

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.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.
PCT/US2024/041774

International filing date (day/month/year)
09.08.2024

Priority date (day/month/year)
11.08.2023

International Patent Classification (IPC) or both national classification and IPC
INV. A61K39/395 C07K16/28

Applicant
PARAGON THERAPEUTICS, 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 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 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 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:



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Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Covone-van Hees, M

Telephone No. -0



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.
 - 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:

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. 4-10(completely); 1-3, 11-44(partially)

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. 4-10(completely); 1-3, 11-44(partially) are so unclear that no meaningful opinion could be formed (*specify*):
see separate sheet
- ☐ 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 the whole application or for said claims Nos. 1-44(partially)
- ☐ 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 13~~ter~~.1(a).
- ☒ See Supplemental Box for further details

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 separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1-44(partially)

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

1. Statement
- | | | |
|-------------------------------|-------------|----------------------------------|
| Novelty (N) | Yes: Claims | <u>1-3, 11-44(all partially)</u> |
| | No: Claims | |
| Inventive step (IS) | Yes: Claims | |
| | No: Claims | <u>1-3, 11-44(all partially)</u> |
| Industrial applicability (IA) | Yes: Claims | <u>1-3, 11-44(all partially)</u> |
| | 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

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 1 refers to TL1A binding protein, comprising HCDR1 seq.3, HCDR2 seq.9, HCDR3 seq.15, LCDR1 seq.21, LCDR2 seq.27, LCDR3 seq.33 or each CDRs with one or two aa substitutions compared to the respective seq.ID etc. followed by a long list of alternative TL1A defined by different CDRs.

Comparing the seq.ID referred to in the first four options of claim 1 and the tables at pg. 74-76 there is no correspondence between the CDR designations and the seq.ID numbering. Since it is impossible to make sense of which antibody is referred to, the options lack clarity to such extent, that said options cannot be searched.

Additionally, for designated Ab70 the claimed LCDR1 is seq.ID 691, but in the tab.pg.83 it corresponds to seq.ID.699.

Claim 2: The same lack of correspondence and major lack of clarity applies for the first 6 options of claim 2, said options cannot be searched.

Claims 4-10: cannot be searched at all, since none of the sequences ID corresponds to the CDRs listed in the tab.1.1-1.3, it follows that the claims lack clarity to such an extent that a search is not possible.

Claims 3,11-16, 28-43: these claims refer in part to the unclear, not searchable subject-matter. The search is accordingly limited to the part referring to anti-TL1A Ab clearly defined by the exact 6 CDRs and/or VH/VL sequences as defined in the tables in the description.

Claim 26, 27, 44: present claims aim to define the antibody by reference to binding to a single amino acid in a conformational epitope (cl.26,27) or by binding to a conformational epitope or as competing to any of the antibodies defined in the previous claims (claim 44). This definition lacks clarity since a) the epitope is not properly defined by only 1 aa, b) competing antibodies may compete by steric hindrance and not bind to the same epitope and c) conformational epitope mapping requires x-ray analysis of crystals of antigen:antibody complexes. All these factors contribute to not clearly define the claimed antibody, rendered a comparison with the many known anti-TL1A impossible. A full search for these claims cannot be therefore done and the search is limited to the exemplified antibodies, defined by structural features i.e. CDRs and VH/VL.

Re Item IV

Lack of unity of invention

The application lacks unity.

The following groups of inventions are not so linked as to form a single general inventive concept as required by Rule 13.1 PCT:

1. claims: 1-44(partially)

TL1A binding protein comprising HCDRs seq.ID 1,11,21 and LCDRs seq.ID 31,41,51, VH/VL seq.ID181,191 and related medical use claims to treat inflammatory diseases, pharmaceutical and injectable compositions, nucleic acid encoding the binding protein, the host cell comprising said nucleic acid, methods to produce said antibody.

- 2-119. claims: 1-44(partially)

TL1A binding protein comprising HCDRs, LCDRs seq.ID 31,41,51 and VH/VL as in tab.1.1-1.3 pg.75-98; tab.2 pg.106-122 and related medical use claims to treat inflammatory diseases, pharmaceutical and injectable compositions, nucleic acid encoding the binding protein, the host cell comprising said nucleic acid, methods to produce said antibody.

The reasons are as follows:

The problem to be solved in the present application and shared by all embodiments of all independent claims is the provision of antibodies binding to TL1A.

The common matter which can be identified as linking the various claimed inventions and which forms a solution to the above mentioned problem is based on the provision of antagonist anti-TL1A antibodies.

This common matter is not novel over at least WO2019209995, US2021093718, US2022390463, all disclosing neutralising anti-TL1A Ab.

In view of the above, the common matter does not comprise any same or corresponding special technical features and is consequently not a single general inventive concept.

Please note that since the claims are convolute and do not refer to the same TL1A Ab, by assignment of the claims to the inventions, all the searchable claims are indicated as partial. Nevertheless, each single invention is defined by the specific CDRs and VH/VL corresponding to the single Ab.

Moreover, the splitting of the claims and the non-unity subject-matter takes also into account the limitation of search as specified under item III.

Starting from the common matter, the following groups of potential inventions are identified:

Invention 1: claims: 1-3, 11-44 (all partially)

TL1A binding protein comprising HCDRs seq.ID 1,11,21 and LCDRs seq.ID 31,41,51, VH/VL seq.ID181,191 and related medical use claims to treat inflammatory diseases, pharmaceutical and injectable compositions, nucleic acid encoding the binding protein, the host cell comprising said nucleic acid, methods to produce said antibody.

Starting from the common matter, this group of claimed invention comprises the additional features of HCDRs seq.ID 1,11,21 and LCDRs seq.ID 31,41,51, VH/VL seq.ID181,191. These features are related to the solution to the problem of providing an alternative antagonist anti-TL1A Ab.

Invention 2-119: claims: 1-3, 11-44(all partially)

TL1A binding protein comprising HCDRs, LCDRs seq.ID 31,41,51 and VH/VL as in tab. 1.1-1.3 pg.75-98; tab.2 pg.106-122 and related medical use claims to treat inflammatory diseases, pharmaceutical and injectable compositions, nucleic acid encoding the binding protein, the host cell comprising said nucleic acid, methods to produce said antibody.

Starting from the common matter, this group of claimed invention comprises the additional features of HCDRs, LCDRs seq.ID 31,41,51 and VH/VL as in tab.1.1-1.3 pg. 75-98; tab.2 pg.106-122. These features are also related to the solution to the problem of providing alternative antagonist anti-TL1A Ab.

The antibodies of the groups of claimed inventions listed above do not share any significant structural elements and each belongs to a different recognised class of antibodies (PCT International Search and Preliminary Examination Guidelines, 10.17).

Consequently, the features of inventions 1-119 which make a contribution over the common matter are different.

Each of these features solves the problem of providing an alternative antagonist anti-TL1A Ab, however as the problem is already known from at least WO2019209995, US2021093718, US2022390463, which also disclose a solution to the same problem, the features are not corresponding either.

There is thus no relationship among these potential inventions which would involve the same or corresponding special technical features, such that the requirement of unity of invention is not met (Rule 13.1 PCT in conjunction with Rule 13.2 PCT).

When indicating the invention to be searched, the Applicant should also indicate which antibody he is interested, to avoid misunderstanding and clearly identify the antibody/ies

of interest. In the absence of this indication, the search will follow the order in the table i.e. according to the numbering of the antibodies from 1-119.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

- 1 The patentability can be dependent upon the formulation of the claims 29-36. 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.
- 2 Cited documents and summary

D1: WO 2019/209995 produces anti-TL1 A Ab, to treat inflammatory bowel disease (see § 141); humanised murine anti-TL1A Ab (see ex.1), shows high affinity and sensitivity (see § 167); CDRs mutation to improve binding in CDRs grafted Ab (see ex.2-7); strong neutralisation of binding (see ex.8) to human and cynomolgous; colitis is improved in rodent animal models (see ex.11) and draft clinical trials (ex.12, no results)

D2: US 2022/390463 relates to human, high-affinity, neutralising anti-TL1A Ab, cross-binding with human, cynomolgous, mouse TL1A, formulations, epitope characterisation, in vivo reduction of allergies in mouse model (see examples)

D3: US 2021/093718 concerns murine and humanised neutralising anti-TL1A Ab in vitro and in vivo in a colitis mouse model, clinical trials to treat Crohn's disease is also outlined (see examples)

D4: US 2019/106486 refers to high affinity, neutralising anti-TL1A Ab, effective in animal models to treat asthma, and other inflammatory diseases (see examples)

Invention 1 [1-3,11-44 (partially); 4-10 (not searched see above)]
- 3 **Novelty and Inventive Step** (Art.33(2) PCT and Art.33(3) PCT)
 - 3.1 An anti-TL1A Ab with HCDRs seq.ID 1,11,21 and LCDRs seq.ID 31,41,51 is not known in the art, claim 1 and claims depending or referring back to it are novel (Art.33(2) PCT).
 - 3.2 D1 or alternatively any of D2-D4, is considered to represent the most relevant state of the art, from which the subject-matter of claim 1 differs in the HCDRs and LCDRs. The provision of alternative anti-TL1A antibodies which do not

show any apparent surprising technical effect over the anti-TL1A antibodies of the prior art D1 or alternatively any of D2-D4 is not considered to involve an inventive step. Indeed, the skilled person, starting from the disclosure of D1 or alternatively any of D2-D4 and confronted to the problem of providing additional anti-TL1A antibodies, would use the common techniques of molecular and cellular biology (the same as the ones used in the present application) to generate, purify and characterise further anti-TL1A antibodies, without applying any inventive skills. The selection of anti-TL1A antibodies without unexpected properties from a group of anti-TL1A antibodies is considered to be arbitrary.

- 3.3 Remaining claims 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: they are mainly standard alternatives in this technical field, which fall within the routine skills of those in the art, and which do not appear to lead to any surprising effects or advantages.

Re Item VII

Certain defects in the international application

- 4 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in D1-D4 is not mentioned in the description, nor are these documents identified therein.