FIDUS LAW CHAMBERS

Litigation | Advisory

To,
The Controller of Patents & Designs,
The Patent Office
Intellectual Property Office
Building, Plot No. 32
Sector 14, Dwarka
New Delhi-110075

Date: May 15th, 2017

RE: POST- GRANT OPPOSITION UNDER SECTION 25 (2) ON PATENT No. 273003 GRANTED FOR APPLICATION NO. 6087/DELNP/2005 DATED DECEMBER 27, 2005 IN THE NAME OF GILEAD PHARMASSET, LLC. BY THE DELHI NETWORK OF POSITIVE PEOPLE (DNP+) AND THE INITIATIVE FOR MEDICINES, ACCESS & KNOWLEDGE, INC (I-MAK)

Dear Sir,

On behalf of our clients Initiative For Medicines, Access & Knowledge, Inc (I-MAKand Delhi Network of Positive People (DNP+), we hereby give notice of opposition to the grant of Indian Patent No. **273003** granted on application No. 6087/DELNP/2005. In this regard please find enclosed:

1. Formal Notice of Opposition on Form 7 under section 25(2) of the Indian Patents Act.
2. A statement of opposition with all its Exhibits (Exhibit I – X)
3. Power of Authority in The name of Constituted attorney Mr. Vishal Vig from the Opponent I-MAK.
4. Board Resolution passed by DNP+ authorizing Mr. Paul Lhungdim appointing him as signatory.

A notarially certified copy of the Power of Authority in the name of the Applicant's Patent Agent will follow separately.

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legal@fiduslawchambers.com

Fee of Rs. 12000/- in this regard is being paid through online fund transfer.

The Learned Controller is requested to take the above mentioned documents on record and in case of any procedural irregularity write to us at legal@fiduslawchambers.com. In any event, no adverse order in respect of the present request or in relation to the Opponents itself, may be passed without giving the applicant an opportunity to be heard.

Yours faithfully

Guruswamy Nataraj
Agent for the Applicant

Encl:

1. Formal Notice of Opposition on Form 7 under section 25(2) of the Indian Patents Act.
2. A statement of opposition with all its Exhibits (Exhibit I – X)
3. Power of Authority in the name of Constituted attorney Mr. Vishal Vig from the Opponent I-MAK.
4. Board Resolution passed by DNP+ authorizing Mr. Paul Lhungdim appointing him as signatory.
5. Fee of Rs. 12000/- (submitted online)

Form 7

THE PATENTS ACT, 1970

(39 OF 1970)

AND

THE PATENT RULES, 2003

NOTICE OF OPPOSITION

[See Section 25(2) and Rule 55A]

We, the Initiative for Medicines, Access & Knowledge (I-MAK), Inc, 16192 Coastal Highway, Lewes, Delaware, 19958-9776, U.S.A. and Delhi Network of Positive People (DNP+), Flat no. A1-5, Property 141 Gali No. 3, Harijan Colony, Neb Sarai, New Delhi, 110068 the hereby give notice of opposition to patent No. 273003 granted on Application No: 6087/DELNP/2005 dated 27th December published on 13th May 2016 in the name of Gilead Pharmasset, LLC. 333 Lakeside Drive, Poster City, California, 94404, U.S.A. on the following grounds:

a. <u>Section 25 (2) (b): Anticipation</u>

That the invention so far as claimed in any claim of the complete specification has been published before the priority date of the claim.

i) in any specification filed in pursuance of an application for a patent made in India on or after the or;

ii) in India or elsewhere, in any other document.

<u>c. Section 25(2)(e): Obviousness/Lack of inventive step</u>

That the invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step having regard to the matter published as

mentioned in clause (b) or having regard to what was used in India before the priority date of the applicant's claim.

d. Section 25(2)(f) –Not an invention/Not Patentable

That the subject of any claim of the complete specification is not an invention within the meaning of this Act, or is not patentable under this Act, in particular under sections 3(d).

e. Section 25(2)(g): Insufficient disclosure

That the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed;

Our Address for service in India:

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Dated May 15, 2017.

Fidus Law Chambers
Attorney for the Opponent

To,
The Controller of Patents,
The Patent Office,
Delhi.

Copy to:
Attorney of Gilead Pharmasset, LLC.
KNS Partners.
109, Sector 44, Gurgaon 122 003
National Capital Region

Online payment of Rs. 12000/- (paid online)

INTHEMATTEROFTHEPATENTSACT,1970ASAMENDED BYTHEPATENTS(AMENDMENT)ACTS1999,2002AND2005 AND INTHEMATTEROFTHEPATENTSRULES,2003ASAMENDEDBYTHE THEPATENTS(AMENDMENT)RULES,2006AND2016

BEFORE THE CONTROLLER OF PATENTS, THE PATENT OFFICE, NEW DELHI
THE PATENTS ACT, 1970 AND THE PATENTS RULES, 2003

IN THE MATTER OF A POST- GRANT OPPOSITION UNDER SECTION 25 (2)

And

IN THE MATTER OF PATENT No. 273003 GRANTED FOR APPLICATION NO. 6087/DELNP/2005 DATED DECEMBER 27, 2005 IN THE NAME OF GILEAD PHARMASSET, LLC. 333 LAKESIDE DRIVE, POSTER CITY, CALIFORNIA, 94404, U.S.A.

…..PATENTEE/RESPONDENT

And

IN THE MATTER OF NOTICE OF OPPOSITION FILED BY THE DELHI NETWORK OF POSITIVE PEOPLE (DNP+) AND THE INITIATIVE FOR MEDICINES, ACCESS & KNOWLEDGE, INC (I-MAK)

.....OPPONENT/PETITIONER

WRITTEN STATEMENT OF OPPOSITION:

1. We, the Initiative For Medicines, Access & Knowledge, Inc (I-MAK) of 16192, Coastal Highway, Lewes, Delaware, 19958-9776 and Delhi Network of Positive People (DNP+) of Flat No. A 1-5, Property 141, Gali No. 3, Harijan Colony, Neb Sarai, New Delhi – 110068 hereby file a post grant opposition on the Patent No. 273003 granted to GILEAD PHARMASSET, LLC. 333

LAKESIDE DRIVE, POSTER CITY, CALIFORNIA, 94404, U.S.A. on their Patent No. 273003.

The grant of the application was published on 13th of May 2016, in the official Journal of the Indian Patent Office. Accordingly, the post grant opposition is filed within the stipulated time period of one year from the date of publication of the grant according to Section 25(2) of the Indian Patents Act, 1970.

2. **Locus Standi:**

The Opponents are the Initiative for Medicines, Access & Knowledge (I-MAK), Inc, a not-for-profit public service organization comprising lawyers and scientists working to protect the public domain against undeserved patents to ensure they do not act as a barrier to research and restrict the public's access to affordable medicines, having its registered address at 16192 Coastal Highway, Lewes, Delaware, 19958-9776, U.S.A. and the Delhi Network of Positive People (DNP+), a community based non-profit organization representing the needs of people living with HIV/AIDS ("PLHAs") and hepatitis C (HCV), registered under Trust Registration No. 8525, Additional Book No. 1423/1-23 IV Sub Registrar, New Delhi, with its registered address at Flat no. A1-5, Property 141 Gali No. 3, Harijan Colony, Neb Sarai, New Delhi, 110068.

3. Background:

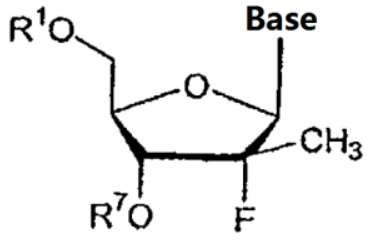
3.1 Patent No. 273003for an invention titled as "(2'R)-2'-DEOXY-2'FLUORO-2'-C-METHYL NUCLEOSIDE" was filed by Gilead Pharmasset, LLC (formerly Pharmasset, Inc.) on December 27, 2005, as a National Phase application (under No. 6087/DELNP/2005) of the PCT application PCT/US2004/012472.PCT/US2004/012472 (published as WO 2005/003147)

was filed by Pharmasset Ltd on 21 April 2004 and published on 13 January 2005 claiming priority from US 60/474,368 dated 30 May 2003. The specification of the invention is enclosed along with the Opposition as **Exhibit I**.

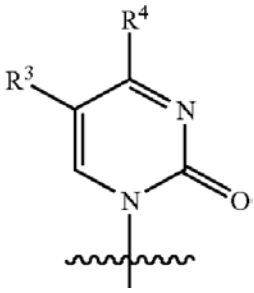
3.2 The application was initially filed with 131 Claims. On the same date, the Patentee submitted a more specific set of Claims reducing the number of Claims to 20 Claims. However, the First Examination Report (FER) was issued on the basis of 131 Claims. While complying with the objections of the FER under Section 21, the Patentee restricted the number of Claims to 20 Claims. Further, under Section 14 hearing on July 21, 2015, the Claims were restricted to 10 Claims. On August 07, 2015, in their reply statement to pre-grant opposition under Rule 55(4), the Patentee again amended Claims to total 16 Claims. Ultimately, Patentee restricted the claims to a total of 8 claims nearly 8 weeks after the application was reserved for orders. Based on these 8 claims the Patent was granted on 9th May 2016.

3.3 The Granted claims currently on record for the present invention **(Exhibit II**) are:

1. A **(**2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D or β-L) or it's pharmaceutically acceptable salt of the structure:



wherein 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

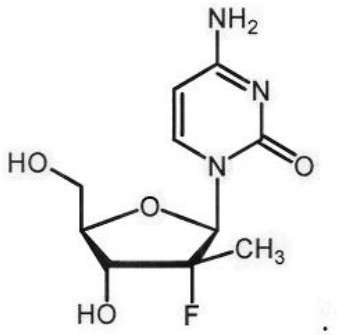
R4 is NH2 or OH.

2.The **(**2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D or β-L) nucleoside as claimed in claim 1 or its a pharmaceutically acceptable salt thereof, wherein R7 is H and R1 is a monophosphate, a diphosphate, or a triphosphate.

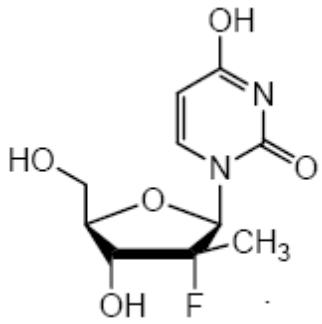
3.The **(**2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D or β-L) nucleoside as claimed in claim 1 or its a pharmaceutically acceptable salt thereof wherein R7 is H and R1 is a triphosphate.

4. The **(**2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D or β-L) nucleoside as claimed in claim 1 or its a pharmaceutically acceptable salt thereof wherein R1 and R7 are H.

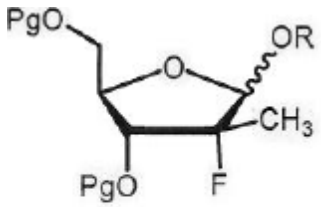
5. A **(**2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D) as claimed in claim 1 or a nucleoside or its pharmaceutically acceptable salt thereof of the formula:



6. A **(**2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D) as claimed in claim 1 or a nucleoside or its pharmaceutically acceptable salt thereof of the formula:



7. A method of synthesizing the **(**2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D or β- L) nucleoside as claimed in claim 1, which comprises glycosylating the pyrimidine with a compound having the following structure:

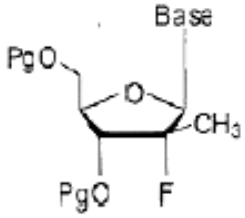


1-4

wherein R is C1-C4 lower alkyl, 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, CH2Ophenyl, CH2O-biphenyl, CH2O-naphthyl, SO2-C1-C10 alkyl, SO2-

phenyl, SO2-biphenyl, SO2-naphtyl, *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl, or both Pg's may come together to form a 1,3-(1,1,3,3-tetraisopropyldisiloxanylidene).

8. A method of synthesizing the **(**2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D or β-L) 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-C10 alkyl, C(O)phenyl, C(O)biphenyl, C(O)naphthyl, CH3, 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-naphtyl, *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl, or both Pg's may come together to form a l,3-(1,1,3,3-tetraisopropyldisiloxanylidene).

4. The dates and events relevant to the case are summarized hereunder:

Date	**Event**
December 27, 2005	Patent application was filed by Patenteewith 131 Claims.
December 27, 2005	Patenteereduced the number of claims to 20.
April 6, 2009	First Examination Report (FER) issued on the basis of 131 Claims.
March 18, 2010	While complying with the objections of the FER, Patentee restricts claims to the 20.
24th July, 2014	Hearing fixed (and thereafter held) by the Controller of Patents under section 14 of the Patent Act, 1970 for

	Patentee to place the application in order for grant. Patentee reduced the number of claims to 10 during the hearing.
December 22, 2014	Opponents objected to a closed-door hearing since its pre-grant opposition was pending and asked that a combined hearing on the merits of the patent application as also the case of the Opponent be scheduled. Opponents' request was refused. Opponents filed a Writ petition **(WP No. 260 of 2015)** before the High Court of Delhi objecting to the fixing of a hearing by the Patent Office which the Opponents were expressly prohibited from attending.
13th January 2015	Controller of Patents passed an order further to the hearing of 24th July 2014 thereby refusing the patent application of Patentee. Writ was withdrawn as infructuous.
January 22, 2015	Patentee filed a Writ Petition (**WP No.687/2015**) against the order of Controller of Patents stating that the latter had erred in considering the contentions in the pre-grant oppositions of *inter alia,* the oppositions and using them as a basis for the order dated 13th January 2015 without serving due notice of the oppositions on the Patentee. They pleaded that the matter be remanded to the Patent Office for fresh consideration.
January 30, 2015	Writ Petition was disposed off by the Hon'ble Delhi High Court directing that the matter be remanded to Controller of Patents for hearing afresh.
August 07, 2015	In reply to the pre-grant opposition, Patenteeagain amended the Claims to increase them to a total of 16

	Claims from the erstwhile 10.
26th February 2016	The Opposition hearings were concluded on the basis of the said 16 claims.
11th March 2016	Note of arguments were filed by all parties.
29th April 2016	Patentee apparently filed an amended set of 8 claims nearly 8 weeks after the matter had been reserved for orders, without notice to the Opponents. No copy of the said amended claims were served on the Opponents.
9th May 2016	Order was passed on the basis of the 8 claims, granting the patent to the Patentee.
12th May 2016	Writ petition [**WP(C) No. 4399 of 2016**] filed in the Delhi High Court by the Petitioners, seeking, *inter alia,* a setting aside of the Patent. The Writ Petition is currently pending.

5. Preliminary submissions

5.1 The present opposition is being filed without prejudice to the writ petition [WP(C) No. 4399 of 2016] that is currently pending adjudication before the High Court of Delhi.

5.2 The Petitioners verily believe that the order of grant of the patent is unsustainable on a number of grounds, which they are actively agitating in the aforesaid writ petition and in respect of which the Petitioners believe that they have a significant likelihood of success.

5.3 The present opposition is being filed only to preserve the Petitioners' legal right within the statutorily prescribed time frame for the filing of a post grant opposition.

5.4 The Petitioner prays that all proceedings in respect of the present post grant opposition be stayed until the outcome of the aforesaid writ petition.

6. Brief history of the Invention:

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

Given the public health crisis around HCV, it is imperative that people living with HCV are able to access the latest and most effective treatments without unmerited patents standing in the way. Undeserved patents of the nature applied for in Patent No. 273003(hereinafter, the impugned patent) affords a company, such as the Patentee, artificial exclusive rights, which then allows it to price a medicine beyond the reach of not only Indian patients, but also many in need in other developing and even developed countries. The Patentee also strategically uses such unmerited patents in its licensing programme in India in order to manage the generic competition and further delay legitimate open competition. By managing the competition the Patentee is able to control the market in India but also in other countries where competitors may otherwise have been able to sell the medicine at more affordable prices.

7. Grounds of Opposition:

- Section 25 (2) (b) - Prior Publication;
- Section 25 (2) (e) – Invention is obvious and lacks inventive step;
- Section 25 (2) (f) – Not an invention;
- Section 25 (2) (g) – Not sufficiently disclosed in the Invention

7.1 Section 25 (2) (b): Prior publication

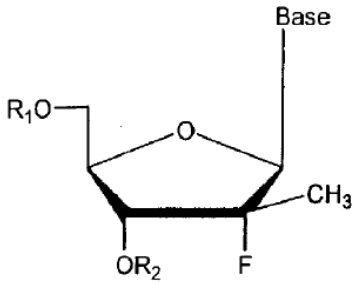
7.1.1 It is respectfully submitted that the subject matter of Claims 1-8 of the impugned patent do not amount to a new invention. According to Section 2(1)(l) of the Patents Act as currently amended a "new invention" means any invention or technology which has not been anticipated by publication in any document or used in the country or elsewhere in the world before the date of filing of patent application with complete specification, i.e. ***the subject matter has not fallen in public domain or that it does not form part of the state of the art.***" (Emphasis Added)

The priority right of 30 May 2003 is not validly claimed

7.1.2 Before setting out the arguments under section 25(2), the Opponentsprovide below whyclaims 1-4 and 6-8 of Patent No. 273003 are not entitled to the priority date of 30 May 2003 from US 60/474,368 (**Exhibit III**).

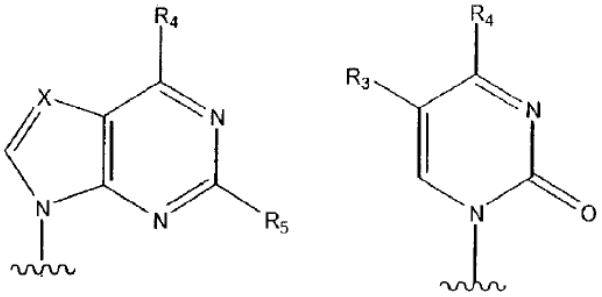
Exhibit III discloses the following subject matter on pages 7-8:

In one embodiment, the anti-virally effective nucleoside is a β-D or β-L nucleoside of the general formula **(I)**:



(I)

wherein base can be



or its pharmaceutically acceptable salt or prodrug thereof, wherein:

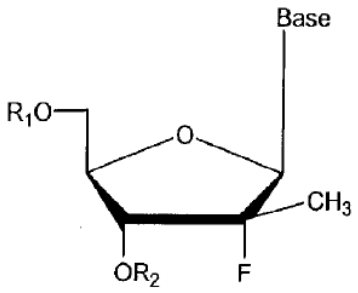
(a) X = N or CH.

(b) R1 and R2 are independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); H-phosphonate (including stabilized H-phosphonates) acyl [including phenyl (optionally substituted), 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 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 is independently H or phosphate. (From WO 01/90121)

(c) R3, R4 and R5 are independently H, halogen (F, Cl, Br, I), OH, OR', SH, SR', NH_2, NHR', NR'$_2$, lower alkyl of C_1-C_6, halogenated (F, Cl, Br, I) lower alkyl of C_1-C_6 such as CF_3 and CH_2CH_2F, lower alkenyl of C_2-C_6 such as $CH=CH_2$, halogenated (F, Cl, Br, I) lower alkenyl of C_2-C_6 such as CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of C_2-C_6 such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C_2-C_6, lower alkoxy of C_1-C_6 such as CH_2OH and CH_2CH_2OH, CO_2H, CO_2R', $CONH_2$, CONHR', CONR'$_2$, $CH=CHCO_2H$, $CH=CHCO_2R'$;

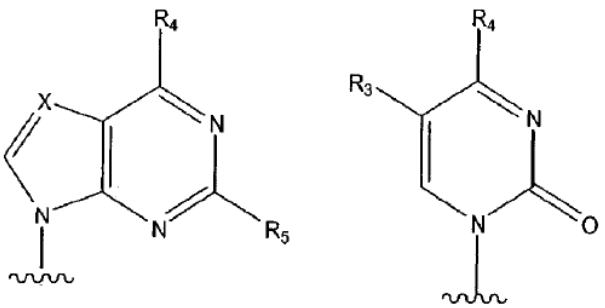
In addition, Exhibit III discloses the following subject matter on pages 15-16:

In one embodiment, the anti-virally or anti-proliferatively effective nucleoside is a β-D or β-L nucleoside of the general formula (I):



(I)

wherein base can be



or its pharmaceutically acceptable salt or prodrug thereof, wherein:

a. X = N or CH.

b. R1 and R2 are independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); H-phosphonate (including stabilized H-phosphonates) acyl [including phenyl (optionally substituted), 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 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 is independently H or phosphate. (From WO 01/90121)

c. R3, R4 and R5 are independently H, halogen (F, Cl, Br, I), OH, OR', SH, SR', NH_2, NHR', NR'$_2$, lower alkyl of C_1-C_6, halogenated (F, Cl, Br, I) lower alkyl of C_1-C_6 such as CF_3 and CH_2CH_2F, lower alkenyl of C_2-C_6 such as $CH=CH_2$, halogenated (F, Cl, Br, I) lower alkenyl of C_2-C_6 such as CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of C_2-C_6 such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C_2-C_6, lower alkoxy of C_1-C_6 such as CH_2OH and CH_2CH_2OH, CO_2H, CO_2R', $CONH_2$, CONHR', CONR'$_2$, $CH=CHCO_2H$, $CH=CHCO_2R'$;

Furthermore, Exhibit III discloses on page 21 that:

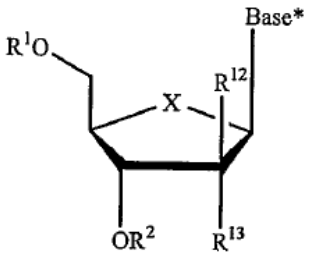
The term "lower alkyl," as used herein, and unless otherwise specified, refers to a C_1 to C_4 saturated straight, branched, or if appropriate, a cyclic (for example, cyclopropyl) alkyl group, including both substituted and unsubstituted forms.

In the above disclosures, as well as other parts of Exhibit III, the subject matter of claims 1-4 and 6-8 of Patent No. 273003 is not specifically disclosed. For example only (but not limited to), Exhibit III does not disclose R1 and R2 (corresponding to R1 and R7 in Patent No.273003) can particularly be C_5-C_{10} alkyl, C_1-C_{10}alkylsulfonyl, or arylC_1-C_{10}alkylsulfonyl.

Accordingly, the subject matter of claims 1-4 and 6-8 of Patent No. 273003 do not derive directly from Exhibit III and are not entitled to the priority date. As a result, the effective date for claims 1-4 and 6-8 of Patent No. 273003 is the filing date of 21 April 2004.Documents published before 21 April 2004 should, therefore, be accepted as prior art for claims 1-4 and 6-8.

7.1.3 International application WO2004002999(**Exhibit IV**) was published on 8 January 2004, i.e. before the effective date of the opposed patent, i.e. 21 April 2004 as discussed above.

Exhibit IV relates to nucleoside compounds for the treatment of Flaviviridae infection, in particular hepatitis C infection. It discloses a compound of the following general formula (IX):



(IX)

or a stereoisomeric, tautomeric or polymorphic form thereof, or a pharmaceutically acceptable salt thereof, wherein:

R^1, R^2 and R^3 are independently H; phosphate; straight chained, branched or cyclic alkyl; acyl; CO-alkyl; CO-aryl; CO-alkoxyalkyl; CO-aryloxyalkyl; CO-substituted aryl; sulfonate ester; benzyl, wherein the phenyl group is optionally substituted with one or more substituents; alkylsulfonyl; arylsulfonyl; aralkylsulfonyl; a lipid; an amino acid; a carbohydrate; a peptide; cholesterol; or a pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1, R^2 and/or R^3 is independently H or phosphate;

X is O, S, SO_2 or CH_2;

Base* is a purine or pyrimidine base;

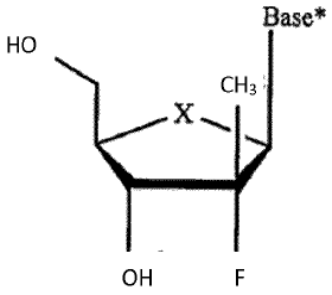
R^{12} is $C(Y^3)_3$;

Y^3 is independently H, F, Cl, Br or I; and

R^{13} is fluoro.

In one subembodiment X is O, and Y^3 is H. In another subembodiment, when X is O and Y^3 is H, R^1, R^2 and R^3 are also H.

As such, the subembodiment of compound (IX) of Exhibit IV (above) discloses the following compounds with Base* = (purine or pyrimidine base) as the only variable:



(IX)

The list of “purine” or “pyrimidine” according to Exhibit IV is defined on page 104, line 15-27 and comprises cytosine and uridine.

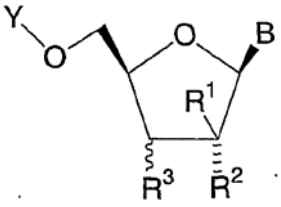
Now, a selection from a single list of specifically disclosed elements does not confer novelty.

Accordingly, the said document discloses both the compounds of claim 5 (above subembodiment of the compound of formula (IX) with Base* = cytosine) and of claim 6 (above sub-embodiment of the compound of formula (IX) with Base* = uridine). Also, these compounds are included in the subject-matter of claims 1 and 4.

Clearly the subject matter of Patent No. 273003 is known in the art as it was published in a document prior to the filing of the invention. Hence, it should be rejected.

7.1.4WO 2002/057425 (**Exhibit V**) published on 25 July 2002 titled "*Nucleoside derivatives as inhibitors of RNA-dependent RNA viral polymerase*" discloses the compounds useful for the treatment of RNA dependent viral infection, in particular as inhibitors of HCV NS5B polymerase, HCV replication and HCV infection. The basic structure of the compounds in Exhibit V is drawn to a sugar attached to a nitrogenous base. The compounds of Patent No. 273003 can be arrived by substitution of various substituents ofthe compounds disclosed in Exhibit V.

The various substituents of Exhibit V include Markush structures at Formula I, II and III. Formula III provides various options for substitutions. As per the various embodiments disclosed, it can be clearly seen that Exhibit V discloses a nitrogenous base, which may be selected from a group of compounds which appear to be derivatives of purine or pyrimidine. In particular, Page 17-19 of Exhibit V discloses Formula III.

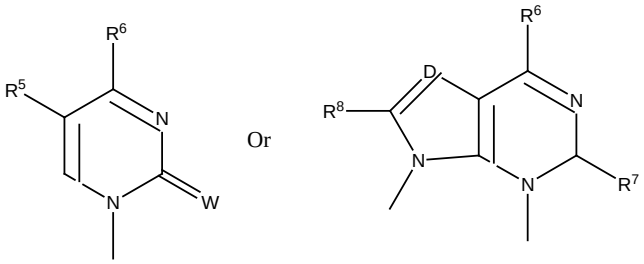


Formula III

wherein Y is H

R^1 is hydrogen, CF^3, or **C_{1-4} alkyl** and one of the R^2 and R^3 is **OH** or C_{1-4} alkoxy and the other of R^2 and R^3 is selected from the group consisting of hydrogen, **hydroxy, fluoro,** C_{1-3} alkyl, trifluoromethyl, C_{1-8} alkylcarbonyloxy, C_{1-3} alkoxy.

Wherein B is



W is O or S

R^5 is H and R^6 is OH.

Further, claims 5 & 6 of WO'425 provides a match as

R^1 is **C_{1-4} alkyl;**

R^3 is **OH;**

$R^2$is **fluoro;**

R^5 is **H**;

R^6 is **OH.**

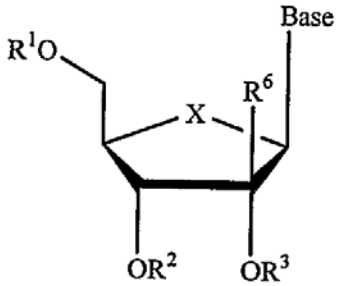
Again, Claims 7 and 8 in Exhibit V, define the base portion of the molecule to be a narrow set of uridine bases where R^5 is H; R^6 is OH and W=O for (2'R)-2'-deoxy-2'-fluoro-2'-methyluridine.From these substitutions, the Opponents submit that the Claims 1-8 of Patent No. 273003 are anticipated by an individual reading ofExhibit V.

Further, the synthesis route (glycosylation) prescribed on page 56 (scheme 1) in Exhibit V is same as discussed in the impugned patent on page 75-76. The method of preparation of compounds by glycosylating an appropriately

modified sugar involving protecting and deprotecting the functional group involving known reagents is disclosed inExhibit V. Therefore, in light of the disclosure made in the Exhibit V application which match all elements of the claimed invention of the impugned patent shows that the Claims 1-8 are not novel and are therefore anticipated.

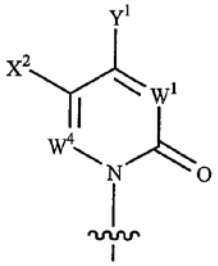
7.2 Section 25 (2) (e) – Invention is obvious and lacks inventive step:

7.2.1 The said application is also obvious and lacks an inventive step. This is apparent from an analysis of Exhibit IV which discloses a compound of the following general formula (III) (see page 19):



(III)

wherein:base may be the following compound (F) (see page 20):



(F)

R1, R2, R3 are as defined above,

which means that:

R1 and R2 may be phosphate including mono-, di- or triphosphate and a stabilized phosphate) (see page 17 lines 24-25);

R3 may be H (see page 17 line 24);

W1 and W1 may be CH (see page 25 line 10);

X2 may be H (see page 26 line 2);
Y1 may be OH or NH2 (see page 26 line 23); and
R6 may be CH3 (see page 26 line 28);

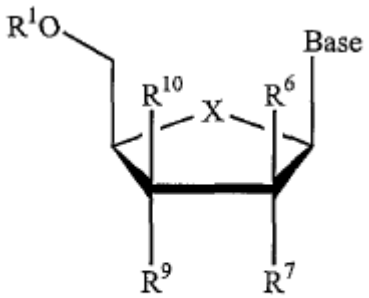
Compounds of claims 2 and 3 of the opposed patent are among the compounds disclosed these combinations.

No experimental data showing a technical effect of compounds of claims 2 and 3 are presented in the opposed patent. Furthermore, no credible technical advance can be imparted to these compounds.

The subject-matter of the claims consists merely in selecting particular chemical compounds from a broader field, i.e. the claimed compounds are an obvious and consequently non-inventive selection among a number of known possibilities. Merely selecting a suitable combination from a list of disclosed chemical groups do not make the invention novel.

7.2.2 The Opponents also rely on**WO0192282**(**Exhibit VI**), which was published on 6 December 2001and **McAtee, *et al.*, 1998 (Exhibit VII),**to show that the impugned patent is obvious.

Exhibit VI relates to β-D- or β-L- nucleosides for the treatment of flavivirus and pestivirus (see top of page 4) and discloses a compound of formula XVII or a pharmaceutically acceptable prodrug thereof (see page 37):



(XVII)

with the following sub-embodiments (see page 41):

(1) Base is cytosine; (2) R^1 is hydrogen; (3) R^6 is methyl; (4) R^7 and R^9 are hydroxyl; (5) R^{10} is hydrogen; and (6) X is O;

(1) Base is uracil; (2) R^1 is hydrogen; (3) R^6 is methyl; (4) R^7 and R^9 are hydroxyl; (5) R^{10} is hydrogen; and (6) X is O;

The two embodiments disclosed in Exhibit VIare depicted below:

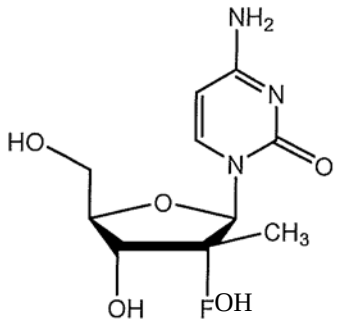
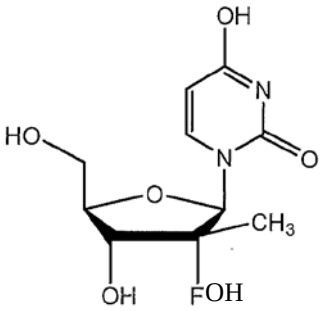
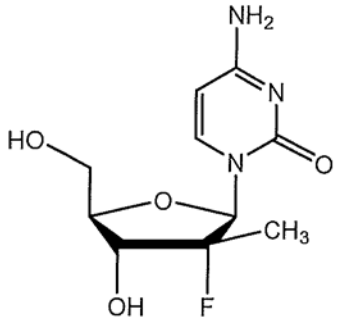
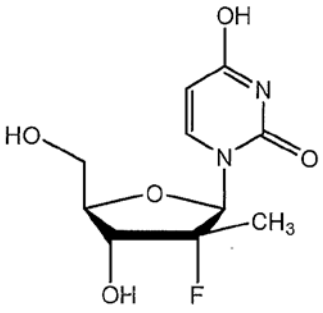
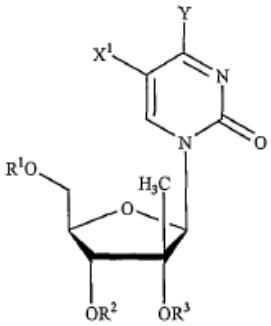
 Subembodiment of the compound of formula (XVII) of Exhibit VIwhere Base is cytosine	 Subembodiment of the compound of formula (XVII) of Exhibit VI where Base is uracil
 Compound of claim 5 of the patent	 Compound of claim 6 of the patent

Exhibit VIalso relates to a compound of formula (V) (see page 125):

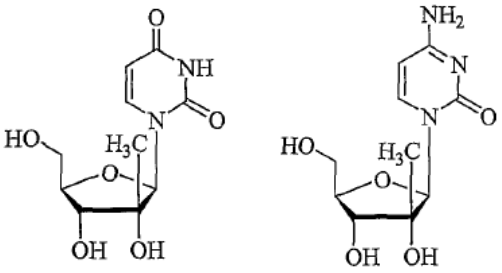


(V)

with the following substituents (see table on pages 125 to 128 of Exhibit V:

R^1	R^2	R^3	X^1	Y
H	H	H	H	OH
H	H	H	H	NH_2
Monophosphate	H	H	H	OH
Monophosphate	H	H	H	NH_2
Diphosphate	H	H	H	NH_2
Diphosphate	H	H	H	OH
Triphosphate	H	H	H	NH_2
Triphosphate	H	H	H	OH

Further, the antiviral activities of β-D-2'-CH3-riboC and β-D-2'-CH3-riboU (see the following formulae) have been evaluated against viruses within the Flavivirus and Pestivirus genuses (virus-cell system BVDV-BT and YFV-BHK) (see table 12 page 191 of Exhibit VI).



β-D-2'-CH_3-riboU β-D-2'-CH_3-riboC

β-D-2'-CH3-riboC shows an EC50 of 3.7 µM and a CC50 >100 µM in BVDV cells and an EC50 of 70 µM and a CC50 >100 µM in YFV cells.

β-D-2'-CH3-riboU show an EC50 of 20 µM and a CC50 >100 µM in BVDV cells and an EC50 of 33 µM and a CC50 >100 µM in YFV cells.

Exhibit VI aims at solving the same general technical problem as the impugned patent, namely it pertains to nucleoside compounds for the treatment of Flaviviridae infections (see the top of page 4 of Exhibit VI and page 8 lines 11 to 16 of the opposed patent). In addition, as seen above, Exhibit VI provides nucleoside compounds with a strong structural resemblance with the compounds claimed by the impugned patent.

7.2.3 The only difference between the compounds of formula (V) of Exhibit VI and the compounds claimed in Patent No. 273003 is the presence of a fluorine atom in the 2'position of the patent under opposition instead of a hydroxyl group in in the compounds of formula (V) of Exhibit VI.

McAtee, *et al.*, 1998,(**Exhibit VII**) discloses several antiviral 2'-fluoronucleosides. Of particular relevance to the present proceedings is the disclosure in the last paragraph in the left column to the second paragraph in the right column on page 2161 of Exhibit VII, which is reproduced below:

"***Fluorine*** *may also serve as an isopolar and* ***isostericmimic of a hydroxyl group*** *since the C-F bond length(1.35 Å) is so similar to the C-O bond length (1.43 Å)and because fluorine is a hydrogen-bond acceptor. Theability of fluorine to mimic a hydroxyl group makes thisatom* ***uniquely suited to nucleoside analogues as areplacement of OH in the sugar portion of a nucleoside****.In addition to our long-standing interest in the synthesisof novel nucleoside analogues, we were interested inincorporating an α-fluorine substituent at the 2' positionof the sugar ring for several reasons. First, the electronegativityof fluorine should stabilize the anomericbond and suppress a significant pathway of in vivodecomposition, thereby improving the acid stability ofthe nucleoside (Scheme 1).*

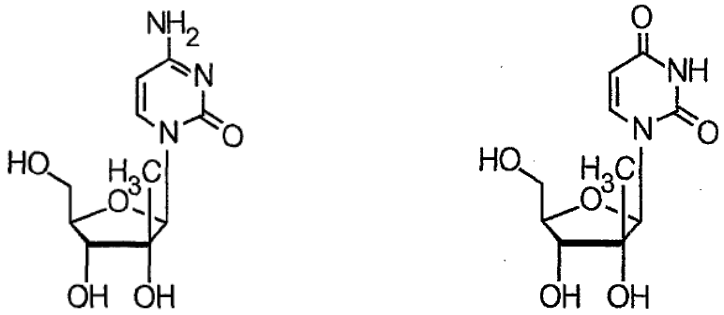
Second, hydroxyl groups often serve as "handles" forthe first step in oxidative degradation of biomolecules invivo. By replacing OH with F, it is possible to create aribo-like sugar that has a substituent at the 2' positionsterically and electronically similar to a hydroxyl group,but which cannot undergo oxidative catabolism. Thus,the in vivo half-life of the compound may be improved."

Exhibit VII explicitly teaches that F and OH are isosteres, and the 2'-α-OH in antiviral nucleosides can be replaced with F to obtain several antiviral 2'-fluoronucleosides, such that the stability and *in vivo* half-life of the nucleosides can be improved. Therefore, on the basis of Exhibit VII, a person skilled in the art would easily predict the compounds of Claim 1 of the impugned patent and their technical effect. Hence, Claim 1 of the patent does not involve an inventive step.

Exhibits VIand VII therefore clearly show that the impugned patent would have been obvious and provides and no technical advance.

7.2.4 The Petitioners also rely on patent application WO0190121A2 (**Exhibit VIII**) and Pankiewicz (2000)(**Exhibit IX)**.

Exhibit VIIIdiscloses a series of anti-HCV nucleoside compounds (see the last paragraph on page 20), and particularly discloses two compounds β-D-2'-CH_3-cytidine and β-D-2'-CH_3-uridine in Figure 1:



which differ from the β-D-(2'R)-2'-deoxy-2'-fluoro-2'-C-methyl cytidine/uridine of Claim 1 of the impugned patent only in that its 2'-C position has an α-OH group while its counterpart in Claim 1 of the impugned patent is

F. Accordingly,Claim 1 of the impugned patent can be easily deduced fromthe compounds disclosed in **Exhibit VIII**and the chemically insignificant difference in the chemical group is merely a poorly veiled attempt to create an illusion ofinventive merit.

7.2.5 Indeed, the article by Pankiewicz (2000) on Carbohydrate Research 327:87-105 **(ExhibitIX),** published on 10 July 2000providesthe possible positions for the introduction of the fluorine atom in nucleoside compounds and the synthetic ways to obtain fluorinated nucleosides have been discussed.

Exhibit IX notably reports that “Since some early-synthesized 2’-deoxy-2’-fluoro nucleosides showed promising therapeutic potential (mainly antiviral and anticancer), the synthesis of new generations of 2%-fluorinated nucleosides flourished in hope of new drug discovery.” (see the paragraph bridging pages 87 and 88).

Moreover, the author has identified 362 structures containing a fluorine atom at the sugar moiety of nucleosides, among which 238 compounds are fluorinates at the C-2’ position of the nucleoside (see page 87 right hand column, lines 1 to 4 of Exhibit VIII). The report also suggests 77% of fluorinated nucleosides synthesized at the date of the article contained fluorine atom(s) at C-2’ of the sugar.

From this derivation any person skilled in the art wishing to solve the objective technical problem would have obviously deduced replacing an α-OH group by a fluorine atom, thereby arriving at the compounds of claims 1 to 6 of the opposed patent.

7.3 Section 25 (1)(f): Not patentable subject matter under Section 3(d)

7.3.1 Claim 1 does not disclose a patentable invention as it is merely a new form of a known substance with no significant difference in properties with regard to efficacy, which cannot be patentable under Section 3(d) of the Act. For the purpose of Section 3(d), substances such as esters, metabolites and ***other derivatives*** of a known substance shall be considered the same substance unless they differ significantly with regard to efficacy.

7.3.2 The decision of the Supreme Court of India in *Novartis AG v Union of India & Others,* Civil Appeal Nos. 2706-2716, 2728 and 2717-2727 of 2013 *(Novartis)* at page 90, paragraph 179 confirmed that the test of efficacy can only be therapeutic efficacy. Pages 90-91, paragraph 180 of *Novartis* states that not all advantageous or beneficial properties are relevant but only such properties that directly relate to efficacy, being therapeutic efficacy in the case ofmedicine.

7.3.3 In view of the prior art discussed, under the definition of Section 3(d), Claim 1 of the impugned patent disclosed a new form of a known substance. The prior art discussed, in particular Exhibits IV, V, VI and VIII, have shown various nucleoside compounds including cytidine and uridine derivatives and their prodrugs, pharmaceutical salts and compositions. Under Section 3(d), Claim 1 at best discloses a derivative of these known forms and, therefore is a new form of a known substance unless it differs significantly with regard to efficacy. In the case of medicines, efficacy is defined as therapeuticefficacy which threshold is clearly not satisfied in the present instance.

7.3.4 The Patentee**had presented no data in their specification to show any activity of the uridine analog claimed in Claim 6.** The only data submitted by the Patentee with their application to show therapeutic activity was for the

cytidine analog (covered in Claim 5) *and not the uridine analog* (Table 1-9 on pages 92-95 of specification).

7.3.5 In view of the above, it is submitted that merely testing the cytidine analog will not accurately represent the therapeutic activity of the either the cytidine analog individually or of the uridine analog.

7.3.6 Further, that the uridine analog claimed in the impugned patent is unable to meet the requirements of Section 3(d) by showing therapeutic efficacy over the known forms in the prior art as it has no antiviral activity. This is shown in the paper by the inventor of the impugned patent i.e. **Clark *et al* at page 5506, right hand column, Table 2 of Exhibit X, which states compound 9 (uridine derivative) demonstrated no anti-HCV activity or cytotoxicity in any assay.** It is therefore submitted that the submission of Clark *et al* is to be treated as an admission in law.

7.3.7 The Patentee has now combined Claims 5 and 6 into one claim, i.e. Claim 1 where *both* the *cytidine analog and the uridine analog* have been claimed jointly so that the data which pertains only to the cytidine analog now appears to pertain to the compound in this claim as a whole. This is an impermissible amendment under the statute and is a mere illusion to overcome a real and credible challenge to the impugned patent under Section 3 (d).

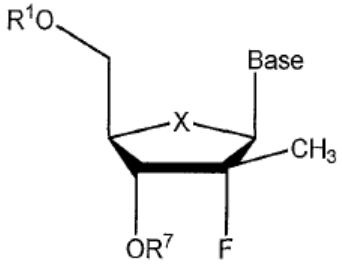
7.3.8 In order for the impugned patent to meet the requirements of Section 3(d) of the Act it must show that Claim 1 and the dependent Claims 5 and 6 enhance the therapeutic efficacy of the already known form. In particular, the patentee has to show data proving the nucleoside compounds (without their prodrug form or as pharmaceutical compositions) claimed in Claim 1 of the impugned patent have greater therapeutic efficacy over the known nucleoside compounds already disclosed in the priorart.

7.3.9 The Opponents note that on pages 92-95ofthe specifications of the impugned patent, the Patenteeonly presents experimental data for a single 2'-methyl-2'flouro nucleoside, namely (2'R)-2'-deoxy-2'-flouro-2'-C-methylcytidine (a compound already disclosed in the prior art). More specifically, the Patentee has failed to present any data showing that other claimed nucleosides, such as the (2'R)-2'-deoxy-2'-flouro- 2'-C-methyluridine derivative that forms the free base for the uridine analog, has antiviral activity that would be effective in treating Flaviviridae infections (including HCV), let alone that they differ significantly in properties with regard efficacy.

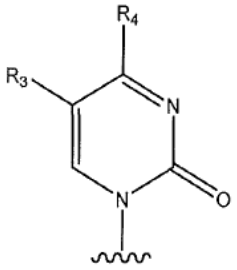
Given the Patentee has not provided the necessary data to meet the requirements of Section 3(d), Claim 1 should not be considered as disclosing a patentableinvention.

7.4 Section 25 (1) (g): Insufficiency of disclosure

7.4.1 Claim 1 of the impugned patent relates to a (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D or β-L) or a pharmaceutically acceptable salt thereof of the structure:



wherein Base is a pyrimidine base represented by the following formula



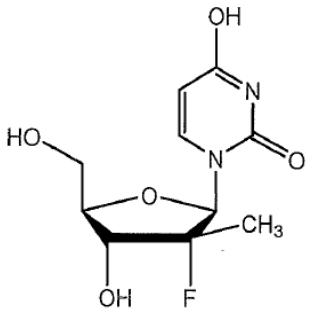
X is O;

R1 and R7 are independently H, a monophosphate, a diphosphate, or a triphosphate;

R3 is H; and

R4 is NH2 or OH.

When R4 is OH, this general formula covers the uridine derivative of (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D or β-L).More particularly, claim 1 encompasses the subject-matter of claim 6 which relates to a (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D) or a pharmaceutically acceptable salt thereof of the formula:



that is (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl uridine (β-D).

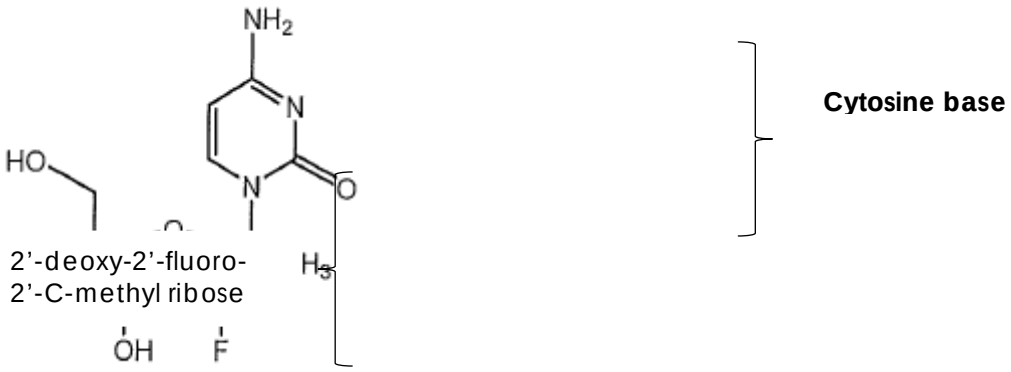
However, no synthetic protocol is given for the uridine derivatives in the patent.

In particular, the opposed patent discloses neither the method of preparation, and optionally of purification, of the (2'R)-2'-deoxy-2'-fluoro-2'-C-methyluridine (β-D) nor the starting materials to obtain it.

As such, one of skill in the art has to devise by himself the complete method of preparation and purification of these compounds.

Hence, the claims are not sufficiently disclosed in the patent specification.

7.4.2 Clark et al. (2005) J. Med. Chem. 48: 5504-5508 **(Exhibit X)** whichdiscusses the scientific disclosures of the impugned patent, reveals that the international application from which it derives was essentially filed to protect 2'-deoxy-2'-fluoro-2'-C-methyl cytidine, which was viewed by the Patentee as a promising anti-HCV compound at the time the application was filed:



2'-deoxy-2'-fluoro-2'-C-methyl cytidine

(Claim 5 of the impugned patent)

A table mentioned in Exhibit X shows the following:

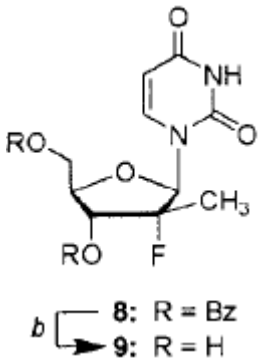


Table 2. Anti-HCV Activity and Cellular Toxicity of Compounds **1**, **9**, 2′-*C*-Methylcytidine (2′-*C*-MeCyd), and 2′-Deoxy-2′-fluorocytidine (2′-FdCyd)

	cpBVDV[a] (MDBK cells)		HCV replicon[b]	
compound	EC_{90} (μM)[b]	CC_{50} (μM)	EC_{90} (μM)	CC_{50}[c] (μM)
1	>100	>100	5.40 ± 2.6	>100
9	>100	>100	>100	>100
2-*C*-MeCyd	2.30 ± 0.1	>100	19.0 ± 5.7	>100
2-FdCyd	>100	>100	6.50 ± 1.6	>100

[a] cpBVDV = cytopathic BVDV. [b] 96 h, average of at least four experiments. [c] MTS CC_{50} was determined in a 4-day assay using the Celltiter 96 nonradioactive cell proliferation assay from Promega (Madison, WI).

In the present case, the impugned patent only presents experimental data for the (2'R)-2'-deoxy-2'-fluoro-2'C-methyl cytidine (see pages 5506of the impugnedpatent). As such, no experimental data showing an antiviral activity

of the claimed uridine derivative forming the subject-matter of Claim 6 is presented in the impugned patent.

Moreover, Exhibit X shows that 2’-deoxy-2’-fluoro-2’-C-methyl uridine (β-D), i.e. the compound of claim 6 of the impugned patent, represented by the following formula 9 in Exhibit X is **not** active in the replicon assay (see page 5506 left hand column last paragraph and table 2 on right hand column of Exhibit X):

The replicon assay is the standard test that allows the determination of the anti-HCV activity of a compound. The HCV replicon assay is used in the opposed patent to evaluate the anti-HCV activity of (2’R)-2’-Deoxy-2’-Fluoro-2’-C-Methyl cytidine (see Example 3 on page 85 of the opposed patent).

The EC_{90} represents the concentration of the tested compound required to achieve 90% inhibition of replicon 96 hours following the administration of the tested compound. The EC_{90} of 2’-deoxy-2’-fluoro-2’-C-methyl uridine is > 100 µM which means that this compound is **therapeutically inactive**.

Hence, the impugned patent does not disclose any qualitative or quantitative data or experimental tests that are sufficient to prove that (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine can produce an expected anti-HCV effect. Furthermore, as a new compound, the subject patent does not provide an effective amount for (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine. Therefore, a person skilled in the art is unable to predict that (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine can product the same or similar effect as (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl cytidine.

Technically, the new compound (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridineClaim 6 which is dependent on and hence derived out of Claim 1of the impugned patent is not sufficiently disclosed in the specification

Prayer:

Based on the grounds and evidence presented above the Opponent prays:

a) That Indian Patent No. 273003 granted in favour of Gilead Pharmasset LLC (formerly Pharmasset, Inc). be refused in its entirety;

b) That the Petitioners/Opponents be awarded the cost of the proceedings.

c) Any other relief deemed appropriate in the facts and circumstances of case may be granted in favour of the Opponents in the interest of justice.

Dated 15th day of May 2017.

For and Behalf of the Opponent:
The Delhi Network of Positive people
and
The Initiative for Medicines, Access & Knowledge, INC (I-MAK)

Mr. Vishal Vig (Constituted Attorney I-MAK)	Mr. Paul Lhungdim (Constituted Attorney DNP+)	Agent of the Opponent

To,
The Controller of Patents,
The Patent Office,
Delhi.

Encl:

1. List of Exhibits enclosed.
2. Online payment of Rs. 12000/- (paid online)

Copy to:
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List of Exhibits:

Exhibit No.	**Name of the documents**
Exhibit I	Power of Attorney of I-MAK
Exhibit II	Power of Attorney of DNP+
Exhibit III	Granted specification of Patent No. 273003
Exhibit IV	Granted claims of Patent No. 273003
Exhibit V	US 60/474,368
Exhibit VI	WO2004002999
Exhibit VII	WO 2002/057425
Exhibit VIII	WO0192282
Exhibit IX	McAtee, *et al.*, 1998
Exhibit X	WO0190121A2
Exhibit XI	Pankiewicz (2000)
Exhibit XII	Clark et al.