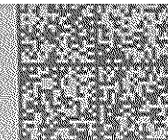


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To: CLARK ZHANG
GOODWIN PROCTER LLP
100 NORTHERN AVENUE/IP DOCKETING 7TH
FL
BOSTON, MA 02210
US

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

To: CLARK ZHANG GOODWIN PROCTER LLP 100 NORTHERN AVENUE/IP DOCKETING 7TH FL BOSTON, MA 02210 US	Date of mailing <i>(day/month/year)</i>
Applicant's or agent's file reference QRL-014WO	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US2022/051713	International filing date <i>(day/month/year)</i> 02 December 2022
Applicant QURALIS CORPORATION	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:
 The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

How? Directly to the International Bureau preferably through ePCT, or on paper to:
 The International Bureau of WIPO, 34, chemin des Colombettes, 1211 Geneva 20, Switzerland
 (Facsimile No.: +41 22 338 82 70)

For more detailed instructions, see the *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:**

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.
☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90bis.1 and 90bis.3).

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices. In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Within 22 months from the priority date, the applicant may request that a supplementary international search be carried out by a different International Searching Authority that offers this service (Rule 45bis.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Taina Matos Telephone No. PCT Helpdesk: 571-272-4300
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PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

To: CLARK ZHANG GOODWIN PROCTER LLP 100 NORTHERN AVENUE/IP DOCKETING 7TH FL BOSTON, MA 02210 US	SEP 06 2023
Applicant's or agent's file reference QRL-014WO	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US2022/051713	International filing date (day/month/year) 02 December 2022
Applicant QURALIS CORPORATION	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:
 The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

How? Directly to the International Bureau preferably through ePCT, or on paper to:
 The International Bureau of WIPO, 34, chemin des Colombettes, 1211 Geneva 20, Switzerland
 (Facsimile No.: +41 22 338 82 70)

For more detailed instructions, see the *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ With regard to any protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.
☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90bis.1 and 90bis.3).

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices. In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Within 22 months from the priority date, the applicant may request that a supplementary international search be carried out by a different International Searching Authority that offers this service (Rule 45bis.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Taina Matos Telephone No. PCT Helpdesk: 571-272-4300
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference QRL-014WO		FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2022/051713	International filing date (<i>day/month/year</i>) 02 December 2022	(Earliest) Priority Date (<i>day/month/year</i>) 03 December 2021	
Applicant QURALIS CORPORATION			

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out 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)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ Certain claims were found unsearchable (see Box No. II).

3. ☒ Unity of invention is lacking (see Box No. III).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

a. the figure of the drawings to be published with the abstract is Figure No. 1

☒ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2022/051713

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out 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.
2. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2022/051713

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 8-83, 88-136, 154, 155, 158, 159, 163-212
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See extra sheet(s).

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 4, 84-87, 162

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2022/051713

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - INV. - C12N 15/113; A61K 31/7125 (2023.01)

ADD. - A61P 25/16; A61P 25/28 (2023.01)

CPC - INV. - C12N 15/113; A61K 31/7125 (2023.08)

ADD. - A61P 25/16; A61P 25/28; C12N 2310/11; C12N 2310/31 (2023.08)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic database consulted during the international search (name of database and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2020/0268907 A1 (THE JOHNS HOPKINS UNIVERSITY) 27 August 2020 (27.08.2020) entire document	1, 4, 84-87, 162
A	US 2020/0032257 A1 (WASHINGTON UNIVERSITY et al.) 30 January 2020 (30.01.2020) entire document	1, 4, 84-87, 162
A	WO 2020/102472 A1 (PRESIDENT AND FELLOWS OF HARVARD COLLEGE) 22 May 2020 (22.05.2020) entire document	1, 4, 84-87, 162
P, X	WO 2022/216759 A1 (MAZE THERAPEUTICS INC.) 13 October 2022 (13.10.2022) entire document	1, 4, 84-87, 162

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

15 August 2023

Date of mailing of the international search report

SEP 06 2023

Name and mailing address of the ISA/

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents

P.O. Box 1450, Alexandria, VA 22313-1450

Facsimile No. 571-273-8300

Authorized officer

Taina Matos

Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2022/051713

Continued from Box No. III Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-7, 84-87, 137-153, 156, 157, and 160-162 are drawn to modified oligonucleotides and methods comprising the same.

The first invention of Group I+ is restricted to a modified oligonucleotide selected to be SEQ ID NO:1, and methods comprising the same. It is believed that claims 1, 4, 84-87, and 162 read on this first named invention and thus these claims will be searched without fee to the extent that they read on SEQ ID NO:1.

Applicant is invited to elect additional modified oligonucleotides, and their respective, corresponding, SEQ ID NOs to be searched in a specific combination by paying additional fee for each set of election. An exemplary election would be a modified oligonucleotide selected to be SEQ ID NO:2, and methods comprising the same. Additional modified oligonucleotides, and their respective, corresponding, SEQ ID NOs will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulas do not share a significant structural element responsible for reducing mis-spliced UNC13A transcripts, requiring the selection of alternative, modified oligonucleotides where "A compound comprising a modified oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof, wherein at least one (i.e., one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage."

Additionally, even if Groups I+ were considered to share the technical features of a compound comprising a modified oligonucleotide comprising a sequence, wherein at least one nucleoside linkage of the oligonucleotide is a non-natural linkage; a compound comprising a modified oligonucleotide; a method for treating a neurological disease in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, or a pharmaceutically acceptable salt thereof, a method for treating Alzheimer's Disease (AD) with frontotemporal dementia (FTD) in a subject in need thereof, wherein the oligonucleotide further comprises a spacer; a method for treating amyotrophic lateral sclerosis (ALS) with frontotemporal dementia (FTD) in a subject in need thereof, an oligonucleotide and a pharmaceutically acceptable excipient, the oligonucleotide; wherein the oligonucleotide is capable of increasing, restoring, or stabilizing expression of the UNC13A mRNA capable of translation of a functional UNC 13A and/or activity and/or function of UNC13A protein in a cell or a human patient of an immune-mediated demyelinating disease, and wherein the level of increase, restoration, or stabilization of expression and/or activity and/or function is sufficient for use of the oligonucleotide as a medicament for the treatment of the immune-mediated demyelinating disease. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 2020/0032257 A1 to Washington University et al. discloses a compound (a Tau antisense compound, Para. [0020]) comprising a modified oligonucleotide comprising a sequence, wherein at least one nucleoside linkage of the oligonucleotide is a non-natural linkage (antisense oligonucleotide comprises at least one modified internucleoside linkage, Para. [0043]); a compound (a Tau antisense compound, Para. [0020]) comprising a modified oligonucleotide (antisense oligonucleotide comprises at least one modified internucleoside linkage, Para. [0043]); a method for treating a neurological disease in a subject in need thereof (methods for treating, preventing or ameliorating a seizure disorder and neurodegenerative diseases by inhibiting expression of Tau, Para. [0014]; "Tau-associated disease" means any neurological or neurodegenerative disease associated with Tau. Non-limiting examples of Tau-associated disorders include Alzheimer's disease, Para. [0436]), the method comprising administering to the subject an oligonucleotide (methods for treating, preventing or ameliorating a seizure disorder and neurodegenerative diseases by inhibiting expression of Tau, Para. [0014]; "Tau-associated disease" means any neurological or neurodegenerative disease associated with Tau. Non-limiting examples of Tau-associated disorders include Alzheimer's disease ... frontotemporal dementia, Para. [0436]) a method for treating Alzheimer's Disease (AD) with frontotemporal dementia (FTD) in a subject in need thereof (methods for treating, preventing or ameliorating a seizure disorder and neurodegenerative diseases by inhibiting expression of Tau, Para. [0014]; "Tau-associated disease" means any neurological or neurodegenerative disease associated with Tau. Non-limiting examples of Tau-associated disorders include Alzheimer's disease ... frontotemporal dementia, Para. [0436]), wherein the oligonucleotide further comprises a spacer (siRNA are linked by means of a nucleic acid based or non-nucleic acid-based linker, Para. [0649]); an oligonucleotide and a pharmaceutically acceptable excipient (pharmaceutically acceptable carriers, adjuvants, and vehicles as desired, Para. [0302]), the oligonucleotide; wherein the oligonucleotide is capable of increasing, restoring, or stabilizing expression of the UNC13A mRNA capable of translation of a functional UNC 13A and/or activity and/or function of UNC13A protein, and wherein the level of increase, restoration, or stabilization of expression and/or activity and/or function is sufficient for use of the oligonucleotide as a medicament for the treatment (expression of the 3R isoform of Tau RNA or protein is increased, Para. [0016]; methods for treating, preventing or ameliorating a seizure disorder and neurodegenerative diseases by inhibiting expression of Tau, Para. [0014]; "Tau-associated disease" means any neurological or neurodegenerative disease associated with Tau. Non-limiting examples of Tau-associated disorders include Alzheimer's disease ... frontotemporal dementia, Para. [0436]).

Further, US 2020/0268907 A1 to The Johns Hopkins University teaches a method for treating amyotrophic lateral sclerosis (ALS) with frontotemporal dementia (FTD) in a subject in need thereof (a method for treating, Para. [0017]; amyotrophic lateral sclerosis ... frontotemporal dementia, Para. [0161]), in a cell or a human patient of an immune-mediated demyelinating disease (a method for treating, Para. [0017]; amyotrophic lateral sclerosis ... frontotemporal dementia, Para. [0161]; human subject, Para. [0016]); comprising a segment with at most 7 linked nucleosides, or a pharmaceutically acceptable salt thereof (sequence is about or more than about 5 ... nucleotides in length, Para. [0083]).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical features.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

To: CLARK ZHANG GOODWIN PROCTER LLP 100 NORTHERN AVENUE/IP DOCKETING 7TH FL BOSTON, MA 02210 US		SEP 06 2023
Applicant's or agent's file reference QRL-014WO		FOR FURTHER ACTION See paragraph 2 below
International application No. PCT/US2022/051713	International filing date (day/month/year) 02 December 2022	Priority date (day/month/year) 03 December 2021
International Patent Classification (IPC) or both national classification and IPC IPC(8) - INV. - C12N 15/113; A61K 31/7125 (2023.01) ADD. - A61P 25/16; A61P 25/28 (2023.01) CPC - INV. - C12N 15/113; A61K 31/7125 (2023.08) ADD. - A61P 25/16; A61P 25/28; C12N 2310/11; C12N 2310/31 (2023.08)		
Applicant QURALIS CORPORATION		

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 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/ Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Date of completion of this opinion 15 August 2023	Authorized officer Taina Matos PCT Helpdesk: 571-272-4300 Telephone No. 571-272-4300
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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US2022/051713

Box No. I Basis of this 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 43*bis*.1(b)).

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 13*ter*.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:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US2022/051713

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 2, 3, 5-83, 88-161, 163-212

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. see claims below are so unclear that no meaningful opinion could be formed (*specify*):

Claims 8-83, 88-136, 154, 155, 158, 159, and 163-212 are multiple dependent claims not drafted in accordance with the second and third sentences of Rule 6.4(a).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☒ no international search report has been established for said claims Nos. 2, 3, 5-83, 88-161, 163-212

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing complying with WIPO Standard ST.26, and such listing was not available to the International Searching Authority in the form, language and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a).

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US2022/051713

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:
- ☐ paid additional fees.
 - ☐ paid additional fees under protest and, where applicable, the protest fee.
 - ☐ paid additional fees under protest but the applicable protest fee was not paid.
 - ☒ not paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with.
 - ☒ not complied with for the following reasons:

<See Supplemental Box>

4. Consequently, this opinion has been established in respect of the following parts of the international application:

- ☐ all parts.
- ☒ the parts relating to claims Nos. 1, 4, 84-87, 162

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2022/051713

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

1. Statement

Novelty (N)	Claims	1, 4, 84-87, 162	YES
	Claims	None	NO
Inventive step (IS)	Claims	1, 4, 84-87, 162	YES
	Claims	None	NO
Industrial applicability (IA)	Claims	1, 4, 84-87, 162	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1, 4, 84-87, and 162 have been analyzed subject to the restriction that the claims read on a modified oligonucleotide selected to be SEQ ID NO:1, and methods comprising the same.

Claims 1, 4, 84-87, and 162 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest:

Regarding claim 1, the prior art of record, individually or in combination, does not teach or fairly suggest a compound comprising a modified oligonucleotide selected to be SEQ ID NO:1.

The following prior art is made of record to support and further define the reasons claim 1 meets the criteria set out in PCT Article 33 (2)-(3):

(i) WO 2020/102472 A1 to President And Fellows Of Harvard College (hereinafter, "Harvard") teaches a nucleic acid comprising 100% sequence identity to instant SEQ ID NO:1 (the agent that increases Ffar2 is an antisense oligonucleotide, Para. [00126]; The gene sequence is shown in SEQ ID NO: 2, Para. [0082]; SEQ ID NO: 2 of Harvard comprises 100% sequence identity to instant SEQ ID NO:1).

None of the prior art taken alone or in combination fairly teach or suggest a nucleic acid sequence consisting of 100% sequence identity to SEQ ID NO:1, as recited above.

Regarding claim 4, the prior art of record, individually or in combination, does not teach or fairly suggest an oligonucleotide comprising a modified oligonucleotide selected to be SEQ ID NO:1, wherein at least one nucleoside linkage of the oligonucleotide is a non-natural linkage.

The following prior art is made of record to support and further define the reasons claim 4 meets the criteria set out in PCT Article 33 (2)-(3):

(i) Harvard teaches a nucleic acid comprising 100% sequence identity to instant SEQ ID NO:1 (the agent that increases Ffar2 is an antisense oligonucleotide, Para. [00126]; The gene sequence is shown in SEQ ID NO: 2, Para. [0082]; SEQ ID NO: 2 of Harvard comprises 100% sequence identity to instant SEQ ID NO:1).

(ii) US 2020/0032257 A1 to Washington University et al. (hereinafter, "Washington") teaches a compound (a Tau antisense compound, Para. [0020]) comprising a modified oligonucleotide comprising a sequence, wherein at least one nucleoside linkage of the oligonucleotide is a non-natural linkage (antisense oligonucleotide comprises at least one modified internucleoside linkage, Para. [0043]).

None of the prior art taken alone or in combination fairly teach or suggest a nucleic acid sequence consisting of 100% sequence identity to SEQ ID NO:1, as recited above.

Regarding claim 84, the prior art of record, individually or in combination, does not teach or fairly suggest a compound comprising an oligonucleotide selected to be SEQ ID NO:1.

The following prior art is made of record to support and further define the reasons claim 84 meets the criteria set out in PCT Article 33 (2)-(3):

(i) Harvard teaches a nucleic acid comprising 100% sequence identity to instant SEQ ID NO:1 (the agent that increases Ffar2 is an antisense oligonucleotide, Para. [00126]; The gene sequence is shown in SEQ ID NO: 2, Para. [0082]; SEQ ID NO: 2 of Harvard comprises 100% sequence identity to instant SEQ ID NO:1).

None of the prior art taken alone or in combination fairly teach or suggest a nucleic acid sequence consisting of 100% sequence identity to SEQ ID NO:1, as recited above.

Claims 86 and 87 depend from claim 84, and therefore meet the criteria set out in PCT Article 33(2)-(3) for at least the same reasons as claim 84.

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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:

Claims 1, 3, 4, 6, 137-141, and 160 contain exemplary claim language (i.e.), which renders the intended scope of the claims unclear. For the purposes of this written opinion, claims 1, 3, 4, 6, 137-141, and 160 have been interpreted without the exemplary claim language.

Claim 66 contains exemplary claim language (i.e.), which renders the intended scope of the claim unclear. Herein, claim 66 has been interpreted without the exemplary claim language.

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

<Box No. IV Lack of unity of invention>

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-7, 84-87, 137-153, 156, 157, and 160-162 are drawn to modified oligonucleotides and methods comprising the same.

The first invention of Group I+ is restricted to a modified oligonucleotide selected to be SEQ ID NO:1, and methods comprising the same. It is believed that claims 1, 4, 84-87, and 162 read on this first named invention and thus these claims will be searched without fee to the extent that they read on SEQ ID NO:1.

Applicant is invited to elect additional modified oligonucleotides, and their respective, corresponding, SEQ ID NOs to be searched in a specific combination by paying additional fee for each set of election. An exemplary election would be a modified oligonucleotide selected to be SEQ ID NO:2, and methods comprising the same. Additional modified oligonucleotides, and their respective, corresponding, SEQ ID NOs will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulas do not share a significant structural element responsible for reducing mis-spliced UNC13A transcripts, requiring the selection of alternative, modified oligonucleotides where "A compound comprising a modified oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof, wherein at least one (i.e., one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage."

Additionally, even if Groups I+ were considered to share the technical features of a compound comprising a modified oligonucleotide comprising a sequence, wherein at least one nucleoside linkage of the oligonucleotide is a non-natural linkage; a compound comprising a modified oligonucleotide; a method for treating a neurological disease in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, or a pharmaceutically acceptable salt thereof, a method for treating Alzheimer's Disease (AD) with frontotemporal dementia (FTD) in a subject in need thereof, wherein the oligonucleotide further comprises a spacer; a method for treating amyotrophic lateral sclerosis (ALS) with frontotemporal dementia (FTD) in a subject in need thereof, an oligonucleotide and a pharmaceutically acceptable excipient, the oligonucleotide; wherein the oligonucleotide is capable of increasing, restoring, or stabilizing expression of the UNC13A mRNA capable of translation of a functional UNC 13A and/or activity and/or function of UNC13A protein in a cell or a human patient of an immune-mediated demyelinating disease, and wherein the level of increase, restoration, or stabilization of expression and/or activity and/or function is sufficient for use of the oligonucleotide as a medicament for the treatment of the immune-mediated demyelinating disease. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 2020/0032257 A1 to Washington University et al. discloses a compound (a Tau antisense compound, Para. [0020]) comprising a modified oligonucleotide comprising a sequence, wherein at least one nucleoside linkage of the oligonucleotide is a non-natural linkage (antisense oligonucleotide comprises at least one modified internucleoside linkage, Para. [0043]); a compound (a Tau antisense compound, Para. [0020]) comprising a modified oligonucleotide (antisense oligonucleotide comprises at least one modified internucleoside linkage, Para. [0043]); a method for treating a neurological disease in a subject in need thereof (methods for treating, preventing or ameliorating a seizure disorder and neurodegenerative diseases by inhibiting expression of Tau, Para. [0014]; "Tau-associated disease" means any neurological or neurodegenerative disease associated with Tau. Non-limiting examples of Tau-associated disorders include Alzheimer's disease, Para. [0436]), the method comprising administering to the subject an oligonucleotide (methods for treating, preventing or ameliorating a seizure disorder and neurodegenerative diseases by inhibiting expression of Tau, Para. [0014]; "Tau-associated disease" means any neurological or neurodegenerative disease associated with Tau. Non-limiting examples of Tau-associated disorders include Alzheimer's disease ...frontotemporal dementia, Para. [0436]) a method for treating Alzheimer's Disease (AD) with frontotemporal dementia (FTD) in a subject in need thereof (methods for treating, preventing or ameliorating a seizure disorder and neurodegenerative diseases by inhibiting expression of Tau, Para. [0014]; "Tau-associated disease" means any neurological or neurodegenerative disease associated with Tau. Non-limiting examples of Tau-associated disorders include Alzheimer's disease ...frontotemporal dementia, Para. [0436]), wherein the oligonucleotide further comprises a spacer (siRNA are linked by means of a nucleic acid based or non-nucleic acid-based linker, Para. [0649]); an oligonucleotide and a pharmaceutically acceptable excipient (pharmaceutically acceptable carriers, adjuvants, and vehicles as desired, Para. [0302]), the oligonucleotide; wherein the oligonucleotide is capable of increasing, restoring, or stabilizing expression of the UNC13A mRNA capable of translation of a functional UNC 13A and/or activity and/or function of UNC13A protein, and wherein the level of increase, restoration, or stabilization of expression and/or activity and/or function is sufficient for use of the oligonucleotide as a medicament for the treatment (expression of the 3R isoform of Tau RNA or protein is increased, Para. [0016]; methods for treating, preventing or ameliorating a seizure disorder and neurodegenerative diseases by inhibiting expression of Tau, Para. [0014]; "Tau-associated disease" means any neurological or neurodegenerative disease associated with Tau. Non-limiting examples of Tau-associated disorders include Alzheimer's disease ...frontotemporal dementia, Para. [0436]).

Further, US 2020/0268907 A1 to The Johns Hopkins University teaches a method for treating amyotrophic lateral sclerosis (ALS) with frontotemporal dementia (FTD) in a subject in need thereof (a method for treating, Para. [0017]; amyotrophic lateral sclerosis ... frontotemporal dementia, Para. [0161]), in a cell or a human patient of an immune-mediated demyelinating disease (a method for treating, Para. [0017]; amyotrophic lateral sclerosis ... frontotemporal dementia, Para. [0161]; human subject, Para. [0016]); comprising a segment with at most 7 linked nucleosides, or a pharmaceutically acceptable salt thereof (sequence is about or more than about 5 ...nucleotides in

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

length, Para. [0083]).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical features.

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

Regarding claim 85, the prior art of record, individually or in combination, does not teach or fairly suggest an oligonucleotide comprising a nucleobase sequence selected to be SEQ ID NO:1.

The following prior art is made of record to support and further define the reasons claim 85 meets the criteria set out in PCT Article 33 (2)-(3):

(i) Harvard teaches a nucleic acid comprising 100% sequence identity to instant SEQ ID NO:1 (the agent that increases Ffar2 is an antisense oligonucleotide, Para. [00126]; The gene sequence is shown in SEQ ID NO: 2, Para. [0082]; SEQ ID NO: 2 of Harvard comprises 100% sequence identity to instant SEQ ID NO:1).

None of the prior art taken alone or in combination fairly teach or suggest a nucleic acid sequence consisting of 100% sequence identity to SEQ ID NO:1, as recited above.

Regarding claim 162, the prior art of record, individually or in combination, does not teach or fairly suggest an oligonucleotide and a pharmaceutically acceptable excipient, the oligonucleotide selected to be SEQ ID NO:1.

The following prior art is made of record to support and further define the reasons claim 162 meets the criteria set out in PCT Article 33 (2)-(3):

(i) Harvard teaches a nucleic acid comprising 100% sequence identity to instant SEQ ID NO:1 (the agent that increases Ffar2 is an antisense oligonucleotide, Para. [00126]; The gene sequence is shown in SEQ ID NO: 2, Para. [0082]; SEQ ID NO: 2 of Harvard comprises 100% sequence identity to instant SEQ ID NO:1), and a pharmaceutically acceptable excipient (a pharmaceutically acceptable carrier or excipient, Para. [00153]).

None of the prior art taken alone or in combination fairly teach or suggest a nucleic acid sequence consisting of 100% sequence identity to SEQ ID NO:1, as recited above.

Claims 1, 4, 84-87, and 162 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

Search History:

Limited Classification Search

The Patent Analyst performed a limited classification search within the following US, IPC, CPC, ECLA, or F-Term classification areas:

CPC Class/Subclass(es): A61K 31/7125; A61P 25/16; A61P 25/28; C12N 15/113; C12N 2310/11; C12N 2310/31 (2023.08)

IPC (8) Class/Subclass(es): A61K 31/7125; A61P 25/16; A61P 25/28; C12N 15/113 (2023.01)

U.S. Class/Subclass(es): 536/24.1

See Global Search Results.

Global Patent Literature Text Search

The Patent Analyst performed the following global text search, which was not limited by classification but may or may not have been limited by other criteria:

Questel Orbit: <https://www.orbit.com>

#	Search query	Results
1	(QURALIS)/PA/OPA/PAH/OWR/REAS	8
2	((HINCKLEY 2D SANDRA)/IN/OIN/INH/INV) OR ((BROWN 2D DUNCAN)/IN/OIN/INH/INV) OR ((ELBAUM 2D DAN+)/IN/OIN/INH/INV) OR ((KAMELGARN 2D MARISA)/IN/OIN/INH/INV)	165
3	((UNC13A)/TI/AB/CLMS/DESC/ODES AND (OLIGONUCLE+)/TI/AB/CLMS/DESC/ODES)	130
4	(MODIF+ S NUCLEOSIDE? S LINK+)/TI/AB/CLMS/DESC/ODES	9308
5	3 AND 4	22
6	(OLIGONUCLE+)/TI/AB/CLMS	60235
7	(MODIF+ S NUCLEOSIDE? S LINK+)/TI/AB/CLMS	1031
8	6 AND 7	815
9	3 AND 8	7
10	C12N-015/113/CPC	23399
11	A61K-031/7125/CPC	821
12	C12N-2310/11/CPC	4007
13	C12N-2310/31/CPC	236
14	A61P-025/16/CPC	15420
15	A61P-025/28/CPC	39507
16	10 AND 11 AND 12	314

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Date of Search: 15 August 2023

17	10 AND 11 AND 12 AND 13	23
18	(10 OR 11) AND 12 AND 13 AND (14 OR 15)	17
19	C12N-015/113/IPC	33633
20	A61K-031/7125/IPC	1997
21	A61P-025/16/IPC	19576
22	A61P-025/28/IPC	53222
23	19 AND 20 AND (21 OR 22)	243
24	23 AND 3	3
25	514044000A/PCL	6817
26	536024100/PCL	4792
27	25 AND 26	411
28	27 AND 3	1

Google Patents: <https://patents.google.com>

#	Search query	Results
1	UNC13a; oligonucle\$; modif\$; internucleoside? OR internucleotide?;	33

Computer Accessed Text Databases Searched

The Patent Analyst searched the following computer accessed text databases:

PubMed.gov (NCBI): <http://www.ncbi.nlm.nih.gov/pubmed>

#	Search query	Results
1	((((Hinckley, Sandra[Author]) OR (Brown, Duncan[Author])) OR (Elbaum, Daniel[Author])) OR (Kamelgarn, Marisa[Author]))	64
2	(UNC13A) AND (oligo*)	7

Google Scholar: <https://scholar.google.com/>

#	Search query	Results
1	UNC13a oligonucleotide modified internucleotide OR internucleoside linkage	3

Date search was completed: 15 August 2023

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