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Date	14.02.2023
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Reference P075467EP	Application No./Patent No. 19827230.4 - 1111 / 3814503 PCT/US2019039558
Applicant/Proprietor Ionis Pharmaceuticals, Inc.	

Communication

The extended European search report is enclosed.

The extended European search report includes, pursuant to Rule 62 EPC, the supplementary European search report (Art. 153(7) EPC) and the European search opinion.

Copies of documents cited in the European search report are attached.

☒ 0 additional set(s) of copies of such documents is (are) enclosed as well.

Refund of the search fee

If applicable under Article 9 Rules relating to fees, a separate communication from the Receiving Section on the refund of the search fee will be sent later.

Should you wish to further prosecute this application in the examination phase, your attention is drawn to the provisions of Rule 70a EPC. An invitation to respond to the extended European search report will be issued shortly (R. 70(2) EPC).



SUPPLEMENTARY EUROPEAN SEARCH REPORT

Application Number
EP 19 82 7230

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
A	HIEN TRAN ZHAO ET AL: "LRRK2 Antisense Oligonucleotides Ameliorate alpha-Synuclein Inclusion Formation in a Parkinson's Disease Mouse Model", MOLECULAR THERAPY-NUCLEIC ACIDS, vol. 8, 1 September 2017 (2017-09-01), pages 508-519, XP055552829, US ISSN: 2162-2531, DOI: 10.1016/j.omtn.2017.08.002 * page 509, left-hand column, paragraph 3 - page 512, right-hand column, paragraph 1 * * table 1 * * figures 1, 2 * -----	1-14	INV. C12N15/113 A61K31/7115 A61K31/712 A61K31/7125
			TECHNICAL FIELDS SEARCHED (IPC)
			C12N A61P
The supplementary search report has been based on the last set of claims valid and available at the start of the search.			
Place of search		Date of completion of the search	Examiner
The Hague		6 February 2023	Solyga-Zurek, A
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			

Information on Search Strategy - Pilot phase (see OJ 2015, A86)

The type of information contained in this sheet may change during the pilot for improving the usefulness of this new service.

Application Number

EP 19 82 7230

TITLE: COMPOUNDS AND METHODS FOR REDUCING LRRK2 EXPRESSION**APPLICANT: Ionis Pharmaceuticals, Inc.****IPC CLASSIFICATION: C12N15/113, A61K31/7115, A61K31/712, A61K31/7125****EXAMINER: Solyga-Zurek, A****CONSULTED DATABASES: BIOSIS, DOSYS, EBI, EMBASE, EPODOC, GOOGLE, MEDLINE, NPL, TXT+, WPI****CLASSIFICATION SYMBOLS DEFINING EXTENT OF THE SEARCH:****IPC:****CPC: C12N15/1137, A61P25/16****FI/F-TERMS:****KEYWORDS OR OTHER ELEMENTS FEATURING THE INVENTION:**

The subject matter of the invention is an antisense gapmer targeting the LRRK2 transcript, and the gapmer for use in a method of treatment of a neurodegenerative disease.

The examination is being carried out on the **following application documents**

Description, Pages

1-209 as published

Sequence listings, SEQ ID NO

1-3848 as published

Claims, Numbers

1-14 filed in electronic form on 16-08-2021

Reference is made to the following document; the numbering will be adhered to in the rest of the procedure.

D1 HIEN TRAN ZHAO ET AL: "LRRK2 Antisense Oligonucleotides Ameliorate alpha-Synuclein Inclusion Formation in a Parkinson's Disease Mouse Model",
MOLECULAR THERAPY-NUCLEIC ACIDS,
vol. 8, 1 September 2017 (2017-09-01), pages 508-519, XP055552829,
US
ISSN: 2162-2531, DOI: 10.1016/j.omtn.2017.08.002

The following document has been cited in the international search report; the numbering will be adhered to in the rest of the procedure.

D2 WO 2017/120365 A1 (IONIS PHARMACEUTICALS, INC.) 13 July 2017
(2017-07-13)

1. Added subject matter (Article 123 (2) EPC)

1.1. The amendments comply with Art. 123(2) EPC.

2. Novelty (Article 54 EPC)

2.1. D1 discloses two modified antisense oligonucleotides (gapmers) targeting LRRK2 and capable of silencing its expression (Table 1, Fig. 1, 2, p. 509, left-hand column, third paragraph to p. 512, right-hand column, first paragraph). The gapmers have a

similar modification pattern as the gapmer defined in claim 1 (the same positions of the 2'-MOE and phosphorothioate modifications) and are shown to be effective in a mouse model of Parkinson's disease. D1 does not disclose the oligonucleotide having a sequence of SEQ ID NO: 3590.

2.2. D2 discloses modified antisense oligonucleotides (gapmers) targeting LRRK2 and capable of silencing its expression (Table 1) and indicated as useful for treatment of Parkinson's disease (Examples 4-7). D2 does not disclose the oligonucleotide having a sequence of SEQ ID NO: 3590.

2.3. The subject matter of **claim 1**, and thus also of **claims 2-14** dependent thereon or referring thereto, appears to be novel (Art. 54(1) and (2) EPC).

3. Inventive step (Article 56 EPC)

3.1. D1 is considered the closest prior art. The subject matter of claim 1 differs from the gapmers disclosed in D1 in that the gapmer of claim 1 has a different sequence (and thus a different target site) as well as in additional 5-methyl cytosine modifications. The effect of the sequence of the gapmer is very good silencing efficacy. The objective technical problem is therefore considered to be the provision of a further effective gapmer targeting LRRK2. This problem is solved by the gapmer as defined in claim 1, which is shown to have strong silencing activity, also *in vivo* (as shown e.g. in Table 48 and Tables 83, 88, 90, 91 in the description).

3.2. There was no suggestion in the prior art that using this specific sequence would result in good silencing effectiveness (especially *in vivo*). Therefore, the subject matter of **claim 1**, and thus also of **claims 2-14** dependent thereon or referring thereto, is considered to involve an inventive step (Art. 56 EPC)

4. Industrial applicability (Article 57 EPC)

4.1. The subject matter of **claims 1-14** is susceptible of industrial application (Art. 57 EPC).

5. Clarity (Article 84 EPC)

5.1. Claim 10 refers to a disease associated with LRRK2. The description does not provide a definition showing which pathologies are considered to be encompassed in this group and it would not be immediately apparent for the skilled person when a disease is considered to be associated with LRRK2. The term therefore renders **claim 10** unclear (Art. 84 EPC).

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