Opposition to patent EP 2 604 620 (Gilead Pharmasset LLC)
Facts and arguments in support of the grounds of opposition

Statement of the joint opponents

1. The Opponent Medici Senza Frontiere Onlus along with the joint opponents, are representing **Médecins Sans Frontières (MSF)**, an independent, medical humanitarian organisation that delivers emergency aid to people affected by armed conflict, epidemics, healthcare exclusion and natural or man-made disasters. MSF began treating people with chronic hepatitis C virus (HCV) with oral direct-acting antivirals (DAAs) in 2015, and is in the process of scaling up treatment programs in several countries. Today, MSF programs are providing HCV treatment to people in Myanmar, Cambodia, India, Pakistan, Iran, Russia, Uzbekistan, Belarus, Mozambique, Uganda, and Kenya.

2. Globally, at least 80 million people have HCV. When untreated, HCV can lead to liver failure and liver cancer - complications that kill over 700,000 each year. For over a decade, the standard treatment for HCV was difficult to deliver, expensive, had debilitating side effects and relatively low cure rates, especially in people with serious liver damage - who needed it most.

3. In 2013, HCV treatment dramatically improved, with the advent of safe, oral DAAs drug combinations that cure over 95% of people who take a 12 to 24-week treatment course. But sky-high prices set by pharmaceutical companies kept DAAs out of reach.

4. Sofosbuvir, the backbone of most treatment regimens, was launched by pharmaceutical corporation Gilead Sciences in the US at $1,000 per pill, although it can be mass produced for less than $1 per pill. High prices have limited access to HCV treatment in many countries - even in high-income countries, where treatment has been rationed.

5. Persistent access barriers have made it challenging for MSF and other treatment providers to scale up HCV treatment access in developing countries. By mid-2016, only 5.4 million people globally, among which one million people in low- and middle-income countries had been treated for HCV. Gilead's voluntary licensing agreements, signed with various manufacturers, have excluded many high-burden, middle income countries and all high-income countries from receiving generic versions of the drug. This has resulted in the fact that DAAs remain unaffordable for millions of people with HCV and their governments.

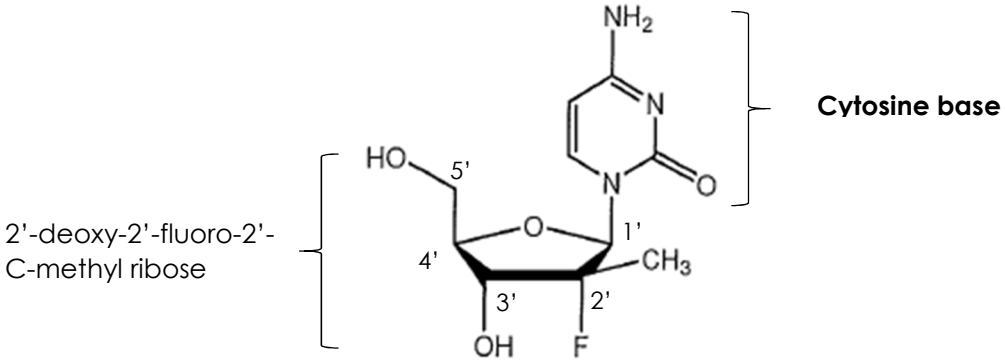
6. Thus, the Opponent and the joint opponents oppose and request the revocation of the European patent **EP 2 604 620** owned by Gilead Pharmasset LLC.

7. The Opponent and the joint opponents emphasise the global public health significance of Hepatitis C treatment and the critical impact of the concerned patent on hindering competition and affordability of sofosbuvir in the Hepatitis C market, alongside the technical grounds below that lead to the Opponent and the joint opponents' belief that the concerned European patent EP 2 604 620 shall be revoked.

Introduction

European patent **EP2604620**, hereafter the "opposed patent" or the "patent", entitled "*Modified fluorinated nucleoside analogues*" was filed on 21 April 2004 as European patent application **13152440.9**, which itself is a divisional application of the earlier European patent application **04775900.6**, the EP regional phase of international application PCT/US2004/12472 (WO2005003147) **(D1)**, naming Jeremy Clark as sole inventor.

As can notably be inferred from the article Clark *et al*. (2005) *J. Med. Chem.* **48**: 5504-5508 **(D2)**, which constitutes the scientific disclosure of the opposed patent, 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 applicant as a promising anti-HCV compound at the time the application was filed:



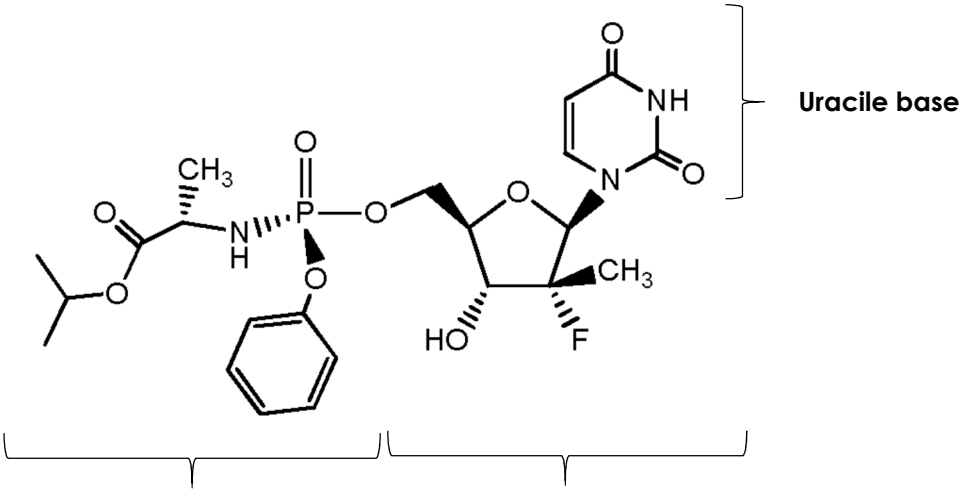
2'-deoxy-2'-fluoro-2'-C-methyl **cytidine**
(claim 5 of the opposed patent)

2'-deoxy-2'-fluoro-2'-C-methyl cytidine is a nucleoside analog constituted of a 2'-deoxy-2'-fluoro-2'-C-methyl ribose moiety and of a cytosine base. Upon its administration to an individual, it penetrates into cells where it is phosphorylated on the 5' OH by intracellular kinases to yield 2'-deoxy-2'-fluoro-2'-C-methyl cytidine monophosphate, diphosphate and eventually triphosphate. 2'-deoxy-2'-fluoro-2'-C-methyl cytidine triphosphate then inhibits HCV RNA-dependent RNA polymerase (RdRp), also known as NS5B.

However, while examination of the earlier application was proceeding, it appeared that 2'-deoxy-2'-fluoro-2'-C-methyl cytidine was not so promising after all. Besides, the applicant developed in parallel another N55B inhibitor which successfully entered on the market as Sofosbuvir (INN). Sofosbuvir is the active principle of Sovaldi®, a drug which price has caused concerns as to the sustainability of health care systems[1] if it were to be distributed to all HCV-infected individuals who need it.

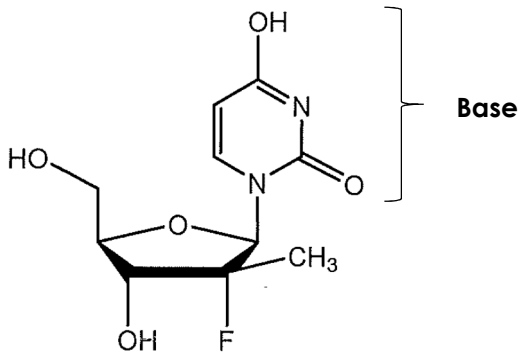
Sofosbuvir is a phosphoramidate derivative of 2'-deoxy-2'-fluoro-2'-C-methyl **uridine:**

[1] "*The price of Sovaldi and its impact on the U.S. health care system*", December 2015, Committee on Finance, United States Senate



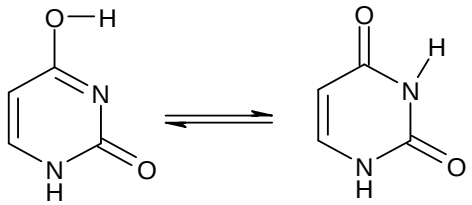
Sofosbuvir is itself attempted to be protected by *i.a.* European patent EP2203462, also in the name of Gilead Pharmasset, filed on 26 March 2008, which has been maintained under amended form after opposition (decision under appeal, T 2643/16).

As such, because two is often better than one, the divisional application from which the present patent derives was filed to reorient the scope of the claims into attempting to specifically cover the 2'-deoxy-2'-fluoro-2'-C-methyl **uridine** part of Sofosbuvir:



2'-deoxy-2'-fluoro-2'-C-methyl **uridine**
(claim 6 of the opposed patent)

In this regard, it is to be noted that although not represented under its predominant tautomeric form at pH 7 the base of the compound of claim 6 of the patent is indeed uracil:



Tautomeric forms of uracil

The lack of the conventional representation of uracil in the patent is particularly revealing in our opinion and brings us to the heart of the problem.

In fact, it was **not** intended, when the International application from which the patent derives was filed, to cover 2'-deoxy-2'-fluoro-2'-C-methyl **uridine**. This was not only because 2'-deoxy-2'-fluoro-2'-C-methyl **cytidine** was viewed as the most promising compound at the time the application was filed, but also because 2'-deoxy-2'-fluoro-2'-C-methyl **uridine** had proved to be **inactive**, as can be seen from the article Clark *et al*. (2005) *J. Med. Chem.* **48**: 5504-5508 (D2) (see page 5506 left hand column last paragraph and Table 2), which constitutes the scientific disclosure of the opposed patent.

It follows therefrom that the patent should be revoked because:

(i) claimed compounds do not have any support in the earlier application as filed (Article 100(c) EPC),

(ii) the synthesis of these compounds is not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Article 100(b) EPC), and

(iii) these compounds do not solve the objective technical problem and therefore lack an inventive step (Article 100(a) EPC).

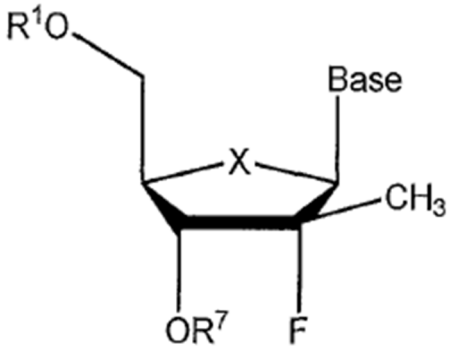
Moreover, claimed compounds are either known from the prior art or obvious in view of the prior art (Article 100(a) EPC).

Cited documents

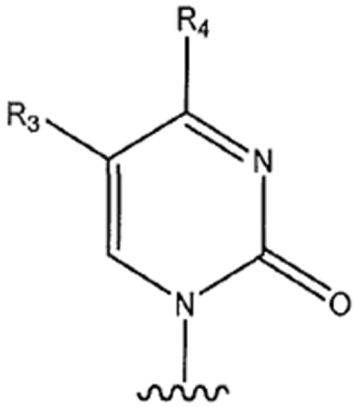
No.	Document	Date of availability to the public
D1	WO2005003147	13 July 2005
D2	Clark *et al*. (2005) *J. Med. Chem.* **48**: 5504-5508	28 March 2005
D3	Perrone *et al*. (2007) J. Med. Chem. **50**: 1840-1849	17 March 2007
D4	US provisional application No. 60/474,368	
D5	Clark employment agreement	
D6	Stuyver employment agreement	
D7	Assent of the assignee to correct inventorship	
D8	WO2004002999	8 January 2004
D9	WO0192282	6 December 2001
D10	Pankiewicz (2000) *Carbohydrate Research* **327**: 87-105	10 July 2000
D11	WO02057425	25 July 2002

I. The subject-matter of the opposed patent extends beyond the content of the earlier application as filed (Article 100(c) EPC)

Claim 1 of the opposed 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;
R^1 and R^7 are independently H, a monophosphate, a diphosphate, or a triphosphate;
R^3 is H; and
R^4 is NH_2 or OH.

This subject-matter has been introduced by the applicant into the claims of the opposed patent when it was filed as a divisional application, without giving the support for this formula in the earlier application as filed.

The closest support for the subject-matter of claim 1 appears to be the eleventh and twelfth embodiments on pages 38-39 of the earlier application as filed (D1). However, these embodiments do not provide that R^1 and R^7 are independently H, a monophosphate, a diphosphate, or a triphosphate. Besides, in the eleventh embodiment X is said to be defined above, that is as defined on the top of page 32 ("X is O, S, CH2, Se, NH, N-alkyl, CHW, $C(W)_2$, wherein W is F, Cl, Br, or I"), *i.e.* X is not simply O.

In fact, R^1 and R^7 can be a monophosphate, a diphosphate, or a triphosphate while R^4 can be OH **only** in the first to eighth embodiments from page 31 to 37 of the earlier application as filed. However, in these embodiments only **lists** of several substituents are given for the various variables. As such, the compound forming the subject-matter

of claim 1 results from the selection of specific substituents within two or more lists of substituents.

The same can be said of claims 2-3 and of claims 7-10, which refer to claims 1-3.

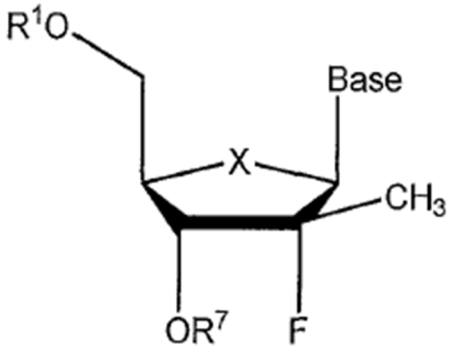
According to the Guidelines for Examination in the EPO (Part G, Chapter VI, Paragraph 8(i)(a)), an individual chemical compound is considered as novel when it results from the selection of specific substituents from two or more "lists" of substituents given in a known generic formula.

In other words, an individual chemical compound cannot be considered as deriving directly and unambiguously from a generic formula when it results from the selection of specific substituents from two or more "lists" of substituents given in the generic formula.

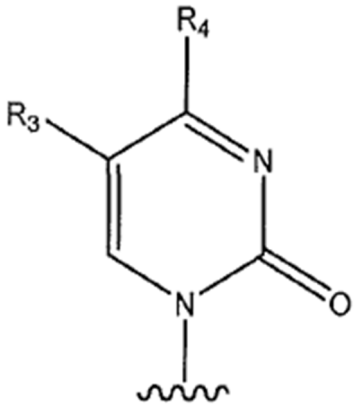
☞ As such, the subject-matter of claims 1-3 and 7-10 extends beyond the content of the earlier application as filed.

II. The opposed patent does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Article 100(b) EPC)

II.1. Claim 1 of the opposed 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:



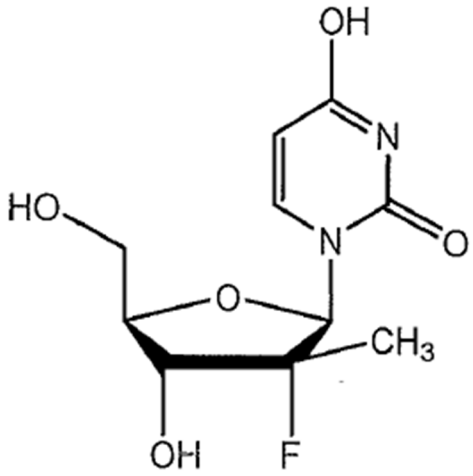
wherein Base is a pyrimidine base represented by the following formula:



X is O;
R^1 and R^7 are independently H, a monophosphate, a diphosphate, or a triphosphate;
R^3 is H; and
R^4 is NH_2 or OH.

When R^4 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-methyle **uridine** (β-D).

However, no synthetic protocol is given for **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-methyl**uridine** (β-D) nor the starting materials to obtain it.

As such, one of skill in the art is left with the **undue burden** of having to devise by himself the complete method of preparation and purification of these compounds.

☞ Accordingly, the subject-matter of claims encompassing uridine derivatives, *i.e.* claims 1 to 4 and 6 to 11 of the opposed patent is not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

II.2. In addition, claims 7 to 11 relate to a pharmaceutical composition comprising a nucleoside of any of claims 1 to 6 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

It should be recalled, in this regard, that according to the Case law of the Boards of Appeal of the European Patent Office, 8th edition 2016, II.C.6.2:
"*In T 1616/09 the board pointed out that, for the purposes of Art. 83 EPC [similar to Art. 100(b) EPC], the level of disclosure in the application which is required for claims directed to pharmaceutical compositions or kits is not the same as that which is required for medical-use claims. For claims directed to pharmaceutical compositions or kits it is in principle sufficient that the application provides information which allows the skilled person to produce the composition or kit,* ***and that there are no substantiated doubts that it could indeed be used in therapy***." (emphasis added).

II.2.1. In the present case, the opposed patent only presents experimental data for the (2'R)-2'-deoxy-2'-fluoro-2'C-methyl cytidine (see Tables 1 to 9 on pages 31 to 33 of the opposed patent). 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 opposed patent.

Moreover, D2 shows that 2'-deoxy-2'-fluoro-2'-C-methyl uridine (β-D), i.e. the compound of claim 6 of the opposed patent, represented by the following formula 9 (framed below) is **not** active in the replicon assay (see page 5506 left hand column last paragraph and table 2 on right hand column of D2):

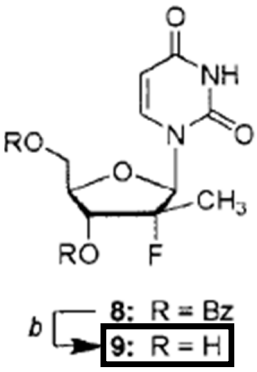


Table 2. Anti-HCV Activity and Cellular Toxicity of Compounds **1**, **9**, 2′-*C*-Methylcytidine (2′-*C*-MeCyd), and 2′-Deoxy-2′-fluorocytidine (2′-FdCyd)

	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).

The replicon assay is the standard test which 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 29 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**.

☞ Accordingly, the subject-matter of the pharmaceutical composition claims covering the compound of claim 6, that is claims 7, 8, 10 and 11 of the opposed patent is not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

II.2.2. Furthermore, it is well known in the art that nucleoside phosphates are unstable in biological media and show poor membrane permeation because of the associated negative charges at physiological pH (see D3, page 1840, right column, 2nd full paragraph).

This is the reason why nucleoside analogues are administered to individuals either under unphosphorylated form, or as a **modified** membrane permeable monophosphorylated form intended to increase the lipophilicity of the nucleoside monophosphate analogue with a consequent increase of membrane permeation and intracellular availability (see D3, page 1840, right column, 3rd full paragraph). An example of such a modified monophosphorylated nucleoside analogue is Sofosbuvir (see Introduction).

Accordingly, it is more than doubtful that the claimed pharmaceutical compositions comprising monophosphates, diphosphates or triphosphates, *i.e*. the pharmaceutical compositions of claims 7-10 could be useful in therapy.

☞ For this reason, the subject-matter of claims 7-10 of the opposed patent is also not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

III. The subject-matter of the opposed patent is not patentable under article 52, 54 and 56 EPC (Article 100(a) EPC)

III.1. The priority right is not validly claimed

The opposed patent was filed on 21 April 2004 and claims the benefit of the priority date of 30 May 2003 from US provisional application No. 60/474,368 (**D4**).

However, the patent is not entitled to the priority date for the following reasons.

III.1.1. Formal reasons

US provisional application No. 60/474,368 was filed in the name of inventors/applicants **Jeremy Clark** and **Lieven Stuyver**. In contrast, the International application from which the opposed patent derives was filed in the name of **Pharmasset, Ltd.** (Barbados).

Article 87 EPC provides that any person who has duly filed, in or for any State party to the Paris Convention for the Protection of Industrial Property or any Member of the World Trade Organization, an application for a patent, a utility model or a utility certificate, or his successor in title, shall enjoy, for the purpose of filing a European patent application in respect of the same invention, a right of priority during a period of twelve months from the date of filing of the first application.

In the present case Pharmasset, **Ltd.** (Barbados) cannot be considered the successor in title of the inventors Jeremy Clark and Lieven Stuyver, because the right of priority has been automatically assigned to Pharmasset, **Inc.** (Georgia, USA), a different legal person, by virtue of their respective employment agreements (see first paragraph on page 1 & part 6. on page 3 of D5, and first paragraph on page 1 & part 6. on page 4 of D6).

☞ As such, none of the claims are entitled to priority and the effective date of the patent is 21 April 2004.

It is noted that the above was discussed in the course of examination and that the Examining division has considered in its communication dated 9 June 2015 that "[…] *in view of the R&D Agreement (whether it was signed or not) and the factual business relation between Pharmasset, Inc. (Georgia) and Pharmasset, Ltd. (Barbados), the corporate tax strategy, the filing of applications in the name of and the confirmatory assignments to the latter, it is considered as sufficiently proven that Pharmasset, Ltd. (Barbados) was the intended recipient of ownership rights, including at the time of the assignment by the inventor Clark, and that the parties' behavior to consider Pharmasset, Ltd. (Barbados) as the "designee" in the sense set forth in section 6.2 of the Employment Agreement.*" (emphasis added).

However, in our opinion, the Examining division did not apply the adequate standard of proof as defined the EPO's Case law. Indeed, as practically all the evidence in support of the transfer of the priority right (unsigned R&D agreement, declarations from

Pharmasset top management, corporate tax strategy) lied within the power and knowledge of the patentee then the adequate standard of proof should have been "**beyond any reasonable doubt**" or "**up to the hilt**".

And indeed there are doubts.

The most important one being that in the assent of the assignee to correct inventorship (D7) of US provisional application No. 60/474,368 (*i.e*. the priority application) received at the USPTO on 13 July 2005 the assignee is expressly mentioned as being Pharmasset, **Inc.** (Georgia), and not the would be "designee" Pharmasset, **Ltd**. (Barbados). This means that in the point of view of the patentee, in 2005 US provisional application No. 60/474,368 was still owned by Pharmasset, Inc. (Georgia).

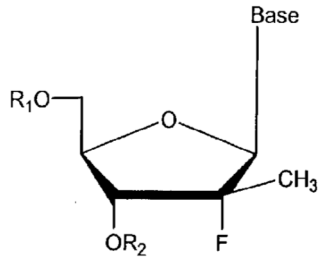
In fact, the above assent of the assignee to correct inventorship shows that it is entirely conceivable that, by virtue of an agreement between them, Pharmasset, **Ltd.** (Barbados) was allowed to **file** in its name patent applications covering inventions made by personnel of Pharmasset, **Inc**. (Georgia), but that where an application was first filed in the name of inventors employed by Pharmasset, Inc. (Georgia) then that application was owned by Pharmasset, Inc. and an express assignment of that application from Pharmasset, Inc. (Georgia) to Pharmasset, Ltd. (Barbados) was needed for the latter to become owner of the application.

III.1.2. Substantive reasons

In the event that Pharmasset, Ltd. would be considered the successor in title of the applicants of the priority application, then we submit that the subject-matter of claims 1-4 and 7-11 does not derive directly and unambiguously from US provisional application No. 60/474,368.

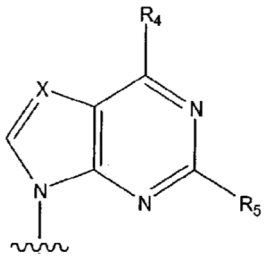
As was noted by the Examining division in its communication dated 9 June 2015, the parts of the priority application (D4) allegedly supporting the claims is to be found on pages 7-8 and 15-16.

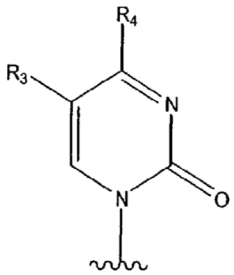
These two sections disclose the same subject-matter, that is a β-D or β-L nucleoside of the general formula (I):



(I)

wherein base can be





and wherein each variable R_1, R_2, R_3, R_4 and R_5 is respectively defined as a list of several dozen substituents.

It can therefore be readily seen that the compounds forming the subject-matter of claims 1-4 and 6 results from the selection of specific substituents within two or more lists of substituents of the compound of formula (I) of the priority document.

As such, the subject-matter of claims 1-4 and 6, as well as that of claims 7-11 which refer to these claims, does not derive directly and unambiguously from the priority document.

☞ As a consequence, the subject-matter of claims 1-4 and 6-11 does not benefit from the priority date and the effective date of the patent is 21 April 2004.

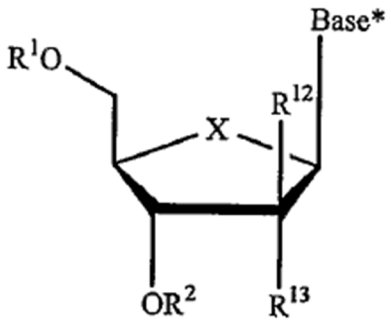
III.2. The subject-matter of the opposed patent is not novel

III.2.1. The subject-matter of claims 1 and 4-6 of the opposed patent is not novel

International application WO2004002999 (**D8**) was published on 8 January 2004, *i.e.* before the effective date of the opposed patent, *i.e*. 21 April 2004, (as has been established previously). Thus, D8 is prior art under article 54(2) EPC.

D8 relates to nucleoside compounds for the treatment of *Flaviviridae* infection, in particular hepatitis C infection (see page 1 lines 10 to 13).

D8 discloses the following compounds of formula (IX) (see page 100):



(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;

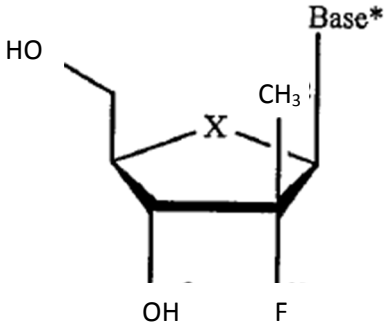
R^{12} is $C(Y^3)_3$;

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 D8 (underlined above), discloses the following compounds with Base* = (purine or pyrimidine base) as only variable:



(IX)

The list of "purine" or "pyrimidine" according to D8 is defined on page 104 line 15-27 and comprises **cytosine** and **uridine**.

According to the Guidelines for examination at the European Patent Office (Part G, Chapter VI, paragraph 8) a selection from a single list of specifically disclosed elements does not confer novelty.

Accordingly, D8 discloses both the compounds of claim 5 (above subembodiment of the compound of formula (IX) with Base* = cytosine) and of claim 6 (above subembodiment of the compound of formula (IX) with Base* = uridine). Besides, these compounds are included in the subject-matter of claims 1 and 4.

☞ As a consequence, the subject-matter of claims 1 and 4-6 lacks novelty.

III.2.2. <u>The subject-matter of claim 7, 8 and 11 is not novel</u>

Should the subject-matter of claims 7-11 be considered sufficiently disclosed, we submit the following.

D8 also discloses pharmaceutical compositions comprising a compound of formula (I) – (XXIII), *i.e*. **in particular a compound of formula (IX) as defined above**, or its pharmaceutically acceptable salt or prodrug thereof, together with a pharmaceutically acceptable carrier or diluent (see page 40 paragraph (d) of D8).

Accordingly, D8 discloses pharmaceutical compositions comprising the compounds of claims 1 and 4-6 of the opposed patent, that is the subject-matter of claims 7, 8 and 11 of the opposed patent.

☞ As a consequence, the subject-matter of claims 7, 8 and 11 also lacks novelty.

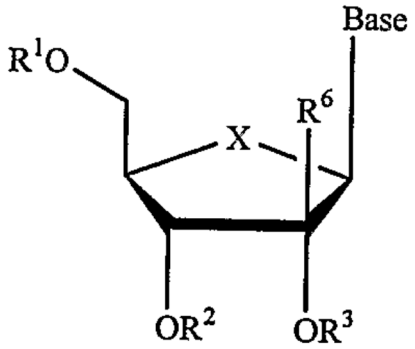
III.3. The subject-matter of the European patent does not involve an inventive step

III.3.1. Lack of inventive step in view of D8 as closest prior art

International application WO2004002999 (**D8**) was published on 8 January 2004, *i.e.* before the effective date of the opposed patent, *i.e*. 21 April 2004 (as has been established previously).

D8 relates to nucleoside compounds for the treatment of *Flaviviridae* infection, in particular hepatitis C infection (see page 1 lines 10 to 13).

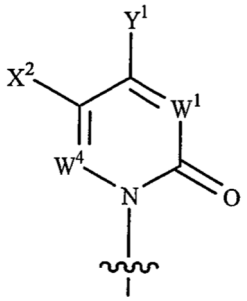
D8 discloses a compound of the following general formula (III) (see page 19):



(III)

wherein:

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



(F)

R^1, R^2, R^3 are as defined above,

which means that:

R^1 and R^2 may be phosphate including mono-, di- or triphosphate and a stabilized phosphate) (see page 17 lines 24-25);

R^3 may be H (see page 17 line 24);

W^1 and W^1 may be CH (see page 25 line 10);

X^2 may be H (see page 26 line 2);

Y^1 may be OH or NH_2 (see page 26 line 23); and

R^6 may be CH_3 (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 effect can be imparted to these compounds (see section **II.2.2.** above).

Accordingly, as is illustrated by the Guidelines for Examination in the EPO, Part G, chapter VII, Annex, paragraph 3.1(iv), the subject-matter of claims 2-3 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.

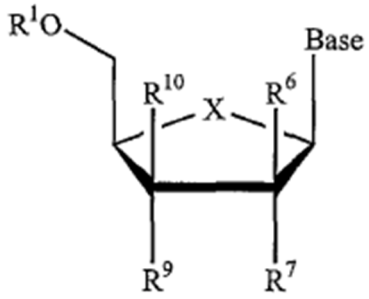
Should the subject-matter of claims 7-11 be considered sufficiently disclosed, in view of D8 also disclosing pharmaceutical compositions comprising a compound of formula (I) – (XXIII), *i.e*. in particular a compound of formula (III) as defined above, or its pharmaceutically acceptable salt or prodrug thereof, together with a pharmaceutically acceptable carrier or diluent (see page 40 paragraph (d) of D8), the foregoing applies *mutatis mutandis* to claims 9 and 10 which relate to pharmaceutical compositions comprising respectively the compounds of claims 2 and 3.

☞ As such, the subject-matter of claims 2, 3 and 9, 10 does not involve an inventive step.

III.3.2. Lack of inventive step in view of D9 as closest prior art and D10

III.3.2.1. International application WO0192282 (**D9**) was published on 6 December 2001, *i.e.* before the priority date claimed by the opposed patent (30 May 2003).

D9 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):



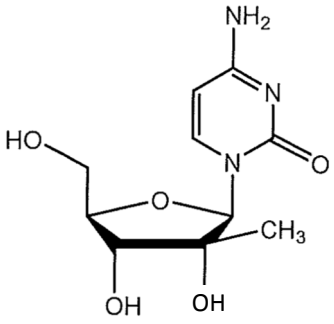
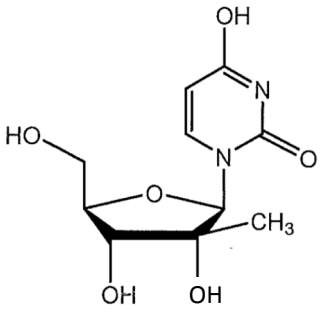
(XVII)

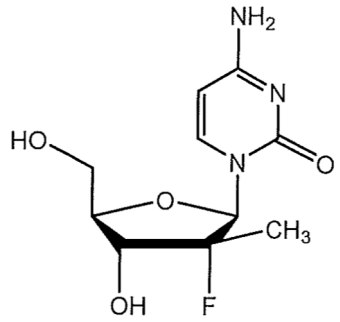
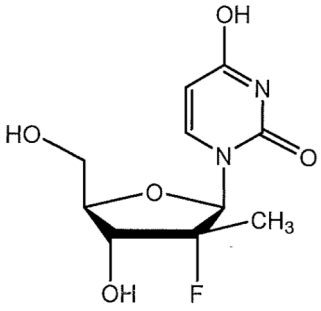
with the following sub-embodiments (see page 41):

(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;

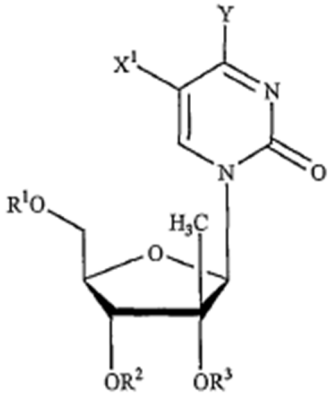
(1) Base is uracil; (2) R^1 is hydrogen; (3) R^6 is methyl; (4) R^7 and R^9 are hydroxyl; (5) R^{10} is hydrogen; and (6) X is O;

The two embodiments are depicted below:

 Subembodiment of the compound of formula (XVII) of D9 where Base is cytosine	 Subembodiment of the compound of formula (XVII) of D9 where Base is uracil

	
Compound of claim 5 of the patent	Compound of claim 6 of the patent

D9 also relates to a compound of formula (V) (see page 125):

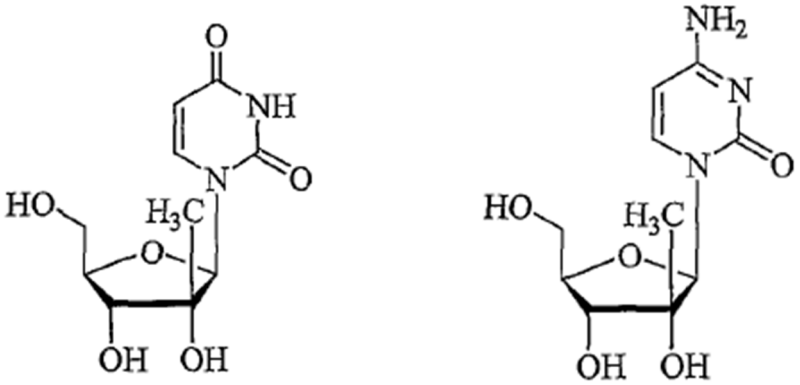


(V)

with the following substituents (see table on pages 125 to 128 of D9):

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

Furthermore, the antiviral activities of β-D-2'-CH_3-riboC and β-D-2'-CH_3-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 D9).



β-D-2'-CH_3-riboU β-D-2'-CH_3-riboC

β-D-2'-CH_3-riboC shows an EC_{50} of 3.7 µM and a CC_{50} >100 µM in BVDV cells and an EC_{50} of 70 µM and a CC_{50} >100 µM in YFV cells.

β-D-2'-CH_3-riboU show an EC_{50} of 20 µM and a CC_{50} >100 µM in BVDV cells and an EC_{50} of 33 µM and a CC_{50} >100 µM in YFV cells.

D9 aims at solving the same general technical problem as the opposed patent, namely providing nucleoside compounds for the treatment of *Flaviviridae* infections (see the top of page 4 of D9 and page 8 lines 11 to 13 of the opposed patent). In addition, as seen above, D9 provides nucleoside compounds with a strong structural resemblance with the compounds claimed by the opposed patent.

D9 therefore qualifies as a closest prior art document according to the problem and solution approach.

The difference between the compounds of formula (V) of D9 and compounds claimed by the opposed patent lies in the presence of a fluorine atom in the 2'position of the nucleoside for the claimed compounds instead of a hydroxyl group in compounds of formula (V) of D9.

The experimental tests in the opposed patent has not been established by comparison to the closets prior art D9. Thus, no technical effect can be associated to the difference between compounds of D9 and compound of the opposed patent.

Accordingly, the objective technical problem can be formulated as providing alternative nucleoside compounds to that of D9 for the treatment of *Flaviviridae* infections.

III.3.2.2. The opposed patent only presents experimental data for the (2'R)-2'-deoxy-2'-fluoro-2'C-methyl cytidine (see Tables 1 to 9 on pages 31 to 33 of the opposed patent). As such, no experimental data making it credible that the claimed uridine nucleoside analogue forming the subject-matter of claim 6 has an effect against *Flaviviridae* infection, *i.e.* that it solves the objective technical problem, is presented in the opposed patent.

Moreover, as seen previously in section **II.2.1.,** it is clear from D2 that 2'-deoxy-2'-fluoro-2'-C-methyl uridine (β-D) represented by formula 9, *i.e*. the compound of claim 6 of the opposed patent, is **not** active in the replicon assay (see page 5506 left hand column last paragraph and table 2 on right hand column of D2).

This establishes that the compound of claim 6 of the opposed patent does not solve the objective technical problem.

Accordingly, the subject-matter of claim 6 of the opposed patent does not involve an inventive step. This applies mutatis mutandis to claims 1, 4, 7, 8 and 11.

Besides, as seen in section **II.2.2.,** it is more than doubtful that the monophosphate, disphosphate and triphosphate nucleosides of claims 2 and 3 could be active as such in therapy because of their instability in biological media and their inability to cross biological membranes to reach their intracellular target. Therefore, the subject-matter of claims 2-3, as that of claims 9 and 10 does not solve the objective technical problem.

Consequently, the subject-matter of claims 1-4 and 6-11 of the opposed patent does not involve an inventive step.

III.3.2.3. Should it be nevertheless considered that the subject-matter of these claims involves an inventive step, and also as regards claim 5, we submit the following.

The article by Pankiewicz (2000) *Carbohydrate Research* 327:87-105 (**D10**) was published on 10 July 2000, *i.e.* before the priority date of the opposed patent (30 May 2003).

D10 is a review relating to fluorinated nucleosides. This article discusses the possible positions for the introduction of the fluorine atom in nucleoside compounds and the synthetic ways to obtain fluorinated nucleosides.

D10 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).

Besides, 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 D10). Moreover, the author reports that 77% of fluorinated nucleosides synthesized at the date of the article contained fluorine atom(s) at C-2' of the sugar.

As such, one of skill in the art wishing to solve the objective technical problem would have been prompted to replace the 2'-hydroxyl group by a fluorine atom in the compounds of formula (V) of D9, thereby arriving at the compounds of claims 1 to 6 of the opposed patent, either as he would have expected this would improve biological activity or as he would have considered this an obvious substitution to try..

☞ Accordingly, the subject-matter of claims 1 to 6 of the opposed patent does not involve an inventive step.

Besides, should the subject-matter of claims 7-11 be considered sufficiently disclosed, D9 also discloses pharmaceutical compositions comprising the active compound, *i.e.* in particular a compound of formula (V) as defined above, or a pharmaceutically acceptable prodrug or salt thereof in the presence of a pharmaceutically acceptable carrier or diluent (see page 55 paragraph V. "Pharmaceutical Compositions" of D9).

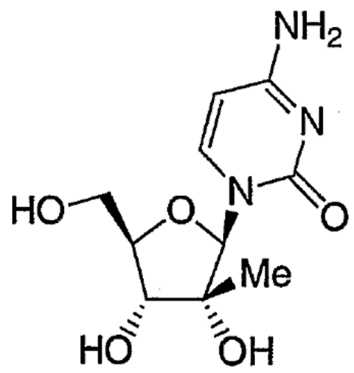
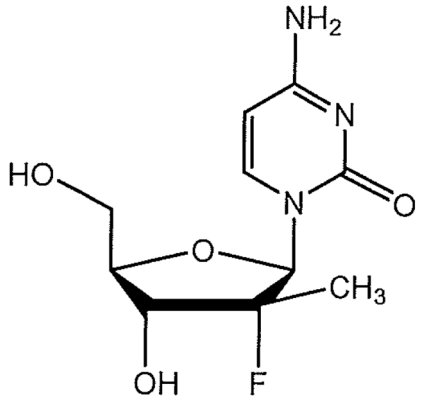
☞ As a consequence, the subject-matter of the pharmaceutical composition claims 7 to 11 does not involve an inventive step.

III.3.3. Lack of inventive step in view of D11 as closest prior art and D10

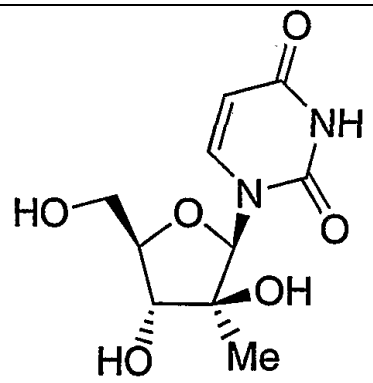
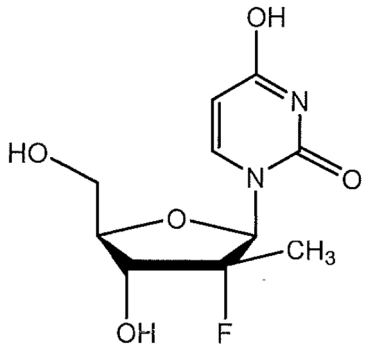
International application WO02057425 (**D11**) was published in 25 July 2002, *i.e.* before the priority date of the opposed patent (30 May 2003).

III.3.3.1. D11 relates to nucleoside derivatives which are inhibitor of RNA-dependent RNA viral polymerase (*i.e.* NS5B) and are useful as inhibitors of HCV and for the treatment of hepatitis C infection (see page 1, lines 6 to 11 of D11).

D11 disclose a 2'C-Methyl-cytidine with the following formula (see example 122 on page 149 of D11):

	
Compound of example 122 of D11	Compound of claim 5 of the patent

In addition, D11 also discloses the compound of example 103 (see page 138):

	
Compound of example 103 of D11	Compound of claim 6 of the patent

D11 aims at solving the same general technical problem as the opposed patent, namely providing nucleoside compounds for the treatment of HCV infections and provides nucleoside compounds with a strong structural resemblance with claimed compounds of the opposed patent. D11 may therefore qualify as closest prior art document according to the problem and solution approach.

The difference between example 122 of D11 and the compound of claim 5 of the opposed patent lies in the presence of a fluorine atom in the 2'position of the nucleosides of the claim 5 of the opposed patent instead of a hydroxyl group.

The experimental tests in the opposed patent have not been established by comparison to the closest prior art D11. Thus, no technical effect can be associated to the difference between the compounds of D11 and the compound of claim 5 of the opposed patent.

Accordingly, the objective technical problem can be formulated as providing alternative nucleoside compounds to that of D11 for the treatment of HCV infections.

☞ As a consequence, applying *mutatis mutandis* the reasoning set forth in the above section **III.3.2.2.**, the subject-matter of claims 1-4 and 6-11 of the opposed patent does not involve an inventive step.

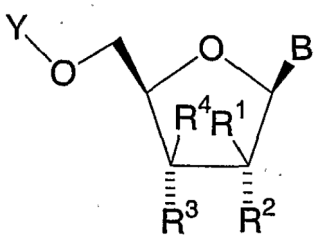
III.3.3.2. Should it be nevertheless considered that the subject-matter of these claims involves an inventive step, and also as regards claim 5, we submit that starting from the compound of example 122 of D11, then the reasoning set forth in the above section **III.3.2.3**. in view of D10 applies *mutatis mutandis* to the subject-matter of claims 1, 4 and 5.

☞ Therefore, the subject-matter of claims 1, 4 and 5 does not involve an inventive step.

Besides, where the subject-matter of claims 7 to 11 be considered sufficiently disclosed, D11 also teaches pharmaceutical compositions comprising the disclosed nucleoside compounds in association with a pharmaceutically acceptable salt (see page 47 lines 30-33).

☞ Consequently, the pharmaceutical compositions comprising the compounds of claims 1, 4 and 5 which form the subject-matter of claims 7, 8 and 11 do not involve an inventive step.

III.3.3.3. In addition, D11 discloses the compound of formula (II)



(II)

which includes the above compound of example 103 of D11 and wherein in particular:

R^1 may be C_{1-4} alkyl (see page 15 line20); and
R^2 may be halogen (see page 16 line 1), the term halogen including fluorine atom (see page 44 line 6).

The compounds of claim 6 of the opposed patent is among the compounds disclosed these combinations.

No experimental data showing a technical effect of the compound of claim 6 is presented in the opposed patent. Furthermore, no credible technical effect can be imparted to this compound (see section **II.2.1.** above).

Accordingly, as is illustrated by the Guidelines for Examination in the EPO, Part G, chapter VII, Annex, paragraph 3.1(iv), the subject-matter of claim 6, as well as that of claims 1 and 4, 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.

☞ The subject-matter of claim 6, as well as that of claims 1 and 4, therefore does not involve an inventive step.

Should the subject-matter of claims 7-11 be considered sufficiently disclosed, in view of D11 also teaching pharmaceutical compositions comprising the disclosed nucleoside compounds in association with a pharmaceutically acceptable salt (see page 47 lines 30-33), the foregoing applies *mutatis mutandis* to claims 7, 8 and 11 which relate to pharmaceutical compositions comprising respectively the compounds of claims 1, 4 and 6.

☞ The subject-matter of claims 7, 8 and 11 therefore also does not involve an inventive step.