PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	06 FEB 2020

Applicant's or agent's file reference	FOR FURTHER ACTION
A3647.10006WO01	See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 19/63044	25 November 2019 (25.11.2019)	26 November 2018 (26.11.2018)

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

IPC - A61K 31/155; A61K 31/337; A61K 31/496 (2020.01)

CPC - A61K 31/155; A61K 31/337; A61K 31/37; A61K 31/496; A61K 31/573; A61K 31/7036

Applicant
AIVIVA BIOPHARMA, 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 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	24 January 2020	Lee Young PCT Help Desk Telephone No. 571-272-4300

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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:

      ☐ 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:

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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. 7-13, 16-19, 28-37

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. 7-13, 16-19, 28-37 are so unclear that no meaningful opinion could be formed *(specify)*:

because they are dependent claims and are 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. 7-13, 16-19, 28-37

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

- ☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details.

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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**

1. Statement

Novelty (N)	Claims	4-6,14,15,20-27,38	YES
	Claims	1-3	NO
Inventive step (IS)	Claims	none	YES
	Claims	1-6,14,15,20-27,38	NO
Industrial applicability (IA)	Claims	1-6,14,15,20-27,38	YES
	Claims	none	NO

2. Citations and explanations:

Claims 1-3 lack novelty under PCT Article 33(2) as being anticipated by US 5,441,732 A to Hoeg et al.(hereinafter Hoeg).

Regarding claim 1; Hoeg discloses a pharmaceutical composition (col 3 ln 50-55; water soluble pharmaceutical medicaments) comprising a reverse thermal gelation material(col 3 ln 40-45; compositions that reversibly gel), wherein the pharmaceutical composition makes a transition from liquid to gel near the body temperature(col 4 ln 20-25; exhibit steady state flow characteristics at or near room temperatures and pH of 2.5-6.5 (this is interpreted as being a liquid at room temperature), yet which almost instantaneously transform to highly viscoelastic gels when exposed to physiological conditions of pH of 7.4 and 37 degrees C) of a mammal (col 12 ln 60-65; present invention can easily be administered to the eye, and col 3 ln 20-25; administered easily by a patient).

Regarding claim 2; Hoeg discloses a composition of claim 1 as discussed. Hoeg further discloses wherein the mammal is a human being (col 3 ln 20-25; administered easily by a patient).

Regarding claim 3; Hoeg discloses a composition of claims 1-2 as discussed. Hoeg further discloses further comprising an active pharmaceutical ingredient (col 3 ln 50-55; water soluble pharmaceutical medicaments).

Claims 14, 15, 20, 21, 27/20 lacks an inventive step under PCT Article 33(3) as being obvious over US 2018/0228903 A1 to Children's Medical Center Corporation (hereinafter Children).

Regarding claim 14; Children discloses a pharmaceutical composition (para [0012], compositions provided herein the combination of the permeation enhancer with the matrix forming agent and therapeutic agent) comprising: an active pharmaceutical ingredient(para [0014], therapeutic agent), methylcellulose(para [0016], matrix forming agent and para [0204], matrix forming compounds methylcellulose), dimethyl sulfoxide(para [0015], penetration enhancer and para [0043], penetration enhancer is dimethyl sulfoxide) and citrate (para [0319], buffering agents include citrate buffer), but does not specifically disclose a specific example/embodiment showing methylcellulose, dimethyl sulfoxide and citrate in a single formulation. However, based on Children's disclosure, it would have been obvious to a person having ordinary skill in the art to identify the composition comprising methylcellulose, dimethyl sulfoxide and citrate by routine experimentation.

Regarding claim 15; Children discloses a composition of claim 14 as discussed. Children further discloses wherein the composition further comprises phosphate (para [0319], phosphate buffer).

Regarding claim 20; Children discloses a pharmaceutical composition (para [0012], compositions provided herein the combination of the permeation enhancer with the matrix forming agent and therapeutic agent) comprising: an active pharmaceutical ingredient(para [0014], therapeutic agent), methylcellulose(para [0016], matrix forming agent and para [0204], matrix forming compounds selected from methylcellulose), dimethyl sulfoxide (para [0015], penetration enhancer and para [0043], penetration enhancer selected from dimethyl sulfoxide) and citrate(para [0319], buffering agents include citrate buffer), wherein the pharmaceutical composition has a first storage modulus (G) at about 37 degrees C (Figure 10 showing the composition having a storage modulus at 37 degrees C) and a second G at about 5 degrees C(Figure 10 showing the composition having a storage modulus at 5 degrees C), wherein the first G is higher than the second G (Figure 10 showing the storage modulus at 37 degrees greater than at 5 degrees C). Although Children does not disclose a specific embodiment that has methylcellulose, dimethyl sulfoxide and citrate; it would have been obvious to a person having ordinary skill in the art to use the disclosure from Children (para [0013]-[0018]; disclosing the composition of the pharmaceutical application) to make this particular composition through routine experimentation.

Regarding claim 21; Children discloses a composition of claim 20 as discussed. Children does not specifically disclose wherein the first G is at least about tenfold higher than the second G; however, Children discloses the increase in the storage modulus with temperature for various compositions (Figure 10); it would have been obvious to a person having ordinary skill in the art to know that this can be tenfold through routine experimentation depending on formulation.

Regarding claim 27/20; Children discloses a composition of claim 20 as discussed. Children further discloses wherein the composition further comprises phosphate (para [0319], phosphate buffer).

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Supplemental Box

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Claim 38 lacks an inventive step under PCT Article 33(3) as being obvious over Hoeg.

Regarding claim 38; Hoeg discloses a method of preparing (col 16 ln 40-50 showing a example of a method of preparation) a pharmaceutical composition (col 3 ln 50-55; water soluble pharmaceutical medicaments) having reverse thermal gelation properties(col 3 ln 40-45; compositions that reversibly gel), comprising: mixing a polymer agent into a slurry (col 16 ln 40-50; to this heated water, methocel was added) containing a gelation modulator and an active pharmaceutical ingredient (col 17 ln 10-15; methocel prepared as in example I was blended with Carbopol and levobunolol), wherein the slurry is formed by a method comprising precipitating the active pharmaceutical ingredient into an aqueous liquid(col 17 ln 10-25; showing the preparation of the active ingredient in a slurry into deionized water), and adding the gelation modulator to the slurry (col 17 ln 10-15; Carbopol was added to the methocel). Hoeg does not disclose wherein the mixing occurs at 60-80 degrees C. Hoeg discloses that the mixing occurs at 90 degrees C (Col 16 ln 40-45; water was heated to 90 degrees C). it would have been obvious to a person having ordinary skill in the art to know that this mixing can be done at 60-80 degrees C through routine experimentation.

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Claims 4-6 lack an inventive step under PCT Article 33(3) as being obvious over Hoeg in view of WO 2018/148653 A1 to Aiviva Holding Limited (hereinafter Aiviva).

Regarding claim 4; Hoeg discloses a composition of claim 3 as discussed. Hoeg does not disclose wherein the wherein the active pharmaceutical ingredient is designed for anti-angiogenesis. However, Aiviva discloses a pharmaceutical composition to treat disease caused by angiogenesis (Abstract) that discloses the use of sustained release preparations (para [0024], compounds may be administered using sustained release capsules and tablets and administered topically, and para [0025], compounds may be used in conjunction with commonly used preparations including polymers). As both Hoeg and Aiviva disclose methods to deliver pharmaceuticals topically; it would have been obvious to a person having ordinary skill in the art to know that the pharmaceutical delivered by Hoeg in a reverse gel formulation can be a anti-angiogenesis composition disclosed by Aiviva, as it provides for extended release (Hoeg, col 3 ln 45-50; sustained release drug delivery systems); through routine experimentation.

Regarding claim 5; Hoeg discloses a composition of claim 3 as discussed. Hoeg does not disclose wherein the wherein the active pharmaceutical ingredient is a multi-kinase inhibitor. However, Aiviva discloses a pharmaceutical composition to treat disease caused by angiogenesis (Abstract); that discloses the use of a multi=kinase inhibitor (para [0016], compounds of the invention possess a spectrum of multi-kinase inhibition activities) that discloses the use of sustained release preparations (para [0024], compounds may be administered using sustained release capsules and tablets and administered topically, and para [0025], compounds may be used in conjunction with commonly used preparations including polymers). As both Hoeg and Aiviva disclose methods to deliver pharmaceuticals topically; it would have been obvious to a person having ordinary skill in the art to know that the pharmaceutical delivered by Hoeg in a reverse gel formulation can be a anti-angiogenesis composition disclosed by Aiviva, as it provides for extended release (Hoeg, col 3 ln 45-50; sustained release drug delivery systems); through routine experimentation.

Regarding claim 6; Hoeg discloses a composition of claim 3 as discussed. Hoeg does not disclose wherein the wherein the active pharmaceutical ingredient wherein the active pharmaceutical ingredient comprises axitinib, nintedanib, pirfenidone, riociguat, sorafenib, sunitinib, lenvatinib, regorafenib, ponatinib, pazopanib, or a combination thereof. However, Aiviva discloses a pharmaceutical composition to treat disease caused by angiogenesis (Abstract); that discloses the use of a multi-kinase inhibitor (para [0016], compounds of the invention possess a spectrum of multi-kinase inhibition activities), wherein the active pharmaceutical ingredient comprises axitinib, nintedanib, pirfenidone, riociguat, sorafenib, sunitinib, lenvatinib, regorafenib, ponatinib, pazopanib, or a combination thereof(para [0021], The multikinase inhibitors may include, but are not limited to, axitinib, nintedanib and lenvatinib), that discloses the use of sustained release preparations (para [0024], compounds may be administered using sustained release capsules and tablets and administered topically, and para [0025], compounds may be used in conjunction with commonly used preparations including polymers). As both Hoeg and Aiviva disclose methods to deliver pharmaceuticals topically; it would have been obvious to a person having ordinary skill in the art to know that the pharmaceutical delivered by Hoeg in a reverse gel formulation can be a anti-angiogenesis composition disclosed by Aiviva, as it provides for extended release (Hoeg, col 3 ln 45-50; sustained release drug delivery systems); through routine experimentation.

Claims 22-26, 27/26 lack an inventive step under PCT Article 33(3) as being obvious over Children in view of Hoeg.

Regarding claim 22; Children discloses a composition of claim 21 as discussed. Children discloses the change in viscosity (para [0197], matrix forming agents may undergo change in viscosity) but does not disclose having a first complex viscosity at about 37 degrees C and a second complex viscosity at about 5 degrees C, wherein the first complex viscosity is higher than the second complex viscosity. However. Hoeg discloses a pharmaceutical composition (col 3 ln 50-55; water soluble pharmaceutical medicaments) comprising a reverse thermal gelation material (col 3 ln 40-45; compositions that reversibly gel), that discloses a change in viscosity with increased concentration (Figure 1). As both Children and Hoeg disclose the use of reverse gel technique to deliver pharmaceuticals; it would have been obvious to a person having ordinary skill in the art to know that the composition disclosed by Children can exhibit viscosity changes as described by Hoeg through routine experimentation.

Regarding claim 23; Children in view of Hoeg discloses a composition of claim 22 as discussed. Neither Children nor Hoeg specifically disclose wherein the first complex viscosity is at least twofold higher than the second complex viscosity. However, Children discloses the rapid transition from viscoelastic to solid at 28 degrees C (para [0514], behaves as a liquid, whereas above 28 degrees C demonstrates a solid like behavior); it would have been obvious to a person having ordinary skill in the art to know that this can also mean that the first complex viscosity is at least twofold higher than the second complex viscosity; through routine experimentation.

Regarding claim 24; Children in view of Hoeg discloses a composition of claim 23 as discussed. Children further discloses having a first loss modulus () at about 37 degrees C and a second at about 5 degrees C, wherein the first G is higher than the second G (Figure 10 showing loss modulus at 37 and 5 degrees where the modulus at 37 higher than at 5 degrees C).

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Supplemental Box

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Regarding claim 25; Children in view of Hoeg discloses a composition of claim 24 as discussed. Although neither Children nor Hoeg specifically disclose wherein the percent gelation at about 37 degrees C is at least 70 percent; Children discloses the gelation as a function of temperature (Figure 13). It would have been obvious to a person having ordinary skill in the art to know that the increase in gelation with temperature as shown by Children can also mean that the percent gelation at about 37 degrees C is at least 70 percent; through routine experimentation.

Regarding claim 26; Children in view of Hoeg discloses a composition of claim 25 as discussed. Although neither Children nor Hoeg specifically disclose wherein the percent gelation at about 5 degrees C is no greater than 20 percent; Children discloses the gelation as a function of temperature (Figure 13). It would have been obvious to a person having ordinary skill in the art to know that the increase in gelation with temperature as shown by Children can also mean the percent gelation at about 5 degrees C is no greater than 20 percent; through routine experimentation.

Regarding claim 27/26; Children in view of Hoeg discloses a composition of claim 26 as discussed. Children further discloses wherein the composition further comprises phosphate (para [0319], phosphate buffer).

Claims 1-6,14,15,20-27,38 have industrial applicability as defined by PCT Article 33(4) because the invention can be made or used in industry.