Borovyk & Partners
PATENT AND TRADEMARK ATTORNEYS

tel.: +38 044 536–03–05
fax: +38 044 529–47–96
www.borovyk.com
info@borovyk.com

Ref. No. **0666-04/15**
of **April 30, 2015**

State Enterprise Ukrainian Intellectual Property Institute (Ukrpatent)

1 Hlazunova Str., Kyiv-42, 01601

Department for Examination of Applications for Inventions, Utility Models and Integrated Circuit Topographies

Division of Pharmaceutics

Expert V.V. Dovgay

Acting under the Power of Attorney from the *All-Ukrainian Network of People Living with HIV/AIDS*, we file materials evidencing that the invention “Nucleosidephosphoramidates” according to Application No. a 2012 12444 of March 31, 2011 fails to meet the patentability criteria in according to Article 7 of the Law "On Protection of Rights to Inventions and Utility Models" (hereinafter the “**Law**”), i.e fails to meet the criterion for “novelty” in according to Part 3 of Article 7 of the Law and fails to meet the criterion for “an inventive step” as defined by Part 7 of Article 7 of the Law.

1. Bibliographic data of the Application No. a 2012 12444 of March 31, 2011 Application No. a 2012 12444 of March 31, 2011 for the invention "Nucleosidephosphoramidates" was submitted in Ukraine as a national phase of international Application PCT/US2011/030725 published under WO2011123645. International Application PCT/US2011/030725 relates to the active substance sofosbuvir. Sofosbuvir is a hepatitis C virus (HCV) NS5B polymerase inhibitor developed by the company Gilead Pharmasset LLC (US), and is used for the treatment of chronic hepatitis C (CHC) as a component of the combination antiviral therapy in adult subjects in combination with other medicines. Pharmaceutical compositions containing sofosbuvir are also known as Sovaldi, Hepcinat, Resof, Hepcvir, SoviHep, Harvoni.

Patent applications, which relate to sofosbuvir, can be divided into primary and secondary (see Thomson Reuters Report prepared for the World Health Organization, available at http://www.who.int/phi/implementation/ip_trade/sofosbuvir_report_updated.pdf). According to the report, the primary patent applications include:

tel.: +38 044 536–03–05
fax: +38 044 529–47–96
www.borovyk.com
info@borovyk.com

- International Application PCT/US2004/012472 of April 21, 2004 published under WO2005003147 that covers the basic compound sofosbuvir,

- International Application PCT/US2008/058183 of March 26, 2008 published under WO2008121634 that covers nucleosidephosphoramidate-based pro-drugs including salts, hydrates, solutions, stereoisomers and crystalline forms and methods of production thereof.

It should be noted that quite a lot of oppositions were filed vs primary patent applications to patent offices of various countries, including the European Patent Office, Patent Office of India and others, because of the claimed inventions fail to meet the patentability criteria for "novelty" and "an inventive step" (see Thomson Reuters Report, p. 14-16).

Application PCT/US2011/030725 (according to WO2011123645), used as a basis for filing of Ukrainian Application No. a 2012 12444, is a secondary patent application (divisional application from the primary application). This application covers the production process of sofosbuvir as an active substance and a crystalline form of nucleosidephosphoramidates, which are used for the treatment of infections caused by hepatitis C virus. In accordance with the Report of the International Searching Authority (WIPO ISR), claims 1-9 of PCT/US2011/030725 covering various forms of crystalline structure of nucleosidephosphoramidates are not new in view of the earlier publication of International Application WO2008121634 (the primary patent application). It is also worth noting that most of the countries prevent to granting patents under secondary applications, which relate to modifications of the already known drugs (see Thomson Reuters Report, p. 6).

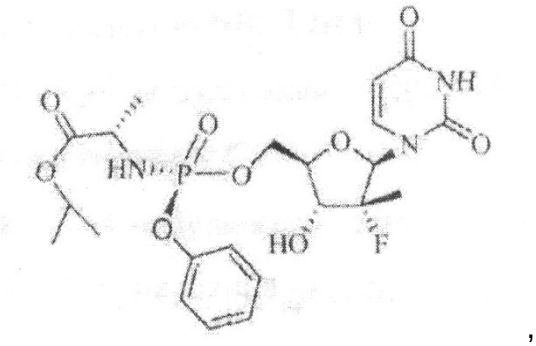
The submitted materials relate to the **amended** claims of the invention "Nucleosidephosphoramidates", filed by the representatives of the applicant, Gilead Pharmasset LLC (US), together with a response to the Preliminary Report of Substantive Examination of January 27, 2015, ref. No. 1720/3A/15.

2. Analysis of the amended claims filed in response to the Preliminary Report of Substantive Examination

The amended claims of the invention "Nucleosidephosphoramidates" comprise a total of 23 claims, which relate to the following objects:

tel.: +38 044 536–03–05
fax: +38 044 529–47–96
www.borovyk.com
info@borovyk.com

- Claim 1 relates to the crystalline compound (S)-isopropyl 2-(((SR, 3R, 4R, 5R)-5-(2,4-dioxo-3,4-dihydropyrimidine-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)metoxy)(phenoxy)phosphoryl)amino)propanoate, represented by formula S_{p-4}:



,

S_{p-4}

with the value of reflection angle 2θ (± 0.2°) on the X-ray powder diffractogram (XRPD) 6,1 and 12,7.

- Claims 2 and 3 of the invention relate to the crystalline compound according to claim 1 and have additional values of angle 2θ (± 0.2°).

- Claim 4 relates to a pharmaceutical composition comprising the crystalline compound according to either claim 1-3 and a pharmaceutically acceptable carrier.

- Claims 5-8 relate to the pharmaceutical composition comprising the crystalline compound according to either claim 1-3 and additionally comprising another antiviral agent, in particular HCV NS3 protease inhibitor (claim 6) or HCV NS5A protease inhibitor (claim 7) or a combination of the said protease inhibitors (claim 8).

- Claim 9 relates to the crystalline compound S_{p-4} according to either claim 1-3 for application in the treatment of an infection caused by hepatitis C virus.

- Claim 10 relates to the combination of the crystalline compound S_{p-4} according to either claim 1-3 and another antiviral agent for application in the treatment of an infection caused by hepatitis C virus.

tel.: +38 044 536–03–05
fax: +38 044 529–47–96
www.borovyk.com
info@borovyk.com

- Claims 11-13 relate to the combination of the crystalline compound S_{p-4} according to either claim 1-3 and another antiviral agent for application in the treatment of an infection caused by hepatitis C virus, wherein HCV NS3 protease inhibitor (claim 11) or HCV NS5A protease inhibitor (claim 12) or a combination of the said protease inhibitors (claim 13) is the other antiviral agent.

- Claim 14 relates to the application of the crystalline compound S_{p-4} according to claims 1-3 for obtaining a medicinal product for the treatment of an infection caused by hepatitis C virus.

- Claim 15 relates to the application of the combination of the crystalline compound S_{p-4} according to either claim 1-3 and another antiviral agent for obtaining a medicinal product for the treatment of an infection caused by hepatitis C virus.

- Claims 16-18 relate to the application of the combination of the crystalline compound S_{p-4} according to either claim 1-3 and another antiviral agent for obtaining a medicinal product for the treatment of an infection caused by hepatitis C virus, wherein HCV NS3 protease inhibitor (claim 16) or HCV NS5A protease inhibitor (claim 17) or a combination of the said protease inhibitors (claim 18) is the other antiviral agent.

- Claim 19 relates to the method of treatment of a human infected with hepatitis C virus by administering the efficient quantity of the compound S_{p-4} according to either claim 1-3.

- Claim 20 relates to the method of treatment of a human infected with hepatitis C virus by administering the efficient quantity of the compound S_{p-4} according to either claim 1-3 in combination with another antiviral agent.

- Claims 21-23 relate to the method of treatment of a human infected with hepatitis C virus by administering the efficient quantity of the compound S_{p-4} according to either claim 1-3 in combination with another antiviral agent, wherein HCV NS3 protease inhibitor (claim 21) or HCV NS5A protease inhibitor (claim 22) or a combination of the said protease inhibitors (claim 23) are the other antiviral agent.

Therefore:

tel.: +38 044 536–03–05
fax: +38 044 529–47–96
www.borovyk.com
info@borovyk.com

- independent claim 1 and dependent claims 2 and 3 of the amended claims have essential features such as structural formula and powder X-ray diffraction diagram expressed in the values of reflection angle 2θ, which characterize the crystalline form of diastereomer according to the formula Sp-4,

- independent claim 4 and dependent claims 5-8 have essential features such as the qualitative compositionof the pharmaceutical composition, wherein the crystalline compound according to claim 1-3 or a combination of that compound with other antiviral drugs is the active ingredient,

- independent claim 9 has essential features such as the use of the crystalline compound according to claim 1-3 for the treatment of infections caused by hepatitis C virus,

- independent claim 10 and dependent claims 11-13 have essential features such as the use of the crystalline compound according to claims 1-3 for the treatment of infections caused by hepatitis C virus, in combination with other antiviral drugs,

- independent claim 14 has essential features such as the use of the crystalline compound according to claim 1-3 for obtaining the medicinal product,

- independent claim 15 and dependent claims 16-18 have essential features such as application of the combination of the crystalline compound according to claims 1-3 with another antiviral agent for obtaining the medicinal product,

- independent claim 19 has essential features such as effect, which describes the method of treatment of a human using the crystalline compound according to claims 1-3,

- independent claim 20 and dependent claims 21-23 have essential features such as effect, which describes the method of treatment of a human using a combination of the crystalline compound according to claims 1-3 with another antiviral agent.

3. Regulations

According to Article 7 of the Law (the citations are italicized hereinbelow):

tel.: +38 044 536–03–05
fax: +38 044 529–47–96
www.borovyk.com
info@borovyk.com

"3. An invention (utility model) shall be considered to be new provided if it does not form part of the state of the art.

4. The state of the art comprises all the facts made available to the public throughout the world before the date of filing of the Application with the Office or, if the priority has been claimed, before the date of its priority.

7. An invention shall be considered as involving an inventive step provided if it is not obvious to a person skilled in the art, i.e. an invention does not proceed obviously from the state of the art."

According to Section 6.5.2.11 of the Rules of Preparing and Filing an Application for Invention and Application for Utility Model (hereinafter, the Rules):

"With regard to an invention, which is found incompliant with the novelty criterion, no further check for an inventive step is done".

According to Section 6.5.3.1 of the Rules:

«An invention has an inventive step if, having regard to the state of the art, it is not obvious to a person skilled in the art. When assessing the inventive step, the claimed invention is compared not only with separate documents or their parts, but with combination of documents or their parts (so called composite prototype), when the possibility of combining the documents or their parts is obvious for a person skilled in the art.

When an inventive step is checked, it is established whether the influence of the combination of the features of the claimed invention on obtaining the technical result indicated by the applicant is known from the state of the art. If this fact is not established, the invention is considered to meet the criterion of an inventive step. (Sec. 6.5.3.2 of the Rules).

The fact that influence of combination of features of the claimed invention on the technical result is known may be proved by combining two or more information sources or their parts, different excerpts from one and the same source or from any different information sources. Involvement of arguments based on knowledge well-known in a specific art without indication to any specific information sources is permissible. (Sec. 6.5.3.6 of the Rules).

tel.: +38 044 536–03–05
fax: +38 044 529–47–96
www.borovyk.com
info@borovyk.com

If the claimed invention meets the criterion of an inventive step with regard to the independent claim(s), the respective dependent claims are not further checked (Sec. 6.5.3.8 of the Rules)".

4. Cited documents

- The following documents are cited in the opposition: Publication of International Application WO 2008/121634 A2 of October 09, 2008, referred to as document **D1** in the Preliminary Report of Substantive Examination,

- Application US 2007/0042988 A1, published on February 22, 2007, referred to as document **D2** in the Preliminary Report of Substantive Examination,

- Publication of the International Application WO 2010/135569 of November 25, 2010, referred to as document **D3** in the Preliminary Report of Substantive Examination,

- Sofia MJ et al "Discovery of a β-d-2'-deoxy-2'-α-fluoro-2'-β-C-methyluridine nucleotide prodrug (PSI-7977) for the treatment of hepatitis C virus", Journal of Medicinal Chemistry, vol. 53, no. 19, 16 September 2010 (2010-09-16), p. 7202-7218, referred to as document **D4** in the Preliminary Report of Substantive Examination.

D1, D2, and D4 have a publication date before the priority dates, of Application No. a 2012 12444 of March 31, 2011 for the invention "Nucleosidephosphoramidates", i.e. March 31, 2010 and May 20, 2010, so the cited documents are prior art for the invention "Nucleosidephosphoramidates" of Application No. a 2012 12444. D3 was cited by the applicant in the description, so it also is the prior art for the invention "Nucleosidephosphoramidates" of Application No. a 2012 12444.

5. The invention according to claims 1-3 fails to meet the patentability criteria for "novelty" and "an inventive step"

According to the independent claim 1 of the claimed invention, the essential features of the invention are **a structural formula of the crystalline compound** (represented by the formula S_{p-4}) and **reflection angle 2θ,** determined by X-ray powder diffraction (XRPD) analysis. Thus, the object of the independent claim 1 is polymorphic modification of the crystalline structure of the compound. In the description, the claimed compound is referred to as form 6 of the crystalline compound represented by the formula S_{p-4}.

tel.: +38 044 536–03–05
fax: +38 044 529–47–96
www.borovyk.com
info@borovyk.com

In according to the Preliminary Report of Substantive Examination of the Application No. a 2012 12444 of March 31, 2011, document D1 discloses the crystalline compound 25 with the structural formula S_{p-4} (claim 2, p. 702), which is completely identical to the structural formula, referred to in claim 1 of the claimed invention. Therefore, the the crystalline structure of claim 1 was known before the date of priority No. a 2012 12444. Further, the crystalline compound found in D1 should have polymorphic modifications of the crystalline structure being formed when it is obtained (i.e. naturally), rather than by taking additional steps aimed at obtaining the required polymorphic modifications of the crystalline structure.

The D2 (p. 10) also discloses the compound 12e with Markush general formula, wherein substituents are shown in Table 2 of the D2. The known compound is the same compound as the one stated at amended claims 1-3. Herewith, the D2 (the description, p. 16, column 2, para. 1), states that the compound 12e may take, in particular the crystalline (polymorphic) form.

The D3 discloses the crystalline compound represented by the formula S_{p-4}, which can be in the crystalline form (p. 97). In this case, D3, p. 102, discloses determination of the crystalline structure of the compound by powder X-ray diffraction (XRPD) analysis.

The D4 discloses the compound 51 described on p. 7209, Fig. 5, and its crystalline form on p. 7214, column 2, which is similar to the crystalline compound in claims 1-3 of the claimed invention. This last paragraph of column 2 in the D4 presents the data of dry powder X-ray diffraction analysis for the compound 51, so obtained along with the results derived for reflection angle 2θ in the range between 5.48° and 50.04°.

Polymorphism is known to be a property of certain substances, which can exist in two or more crystalline forms. These forms are called polymorphic modifications or polymorphic variations, and polymorphic transformation is the transfer of one modification to another one (А.І. Гончаров, М.Ю.Корнілов «Довідник з хімії», ВО «Вища школа», Головне видавництво, Київ, 1974р. – стор. 212) [A.I. Goncharov, M.Yu. Kornilov "Handbook of Chemistry", VO Vyscha Shkola, Central Publishing, Kyiv, 1974. - p. 212, *in Ukrainian*]. Polymorphism occurs at certain temperatures or under certain parameters of pressure. For example, more than forty modifications of silicone carbide SiC are known. Transfer to the next polymorphic modification, characterized by a less dense crystal structure, takes place in response to heating to a certain temperature («Курс общей химии» під редакцією Н.В.Коровина, 2 видання, «Высшая школа», Москва, 1990 – 245 стор.) ["A Course in

tel.: +38 044 536–03–05
fax: +38 044 529–47–96
www.borovyk.com
info@borovyk.com

General Chemistry" edited N.V. Korovin, 2nd Edition, Vyschaya Shkola, Moscow, 1990. - 245 p., *in Russian*]. In particular, there are polymorphic modifications of sulfur having the form of rhombic sulfur and monoclinic sulfur characterized by different physical parameters (rhombic sulfur has a more stable structure), (Оганесян Є.Т. «Руководство по химии поступающим в ВУЗы: Справочное пособие», 2 видання, «Высшая школа», Москва, 1990 – стор. 201 [Oganesyan E.T. "Guide to Chemistry for Prospective Students: Reference Book", 2nd edition, Vyschaya Shkola, Moscow, 1990 - p. 201, *in Russian*). It is also known, that under normal conditions iron crystallizes in a body-centered cubic lattice, and in the temperature range of 910-1390 °C iron forms a face-centered cubic lattice. The said different types of the same crystalline structure are caused by polymorphism (Хомченко І. Г. «Загальна хімія», Підручник, Київ, «Вища школа», 1993 - 250 стор. [Khomchenko I.G. "General Chemistry", Textbook, Kyiv, Vyscha Shkola, 1993. - 250 p., *in Ukrainian*).

Powder X-ray diffraction (XRPD) analysis is a method to study the structure of a substance using phenomenon of X-ray diffraction on its crystal lattice. The X-ray diffraction method allows us to obtain not only qualitative and quantitative data about the structure of the substance, but the information on the nature and extent of defects in its crystalline structure. The resulting X-ray diffraction analysis diagram characterizes the substance based on its crystal structure. Thus, the presence of defects in the crystal structure of the substance is determined by reflection angle 2θ (Bragg angle).

Thus, any polymorphic forms (modifications) of the known crystalline compound, namely, the compound of the formula $S_{p\text{-}4}$, are not new, since the crystalline compound is known itself based on the fact that:

- this is a form of existence of the same crystalline compound, i.e. of the same substance, which is unstable and which, under certain conditions, transfers to another state (polymorphic modification) to achieve a polymorphic modification of certain stability, i.e. the crystalline compound to be used should reach its stable form in any case,

- parameters of the certain polymorphic modification, which have not been described before, do not allow to find a novelty, because these options have been already characterized by the crystalline compound, which facts are known from the prior art.

This is further confirmed by the International Search Report (WIPO ISR). The expert concluded about the lack of novelty in the compound according to claims 1-9 under the international publication since the features of the said claims are known from the D1.

tel.: +38 044 536–03–05
fax: +38 044 529–47–96
www.borovyk.com
info@borovyk.com

Herewith, the D1 does not directly indicate any reflection angle 2θ. This suggests that parameters of crystal lattice of the compound are known as the compound itself is known. It should be noted that reflection angles 2θ referred to in claims 1-9 according to the international publication (not new in according to the D1) were included by the applicant to amended claims 1-3.

This approach is confirmed by Guidelines for the examination of inventions in the field of pharmaceuticals (Guidelines for the examination of pharmaceutical patents: developing a public health perspective, a Working Paper), developed by international organizations such as International Centre for Trade and Sustainable Development (ICTSD), World Health Organization (WHO) and United Nations Conference on Trade and Development (UNCTAD), available at http://apps.who.int/medicinedocs/documents/s21419en/s21419en.pdf. The said recommendations were developed due to consideration of the balance of interests of patent holders and potential users of proprietary objects and provisions of the Agreement TRIPS Agreement ratified by Ukraine on 5 February 2008.

The said Guidelines contain a section describing the approach to examination of inventions, the object of which is a polymorphic modification of the known crystalline compound (see Section 2.5 “POLYMORPHS”, p. 10-11). Polymorphism is recognized as a natural quality of compounds in their solid (crystalline) form. Polymorphic modification may not be an object of the invention, but rather the object of study of the already known compound, for example, maintenance of crystal structure parameters, including reflection angle 2θ for the purposes of its identity. Therefore, any polymorphic forms of the known compound, even though their new therapeutic effect was discovered, are known in the art and, as such, are not patentable. Submission of applications for such forms (secondary, derivative applications) is an attempt of primary patent owners to extend their action (in the case of expiry of legal protection) or to extend their effect on other countries not covered by primary patents. Herewith, the Guidelines note that in some cases the process (method) for obtaining certain polymorphic modifications, including obtaining of a stable form of a crystalline compound, can be considered as a new one or as one involving an inventive step. This is logical given the fact that such process can have features previously unknown and unobvious to a person skilled in the art.

But the claimed invention according to the amended claims do not apply to the process (method) of obtaining form 6 of the crystalline compound, and, therefore, do not have features that would be unknown from the prior art.

tel.: +38 044 536–03–05
fax: +38 044 529–47–96
www.borovyk.com
info@borovyk.com

Thus, all the essential features of the invention according to claims 1-3, and the very existence of the crystalline form of the compound according to the formula S_{p-4} and reflection angles 2θ, which are inherent in the crystalline form, have been disclosed in each of the documents D1-D4, and therefore has been known from the prior art.

Moreover, the document D4 directly provides information about the value of reflection angles 2θ in the range between 5.48° and 50.04° for the claimed compound according to the formula S_{p-4}, which indicates that this feature was directly disclosed in D4 and, as such, is known in the prior art. Thus, the invention according to claims 1-3 is not new in according to Part 3 of Article 7 of the Law based on the assumption that all the essential features of the invention according to claims 1-3 has been known in the prior art, i.e. is contained in each of the documents D1-D4.

The invention according to claims 1-3 does not involve an inventive step based on the following considerations

As noted above, the reflection angle 2θ of the crystalline structure (i.e., the parameter that characterizes the specific form of the crystalline compound, form 6 according to the description of the invention) is a characteristic parameter of a polymorphic modification of any crystalline compound determined by measuring other parameters of the crystalline compound known in the prior art.

Therefore, reflection angle 2θ is obvious to a person skilled in the art and can be determined, for example, by obtaining powder of the previously known crystalline compound according to the information contained in the documents D1-D4 and by studying the powder by X-ray diffraction analysis. Obviously, the compound parameters are not changed. That is, as noted above, the polymorphic forms are a natural quality of the already known crystalline structure, that is why a polymorphic form is neither created nor invented by the inventor, but rather is the result of study of parameters of the already established active compound, in this case the crystalline compound according the formula S_{p-4} known from the documents D1-D4. Thus, the invention according to the amended claim 1 does not involve an inventive step within the meaning of Part 7 of Article 7 of the Law.

Dependent claims 2, 3, which relate to the crystalline compound according to the formula S_{p-4} with additional reflection angles 2θ, have no features other than those of the known structural formula of the compound and additional values of reflection angles 2θ, which, as established above, were found to be known from the prior art, namely the documents D1-

tel.: +38 044 536–03–05
fax: +38 044 529–47–96
www.borovyk.com
info@borovyk.com

D4. Thus, the features of dependent claims 2, 3 of the formula are known in the prior art, and additional reflection angles 2θ can be identified by studying the previously known compound by method of powder X-ray diffraction (XPRD) analysis. Thus, dependent claims 2, 3 are also not new and do not involve an inventive step within the meaning of Part 7 of Article 7 of the Law, even when combined with features of independent claim 1 of the invention.

The disclosed invention according to amended claims 1-3 may not be defined as an invention by selection. According to Section 6.5.3.3 of the Rules, *the following, in particular, meet the criterion of inventive step: an individual compound falling into the general structural formula of a group of known compounds, but not described as specially obtained and explored and at the same time demonstrating new features unknown for this group of compounds in quantitative and (or) qualitative respect (invention by selection).*

As stated by the applicant in the reply, the claimed compound is a polymorphic form of the crystalline compound of the known crystalline structure (form 6), while previously known forms 1-5 of this compound are unstable and transform into this stable form over time. Thus, it is clear that a more stable polymorphic form (form 6), compared with previous forms (forms 1-5), requires a higher melting point, since conversion of one polymorphic form into another one (i.e. instability of the form) takes place under the influence of external conditions, preferably temperature. So, the form 6 is not specifically obtained and investigated, but rather is a form of the crystalline compound, in which the known forms 1-5 are converted in any case.

Please note that the invention according to Application No. a 2012 12444 of March 31, 2011 is based on creating nucleosidephosphoramidates for their use as agents for the treatment of viral diseases, including the treatment of hepatitis C infection in mammals, that involves biological impact of nucleosidephosphoramidates as inhibitors of RNA-dependent replication of viral RNA (HCV NS5A polymerase inhibitors), Section “Field of Technology” of the description of the claimed invention. Thus, to allow a polymorphic form of the crystalline compound according to the formula S_{p-4} as an invention by selection, properties unknown for this compound must be identified, and such properties may involve previously unknown biological activity on mammals, such as bioavailability, absorbability etc. So the applicant must describe the new, unknown therapeutic effect caused by form 6 of the crystalline compound.

tel.: +38 044 536–03–05
fax: +38 044 529–47–96
www.borovyk.com
info@borovyk.com

The applicant's responce as well as the description of the disclosed invention, provide no unknown properties of form 6, which involve new biological impact or new influence on mammals, in particular in the treatment of infections caused by hepatitis C virus. So the applicant fails to provide any new unknown biological properties of the form 6, which are essential to recognize this invention as the invention by selection.

Thus, according to the applicant, the properties of the crystalline compound, i.e. its stability, are new and unobvious. However, the prior art (D1-D4) found certain compounds, similar to the claimed one, and were used for the treatment of viral infections, in particular hepatitis C, and the data presented on the biological activity of these compounds. It is quite logical that the known compounds must have stable forms to be used in the treatment of hepatitis C and to study relevant biological effects on mammals.

Therefore, the disclosed invention according to the amended claims 1-3 is not an invention by selection within the meaning of Section 6.5.3.3 of the Rules.

6. The invention according to claims 4-23 is incompliant with the patentability criteria for "novelty" and "an invention step".

The independent claim 4 and dependent claims 5-8 contain essential features such as qualitative composition, which describes a pharmaceutical composition, wherein the crystalline compound according to claims 1-3 or a combination of the said compound with other antiviral drugs is an active ingredient. The document D1 discloses a pharmaceutical composition for the treatment and/or prevention of a viral disease (claim 4, the crystalline compound 25), including those caused by hepatitis C virus (see Section "Field of invention" of the description), which contains the crystalline compound according to the formula S_{p-4} and a pharmaceutically acceptable carrier (D1, p. 710). Further, D1 (see Section "Field of invention" for description) discloses the use of the crystalline compound according to the formula S_{p-4} both separately and in combination with any antiviral agent known in the art, in particular HCV NS3 and HCV NS5A protease inhibitors (see Section "Background"). Thus, D1 discloses all the essential features of the claimed invention according to claim 4 and claims 5-8.

Further, documents D2-D4 disclose the pharmaceutical composition comprising a crystalline compound according to the formula S_{p-4} and a pharmaceutically acceptable carrier. The compound is intended for the treatment and/or prevention of diseases caused by hepatitis C virus (D3, p. 98). Therefore, D2-D4 also disclose all the essential features of the claimed invention according to claim 4 and claims 5-8.

tel.: +38 044 536–03–05
fax: +38 044 529–47–96
www.borovyk.com
info@borovyk.com

In other words, the claimed invention according to independent claim 4 and dependent claims 5-8 is not a new one.

The independent claim 4 and dependent claims 5-8 do not contain features other than those described above. Production of a pharmaceutical agent using specific polymorphic modification of the crystalline compound (form 6 characterized by deflection angles 2θ referred to in claims 1-3), even if it is more stable compared to other forms, is obvious for a person skilled in the art due to consideration of the fact of the crystalline compound. Thus, the claimed invention according to the independent claim 4 and dependent claims 5-8 clearly follows from the prior art, and therefore does not meet the requirements of the patentability criterion for “an inventive step".

Similarly, the use of the crystalline compound according to claim 1-3 for the treatment of infections caused by hepatitis C virus (independent claim 9) separate or in combination with other antiviral drugs (independent claim 10 and dependent claims 11-13) or for obtaining of the medicinal product (independent claim 14) separate or in combination with other antiviral agents (independent claim 15 and dependent claims 16-18) are also known from the D1-D4.

Therefore, the claimed invention under claims 9-18 is not a new one.

Also, these claims do not include features other than the use of the specific polymorphic modification of the crystalline compound, which form is obviously determined by a person skilled in the art, and the use of other antiviral agents known in the art. In this case, the applicant fails to state, in particular in the description, any new result, which may be caused by the combination of the claimed compound and other antiviral agents, i.e. the effect of these features for the invention was not confirmed.

Therefore, the disclosed invention according to claims 9-18 clearly follows from the prior art, and therefore is not meet patentability criteria for “an inventive step”.

The method of treatment of a human with the crystalline compound according to claims 1-3, is characterized in independent claims 19, 20 and dependent claims 21-23, and is also disclosed in the D1-D4 listed above, especially given the purpose of the invention.

Therefore, the claimed invention according to claims 19-23 is not a new one.

tel.: +38 044 536–03–05
fax: +38 044 529–47–96
www.borovyk.com
info@borovyk.com

Herewith, the said claims do not include features other than the use of the crystalline compound according to claims 1-3 alone or in combination with other known antiviral agents.

Therefore, the disclosed invention according to claims 19-23 clearly follows from the prior art, and therefore is not meet patentability criteria for “an inventive step”.

For these reasons, the all claims of the invention "Nucleosidephosphoramidates" according to Application No. a 2012 12444 of March 31, 2011 fail to meet a patentability criterion for “novelty” as defined by Part 3 of Article 7 of the Law as well as patentability criterion for “an inventive step” as defined by Part 7 of Article 7 of the Law.

With regard to the patents granted in other countries for the same invention, as referred to in applicant’s reply, please note that this may be caused by different approaches to examination of secondary (derivative) patents and their qualification as inventions by selection. In particular, the description of the claimed invention (which was also submitted in other countries) states data on the biological activity for the compound represented by formula 4, and its respective phosphorus-based diastereomers represented by formula R_{p-4} and S_{p-4} (example 33 in the description). However, these data are not a feature of form 6 of the crystalline compound only, but is rather common for a general compound and its diastereomers and therefore cannot evidence the new impact of the application of the form 6 on mammals. However, such data could be taken into account for examination in other countries, so as to prove the existence of the new properties unknown for this group of compounds, but they are false.

Furthermore, on behalf of the principal, we would like to provide the additional information, which is not related to the essence of the invention, but rather intended to explain the motivation of the objection filed by a legal entity, which is a charitable non-for-profit organization and, as such, may neither manufacture, nor distribute medicinal products and, hence, cannot compete with the applicant in Ukraine.

Hepatitis C virus (HCV) is a major global problem for public health. The virus is transmitted by direct contact with blood of an infected person. People with injuries from needles, healthcare professionals working with blood/blood products, recipients of transfusions/blood products, organ transplant recipients and injection drug users are among the risk groups for HCV infection. According to the World Health Organization, 170+ million people are chronic carriers of hepatitis B virus which can cause cancer and/or

tel.: +38 044 536–03–05
fax: +38 044 529–47–96
www.borovyk.com
info@borovyk.com

cirrhosis. Ukraine has about 1.2 million people who are chronically infected with HCV[1]. Today, about 66 thousand patients with HCV[2] require therapy, while the National Targeted Programme for Prevention, Diagnosis and Treatment of Viral Hepatitis for the Period until 2016 provides treatment to about 1,300 patients only due to high treatment costs.

In addition, there are about 231,409 people living with HIV (PLHIV) in Ukraine[3]. Given global co-infection rate is 15%, which means that about 34,000 people living with HIV are also infected with HCV. HIV affects the progression of HCV, which leads to higher rates of HCV progression in a chronic form, accelerates progression of HCV infection and contributes to high mortality. In the era of antiretroviral therapy, patients co-infected with HIV/HCV are at higher risk of morbidity and mortality compared to patients with HIV infection only and those with chronic hepatitis C alone.

HIV-infected patients still demonstrate a five times greater mortality rate compared to non-HIV-infected people, and chronic hepatitis C is associated with a 50% increase in mortality rate among patients diagnosed with AIDS.[4]

Taking into consideration the crisis related to HCV and HIV/AIDS in Ukraine's public health, it is important that people living with HCV and HIV can get access to the latest and most effective treatment methods without "evergreen" patents, which stand on their way. "Evergreen" patents allow a company to obtain "artificial" exclusive rights. This allows the company setting extremely high prices for medicines making them absolutely unaffordable for Ukrainian patients. For example, Gilead set the price for a treatment course with Sovaldi as high as EUR 41,000.00 and USD 84,000 in France and in USA, respectively.

---

1 Уніфікований клінічний протокол: вірусний гепатит С, затверджений наказом МОЗ № 233, від 02 березня 2014, стор. 7 [Unified Clinical Protocol: Viral Hepatitis C approved by MoH Order No. 233 dd. March 02, 2014, p. 7, *in Ukrainian*]
http://www.dec.gov.ua/mtd/dodatki/2014_233VirysGepatitC/2014_233_YKPMD.doc

2 http://hvstop.org/news.php?id_news=168

3 Український центр контролю за соціально небезпечними хворобами, Інститут епідеміології та інфекційних хвороб імені Л. В. Громашевського, Інформаційний бюлетень № 40, Київ, 2013, стор. 14. http://ucdc.gov.ua/uk/statystyka/informatsijni-byuleteni/vil-infektsiya [Ukrainian Center for Control over Socially Dangerous Diseases, L.V. Gromashevsky Institute for Epidemiology and Infectious Diseases, Information Bulletin No. 40, Kyiv, 2013, p. 14 *in Ukrainian*]

4 Branch AD, Van Natta ML, Vachin ML, et al. Mortality in HCV-infected patients with a diagnosis of AIDS in the era of combination anti-retroviral therapy. Clin Infect Dis 2012;55:137-144

tel.: +38 044 536–03–05
fax: +38 044 529–47–96
www.borovyk.com
info@borovyk.com

We kindly ask the expert to review the submitted materials and the information about lack of patentability criteria for the claimed invention and take them into account under examination of the claimed invention.

Enclosure:

- Power of Attorney issued by *All-Ukrainian Network of People Living with HIV/AIDS*, 1 page 1 copy

Sincerely,

Patent Attorney

Borovyk Petro

Borovyk & Partners
PATENT AND TRADEMARK ATTORNEYS

tel.: +38 044 536–03–05
fax: +38 044 529–47–96
www.borovyk.com
info@borovyk.com

Ref. No. 1174-08/15
of August 07, 2015

State Enterprise Ukrainian Intellectual Property Institute (Ukrpatent)

1 Hlazunova Str., city of Kyiv-42, 01601

Department for Examination of Applications for Inventions, Utility Models and Integrated Circuit Topographies

Division of Pharmaceutics

Expert V.V. Dovgay

Acting under the Power of Attorney from the *All-Ukrainian Network of People Living with HIV/AIDS*, we file additional materials to those sent on April 30, 2015 evidencing that the invention "Nucleosidephosphoramidates" according to Application No. a 2012 12444 of March 31, 2011 fails to meet the patentability criteria.

The additional materials take into account the applicant's reply to the Preliminary Report of Substantive Examination of May 25, 2015, Ref. No. 10779/3A/15 (hereinafter, the reply).

The said reply contains the **amended** claims of the invention "Nucleosidephosphoramidates" and explanations with regard to the invention in view of the patentability criterion for "an inventive step". In particular, the applicant states in the reply that "*The **object** to be solved by the proposed invention was to provide a new crystalline form of the compound Sp-4 with better characteristics compared with known solid forms of this compound. In this regard, **the technical result** of the claimed invention is primarily the fact of obtaining a new crystalline form, because the process of obtaining a chemical compound in a new crystalline form (i.e. selecting certain conditions of crystallization, such as temperature, solvents and others) is always unpredictable for a person skilled in the art. The prior art does not contain any motivation to obtain crystalline form 6".* Applicant's further justification of an inventive step is based on that the obtaining of crystalline form 6 is not known in the prior art and that the prior art does not disclose information on the benefits of crystalline form 6 over form 1 and other crystalline forms of compound Sp-4 referred to in the claims.

The applicant's arguments that the invention was aimed precisely at obtaining crystalline form 6 of compound Sp-4, which has advantages, compared to previously known crystalline forms, and that the technical result of the invention is the fact of obtaining crystalline form 6, are not valid.

tel.: +38 044 536–03–05
fax: +38 044 529–47–96
www.borovyk.com
info@borovyk.com

The description of the invention (p. 1, Section “Field of Technology”) states that the object of the invention is **to create nucleosidephosphoramidates for their use as agents for the treatment of viral diseases, in particular for the treatment of hepatitis C infection in mammals** that involves biological impact of nucleosidephosphoramidates as inhibitors of RNA-dependent replication of viral RNA (HCV NS5A polymerase inhibitors). The technical result of the invention is **obtaining nucleosidephosphoramidate pro-drugs with improved physicochemical and pharmacokinetic properties compared specifically to nucleosides,** which use as therapeutic agents, i.e. inhibitors of replication of hepatitis C virus in mammals, that is well known in the art (p. 6 of the description). In other words, the object of the invention is to obtain the compound and its forms, which have new features of biological impact on mammalian body compared to the well-known nucleosides.

According to the description, the invention is targeted at solvation an entirely different problem rather than obtaining of the stable crystalline form 6 of compound Sp-4. Further, the technical result of the invention is not the fact of obtaining of the stable crystalline form 6, but rather obtaining of new compounds – nucleosidephosphoramidates represented by formula 4 and their respective phosphorus-based diastereomers represented by formula Sp-4 including crystalline forms of compound Sp-4.

Therefore, the object of the invention and the technical results in according to the reply, have been defined for the first time in this reply, and it is beyond the scope of the application documents originally filed. It is also worth noting that the facts about additional tests conducted by the applicant in respect of the benefits of form 6 over the other crystalline forms of the compound, particularly over the form 1 (p. 4-7 of the reply) are not included in the description of the invention and are also beyond originally submitted application documents, and therefore cannot be taken into account under examination.

According to Section 6.5.3.2 of the Rules of Examination of the Application for Invention and Application for Utility Model, *when an inventive step is checked, it is established whether the influence of the combination of the features of the claimed invention on obtaining the technical result* ***indicated by the applicant*** *is known from the state of the art.*

Herewith this description does not include the facts **about a new biological activity** of crystalline form 6 of compound Sp-4 compared to other crystalline forms described in this invention and compared to previously known nucleosides. The facts that the crystalline form 6 of compound Sp-4 is more stable during storage compared to other crystalline forms, also described in this application, does not affect the biological activity of the compound and therefore cannot be considered in identifying the impact of a set of attributes of the invention claimed on the achievement of the technical result claimed by the applicant.

tel.: +38 044 536–03–05
fax: +38 044 529–47–96
www.borovyk.com
info@borovyk.com

Further, the International Preliminary Report on patentability of the invention of International Application PCT/US2011/030725 (attached) contains an expert's statement that the invention does not involve an inventive step, particularly according to independent claim 2 of the international application. The independent amended claim 1 contains, as stated in the applicant's reply, a set of essential features that are fully identical to those of independent claim 2 according to International Application PCT/US2011/030725, which does not involve an inventive step. The set of essential features varies by reflection angle 2θ (± 0.2°), which may be inherent to an X-ray powder diffraction (XRPD) analysis and is quite obvious to a person skilled in the art. Thus, the independent amended claim 1 does not contain any new essential features and, as such, does not involve an inventive step within the meaning of Part 7 of Article 7 of the Law "On Protection of Rights to Inventions and Utility Models". Accordingly, other claims 2-22, which are entirely based on independent claim 1, do not contain new essential features which would be unobvious and, therefore, do not involve an inventive step in according to Part 7 of Article 7 of the Law "On Protection of Rights to Inventions and Utility Models".

Please take into account that the examination of patentability of the invention is independent and is based on various approaches in studying objects of different types, including in particular polymorphic modifications of known crystalline compounds, therefore the information about granting of patents in other countries based on corresponding applications may not serve as a significant argument in favor of granting a patent in Ukraine.

We also kindly ask the expert to take into consideration the additional information provided by us in previous materials on principal's behalf, which does not apply to the essence of the invention, but is intended to explain the reasons for filing objections, namely concerning access to the latest and most effective methods of treatment for patients with hepatitis C for whom "evergreen" patents serve as a barrier.

We kindly ask the expert to further review the submitted materials and the information about lack of patentability criteria for the claimed invention and take them into account under examination.

Enclosure:

- International Preliminary Report on Patentability of Invention of Application PCT/US2011/030725, 17 pages 1 copy
- Power of Attorney issued by *All-Ukrainian Network of People Living with HIV/AIDS* (a photocopy), 1 page 1 copy

Sincerely,

tel.: +38 044 536–03–05
fax: +38 044 529–47–96
www.borovyk.com
info@borovyk.com

Patent Attorney

P.A. Borovyk

Borovyk & Partners
PATENT AND TRADEMARK ATTORNEYS

tel.: +38 044 536–03–05
fax: +38 044 529–47–96
www.borovyk.com
info@borovyk.com

Ref. No. 0903-06/16
of June 13, 2016

State Enterprise Ukrainian Intellectual Property Institute (Ukrpatent)

1 Hlazunova Str., city of Kyiv-42, 01601

Department for Examination of Applications for Inventions, Utility Models and Integrated Circuit Topographies

Division of Pharmaceutics

Expert V.V. Dovgay

RE: *Preliminary Report of Substantive Examination of September 25, 2015*

Application No. a201212444

Title of the invention: Nucleosidephosphoramidates

Applicant: GILEAD PHARMASSET LLC (US)

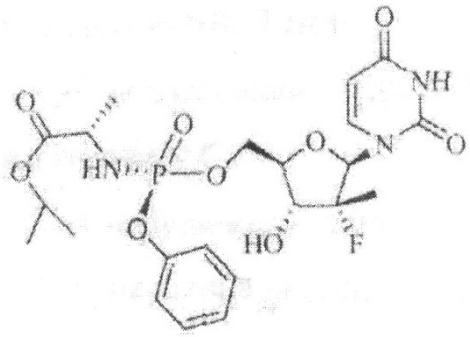
Date of filing: March 31, 2011

Acting under the Power of Attorney from the *All-Ukrainian Network of People Living with HIV/AIDS*, we file for your kind attention additional materials to those sent on August 07, 2015 evidencing that the invention “Nucleosidephosphoramidates” according to Application No. a 2012 12444 of March 31, 2011 fails to meet the patentability criteria in according to Article 7 of the Law of Ukraine "On Protection of Rights to Inventions and Utility Models".

The additional materials take into account the applicant’s reply to the Preliminary Report of Substantive Examination of September 25, 2015, Ref. No. 20375/3A/15 (hereinafter, the reply).

The said reply contains the amended claims and explanations with regard to compliance of the invention with the patentability criterion for “an inventive step” according to the amended claims. In accordance with the amended claims, the subject of the invention according to claim 1 is a crystalline compound (S)-isopropyl 2-(((SR, 3R, 4R, 5R)-5-(2,4-dioxo-3,4-dihydropyrimidine-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)metoxy)(phenoxy) phosphoryl)amino)propanoate represented by formula Sp-4:

tel.: +38 044 536–03–05
fax: +38 044 529–47–96
www.borovyk.com
info@borovyk.com



,

S_{p-4}

with the value of the reflection angle of 2θ (± 0.2°) on the X-ray powder diffractogram (XRPD) 6,08, 8,2, 10,38, 12,17, 12,7, 13,73, 14,1, 15,91, 16,83, 17,17, 17,66, 17,95, 18,79, 19,1, 19,41, 19,8, 20,11, 20,82, 21,81, 22,03, 23,03, 23,26, 23,64, 23,89 and 24,73. Other independent and dependent claims are based on the crystalline compound according to claim 1 of the invention, in particular concern its use in the treatment of hepatitis C or production of drugs based on this compound. In accordance with the information from previous oppositions with regard to compatibility of the invention according to Application No. a 2012 12444 with patentability criteria, this compound is a crystalline form 6 of sofosbuvir, a nucleotide analogue, used in combination with other medicinal products for the treatment of hepatitis C (hereinafter referred to as form 6 of sofosbuvir).

Claim 1 of WO 2008/121634 A2 published on October 09, 2008 (D1) describes compounds, in particular those presented by formula Sp-4 (sofosbuvir), which has the form of "… hydrates, solvates and **crystalline form**" (page 698, para. 1). Therefore, compounds according to claim 1 of WO 2008/121634 A2 refer to all and any of the known crystalline forms of sofosbuvir, including form 6 of the crystalline compound.

The applicant points to relative stability of the form 6 compared to other forms 1-5 of this crystalline compound. However, form 6, taking into consideration its previous disclosure in D1 and its characteristics, in particular results of X-ray diffraction (XRD) analysis, differential scanning calorimetry and thermogravimetric (DSC/TGA) analysis and others, which are specific to the compound produced with the method described in WO 2008/121634 A2. Therefore, WO 2008/121634 A2 discloses the general method for obtaining many compositions including composition 25 (sofosbuvir) from the table on p. 695 of WO 2008/121634 A2. The method includes purification by high-performance gas-liquid chromatography (HPLC) using acetonitrile, wherein water is used as a mobile phase followed by separation of the composition by removing acetonitrile and water under low

tel.: +38 044 536–03–05
fax: +38 044 529–47–96
www.borovyk.com
info@borovyk.com

pressure. Then the pure compound is obtained by evaporating the solution under low pressure.

This general method is also described in Application US 2007/0042988 A1 (D2) and in the Sofia MJ et al “Discovery of a β-d-2'-deoxy-2'-α-fluoro-2'-β-C-methyluridine nucleotide prodrug (PSI-7977) for the treatment of hepatitis C virus”, Journal of Medicinal Chemistry (**D4**). Since form 6 of sofosbuvir is obtained by solving compound sofosbuvir in water, one may assume that the described methods for obtaining purified sofosbuvir by evaporating acetonitrile and water are obvious for obtaining form 6 as a crystalline form of the purified material.

Other methods for purifying sofosbuvir by crystallization include re-crystallization. WO 2010/135569 (D3) states that crystalline form similar to form 6 is obtained by re-crystallization from isopropanol/heptane based on the melting point. This corresponds to the methods for obtaining sofosbuvir described in earlier applications, thus form 6 of sofosbuvir may be obtained obviously, though it is not directly described in earlier applications.

Reflection angles 2θ (± 0.2°) on X-ray powder diffractogram (XRPD) as disclosed in the claims, are an inherent property of the crystalline form of the compound as a parameter of any form of the compound. The parameters of certain properties, which are inherent to the already known form of the compound, may not be unobvious due to the fact that they are merely measured parameters of certain property of the known compound. If such invention may be recognized as unobvious, then any parameters of already known compounds, not described directly in the prior art, may also be claimed as an invention and may be recognized as unobvious, in particular the known compounds, which are additionally described using their common physical properties, such as density, internal pressure, boiling point or crystallization of the compound, which are their typical and unchangeable property.

Therefore, form 6 of sofosbuvir is obvious according to the disclosure of crystalline forms of sofosbuvir in WO 2008/121634 A2 as a property of the already known compound, and may not be recognized as unobvious, even if a number of reflection angles 2θ (± 0.2°) on the X-ray powder diffractogram (XRPD), a common parameter of this known property, is taken into account.

The crystalline form of the known compound may be obtained by a chemist without excessive effort by fulfilling a large number of various, but standard conditions, including formation of crystals by evaporating solution, using various solutions for obtaining crystalline forms, hydrates, solvates and anhydrous forms of medicines. This is usual activity of a person skilled in the art and is not a result of human’s intellectual activity and

tel.: +38 044 536–03–05
fax: +38 044 529–47–96
www.borovyk.com
info@borovyk.com

is not an invention in according to the Article 1 of the Law of Ukraine “On Protection of Rights to Inventions and Utility Models”.

Such application may relate to the establishment of a certain standard for production of the compound 6 (claim 1), which will describe proved identification technologies for a certain crystalline form of the compound (screening).

The use of water for obtaining possible crystalline forms and hydrates of a medicinal compound is known in essence from the prior art and is compulsory for obtaining crystalline forms when medicines are invented. Water is essentially present in such chemical processes as a result of contact of a compound molecule with air (humidity) and during storage of active pharmaceutical ingredients and final dosage forms of medicines. Therefore, use of water for obtaining form 6 of sofosbuvir is obvious for a chemist.

Furthermore, enhancing stability of the compound itself is not sufficient to satisfy the criterion for an inventive step as defined by Part 7 of Article 7 of the Law of Ukraine “On Protection of Rights to Inventions and Utility Models”, because such result is obvious and is expected when the compound is produced.

With regard to compositions using sofosbuvir (claims 2-6) claimed in the invention, it should be noted that pharmaceutical compositions, which contain sofosbuvir for the treatment of viral diseases including hepatitis C as such (as monotherapy) or in combination with other known antiviral medicines are obvious in view of the prior art. Therefore, the use of the most stable polymorphic form of the composition is, in most cases, expected and essential for testing medicines and preparation of their dosage forms. This is especially important for sofosbuvir, taking into consideration its high solubility in water and sufficient absorption parameters and crystal distribution by size. Lack of stability in other crystalline forms 1-5, as claimed by the applicant in the reply to the Preliminary Report, shows that the choice of form 6 for further pharmaceutical research and creation of the pharmaceutical composition is expected and is obvious.

With regard to other claimed subjects of the invention, i.e. crystalline compounds of sofosbuvir according to form 6 (claims 7-11) and use of crystalline compound of sofosbuvir according to form 6 for obtaining a medicines (claims 12-16), the method of treatment of a human infected with hepatitis C virus (claims 17-21), tablets (claims 22-25) and its use (claims 26-30) for the treatment of infection as monotherapy or in combination with other known antiviral medicines, it should be noted that the mentioned above inventions are also obvious in view of the prior art, taking into consideration that antiviral activity of sofosbuvir and its analogues, in particular crystalline form 6, is known from the prior art.

Therefore, the inventions according to the amended claims, even though taking into account the arguments presented in the reply in favor of unobvious nature of the claimed

tel.: +38 044 536–03–05
fax: +38 044 529–47–96
www.borovyk.com
info@borovyk.com

inventions, fail to meet the patentability criterion for “an inventive step” as defined by Part 7 of Article 7 of the Law of Ukraine “On Protection of Rights to Inventions and Utility Models”.

We kindly ask the expert to review the submitted materials and the information and to take them into account under examination.

Enclosure:

- a photocopy of the Power of Attorney issued by *All-Ukrainian Network of People Living with HIV/AIDS* (a photocopy), 1 page 1 copy

Sincerely,

Patent Attorney

Borovyk Petro