

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 220703-010508PCT	FOR FURTHER ACTION		See Form PCT/IPEA/416
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 national classification and IPC INV. A61K39/395			
Applicant PARAGON THERAPEUTICS, INC.			
1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of <u>9</u> sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. ☒ a total of <u>317</u> sheets, as follows: ☒ sheets of the description, claims and/or drawings which have been amended and/or sheets containing rectifications authorized by this Authority, unless those sheets were superseded or cancelled, and any accompanying letters (see Rules 46.5, 66.8, 70.16, 91.2, and Section 607 of the Administrative Instructions). ☐ sheets containing rectifications, where the decision was made by this Authority not to take them into account because they were not authorized by or notified to this Authority at the time when this Authority began to draw up this report, and any accompanying letters (Rules 66.4bis, 70.2(e), 70.16 and 91.2). ☐ superseded sheets and any accompanying letters, where this Authority either considers that the superseding sheets contain an amendment that goes beyond the disclosure in the international application as filed, or the superseding sheets were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in item 4 of Box No. I and the Supplemental Box (see Rule 70.16(b)). b. ☐ a separate electronic file containing a sequence listing (<i>sent to the International Bureau only</i>)			
4. 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			
Date of submission of the demand 11.06.2025		Date of completion of this report 09.10.2025	
Name and mailing address of the international preliminary examining authority:  European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040		Authorized officer Covone-van Hees, M Telephone No. +31 70 340-4416	



INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2024/041774

Box No. I Basis of the report

1. With regard to the **language**, this report is based on
- ☒ 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 (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a) and (b))
2. With regard to the **elements*** of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

Description, Pages

1-236 filed in electronic form on 11-06-2025

Sequence listings, SEQ ID NO

1-2595 as originally filed

Claims, Numbers

1-44 as amended (together with any statement) under Art. 19 PCT

Drawings, Sheets

1/26-26/26 as originally filed

- ☒ a sequence listing - see Supplemental Box Relating to Sequence Listing.
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since either they are considered to go beyond the disclosure as filed, or they were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in the Supplemental Box (Rules 70.2(c) and (c-bis)):
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):

5. ☐ This report has been established:
- ☐ taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rules 66.1(d-bis) and 70.2(e)).
 - ☐ without taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91(Rules 66.4bis and 70.2(e)).
6. ☒ With regard to top-up searches (Rules 66.1ter and 70.2(f)):
- ☒ A top-up search was carried out by this Authority on 23.06.2025 (all discovered documents are listed in the Supplemental Box Relating to Top-up Search).
 - ☐ Additional relevant documents have been discovered during the top-up search.
 - ☐ No top-up search was carried out by this Authority because it would serve no useful purpose.
7. ☐ Supplementary international search report(s) from Authority(ies) has/have been received and taken into account in establishing this report (Rule 45bis.8(b) and (c)).

* If item 4 applies, some or all of those sheets may be marked "superseded".

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. 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 preliminary examination (*specify*):
 - ☐ 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 the said claims Nos. 4-10(completely); 1-3, 11-44(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 Preliminary Examining 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 Rules 13ter.1(a) and 13ter.2.
 - ☒ See separate sheet for further details

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/US2024/041774

Box No. V Reasoned statement under Article 35(2) 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</u>
	No: Claims	

2. Citations and explanations (Rule 70.7):

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

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, 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 and/or examination,
 - ☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
 - c. ☐ furnished to this Authority as an amendment* under PCT Article 34 on .
 2. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established to the extent that a meaningful opinion referred to in Article 33(1) could be formed without a WIPO Standard ST.26 compliant sequence listing.
 3. Additional comments:
- * *If item 4 in Box No. I applies, the sequence listing, which forms part of the basis of the report, may be marked "superseded."*

Re Item I

Basis of the report

- 1 The applicant wishes the international preliminary examination to start on the basis of the claims 1-44 as amended under Article 19 and description pages 1-236 under Article 34 PCT.

Re Item III

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

- 1 The applicant/representative is informed that the search is the responsibility of the ISA under Chapter I of the PCT, the procedure before the ISA is closed and that there is no provision in the PCT for a review of or an appeal against the findings of the ISA by the IPEA. Therefore, what was not searched will not be examined. During ISA as Chapter I, claims 1-16,26-44 have been objected under lack of clarity and disclosure as detailed below and only partially searched:
- 2 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.
- 2.1 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 is impossible to make sense which antibody is referred to, the options lack clarity to such extent, that said options cannot be searched.
- 2.2 Additionally, for designated Ab70 the claimed LCDR1 is seq.ID 691, but in the tab.pg.83 corresponds to seq.ID.699.
- 3 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.
- 4 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.
- 5 Claims 3,11-16, 28-43: these claims refer in part to the unclear, not searchable subject-matter.

- 5.1 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.
- 6 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 therefore be done and the search is limited to the exemplified antibodies, defined by structural features i.e. CDRs and VH/VL.
- 7 An objection of lack of unity was raised during chapter I and 119 groups of inventions were identified:
- 7.1 Please note that the claims filed during chapter I were convolute and did not refer to the same TL1A Ab of tab.1.1-1.3 pg.75-98. By assignment of the claims to the inventions, all the searchable claims were indicated as partial. Nevertheless, each single invention has been defined by the specific CDRs and VH/VL corresponding to the single Ab, in particular the first invention refers to the first antibody referred to in Tab.1.1.
- 7.2 Moreover, the splitting of the claims and the non-unity subject-matter took also into account the limitation of search as specified above
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 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.

- 7.3 The Applicant did not reply to the invitation to pay additional fees and accordingly the search was limited to invention 1.

Re Item V

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

- 1 As noted above under item III, the search is the responsibility of the ISA under Chapter I of the PCT, the procedure before the ISA is closed and there is no provision in the PCT for a review of or an appeal against the findings of the ISA by the IPEA.
- 1.1 Moreover, the Applicant did not pay additional search fees upon invitation, the search was therefore limited to anti-TL1A Ab with HCDRs seq.ID 1,11,21 and LCDRs seq.ID 31,41,51
- 1.2 What was not searched will not be examined
- 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.
- 4 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.

Re Item VII

Certain defects in the international application

- 5 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.