PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2019/039156	26.06.2019	27.06.2018

International Patent Classification (IPC) or both national classification and IPC
INV. C07D401/14 A61P25/28 A61K31/444

Applicant
BIOGEN MA 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 43*bis*.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 notifed the International Bureau under Rule 66.1*bis*(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/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Weisbrod, Thomas Telephone No. +49 89 2399-0

Box No. I Basis of the opinion

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 43*bis*.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 13*ter*.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 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.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 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-20
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-20
Industrial applicability (IA)	Yes:	Claims	1-20
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

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

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Claims 19-20 relate to a subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv)/67.1(iv) PCT. 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 a first or further medical treatment.

2 Reference is made to the following documents.

D1 LOVERING ET AL. EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY 2017, 145, 606-621, XP055611432.

D2 US 2011/009410 A1, 13 January 2011.

D3 WO 2018/151830 A1, 23 August 2018.

Under the assumption that the priority is valid, the P-document D3 is not considered as prior art under Rule 64.1 PCT.

3 Novelty

D1 and D2 disclose ASK1 inhibitors (cf. D1, pages 612-614, tables 1-3: compounds 18, 19, 20, 21, 25, 26, 27, 31, 36, 38, 45; D2, claim 1 wherein R1 can be alkyl, X1 = X2 = X6 can be N, X5 can be CR4, R4 can be alkoxy, and R3 is a ring). The present claims are novel over D2 on account of the pyridin ring nitrogen next to the group OR2 in the compounds (I). The compounds of D1 have a benzene rather than a pyridine ring in the coresponding position. The present claims are novel over D2 on account of R1 in the compounds (I); which does not comprise the ring values of the corresponding variable R3 of D2.

4 Inventive step

The application describes the synthesis of certain compounds (I) and shows in-

ter alia that they inhibit ASK1 (cf. page 35, line 29 to page 36, line 2; page 36, line 27 to page 37, line 4). Accordingly, they are potentially useful for the indications of claim 18.

D1 is the closest prior art, because it shows a series of ALK1 inhibitors from whicb the present compounds (I) differ merely in having a pyridine nitrogen rather than ring CH group next to the methoxy substituent (cf. D2, compounds 18, 19, 20, 21, 25, 26, 27, 31, 36, 38, 45). In view of D1 the problem to be solved lies in the provision of further ALK1 inhibitors. D2 teaches already that a nitrogen atom in the position of the left ring in present formula (I) is compatible with the desired activity (cf. D2, claim 1 when X6 = N). Hence, in view of D1 in combination with D2, the present compounds (I) are merely obvious alternatives of the compounds of D1. In the absence of any substantiated unexpected effect of the present compounds (I) in comaprison with the structurally most similar example(s) of D1, no inventive step would be acknosledged for the present claims 1-20.

Re Item VI

Certain documents cited

D3 discloses ASK1 inhibitors which overlap with the present compounds (I) (cf. claim 1 when Y2 = N and R63 = OR63) but D3 does not specifically disclose a present compound (I). The most similar examples of D3 comprise on the left side an N-methyl-pyridin-2-one ring rather than a 2-(R2O)-substituted pyridine ring. Hence, the subject-matter of the present claims is a novel selection of D3, with the unsubstituted pyridine ring nitrogen atom as novel technical feature.

Re Item VII

Certain defects in the international application

It would appear that D1-D2 are not cited in the description (Rule 5.1(a)(ii) PCT).

Re Item VIII

Certain observations on the international application

Claims 17 and 19 do not comply with Article 6 PCT, because the therapeutic application is functionally defined by a mechanism of action which does not allow any practical application in the form of a defined, real treatment of a pathological condition. This objection may be overcome by introducing in the claims a list of pathological conditions cited in the application.

The category of dependent claim 18 lacks clarity (Article 6 PCT). This objection may be overcome by replacing the phrase "the compound of claim 17" with "the compound for use of claim 17".

The claims like clauses at pages 40-35 render the claims unclear (Article 6 PCT).