

Before the Controller of Patents, New Delhi

**In the matter of section 25(1) of the Patents Act,
1970;**

AND

In the matter of the Patents Rules, 2003

AND

**In the matter of Patent Application No.
6087/DELNP/2005 filed by Gilead Pharmasett
LLC on 27 December 2005 titled “A (2’R)-2’-
Deoxy-2’Fluoro-2’-C-Methyl Nucleoside”**

AND

**In the matter of representation by way of
opposition by Sankalp Rehabilitation Trust
(Opponent)**

STATEMENT OF FACTS AND EVIDENCE

I. INTRODUCTION

1. The Opponents are community based, non-profit organizations representing the needs of people living with Hepatitis-C and HIV/AIDS.
2. Sankalp Rehabilitation Trust is a community-based organisation, registered under the Bombay Public Trusts Act, 1950 bearing registration No. E15459 having its office at SS Bengali Municipal School, First floor, Thakurdwar road, Charni road east, Mumbai- 400 002. The Opponent provides care, treatment and rehabilitation services for injecting drug users. The Opponent has over a thousand beneficiaries who are injecting drug users and who need treatment for Hepatitis C. Injecting drug users are particularly vulnerable to infection with HIV and Hepatitis-C. With respect to health status, HIV as well as Hepatitis-C are a major cause of concern amongst drug users. A survey carried out as part of the sentinel

survey in 2003 revealed that 79% of 250 drug user-patients of the Applicant tested positive for Hepatitis C. In July 2011, 41 of 95 of the Applicant's drug user patients tested positive for Hepatitis C. Out of these, only two who are also co-infected with HIV are on treatment that is being provided free of cost by an international aid agency.

3. Often the high cost of medicines is exacerbated by patent protection. It is well known that product patent on a medicine allows the patent holder to exclude other pharmaceutical companies from manufacturing the medicine for a period of twenty years and thereby allows it to set monopolistic prices for the medicine. The opponents are therefore concerned about the impact of product patent on access to safe, effective and affordable treatment for Hepatitis C. It is established that grant of patents to routine modification to already known drugs to overcome known problems will place life-saving drugs out of the reach of thousands of patients who require it. The high costs of patented medicines also impact the ability of government to procure these medicines for the national treatment programme.
4. The present Application was filed at the Patent Office in Delhi. Therefore, the Hon'ble Patent Controller has the jurisdiction to hear and decide this pre-grant opposition in Delhi.
5. The present specification relates to, 2' methyl-2'fluoro-nucleoside analogues, dosages, and compositions involving the same for the treatment of *flaviviridae* infections which include HCV.
6. Thus, while examining the present Application and the present pre-grant opposition, the Hon'ble Patent Controller must strictly interpret the higher standards of patentability criteria set by the Indian Parliament in order to ensure that pharmaceutical companies are not able to obtain patents over new forms of already known substances and that patents are granted only to genuine inventions.

II. ACCESS TO MEDICINES AND STRICT INTERPRETATION OF PATENTABILITY STANDARDS

7. The present Application pertains to nucleoside analogues for the treatment of viral diseases, particularly Hepatitis C. These compounds are inhibitors of RNA-dependent RNA viral replication and are useful as inhibitors of the virus.
8. HCV NS5B polymerase is required for the synthesis of a double-stranded RNA from a single-stranded viral RNA that serves as a template in the replication cycle of HCV. Therefore, NS5B polymerase is considered to be an essential component in the HCV replication complex. A number of effective targets for drug development against HCV therapeutics include NS5B polymerase.
9. Nucleoside inhibitors of NS5B polymerase can act either as a non- natural substrate that results in chain termination or as a competitive inhibitor which competes with nucleotide binding to the polymerase. To function as a chain terminator the nucleoside analog must be taken up by the cell and converted *in vivo* to a triphosphate to compete for the polymerase nucleotide binding site.
10. Present application claims allegedly novel nucleoside analogues for the treatment of viral infections mainly HCV.
11. The most effective way to lower the cost of these essential medicines is to promote competition. However, in order for there to be any effective generic competition, it is imperative that patents not be granted in India for uninventive, incremental improvements or to inventions that do not meet the strict patentability standards set by India.
12. Although India was constrained by its WTO obligations to introduce product patent protection for pharmaceutical products through the Patents (Amendment) Act of 2005, India retains full sovereignty in determining the standards that must be met with respect to patentability. India is under no obligation to follow the perilous path that many developed nations have taken in setting low standards for novelty and inventive step that result in

patent protection for incremental innovations, all too often at the cost of public health. This has been recognised by the Hon'ble Supreme Court of India too in *Novartis AG v. Union of India and others*, (2013) 6 SCC 1.

13. Cognisant of public health concerns and the Doha Declaration on the TRIPS Agreement and Public Health (2001), Parliament introduced certain provisions, while passing the Patents (Amendment) Act, 2005 to amend the Patents Act, 1970 (hereinafter referred to as the "Patents Act"), to ensure that patents are granted only for genuine inventions and to prevent "evergreening", i.e. creation or extension of monopolies through patent terms by obtaining patents for minor or routine modifications. Indian Parliament also set a higher standard of inventive step.
14. The Patents Act should be interpreted by the Hon'ble Patent Controller in light of all the relevant circumstances surrounding the Amending Act. The Hon'ble Madras High Court, in *Novartis AG v. Union of India and Others*, (2007) 4 MLJ 1153, while upholding Section 3(d) against a constitutional challenge, stated: "We have borne in mind the object which the Amending Act wanted to achieve namely, ***to prevent evergreening; to provide easy access to the citizens of this country to life saving drugs and to discharge their Constitutional obligation of providing good health care to its citizens.***" [see para 19] (emphasis added). As such, the Opponent submits that the Hon'ble Patent Controller, while considering the present pre-grant opposition and while interpreting the provisions of the Patents Act, must bear in mind the intent of Parliament in enacting the Patents (Amendment) Act, i.e. to ensure India's compliance with its obligations under the Agreement on Trade Related Aspects of Intellectual Property Rights while ensuring that patent protection does not come in the way of India's fundamental duty to provide good health care to its citizens.
15. The Opponents firmly believe that a proper application of the patentability standards set out in Section 3(d) of the Patents Act, as well as those embodied in Section 2(1)(j) and Section 2(1)(ja) of the Patents Act, in a manner that fully carries out the objectives of the Amending Act, will

result in the rejection of the present application. The Opponents, therefore, humbly requests that the Hon'ble Patent Controller scrutinise the present application with special care, as its decision will determine whether millions of people will have affordable access to lifesaving treatment.

III. BACKGROUND OF ALLEGED INVENTION

16. On 21 April 2004, the Patent Applicant filed the national phase entry of International Application No. PCT/US2004/012472 (international Publication No. WO 2005/003147) in India, which was subsequently allotted Indian Patent Application No. 6087/DELNP/2005, i.e. the present Application.

III.A. Nucleoside analogues were known

17. Admittedly, as of the earliest priority date, nucleoside analogues were known for their activity in flavivirdae including hepatitis C.

18. At the time of the alleged invention, as will be explained below, the following were well known to persons skilled in the art:

- (i) The Applicant in the present Specification admits that HCV NS5B polymerase is required for the synthesis of a double-stranded RNA from a single-stranded viral RNA that serves as a template in the replication cycle of HCV.[As admitted on page 3, para 1, *placitum* 6-9 of the Present Specification]
- (ii) The applicant also admits that a wide range of nucleoside analogues with 2' methyl and 2' fluorine substitutions have been discovered. [As admitted on page 9, para 2, *placitum* 8-16 of the Present Specification]
- (iii) The Applicant also admits that nucleoside analogues have been developed for the treatment of flaviviridae infections. Also, certain branched nucleosides useful in the treatment of flaviviruses including HCV and pestiviruses are disclosed in International publication Nos. WO 01/90121 and WO 01/92282. Further, it is

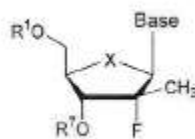
also admitted that WO 2004/002422 by Idenix pharmaceuticals discloses a family of 2' methyl nucleosides for the treatment of flavivirus infection. Also WO 2004/002999 by Idenix published January 2004 discloses a series of 2' or 3' prodrugs of 1', 2', 3', or 4' branch nucleosides for the treatment of flavivirus infections including HCV infections. [As admitted on page 12, para 4-6, *placitum* 11-26 of the Present Specification]

- (iv) The patentee admits a host of patent documents including PCT/CAOO/01316 (WO 01/60315; PCT/US02/01531 (WO 01/57425 and PCT/US02/03086 (WO 02/057287, PCT/EPOT/09633 (WO/018404); and PCT WP 01/79246, WO 02/3290 and WO 02/48165. [As admitted by the Applicant on page 12-13, para 7, *placitum* 27-30 of the Present Specification]

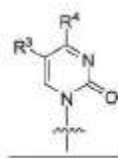
IV. SUMMARY OF CLAIMS

19. The claims of the present application can be summarised as follows:

- (i) Claim 1 is an independent claim and relates to a nucleoside or its pharmaceutically acceptable salt of the structure:

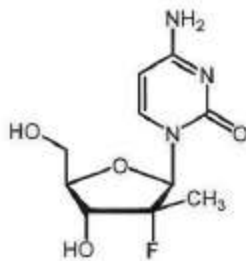


Wherein the Base is a pyrimidine base represented by the following formula

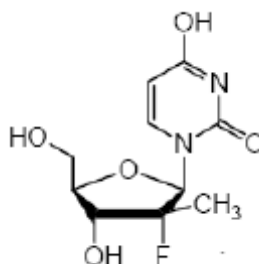


X is O; R¹ and R⁷ are independently H, a monophosphate, a diphosphate, or a triphosphate; and R³ is H and R⁴ is NH₂ or OH.

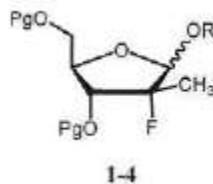
- (ii) Claim 2 is a dependent on claim 1 and relates to the nucleoside as claimed in claim 1, wherein R^7 is H and R^1 is a monophosphate, a diphosphate, or a triphosphate.
- (iii) Claim 3 is a dependent on claim 1 and relates to the nucleoside nucleoside as claimed in claim 1, R^7 is H and R^1 is a diphosphate or a triphosphate.
- (iv) Claim 4 is a dependent on claim 1 and relates to the nucleoside wherein R^7 is H and R^1 is triphosphate.
- (v) Claim 5 is a dependent on claim 1 wherein R^1 and R^7 are H.
- (vi) Claim 6 is an independent claim and relates to a nucleoside or its pharmaceutically acceptable salt thereof of the formula:



- (vii) Claim 7 is an independent claim and relates to a nucleoside or its pharmaceutically acceptable salt thereof of the formula:

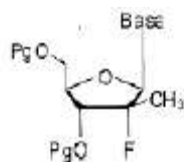


- (viii) Claim 8 is a process claim and relates to the method of synthesizing the nucleoside as claimed in claim 1, which comprises glycosylating the pyrimidine with a compound having the following structure:



Wherein R is C₁-C₄ lower acyl, benzoyl, or mesyl; and Pg is selected from among C(O)-C₁-C₁₀ alkyl, C(O)phenyl, C(O)biphenyl, C(O)naphthyl, CH₂-C₁-C₁₀ alkyl, CH₂-C₁-C₁₀ alkenyl, CH₂-phenyl, CH₂-biphenyl, CH₂-naphthyl, CH₂O-C₁-C₁₀ alkyl, CH₂O-phenyl, CH₂O-biphenyl, CH₂O-naphthyl, SO₂-C₁-C₁₀ alkyl, SO₂-phenyl, SO₂-biphenyl, SO₂-naphthyl, tert-butyl dimethylsilyl, tert-butyl diphenylsilyl, or both Pg's may come together to form a 1,3-(1,1,3,3-tetraisopropylidisiloxanylidine).

- (ix) Claim 9 is a process claim which relates to a method of synthesizing the nucleoside as claimed in claim 1, which comprises selectively deprotecting a 3'-OPg or a 5'-OPg of a compound having the following structure:



Wherein, each Pg is independently a protecting group selected from among C(O)-C₁-C₁₀alkyl, C(O)phenyl, C(O)biphenyl, C(O)naphthyl, CH₃, CH₂-C₁-C₁₀ alkyl, CH₂-C₁-C₁₀alkenyl, CH₂O-phenyl, CH₂O-biphenyl, CH₂O-naphthyl, SO₂-C₁-C₁₀ alkyl, SO₂-phenyl, SO₂-biphenyl, SO₂-naphthyl, tert-butyl dimethylsilyl, tert-butyl diphenylsilyl, or both Pg's may come together to form a 1,3-(1,1,3,3-tetraisopropylidisiloxanylidene).

- (x) Claim 10 is dependent on claim 1-7 and relates to the nucleoside as and when used for the preparation of a pharmaceutical composition or medicament.

V. SUMMARY OF GROUNDS OF OPPOSITION

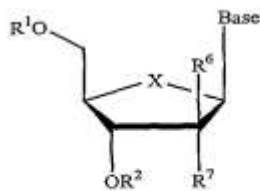
20. The Opponent brings this opposition under the following grounds, amongst others, each of which are without prejudice to one another:
21. Claims 1-10 of the present application are not new, are anticipated and lack novelty, and therefore fail under Section 2(1)(j) of the Patents Act. Therefore, the Opponent brings this opposition under 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 in India or elsewhere in any document;
22. Claims 1 to 10 of the present application lack inventive step, and therefore fail under Sections 2(1)(j) and 2(1)(ja) of the Patents Act. Therefore, the Opponent brings this opposition under Section 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;
23. Claims 1-7 and 10 of the present application do not satisfy the test of Section 3(d) of the Patents Act in as much as the subject matter does not exhibit enhanced therapeutic efficacy. Therefore, the Opponent brings this opposition under Section 25(1)(f)—that the subject of any claim of the complete specification is not an invention within the meaning of this Act.
24. The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed. Therefore, the Opponent brings this opposition under Section 25(1)(g) of the Act—that that complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed; and
25. The Patent Applicant has failed to comply with the requirements of Section 8 of the Patents Act. Therefore, the Opponent brings this opposition under Section 25(1)(h) of the Act—that the Patent Applicant has failed to disclose the Controller information required by Section 8 or

has furnished information which in any material particular was false to his knowledge.

VI. DETAILED GROUNDS

VI.A. Claim 1-10 are not new, lack novelty, are anticipated by prior publication and, therefore, should be rejected under Section 25(1)(b)(ii) of the Patents Act.

26. Section 2(1)(j) of the Patents Act defines an “invention” as “a *new* product or process involving an inventive step and capable of industrial application” (emphasis added). Section 25 (1)(b)(ii) provides a ground for opposition if the alleged invention, in so far as claimed in any claim of the complete specification, is not new, having been published before the priority date of the claim in India or elsewhere, in any other document. Thus, if a publication, published prior to the priority date of a patent application, discloses the claimed invention, then the claims of the patent application are not new, lack novelty, are anticipated by prior publication and must be rejected.
27. “Newness” or novelty is to be determined by comparing the claims of a patent application to the disclosures in the prior art, read in light of the general knowledge available to a person skilled in the art.
28. It is submitted that claim 1-10 lack novelty in light of each WO 01/92282 A2, WO 02/057425 or WO 01/90121, as shown below:
29. Without prejudice to other grounds raised herein, WO 01/92282 A2 titled ‘Methods and compositions for treating flaviviruses and pestiviruses’, published on December 6, 2001, hereinafter ‘282 Application’ a copy of which is attached herein and marked at ‘**Exhibit A**’ discloses nucleoside analogues with 2’-methyl & 2’ fluorine substitution.
30. Embodiment XI of the ‘282 Patent discloses the compound of the following formula disclosed on internal page 26:



(XI)

Wherein:

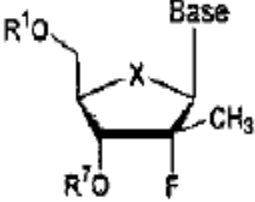
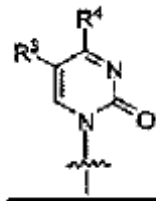
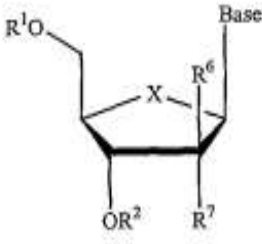
Base is a purine or **pyrimidine** base as defined herein;

R¹, R² and R³ are independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilised phosphate prodrug); acyl (including lower acyl); alkyl; alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an aminoacid; 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, R² and R³ is independently H or phosphate;

R⁶ is hydrogen, hydroxyl, alkyl (including lower alky), azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(lower alkyl), -O(acyl), _O(lower acyl), -O(alkyl), -O(loweralkyl), -O(alkenyl), chloro, bromo, **fluoro**, iodo, NO₂, NH₂, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)₂, -N(acyl)₂

R⁷ is hydrogen, OR³, hydroxyl, **alkyl (including lower alkyl)**, azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -O(acyl), _O(lower acyl), -O(alkyl), -O(loweralkyl), -O(alkenyl), chlorine, bromine, iodine, NO₂, NH₂, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)₂, -N(acyl)₂; and

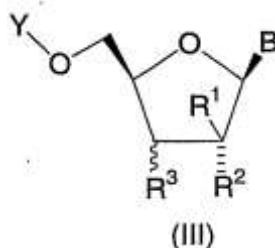
X is O, S, SO₂ or CH₂ which when substituted leads to the impugned compound claimed in claim 1 of the present application. A comparison of the structures of the claimed compound and the compound disclosed in the '282 application can be shown in the table below:

Elements of claimed invention in present application	Features disclosed in prior art document ('282 Application) Exhibit A
<p>Claims 1-7- β-D and β-L compounds of</p>  <p>Wherein the Base is a pyrimidine represented by the formula:</p>  <p>X=O, R¹ & R⁷ are independently H, a monophosphate, a diphosphate, a triphosphate... With pharmaceutically acceptable salts and carriers.</p>	<p>β-D and β-L compounds of</p>  <p>(XI)</p> <p>Base is pyrimidine base which includes Uracil; R₁, R₂ and R₃ are independently H; phosphate (including monophosphate, diphosphate, triphosphate; R₆ is fluoro R₇ is alkyl (including lower alkyl), X is O (See internal page 26)</p>
<p>Claims 8- Method of synthesizing nucleoside by glycosylating the pyrimidine with appropriately modified sugar.</p> <p>Claim 9- Method of synthesizing the nucleoside as claimed in claim 1, which comprises selectively deprotecting the nucleoside.</p>	<p>Glycosylating of the nucleobases with appropriately modified sugar which is optionally protected is coupled to the BASE by methods well known to person skilled in the art. (See page 62-63)</p>
<p>Claims 10- Use in pharmaceutical composition or a medicament.</p>	<p>Compositions are disclosed. (see page 55-56)</p>

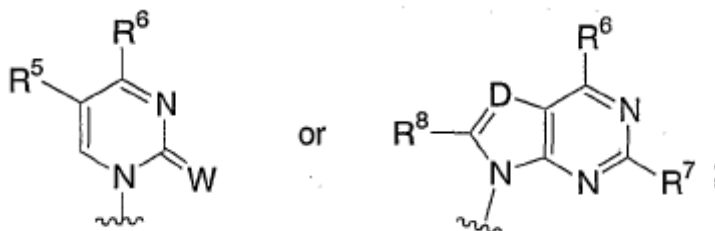
31. Therefore, in light of the disclosures made in the '282 Application which match all features in the structure of the Present Application showing that the compound claimed in claim 1 -10 are not novel.
32. WO 02/057425 titled 'Nucleoside derivatives as inhibitors of RNA dependent RNA viral polymerase', which was published on July 25, 2002,

a copy of which is annexed hereto and marked as “**Exhibit B**” anticipates the impugned invention disclosed in the present application.

33. Embodiment III of the ‘425 Application discloses compounds of the following formula: (See Exhibit B, internal page 17)



wherein **B** is



D is N, CH, C-CN, C-NO₂, C-C₁₋₃ alkyl, C-NHCONH₂, C-CONR¹¹R¹¹, C-CSNR¹¹R¹¹, C-COOR¹¹, C-hydroxy, C-C₁₋₃ alkoxy, C-amino, C-C₁₋₄ alkylamino, C-di(C₁₋₄ alkyl) amino, C-halogen, C-(1,3-thiazol-2-yl), or C-(imidazol-2-yl); wherein alkyl is unsubstituted or substituted with one to three groups independently selected from halogen, amino, hydroxyl, carboxy, and

C₁₋₃ alkoxy;

W is O or S;

Y is H, C₁₋₁₀ alkylcarbonyl, P₃O₉H₄, P₂O₆H₃, or P(O)R⁹R¹⁰;

R¹ is hydrogen, CF₃, or C₁₋₄ alkyl and one of R² and R³ is OH or C₁₋₄ alkoxy and the other of R² and R³ is selected from the group consisting of hydrogen,

hydroxy,

fluoro,

C₁₋₃ alkyl,

Trifluoromethyl,

C₁₋₈ alkylcarbonyloxy,

C₁₋₃ alkoxy; or

Amino; or

R² is hydrogen, CF₃, or C₁₋₄ alkyl and one of R¹ and R³ is OH or C₁₋₄ alkoxy and the other of R¹ and R³ is selected from the group consisting of hydrogen,

hydroxyl,

fluoro,

C₁₋₃ alkyl,

trifluoromethyl,

C₁₋₈ alkylcarbonyloxy,

C₁₋₃ alkoxy, and

amino; or

R¹ and R² together with the carbon atom to which they are attached form a 3- to 6- membered saturated monocyclic ring optionally containing a heteroatom selected from O, S, and NC₀₋₄ alkyl;

R⁶ is H, OH, SH, NH₂, C₁₋₄ alkylamino, di(C₁₋₄ alkyl) amino,

C₃₋₆ cycloalkylamino, halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, or CF₃;

R⁵ is H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ alkylamino, CF₃, or halogen;

R₇ is hydrogen, amino, C₁₋₄ alkylamino, C₃₋₆ cycloalkylamino, or

Di(C₁₋₄ alkyl)amino;

Each R¹¹ is independently H or C₁₋₆ alkyl;

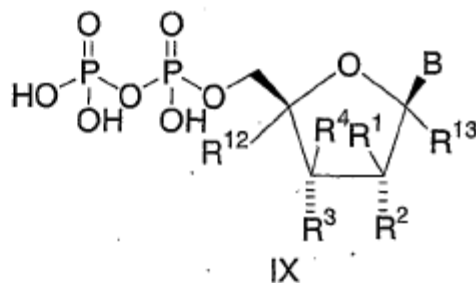
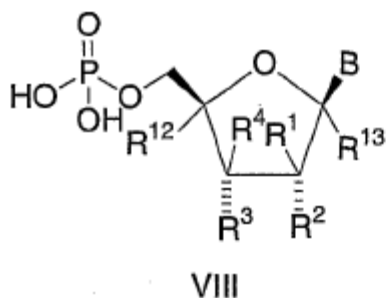
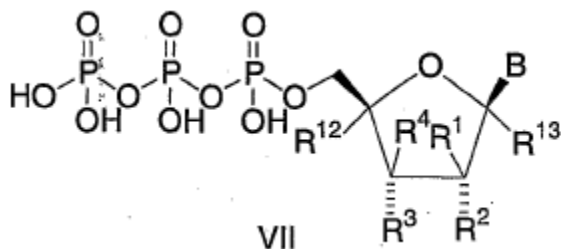
R⁸ is H, halogen, CN, carboxy, C₁₋₄ alkyloxycarbonyl, N₃, amino, C₁₋₄ alkylamino, di(C₁₋₄ alkyl)amino, hydroxyl, C₁₋₆ alkoxy, C₁₋₆ alkyl thio, C₁₋₆ alkylsulfonyl, or (C₁₋₄ alkyl)₀₋₂ aminomethyl; and

R⁹ and R¹⁰ are each independently hydroxyl, OCH₂CH₂SC(=O)t-butyl, or OCH₂O(C=O)iPr;

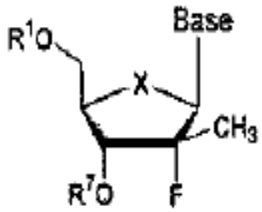
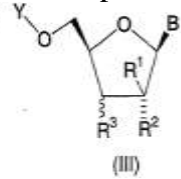
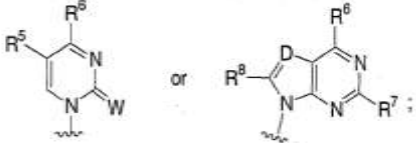
with the provisos that (a) when R¹ is hydrogen and R² is fluoro, then R³ is not hydrogen, trifluoromethyl, fluoro, C₁₋₃ alkyl, amino, or C₁₋₃ alkoxy; (b) when R¹ is hydrogen and R² is fluoro, hydroxyl, or C₁₋₃ alkoxy, then R³ is

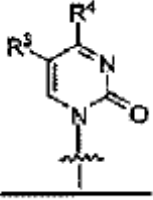
not hydrogen or fluoro; and when R¹ is hydrogen and R² is hydroxyl, then R³ is not β-hydroxy.

34. The '425 application also encompasses mono, di and tri phosphate derivatives in embodiments VII, VIII and IX (See internal page 44, Exhibit B).



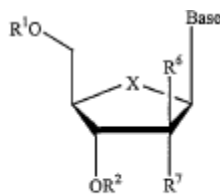
- 35.

Elements of claimed invention in present application	Features disclosed in prior art document ('425 Application) Exhibit B
<p>Claims 1-7- β -D and β-L compounds of</p>  <p>Wherein the Base is a pyrimidine represented by the formula:</p>	<p>β -D and β-L compounds of</p>  <p>(III)</p> <p>wherein B is</p>  <p>or</p> <p>R¹ = C₁₋₄ alkyl R² = fluoro R³ = OH Y = H Monophosphates, Diphosphates and tri</p>

 <p>X=O, R¹ & R⁷ are independently H, a monophosphate, a diphosphate, a triphosphate... With pharmaceutically acceptable salts and carriers.</p>	<p>phosphates are disclosed as structures VII, VIII & IX (<i>see</i> internal page 17)</p>
<p>Claims 8- Method of synthesizing nucleoside by glycosylating the pyrimidine with appropriately modified sugar.</p> <p>Claim 9- Method of synthesizing the nucleoside as claimed in claim 1, which comprises selectively deprotecting the nucleoside.</p>	<p>Glycosylating of the nucleobases with appropriately modified sugar which is optionally protected is coupled to the base to yield preferred nucleoside analogues. (<i>See</i> internal page 55-56)</p>
<p>Claims 10- Use in pharmaceutical composition or a medicament.</p>	<p>Compositions are disclosed. (<i>See</i> internal page 45).</p>

36. Therefore, in light of the disclosure made in the '425 Application which match all elements of the claimed invention in Present Application shows that the claims 1 -10 are not novel.
37. It is submitted that WO 01/90121 titled 'Methods and compositions for treating Hepatitis C virus' published on November 29, 2001, a copy of which is hereto annexed and marked as "**Exhibit C**" also discloses the claimed invention in the impugned specification. The '121 Application discloses β-D-or β-L-nucleosides for treatment of HCV.

38. In the XI embodiment of the invention in the '121 Application, compounds encompassed by the structure shown below are disclosed: (See internal pages 13-14 Exhibit C)



(XI)

wherein:

Base is a purine or **pyrimidine** base as defined herein;

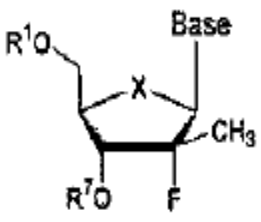
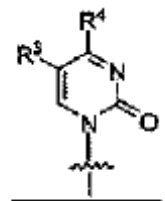
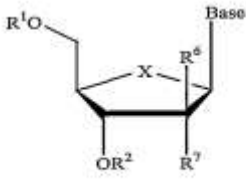
R¹, R² and R³ are independently **H**; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilised phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methane sulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an 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 R² or R³ is independently **H** or phosphate;

R⁶ is hydrogen, hydroxyl, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(lower alkyl), -O(acyl)_m - O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), chloro, bromo, **fluoro**, iodo, NO₂, NH₂, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)₂, -N(acyl)₂;

R⁷ is hydrogen, OR³, hydroxyl, **alkyl (including lower alkyl)**, azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O (lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), chlorine, bromine, iodine, NO₂, NH₂, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)₂, -N(acyl)₂; and

X is O, S, SO₂ or CH₂.

39. The method of preparation of compounds is also disclosed by glycosylating an appropriately modified sugar involving protecting and deprotecting the functional groups involving known chemical reagents. (See Exhibit C internal page 66-69)

Elements of claimed invention in present application	Features disclosed in prior art document ('121 Application) Exhibit C
<p>Claims 1-7- β -D and β-L compounds of</p>  <p>Wherein the Base is a pyrimidine represented by the formula:</p>  <p>X=O, R¹ & R⁷ are independently H, a monophosphate, a diphosphate, a triphosphate... With pharmaceutically acceptable salts and carriers.</p>	<p>β -D and β-L compounds of</p>  <p>(XI)</p> <p>Base is a purine of pyrimidine base as defined herein R6=Fluoro R7= alkyl (including lower alkyl) R2=H R1= H (including monophosphate, diphosphate, triphosphate, or a stabilised phosphate prodrug) (See page 13-14)</p>
<p>Claims 8- Method of synthesizing nucleoside by glycosylating the pyrimidine with appropriately modified sugar.</p> <p>Claim 9- Method of synthesizing the nucleoside as claimed in claim 1, which comprises selectively deprotecting the nucleoside.</p>	<p>Glycosylating of the nucleobases with appropriately modified sugar which is optionally protected is coupled to the base to yield preferred nucleoside analogues. (See page 66-69)</p>
<p>Claims 10- Use in pharmaceutical composition or a medicament.</p>	<p>Compositions are also disclosed. see internal page 59-61</p>

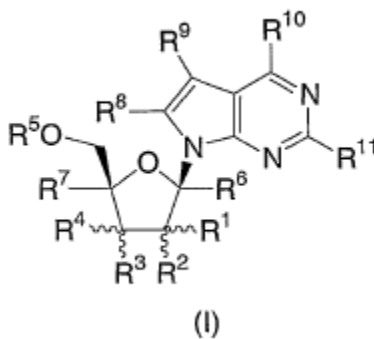
40. Therefore, in light of disclosure made in either '282, or '425 or '121 Application, claims 1-10 of the present application are not new, lack novelty and are anticipated and therefore ought to be rejected.

VI.B. Claims 1 to 20 are obvious, do not involve a technical advance and lack inventive step as defined under Section 2(1)(ja) and are, therefore, should be rejected under Section 25(1)(e) of the Patents Act.

41. Section 2(1)(j) defines an "invention" as "a new product or process involving an *inventive step* and capable of industrial application". (emphasis added). Therefore, all alleged inventions, in order to qualify for a patent, must satisfy the criteria of inventive step. Section 2(1)(ja) of the Patents Act defines an inventive step as "a feature of an invention that involves technical advance as compared to the existing knowledge ... and that makes the invention not obvious to a person skilled in the art".
42. Sub-sections (j) and (ja) of Section 2(1) of the Patents Act thus require a Patent Applicant to show that the feature of the alleged invention involves a technical advance and that it is not obvious to a person skilled in the art. These requirements are laid down to ensure that patents, which result in a monopoly, are granted only to genuine inventions.
43. Section 25(1)(e) of the Patents Act provides a ground for opposition if the alleged invention is obvious and does not involve an inventive step having regard to matter published, as described in Section 25(1)(b) of the Patents Act. Section 25(1)(b) sets out that such published matter includes matter published in India or elsewhere in any document before the priority date of the alleged invention.
44. The present specification deals with 2' methyl up, 2' fluoro down nucleoside analogues as effective for treatment of HCV. Nucleoside analogues are substrate analogues that need to be phosphorylated to their corresponding nucleoside triphosphate (nucleotide) in the cytoplasm of infected cells in order to become active against the viral polymerases. The

nucleotide may be incorporated by the polymerase during processive nucleic acid synthesis, leading to early termination of the elongation reaction and thus inhibition of the virus life cycle. Nucleoside inhibitors of the viral polymerase are used therapeutically for HIV, hepatitis B and herpes viruses.

45. Nucleoside analogue drugs which are long known for their application in competitive inhibition/ chain termination and resultant antiviral effect, have been used in the treatment of cancers and HIV. AZT (INN name- zidovudine), the first revolutionary breakthrough drug approved for treatment of HIV was first synthesized back in 1964.
46. It is submitted that a significant amount of work relating to nucleoside analogues was being undertaken during the 1990's for their activity against HCV which is illustrated by several patent documents including the '121 Application, '282 Application etc, which report a range of 2'-methyl-up 2'-fluorine- down as well as 2'-methyl-up 2'-hydroxy- down and nucleoside analogues showing antiviral activities against *flaviviridae* including Hepatitis C.
47. In addition to that, WO 02/057287 titled 'Nucleoside derivatives as inhibitors of RNA- dependent RNA viral polymerase' published on July 25, 2002, hereinafter '287 Application, a copy of which is annexed herewith and marked "**Exhibit D**" discloses 2'-methyl-up 2'-fluorine-down nucleoside analogues in its embodiment I as below (*See* internal page 5-6):



or a pharmaceutically acceptable salt thereof:

wherein R¹ is C₂₋₄ alkenyl, C₂₋₄ alkynyl, or **C₁₋₄ alkyl**, wherein alkyl is unsubstituted or substituted with hydroxy, amino, C₁₋₄ alkoxy, C₁₋₄ alkylthio, or one to three fluorine atoms;

R² is hydrogen, **fluorine**, hydroxyl, mercapto, C₁₋₄ alkoxy, or C₁₋₄ alkyl; or R¹ and R² together with the carbon atom to which they are attached to form a 3-6-membered saturated monocyclic ring system optionally containing a heteroatom selected from O, S, and NC₀₋₄ alkyl;

R³ and R⁴ are each independently selected from the group consisting of **hydrogen**, cyano, azino, halogen, **hydroxy**, mercapto, amino, C₁₋₄ alkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, and C₁₋₄ alkyl, wherein alkyl is unsubstituted or substituted with hydroxy, amino, C₁₋₄ alkoxy, C₁₋₄ alkylthio, or one to three fluorine atoms;

R⁵ is hydrogen, C₁₋₁₀ alkylcarbonyl, P₃O₉H₄, P₂O₆H₃, or P(O)R₁₃R₁₄;

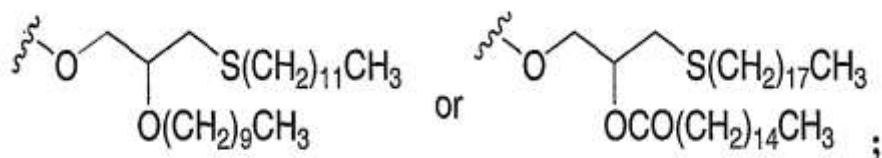
R⁶ and R⁷ are each independently **hydrogen**, methyl, hydroxymethyl, or fluoromethyl;

R⁸ is hydrogen, C₁₋₄ alkyl, C₂₋₄ alkynyl, halogen, cyano, carboxy, C₁₋₄ alkyloxycarbonyl, azido, amino, C₁₋₆ alkylsulfonyl, (C₁₋₄ alkyl)₀₋₂ aminomethyl, or C₄₋₆ cycloheteroalkyl, unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, amino, C₁₋₄ alkyl, and C₁₋₄ alkoxy;

R⁹ is hydrogen, cyano, nitro, C₁₋₃ alkyl, NHCONH₂, CONR¹²R¹², CSNR¹²R¹², COOR¹², C(=NH)NH₂, hydroxyl, C₁₋₃ alkoxy, amino, C₁₋₄ alkylamino, di(C₁₋₄ alkyl)amino, halogen, (1,3-oxazol-2-yl), (1,3-thiazol-2-yl), or (imidazol-2-yl); wherein alkyl is unsubstituted or substituted with one to three groups independently selected from halogen, amino, hydroxyl, carboxy, and C₁₋₃ alkoxy;

R¹⁰ and R¹¹ are each independently hydrogen, hydroxy, halogen, C₁₋₄ alkoxy, amino, C₁₋₄ alkylamino, di(C₁₋₄ alkyl)amino, C₃₋₆ cycloalkylamino, di(C₃₋₆cycloalkyl)amino, or C₄₋₆ cycloheteroalkyl, unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, amino, C₁₋₄ alkyl, and C₁₋₄ alkoxy;

Each R¹² is independently hydrogen or C₁₋₆ alkyl; and
 R¹³ and R¹⁴ are each independently hydroxyl, OCH₂CH₂SC(=O)C₁₋₄alkyl,
 OCH₂O(C=O)OC₁₋₄alkyl, NHCHMeCO₂Me, OCH(C₁₋₄alkyl)O(C=O)C₁₋₄
 alkyl,



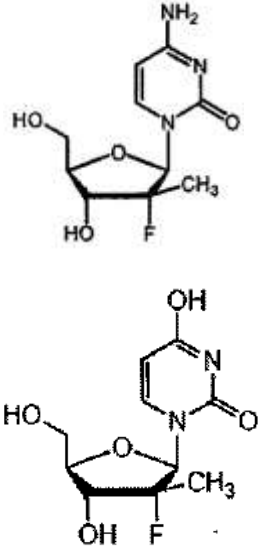
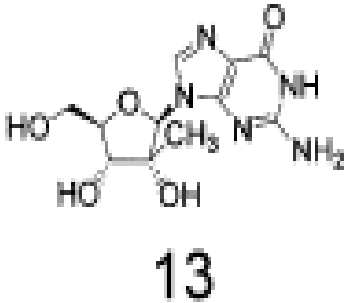
with the proviso that when R¹ is β-methyl and R⁴ is hydrogen or R⁴ is β-methyl and R¹ is hydrogen, R² and R³ are α-hydroxy, R¹⁰ is amino, and R⁵, R⁶, R⁷, R⁸, and R¹¹ are hydrogen, then R⁹ is not cyano or CONH₂.

Compound claimed in Claims 6&7	Compound disclosed in '287 application, Exhibit D
 	 (I) R⁶=H R¹=CH₃ R²=F R³=H R⁴=OH R⁵=H R⁷=H (see internal page 5-6)

48. It can therefore be seen that the '287 application discloses nucleoside analogues with 2'methyl-up-2' fluorine-down compounds. Barring disclosing the base of the nucleoside analogue, the '287 application discloses all limitations of the present invention.

49. It is submitted that the '287 application also discloses several 2'-methyl-up-2' hydroxy-down compounds which were known to have anti- HCV activity at the time of filing of the Present Application.
50. It is submitted that at the time of priority of the present application it was common general knowledge that 2'-methyl-up-2'-hydroxy- down nucleoside analogues had the potential to be therapeutically efficacious in treating HCV. As will be substantiated below, it was also common general knowledge that certain 2'-methyl-up-2'-hydroxy- down nucleoside analogues had activity in the HCV replicon assay and acted as chain terminators of the HCV chain terminators of the HCV RNA- dependent RNA polymerase.
51. Firstly, Raffaele De Francesco and Charles Rice "New therapies on the horizon for hepatitis C: are we close?", (2003) *Clin Liver Dis.*, 7, 211-243, published on or about February 2003, a copy of which is hereto annexed and marked as "**Exhibit E**" discloses various strategies for treating HCV that were being pursued for treating HCV. These strategies include the use of nucleoside analogues to inhibit NS5B enzymatic activity. Francesco and Rice confirm that NS5B had been identified as a target for the development of anti HCV therapies by early 2003 and suggest that inhibition of this pivotal enzyme would lead to the suppression of HCV replication in infected cells (*see* Francesco and Rice, Exhibit E, page 225 paragraph 3, *placitum* 36-43). The article further identifies that novel series of nucleosides that are candidates for the treatment of HCV. It also identifies β -D-2'-methyl-ribofuranosyl-guanosine which was found to be phosphorylated in cultured cells and was also found to be orally bioavailable in primates. (*see id.*Exhibit E internal page 228-229, paragraph 3-5, *placitum* 23-43). The structure of β -D-2'-methyl-ribofuranosyl-guanosine is outlined: (*See id.* Exhibit E, internal page 226, figure 6B compound 13:

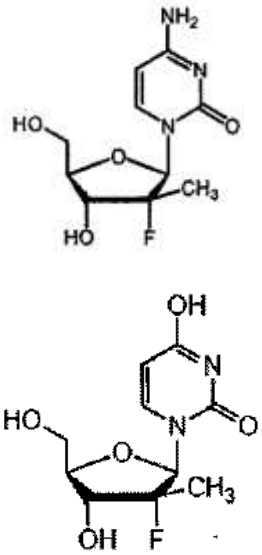
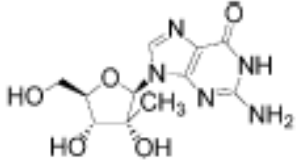
Compound claimed in Claims	Figure 6B, compound 13, Exhibit
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6&7	E, (see internal page 226)
	

52. Francesco and Rice further outline that a myriad of new therapies including inhibitors of polymerase are in the process of development and the next few years signal widespread clinical use. (see *id.* Exhibit E internal page 233, *placitum* 9-20).
53. The skilled person in the art therefore knew that nucleoside analogues with 2' methyl up and 2' hydroxyl down substitutions were one of the compounds in the process of development for treatment of HCV and had bright future prospects.
54. Secondly, Raffaele De Francesco, Licia Tomei, Sergio Altamura, Vincenzo Summa, Giovanni Migliaccio, "Approaching a new era for Hepatitis C virus therapy: inhibitors of the NS3-4 serine protease and the NS5B RNA RNA –dependent RNA polymerase", (2003) *Antiviral Research*, 58, 1-16 published on or about March 2003, a copy of which is annexed hereto marked as, "**Exhibit F**", also identifies NS5B to be pivotal in viral genome replication and teaches that specific inhibitors of this enzyme could be found that block HCV replication. (See Francesco *et al*, Exhibit F, internal page 8, column 2, *placitum* 43-51 and page 9, column

1, *placitum* 1-2). It also reports that the only nucleoside which had been shown to be therapeutically useful against HCV i.e. ribavirin could also have a mechanism of action whereby it is incorporated by NS5B into the nascent viral genome. (*See id.* Exhibit F, internal page 10, column 2, *placitum* 42).

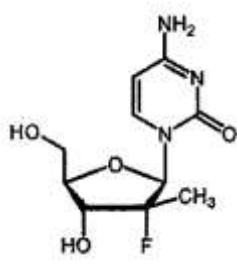
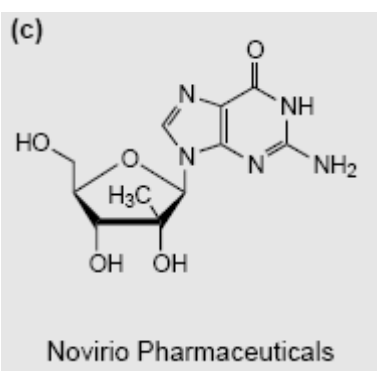
55. Francesco *et al* identify β -D-2'-methyl-ribofuranosyl-guanosine as having NS5B activity (*see id.* Exhibit F, internal page 11, figure 5, compound 11).

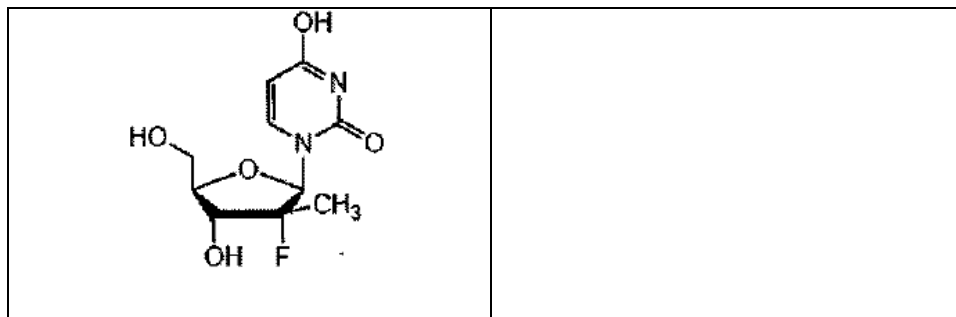
Compound claimed in Claims 6&7	Figure 5, compound 11, <i>see</i> internal page 11, Exhibit F
	 <p style="text-align: center;">11</p>

56. The compound 11 disclosed on internal page 11 is same as the compound 13 disclosed in figure 6B of Exhibit E.
57. Francesco *et al*, therefore confirm the teachings of Francesco and Rice (see Exhibit E) and reaffirm that inhibitors of NS3-4 A and NS5B constitute the most promising targets for the development of novel anti-HCV compounds. (*See* Exhibit F, internal page 12, column 2, *placitum* 5-7)
58. Thirdly, Michelle Walker and Zhi Hong, "HCV RNA-dependent RNA polymerase as a target for antiviral development", *Current Opinion in Pharmacology*, (2002) 2, 1-9 published on or about October 2002, hereinafter 'Walker and Hong', a copy of which is hereto annexed and

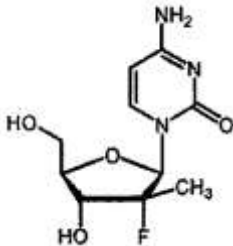
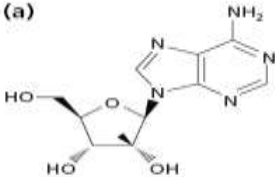
marked “**Exhibit G**” report that RNA dependent RNA polymerase being a vital target for viral replication, has been the focus of intense drug discovery activity. Walker and Hong further report that both nucleoside and non- nucleoside inhibitors of HCV polymerase with encouraging profiles have been identified, could be further developed into therapeutics once clinical trials initiate in near future. (See Walker and Hong, Exhibit G abstract on internal page 1)

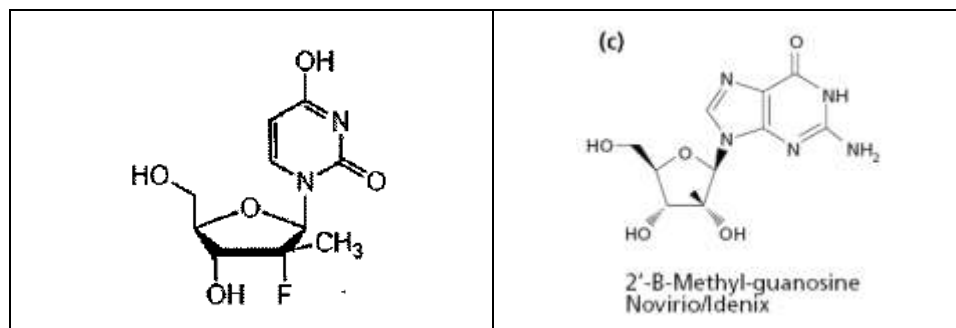
59. Walker and Hong therefore reaffirm that the polymerase inhibitors were promising drug candidates in 2003. They identify that at that time there were several compounds with the potential to inhibit various targets encoded by HCV, however, the primary focus at the time was on finding inhibitors of the NS5B polymerase which was apparent from numerous patents filed within the past year laying claims to new compound entities and new therapeutic utilities related to HCV treatment. (See *id.* Exhibit G internal pages 4, column 2, *placitum* 20-32& page 5 column 1&2)
60. Walker and Hong further disclose that Norvirio Pharmaceuticals (now Idenix Pharmaceuticals Inc., Cambridge, MA) had also disclosed a broad series of nucleosides with extensive sugar modifications. (See *id.* Exhibit G internal page 6, column 1, *placitum* 1-6) The article further discloses that structure of β -D-2'-methyl-ribofuranosyl-guanosine as compound (c) on internal page 5:

Structure of compounds claimed in claim 6 & 7	Figure 5, compound (c), see internal page 5, Exhibit G
	



61. The compound (c) i.e. β -D-2'-methyl-ribofuranosyl-guanosine is identical to the compounds disclosed in the previous articles in Exhibits E & F.
62. Fourthly, Walker, Todd C Appleby, Weidon Zhong, Johnson YN Lau and Zhi Hong, "Hepatitis C virus therapies: current treatments, targets and future perspectives", *Antiviral Chemistry & Therapy*, (2003) 14, 1-21 published on or about January 2003, a copy of which is hereto annexed and marked "**Exhibit H**" suggest chain terminators and non chain terminators for nucleoside inhibitors. They admit that recent studies suggest that some of the antiviral activity of ribavirin may be due to its ability to misincorporate into the viral genome. In addition to that they predict RNA chain terminators to work in a manner similar to DNA polymerase inhibitors. They further report that Merck had indeed recently described two nucleoside analogues that appear to act as chain terminators. (*See id.*, Exhibit H, Walker *et al*, internal page 11, column 2, *placitum* 26-29)The compounds are 2' methyl-adenosine (2' Me-A) and 2'-O-methyl-cytidine (2'O-Me-C) of formula as shown below (*see id.*, Exhibit H internal page 12, figure 6):

Compound claimed in Claims 6&7	Figure 6, compound (a) & (c), see internal page 12, Exhibit H
	<p>(a)</p>  <p>2'-Methyl-adenosine Merck Ki=0.9 μM</p>

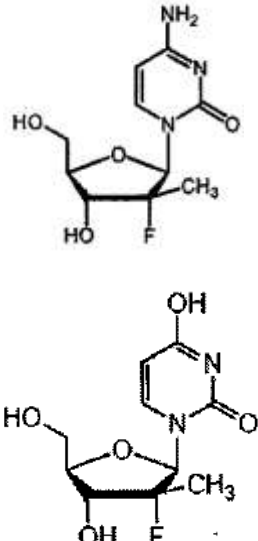
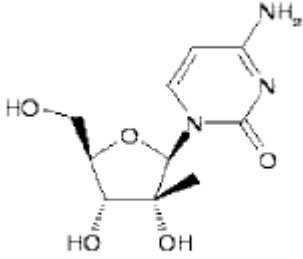


63. It may be noted that the compound (c) in figure 6 in Exhibit H is the same as the abovementioned compound disclosed in Exhibit G, E & F).
64. Walker *et al* further disclose that the 2'- methyl- guanosine and additional nucleosides described by Novirio/ Idenix act in a manner similar to the compounds disclosed by Merck. (*See id.*, Exhibit H, internal page 39-42). Walker *et al* identify this class of drugs as having great potential to serve as potent anti- HCV therapies. (*See id.* Exhibit H, internal page 11, column 2, *placitum* 48-53).
65. Fifthly, Steven Carroll *et al.*, "Inhibition of Hepatitis C Virus RNA Replication by 2'-Modified Nucleoside Analogues" (2003), *J.Biol.Chem.*, 278, 11979-11984, first published online on 27 January, 2003 and in print on 4 April 2003, a copy of which is hereto annexed and marked "**Exhibit I**" not only validate the RNA-dependent RNA polymerase (NS5B) of hepatitis C virus as essential for the replication of viral RNA, but also describe 2'- substituted nucleosides as inhibitors of HCV replication. Carroll *et al* teach that 5'- triphosphates of 2'-C-methyladenosine and 2'- O-methyl-cytidine as inhibitors of NS5B- catalyzed RNA synthesis in vitro, in a manner that is competitive with substrate nucleoside triphosphate. They report that both compounds are found to inhibit HCV RNA replication in a replicon cell line. They conclude that 2' modifications of natural substrate nucleosides transform these molecules into potent inhibitors of HCV replication. (*See Carroll et al.*, Exhibit I, abstract internal page 1.). Carroll *et al* therefore establish the activity of

2'-C-methyladenosine and 2'-O-methyl-cytidine as inhibitors of NS5B-catalyzed RNA polymerase in HIV infected cells.

66. Sixthly, the importance of 2' nucleosides was highlighted by three presentations in the 16th International Conference on Antiviral Research held at Savannah, Georgia, USA between 27th April and 1 May 2003. The abstracts of these presentations were published in the journal Antiviral Research volume 57 issue 3 dated February 2003, a copy of which is hereto annexed and marked as "**Exhibit J**". The three presentations were held during Oral Session V: Hepatitis C virus, Flaviviruses given at 08:30, 08:45 and 09:00 am respectively on 30th April 2004. The first presentation was made by Eldrup *et al*, "Structural Activity Relationship of 2' Modified Nucleosides for Inhibition of Hepatitis C Virus" (Abstract 119). The 119 abstract states that two 2' modified ribonucleosides were evaluated for anti HCV activity and found to be potent inhibitors of HCV RNA replication in vitro. The presentation describes a series of related 2' modified ribonucleosides; including introduction of modified bases, with various substitutions, and change of stereo- and region- chemistry on the sugar moieties. The structures of the compounds were described in the presentations. The Opponents are in the process of obtaining copies of the presentation and crave leave to rely on them at the time of oral hearing.
67. Abstract 120 titled "Synthesis and Pharmacokinetic Properties of Nucleoside Analogues as Possible Inhibitors of HCV RNA Replication, Bhat *et al*. Abstract 120 reports that a large number of diverse molecules have found several 2'- modified nucleosides that demonstrate potent inhibitory activity in a cell based replicon assay. Out of these compounds some of the compounds have been reported to display promising pharmacokinetic properties *in vivo*. The abstract also reports a series of compounds which were investigated for a structure activity relationship. The Opponents are in the process of obtaining copies of the presentation and crave leave to rely on them at the time of oral hearing.

68. Abstract 121 titled “2’ Modified Nucleoside Analogues as Inhibitors of Hepatitis C RNA Replication” reports that 2’ modified nucleoside analogues were found to inhibit the synthesis of viral RNA in a cell based replicon assay in the absence of cytotoxicity. The abstract reports that the corresponding 5’- triphosphates were found to inhibit the synthesis catalysed by HCV RNA polymerase. It further reports that gel-based incorporation assays indicated that the RNA polymerase is capable of incorporating these analogues on to a growing RNA strand. Some pharmacokinetic complications are also reported. The Opponents are in the process of obtaining copies of the presentation and crave leave to rely on them at the time of oral hearing.
69. The three abstract presentations therefore establish the role of 2’ modified nucleoside analogues in inhibition of viral replication was reported in several scientific journals.
70. It is further submitted 2’-C-methyl-cytidine was already being tested in chimpanzees for anti- HCV activity in early 2003. It was reported as a ribonucleoside analogue designated as NM107. *See* Standring, D. N., *et al.* ‘NM 283 has potent antiviral activity against genotype 1 chronic hepatitis C virus (HCV-1) infection in the chimpanzee.’ *Journal of Hepatology* (2003)38: 3 published on or about March 2003, a copy of which is annexed hereto and marked as “**Exhibit K**”.
71. NM107 was discovered as a potent and selective inhibitor of flavi- and pesti-virus replication in cell culture. NM283 which is a prodrug form of NM107 with improved bioavailability was tested for activity against HCV-1 in chronically infected chimpanzees. The compound was shown to be a competitive inhibitor of purified RNA polymerase in vitro. Its prodrug NM283 had a favourable profile with respect to in vitro toxicity. The publication concludes that NM283 as promising antiviral agent for chronic HCV infection, regulatory filings to initiate human trials of NM283 were underway. (*see id.*, column 2, *placitum* 16-52)
72. The structure of NM107 was made available later:

Compound claimed in Claims 6&7	Structure of NM107
	 <p data-bbox="1016 663 1159 705">NM107</p>

73. It is submitted that fluorine and hydroxyl groups are classical isosteres as a result of the direct adaptation of the Grimm's hydride Displacement Law, i.e. having the same number of valence electrons, thereby making them obvious alternatives for substitution in medicinal chemistry. Fluorine substitution can have a profound effect to improve drug disposition, in terms of distribution, drug clearance, route(s), and extent of drug metabolism. The isosteris replacement of the hydroxyl group is a commonly used strategy in medicinal chemistry. (See B Kevin Park, Neil R Kitteringham, and Paul M O'Neill, 'Metabolism of Fluorine-Containing Drugs 2001 *Annu. Rev. Pharmacol. Toxicol.* 41:443-70, a copy of which is hereto annexed and marked "**Exhibit L**", internal page 445, *placitum* 24-25). It is therefore obvious for a person skilled in the art fluorine as a substituent in place of hydroxyl. (*see id.*, Exhibit L, internal page 3152 Exhibit L).
74. The Patent Applications '282, '425 and '121 discussed above also disclose fluorine substitution at 2'-position rendering the claimed invention obvious.

Methods of fluorinating nucleoside analogues was also known to a person skilled in the art

75. R.P. Singh and J.M. Shreeve, 'Recent advances in nucleophilic fluorination reactions of organic compounds using deoxofluor and DAST', *Synthesis*, (2002) 2561-2578 a copy of which is hereto annexed and marked as "**Exhibit M**" disclose that fluorination of tertiary alcohols can be successfully achieved by using DAST and deoxofluor as reagents by a person skilled in the art. (*see* Singh and Shreeve, Exhibit M, internal page 2562-2564)
76. Furhter, J. Wachtmeister *et al*, "Synthesis of 4-substituted carbocyclic 2,3-dideoxy-3-C-hydroxymethyl nucleoside analogues as potential ant-viral agents", *Tetrahedron*, 55, 10761-10770, a copy of which is hereto annexed and marked "**Exhibit N**" disclose that fluorination of a tertiary alcohol in a cyclopentanol compound with DAST-25% yield With Deoxo-Fluor-43% yield. It discloses that fluorination of a tertiary alcohol in a cyclopentanol compound with inversion of stereochemistry can be carried out with DAST with a yield of 25% as well as with deoxo- fluor with a yield of 43%. This means that a person skilled in the art has two alternatives to proceed with the fluorination of tertiary alcohol, first with deoxo-fluor and then with DAST. (*see id.* internal page 10763, *placitum* 13-17)

Summary

77. In light of the above, it is established that NS5B had been identified as a vital target for the development of anti HCV therapies by early 2003 and that inhibition of this pivotal enzyme would lead to the suppression of HCV replication in infected cells. It was also known that 2' modified nucleoside analogues were widely being investigated and their anti- HCV activity in vitro as well as in vivo was also known to a person skilled in the art.
78. Claims 1 to 10 of the present application are therefore obvious to a person skilled in the art. They do not involve any technical advance over the

existing knowledge. They lack inventive step. The mere fact that routine tests and experiments would have to be conducted in order to verify the expected advantages does not confer inventive step to the alleged invention described in the present application. Therefore, Claims 1 to 10 should be rejected under Section 25 (1)(e) of the Patents Act.

VI.C. Claims 1-7 and 10 fail under Section 3(d), are not an invention within the meaning of this Act and should be rejected under Section 25(1)(f) of the Patents Act.

79. Section 25(1)(f) of the Patents Act provides a ground for opposition if the subject matter of any claim of the Complete Specification is not an invention within the meaning of the Act.
80. 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 efficacy over the known efficacy of the known substance. The explanation to Section 3(d) states that combinations of known substances are to be considered to be the same substance.
81. Section 3(d) of the Patents Act was amended in 2005 to prevent patents on modifications of known substances, such as combinations and salts, esters, ethers and other derivatives of known substances. 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.
82. It is an established position of law that Section 3(d) has to be satisfied independently of Sections 2(1)(j) and 2(1)(ja) [*see Novartis AG v. Union of India and others*, (2013) 6 SCC 1].
83. As held by the Hon'ble Madras High Court, the burden of proof is on the patent applicant to satisfy the requirements of Section 3(d), i.e. that of showing enhanced efficacy [*see Novartis AG and another v. Union of India and others*, (2007) 4 MLJ 1153, para 13]. As held by the Hon'ble Intellectual Property Appellate Board, this data is required to be in the

Complete Specification [*Novartis AG v. Union of India and others*, MIPR 2009 (2) 0345, para 9(xvii)].

84. It is also an established position of law that the term “efficacy” in Section 3(d) means therapeutic efficacy for pharmaceutical products [*see Novartis AG v. Union of India and others*, (2013) 6 SCC 1].
85. In order to discharge the burden of Section 3(d), the Applicant ought to have compared therapeutic efficacy of at least one 2’methyl-up - 2’hydroxy down nucleoside analogues including those disclosed in the ‘282 Application, ‘425 application and the ‘121’ application as well as the compound 13 disclosed in Exhibit E with the 2’methyl-up 2’ fluoro-down compounds claimed in the present application. The Patent Applicant has failed to discharge this burden. This data supplied by the Applicant cannot be considered to be evidence of improvement in therapeutic efficacy over the 2’methyl-up - 2’hydroxy down nucleoside analogues.
86. In view of the above, the subject matter claimed in the present invention amounts to a new use of a known substance and therefore not an invention in accordance with Section 3(d) of the Patents Act.

VI.F. The complete specification does not sufficiently and clearly describe the invention as claimed in Claims 10 and should be rejected under 25(1)(g) of the Patents Act.

87. Section 25(1)(g) of the Patents Act provides a ground for opposition if the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.
88. Section 10(4) of the Patents Act requires the complete specification to fully and particularly describe the inventions and its operation or use.
89. Without prejudice to other grounds raised herein, the complete specification does not sufficiently and clearly describe all the claims of the present application.
90. Claim 10 relates to compositions or medicament comprising compounds claimed in claims 1-7. The specification does not support the claims with

adequate description as to how a person skilled in the art can arrive at the composition. The specification on page 49 broadly defines excipients, carriers and diluents with no specific identification the excipients/ carriers without any specific guidance on the claimed compound.

VI.G. The Patent Applicant has not complied with the requirements of Section 8. Therefore, the present application should be rejected under Section 25(1)(h) of the Patents Act.

91. Section 25(1)(h) of the Patents Act provides a ground for opposition if the Patent Applicant has not furnished information required under Section 8 of the Patents Act, within the time prescribed by law.
92. Without prejudice to other grounds raised herein, the present application should be rejected because the Patent Applicant has not complied with the mandatory requirements of Section 8 of the Patents Act.
93. Section 8 of the Patents Act read with rule 12(1) of the Patents Rules requires, *inter alia*, a patent applicant, who is prosecuting, either alone or jointly with any other person, an application for a patent in any country outside India in respect of the same or substantially the same invention, to file a statement setting out the particulars of such application (Form 3) within six months of the date of filing of such application in India. Along with such statement, the patent applicant is also required to furnish an undertaking that, up to the grant, it would keep the Controller informed in writing, from time to time, of detailed particulars of applications filed in other jurisdictions after Form 3 was filed in India within six months of the date of such filing in other jurisdictions. This is done by filing Form 3 as prescribed by the Patents Rules. The Patent Applicant is also required to keep the Hon'ble Patent Controller informed of the developments of the corresponding or similar patent applications in other jurisdictions.
94. The prosecution history for the present application, available online on the IPAIRS website, shows that the Patent Applicant had not furnished the information required under Section 8 of the Patents Act, within the time

prescribed by law. Thus, *prima facie*, the Patent Applicant has not complied with the requirements of Section 8 of the Patents Act.

95. In the present case, the patentee has filed Form 3 at three instances dated May 23, 2006, May 13, 2014 and June 25, 2014. These three documents are annexed herewith as **Exhibit N, O & P** respectively. The patent Applicant had also filed a petition under rule 137 dated 26 June 2014 for condonation of delay in filing details of corresponding applications. The petition states that the Indian agents would submit the consolidated details of the corresponding applications to the Indian patent office. None of these Form 3s disclose several pending litigations as outlined below. Moreover, it appears that no For-3 post filing of this petition has been filed with the Patent office. Further there has been no information regarding various litigations which have ensued in other jurisdictions.
96. In August 2013, Idenix Pharmaceuticals initiated a request with the Chinese Patent Office's Patent Re-examination Board to invalidate Gilead's Chinese Patent CN100503628C.
97. In February 2012, the USPTO initiated an interference involving an Idenix patent application that was pending (US patent Application 12/131,868) covering certain 2'-methyl, 2'-fluoro nucleoside compounds, and a patent granted to Gilead (US 7429,572) that was related to the same nucleoside compounds. The outcome of the interference was in favour of Gilead. This decision of the USPTO was challenged by Idenix before the District Court of Delaware on 29 January 2014 which was brought for review by the Patent Trial and Appeal Board (PTAB) of the USPTO for correction of the decision and judgment of priority. The case is currently active (Case NO. 1:14cv00109)
98. In December 2013, the USPTO declared a second patent interference between Idenix's U.S. Patent 7,608,600 and Gilead's United States Publication US20080070861A1, both related to the use of 2'-methyl-2'-fluoro nucleoside compounds to treat HCV infections.

99. On 1 December 2013, Idenix announced that it filed a separate patent infringement and interference lawsuit in the United States District Court in Wilmington, Delaware (Idenix U.S. Patent 7,608,600 and Gilead U.S. Patent 8,415,322) which is still active.
100. At the time of filing Form- 3 in 2014, the patent applicant was aware of the ensuing litigations. The petition for condonation of delay under rule 137 merely craves for condonation of delay in disclosing the new applications which are filed in other jurisdictions and is mum on any of the abovementioned litigations which shows the malafide conduct of the Patent Applicant. The patent applicant is called upon to justify why these litigations and interferences were not disclosed to the Indian patent Office.
101. Therefore, the Patent Applicant has failed to comply with the requirements of Section 8 of the Patents Act.
102. The Opponent submits that even if the Patent Applicant were to file any further petition to condone the delay or irregularity caused by the delay in filing the information required under Section 8 of the Patents Act, such petition must be decided in favour of the Patent Applicant only if it provides sufficient and clear and convincing reason for failure to provide the data within the time prescribed by the law. Such delay should not be condoned where the Patent Applicant has failed to exercise due diligence, has been negligent or has delayed the submission of such information in a *mala fide* manner to prevent such information from being available to the Patent Office. Otherwise, the provisions of Section 8 of the Patents Act read with rule 12 of the Patents Rules that mandates timely filing will be rendered otiose. The Patent Applicant should be put to the strict proof of its pleadings in any such application/petition.
103. Therefore, in view of the fact that the Patent Applicant has evidently not complied with the requirements of Section 8 of the Patents Act, the Patent Application should be rejected under Section 25(1)(h) of the Patents Act.

VII. HEARING REQUESTED

104. The Opponents hereby request a hearing under Section 25(1) of the Patents Act and rule 55 of the Patents Rules.

VIII. CONCLUSION

105. Given all of the foregoing, the Opponents humbly pray:

- (i) For an order rejecting patent application 6087/DELNP/2005 for reasons as stated above:
- (ii) For leave to amend the opposition in case the patent applicant amends the claims.
- (iii) For leave to rely on additional documents at the time of oral hearing.
- (iv) For such further and other orders as may become necessary in the facts and circumstances of the case or in the interest of justice, equity and good conscience.

Drafted by: Geetanjali Sharma, Advocate

Settled by: Anand Grover, Senior Advocate

Place: New Delhi

Date: 30 January, 2015

On Behalf of _____

(Eldred Tellis, Authorised signatory, Sankalp Rehabilitation Trust)