

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

|                                                                                                               |                                                          |                                                                                                                              |  |
|---------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|--|
| To:<br><br><br><br><br><br><br><br><br><br>see form PCT/ISA/220                                               |                                                          | <b>PCT</b><br><br><br><br><b>WRITTEN OPINION OF THE<br/>INTERNATIONAL SEARCHING AUTHORITY</b><br>(PCT Rule 43 <i>bis</i> .1) |  |
|                                                                                                               |                                                          |                                                                                                                              |  |
|                                                                                                               |                                                          | Date of mailing<br>(day/month/year) see form PCT/ISA/210 (second sheet)                                                      |  |
| Applicant's or agent's file reference<br>see form PCT/ISA/220                                                 |                                                          | <b>FOR FURTHER ACTION</b><br>See paragraph 2 below                                                                           |  |
| International application No.<br>PCT/US2018/035660                                                            | International filing date (day/month/year)<br>01.06.2018 | Priority date (day/month/year)<br>22.09.2017                                                                                 |  |
| International Patent Classification (IPC) or both national classification and IPC<br>INV. A61K47/64 A61P21/00 |                                                          |                                                                                                                              |  |
| Applicant<br>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 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 notified 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:<br><br><br>European Patent Office<br>P.B. 5818 Patentlaan 2<br>NL-2280 HV Rijswijk - Pays Bas<br>Tel. +31 70 340 - 2040<br>Fax: +31 70 340 - 3016 | Date of completion of<br>this opinion<br><br>see form<br>PCT/ISA/210 | Authorized Officer<br><br>Hoff, Philippe<br><br>Telephone No. +31 70 340-0 |  |
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**Box No. I Basis of the opinion**

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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:

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**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**

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1. Statement

|                               |             |             |
|-------------------------------|-------------|-------------|
| Novelty (N)                   | Yes: Claims |             |
|                               | No: Claims  | <u>1-31</u> |
| Inventive step (IS)           | Yes: Claims |             |
|                               | No: Claims  | <u>1-31</u> |
| Industrial applicability (IA) | Yes: Claims | <u>1-31</u> |
|                               | No: Claims  |             |

2. Citations and explanations

**see separate sheet**

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**Box No. VI Certain documents cited**

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1. Certain published documents (Rules 43bis.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

**see form 210**

**Re Item V**

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

Reference is made to the following documents:

- D1 WO 2017/062835 A2 (SAREPTA THERAPEUTICS INC [US]) 13 April 2017 (2017-04-13)
- D2 WO 2014/153240 A2 (SAREPTA THERAPEUTICS INC [US]) 25 September 2014 (2014-09-25)
- D3 WO 2012/150960 A1 (AVI BIOPHARMA INC [US]; HANSON GUNNAR J [US]) 8 November 2012 (2012-11-08)
- D4 WO 2014/100714 A1 (SAREPTA THERAPEUTICS INC [US]) 26 June 2014 (2014-06-26)
- D5 US 2010/168212 A1 (POPPLEWELL LINDA [GB] ET AL) 1 July 2010 (2010-07-01)
- D6 WO 2018/118662 A1 (SAREPTA THERAPEUTICS INC [US]) 28 June 2018 (2018-06-28)

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.

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

Document D1 discloses an antisense oligomer conjugate of formula (I), wherein the targeting sequence is SEQ ID no. 1 (5' gttgcctccggttctgaaggtgttc-3'). More particularly, the phosphorodiamidate morpholino (PMO) antisense oligonucleotide having the base sequence SEQ ID No.1 is conjugated at the 3' terminal end to the oligo-arginine R<sub>6</sub> using glycine as a linker, forming the peptide conjugated PMO of formula (I): R<sub>6</sub>-G-

PMO. The antisense oligomer conjugate is used for treating Duchenne muscular dystrophy (page 3, paragraph 12 - paragraph 14; page 12, paragraph 34 - page 16, paragraph 37; page 23, paragraph 58; page 69, paragraph 211; page 107, paragraph 333 - page 109, paragraph 339; sequence 84; claims).

Document D2 discloses an antisense oligomer conjugate of formula (I), wherein the targeting sequence is complementary to an exon 53 annealing site in the dystrophin pre-mRNA designated as H53A(+36+60) and more particularly having the base sequence SEQ ID No.1 (5' gttgcctccggttctgaaggtgttc-3'). The phosphorodiamidate morpholino (PMO) antisense oligonucleotide having the base sequence SEQ ID No.1 can be conjugated at the 3' terminal end to the oligo-arginine R<sub>6</sub> using glycine as a linker, forming the peptide conjugated PMO of formula (I): R<sub>6</sub>-G-PMO. The antisense oligomer conjugate is used for treating Duchenne muscular dystrophy (abstract; page 4, line 16 - line 34; page 6; page 37, line 10 - line 24; table 1; examples 2,7; sequence 1; claims).

Thus, D1 and D2 are prejudicial to the novelty of the subject-matter of claims 1-31 of the present application.

2. Should the Applicant overcome the objections of lack of novelty raised above, an inventive step has to be demonstrated over D1 and D2 as the present subject-matter of claims 1-31, as far as novel, appears to be an obvious alternative over said documents (Article 33(3) PCT).

The antisense oligomer having the sequence SEQ ID no.1 is known to be suitable for exon 53 skipping in the human dystrophin gene. Its conjugation at the 3' terminal end with the oligo-arginine R<sub>6</sub> using glycine as a linker is unambiguously disclosed in D1 and D2.

## **Re Item VI**

### **Certain documents cited**

The examination has been carried out assuming that the priority of the application is valid. However, attention is drawn to the fact that the document D6 which has been cited in the search report as "E" document may become relevant in the national/regional examination phase.

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING  
AUTHORITY (SEPARATE SHEET)**

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International application No.

PCT/US2018/035660