

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
see form PCT/ISA/220

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/US2019/065581	International filing date (day/month/year) 11.12.2019	Priority date (day/month/year) 13.12.2018
International Patent Classification (IPC) or both national classification and IPC INV. C12N15/13		
Applicant SAREPTA THERAPEUTICS, 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>8, 18, 21-24</u>
	No: Claims	<u>1-7, 9-17, 19, 20, 25-29</u>
Inventive step (IS)	Yes: Claims	<u>8, 18, 21, 23, 24</u>
	No: Claims	<u>1-7, 9-17, 19, 20, 22, 25-29</u>
Industrial applicability (IA)	Yes: Claims	<u>1-29</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 WO 2017/062835 A2 (SAREPTA THERAPEUTICS INC [US]) 13 April 2017 (2017-04-13)
- D2 EP 2 799 548 A1 (NIPPON SHINYAKU CO LTD [JP]; NAT CT NEUROLOGY & PSYCHIATRY [JP]) 5 November 2014 (2014-11-05)
- D3 WO 2010/048586 A1 (AVI BIOPHARMA INC [US]; SAZANI PETER [US]; KOLE RYSZARD [US]) 29 April 2010 (2010-04-29)
- D4 WO 2012/109296 A1 (CHARLOTTE MECKLENBURG HOSPITAL [US]; LU QI LONG [US]) 16 August 2012 (2012-08-16)
- D5 WO 2012/150960 A1 (AVI BIOPHARMA INC [US]; HANSON GUNNAR J [US]) 8 November 2012 (2012-11-08) cited in the application

1 Novelty

The present application does not meet the criteria of Article 33(2) PCT, because the subject-matter of claims 1-7, 9-17, 19, 20 & 25-29 is not novel.

1.1 The document D2 discloses:

method of treating Duchenne's muscular dystrophy using a morpholino antisense oligomer capable of exon skipping in human dystrophin (cl. 60) with a "T" moiety as depicted in claim 7 at the 5' end (cl. 66, 67) and an arginine-rich cell-penetrating peptide at the 3' end (cl. 60; SEQ ID NO: 3486-3501), e.g. GLY-ARG₆-Ac (§ 338-339), wherein the targeting sequence of said oligomer consists of SEQ ID NO: 2 (cl. 64; SEQ ID NO: 81, 892); said sequence comprises the base sequences of SEQ ID NO: 1, 3, 4, 6, 8 of the application; or wherein the targeting sequence of said oligomer comprises the SEQ ID NO: 5 (cl. 64; SEQ ID NO: 1042)

The subject-matter of claims 1-7, 9-17, 19, 20 & 25-29 is not novel in view of D1.

1.2 The document D2 discloses:

- a morpholino antisense oligomer capable of skipping exon 50 in human dystrophin (fig. 13; table 15) consisting of a sequence of 5'-GGGATCCAGTATACTTACAGGCTCC-3', i.e. SEQ ID NO: 2, complementary to positions 103-127 counted from the 5' end of exon 50 (table 15; SEQ ID NO: 102; § 134, 135); said sequence comprises the base sequences of SEQ ID NO: 1, 3, 4, 6, 8 of the application
- a morpholino antisense oligomer capable of skipping exon 50 in human dystrophin consisting of a sequence complementary to positions 106-127 counted from the 5' end of exon 50 (cl. 3, 17-19); said positions correspond to the base sequence of SEQ ID NO: 1 of the application
- pharmaceutical composition comprising said oligomer or a pharmaceutically acceptable salt thereof for the treatment of muscular dystrophy (cl. 20), e.g. Duchenne's muscular dystrophy (§ 16, 136)

The subject-matter of claims 1, 2, 6 & 25-29 is not novel in view of D2.

1.3 The document D3 discloses:

- composition for use in skipping exon 50 in human dystrophin (i.e. restoring the mRNA reading frame) comprising a morpholino antisense oligomer targeting the splice donor site of exon 50 of human dystrophin (cl. 24; fig. 3; ex. 2) consisting of a base sequence of 5'-GGGATCCAGTATACTTACAGGCTCC-3', i.e. SEQ ID NO: 2 (SEQ ID NO: 585); said sequence comprises the base sequences of SEQ ID NO: 1, 3, 4, 6, 8 of the application; said oligomer conjugated at the 3' end to an arginine-rich peptide (p. 8, l. 25-27; cl. 26; SEQ ID NO: 570-578)
- said composition for use in treating muscular dystrophy (cl. 48, 57), e.g. Duchenne's muscular dystrophy (cl. 49)

The subject-matter of claims 1, 3-6 & 25-29 is not deemed novel in view of D3.

1.4 The document D4 discloses:

- a morpholino antisense oligomer capable of skipping exon 50 in human dystrophin (cl. 1, 4; table 3, SEQ ID NO: 97; fig. 3, 4) consisting of a sequence of 5'-GGGATCCAGTATACTTACAGGCTCC-3'; said sequence comprises the base sequences of SEQ ID NO: 1, 3, 4, 6, 8 of the application

- a morpholino antisense oligomer capable of skipping exon 50 in human dystrophin (cl. 1, 4; table 3, SEQ ID NO: 79; fig. 3, 4) consisting of a sequence of 5'-AACTTCCTCTTTAACAGAAAAGCATAC-3; said sequence comprises the base sequence of SEQ ID NO: 5 of the application
- pharmaceutical composition comprising said oligomer for the treatment of Duchenne's muscular dystrophy (cl. 7)

The subject-matter of claims 1, 6 & 25-29 is not novel in view of D4.

2 Inventive Step

The present application does not meet the criteria of Article 33(3) PCT, because the subject-matter of claim 22 does not involve an inventive step.

2.1 Document D1 is regarded as being the closest prior art to the subject-matter of independent claim 22, and discloses:

a pharmaceutically acceptable salt of a morpholino antisense oligomer capable of exon skipping in human dystrophin (cl. 60) with a "T" moiety as depicted in claim 7 at the 5' end (cl. 66, 67) and an arginine-rich cell-penetrating peptide at the 3' end (cl. 60; SEQ ID NO: 3486-3501), e.g. GLY-ARG₆-Ac (§ 338-339), wherein the targeting sequence of said oligomer consists of SEQ ID NO: 2 (cl. 64; SEQ ID NO: 81, 892); said sequence comprises the base sequences of SEQ ID NO: 1, 3, 4, 6, 8 of the application; or wherein the targeting sequence of said oligomer comprises the SEQ ID NO: 5 (cl. 64; SEQ ID NO: 1042)

2.2 The subject-matter of claim 22 therefore differs from this known oligomer salt in that the oligomer is present as a hexahydrochloride salt.

2.3 No comparison has been made. Hence, no technical effect resulting from the differences can be stated.

2.4 The problem to be solved by the present invention may therefore be regarded as the provision of a further morpholino oligomer compound.

2.5 The solution proposed in claim 22 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons:

A hexahydrochloride salt is one of the straightforward possibilities the skilled person would choose from without exerting any inventive skill when trying to solve the problem posed. The application does not provide any unexpected technical effect on which acknowledgement of an inventive step could be based.

- 2.6 In contrast, an inventive step can be acknowledged for the subject-matter of claims 8, 18, 21, 23 & 24 all relating to an oligomer defined by SEQ ID NO: 3 with a triethylene glycol group at the 5' end. The potency of said oligomer is comparable with the one of the slightly longer oligomer consisting of SEQ ID NO: 2. Yet, according to example 1 the shorter oligomer is easier to purify after synthesis than the longer one known from the prior art.

3 Industrial Applicability and Patentability

The subject-matter of claims 1-29 is considered industrially applicable.

However, claims 26-29 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.

Re Item VIII

Certain observations on the international application

Claims 7, 17 & 22 define the base sequence "Nu from 1 to n" of the oligomer by reference to SEQ ID NO: 1-9. The formulae (I), (III) and (IV), however, comprise additional bases ("Nu" outside bracketed part). This inconsistency leads to a lack of clarity (Article 6 PCT). This is also illustrated by formula (IVa) wherein the whole base sequence of the oligomer corresponds to SEQ ID NO: 3.