PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: WARREN VOLLES
IPRAXUS LEGAL, LLC
P.O. BOX 689
67 STERLING HILL ROAD
OLD LYME, CT 06371

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	12 NOV 2019
Applicant's or agent's file reference 20063-PCT	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 19/42718	20 July 2019 (20.07.2019)	22 July 2018 (22.07.2018)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 31/428; C07D 277/82; A61P 25/28 (2019.01)
CPC - A61K 31/428; C07D 277/82

Applicant BIOHAVEN THERAPEUTICS LTD.

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 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/US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	01 October 2019	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 19/42718

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(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 13*ter*.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 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.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:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 19/42718

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-17	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-17	NO
Industrial applicability (IA)	Claims	1-17	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-15 lack an inventive step under PCT Article 33(3) as being obvious over US 2018/0037557 A1 to Biohaven Pharmaceutical Holding Company Ltd. (hereinafter .Biohaven.).

Regarding claim 1, Biohaven teaches a method of treating a neurological disorder that includes Alzheimer's Disease in a patient in need thereof (para [0080], [0144]), comprising administering to the patient a therapeutically effective amount of a riluzole prodrug (para [0072]-[0075], [0080]). While Biohaven does not specifically teach treating Alzheimer.s disease in a patient in need thereof, based on the teachings of Biohaven described above, it would have been obvious to one of ordinary skill in the art to design such a method, through routine experimentation, in order to effectively treat Alzheimer.s disease in said patient.

Regarding claim 2, Biohaven teaches the method of claim 1, as above, wherein the riluzole prodrug has the formula shown in the claim, and pharmaceutically acceptable salts thereof, wherein R23 is selected from H (para [1270], Example 204; para [1272], trifluoroacetic acid salt).

Regarding claim 3, Biohaven teaches the method of claim 2, wherein the riluzole prodrug has the formula shown in the claim (para [1270], Example 204).

Regarding claim 4, Biohaven teaches the method of claim 1, as above, but does not specifically teach wherein the riluzole prodrug is administered to the patient at a dosage of from about 100 to 400 mg per day. However, Biohaven does teach the pharmacokinetic properties of the riluzole prodrug administered orally at a dose of 5 mg/kg (para [1464], Table 5; Fig 3; Fig 5) and further teaches that the effective amount of the riluzole prodrug in a pharmaceutical composition ranges from 1 mg/kg to 500 mg/kg (para [1413]). Based on such teachings of Biohaven described above, it would have been obvious to one of ordinary skill in the art to determine the daily dosage of riluzole prodrug to be administered to the patient, by taking into consideration, the age, weight and the medical condition of said patient, through routine experimentation, in order to effectively treat Alzheimer.s disease in said patient.

Regarding claim 5, Biohaven teaches the method of claim 4, as above, but does not specifically teach wherein the riluzole prod rug is administered to the patient at a dosage of about 110, or 140, or 150, or 210, or 280, or 350 mg per day. However, Biohaven does teach the pharmacokinetic properties of the riluzole prodrug administered orally at a dose of 5 mg/kg (para [1464], Table 5; Fig 3; Fig 5) and further teaches that the effective amount of the riluzole prodrug in a pharmaceutical composition ranges from 1 mg/kg to 500 mg/kg (para [1413]). Based on such teachings of Biohaven described above, it would have been obvious to one of ordinary skill in the art to determine the daily dosage of riluzole prodrug to be administered to the patient, by taking into consideration, the age, weight and the medical condition of said patient, through routine experimentation, in order to effectively treat Alzheimer.s disease in said patient.

Regarding claim 6, Biohaven teaches the method of claim 5, as above, but does not specifically teach wherein the riluzole prod rug is administered to the patient at a dosage of 280 mg, once per day. However, Biohaven does teach the pharmacokinetic properties of the riluzole prodrug administered orally at a dose of 5 mg/kg (para [1464], Table 5; Fig 3; Fig 5) and further teaches that the effective amount of the riluzole prodrug in a pharmaceutical composition ranges from 1 mg/kg to 500 mg/kg, that can be administered as single dose or in two or more doses (para [1413]). Based on such teachings of Biohaven described above, it would have been obvious to one of ordinary skill in the art to determine the daily dosage of riluzole prodrug to be administered to the patient, by taking into consideration, the age, weight and the medical condition of said patient, through routine experimentation, in order to effectively treat Alzheimer.s disease in said patient.

Regarding claim 7, Biohaven teaches the method of claim 6, as above, but does not specifically teach wherein the riluzole prod rug is administered to the patient at a dosage of 140 mg, twice per day. However, Biohaven does teach the pharmacokinetic properties of the riluzole prodrug administered orally at a dose of 5 mg/kg (para [1464], Table 5; Fig 3; Fig 5) and further teaches that the effective amount of the riluzole prodrug in a pharmaceutical composition ranges from 1 mg/kg to 500 mg/kg, that can be administered as single dose or in two or more doses (para [1413]). Based on such teachings of Biohaven described above, it would have been obvious to one of ordinary skill in the art to determine the daily dosage of riluzole prodrug to be administered to the patient and the mode of administering said dosage, by taking into consideration, the age, weight and the medical condition of said patient, through routine experimentation, in order to effectively treat Alzheimer.s disease in said patient.

---Continued in Supplemental Box----

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 19/42718

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box V.2. Citations and Explanation:

Regarding claim 8, Biohaven teaches the method of claim 1 wherein the riluzole prodrug is administered to the patient once per day (para [1406], [1413], single dose).

Regarding claim 9, Biohaven teaches the method of claim 1 wherein the riluzole prodrug is administered to the patient twice per day (para [1406], multiple time per day dosage; para [1413], in two or more doses).

Regarding claim 10, Biohaven teaches the method of claim 1 wherein the riluzole prodrug is administered to the patient in the form of a capsule (para [1413]).

Regarding claim 11, Biohaven teaches the method of claim 1 wherein the riluzole prodrug is administered to the patient in the form of a tablet (para [1413]).

Regarding claim 12, Biohaven teaches the method of claim 1, as above, but does not teach wherein the riluzole prodrug is administered to the patient for a duration of from about 8 weeks to 48 weeks. However, Biohaven does teach the pharmacokinetic properties of the riluzole prodrug administered orally at a dose of 5 mg/kg (para [1464], Table 5; Fig 3; Fig 5). Based on the teachings of Biohaven, it would have been obvious to one of ordinary skill in the art to determine the duration for administering the riluzole prodrug, by taking into consideration, the medical condition of said patient and the response to treatment, through routine experimentation, in order to effectively treat AlzheimerLs disease in said patient.

Regarding claim 13, Biohaven teaches the method of claim 1, as above, but does not teach wherein the riluzole prodrug is administered to the patient for a duration of from the onset of treatment to the end of the patient's life. However, Biohaven does teach the pharmacokinetic properties of the riluzole prodrug administered orally at a dose of 5 mg/kg (para [1464], Table 5; Fig 3; Fig 5). Based on the teachings of Biohaven, it would have been obvious to one of ordinary skill in the art to determine the duration for administering the riluzole prodrug, by taking into consideration, the medical condition of said patient and the response to treatment, through routine experimentation, in order to effectively treat AlzheimerLs disease in said patient.

Regarding claim 14, Biohaven teaches a method for improving a response in a patient afflicted with a neurological disorder that includes Alzheimer's disease (para [0080], [0139], [0144]), comprising administering to the patient in need thereof, a therapeutically effective amount of a riluzole prodrug (para [0072]-[0075], [0080]). While Biohaven does not specifically teach treating a patient afflicted with AlzheimerLs disease, based on the teachings of Biohaven described above, it would have been obvious to one of ordinary skill in the art to design such a method, through routine experimentation, in order to effectively treat AlzheimerLs disease in said patient.

Regarding claim 15, Biohaven teaches the method of claim 14, wherein the improved response is one or more of overall survival, quality of life, overall response rate, duration of response, delay of onset (para [0139], preventing the disease or condition from occurring in the subject), or patient reported outcome.

Claims 16-17 lack an inventive step under PCT Article 33(3) as being obvious over Biohaven in view of US 2013/0064775 A1 to Busserolles et al. (hereinafter LBusserollesL).

Regarding claim 16, Biohaven teaches the method of any of claims 1-15, as above, but does not specifically teach a kit for the treatment of AlzheimerLs disease comprising:
(a) a riluzole prodrug; and
(b} instructions for administering the riluzole prodrug in said method. However, Biohaven does teach packaged unit dosage forms of a riluzole prodrug (para [1270], Example 204; para [1413]), useful in the treatment of AlzheimerLs disease in a patient (para [0080], [0144]). In a similar invention, Busserolles teaches a kit for the treatment of a disease (para [0042]; claims 12 and 13) comprising: riluzole and instructions for administering riluzole to treat said disease (para [0042], [0045]). It would have been obvious to one of ordinary skill in the art to combine the teachings of Biohaven and Busserolles, as both are directed to therapeutic use of riluzole or a riluzole prodrug, and formulate the riluzole prodrug disclosed in Biohaven in a kit with instructions for administration, as disclosed in Busserolles, in order to enhance the ease of treating AlzheimerLs disease in a patient (Biohaven, para [0080]).

Regarding claim 17, Biohaven and Busserolles teach the kit of claim 16, as above, wherein Biohaven further teaches that the prod rug has the formula shown in the claim (para [1270], Example 204).

Claims 1-17 have industrial applicability as defined by PCT Article 33(4), because the subject matter can be made or used in industry.