

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

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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/US2024/013683

International filing date (day/month/year)
31.01.2024

Priority date (day/month/year)
01.02.2023

International Patent Classification (IPC) or both national classification and IPC
INV. C12N15/86

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:



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Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Stoyanov, Borislav

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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.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13ter.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. 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>2, 7</u>
	No: Claims	<u>1, 3-6, 8</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-8</u>
Industrial applicability (IA)	Yes: Claims	<u>1-8</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

Reference is made to the following documents:

- D1 WO 2020/172624 A1 (LIFE TECHNOLOGIES CORP [US]) 27 August 2020 (2020-08-27)cited in the application
- D2 WO 2018/226887 A1 (SPARK THERAPEUTICS INC [US]) 13 December 2018 (2018-12-13)cited in the application

Item V

Novelty (Article 33(2) PCT)

D1 discloses an AAV production system, including HEK293 cells, an AAV transfer vector, a packaging plasmid, an AAV production enhancer, and cell culture media that supports growth and expansion of the HEK293 cells. In embodiments, the AAV production enhancer includes one or more of a histone deacetylase (HDAC) inhibitor, sodium propionate, egg lecithin, lithium acetate, trichostatin hydroxyurea, nocodazole-DMSO, NaCl, and caffeine. In embodiments, the HDAC inhibitor is apicidin, belinostat, CI- 994, CRA-024781, curcumin, panobinostat, sodium butyrate, sodium phenylbutyrate, suberoylanilide hydroxamic acid, trichostatin A, and/or valproic acid. In embodiments, the HDAC inhibitor is sodium butyrate, sodium phenylbutyrate, trichostatin A, and/or valproic acid. In embodiments, the AAV enhancer is added between about 0 hour and about 6 hours after transfection (see e.g. [0012]).

In embodiments, the HD AC inhibitor is included at a concentration (final concentration contacted with the cells) from about 0.1 mM to about 100 mM. In

embodiments, the HD AC inhibitor is included at a concentration from about 0.1 mM to about 75 mM. In embodiments, the HD AC inhibitor is included at a concentration from about 0.1 mM to about 50 mM. In embodiments, the HD AC inhibitor is included at a concentration from about 0.1 mM to about 25 mM. In embodiments, the HD AC inhibitor is included at a concentration from about 0.1 mM to about 10 mM. In embodiments, the HD AC inhibitor is included at a concentration from about 0.1 mM to about 9 mM. In embodiments, the HDAC inhibitor is included at a concentration from about 0.1 mM to about 8 mM. In embodiments, the HDAC inhibitor is included at a concentration from about 0.1 mM to about 7 mM. In embodiments, the HDAC inhibitor is included at a concentration from about 0.1 mM to about 6 mM. In embodiments, the HDAC inhibitor is included at a concentration from about 0.1 mM to about 5 mM. In embodiments, the HDAC inhibitor is included at a concentration from about 1 mM to about 100 mM. In embodiments, the HDAC inhibitor is included at a concentration from about 1 mM to about 50 mM. In embodiments, the HDAC inhibitor is included at a concentration from

about 1 mM to about 25 mM. In embodiments, the HDAC inhibitor is included at a concentration from about 1 mM to about 10 mM. In embodiments, the HDAC inhibitor is included at a concentration from about 1 mM to about 9 mM. In embodiments, the HDAC inhibitor is included at a concentration from about 1 mM to about 8 mM. In embodiments, the HDAC inhibitor is included at a concentration from about 1 mM to about 7 mM. In embodiments, the HDAC inhibitor is included at a concentration from about 1 mM to about 6 mM. In embodiments, the HDAC inhibitor is included at a concentration from about 1 mM to about 5 mM. The concentration may be any value or subrange within the recited ranges, including endpoints.

In some embodiments, the AAV enhancer is added at one or more than one time point, such as at the time of transfection (about hour 0) until about 48 hours after transfection. The AAV enhancer may be added at about 1 hour to about 16 hours after transfection to boost cell packaging of AAV vectors. In some embodiments, the AAV enhancer may be added at the time of transfection. In some embodiments, the AAV enhancer may be added at the time of transfection and at about 1 hour to about 16 hours after transfection. In some embodiments, AAV enhancer may be added from about 4 to 5 hours after transfection. In some embodiments, AAV enhancer may be added from about 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10,

11, 12, 16, 24, 36, or 48 hours after transfection. The AAV enhancer may be added at any time (or subrange) within the recited ranges, including endpoints. (see e.g. [0093] - [0095]).

Therefore, claims 1, 3-5, 6 and 8 are not new over D1 (Article 33(2) PCT).

Inventive step (Article 33(3) PCT)

Closest prior art is D1. In view of D1 the technical problem underlying the present claims 2 and 7 could be formulated as being the provision of alternative method for producing rAAV. The proposed solution could be seen in the use of a defined DMSO concentration range.

However, the elaboration of a particular DMSO concentrations is considered as being a routine laboratory practice for the person skilled in the art.

Therefore, the proposed in claims 2 and 7 solution for the underlying technical problem is seen as being obvious for the person skilled in the art.

Consequently, claims 2 and 7 are not inventive (Article 33(3) PCT).

Item VIII

Clarity (Article 6 PCT)

The present claims 1 and 6 relate to the feature "low dose" which is open for interpretation. This feature renders the claims 1 and 6 unclear (Article 6 PCT).

Therefore, dependant claims 2-5 and 7-8 unclear too (Article 6 PCT).

In addition, in claim 3 the dose of the valproic acid can apparently be "0 mM". This is inconsistent with the feature "low dose" recited in claim 1. Therefore, claim 3 is unclear (Article 6 PCT).