PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)
(PCT Rule 44bis)

FOR FURTHER ACTION
See item 4 below

<table>
<thead>
<tr>
<th>Applicant’s or agent’s file reference</th>
<th>SBA013PCT</th>
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<tr>
<td>International application No.</td>
<td>PCT/IL2015/05872</td>
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<tr>
<td>International filing date (day/month/year)</td>
<td>30 August 2015 (30.08.2015)</td>
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<td>Priority date (day/month/year)</td>
<td>31 August 2014 (31.08.2014)</td>
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International Patent Classification (8th edition unless older edition indicated)
See relevant information in Form PCT/ISA/237

Applicant:
TEL HASHOMER MEDICAL RESEARCH INFRASTRUCTURE AND SERVICES LTD.

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the
   International Searching Authority under Rule 44 bis.1(a).

2. This REPORT consists of a total of 8 sheets, including this cover sheet.
   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a
   reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:
   - Box No. I Basis of the report
   - 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 Article 35(2) with regard to novelty, inventive step or
     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

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1
   but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from
   the priority date (Rule 44bis .2).

Date of issuance of this report
28 February 2017 (28.02.2017)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No. +41 22 338 82 70

Authorized officer
Simin Baharlou

e-mail: pct.team9@wipo.int

Form PCT/IB/373 (January 2004)
PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
WEBB & CO.
P.O. Box 2189
Rehovot 76121
Israel

PCT
WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) 07 Jan 2016

Applicant’s or agent’s file reference
SBA013PCT

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/IL2015/008872

International filing date
(day/month/year) 30 Aug 2015

Priority date
(day/month/year) 31 Aug 2014

International Patent Classification (IPC) or both national classification and IPC
IPC (2015.01) A61K 38/22 A61K 38/24 A61P 15/00 A61P 15/18

Applicant
TEL HASHOMER MEDICAL RESEARCH INFRASTRUCTURE AND SERVICES LTD.

1. This opinion contains indications relating to the following items:
   - [X] Box No. I Basis of the opinion
   - [ ] Box No. II Priority
   - [X] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - [ ] Box No. IV Lack of unity of invention
   - [X] 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
   - [X] 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 Authority has notified the International Bureau under Rule 66, 43bis(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:
Israel Patent Office
Technology Park, Bldg. 5, Malcha, Jerusalem, 9695101, Israel
Facsimile No. 972-2-5651616

Date of completion of this opinion
06 Jan 2016

Authorized officer
HERMAN Karin

Telephone No. 972-2-5651749

Form PCT/ISA/237 (cover sheet) (January 2015)
1. With regard to the language, this opinion has been established on the basis of:
   X the international application in the language in which it was filed.
   □ a translation of the international application into ________, which is the language of a
translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. □ This opinion has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established on the basis of a sequence listing:
   a. □ forming part of the international application as filed:
      □ 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 13ter.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 13ter.1(a)).
      □ on paper or in the form of an image file (Rule 13ter.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

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. 1-14

because:

☒ the said international application, or the said claims Nos. 1-14 relate to the following subject matter which does not require an international search (specify):

Claims 1-14 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

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

☐ 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. ______________________

☐ 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 a 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 a 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 13ter.1(a) or (b).

☐ See Supplemental Box for further details.

Form PCT/ISA/237 (Box No. III) (January 2015)
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

<table>
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<tr>
<th></th>
<th>Claims</th>
<th>Novelty (N)</th>
<th>4-9, 12, 15-18</th>
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<td></td>
<td>Claims</td>
<td>Inventive step (IS)</td>
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<tr>
<td></td>
<td>Claims</td>
<td>Industrial applicability (IA)</td>
<td>15-18</td>
<td>YES</td>
</tr>
</tbody>
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2. Citations and explanations:

2.1. **Reference is made to the following documents:**

- **D1** WO2009052119 (A1); 23.04.2009; UNIV COLUMBIA [US]; WANG JEFF [US]; TORTORIELLO DREW [US]
- **D2** WO 0108695 (A2); 08.02.2001; UNIV ERASMUS [NL]; GROOTEGOED JOHAN ANTON [NL]; THEMMELEN AXEL PETER NICO [NL]

3. **Novelty Article 33(1)PCT, Article 33(2)**

3.1. The present application meets the criteria of Article 33(1) PCT since none of the prior art discloses: a method or kit of inhibiting premature follicle activation induced by transplantation of ovarian tissue or whole ovary or by chemotherapeutic drug comprising administering a pharmaceutical composition comprising anti-mullerian hormone, agonist or anti MIR. Hence the subject-matter of claims 4-9, 12, 15-18 is new in the sense of Article 33(2) PCT.

3.2. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-3, 10-11, 13-14 is not new in the sense of Article 33(2) PCT.

3.3. Claims 1-3, 10-11, 13-14 relate to a method of inhibiting premature follicle activation induced by an acute insult, which can be endometriosis, comprising administering a pharmaceutical composition comprising anti-mullerian hormone, agonist or anti MIR.

3.4. D1 discloses a method for treating endometriosis in a female animal, comprising administering a therapeutically effective amount of Mullerian inhibiting substance (MIS), or a biologically active fragment or variant thereof (whole document). Mullerian Inhibiting Substance (MIS) is also known as Anti-Mullerian hormone (AMH), Mullerian inhibiting factor (MIF), and Mullerian inhibiting hormone (M1H) (para. 0017). In vitro experiments suggest that MIS partially inhibits the initial recruitment of primordial follicles and antagonizes subsequent FSH-dependent follicular growth. Supporting these observations, female MIS knockout mice exhibit increased recruitment of primordial follicles during the prepubertal period, resulting in the premature exhaustion of the
3.5. Therefore, D1 anticipates the subject-matter of claims 1-3, 10-11, 13-14 (Article 33(2) PCT).

4. 

4.1. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-18 is not inventive in the sense of Article 33(3) PCT.

4.2. The subject-matter of claims 1-3, 10-11, 13-14 is not new and therefore cannot involve an inventive step in the sense of Article 33(3) PCT.

4.3. Claims 4-6, 8-9, 15, 18 relate to a method and kit of inhibiting premature follicle activation induced by transplantation of ovarian tissue or whole ovary or by chemotherapeutic drug, comprising administrating a pharmaceutical composition comprising anti-mullerian hormone, agonist or anti MIR.

4.4. D2 discloses the use of exogenous AMH and/or AMH agonists and/or AMH antagonists for long-term control of female fertility (whole document). Women of various ages can be treated with AMH and/or AMH agonists and/or AMH antagonists for various reasons, such as contraception, extension of the fertile period, postponement of menopause, control of follicle development, etc. The method may seek to inhibit recruitment of primordial follicles into the pool of growing follicles, in particular in order to obtain contraception and/or prolong the duration of fertility and/or postpone the menopause. For this purpose, it is preferred to administer AMH and/or an AMH agonist (page 4 lines 22-26).

4.5. D3 discloses model simulations using the administration of exogenous AMH that show that the transfer of non-growing primordial follicles to the active state can be slowed enough to provide more follicles for development later in life and to cause a delay in the onset of menopause as measured by the number of primordial follicles remaining in the ovaries (abstract). Section 5 demonstrates how exogenous AMH inputs, AMH agonists and AMH antagonists affect model behavior. Fig. 7 shows that treatments with various doses of AMH may reduce the number of follicles entering the active pool and, hence, delay menopause as measured by the number of primordial follicles remaining in the ovaries.

4.6. D4 discloses the implication of the “burnout” phenomenon for ovarian tissue transplantation. The duration of graft survival following ovarian tissue transplantation can be as short as a few months, largely due to massive loss of primordial follicles during processing, freezing, and thawing. D4 also discloses that Ovotoxic chemotherapy agent cyclophosphamide (Cy) triggers upregulation of the PI3K pathway, initiating a wave of follicle recruitment and growth and, ultimately, burnout of the ovarian follicle reserve. Fig. 1B suggests that ovarian tissue grafts undergo a similar process of follicle activation and “burnout” to that seen following Cy treatment. AMH levels reflect the decline in ovarian follicle reserve and indicate a decrease in inhibition exerted on the same population of follicles. Co-administration of AS101 was shown to attenuated follicle burnout via its effect on the PI3k pathway and by reducing apoptosis in growing follicles. This raised the possibility that other agents that act on this crucial activation pathway may have the potential to reduce follicle burnout and preserve ovarian follicle reserve in the face of ovotoxic treatments or ovarian tissue transplantation.

4.7. D2 or D3 relates to a method of inhibiting premature follicle activation comprising administrating a pharmaceutical composition comprising anti-mullerian hormone or agonist. D2 or D3 does not teach that the premature follicle activation is induced by chemotherapy treatment or ovarian tissue transplantation. However D4 teaches that premature follicle activation (burnout) may be induced
by chemotherapy treatment or ovarian tissue transplantation. Hence, the skilled man in the art
could apply AMH or AMH agonist of D2 or D3 as an alternative to AS101 known from D4 for
treating premature follicle activation induced by chemotherapy treatment or ovarian tissue
transplantation without an inventive step. Thus the subject-matter of claims 4-6, 8-9, 15, 18 is not
inventive in the sense of Article 33(3) PCT.

4.8. The dependent claims 7, 12, 16-17 do not appear to contain any additional features which, in
combination with the features of any claim to which they refer, meet the requirements of the PCT
with respect to inventive step PCT Article 33(3) PCT.

5. **Industrial Applicability** Article 33(1)PCT and Article 33(4) PCT

5.1. The subject-matter of claims 15-18 is considered to be industrially applicable in the sense of Article
33(4) PCT.

5.2. For the assessment of the present claim 1-14 on the question whether they are industrially
applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be
dependent upon the formulation of the claims. The ILPO, for example, does not recognize as
industrially applicable the subject-matter of claims relating to a method of medical treatment of the
human body, but may allow claims relating to a compound for use in the medical treatment of the
human body or relating to use of a compound in the manufacture of a medicament.
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, 14, 15 do not meet the requirements of PCT Article 6, since the subject matter for which protection is sought is broadly defined. The description of the application relates only to a female subject, and not to any subject in need.