comprising compounds of any of claims 1-3, and that nowhere in the impugned application, the Applicant has provided any example illustrating preparation of a suitable composition, making it clear that the pending claim 4 is in contravention of provisions of S. 10(4)(b), and for this reason alone, pending claim 4 ought to be refused.

Based on submission made supra, it is evidently clear that there is absolutely no disclosure of the exact process of preparation/synthesis of the compounds as claimed in the impugned Application, and for this reason alone, each of the claims 1-5 ought to be refused.

11(b) Hearing submission by the applicant on section 25(1)(g)-

i. Opponents argued that compound of claim 1 and its specific diastereomers of claims 2-3 are not clearly and sufficiently disclosed in the specification.

ii. Applicant strongly defers with this allegation and respectfully submits that claim 1 is directed to a compound represented by the formula
The compound has six chiral centers. The stereochemistry at five of the chiral centers is depicted in claim 1. The stereochemistry at the phosphorus atom is not specified in the formula above. The claim 1 therefore encompasses any compound that may be represented by the formula of claim 1 and encompasses mixtures of diastereomers and isolated diastereomers in which the stereochemistry at the P atom is either Sr or Rr. In other words, above formula of claim 1 encompasses compounds regardless of stereochemistry at the phosphorus atom, i.e. it encompasses both diastereomeric mixture and the individual diastereomers.

iii. The lines at the phosphorus atom in the formula above do not show three-dimensional geometry at the atom. It is noted on page 100 of the specification that such a structure includes all possible stereochemical configurations at the phosphorous atom. There is, therefore, no feature in claim 1 that has any limiting effect regarding the stereochemistry at the phosphorus atom. The formula of claim 1, therefore, clearly encompasses both diastereomeric mixture and individual diastereomers.

iv. Claims 2 and 3 are directed to the specific diastereomers, respectively, i.e.: 

v. Applicants submits that the complete specification at page 20, under "definitions of the invention" with respect to compounds in which the P atom
is chiral, the resolved diastereomers are explicitly disclosed as embodiments of the invention. The paragraph reads as below:

"The term "P*" means that the phosphorous atom is chiral and that it has a corresponding Cahn-Ingold-Prelog designation of "R" or "S" which have their accepted plain meanings. It is contemplated that compounds of the formula I are racemic because of the chirality at phosphorous. Applicants contemplate use of the racemate and/or the resolved enantiomers. In some instances, an asterisk does not appear next to the phosphoramidate phosphorous atom. In these instances, it is understood that the phosphorous atom is chiral and that one of ordinary skill understands this to be so unless the substituents bound to the phosphorous exclude the possibility of chirality at phosphorous, such as in P(O)Cl/’, (emphasis added).

Thus, the present specification discloses a chiral phosphorus atom and that use of either a mixture of diastereomers and/or the resolved diastereomers is disclosed in the specification.

vi. Further, on page 8-9 of the complete specification there is disclosed a compound of formula (I)

\[
\begin{align*}
\text{in order for general formula (I) to include the compound of claim 1 the following matches must hold:}
\end{align*}
\]

R1 = phenyl; R2 = hydrogen; R3a = hydrogen; R3b = methyl; R4 = isopropyl; R5 = hydrogen; R6 = methyl; X = F; Y = OH; Base = Uracil, for that base has to be formula b with R7 and R8 being hydrogen.

From the definitions of various substituents on page 9 of the priority document, it is clear that R1 is aryl which includes phenyl, (page 9, line 1-
2); R2 is hydrogen, (page 9, line 7); R3a is H and R3b is independently selected from H, CH3....(page 9, line 20); R4 is C1-10 alkyl, (page 10, line 1) and the definition of alkyl covers isopropyl (page 13 line 10); R5 is hydrogen (page 10 line 3); R6 is CH3 (page 10 line 11); X is F (page 10 line 12); Y is OH (page 10 line 13); Base is formula b wherein R7 and R8 are independently hydrogen (page 11).

vii. On page 36 of the complete specification, the first aspect of the second embodiment is directed to a compound of formula (1-3) which also covers and supports the specific compound of claim 1.

viii. Further, on page 42 of complete specification, the fifth aspect of second embodiment is directed to a compound of formula (I-4) which defines the stereochemistry around the chiral carbon atom and covers or supports the compounds of claims 1, 2 & 3.

ix. In case of IX-25-2 each of R2-R9 have been specified and should be read in combination with formula IX on page 243. The applicant considered that the passage on page 96 referring to the first orientation of R3a and R3b is a preferred variation as is further shown e.g. by example 82 on page 695 where all the tested compounds have this configuration. There is also no selection from lists involved because all the substituents in formula (II) are set out in a single line. This should be combined with the statement of all possible stereochemical configurations possible for phosphorus and IX-25-2 which is considered to be directly related to it, thereby directly individualizing the diastereomers of claim 2 and 3.

x. The Applicant also refers back to page 18 of the complete specification, which reads "It is contemplated that compounds of formula I are racemic because the chirality at phosphorous. Applicant contemplate use of the racemate and/or the resolved enantiomers".

xi. The Example in the specification which is most relevant to the claimed subject matter is Example 25. That Example discloses the preparation of a
compound according to claim 1, as a diastereomeric mixture (see page 683 of corresponding WO 2008/121634 A2). The specification explains that the compounds of Example 25 can be prepared “using similar procedures described for Examples 5-8” (see id. at page 682).

xii. Examples 5 to 8 can be found at pages 675 to 678 of PCT publication WO 2008/121634 A2. Each of Examples 5 to 8 exemplify the same general synthetic process. In each case the process described includes dissolving the appropriate phosphorochloridate (depending upon the particular phosphoramidate promoiety desired) in tetrahydrofuran (THF), adding that solution to a mixture of 2'-deoxy-2'-fluoro-2'-Cmethyluridine and N-methylimidazole with vigorous stirring at room temperature, and then stirring overnight. Examples 5 to 8 clearly demonstrate that regardless of the particular phosphorochloridate utilized as starting material, the reaction is carried out in the same manner under the same conditions and produces the corresponding prodrug.

xiii. Given this demonstration that varying the phosphorochloridate did not impact the reliability of the reaction, these Examples demonstrate that a skilled person would reasonably and correctly understand that utilizing the same reaction conditions and the same process with the appropriate phosphorochloridate would, and in fact did, produce the compound of Example 25.

xiv. It would be quite evident to a person skilled in the art that the corresponding reaction done in Example 25 of ‘3658 involved the addition of phenyl isopropoxyalaninyl phosphorochloridate dissolved in THF to a mixture of 2'-deoxy-2'-fluoro-2'-Cmethyluridine and N-methylimidazole in the same way as in Examples 5 to 8. The reaction scheme is shown below and follows that in Examples 5 to 8.

\[
\begin{align*}
\text{Phenyl isopropoxyalaninyl phosphorochloridate} & \quad \text{2'-deoxy-2'-fluoro-2'-Cmethyluridine and N-methylimidazole}
\end{align*}
\]

xv. The specification teaches how to prepare the appropriate phosphorochloridate in Example 2 (id. at pages 672-673). The specification
also teaches how to prepare the appropriate 2'-deoxy-2'-fluoro-2'-C-methyluridine in Example 4 (id. at pages 674-675).

xvi. The specification confirms that the reaction of 2'-deoxy-2'-fluoro-2'-C-methyluridine and the appropriate phosphorochloridate according to the procedure set forth in Examples 5 to 8 was in fact completed, and that the compound of Example 25 was obtained and isolated. NMR data for the compound of Example 25 are provided (id. at page 683) and activity data are provided (id. at page 695).

xvii. It is simply not credible to assert that any skilled chemist would have difficulty in repeating the procedures set out in the specification to produce the compound of Example 25. Further, any skilled chemist would also have been well able to follow the teaching of Example 81 to resolve the individual diastereomers, as explained in detail below.

xviii. Claims 2 and 3 are directed to specific diastereomers of a compound as claimed in claim 1. These diastereomers arise from the chiral center at the phosphorus atom.

xix. Example 81 on page 694, makes it clear that diastereomers of the application have been separated and isolated. Example 81 explains that diastereomeric mixtures arising from the chiral center at the P atom can be resolved using Supercritical Fluid Chromatography (SFC) on a Chiralpak-AS-H (2 x 25) column using 20% methanol in carbon dioxide as solvent. Claim 2 covers the compound of example 25 and this only gives the possibility of the two diastereomers at the phosphorous atom. As there is direct disclosure of a single compound which includes the two diastereomers, the skilled person knows that these are at phosphorous atom and knows how to extract them. Applicant submits that complete specification makes specific reference to the two diastereomers and that these have effectively been individualized. When reading the table (i.e. for IX-25-2) both configurations for the phosphorous center have to be read into the table, thereby providing a simple and direct disclosure. As there are only two possibilities, R and S at the phosphorous atom, the compounds of claims 2 and 3 are also not just covered but also disclosed. A skilled chemist would have had no difficulty in applying the technique described in Example
81 to other compounds, such as that of Example 25, with a reasonable expectation that they would be able to resolve the specific diastereomers from the diastereomeric mixture.

xx. Further, as filed specification mentions in Example 81 that certain exemplified compounds were obtained as mixture of diastereomers because of chirality at Phosphorous. These diastereomers were separated as fast eluting and slow eluting isomers and, representative examples have been provided for compounds of examples 15, 39 and 49. A person skilled in the art will be able to separate two diastereomeric compounds of claim 2 and 3 from compound claimed in claim 1, in view of the teaching provided for other exemplified compounds. The specification is meant to be read by a person skilled in the art, not by diamond merchant. Therefore, opponent's allegation are incorrect and misleading that Applicant did not separate and possess two diastereomers. Applicant submits that the two diastereomers were separated and applicant possessed two diastereomeric compounds of claim 2 and 3.

xxi. In brief, compound of claim 1 is fully enabled in the specification along with the activity data (compound IX-25-2). Further, specification specifically provides embodiment which is directed to a compound of formula (I-4) which defines the stereochemistry around the chiral carbon atom and covers or supports the compounds of claims 2 & 3. Further, page 18 of the complete specification, reads "It is contemplated that compounds of formula I are racemic because the chirality at phosphorous. Applicant contemplate use of the racemate and/or the resolved enantiomers". In view of this, it is amply clear to the person skilled in the art that claimed compound 1 (compound IX-25-2) would exist in two diastereomers forms because of the chirality at the phosphorous atom; corresponding compounds are claimed in Claims 2 and 3. Even otherwise, as admitted by the Opponent on page 29 of their opposition petition that it is clear to the skilled person and part of his common general knowledge that stereoisomers may be provided in a (S)- or (R)- form. A person skilled in the art would generally recognized how to separate various stereoisomers such as pending Claims 2 and 3 from a
racemic mixture. Accordingly, the present specification provides sufficient support for pending Claims 2 and 3.

xxx. As per the well accepted International patent practice, the Applicant has right to claim the base compound along with its possible diastereomers which are well within the ambit of skilled person. Further Indian Patent Act defines “invention” and “capable of industrial application” as below: 2(j) "invention” means a new product or process involving an inventive step and capable of industrial application; 2(ac) "capable of industrial application", in relation to an invention, means that the invention is capable of being made or used in an industry.

It is humbly submitted that Claim 2 and 3 meets the criteria of above definitions. Claims 2 and 3 are capable of being made and used in an industry, accordingly, it is not required by the Indian patent Act to provide activity of each and every diastereomers which are encompassed in the compound claim.

ii. In addition, pending Claims 2-3 have been recognized and granted in many corresponding jurisdictions including the country where the provisional priority application was filed i.e. US. In view of the above submissions, it is clear that the compounds of claims 2 and 3 are well supported by the original disclosure of complete specification.

12. Ground (V) : Section 25(1)(h)- that the applicant has failed to disclose to the Controller the information required by section 8 or has furnished the information which in any material particular was false to his knowledge

12(a) Hearing submission by the opponents on section 25(1)(h)-

No Submission filed by opponent O4, O5, O7 & O10. Oppinents O1 and O11 submitted as follows-

The Applicant has not submitted information in respect to the corresponding applications filed in foreign countries and particulars of amendments made in order to respond to FER and pre-grant oppositions in the said countries. For example, the Applicant has failed to disclose the rejection of its Chinese patent application for the same subject matter. The Applicant filed a fresh Form 3 showing the status of the corresponding
foreign patent application on 3rd December 2018 (after the hearing). The status of the Chinese patent application CN2008800180242 has been marked as "Published" in the said document which is a categorical misstatement. The status page of CN2008800180242 from the State Intellectual Property Office (SIPO) of China showing that the patent application in question has in fact been rejected is submitted herewith as Annexure A. The Opponent reiterates that in the pre-grant opposition pertaining to the corresponding European patent, the opposition board in their decision accepted the arguments of the opponents and rejected claims 2 and 3 and the dependent claims relating to the isomeric forms of the compositions comprising the compounds and pharmaceutically acceptable medium thereof. However, this fact has not been disclosed by the Applicant to the Indian Patent Office and amounts to a material non-disclosure which ought to result in the rejection of the patent under Section 25(1)(h).

The corresponding substantially equivalent applications were rejected by Egyptian Patent Office (EGPO). We are in touch with the officials at Egyptian patent office to procure the file wrapper of respective refusals/rejections. In the interim, please note the corresponding Egyptian patent application number as “EG2011001955” that is rejected by the EGPO. Similar situation exists in Russia, Japan, Brazil and China the application and publication number details are provided in the below table

<table>
<thead>
<tr>
<th>Name of the Country</th>
<th>Publication No. &amp; Application No.</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Russia</td>
<td>RU2651892C3 &amp; RU2009139968A</td>
<td>Invalidation on specific aspects of the patent specification.</td>
</tr>
<tr>
<td></td>
<td>RU2012152811A</td>
<td>Application was withdrawn by the applicants in view of the office action.</td>
</tr>
</tbody>
</table>
From the above, it is clear that the Applicant’s is hiding this sensitive and crucial information from Indian Patent Office (IPO) to gain undue advantage in the Indian market by falsely procuring and enforcing the rights in the territory of India against the local pharmaceutical companies. This inequitable conduct of the Applicant in itself is an admission that they are on the shaky grounds with unclean hands in front of the IPO. In short, the Applicant has fully and completely failed to meet the requirement of Section 8. In light of the rejections in the corresponding Russian and Egyptian applications, we humbly request the Ld. Controller to reject the present patent application of the applicant.

12(b) Hearing submission by the applicant on section 25(1)(h)-
During the Hearing, Opponent urged that relevant information under section 8 has not been submitted by the Applicant. Specially, Opponent urged that Applications in Russia and Egypt are refused and the same has not been submitted to IPO. It is important, however, to mention herein that there is no such allegation in Opposition petition. Most importantly, Opponent did not produce any document or evidence in support of these allegations made during hearing. Even the Opponent did not provide any patent application number for the application filed in said countries. Without prejudice, Applicant submits that the allegations of the Opponent are completely false and frivolous for the following reasons-
1. There is no corresponding Egyptian patent application.
2. As regards Russia, details of four applications has been submitted in previous form 3, and further updated status is as under:

<table>
<thead>
<tr>
<th>Country Name</th>
<th>Status</th>
<th>Application Number</th>
<th>Date Filed</th>
<th>Patent Number</th>
<th>Grant Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Russian Federation</td>
<td>Abandoned</td>
<td>2012152811</td>
<td>Mar 26, 2008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Russian Federation</td>
<td>Pending</td>
<td>2018103329</td>
<td>Mar 26, 2008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Russian Federation</td>
<td>Granted as replacing 2478104</td>
<td>2009139968</td>
<td>Jun 16, 2016</td>
<td>2651892</td>
<td>Apr 24, 2018</td>
</tr>
</tbody>
</table>

Applicant submits that one application (App. No. 2012152811) is abandoned, and other application (App. No. 2018103329) is currently pending. Russian Patent No. 2651892 is a reissued patent replacing partially invalidated Russian Patent No. 2478104. PTE has been granted for Russian Patent No. 2651892 (March 26, 2028, to March 25, 2031). The Russian IP Court has finally decided in favor of Gilead and confirmed that the new Russian Patent No. 2651892 and the corresponding PTE case stand.

**CONTROLLER ANALYSIS AND OPINION**

**13. ANALYSIS OF PRIOR ART DOCUMENTS**

The documents cited by the opponents during hearing are discussed herewith in sequence of publication of such documents in order to better understand the chronology of the prior art knowledge available to a person skilled in the art and its relevance thereof.

**Year -1994**

**D8** (1994) is a non patent literature published in 1994 which reports that certain triester derivatives of the inactive nucleoside analogue, dideoxy uridine (ddU) are inhibitors of HIV replication at μM levels.
dideoxy uridine

It further recognizes the need for masking the highly charged phosphate groups in order to facilitate intracellular release of nucleoside and found aryloxyphosphoramidates are useful as masking agents for AZT. It is observed that dideoxy uridine (ddU) and its derivatives (3a, 3b, 3c) are reported for HIV activity and are structurally very different from the claimed compound, w.r.t. nucleoside moiety and the phosphoramidate moiety.

**Year 1995**

D18 (1995) is a review paper capturing different literatures known in the field of nucleotide prodrugs. It discloses the following compounds:
It is observed that D18 does not disclose or suggests a prodrug comprising the claimed nucleoside moiety and phosphoramidate moiety.

**Year 1996**

**D10** (published on 12 April 1996) reports the new phosphate derivatives of the anti-HIV nucleoside analogue d4T as potential membrane-soluble prodrugs of the bioactive free nucleotide.

It further suggests the successful intracellular delivery of free nucleotides by the masked phosphate triester prodrugs. The phosphoramidate derivatives of d4T show advantage over d4T itself particularly in thymidine kinase deficient cells.

It is observed that disclosed compounds are structurally completely different from the claimed compounds and reports HIV activity.

**D11** (July 1996) discloses So324 which is a 2’,3’-dideoxy-2’,3’-didehydrothymidine-5’-monophosphate (d4T-MP) prodrug containing at the phosphate moiety a phenyl group and the methylester of alanine linked to the phosphate through a phosphoramidate linkage. So324 has anti-HIV activity in human CEM, MT4, and monocyte/macrophage cells that is superior to that of d4T.
It is observed that D11 discloses phosphoramidates prodrugs of the d4T which are structurally completely different from the claimed compounds and have anti-HIV activity.

**Year 1999**

**D19** (published on 02.09.1999) & **D20** (published on 19.02.2002)-

It may be noted that D20 is the family document of D19 hence both the documents are discussed together. D19 & D20 discloses a family of 2'-fluoronucleosides of several general formulae useful for treating HCV.

D19/D20 provides a general definition of R2 as “stabilized phosphate prodrug”.

It is observed that neither there is any specific teaching or disclosure for a phosphoramidate group at R2 nor any disclosure or suggestion regarding a nucleoside group with a 2'-fluoro (down) – 2'-methyl (up) substitution pattern.

**D12** (1999) investigates the metabolism of phosphoramidate triester prodrugs of 2',3'-didehydro-2',3'-dideoxythymidine(d4T) and 3'-azido-2',3'-dideoxythymidine (AZT) with reference to anti-HIV activity.
It further states that for both the d4TMP and AZTMP phosphoramidate derivatives, L-alanine was shown to be preferred amino acid.

It is observed that D12 discloses phosphoramidates prodrugs of the d4T and AZT both of which are structurally completely different from the claimed compounds and have anti-HIV activity.

**Year 2000**

**D13** (2000) reports the synthesis and anticancer activity of a series of AZT phosphoramidate monoesters containing amino acid methyl ester (3a-11a) and N-alkyl amide (3b-11b, 9c-9f) moieties. Marked stereochemical preference for the L-amino acid stereochemistry in MCF-7 cells is observed during study. D13 reports that anti-cancer activity of amino acid phosphoramidate is enhanced by an aromatic amino acid side chain preferably L-indolyl methyl group.

It is observed that D13 discloses amino acid phosphoramidate prodrugs of AZT which are structurally completely different from the claimed compounds and have anti-cancer activity.

**Year 2001**

**D22** (published on 29.11.2001)

D22 discloses markush structure for 3-D- or 3-L-nucleoside having formulas (I) to (XVIII) and compositions thereof for the treatment of hepatitis C infection. D22 discloses compound of formula XI -
wherein base is a purine or pyrimidine base (which includes, but is not limited to uracil); and among list of chemical groups for different substituents R1-R7, R1 includes phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); X is O; R2 includes H; R6 includes alkyl (including lower alkyl) and R7 includes chlorine, bromine, iodine.

It is observed that D22 discloses generic compounds of formula I-XVIII and the compound of formula XI referred by the opponents does not disclose fluorine group for R7. D22 does not disclose any nucleoside moiety with a 2'-fluoro (down) and 2'-methyl (up) substitution pattern on the sugar ring. Further none of the eighteen Markush formulas of D22 discloses a phosphoramidate moiety.

D3 (published on 06.12.2001) discloses markush structures of 3-D- or -L-nucleoside of the Formulas (I) to (XVIII) (encompassing several thousand compounds), methods and compositions for the treatment of a host infected with a flavivirus or pestivirus infection. D3 discloses prodrug of compounds of formula XI & XVI-

![Diagram](image)

wherein there is list of chemical groups defined for each substituent R1-R7. It is observed that for formula XI, definition of R7 does not include fluorine and definition of R1 include only phosphate. Further for formula XVI, definitions of R7 and R8 does not include fluorine and definition of R1 include only phosphate hence a nucleoside moiety with a 2'-fluoro (down) – 2'-methyl (up) substitution pattern on the sugar ring is neither disclosed nor suggested. It is observed that eighteen Markush formulas of D3 neither discloses a phosphoramidate moiety nor suggest combining phosphoramidates with the required nucleoside at the 5'-carbon of the sugar moiety.
**Year 2002**

**D17** (published on 31.01.2002) relates to prodrugs of methoxyphosphonate nucleotide analogues having anti-HIV activity and identified GS 7340 as a preferred embodiment.

![Chemical structure of GS-7340](image.png)

GS-7340 is a prodrug containing at the phosphate moiety a phenyl group and the Isopropylester of alanine linked to the phosphate through a Phosphoramidate linkage. D17 also discloses the stereoisomers of GS 7340. It is observed that the disclosed compounds do not disclose the claimed nucleoside moiety.

**Year 2004**

**D25** (published on 08.01.2004) discloses various generic compounds representing modified 2' and 3' nucleoside prodrugs for treating flaviridae infections. D25 discloses the compound of formula (IV)-

![Chemical structure of D25 compound](image2.png)

wherein definition of substituents for R1, R2, R6 & R7 includes large number of substituents which also includes R1 as phosphate (including mono-, di- or triphosphate and a stabilized phosphate) or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein R1 is phosphate (including mono-, di- or triphosphate); wherein in one embodiment R2 and/or R3 is not phosphate (including mono-, di- or triphosphate or a stabilized phosphate prodrug). R2 as H; X as -O; R6 as methyl (-CH3); R7 as Fluoro (F); Base as formula (F)
where W1 is N; W4 is CH; X2 is H; Y1 is OH.

It is observed that for base of formula (F), W4 cannot be CH if W1 is N hence excluding uracil base therein. D25 neither discloses any phosphoramidate moiety nor suggests the use of a phosphoramidate moiety at 5’ carbon of the sugar.

D9 (2004 Mar-Apr) reports that amino acid phosphoramidates of nucleosides have been shown to be potent antiviral and anticancer agents with the potential to act as nucleoside monophosphate prodrugs. Therefore, the authors investigated their ability to deliver 3’-azido-3’-deoxythymidine (AZT) 5’-monophosphate to cells and mechanism thereof.

D9 demonstrated that 3’-azido-3’-deoxythymidine (AZT) amino acid phosphoramidates are potent, nontoxic antiviral, and/or anticancer agents. It is observed that compounds disclosed in D9 are structurally completely different from the claimed compounds both in terms of nucleoside and phosphoramidate moiety.

D15 (2004) is a review article wherein the authors attempted to find out whether there was any general phosphoramidate motif that could be applied to all nucleosides. While no such motif was found, some general principles were established. A dependence of length of amino acid on anti-viral activity was found and alanine was found most efficacious. On the other hand, the alkyl side chain could be between 1-6 carbon atoms. Final reference was given to phenolmethoxyalaninyl group.
D15 also reports preferred moieties for a successful phosphoramidate triester outcome.

It is observed that D15 primarily discusses nucleoside analogues AZT and d4T both of which are thymidine analogues in reference to anti HIV activity and structure activity relationships studies referred therein are based on such nucleoside analogues. Further D15 concludes that aryloxy phosphoramidate approach works poorly for AZT but well for d4T and a range of dd and d4 nucleosides. D15 does not disclose any compound with claimed nucleoside moiety and phosphoramidate moiety and not suggests use of such nucleoside in treatment of HCV.

**D27** (published on 11.11.2004) discloses a conjugate comprising an antiviral compound linked to one or more phosphonate groups or pharmaceutically acceptable salt or solvate thereof. D27 provides large number of such conjugates having formulas 502-569.

It is observed that D27 does not disclose even a single compound with 2'-fluoro (down) and 2'-methyl (up) substitution at deoxyribose sugar ring of nucleoside moiety containing uracil base.

**Year 2005**

**D1** (published on 13.01.2005) discloses a (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D or β-L) or its pharmaceutically acceptable salt or prodrug thereof of the structure:

![Chemical structure](image)

wherein Base is a purine or pyrimidine base; X is O, S, CH2, Se, NH, N-alkyl, CHW (R, S, or racemic), C(W)2, wherein W is F, Cl, Br, or I; and, R1 and R7 are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate.
prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid, a carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein R1 or R7 is independently H or phosphate; R1 and R7 can also be linked with cyclic phosphate group and methods for the treatment of Flaviviridae infections, especially hepatitis C virus (HCV). D1 refers to certain prodrugs generally and the structure of prodrugs provided in the specification are either N-acyl prodrugs or amide ester prodrugs at 3'- or 3'- and 5'- amide ester prodrugs.

It is observed that D1 does not disclose or describe any aryloxy phosphoramidate. As the definitions provided for “pyrimidine” base in D1 includes uracil so D1 can be considered to generically disclose (2'R)-2'-deoxy-2'-fluro-2'-C-methyl nucleosides having uracil base but it does not disclose any specific example or reference of (2'R)-2'-deoxy-2'-fluoro-2'-C-methyluridine and the examples disclosed relates to (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine (see example 1 & 2), (2'R)-6-Chloro-2'-Deoxy-2'-Fluoro-2'-C-Methylpurine (see example 2) and (2'R)-2'-Deoxy-2'-Fluoro-2'-C-Methyladenosine (see example 3) only. Further D1 refers to certain prodrugs in general, but does not disclose any type of phosphoramidate moiety.

D2 (published on 10.02.2005) discloses nucleotide derivatives of formula (I) and their use in the treatment of cancer-

![Chemical structure](image)

wherein:
R is selected from the group comprising alkyl, aryl and alkylaryl; R' and R" are independently selected from the group comprising H, alkyl and alkylaryl,
or R' and R" together form an alkylene chain so as to provide, together with the C atom to which they are attached, a cyclic system; Q is selected from the group comprising -O- and -CH2-; X and Y are independently selected from the group comprising H, F, Cl, Br, I, OH and methyl (-CH3); Ar is a monocyclic aromatic ring moiety or a fused bicyclic aromatic ring moiety, either of which said ring moieties is carbocyclic or heterocyclic and is optionally substituted; Z is selected from the group comprising H, alkyl and halogen; and n is 0 or 1, wherein when n is 0, Z' is -NH2 and a double bond exists between position 3 and position 4, and when n is 1, Z' is =O; or a pharmaceutically acceptable derivative or metabolite of a compound of formula I; with the proviso that, except where R is 2-Bu (-CH2-CH(CH3)2) and one of R' and R" is H and one of R' and R" is methyl (-CH3), when n is 1 and X and Y are both H, then Ar is not unsubstituted phenyl (-C6H5).

Further, D2 also discloses that changes to the ester derivative indicated significant changes in potency by referring to ca 4-fold potency boost of phosphoramidate of d4T (10) over phosphoramidate of d4T (9):

It is observed that D2 does not specifically disclose any compound with unsubstituted uracil base attached to sugar and the unique substitution pattern of 2'-fluoro (down) and 2'-methyl (up) at 2'-position of sugar ring and phosphoramidate with isopropyl ester of alanine amino acid. The compounds disclosed are anticancer compounds and no HCV activity is shown therein.

D7 is a non patent literature published in April 2005, which studies anticancer floxuridine amino acid ester prodrugs compounds synthesized using aspartic acid, lysine, and proline amino acids.
D7 also discuss that, “Prodrug strategies are generally adopted to improve the undesirable properties of therapeutic drugs to overcome barriers, such as poor oral absorption, chemical instability, and toxicity. The design of amino acid ester prodrugs offers a high degree of flexibility, because there are a large variety of amino acids available for optimization of prodrugs.” and concludes that, “A carefully selected amino acid can also make a nucleoside analogue, such as floxuridine into a carrier-mediated substrate. Peptide transporter-mediated uptake of these prodrugs could potentially increase intestinal absorption if delivered orally or be used to target specific cancer cell types expressing these transporters. Further studies with more structurally diverse amino acids and nucleoside analogues could eventually lead to the development of a structure-activity and structure-transport relationship database that could facilitate optimal prodrug design.”

It is observed that floxuridine amino acid ester prodrugs compounds disclosed in D7 lacks 2’-fluoro (down), 2’-methyl (up) substitution of the ribose ring and have fluoro substituted uracil base. Further there is no disclosure or suggestion to use phosphoramidate moiety in D7. 

D21 (published on web on 26/07/2005) describes the synthesis and biological activity of β-D-2’-deoxy-2’-fluoro-2’-C-methyl cytidine (compound 1) as a potent anti-HCV agent. Further D21 also discloses β-D-2’-deoxy-2’-fluoro-2’-C-methyl uridine (compound 9)

Both compound 1 and compound 9 were tested for anti-HCV activity in both a cell based quantitative real time RT-PCR assay and surrogate bovine viral
diarrhea virus (BVDV) assay. It was found that compound 9 demonstrated no activity or cytotoxicity in any assay whereas compound 1 demonstrated potency but no cytostasis in HCV replicon assay but was inactive in BVDV assay. D1 under the heading 'Stereoisomerism and Polymorphism' (pages 51-54) discusses how the nucleoside compounds covered have several chiral centres and may exist in and be isolated in optically active and racemic forms, as do most amino acids which can exist as separate enantiomers. Pages 52-53 then set out commonly known techniques in the art for obtaining optically active materials.

It is observed that though the claimed nucleoside moiety, β-D-2'-deoxy-2'-fluoro-2'-C-methyl uridine, was disclosed in D21 but it was found to be inactive for anti-HCV activity. Further D21 does not disclose any prodrugs for the disclosed compounds.

D26 (published on 02.02.2006) provides a method for preparing the anti-HCV nucleosides containing the 2-deoxy-2-fluoro-2-C-methyl-β-D-ribofuranosyl nucleosides from a preformed, preferably naturally-occurring, nucleoside. D26 also provides a process for preparing a 2-deoxy-2-fluoro-2-methyl-D-ribonolactone derivative and conversion of the lactone to nucleosides with potent anti-HCV activity, and their analogues.

It is observed that D26 discloses nucleosides having different structure and does not disclose phosphoramidates.

D4 (published on 02.02.2006) discloses nucleoside aryl phosphoramidates of formula

![Chemical structure](attachment:chemical_structure.png)

their synthesis and use as precursors to inhibitors of RNA-dependent RNA viral polymerase (including precursors to inhibitors of hepatitis C virus (HCV) NS5B polymerase). Further, it discloses that, “the aryl phosphoramidates of the present invention act as prodrugs of the
corresponding nucleoside 5'-monophosphates. Endogenous kinase enzymes convert the 5'-monophosphate into their 5'-triphosphate derivatives which are the inhibitors of the RNA-dependent RA viral polymerase. Thus, the aryl phosphoramideates may provide for efficient target cell penetration than the nucleoside itself, may be less susceptible to metabolic degradation, and may have the ability to target a specific tissue, such as the liver, resulting in a wider therapeutic index allowing for lowering the overall dose of the antiviral agent”.

It is observed that it discloses phosphoramide derivative of only purine bases with methyl (up) and hydroxy (down) substitution pattern at 2'-position. D4 suggests that aryl phosphoramideates of disclosed compounds act as prodrugs of the corresponding nucleoside 5'-monophosphates and the aryl phosphoramideates may provide for efficient target cell penetration than the nucleoside itself but no actual activity is reported specifically for any of the five compounds synthesized therein. D4 neither discloses nucleosides with pyrimidine base having methyl (up) and fluoro (down) substitution pattern at 2'-position, nor does it discloses/suggests claimed phosphoramide moiety having specific substituents thereon. D16 (published on 29.06.2006) discloses uridine derivatives of the compound of formula-

![Image of uridine derivative]

Wherein substitutions includes \( R_1: \) H, monohalogenated alkynyl or dihalogenated alkenyl; \( R_2: \) a halogen ; \( R_3: \) hydroxy; \( R_4: \) O-phosphate as well as its possible tautomers, its possible pharmaceutically acceptable additions salts with an acid or a base, and its N-oxide forms and such other
prodrugs include for instance, esters, such as amino acid esters, e.g. alanine esters having activity against flaviviridae including HCV.

It is observed that the disclosed compounds are structurally completely different from the claimed compounds w.r.t. nucleoside moiety and does not disclose phosphoramidate moiety.

**Year 2007**

**D5** (published on 22.02.2007) discloses novel nucleoside compounds (phosphoramidate esters of 4'-substituted nucleosides) of formula I which are useful for the treatment of Hepatitis C Virus (HCV) mediated diseases.

![Formula I]

Further D5 also discusses that claimed aryloxy phosphoramidate derivatives overcome the problems associated with the nucleosides regarding suboptimal physical properties, poor pharmacokinetics and kinase-mediated phosphorylation to generate the nucleoside triphosphate. It is observed that D5 discloses nucleoside compounds which are substituted at 5'-position with either azido or alkynyl or -\((Z)\)-CH=CHCl group.

**D6** is a non patent literature published in Feb 2007, which discloses that \(\beta\)-D-2'-deoxy-2'-fluoro-2'-C-methylcytidine (PSI-6130) is a potent specific inhibitor of hepatitis C virus and further investigates the phosphorylation of PSI-6130 and inhibition of HCV NSSB.

![PSI-6130]

The enzymatic studies, using cloned human enzymes, performed therein focused on understanding the conversion of \(\beta\)-D-2'-deoxy-2'-fluoro-2'-C-methylcytidine to its monophosphate, diphosphate, and then triphosphate forms and an enzymatic phosphorylation pathway for PSI-6130 is proposed.
Based on results obtained in studies paper suggests that PSI-6130 is worthy of further investigation as a treatment for HCV infection.

It is observed that PSI-6130 is a nucleoside having cytosine base and mono, di and tri phosphates of PSI-6130 are disclosed in D6. There is no reference or suggestion to use uracil base or phosphoramidate moiety in D6.

**D14** (published on web on 17/3/2007) reports application of phosphoramidate ProTide technology to the ribonucleoside analogue of 4'-azidouridine to generate novel antiviral agents for the inhibition of HCV. Twenty-two phosphoramidates (compound numbers 11, 12, 14-20, 22-25, 27-35) were prepared, including variations in the aryl, ester and amino acid regions and tested for HCV activity.

<table>
<thead>
<tr>
<th>compound</th>
<th>amino acid</th>
<th>ester</th>
<th>EC50 (µM)</th>
<th>CC50 (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>L-Ala</td>
<td>Me</td>
<td>3.1</td>
<td>&gt;100</td>
</tr>
<tr>
<td>12</td>
<td>L-Ala</td>
<td>Et</td>
<td>1.3</td>
<td>&gt;100</td>
</tr>
<tr>
<td>13</td>
<td>L-Ala</td>
<td>Bu</td>
<td>1.2</td>
<td>&gt;100</td>
</tr>
<tr>
<td>14</td>
<td>L-Ala</td>
<td>2-Bu</td>
<td>0.33</td>
<td>&gt;100</td>
</tr>
<tr>
<td>15</td>
<td>L-Ala</td>
<td>iBu</td>
<td>0.77</td>
<td>&gt;100</td>
</tr>
<tr>
<td>16</td>
<td>L-Ala</td>
<td>tBu</td>
<td>5.1</td>
<td>&gt;100</td>
</tr>
<tr>
<td>17</td>
<td>L-Ala</td>
<td>Bu</td>
<td>0.61</td>
<td>&gt;100</td>
</tr>
<tr>
<td>18</td>
<td>MeGly</td>
<td>Et</td>
<td>10.3</td>
<td>&gt;100</td>
</tr>
<tr>
<td>19</td>
<td>MeGly</td>
<td>Bu</td>
<td>3.4</td>
<td>&gt;100</td>
</tr>
<tr>
<td>20</td>
<td>dPhnGly</td>
<td>Et</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>21</td>
<td>dPhnGly</td>
<td>Bu</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>22</td>
<td>Phn</td>
<td>Et</td>
<td>1.37</td>
<td>&gt;100</td>
</tr>
<tr>
<td>23</td>
<td>Phn</td>
<td>Bu</td>
<td>&lt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>24</td>
<td>Val</td>
<td>Bu</td>
<td>&lt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>25</td>
<td>Gly</td>
<td>Bu</td>
<td>1.6</td>
<td>&gt;100</td>
</tr>
<tr>
<td>26</td>
<td>&gt;-Ala</td>
<td>Bu</td>
<td>1.2</td>
<td>&gt;100</td>
</tr>
<tr>
<td>27</td>
<td>Leu</td>
<td>Et</td>
<td>2.3</td>
<td>&gt;100</td>
</tr>
<tr>
<td>28</td>
<td>Pro</td>
<td>Et</td>
<td>6.0</td>
<td>&gt;100</td>
</tr>
<tr>
<td>29</td>
<td>Met</td>
<td>Et</td>
<td>14</td>
<td>&gt;100</td>
</tr>
<tr>
<td>30</td>
<td>N-MeGly</td>
<td>Et</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>31</td>
<td>iPrGly</td>
<td>Et</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>32</td>
<td>β-Ala</td>
<td>Et</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>

D14 reports that 1-naphthyl phosphoramidate has increased potency as compared to corresponding phenyl phosphoramidate (in anti-cancer assay). The most active compound in D14 was 1-naphthyl L-alanine benzyl ester phosphoramidate. The author states that “the generic message is that the Pro Tide synthesis from inactive parent nucleosides may be a warranted drug discovery strategy”.

221
**D23 was published on Sept 9-13, 2007 i.e. after earliest priority date of the present application which is 30/03/2007 hence is not a valid prior art document.**

D23 is a poster presented during 9-13 September 2007 which discloses compound PSI-6206 which is 2’-deoxy-2’-fluoro-2’-C-methyluridine and compound PSI-6130 which is its corresponding 2'-methylcytidine.

![PSI-6206 and PSI-6130](image)

D23 taught that phosphoramidates of PSI-6206 are more potent, as much as 100X, than the cytidine analog PSI-6130. The structure of PSI-6206 phosphoramidate and a general scheme of preparing PSI-6206 is also disclosed-

![Scheme 1: Preparation of Phosphoramidates](image)

It is observed that D23 does not provide any definition for the substituents R1, R2 and R3.

**D24 was published on October 12, 2007 i.e. after earliest priority date of the present application hence is not a valid prior art document.**

D24 discloses that β-D-2’-deoxy-2’-fluoro-2’-C-methylcytidine (PSI-6130) is a potent inhibitor of hepatitis C virus (HCV) replication in the subgenomic HCV replicon system, and its corresponding 5’-triphosphate is a potent inhibitor of the HCV RNA polymerase in vitro. In addition the deaminated derivative of PSI-6130, β-D-2’-deoxy-2’-fluoro-2’-Cmethyluridine (RO2433, PSI-6026) and its corresponding phosphorylated metabolites were identified.
in human hepatocytes after incubation with PSI-6130 i.e. 5’-triphosphate (TP) of PSI-6130 (PSI-6130-TP) and RO2433 (RO2433-TP).
The structures of PSI-6130 (fig. 1), RO2433 (fig. 2) and RO2433-TP (fig. 3) are as follows-

![Fig. 1](image1.png)  ![Fig. 2](image2.png)  ![Fig. 3](image3.png)

**D28** is a document which is published in 2010 and hence not considered as prior art document and therefore not discussed herein.

**D29** is a Ph.D. thesis submitted by Plinio Perrone in 2007 to Cardiff University. There is no evidence provided by the opponent which unambiguously prove the public access to such thesis in 2007. The copy of document provided shows 2013 as publication year. Hence D29 is not considered as a valid prior art document for present invention and not discussed herein.

**Discussion and opinion on validity of first priority date i.e. 30/03/2007 of present application**

14. With reference to the documents D23 and D24, the opponents have taken the argument that said documents are valid prior art documents as first priority date of 30/03/2007 derived from patent application US60/309915 is not valid. In this regard it is to be noted that said arguments are not found to be persuasive vis a vis invalidity of priority date of priority document number US60/309915 dated 30 March 2007. On going through the priority document US60/309915 dated 30 March 2007 it is observed that on page 187 compound IX is disclosed and further on page 195 various substituents corresponding to the claimed compound are disclosed (see IX-25-2)
Further on pages 63-64 of said priority document, the stereochemical configurations for the phosphoramidate moiety w.r.t. substituents R3a and R3b alongwith the phosphorous atom is disclosed. For phosphorous atom, it is stated that “Additionally, the inventors recognize that the phosphorus atom of the phosphoramidate moiety is another source of chirality. Although the structures below do not specifically depict chirality at phosphorus, the inventors recognize that stereochemical configurations are possible such that in a staggered (or zigzag) line structure the oxo-substituent projects towards the viewer while the OR1 substituent projects away from the viewer, and vice versa. Therefore, the structures below include all possible stereochemical configurations possible for phosphorus.”.

As the priority document US60/309915 is found to have disclosure for the claimed compound and its stereochemical configurations (implicit disclosure), hence the Controller is of the view that priority date of 30/03/2007 derived from US60/309915 is valid and accordingly documents published after 30/03/2007 are not considered as valid prior art documents.

Prejudice to that opinion has been given on D23 and D24 also while deciding upon the novelty, inventive step and patentability of the present invention.

**Opinion of the Controller on the ground under Section 25(1)(b)-**

15. The present invention relates to a compound having formula

| IX-25-1 | Ph | H | H | H |
| IX-25-2 | Ph | H | H | CH₃ |
| Pr | H | CH₃ | F | OH | H | H |
| Pr | H | CH₃ | F | OH | H | H |
D1 (WO2005003147) discloses a (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D or β-L) or its pharmaceutically acceptable salt or prodrug thereof of the structure:

wherein Base is a purine or pyrimidine base; X is O, S, CH2, Se, NH, N-alkyl, CHW (R, S, or racemic), C(W)2, wherein W is F, Cl, Br, or I; and, R1 and R7 are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid, a carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein R1 or R7 is independently H or phosphate; R1 and R7 can also be linked with cyclic phosphate group and methods for the treatment of Flaviviridae infections, especially hepatitis C virus (HCV).

As per the definitions provided for “pyrimidine” base it includes uracil also so D1 generically discloses (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleosides with uracil base but it does not disclose any type of phosphoramidate moiety as present in claimed compound. Further the examples disclosed in D1 relates to (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine (see example 1 & 2), (2'R)-6-Chloro-2'-Deoxy-2'-Fluoro-2'-C-Methylpurine (see example 2) and
(2'R)-2'-Deoxy-2'-Fluoro-2'-C-Methyladenosine (see example 3) but no specific example is provided for (2'R)-2'-deoxy-2'-fluoro-2'-C-methyluridine or process of preparing the same and also there is no reference suggesting to pick uracil as preferred base. Hence the claimed compound is structurally different from the compounds disclosed in D1 and does not anticipate the subject matter of the claims 1-5. Hence claims 1-5 are novel over the cited document D1.

16. D2 discloses chemical compound of formula I having anti-cancer property:

![Chemical Structure]

Wherein R is selected from the group comprising alkyl, aryl and alkylaryl; R' and R" are independently selected from the group comprising H, alkyl and alkylaryl, or R' and R" together form an alkylene chain so as to provide, together with the C atom to which they are attached, a cyclic system; Q is selected from the group comprising -O- and -CH2-; X and Y are independently selected from the group comprising H, F, Cl, Br, I, OH and methyl (-CH3); Ar is a monocyclic aromatic ring moiety or a fused bicyclic aromatic ring moiety, either of which said ring moieties is carbocyclic or heterocyclic and is optionally substituted; Z is selected from the group comprising H, alkyl and halogen; and n is 0 or 1, wherein when n is 0, Z' is -NH2 and a double bond exists between position 3 and position 4, and when n is 1, Z' is =O; or a pharmaceutically acceptable derivative or metabolite of a compound of formula I; with the proviso that, except where R is 2-Bu (-CH2-CH(CH3)2) and one of R' and R" is H and one of R' and R" is methyl (-CH3), when n is 1 and X and Y are both H, then Ar is not unsubstituted phenyl (-C6H5).

17. There is no specific disclosure of claimed compound having specific nucleoside and phosphoramidate moiety is there or process of preparation thereof in D2. A person skilled in the art needs to make selection from numerous definitions of the substituents to reach the claimed compound
and there is no suggestion to cherry pick claimed substituents, as such
substituents are neither preferred nor exemplified in the specification hence
the disclosure can also not be considered as implicit disclosure. The claimed
compound is considered to be structurally different from the compounds
disclosed in D2 and does not anticipate the subject matter of the claims 1-5.
Hence claims 1-5 are novel over the cited document D2.

18. D23 can not be considered as prior art as it was published after priority
date of instant application and opponent arguments are not found to be
persuasive vis a vis invalidity of priority date of priority document number

19. Prejudice to that even if one consider D23, it discloses compound PSI-
6206 and a process of its preparation (scheme 1)

But no definition is provided for the substituents R1, R2 and R3 and hence
said compound and the process do not anticipate the claimed invention.
Hence claims 1-5 are novel over the cited document D23.

**Opinion of the undersigned on the ground under Section 25(1)(e)**

20. The claimed compound can be broadly said to be consists of two
moieties-

(i) a **nucleoside moiety** containing
- unsubstituted uracil as pyrimidine base; and
- a specific modified deoxyribose sugar ring with methyl substitution
in up and fluorine substitution in down at the 2' position of the sugar
&

(ii) a **phosphoramidate moiety** (attached to hydroxyl group of 5’
position of nucleoside unit) having unsubstituted phenyl group
attached to phosphorus via oxygen, an amide ester with L-alanine
amino acid moiety, and isopropyl ester at carboxyl group of L-alanine amino acid.

21. O1 argued that D1 in claim-6 discloses the structure of base compound for claimed produg including its monophosphate, diphosphate, triphosphate or a stabilised phosphate prodrug and then relied on D8, D10 D14 to demonstrates the success of using the ProTide prodrug strategy to activate the intracellular presence of active triphosphates of an inactive HIV compound ddU (D8) and cite the use of the phosphoramidate prodrugs (D10, D14, D15, D17). D16 referred to as it discloses uridine nucleoside derivatives as antiviral drugs and alanine ester as potential prodrugs for said derivatives. Though the applicant has provided submission for each cited document but has argued that only D1, D14, D16 are relevant for inventive step analysis as they relate to treatment of HCV.

22. It may be noted that none of the documents cited by O1, independently or in combination with each other, either discloses the claimed nucleoside moiety or claimed phosphoramidate moiety. Though D1 generically discloses a nucleoside unit in claim-6 which having pyrimidine base may include uracil (but no specific example with uracil as base is provided in the description) but it lacks phenyl phosphoramidate moiety. D8, D10, D14, D15, D16 & D17 generally suggests use of the phosphoramidate ProTide technology to various nucleosides analogues like 4’ azidouridine (D14), ddU (D8), d4T (D10) but there is neither any disclosure of specific phosphoramidate moiety claimed in present invention nor any suggestion to modify the known phosphoramidate moieties by having specific substituents therein. On the basis of mere disclosure of phosphoramidate moieties attached to structurally different nucleoside moiety it is not reasonable to
consider that such teachings can be extended to nucleoside moieties having different sugar molecule with different substituents pattern. Even selection of substituents of phosphoramidate moiety disclosed in cited prior art documents and activity shown thereof is in relation with nucleoside to which it is attached. The opponents have failed to provide any document which suggests such general teaching which states that selected specific substituents on phosphoramidate will show same activity for every nucleoside moiety irrespective of its structure. The selection of specific nucleoside moiety having specific substituents thereon and selection of specific substituents in phosphoarmidate moiety of present invention is considered as non obvious. Therefore claimed compound, its stereoisomers and pharmaceutically composition thereof are considered to be inventive. Further none of the cited prior art documents disclose a process of preparing claimed compound having specific nucleoside and phosphoramidate moiety. Hence the subject matter of claims 1-5 is considered to involve an inventive step.

23. O4 has submitted that the Applicant has put together following known features disclosed in the cited prior art documents to arrive at the claimed compound-

(a) 2’-deoxy-2’-fluorouridine was known an anti-HCV agent (reference is made to documents D1, D2 & D3);
(b) ProTide approach to activate an inactive nucleoside by phosphate prodrug formation was known (reference is made to documents D4, D5, D6, D7, D8 & D9);
(c) L-alanine was a preferred amino acid in ProTide approach (reference is made to documents D10, D11, D11, D12, D13, D14, D15 & D16);
(d) Isopropyl moiety in prodrug compounds were known to show better activity (reference is made to D17).

The applicant has submitted that the arguments of the O4 on the ground of lack of Inventive Step are two-fold;

a. That the class of nucleosides was known for antiviral activity and all that required was to make a suitable phosphoramidates (PPA) kind
of prodrugs which can improve and facilitate the drug absorption or activity.

b. Alternatively, it was argued by the O\textsuperscript{4} that the exact nucleoside for HCV were known and that there was enough motivation for the person skilled in the art to employ the use of an L-alanine based aryloxy phosphate prodrug using the Pro-Tide approach, and hence the compounds of the present invention are obvious.

The applicant argued that a bare reading of all the prior art documents relied upon by the Opponent would show that Opponent has tried to combine prior documents from the field of HIV, Cancer and HCV infection, and further different kind of nucleosides are relied upon to generalize the arguments. Applicant argued that to analyze inventive step of the present invention only those documents wherein disclosed compounds have reported HCV activities having similar nucleosides should be considered.

\textbf{24.} Regarding the first feature O\textsuperscript{4} has relied on D1, D2 & D3 but none of the cited document discloses specific nucleoside moiety containing unsubstituted uracil as base and a deoxyribose sugar ring with methyl substitution in up and fluorine substitution in down at the 2’ position. Though D2 discloses nucleotide derivatives but same is used for treatment for cancer and O\textsuperscript{4} has failed to show how such compound can be considered as anti-HCV agent. D1 is found to be closest prior art w.r.t the first feature as it discloses (2′R)-2′-deoxy-2′-fluoro-2′-C-methyl nucleoside for treatment of HCV, D3 is also found to be not relevant due to difference in nucleoside moiety w.r.t. substituent on deoxyribose sugar ring as fluorine is missing as substituent at 2’ position. Regarding the second feature O\textsuperscript{4} has relied on D4, D5, D6, D7, D8 & D9 each of which relates to nucleoside compounds with different structure. D4 discloses phosphoramidate derivative of only purines bases with methyl (up) and hydroxy (down) substitution pattern at 2’-position. D5 discloses phosphoramidates of nucleoside which are substituted at 5’-position with either azido or alkynyl or –(Z)-CH=CHCl group and differ significantly in respect of substitution at 2’-position as it does not include methyl and fluoro at all. D6 discusses enzymatic studies focused on understanding the conversion of β-D-2′-deoxy-2′-fluoro-2′-C-
methylcytidine (PSI-6130) [a cytosine based nucleoside] to its monophosphate, diphosphate, and then triphosphate forms and it is silent on prodrugs or phosphoramidates. D7 is considered to be general art which discloses amino ester prodrugs of an anti-cancer drug, floxuridine and is not related to phosphoramidate at all. D8 reports the success of the ProTide strategy using ddU and AZT for treatment of HIV and use of the aryloxyphosphoramidates as masking agent. D9 demonstrated that 3'-azido-3'-deoxythymidine (AZT) amino acid phosphoramidates are potent, non-toxic antiviral and/or anticancer agents but does not talks about the aryloxyphosphoramidates. Regarding the third and fourth feature O4 has relied on documents D10-D17 to show that L-alanine was a preferred amino acid in ProTide approach and Isopropyl moiety in prodrug compounds were known to show better activity. D10-D17 in general refer to role of linkage of L-Alanine unit (as alaninyl unit or isopropyl ester of alanine) with phosphate in phosphoramidate moiety in anticancer or antiviral activity of corresponding compounds/prodrugs of d4T (in D10, D11, D12), AZT (in D12) etc. But the opponent fails to provide any substantial evidence on the basis of which it can be reasonably presume that such use of L-alanine or isopropyl unit in different phosphoramidate moiety will always result in similar activity irrespective of other factors also like nature of nucleoside used, nature and type of substituents attached to other parts of phosphoramidate moiety etc. The selection of specific nucleoside moiety having specific substituents thereon and selection of specific substituents in phosphoarmidate moiety of present invention is considered as non obvious. Therefore claimed compound, its stereoisomers and pharmaceutically composition thereof are considered to be inventive. Further none of the cited prior art documents disclose a process of preparing claimed compound having specific nucleoside and phosphoramidate moiety. Hence the subject matter of claims 1-5 is considered to involve an inventive step.

25. O5 & O7 argued that it was known in the art that full potential of nucleosides that are either inactive or that do not exhibit sufficient activity can be realized by using the ProTide approach i.e. by coupling the nucleoside with a phosphate moiety. Then they refer to documents D8, D18,
D10, D11, D12, D15, D14 and concluded that the general architecture of a phosphoramidate (part) of a prodrug includes an ester linked to amino acid and phosphate group is known with alanine is the most preferred amino acid and isopropyl ester is the most preferred ester (D14) and such combination was found to undergo hydrolysis and liberate the nucleoside in phosphate form (intra-cellularly). Thereafter they argued that prior to 2005 various nucleosides were known, such as AZT, ddu etc. which exhibited anti-viral activity. Further referring to documents D20, D1, D21, D6 they concluded that the prior art provides the following teachings prior to the priority date of March 2007:

a) Native nucleosides are per se inactive and not suitable for direct administration to patient; hence, to overcome the limitation of nucleosides, ProTide approach was developed;

b) Proposals for possible structures of various ProTides was proposed and experimented on various nucleosides such as AZT, D4T, ddU etc. and found to be successful; experimental prodrugs using various nucleosides were also prepared in the art and found to exhibit excellent antiviral activity;

c) In particular, prodrug moiety comprising isopropyl ester with L-alanine amino acid was found to be most efficacious when combined with nucleosides to activate the concerned nucleoside (D14);

d) The Nucleoside which is to be activated may be selected from any nucleoside including those taught by D1. In fact, D1 itself recommends that prodrugs may be found in order to activate the nucleosides disclosed therein. The application clearly states that conventionally known prodrug moieties may be used, including alkyl ester moieties. D14 suggests the use of isopropyl alaninyl moiety.

e) The process of formation of activated nucleoside or ProTide is also known and documented i.e. condensation of nucleoside with selected phosphate ester.

f) The site at which the condensation is to occur, is also known and disclosed by D1 i.e. 5’ position.
g) There is sufficient motivation to prepare such prodrugs as prodrugs have been commonly prepared in case of all nucleosides that are inactive or poorly phosphorylated within a cell. As per the applicant such arguments are based on hindsight analysis as the opponent has tried to combine prior documents from the field of HIV, Cancer and HCV infection, and further different kind of nucleosides are relied upon to generalize the arguments. As per the applicant only those documents wherein disclosed compounds have reported HCV activities having similar nucleosides are relevant for the combining them to analyze inventive step of the present invention.

26. It is observed that D8, D18, D10, D11, D12, D15, cited by the opponents O5 and O7 relate to treatment of HIV and none of the cited prior art document discloses the nucleoside moiety present in the claimed compound. The subject matter of D1, D6, D14, D20, D21 relates to treatment of HCV wherein D1 discloses a (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside, D6 discloses β-D-2'-deoxy-2'-fluoro-2'-C-methylcytidine, D14 discloses application of phosphoramidate ProTide technology to the ribonucleoside analogue of 4'-azidouridine, D20 discloses a family of 2'-fluoronucleosides and D21 discloses nucleoside moiety, β-D-2'-deoxy-2'-fluoro-2'-C-methyl uridine but it was found to be inactive for anti-HCV activity. As can be seen prior to 2005 claimed nucleoside is not known and there is no teaching in the cited prior art documents which will motivate a person skilled in the art to carry out specific modifications in known nucleosides in order to reach the nucleoside moiety claimed in present invention. D1 generically discloses such nucleoside moiety and D21 specifically reported that claimed nucleoside is inactive. D14 relates to different type of nucleoside and there is no teaching therein to use specific nucleoside moiety as used in present invention or to extend use of phosphoramidate moiety disclosed therein to nucleosides as referred in present invention. Even if one considers that a person skilled in the art is motivated to use phosphoramidate ProTide approach to claimed nucleoside moiety in view of D14, one would have prefer benzyl ester and not the isopropyl ester for phenyl phosphoramidate nucleotide analogue and would
have prefer 1-naphthyl phosphoramidates over phenyl phosphoramidates. Hence claimed invention can not be considered obvious in view of the cited prior art documents and considered to involve an inventive step. It may be noted that though the cited prior art documents independently suggests use of specific substitutents in phosphoarmidate unit when attached to a different type of nucleoside for treatment of diseases like HIV/cancer but it is not reasonable to consider that such teachings can be extended to nucleoside moieties having different sugar molecule with different substitutents pattern for treatment of a different disease i.e. HCV. Even selection of substituents of phosphoramidate moiety disclosed in cited prior art documents and activity shown thereof is in relation with nucleoside to which it is attached. The opponents have failed to provide any document which suggests such general teaching which states that selected specific substituents on phosphoramidate will show same activity for every nucleoside moiety irrespective of its structure. The selection of specific nucleoside moiety having specific substitutents thereon and selection of specific substituents in phosphoarmidate moiety of present invention is considered as non obvious. Therefore claimed compound, its stereoisomers and pharmaceuticaal composition thereof are considered to be inventive. Further none of the cited prior art documents disclose a process of preparing claimed compound having specific nucleoside and phosphoramidate moiety. Hence the subject matter of claims 1-5 is considered to involve an inventive step.

27. O9 has relied on D3, D22, D23 D24, D25, D14, D26 and D2 for inventive step. Both D3 and D22 do not disclose any nucleoside moiety with a 2'-fluoro (down) and 2'-methyl (up) substitution pattern on the sugar ring and any type of phosphoramidate moiety. D25 neither discloses a nucleoside moiety with a uracil base nor discloses use of a phosphoramidate at the 5’-carbon of the sugar moiety. D26 discloses compounds which are structurally different from the claimed compounds. D14 discloses 4’-azido, 2’-hydroxy pronucleotides compounds having phosphoramidate unit but it discloses that 1-naphthyl phosphoramidate has increased potency as compared to corresponding phenyl phosphoramidate (in anti-cancer assay).
The most active compound as reported in Perrone was 1-naphthyl L-alanine benzyl ester phosphoramidate. Further D14 clearly states that "a separate ProTide motif optimization process is needed for each nucleoside analogue versus a given target". D2 does not specifically disclose any compound with unsubstituted uracil base attached to sugar and the unique substitution pattern of 2’-fluoro (down) and 2’-methyl (up) at 2’-position of sugar ring and phosphoramidate with isopropyl ester of alanine amino acid. The compounds disclosed in D2 are anticancer compounds and no HCV activity is shown therein. As evident, the opponent has failed to provide any cited prior art document which either discloses nucleoside moiety and phosphoramidate moiety as present in the claimed invention or suggests modifying the existing nucleoside and phosphoramidate moieties so as to reach the claimed compound. With reference to D23 and D24 even if one consider them to be relevant prior art documents there is no teaching in other cited prior art documents which will motivate a person skilled in the art to pick up specific substituents and substitute them in order to get nucleoside and phosphoramidate units claimed in present in invention with reasonable expectation of success. The selection of specific nucleoside moiety having specific substituents thereon and selection of specific substituents in phosphoramidate moiety of present invention is considered as non obvious. Therefore claimed compound, its stereoisomers and pharamaceutical composition thereof are considered to be inventive. Further none of the cited prior art documents disclose a process of preparing claimed compound having specific nucleoside and phosphoramidate moiety. Hence the subject matter of claims 1-5 is considered to involve an inventive step.

28. O10 has primarily relied on D27 to show that it encompasses claimed compounds but it may be noted that D27 does not disclose even a single compound with 2’-fluoro (down) and 2’-methyl (up) substitution at deoxyribose sugar ring of nucleoside moiety containing uracil base. D23 and D24 are also not valid prior art documents and even if they are considered there is no teaching in either in D27 or in other cited prior art documents D14, D10, D2, D21, D25 and D27 independently or in combination for a
person skilled in the art to pick up specific substituents in order to prepare the claimed nucleoside and phosphoramide moiety. D28 is published in 2010 and hence is not considered to be a valid prior art document for inventive step analysis. The selection of specific nucleoside moiety having specific substituents thereon and selection of specific substituents in phosphoramide moiety of present invention is considered as non obvious. Therefore claimed compound, its stereoisomers and pharmaceutical composition thereof are considered to be inventive. Further none of the cited prior art documents disclose a process of preparing claimed compound having specific nucleoside and phosphoramidate moiety. Hence the subject matter of claims 1-5 is considered to involve an inventive step.

29. O11 has relied on D2, D14, D24, D23, D21, D3, D22, D25, D26 and D29. D29 is not considered as valid prior art document as opponent has failed to provide any substantial evidence to show that same is published in 2007 and said document shows 2013 as year of publication. Further D23 and D24 are also not considered as relevant prior art document. Prejudice to that even if one consider D23 and D24 there is no teaching in other cited prior art documents which will motivate a person skilled in the art to pick up specific substituents and substitute them in order to get nucleoside and phosphoramide units claimed in present invention with reasonable expectation of success. Both D3 and D22 do not disclose any nucleoside moiety with a 2'-fluoro (down) and 2'-methyl (up) substitution pattern on the sugar ring and any type of phosphoramide moiety. D25 neither discloses a nucleoside moiety with a uracil base nor discloses use of a phosphoramide at the 5'-carbon of the sugar moiety. D26 discloses compounds which are structurally different from the claimed compounds. D14 discloses 4'-azido, 2'-hydroxy pronucleotides compounds having phosphoramide unit but it discloses that 1-naphthyl phosphoramide has increased potency as compared to corresponding phenyl phosphoramide (in anti-cancer assay). The most active compound as reported in Perrone was 1-naphthyl L-alanine benzyl ester phosphoramide. Further D14 clearly states that "a separate ProTide motif optimization process is needed for each nucleoside analogue versus a given target". D2 does not specifically disclose any compound with
unsubstituted uracil base attached to sugar and the unique substitution pattern of 2’-fluoro (down) and 2’-methyl (up) at 2’-position of sugar ring and phosphoramidate with isopropyl ester of alanine amino acid. The compounds disclosed in D2 are anticancer compounds and no HCV activity is shown therein. D21 discloses nucleoside moiety, β-D-2’-deoxy-2’-fluoro-2’-C-methyl uridine but it was found to be inactive for anti-HCV activity. The opponent has failed to provide any evidence which suggests modifying the existing nucleoside and phosphoramidate moieties so as to reach the claimed compound resulting in claimed HCV activity. It may be noted that ProTide approach is known in cited prior art documents but none of the cited prior art documents suggests specific selection of specific substituents on phosphoramidate unit and use thereof with the nucleoside moiety disclosed in D21. There is variation in the sugar molecule or base of nucleoside moiety in prior art documents and inferences drawn therein for various substituents of phosphoramidate moiety is in context with such different nucleosides unit present therein. It is not reasonable to presume that such teachings can be simply extended to a different nucleoside (having different sugar molecule and base combination) to have similar desired effect in terms of activity without considering various structural activity relationships in terms of size, nature, stereochemistry of the substituents etc. which actually plays important role in activity of any compound. The selection of specific nucleoside moiety having specific substituents thereon and selection of specific substituents in phosphoramidate moiety of present invention is considered as non obvious. Therefore claimed compound, its stereoisomers and pharmaceutically composition thereof are considered to be inventive. Further none of the cited prior art documents disclose a process of preparing claimed compound having specific nucleoside and phosphoramidate moiety. Hence the subject matter of claims 1-5 is considered to involve an inventive step.

30. O12 has neither filed any written submission nor put forward any substantial arguments during oral hearing for inventive step. It was merely stated that opponent is relying on statement provided in pre-grant opposition filed for inventive step. D23, D14, D24, D10, D2, D21, D25, D27
are the documents cited in the opposition. As discussed earlier D23 and D24 are not valid prior art documents. Prejudice to that even if one considers D23 and D24 in combination with other cited prior art documents there is no teaching in D14, D10, D2, D21, D25 and D27 which guides a person skilled in the art to select specific substituents for known nucleoside and phosphoramidate moiety in order to reach the claimed compounds. The selection of specific nucleoside moiety having specific substituents thereon and selection of specific substituents in phosphoramidate moiety of present invention is considered as non obvious. Therefore claimed compound, its stereoisomers and pharamaceutical composition thereof are considered to be inventive. Further none of the cited prior art documents disclose a process of preparing claimed compound having specific nucleoside and phosphoramidate moiety. Hence the subject matter of claims 1-5 is considered to involve an inventive step.

31. O13 has relied on documents D23, D24, D25, D22 and D20. As discussed earlier D23 and D24 are not valid prior art documents. Prejudice to that even if one considers D23 and D24 in combination with other cited prior art documents there is no teaching in cited prior art documents D5, D20 and D22 which guides a person skilled in the art to select specific substituents for known nucleoside and phosphoramidate moiety in order to reach the claimed compounds. The selection of specific nucleoside moiety having specific substituents thereon and selection of specific substituents in phosphoramidate moiety of present invention is considered as non obvious. Therefore claimed compound, its stereoisomers and pharamaceutical composition thereof are considered to be inventive. Further none of the cited prior art documents disclose a process of preparing claimed compound having specific nucleoside and phosphoramidate moiety. Hence the subject matter of claims 1-5 is considered to involve an inventive step.

Opinion of the Controller on the ground under Section 25(1)(f)

32. The subject matter is not patentable if it falls under section 3(d) of the Patents Act, 1970 which read as follows-
“the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of the substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.

“Explanation—For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy”.

On a plain reading of section 3(d) it’s clear that section 3(d) is applicable in case of

- the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of the substance or
- the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.

33. The opponents have primarily argued that the claimed invention is mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of the substance. To apply said clause pre condition is existence of a known substance with a known efficacy and then one need to show that claimed substance is new form of such known substance.

34. In the present case, all the opponents have argued that the subject matter of the claims 1-3 falls within the section 3(d) of the Patents Act, 1970 and primarily they have relied on the documents D1, D2, D21, D23 and D27. O1 has identified (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl cytidine as known substance for the claimed compound. As the nucleoside moiety of the claimed compound is structurally different from such known substance hence claimed compound cannot be termed as ester of such known substance. Other opponents have merely referred to D1 without identifying
any compound which can be considered as known substance. After going through D1 it is observed that it does not exemplify any compound having uracil base nucleoside which can be considered as a known substance for the claimed compound. The opponents have also cited D2, without referring to any specific compounds as known substance for claimed compounds. D2 discloses markush structure of formula (I) which encompasses large number of compounds compounds which are useful in treatment of cancer but exemplify compounds include only bromo vinyl uridine (BVU) and gemcitabine (GemCyt) which are referred as similar nucleotides by the opponents. Said exemplify compounds are structurally different from the claimed compounds (and also have have anti cancer activity instead of HCV activity) hence such compounds disclosed in D2 can not be considered as known substance for claimed compound. D21 is referred by the opponents O5, O7, O12 wherein compound 9 of said document is identified as known substance for the claimed compound. Compound 9 (-D-2’-deoxy-2’-fluoro-2’-C-methyl uridine) was found to be inactive for anti-HCV activity and the opponents have failed to show how claimed compound which comprises of phosphoramidate moiety (phenoxy phosphoramidate of isopropyl ester of L-alanine amino acid) attached to a nucleoside moiety can be considered as derivatives of such known compound 9. The opponents have referred claimed compound as prodrug of compound 9 of D21 and submitted that prodrugs are not patentable under section 3(d) of the Patents Act (reliance is placed on F. Hoffmann-La Roche Ltd. and Ors. v. Cipla Ltd. 2016(65) PTC l(Del)). In this regard it is to note that even if one consider compound 9, having no activity in HCV replicon assay, as known substance for the claimed compound then also the applicant has shown the efficacy for the claimed compound (as compound 25) in HCV replicon assay in table on pages 696-697 of the complete specification. Further D23 is referred by the opponents with PSI-6206 as the closest compound. D23 is not a valid prior art document as it is published after the priority date of the present invention. Prejudice to that even if one consider D23, the markush structure PSI-6206 lack any definition for the substituents hence can not be considered as a known substance for the claimed compound. With reference
to D27 the opponent fails to show any known substance. The compound as referred by the opponent for comparison with claimed compound is a hypothetical compound which is not specifically disclosed in D27. The compound disclosed in D27 are structurally different from the claimed compound and hence same can not be considered as known substance for the claimed compound. Hence claimed invention does not fall within the scope of section 3(d) of the Patents Act.

35. Section 3(e) and Section 3(i) was also raised by some opponents in the opposition. As method of treatment claims are not on record hence section 3(i) is not applicable. Further with respect to the composition claim the opponents argument is not found to be persuasive w.r.t. section 3(e) as claimed composition comprises of novel and inventive compound alongwith pharmaceutically acceptable medium. Hence the subject matter of claims 1-5 does not fall within the scope of section 3(e) and 3(i) of the Patents Act.

Opinion of the Controller on the ground under Section 25(1)(g)

36. The opponents have primarily raised the ground of insufficiency of disclosure w.r.t. stereochemistry of the claimed compounds and the process of preparation of claimed compounds. Following compound is claimed along with its stereoisomers in claim-1

![Chemical structure]

Further diastereomers of the compound of claim 1, based on the stereochemistry at ‘P’ atom, are claimed in claims 2 and 3
37. Before deciding upon the ground of insufficiency I would like to discuss the relevant subject matter referred in the description.

On page 8 of the description under the paragraph “Summary of the invention” it is disclosed that the present invention is directed toward novel phosphoramidate prodrugs of nucleoside derivatives for the treatment of viral infections in mammals, which is a compound, its stereoisomers, salts (acid or basic addition salts), hydrates, solvates, or crystalline forms thereof, represented by the following structure of formula I:

![Formula I](image)

It may be noted that said structure of formula I was claimed as claim-1 in claims originally filed during national phase entry of the application in India.

On page 18-19 of the description, under the paragraph of “Definitions” it is disclosed that the term "P*" means that the phosphorous atom is chiral and that it has a corresponding Cahn-Ingold-Prelog designation of "R" or "S" which have their accepted plain meanings. It is contemplated that compounds of the formula I are racemic because the chirality at phosphorous. Applicants contemplate use of the racemate and/or the resolved enantiomers. In some instances, an asterisk does not appear next to the phosphoroamidate phosphorous atom. In these instances, it is understood that the phosphorous atom is chiral and that one of ordinary skill understands this to be so unless the substituents bound to the phosphorous exclude the possibility of chirality at phosphorous, such as in P(O)Cl₃.

On page 42, one of the embodiments of the invention is disclosed as formula I-IV represented as follows-
It may be noted that the stated formula discloses all the possible stereochemical configurations for the claimed compounds including that of amino acid and P atom (based on definition of P*).

The paragraph on pages 96-97 discloses how to read the structures of the compounds in the tables disclosed subsequently. It states that in each of the presented tables, the phosphoramidate substituent containing the substituents R³α and R³β are depicted without reference to stereochemical structure (cf. structures 1-1, 1-3, 1-5, 1-7, and 1-9 above). It is contemplated that the compounds recited below embody compounds in which R³α projects toward the viewer while R³β projects away from the viewer (cf. structures 1-2, 1-4, 1-6, 1-8, and 1-10). Moreover, it is contemplated that the compounds recited below also embody compounds in which R³α projects away from the viewer while R³β projects towards the viewer. Not meant to be limiting, however, it is contemplated that preferred compounds are those in which R³α projects towards the viewer and R³β projects away from the viewer such that the natural L-amino acid (S)-configuration is presented. Additionally, the inventors recognize that the phosphorus atom of the phosphoramidate moiety is another source of chirality. Although the structures below do not specifically depict chirality at phosphorus, the inventors recognize that stereochemical configurations are possible such that in a staggered (or zig-zag) line structure the oxo-substituent projects towards the viewer while the OR¹ substituent projects away from the viewer, and vice versa, i.e., where the Cahn-Ingold-Prelog stereochemical designation of phosphorous is either R or S. Therefore, the structures below include all possible stereochemical configurations possible for phosphorus.

On page 243, the structure of the compound of formula IX is disclosed as-
Further, in Table IX-25 the compound IX-25-2 is disclosed.

<table>
<thead>
<tr>
<th>No</th>
<th>R^1</th>
<th>R^2</th>
<th>R^2^1</th>
<th>R^2^2</th>
<th>R^3</th>
<th>R^4</th>
<th>R^5</th>
<th>X</th>
<th>Y</th>
<th>R^7</th>
<th>R^8</th>
</tr>
</thead>
<tbody>
<tr>
<td>IX-25-1</td>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>1Pr</td>
<td>H</td>
<td>CH_3</td>
<td>F</td>
<td>OH</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>IX-25-2</td>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>CH_3</td>
<td>1Pr</td>
<td>H</td>
<td>CH_3</td>
<td>F</td>
<td>OH</td>
<td>H</td>
<td>H</td>
</tr>
</tbody>
</table>

Further the claimed compound is disclosed and characterized in description as example 25.

<table>
<thead>
<tr>
<th>Ex.</th>
<th>R^1</th>
<th>R^2</th>
<th>R^3</th>
<th>R^4</th>
<th>NMR/MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>i-Pr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1H NMR (DMSO-d_6) δ 1.13-1.28 (m, 12H), 3.74-3.81 (m, 2H), 3.95-4.08 (m, 1H), 4.20-4.45 (m, 2H), 4.83-4.87 (m, 1H), 5.52-5.58 (m, 1H), 5.84-6.15 (m, 3H), 7.17-7.23 (m, 3H), 7.35-7.39 (m, 2H), 7.54-7.57 (m, 1H), 11.50 (s, 1H) ; MS, m/e 530.2 (M+1)^+</td>
</tr>
</tbody>
</table>

38. In view of the above stated references to the description of the present invention I am of the view that the stereochemistry for the claimed compounds is clearly disclosed. The stereochemistry of the basic structure of the claimed compound is sufficiently disclosed in the description, be it S-configuration of amino acid or R- & S- configuration of P atom and same is considered to be sufficiently enabled for a person skilled in the art to determine the possible stereoisomers for the claimed compound without any undue burden.

39. Further with reference to the preparation of the claimed compound it is stated on page 684 of the description that *Example numbers 13-54 and 56-66 are prepared using similar procedures described for examples 5-8.*
Based on the structure of the claimed compound and the process claimed in claim-5 the closest example of process for preparing claimed compound is Example 5 which discloses following process scheme-

![Diagram of chemical reaction]

The compound prepared in Example 5 differs from the claimed compound only in that it is a methyl ester whereas compound of claim 1 is an isopropyl ester hence it is considered that the process claimed in claim-5 of the instant invention can be carried out by the person skilled in the art by simply exchanging methyl group with isopropyl without undue burden.

40. Further the example 81 of the description discloses the process of separation of diastereomers of exemplified compounds and states that "certain exemplified compounds were obtained as mixture of diastereomers because of the chirality at phosphorous. The diastereomers were separated on a Chiralpak-AS-H (2 X 25 cm) column under Supercritical Fluid Chromatography (SFC) conditions using 20% methanol in carbon dioxide as solvent. The absolute stereochemistry of the P-chiral center of the diastereomers were not determined. However, chromatographic resolution of these two diastereomers provides for isomers that are characterized as fast eluting and slow eluting isomers. Some examples are shown below.

<table>
<thead>
<tr>
<th>Compound</th>
<th>EC90 (uM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example 15 (Diastereomeric mixture)</td>
<td>0.86</td>
</tr>
<tr>
<td>Fast Moving isomer of Example 15</td>
<td>1.35</td>
</tr>
<tr>
<td>Slow Moving isomer of Example 15</td>
<td>0.26</td>
</tr>
<tr>
<td>Example 39 (Diastereomeric mixture)</td>
<td>0.47</td>
</tr>
<tr>
<td>Fast Moving isomer of Example 39</td>
<td>0.78</td>
</tr>
<tr>
<td>Slow Moving isomer of Example 39</td>
<td>0.02</td>
</tr>
<tr>
<td>Example 49 (Diastereomeric mixture)</td>
<td>0.126</td>
</tr>
<tr>
<td>Fast Moving isomer of Example 49</td>
<td>0.03</td>
</tr>
<tr>
<td>Slow Moving isomer of Example 49</td>
<td>5.78</td>
</tr>
</tbody>
</table>
As can be seen from stated example, a process for separation of diastereomers from a mixture of diastereomers, resulting because of the chirality at phosphorous, is provided. The opponent’s argument that processes disclosed cannot be used without undue burden on the person skilled in the art for separation of diastereomers of compound 25 is not found to be persuasive. The opponent has failed to show any evidence that the process as disclosed in example 81 for compound of formula 39 is not suitable for separation of diastereomers of compound 25. Hence I am of the opinion that ground under section 25(1)(g) of the Patents Act is not valid.

**Opinion of the undersigned on the ground under Section 25(1)(h)**

41. Though the ground under section 25(1)(h) was raised in the opposition notice by the opponents O1, O4, O5, O7, O10 and O11. The said ground was neither argued (during oral hearing) nor was any written hearing submission filed by the opponents O4, O5, O7 and O10. The remaining opponents O1 and O11 failed to show any lapse at the end of the applicant in filing of information under section 8. As the opponents have failed to show any irregularity by the applicant in filing of requirements under section 8, the applicant submission in this regard is found to be satisfactory hence I am of the opinion that ground under section 25(1)(h) of the Patents Act is not valid.

**CONCLUSION:**

42. After thorough and careful consideration of the pre-grant opposition filed by all the opponents under section 25(1) of the Act, statements and evidences produced by all the opponents and the applicant before and at the time of hearing, arguments presented by all the opponents and the applicant during hearing, written submissions by all the opponents and the applicant filed after hearing and in view of my above stated analysis and findings I reject all the pre-grant representations filed in the present application as none of the grounds raised therein were found to be valid. Therefore, I hereby proceed with the grant of patent for the instant application number 3658/KOLNP/2009 with five (05) claims.
The case is hereby disposed of under section 25(1) of The Patents Act, 1970 (as amended) and corresponding rule 55 of The Patents Rules, 2003 (as amended). There is no award of costs to either party.

Dated this 28th day of December 2023

Sd/-

(DR. ROHIT RATHORE)
Deputy Controller of Patents & Designs