

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.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. PCT/US2020/042312	International filing date (day/month/year) 16.07.2020	Priority date (day/month/year) 19.07.2019
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International Patent Classification (IPC) or both national classification and IPC
INV. C12N15/113 A61K31/712 A61K31/7125

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 43bis.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 66.1bis(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:  European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Spindler, Mark-Peter Telephone No. +31 70 340-0	
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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 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:

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

1. Statement

Novelty (N)	Yes: Claims	<u>1-30</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-30</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-30</u>
	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

Re Item V

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

The following documents appeared to be relevant; the numbering will be adhered to in the rest of the procedure:

- D1 FINKEL RICHARD S ET AL: "Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study", THE LANCET, vol. 388, no. 10063, 7 December 2016 (2016-12-07), pages 3017-3026, XP029849269
- D2 RICHARD S. FINKEL ET AL: "Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy", NEW ENGLAND JOURNAL OF MEDICINE, vol. 377, no. 18, 2 November 2017 (2017-11-02), pages 1723-1732, XP055528610
- D3 WO 2014/110291 A1 (ISIS PHARMACEUTICALS INC [US]) 17 July 2014 (2014-07-17)

1 Patentability

Claims 1-30 encompass or relate to methods of treatment. 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.

It is noted that independent claims 2, 11 & 13 also encompass non-therapeutic purposes which would not be limiting upon reformulation of the claims.

2 Novelty

None of the documents cited discloses a method wherein an oligonucleotide as defined by the depicted structures ("nusinersen" marketed as SPINRAZA) is administered applying the dosage regimen as specified in the independent claims. The subject-matter of claims 1-30 is hence novel within the meaning of Article 33(2) PCT.

3 Inventive Step

The subject-matter of claims 1-30 can be considered to involve an inventive step within the meaning of Article 33(3) PCT.

3.1 Document D1 to D3 might all be regarded as closest prior art to the subject-matter of claim 1. Exemplarily, D1 is chosen and discloses:

method of treating SMA (fig. 1) with "nusinersen" using 12 mg as loading and maintenance dose (p. 3018, rh. col.)

3.2 The subject-matter of claim 1 therefore differs from this known SMA therapy in that a different dosage regimen is used.

3.3 No clinical data are disclosed in the application. Yet, from the modelling/simulating provided it appears that this difference would result in a faster and/or better therapeutic effect.

3.4 The problem to be solved by the present invention may therefore be regarded as the provision of an improved method of treating SMA.

3.5 The solution proposed in claim 1 of the present application can be considered as involving an inventive step (Article 33(3) PCT) for the following reasons:

It is deemed at least plausible that the problem is solved by the subject-matter of claim 1. Even though the mere administration of two times "about" 50 mg will not be sufficient for permanently treating SMA it appears likely that this treatment will have a beneficial short-term effect over the known dosage regimen.

There is no pointer in the prior art that would prompt the skilled person to a dosage regimen comprising a double loading dose of 50 mg of "nusinersen". The approved regimen (as reflected by D1 and D2) uses 12 mg as loading and maintenance dose. D3 uses up to 9 mg (ex. 13, 14) and suggests 15 mg "nusinersen" as loading and maintenance dose (p. 55). D3 further refers generically to a single dose of up to 200 mg oligonucleotide (p. 65).

Thus, the skilled person would require at least some inventive skill in order to arrive at the subject-matter of claim 1.

3.6 The same reasoning applies, mutatis mutandis, to the subject-matter of the corresponding independent claims 2 & 10-13, which therefore are also considered inventive.

4 Industrial Applicability

The subject-matter of claims 1-30 is considered industrially applicable.

Re Item VIII

Certain observations on the international application

The term "about" used throughout the claims is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claims unclear, Article 6 PCT. The claims should be clear from their wording alone.

Claims 23-30 refer to a further step of detecting a neurofilament level in the treated subject thereby rendering the nature of the claimed method unclear as the method covers therapeutic and monitoring steps.