PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.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.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IL2020/050011	05.01.2020	06.01.2019

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/7076 A61K31/4706 A61P3/04 A61P3/06

Applicant
CAN-FITE BIOPHARMA 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 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 notifed 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:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Uryga-Polowy, V Telephone No. +49 89 2399-0

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IL2020/050011

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 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:

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)	Yes:	Claims	10
	No:	Claims	1-9, 11-22
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-22
Industrial applicability (IA)	Yes:	Claims	1-22
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

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

Re Item V.

1 Cited documents

Reference is made to the following documents:

D1 WO 2017/090036 A1 (CAN-FITE BIOPHARMA LTD [IL]) 1 June 2017 (2017-06-01)cited in the application

D2 KR 101 881 441 B1 (SEOUL NAT UNIV R&DB FOUNDATION [KR]) 24 July 2018 (2018-07-24)

D3 NEDA RASOULI ET AL: "Ectopic fat accumulation and metabolic syndrome", DIABETES, OBESITY AND METABOLISM, vol. 9, no. 1, 1 January 2007 (2007-01-01), pages 1-10, XP055682029, ISSN: 1462-8902, DOI: 10.1111/j.1463-1326.2006.00590.x

D4 ERSILIA NIGRO ET AL: "New Insight into Adiponectin Role in Obesity and Obesity-Related Diseases", BIOMED RESEARCH INTERNATIONAL, vol. 2014, 1 January 2014 (2014-01-01), pages 1-14, XP055486972, ISSN: 2314-6133, DOI: 10.1155/2014/658913

Re Item V.

2 Novelty - Article 33(2) PCT

2.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-9, 11-22 is not new within the meaning of Article 33(2) PCT.

2.2 Document D1 discloses the effective reduction of fat/lipid accumulating in ectopic sites by an A3AR ligand, activator of the A3AR, be it an A3AR agonist or an A3AR allosteric enhancer; D1 also discloses a pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredient an A3AR ligand in an amount effective to reduce ectopic lipid accumulation in a tissue of a subject, suitable for daily administration; a unit dosage form for oral administration is also disclosed; various specific compounds are disclosed, and

among them all specific compounds of present claims 6, 7, 9, 17 and 19.

The subject-matter of claims 1-9, 11-20, 22 is therefore not new (Article 33(2) PCT).

2.3 Document D2 discloses A3AR ligands of formula (I) or (II) for use in treating obesity or diabetes, such as e.g. IB-MECA, Cl-IB-MECA, Thio-IB-MECA, Thio-Cl-IB-MECA; pharmaceutical compositions suitable for oral administration, for daily administration are also disclosed; D2 discloses the adiponectin-increasing activity of said compounds, as demonstrated in vitro in hBM-MSC cells.

The subject-matter of claims 1-7, 11-17, 20-22 is therefore not new (Article 33(2) PCT).

3 Inventive step - Article 33(3) PCT.

3.1 The present application does not meet the requirements of Article 33(1) PCT because the subject-matter of claims 1-22 does not involve an inventive step within the meaning of Article 33(3) PCT.

3.2 The subject-matter of claims 1-9, 11-22 is not new and therefore cannot involve an inventive step.

3.3 Dependent claim 10 does not appear to contain any additional feature which, in combination with the features of any claim to which they refer, meet the requirements of the PCT with respect to novelty and/or inventive step. The combined use with another antidiabetic agent is namely a usual option for the skilled person, and no special, surprising technical effect has been achieved for such a combination.

3.4 In addition, considering D4 as closest prior art, which discloses that increasing adiponectin expression or activity is beneficial in the prevention and/or treatment of obesity, together with the teaching of D2, which discloses the adiponectin increasing activity of the claimed compounds, also renders the present claims obvious.

Re Item VII.

4 **Form of the claims**

Claims 20 and 21 relate to subject-matter considered by this Authority to be covered by the provision of Rule 39.1(iv) PCT.

The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a **product**, in particular substances or compositions **for use in** a first or further medical treatment.

5 **Prior art**

To meet the requirements of Rule 5.1(a)(ii) PCT, the relevant prior art documents should be identified in the description and the relevant background art disclosed therein should be briefly discussed.

Re Item VIII.

6 **Clarity - Article 6 PCT**

6.1 The application does not meet the requirements of Article 6 PCT, because the subject matter of claims 1, 11, 21, 22 is not clear.

6.2 Independent claim 1 is formulated in the "second medical use" claim format, but is not only comprising therapeutic uses: whereas treating obesity is clearly therapeutic, reducing weight or reducing body fat mass are non therapeutic aspects.

6.2.1 In claims 1, 11, 21, 22, the application of the products (d) is functionally defined by a mechanism of action: "inhibiting adipocyte proliferation" , which does not allow the skilled person to clearly identify which concrete pathological conditions fall into that definition, rendering the scope of this claim unclear (Article 6 PCT).