PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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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/IB2021/050464	21.01.2021	24.01.2020

International Patent Classification (IPC) or both national classification and IPC
INV. A61P7/00 C07K16/28 ADD. A61K39/00

Applicant
PFIZER 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 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	Malamoussi, A Telephone No. +49 89 2399-0

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IB2021/050464

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. 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, 5, 7-40(all 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. 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 whole application or for said claims Nos. 1, 5, 7-40(all 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 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

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	2-4, 6(completely); 1, 5, 7-12, 15, 21, 23-25, 28-35, 37, 39, 40(partially)
	No:	Claims	13, 14, 16-20, 22, 26, 27, 36, 38(all partially)
Inventive step (IS)	Yes:	Claims	
	No:	Claims	2-4, 6(completely); 1, 5, 7-40(partially)
Industrial applicability (IA)	Yes:	Claims	2-4, 6(completely); 1, 5, 7-40(partially)
	No:	Claims	

2. Citations and explanations

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 III

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

1.1 The present application comprises claims relating to several thousand possible anti-E-selectin antibodies. According to Rule 6.1(a) PCT, the number of claims shall be reasonable in consideration of the nature of the invention claimed, which is not the case here.

1.2 The application relates to sequence combinations, which may or may not generate an antibody with defined technical properties. The examiner is unable to search the thousands of combinations claimed without undue burden.

1.3 For the purposes of an incomplete search, the applicant was requested to identify the subject matter to be searched in more detail, for example, with reference to fully defined antibodies disclosed in the application and claims.

1.4 In their reply to invitation to provide informal clarification according to PCT/GL/IPSE paragraphs 9.34 and 9.35, the applicant requested that antibody 1444 (optimized) is searched.

1.5 Present search is thus restricted to the subject matter relating to antibodies comprising the particular CDR combinations with the order as shown in table 3 on p. 87 as far as relating to antibody 1444 (optimized), i.e. an antibody comprising HCDR1-3 with SEQ ID No 8-10, and LCDR1-3 with SEQ ID No 2-4, respectively.

Re Item V

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

2 "Method of treatment" **claims 22-33 and "Swiss type" claims 38-39**

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. An opinion is given on novelty and inventive step on the basis of the alleged effect of the product/composition.

3 "First/second medical use" **claims 36-37** and **40**

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.

Patentability, in particular novelty and inventive step, of claims **36-37** and **40** has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

4 In case the application enter the European Regional Phase, the applicant is informed that

1) claims in the format "Substance/composition X for use in the treatment of disease Y" are considered allowable (c.f. claim 36) , and

2) a claim in the form "Use of a substance or composition X for the manufacture of a medicament for therapeutic application Z" is allowable for either a first or "subsequent" (second or further) such application ("Swiss-type" claim), if this application is new and inventive and has a filing or earliest priority date before 29 January 2011 (which is presently not the case).

5 **Most relevant prior art documents**

D1 teaches the in vivo and in vitro characterization of an engineered human antibody to E-selectin, termed **SPLAT-1** (abstract). The antibody was engineered based on a known murine antibody ENA-2 (p. 110, right col., paragraph 2-p. 112, left col., paragraph 1). The affinity of SPLAT-1 was measured by Biacore and found to be 1.6 nM (p. 112, left col., paragraph 2). SPLAT-1 blocks the binding of human leukocytes to E-selectin (abstract, fig. 2) and does not mediate ADCC or complement-mediated lysis of endothel cells (abstract, fig. 3, 4). In vivo, SPLAT-1 inhibits the recruitment of leukocytes to cytokine-inflamed skin grafted on to SCID mice and has a long circulating half-life in primates, making the antibody suitable for use in human therapy (abstract, fig. 5). SPLAT-1 had a half life of 12-14 days in healthy cynomolgous monkeys and even after prolonged exposure to the antibody, the primates did not produce a detectable immune response to the antibody (p. 115, left col., paragraph 2).

D2 relates to humanized antibodies that bind to E-selectin (abstract), in particular the antibody **CY1788** (example 2). CY1788(V_{HF}/V_{LA})-IgG4 inhibited the adhesion of human neutrophils to rIL-1β activated HUVECs (p. 51, l. 17-19).

D3 discloses the antibody **Mab18/7** which is specific for E-selectin and inhibits the adhesion of PMN and HL-60 cells to activated HEC monolayers (example 3).

D4 describes antibodies binding to ELAM-1 (E-selectin), in particular CL2 (p. 13, paragraph 4-p. 14, paragraph 1), which significantly attenuated total leukocyte infiltration and the number of infiltrating neutrophils in treated animals (p. 16, paragraph 2). Moreover, CL2 treatment resulted in a significant reduction in late-phase bronchoconstriction but had no apparent effect on the acute response (p. 16, paragraph 2).

D5 discloses antibodies that cross react with E- and P-selectin, as well as antibodies that are reacting with E-selectin only, in particular antibodies 1E4 and 2D4 (p. 36, l. 37-38). 1E4 blocked normal human peripheral blood neutrophil binding to TNF-α activated HUVEC (p. 40, l. 5-10).

D6 discloses the blocking anti-CD62E (E-selectin) antibody **P6E2** (abstract).

D7 describes a blocking monoclonal antibody to ELAM1 (E-selectin), termed **BB11** (abstract).

6 Novelty (Art. 33(3) PCT)

6.1 **Claim 13** aims at providing an antibody that competes for binding to human E-selectin with 1444 (optimized). **Claims 13-40** are dependent on **claims 1-13**, i.e. including the subject matter of **claim 13**. The prior art documents **D1** to **D7** all disclose antibodies that bind to E-selectin (see above). It is noted that a competing antibody might not necessarily bind to the same epitope as an antibody being defined in **claims 1-12**. Antibodies can compete for binding through steric hindrance, without necessarily binding to the same epitope, or having any of the technical properties associated with the antibody with which they should compete. Since it cannot be excluded beyond reasonable doubt that the known antibodies compete for binding with the antibody 1444 (optimized), the subject matter of **claim 13** is not considered to be novel in view of any one of **D1** to **D7** (**Art. 33(2) PCT**).

6.2 Moreover, **D1** discloses a method of making an antibody of **claim 13** (see p. 108, right col.), a pharmaceutical composition comprising said antibody, a method of treating a medical condition associated with expression of E-selectin (see p. 113, left col., paragraph 1 and fig. 5), and a method of decreasing an E-selectin biological activity in a subject (see p. 113, left col., paragraph 1 and fig. 5), therefore, the subject matter of **claims 19-20, 22, 26-27, 36** and **38** does not appear to be novel in view of **D1.**

6.3 **D2** teaches nucleic acids, vectors, host cells (CHO), methods of making an antibody (see example 4), therefore, the subject matter of **claims 14, 16-20** does not appear to be novel in view of **D2.**

6.4 Since **D4** discloses the in vivo administration of a pharmaceutical composition comprising the anti-E-selectin antibody CL2, which significantly attenuated both the total leukocyte infiltration and the number of infiltrating neutrophils in the treated animals (p. 13, paragraph 4- p. 14, paragraph 1 and p. 16, paragraph 2), the subject matter of **claims 20, 22, 26-27, 36, and 38** does not appear to be novel in view of **D3** (**Art. 33(2) PCT**).

6.5 The prior art documents at hand do not appear to disclose an isolated antibody, or antigen binding fragment thereof, that specifically binds to human E-selectin comprising heavy and light chain variable region CDRs with SEQ ID No with SEQ ID No 8-10, and SEQ ID No 2-4, respectively, i.e. relating to antibody 1444 (optimized), or the subject matter of **claims 15, 21, 23-25, 28-35, 37, 39** and **40**, only as far as relating to antibody 1444 (optimized).

6.6 Therefore, the subject matter of **claims 1-12, 15, 21, 23-25, 28-35, 37, 39** and **40,** only as far as relating to the antibody 1444 (optimized) appears to be novel (**Art. 33(2) PCT**).

7 Inventive Step (Art. 33(3) PCT)

7.1 **D1** might be considered to represent the closest prior art document for the subject matter of **claim 1**. Alternatively any one of **D2** to **D7**, each taken separately and independently, might be the closest prior art document.

7.2 The subject matter of **claim 1**, only as far as relating to an antibody comprising the three heavy and three light chain CDR sequences of antibody 1444 (optimized) (see point 1.5) differs from **D1** (or any one of **D2** to **D7**) in that it comprises the particular CDR sequences.

7.3 There does not appear to be a technical effect caused by this difference, since the antibodies of **D1** (or any one of **D2** to **D7**) and the claimed antibodies specifically bind to human E-selectin.

7.4 The objective technical problem may thus be regarded as the provision of an alternative anti-human E-selectin antibody.

7.5 The solution disclosed in **claim 1** with the restriction as provided under point 1.5, does not involve an inventive step for following reasons:

7.6 The procedure to obtain, screen and produce monoclonal antibodies specifically recognizing well known proteins such as human E-selectin, is considered routine procedure for the skilled artisan. Therefore, the production of monoclonal antibodies directed against human E-selectin is considered to represent a routine procedure (see for example **D1-D7**) and, in the absence of evidence to the contrary, the antibodies as defined in the claims do not solve a previously unforeseeable technical problem and do not lead to an unexpected and surprising technical effect.

7.7 If a novel antibody binds to the same antigen as known antibodies, inventive step is not acknowledged solely on the basis that the novel antibody is structurally different from the known antibodies. Arriving at alternative antibodies by applying techniques know in the art is considered to be obvious to the skilled person. The fact that the structure of the thus obtained alternative antibodies, i.e. their amino acid sequences of the six CDRs, is not predictable is not a reason for considering these antibodies as non-obvious.

7.8 Therefore, the subject matter of **claims 1-12** does not appear to involve an inventive step in view of **D1** or any one of **D2-D7** (**Art. 33(3) PCT**).

7.9 Even if **claim 13** was considered novel, it would not be regarded as involving an inventive step for the following reasons. There are not effects associated with the antibodies of claim 13. They do not have to exhibit any of the activities attributed to or shown for antibody 1444 (optimized), since the antibodies may compete and yet do not share functional properties. For instance, the antibodies may bind overlapping epitopes, or even distinct epitopes and merely sterically hinder binding of each other.

7.10 The additional features of independent **claims 15** and dependent **claims 21, 23** and **28-35** were not shown to relate to any surprising effect and thus are, in view of **D1**, or any one of **D2-D7**, and the general knowledge in the art, not inventive (**Art. 33(3) PCT**).

7.11 Even if a product claim to a monoclonal anti-human E-selectin antibody were considered novel and inventive, a claim drawn to a polynucleotide comprising a nucleic acid encoding only the light **or** heavy chain of an antibody as currently worded in **claim 15** would not be considered inventive as it only refers to part of an antibody which cannot display the same features as the full antibody comprising heavy and light chains. The polynucleotide of the VH or VL alone is not an intermediate for the production of the full antibody, since, most plausibly, the VH or VL does not have the same binding capacity as the full antibody VH and VL.

7.12 **Claims 24-25, 37, 39** and **40** aim at providing an antibody for the treatment of SCD.

7.13 **D8** might be considered to represent the closest prior art document for the subject matter of **claims 24-25, 37, 39** and **40**, since it discloses the treatment of SCD with E-selectin specific inhibitors.

7.14 **D8** discloses the use of the pan-selectin inhibitor GMI-1070, which was designed on the basis of the bioactive conformation of sLex in the carbohydrate-binding domain of E-selectin and preferentially inhibits E-selectin over P- or L-selectin (p. 1781, right col., paragraph 1). **D8** teaches that the dramatic effect of GMI-1070 on leukocyte rolling velocities is consistent with efficient in vivo blockade of E-selectin function (p. 1783, left col., paragraph 1). Administration of GMI-1070 reversed sickle cell crisis by improving blood flow and survival of SCD mice (p. 1783, right col., paragraph 2). **D8** concludes that E-selectin plays a major role in red blood cells (RBC)-white blood cells (WBC) interactions, improved blood flow and survival of SCD mice (p. 1784, right col., paragraph 2-p. 1785, left col., paragraph 1).

7.15 The subject matter of **claims 24-25, 37, 39** and **40** differs from **D8** in that the agent used to treat SCD is an anti-E-selectin antibody.

7.16 There does not appear to be a technical effect caused by this difference.

7.17 The objective technical problem may be regarded as the provision of an alternative agent for use in the treatment of SCD.

7.18 Starting from the disclosure of **D8**, the person skilled in the art looking for an alternative agent for use in the treatment of SCD would consider to use an anti-E-selectin antibody, instead of the inhibitor GMI-1070. In view of **D8** which underlies the role of E-selectin in SCD, the skilled person being aware of the advantages offered by monoclonal antibodies in terms of specificity, would be motivated to provide a specific inhibitor in form of a monoclonal antibody binding

to E-selectin and would thus arrive at the subject matter of **claims 24-25, 39** and **40** in an obvious manner, without being inventive. As discussed herein above, the mere provision of anti-human E-selectin antibodies does not involve an inventive step in view of any one of **D1** to **D7**. Consequently, **claims 24-25, 37, 39** and **40** do not appear to involve an inventive step in view of **D8** and any one of documents **D1** to **D7** (**Art. 33(3) PCT**).

Re Item VIII

8 **Certain observations on the international application**

8.1 Since the three CDRs of each of the variable domains of the light and heavy chains are normally responsible for binding to the antigen, the conventional antibody, in order to be uniquely defined by its structure only and have its characteristic binding specificity, needs to be defined by at least these six CDRs to fulfil the requirements of **Art. 6 PCT**.

8.2 Regarding **claim 2:** CDRs when not defined by their specific sequence must be defined according to a numbering scheme, for example, chosen from that of Kabat, Chothia or IMGT.

8.3 **Claim 9** aims at providing a camelid antibody. It is known in the art that camelids produce functional antibodies devoid of light chains. The present application shows in the examples the production of antibodies comprising heavy and light chain sequences, however, does not provide clear and complete disclosure of how to provide different antibody formats such as camelid antibodies being devoid of a light chain. The skilled person is thus left with the task and burden to find how the teaching related to antibody 1444 (optimized) could be extended to products of different origin, contrary to the requirements of **Art. 5 PCT**.

8.4 Limitation to specific K_D, K_{on} or K_{off} values, IC_{50} e.g. in **claims 10-12**, without indication of the minimal assay conditions in the corresponding claim, and a detailed assay protocol in the examples is meaningless, given that said values depend in the specific assay conditions chosen. Choosing the right assay conditions will result in one of the specifically indicated values. Hence, as presently used, said parameters are considered to be non-limiting (**Art. 6 PCT**).

8.5 The term "optionally" in **claim 12** renders the subsequent text meaningless.

8.6 Regarding **claim 13**: depending on the order of binding an antibody can be competing or not. Thus the boundaries of the claim is not clear without further defining the competition assay (**Art. 6 PCT**). Please see **XP55572134**, table 2 where INIA6D8 is not competing (0%) with JM7A11 but vice-versa JM7A11 is competing with INIA6D8 (53%).

8.7 The term "PER.C6" appears to be a trademark. Trademarks and similar expressions characterize the commercial origin of goods, rather than the properties of the goods (which may change from time to time) relevant to the invention. Therefore, trademarks and similar expression should be removed from claims (**Art. 6 PCT**, Guidelines 5.39).

8.8 **Claim 22** refers to a functionally defined disease, namely characterized by "mediated by or associated with expression of E-selectin and/or binding of E-selectin to a ligand". Such a functional definition does not allow to clearly determine the scope of the claim without undue burden. In a second medical use claim, the pathology to be treated must be clearly defined.

8.9 **Claims 26** and **40** do not define a specific medical use of the claimed product. The therapeutic application in **claims 26** and **40** is functionally defined as "decreasing an E-selectin biological activity in a subject" (**claim 26**) or "reducing E-selectin activity in a subject" (**claim 40**), which does not allow for any practical application in the form of a real, defined treatment of a pathological condition (disease). It is the mere mechanism which may underlie a potential therapy and thus cannot be the subject of a therapeutic use claim (**Art. 6 PCT**). Moreover the "biological activity" is not further defined, leaving the reader in doubt of the activity to be reduced.

8.10 The term "IW-1701" appears to be an internal designation which has no generally recognized meaning and thus, leaves the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the definition of the subject-matter of **claim 29** unclear.

8.11 **Claim 30** provides for compounds that are characterized by the properties they should have, i.e. "a compound that modulates HbS so as to maintain it in its R state", " a compound that targets HbS multimerization by modulating generation of 2, 3-diphosphoglyceric acid" etc. The functional definitions solely refer to technical effects of the desired compounds and in no way provide information as to the structural and technical features thereof. Apart from rendering the claims unclear, said functional definitions put an undue burden on the skilled

person seeking to establish the scope of the referred functional feature, so as to be able to carry out the invention over the whole scope of the claims (**Art. 5 and 6 PCT**).

8.12 In a later European regional phase objections might be raised against any expression within the description such as "...incorporated by reference..." (e.g. on page1) as the regional patent law requires that the application is self-contained.

8.13 The vague statements in the description in paragraph [0390] imply that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (**Art. 6 PCT**) when used to interpret them.