

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

|                                                                                                                                                         |                                                          |                                                                                                                          |  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|--|
| To:<br><br><br><br><br><br><br><br><br><br>see form PCT/ISA/220                                                                                         |                                                          | <b>PCT</b><br><br><br><b>WRITTEN OPINION OF THE<br/>INTERNATIONAL SEARCHING AUTHORITY</b><br>(PCT Rule 43 <i>bis</i> .1) |  |
|                                                                                                                                                         |                                                          |                                                                                                                          |  |
|                                                                                                                                                         |                                                          | Date of mailing<br>(day/month/year) see form PCT/ISA/210 (second sheet)                                                  |  |
| Applicant's or agent's file reference<br>see form PCT/ISA/220                                                                                           |                                                          | <b>FOR FURTHER ACTION</b><br>See paragraph 2 below                                                                       |  |
| International application No.<br>PCT/IB2015/055597                                                                                                      | International filing date (day/month/year)<br>23.07.2015 | Priority date (day/month/year)<br>06.08.2014                                                                             |  |
| International Patent Classification (IPC) or both national classification and IPC<br>INV. C07D487/04 A61K31/5025 A61P9/00 A61P11/00 A61P25/00 A61P27/02 |                                                          |                                                                                                                          |  |
| Applicant<br>PFIZER 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 notified 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:<br><br><br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0<br>Fax: +49 89 2399 - 4465 | Date of completion of<br>this opinion<br><br>see form<br>PCT/ISA/210 | Authorized Officer<br><br>Beligny, Samuel<br><br>Telephone No. +49 89 2399-0 |  |
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**Box No. I Basis of the opinion**

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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:

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**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**

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1. Statement

|                               |             |             |
|-------------------------------|-------------|-------------|
| Novelty (N)                   | Yes: Claims | <u>1-25</u> |
|                               | No: Claims  |             |
| Inventive step (IS)           | Yes: Claims | <u>1-25</u> |
|                               | No: Claims  |             |
| Industrial applicability (IA) | Yes: Claims | <u>1-25</u> |
|                               | No: Claims  |             |

2. Citations and explanations

see separate sheet

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**Box No. VII Certain defects in the international application**

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

see separate sheet

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**Box No. VIII Certain observations on the international application**

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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**

Reference is made to the following documents:

- D1        DONNELL A F ET AL: "Identification of pyridazino[4,5-*b*]indolizines as selective PDE4B inhibitors",  
BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON,  
AMSTERDAM, NL,  
vol. 20, no. 7, 13 February 2010 (2010-02-13), pages 2163-2167,  
XP026971036,  
ISSN: 0960-894X  
[retrieved on 2010-02-13]  
cited in the application
- D2        NAGANUMA K ET AL: "Discovery of selective PDE4B inhibitors",  
BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON,  
AMSTERDAM, NL,  
vol. 19, no. 12, 15 June 2009 (2009-06-15), pages 3174-3176,  
XP026138493,  
ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2009.04.121  
[retrieved on 2009-05-03]  
cited in the application
- D3        WO 2011/051342 A1 (JANSSEN PHARMACEUTICA NV [BE]; PASTOR-  
FERNANDEZ JOAQUIN [ES]; BARTOLOM) 5 May 2011 (2011-05-05)

*Novelty*

1. D1 discloses pyridazino[4,5-*b*]indolizine derivatives as selective PDE4B inhibitors over PDE4D (see D1, abstract, and compounds 1, 7a-7f, 8a-8g, 13a-13d, 14a-14h, 15, 16 in Tables 1-5). The compounds of the present application differ from the compounds of D1 in that they are based on an imidazo[1,2-*b*]pyridazine core rather than on a pyridazino[4,5-*b*]indolizine core.

D2 discloses pyrimidine based selective PDE4B inhibitors over PDE4D (see D2, abstract, and compounds 1-35 in tables 1-4). The compounds of the present application differ from the compounds of D2 in that they are based on an imidazo[1,2-*b*]pyridazine core rather than on a pyrimidine core.

D3 discloses imidazo[1,2-*b*]pyridazine based PDE10 inhibitors (see p. 1, l. 5-12, and claim 1). The compounds of the present application differ from the compounds of D3 in that the substituent at the 2-position of the imidazo[1,2-*b*]pyridazine core is a carboxamide derivative rather than hydrogen, alkyl, trifluoromethyl, cycloalkyl or alkoxy (see definition of the corresponding R<sup>2</sup> substituent in claim 1 of D3).

Thus the compounds of the present application are new, and the subject-matter of claims 1-25 is new (Article 33(2) PCT).

### *Inventive Step*

2. D3 is regarded as being the prior art closest to the subject-matter of the present application.

The problem to be solved by the present invention may be regarded as the provision of further PDE4B inhibitors selective over PDE4D.

The solution to this problem proposed in claim 1 of the present application is considered as involving an inventive step (Article 33(3) PCT) for the following reasons:

The data on p. 88-105 show that the compounds of the present application have the desired activity and selectivity.

Moreover, even though D3 shows that imidazo[1,2-*b*]pyridazine can be useful in targeting phosphodiesterases such as PDE10, the prior art does not suggest that imidazo[1,2-*b*]pyridazine bearing a carboxamide at the 2-position and a ring directly attached, or attached via an alkyl chain at the 3-position as in the present application, could be selective PDE4B inhibitors over PDE4D.

The compounds of the present application are thus considered to be inventive, and an inventive step is acknowledged to the subject-matter of claims 1-25 (Article 33(3) PCT).

### *Industrial Application*

3. The subject-matter of claims 1-25 can find industrial applicability in the field of pharmacy, thus meets the requirements of Article 33(4) PCT.

**Re Item VII**

**Certain defects in the international application**

4. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in D3 is not mentioned in the description, nor is this document identified therein.

**Re Item VIII**

**Certain observations on the international application**

5.1 Each of independent claims 20-23, concerning specific compounds of the present application, comprises all the features of claim 1 and are therefore not appropriately formulated as claims dependent on the latter (Rule 6.4 PCT).

5.2 Claim 25 relate to 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 use in a first or further medical treatment.

5.3 It should be noted that in the Regional phase, this Authority does not accept references to methods of treatment, to the metabolites or prodrugs of the claimed compounds or the expression "incorporated by reference" in the description.