PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA220

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA210 (second sheet)

FOR FURTHER ACTION
See paragraph 2 below

Applicant's or agent's file reference
see form PCT/ISA220

International application No.
PCT/US2015/051055

International filing date (day/month/year)
18.09.2015

Priority date (day/month/year)
19.09.2014

International Patent Classification (IPC) or both national classification and IPC
INV. C07D401/12 A61P35/00 A61K31/4704 A61K31/4709 C07D471/04 C07D401/14

Applicant
FORMA THERAPEUTICS, INC.

1. This opinion contains indications relating to the following items:

☐ Box No. I  Basis of the opinion
☐ Box No. II  Priority
☐ Box No. III  Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐ Box No. IV  Lack of unity of invention
☒ Box No. V  Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
☐ Box No. VI  Certain documents cited
☐ Box No. VII  Certain defects in the international application
☒ Box No. VIII  Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority (“IPEA”) except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA220.

Name and mailing address of the ISA:
European Patent Office
D-80296 Munich
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Fax: +49 89 2399 - 4465

Date of completion of this opinion
see form PCT/ISA210

Authorized Officer
Fanni, Stefano
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Form PCT/ISA237 (Cover Sheet) (January 2015)
1. With regard to the language, this opinion has been established on the basis of:
   ☑ the international application in the language in which it was filed.
   ☐ a translation of the international application into, which is the language of a translation furnished for the
     purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the rectification of an obvious mistake authorized
   by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this
   opinion has been established on the basis of a sequence listing:
   a. ☐ forming part of the international application as filed:
      ☐ in the form of an Annex C:ST.25 text file.
      ☐ on paper or in the form of an image file.
   b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of
      international search only in the form of an Annex C:ST.25 text file.
   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
      ☐ in the form of an Annex C:ST.25 text file (Rule 13ter.1(a)).
      ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section
        713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished,
   the required statements that the information in the subsequent or additional copies is identical to that
   forming part of the application as filed or does not go beyond the application as filed, as appropriate, were
   furnished.

5. Additional comments:
Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)  
Yes: Claims  1-34  
No: Claims

Inventive step (IS)  
Yes: Claims  1-34  
No: Claims

Industrial applicability (IA)  
Yes: Claims  1-34  
No: Claims

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet
ITEM V

With regard to claims 28-32 and 34, the patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

The present subject matter is directed towards compounds of formula:

![Chemical Structure (I)](image)

as inhibitors of mutant isocitrate dehydrogenase (mt-IDH) proteins with neomorphic activity, useful in the treatment of e.g. cancers.

Reference is made to the following documents:

<table>
<thead>
<tr>
<th>Document</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1</td>
<td>WO 2013/102431 A1</td>
</tr>
<tr>
<td>D2</td>
<td>WO 2014/141153 A1</td>
</tr>
<tr>
<td>D3</td>
<td>WO 2011/072174 A</td>
</tr>
</tbody>
</table>

NOVELTY (Article 33(2) PCT)

The present subject matter differs from D1-D3 on account of the present bicyclic, N-containing core structure.

INVENTIVE STEP (Article 33(3) PCT)

D2 may be considered the closest prior art and discloses compound of formula:

![Chemical Structure (II)](image)

which are inhibitors of mutant IDH proteins having a neomorphic activity and are useful in the treatment of e.g. cancer.
The problem to be solved by the present subject matter vis-à-vis D2 is considered to
be the provision of further inhibitors of mutant IDH proteins.

As a solution to this problem, the present application proposes the compound of
formula I above, which is mainly characterised by a 3-(substituted)aminomethyl-2-
isooquinolone core structure.

The problem appears to be solved (cf page 108, table 6).

The question to be addressed when assessing the inventive step of the present
subject matter appears to be whether the skilled person would be motivated to replace
the pyrimidine core-structure of D2 with a bicyclic, N-containing core structure, in
order to solve the given problem.

Inhibitors of mutant IDH proteins are disclosed also in D1 and D3. However, neither
D1 nor D3 appear to disclose or even suggest that compounds based upon a N-
containing, bicyclic structure may provide a solution to the given problem.

The novel part of the present subject matter is therefore based upon an inventive step.

ITEM VIII

The term "prodrug" is a functional expression, i.e. an expression attempting to define
the subject matter in terms of a desired property instead of indicating precisely the
technical measures (i.e. in this case the chemical structures) specifically designed to
solve the problem.

Similarly, the term "isomers" encompasses compounds (e.g. positional isomers) which
may have a quite different structure compared to the structure of compound of formula
(I) as defined above.

The two expression "prodrugs" and "isomers" as used in the claims do not fulfil
therefore the requirements of Article 6 PCT.