

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

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/US2019/041154

International filing date (day/month/year)
10.07.2019

Priority date (day/month/year)
11.07.2018

International Patent Classification (IPC) or both national classification and IPC
INV. C07K16/28 A61P35/00 A61P35/02 A61P35/04 A61K39/395

Applicant
FIVE PRIME 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:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0
Fax: +49 89 2399 - 4465

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Irion, Andrea

Telephone No. +49 89 2399-0



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 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:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

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>160-167</u>
	No: Claims	<u>1-159, 168-171</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-171</u>
Industrial applicability (IA)	Yes: Claims	<u>1-171</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

Item V

V.1 Reference is made to the following documents:

- D1 WO 2012/033953 A1 (HALOZYME INC [US]; KODANDAPANI LALITHA [US] ET AL.) 15 March 2012 (2012-03-15)
- D2 WO 2014/039983 A1 (DARTMOUTH COLLEGE [US]) 13 March 2014 (2014-03-13)
- D3 WO 2015/097536 A2 (JANSSEN PHARMACEUTICA NV [BE]) 2 July 2015 (2015-07-02)
- D4 WO 2016/207717 A1 (JANSSEN PHARMACEUTICA NV [BE]) 29 December 2016 (2016-12-29)
- D5 WO 2017/137830 A1 (JANSSEN PHARMACEUTICA NV [BE]) 17 August 2017 (2017-08-17)
- D6 DATABASE EMBASE [Online]
- Pdoc ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL; 1 July 2019 (2019-07-01), JOHNSTON R J ET AL: "Acidic pH selective binding of VISTA to PSGL-1 and anti-tumor activity of combined VISTA and PD-1 blockade", Database accession no. EMB-628912926 ; & JOHNSTON R J ET AL: "Acidic pH selective binding of VISTA to PSGL-1 and anti-tumor activity of combined VISTA and PD-1 blockade", CANCER RESEARCH 20190701 AMERICAN ASSOCIATION FOR CANCER RESEARCH INC. NLD, vol. 79, no. 13, Supplement, 1 July 2019 (2019-07-01), ISSN: 1538-7445
- D7 WO 2018/169993 A1 (FIVE PRIME THERAPEUTICS INC [US]; SQUIBB BRISTOL MYERS Pdoc CO [US]) 20 September 2018 (2018-09-20)
- D8 WO 2019/183040 A1 (FIVE PRIME THERAPEUTICS INC [US]; SQUIBB BRISTOL MYERS Edoc CO [US]) 26 September 2019 (2019-09-26)
- D9 WO 2019/185879 A1 (HUMMINGBIRD BIOSCIENCE HOLDINGS PTE LTD [SG]; CLEGG Edoc RICHARD IAN [GB]) 3 October 2019 (2019-10-03)

V.2 Novelty (Article 33(2) PCT)

V.2.1 Prior art documents

Document D1 describes methods for identifying antibodies showing pH-dependent binding. Anti-tumor antibodies capable of preferably binding to an antigen under acidic conditions (tumor-microenvironment) are disclosed (p. 3 l. 30 - p. 4 l. 3, p. 4 l. 17-24). Said antibodies are more active in low pH than at neutral or physiological pH (p. 5 l. 23-31). See also Examples 8 and 9.

Document D2 describes antibodies directed against VISTA used for the treatment of cancer (p. 69 3rd paragraph). Said antibodies are used for upregulating an immune response by inhibiting the VISTA-mediated suppression of immune responses (p. 9 I. 1-4, p. 15 4th and 5th paragraph, p. 24 4th paragraph, p. 77 2nd paragraph - p. 80 3rd paragraph).

Documents D3 and D4 describe antibodies raised against cynoVISTA that bind also human VISTA. Said antibodies activate T cells and monocytes and have anti-bladder tumor properties. VSTB95 and VSTB112 bind to epitopes comprising aa 27-36 and 54-65. Said antibodies bind to the FG loop of huVISTA. (see D3: Examples 4, 7-15; D4: Example 4, 7-15, 27)

Document D5 describes anti-VISTA antibodies interacting with cynoVISTA and huVISTA. Said antibodies show anti-tumor effects in murine bladder tumor model (Example 12). Epitopes bound by said antibodies are aa 27-36 and aa 54-65 (Example 13). Said antibodies activate T cells and monocytes (Example 15).

V.2.2 With respect to claims 1-159 and 168-171

Due to the unclear meaning of several features in the claims (see items V.5.2-V.5.22 below) claims 1-159 and 168-171 are not considered novel over the disclosure of each of D2-D5. Therefore, claims 1-159 and 168-171 do not meet the requirements of Article 33(2) PCT.

V.2.3 With respect to claims 160-167

None of the cited prior art documents describes an anti-VISTA antibody comprising the HCDRs of SEQ ID NO. 503-517. Therefore, the subject-matter of claims 160-167 are considered novel in the sense of Article 33(2) PCT.

V.3 Inventive step (Article 33(3) PCT)

V.3.1 With respect to claims 160-167

The subject-matter of claims 160-167 differs from each of the documents D2-D5 in the sequence of the HCDRs. The technical effect based on said difference is not apparent from the application as originally filed since comparative data are missing.

The technical problem to be solved may be regarded as providing alternative anti-VISTA antibodies. (NOTE: Antibodies of claims 160-167 are not limited by showing pH sensitive or dependent binding)

The mere provision of an alternative can only be regarded as demonstrating inventive step when the alternative provides some sort of technical advantage, otherwise the specific choice is merely an arbitrary selection of one among a number of equally viable known alternatives.

Hence the subject-matter of claims 160-167 does not meet the requirements of Article 33(3) PCT.

V.4 Industrial applicability (Article 33(4) PCT)

V.4.1 With respect to claims 1-171

The subject-matter of claims 1-171 appears to be susceptible of industrial application.

V.5 Further remarks

V.5.1 With respect to claims 150-158, and 168-171

The subject-matter of claims 150-158 and 168-171 is considered to be a method of treatment by therapy of the human or animal body.

For the assessment of the present claims 150-158 and 168-171 on the question whether they are patentable, no unified criteria exist in the PCT Contracting States. 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 150-158 and 168-171 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

V.5.2 With respect to claims 3-37, 39-45 and 48

The subject-matter of claims 3-37, 39-45, 48 refers to the binding of anti-VISTA antibodies in acidic conditions with a KD that is lower than its KD in neutral or physiological conditions, or with a specific koff value. The method measuring said KD or koff is not defined (Article 6 PCT).

V.5.3 With respect to the expressions "acidic condition", "neutral condition" and "physiological condition"

It is not clear where the limit pH value of an acidic condition should be located in order to distinguish an acidic pH from a neutral pH. Furthermore, in order to meet the requirements of Article 6 PCT a "physiological pH" or "physiological condition" should be defined by a numeric value, since a cancer has also its physiological pH.

V.5.4 With respect to claim 60

Claim 60 reads

The isolated antibody of any one of claims 55, 57 or 59, wherein a condition having a pH of less than pH 7.0 is a tumor or any diseased area having a pH of less than pH 7.0 in a subject and in which an immune stimulation is desired. (emphasis added)

The underlined feature is unclear in the sense of Article 6 PCT.

V.5.5 With respect to claim 67

Claim 67 reads

The isolated antibody of any one of claims 1-66, wherein the antibody has been engineered to bind to hVISTA at acidic pH, but wherein the antibody does not bind specifically to hVISTA at neutral or physiological pH. (emphasis added)

Having an antibody in his/her hand the skilled person does not know whether said antibody has been engineered to bind hVISTA at acidic pH or not. Therefore, claim 67 does not meet the requirements of Article 6 PCT.

V.5.6 With respect to claims 68, 69, 82, 91, 92

Claim 68 reads

The isolated antibody of any one of claims 1-67, wherein the antibody binds at or near the histidine rich region of hVISTA, such as the histidine-rich B-sheet extension. (emphasis added)

Claim 69 reads

The isolated antibody of claim 68, wherein the antibody binds at or near the histidine rich region of hVISTA, such as the histidine-rich B-sheet extension, in conditions having a pH of 6.0-6.5.

The term "near" used in claim 68 is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claim unclear, Article 6 PCT.

Furthermore, the expressions "histidine rich region" and "the histidine-rich beta-sheet extension" are not defined (how many histidine residues should be present in a region in order to be "histidine-rich") (Article 6 PCT).

Same consideration applies to claims 82, 91 and 92.

V.5.7 With respect to claims 70

Claim 70 refers to an antibody that competes or cross-competes for binding to hVISTA. The claim does not indicate the method used for measuring said competing activity ("determined, e.g., by the competitive BLI epitope binning assay described in Example 15" is considered to be optional) (Article 6 PCT). Furthermore, reference anti-VISTA antibodies are referred to via internal designations such as "P1-061029" which do not have a generally recognized meaning (Article 6 PCT).

Furthermore, the expression "derivative thereof" renders the subject-matter unclear (Article 6 PCT).

V.5.8 With respect to claim 71

Claim 71 reads

The isolated antibody of any one of claims 1-70, wherein the antibody binds to epitope Group A, as determined, e.g., by the competitive BLI epitope binning assay described in Example 15.

The expression "epitope Group A" is an internal designation with no generally recognized meaning (Article 6 PCT).

V.5.9 With respect to claims 72-75

Claims 72-75 refers to an anti-VISTA antibody that does not bind (under what circumstances?) significantly to hVISTA in which one or more amino acids have been mutated.

Claims 72-75 do not meet the requirements of Article 6 PCT because the matter for which protection is sought is not clearly defined. The claim attempts to define the subject-matter in terms of the result to be achieved, not binding to mutated hVISTA, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.

V.5.10 With respect to claims 78-80

Claim 78 reads

An isolated antibody (Ab) that binds specifically to hVISTA under acidic conditions, e.g., at a pH of 6.5 (as measured, e.g., by one of the assays described in the Examples), wherein the Ab inhibits the interaction between VISTA and (a) T cells or (b) PSGL-1, and wherein the Ab contacts hVISTA through one or more (e.g., at least 1-3, 1-5, 1-10, 5-10, 5-15 or all) energetically important contact residues of an antibody described herein, such as VISTA.4, P1-070976, P1-065333, P1-070976 H95D, P1-070976 E97P, P1-061015, P1-061029, PI-068761, or P1-06876Z, [...]

The underlined features are considered to be unclear (Article 6 PCT).

Similar consideration applies to claims 79 and 80.

V.5.11 With respect to claims 61, 73, 76, 79, 82, 83, 85, 88-92, 94-98

Claims 61, 73, 76, 79, 82, 83, 85, 88-92, 94-98 refer to methods "as described, e.g. in the Examples" (or equivalent expressions). This reference to the Examples in general renders the subject-matter unclear (Article 6 PCT).

V.5.12 With respect to parameters used in the claims 1-171

References to a parameter without defining the method used for determining said parameter render said parameter unclear in the sense of Article 6 PCT.

V.5.13 With respect to internal designations

Internal designations, such as VISTA.4, P1-070976, IgG1.3, VK1.A64G..., do not have a generally recognized meaning (Article 6 PCT).

V.5.14 With respect to claim 107-109, 116-121

Claim 107 reads

An isolated antibody, or an isolated antibody of any one of claims 1-106, wherein the antibody is 41F11 or VISTA.4 or a variant thereof.

Neither "41F11", "VISTA.4" nor "variant thereof" is clear (Article 6 PCT).

Same consideration applies to claims 108, 109, and 116-121

V.5.15 With respect to claims 78-80, 83, 86, 88-92, 94-98, 100, 108, 109, 125-133, 160, 161

Features written within brackets are considered being optional and are, therefore, not limiting. Furthermore, optional features ("e.g.", "such as", "for example", "optionally") do not have a limiting character.

V.5.16 With respect to claim 171

Claim 171 reads

The method of any one of claims 168-170, wherein the antibody that binds specifically to hVISTA is an antibody described herein.

This claim appears to be redundant (Article 6 PCT).

V.5.17 With respect to claims 76-87, 91 and 92

Claims 76-87, 91-92 intend to define the anti-VISTA antibodies by their binding characteristic (epitope, "energetically important contact residues", Ab contacts through specific CDRs, Ab contacts through specific amino acids in the CDRs). The binding characteristic of an antibody is an inherent property of an antibody. In the absence of any proof/evidence to the contrary, the antibody of the prior art fall under this functional definition.

V.5.18 With respect to claims 88-90

Claims 88-90 appears to be redundant (Article 6 PCT).

V.5.19 With respect to claims 91 and 92

Claims 91 and 92 refer to an antibody that "has low or undetectable levels of neutropenia". An antibody cannot have any level of neutropenia (Article 6 PCT).

V.5.20 With respect to claims 94-98

Claims 94 and 95 refer to parameter aggregation/viscosity/hydrodynamic radius/melting temperature/HMW being similar or lower to that of VISTA.4 or a derivative thereof. The term "derivative" is unclear (Article 6 PCT). In its broadest sense any anti-VISTA antibody is a derivative of VISTA.4. Furthermore, the terms "VISTA.4" and "similar" are unclear. The method for measuring said parameter is not defined (Article 6 PCT).

V.5.21 With respect to antibodies in general

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain regions in order to form functional antigen binding sites.

A claim to an antibody which is structurally characterised by less than the full sequence of all the CDRs, and their specific order, cannot be seen to sufficiently disclose an antibody with any particular properties.

Furthermore, even single changes in the amino acid sequences of the heavy and light chain variable regions, particularly in the CDRs may dramatically affect antigen-binding function.

V.5.22 With respect to claims 160-161

Claims 160 and 161 refer to the CDRs of a VH and VL. It appears that there are different numbering schemes suitable for locating the CDRs of an antibody (i.e. Kabat, Chothia, Martin, Gelfand, IMGT, Aho's). It is unclear what numbering scheme should be used (Article 6 PCT).

Item VI

VI.1 With respect to documents D6-D9

The examination report has been based on an assumed valid priority for the present application. Should the priority of the present application not be valid, the above cited documents D6-D7 would be relevant with respect to novelty and inventive step (Article 33(2) and (3) PCT). Furthermore, should the present application be entered into the regional phase, the documents D7-D9 could be relevant to the question of novelty