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/US2022/081334	12.12.2022	13.12.2021

International Patent Classification (IPC) or both national classification and IPC
INV. C12N15/113 A61K31/713 ADD. A61P25/28

Applicant
ELI LILLY AND COMPANY

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	Andres, Serge Telephone No. -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.

   b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)),

      ☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.

4. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established to the extent that a meaningful opinion could be formed without a WIPO Standard ST.26 compliant sequence listing.

5. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 1-45(partially)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 1-45(partially)

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing complying with WIPO Standard ST.26, and such listing was not available to the International Searching Authority in the form, language and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a).

☐ See Supplemental Box for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:

   ☐ paid additional fees

   ☐ paid additional fees under protest and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☒ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-45(partially)

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	2, 3, 9-18, 25-30(all partially)
	No:	Claims	1, 4-8, 19-24, 31-45(all partially)
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-45(partially)
Industrial applicability (IA)	Yes:	Claims	1-45(partially)
	No:	Claims	

2. Citations and explanations

see separate sheet

Prior art

Reference is made to the following documents:

D1	WO 2021/188626 A1 (23 September 2021)
D2	SIGNAL TRANSDUCTION AND TARGETED THERAPY, vol. 5, Art. 101, (December 2020), pages 1-25 [XP055801687] cited in the application
D3	WO 2004/058940 A2 (15 July 2004)
D4	WO 2021/202511 A2 (7 October 2021)
D5	WO 2016/151523 A1 (29 September 2016)

Item IV.

Lack of unity of invention

1 The use of chemically modified interfering RNAs, targeting MAPT, for treating tauopathies has been well documented in the prior art :

1.1 Document D1 discloses various chemicallydified interfering RNAs which target MAPT in different regions (see e.g. [014]; [0171]-[0175]; [0196]; [0201]-[0207]; Tables; Examples; Claims), for use in the treatment of tauopathies such as Alzheimer's disease (AD), progressive supranuclear palsy (PSP) or frontotemporal dementia (FTD) (see e.g. [0204]; [0508]; Claims).

1.2 Similarly does document D3 also disclose chemically modified dsRNAs for silencing MAPT expression in the treatment of tauopathies (see e.g. page 18, lines 6-16; page 81, line 17 - page 82, line 3; page 92, lines 24-26).

1.3 Document D4 also discloses inhibition of MAPT expression with dsRNAs (see page 2, lines 6-24; pages 8-14; page 53, 1st §; pages 61 and 62; page 71, last §; page 77; Tables 3-8; Claims).

1.4 Document D5 discloses interfering RNAs targeting exon 10 of MAPT for treating neurodegenerative diseases ('Summary of the Invention'; § bridging pages 6 and 7; page 10, lines 25-35; Examples; Claims).

2 In view of said prior art, the problem underlying the application can be defined as the provision of further dsRNAs targeting MAPT for use in the treatment of tauopathies. The solutions proposed in underlying application can be summarised as the interfering RNAs targeted to the various regions of MAPT as defined in Table 1.

3 Due to the fact that the use of chemically modified interfering RNAs, targeting MAPT, for treating tauopathies is known in the prior art, due to the essential difference in primary structure of the different groups of solutions, and due to the fact that no other technical features, especially not the chemical modification patterns (see D1, D2, D4), can be distinguished which, in the light of the prior art could be regarded as special technical features, the ISA is of the opinion that there is no single inventive concept underlying the plurality of claimed inventions of the present application in the sense of rule 13.1 PCT. Consequently there is lack of unity.

4 The various compounds claimed have been tentatively regrouped according to the target regions of MAPT, as defined from the data of Table 1.

5 As no additional search fee has been (timely) paid, the present opinion is restricted to the searched subject, i.e. the subject-matter of present claims 1-45, as far as concerning the MAPT target region defined by nucleotides 1066-1075 in Table 1.

Item V.

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

6 Concerning claims 32-37, it is noted that 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.

7 NOVELTY (Art. 33(2) PCT)

7.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1, 4-8, 19-24, 31-45 is not new in the sense of Article 33(2) PCT.

7.2 Indeed, documents D1 and D3, of which the teachings have already been summarised above (see points 1.1 and 1.2), describe interfering RNAs targeting MAPT in the claimed region (see D1: page 158, MAPT_2034; page 175, MAPT_2027 to _2038; D3: page 92).

8 INVENTIVE STEP (Art. 33(3) PCT)

8.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-45 does not involve an inventive step in the sense of Article 33(3) PCT.

8.2 The document D1 is regarded as being the closest prior art to the subject-matter of said claims, and its disclosure has already been summarised above (see points 1.1 and 7.2).

8.3 The subject-matter of the claims therefore differs from this known teaching in the specific chemical patterns claimed. The application does not associate any special technical effect to said patterns. The problem to be solved by the present invention may therefore be regarded as the provision of further chemically modified interfering RNAs, targeting MAPT in the region defined ny nucleotides 1066-1075, for use in the treatment of tauopathies.

8.4 The solution proposed in the claims of the present application cannot be considered as involving an inventive step (Article 33(3) PCT). Indeed, some of the specific modifications have already been suggested in e.g. documents D1 or D4, and the various patterns have been shown in document D2 to be applicable to therapeutically active interfering RNAs. Hence, the various embodiments present in the claims have to be seen as straightforward and obvious alternatives to those disclosed in D1.

9 INDUSTRIAL APPLICABILITY (Art. 33(4) PCT)

The subject-matter of claims 1-45 is considered as being industrially applicable in the sense of Art. 33(4) PCT.