PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 915-WO	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/EP2020/050798	International filing date *(day/month/year)* 14 January 2020 (14.01.2020)	Priority date *(day/month/year)* 15 January 2019 (15.01.2019)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant UNION THERAPEUTICS A/S		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	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 Article 35(2) with regard to novelty, inventive step or 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

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 16 June 2021 (16.06.2021)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Nora Lindner e-mail pct.team5@wipo.int

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/EP2020/050798	14.01.2020	15.01.2019

International Patent Classification (IPC) or both national classification and IPC
INV. A61K9/20 A61K9/28 A61K31/443

Applicant
LEO PHARMA A/S

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 P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	see form PCT/ISA/210	Muller, Sophie Telephone No. +31 70 340-0

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2020/050798

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	8, 9, 12, 15, 18, 19
	No:	Claims	1-7, 10, 11, 13, 14, 16, 17
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-19
Industrial applicability (IA)	Yes:	Claims	1-19
	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

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

1. Cited Documents

The following documents are referred to in this communication:

D1 US 2005/186276 A1 (BERCHIELLI ALFRED [US] ET AL) 25 August 2005 (2005-08-25)

D2 US 2007/104792 A1 (JENKINS SCOTT [US]) 10 May 2007 (2007-05-10)

D3 WO 2011/160632 A1 (LEO PHARMA AS [DK]; NIELSEN SIMON FELDBAEK [DK]) 29 December 2011 (2011-12-29)cited in the application

2. Novelty

Example 4 of D1 discloses a long duration matrix tablet comprising: 2% w/w PDE 4D inhibitor, 35% w/w Methocel K4M CR as matrix polymer, 62% w/w lactose as diluent and 1% w/w Mg stearate as lubricant.

The subject-matter of claims 1-7,10,11,13,16,17 is therefore not new in view of example 4 of D1 (Article 33(2) PCT)

D2 discloses (see paragraph [0129] - paragraph [0130] on page 12; paragraph [0140] - paragraph [0142] and claims 1-20) a tablet formulation comprising: the PDE5 inhibitor Tadalafil, Hypromellose, Lactose monohydrate, Silicified Microcrystalline cellulose, Magnesium stearate.

The subject-matter of claims 1-7,10,11,16,17 is therefore not new in view of D2 (Article 33(2) PCT).

D3 discloses (see page 12, line 24 - page 13, line 10; example 8 on page 28 - page 30 and the claims) the synthesis of compound of formula (I) of claim 14. Formulations comprising compound of formula (I) suitable for oral administration may be in form of tablets and may comprise HPMC, lactose, magnesium stearate,...

The subject-matter of claims 1 and 14 is therefore not new in view of D3 (Article 33(2) PCT).

3. Inventive Step

3.1. The subject-matter of claims 1-7,10,11,13,14,16,17 is not new and can therefore not involve an inventive step in the meaning of Article 33(3) PCT.

3.2. Dependent claims 8,9,12 are not considered inventive with respect to D1 and D2, insofar as they do not appear to comprise any technical features which lead to a non-obvious solution of a technical problem (Article 33(3) PCT).

3.3. From common general knowledge it is known that the systematic investigation of a compound to determine whether it is prone to polymorphism is routine practice in the pharmaceutical industry. Therefore dependent claim 15 is not considered inventive with respect to D3 (Article 33(3) PCT).

3.4. Inventive step of claims 18 and 19 is assessed using the following Problem-Solution-Approach reasoning:

D3 is considered as being the closest prior art.

D3 discloses (see page 12, line 24 - page 13, line 10; example 8 on page 28 - page 30 and the claims) the synthesis of compound of formula (I). Formulations comprising compound of formula (I) suitable for oral administration may be in form of tablets and may comprise HPMC, lactose, magnesium stearate,...

Claims 18 and 19 differ from D3 in some specific modified release tablet formulations comprising hypromellose (HPMC), lactose monohydrate, colloidal silicon dioxide and magnesium stearate.

The effect of selecting these excipients lies in the obtention of a modified release tablet formulation.

The objective technical problem may therefore be formulated as how to provide a modified release formulation of compound (I).

As can be seen from e.g example 4 of D1, using HPMC, lactose and magnesium stearate for making a modified release tablet formulation comprising a PDE inhibitor is well known.

Starting from D3 and looking at the modified release formulations of e.g example 4 of D1, the skilled person seeking to provide a modified release tablet formulation of compound (I) would have: a) used the excipients HPMC, lactose monohydrate, Magnesium stearate and b) by using his common knowledge he would also have used the glidant colloidal silicon dioxide in the claimed amounts.

Claims 18 and 19 are therefore not regarded as being inventive in view of D3 in combination with D1 (Article 33(3) PCT).

4. Industrial applicability

Claims 1-19 satisfy the criterion of industrial applicability set forth in Article 33(4) PCT.

Re Item VIII

Certain observations on the international application

Terms like "hypromellose 2910", "hypromellose 2208" used in claim 3 appear to be registered trademarks: they have no precise meaning as it is not internationally accepted as standard descriptive terms, thereby rendering the definition of the subject-matter of said claim unclear, Article 6 PCT.