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PCT

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

Date of mailing
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Applicant's or agent's file reference
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FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2015/075628

International filing date (day/month/year)
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International Patent Classification (IPC) or both national classification and IPC
INV. C07K16/46 C07K16/28 A61K39/395

Applicant
GLENMARK PHARMACEUTICALS S.A.

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 notified 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:



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Date of completion of
this opinion

see form
PCT/ISA/210

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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. 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>3, 4, 6-9</u>
	No: Claims	<u>1, 2, 5, 10-15</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-15</u>
Industrial applicability (IA)	Yes: Claims	<u>1-15</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 following documents

- D1 WO 2011/154453 A1 (GENMAB AS [DK]; WEERS MICHEL DE [NL]; WALSETH TIM [US]; WINKEL JAN VAN) 15 December 2011 (2011-12-15)
- D2 ELLIS J H ET AL: "Engineered anti-CD38 monoclonal antibodies for immunotherapy of multiple myeloma", THE JOURNAL OF IMMUNOLOGY, vol. 155, no. 2, 1 January 1995 (1995-01-01), pages 925-937, XP002146232
- D3 WO 2014/068114 A1 (MORPHOSYS AG [DE]) 8 May 2014 (2014-05-08)
- D4 DECKERT J ET AL: "SAR650984, A Novel Humanized CD38-Targeting Antibody, Demonstrates Potent Antitumor Activity in Models of Multiple Myeloma and Other CD38+ Hematologic Malignancies", CLINICAL CANCER RESEARCH, vol. 20, no. 17, 1 September 2014 (2014-09-01), pages 4574-4583, XP055239997
- D5 WO 2008/047242 A2 (SANOFI AVENTIS [FR]; PARK PETER U [US]; BARTLE LAURA M [US]; SKALETSKA) 24 April 2008 (2008-04-24)
- D6 DE WEERS M ET AL: "Daratumumab, a Novel Therapeutic Human CD38 Monoclonal Antibody, Induces Killing of Multiple Myeloma and Other Hematological Tumors", THE JOURNAL OF IMMUNOLOGY, vol. 186, no. 3, 27 December 2010 (2010-12-27), pages 1840-1848, XP55210884
- D7 WO 2012/092612 A1 (TAKEDA PHARMACEUTICAL [JP]; ELIAS KATHLEEN ANN [US]; LANDES GREGORY [U]) 5 July 2012 (2012-07-05)
- D8 WO 2015/063339 A1 (GLENMARK PHARMACEUTICALS SA [CH]) 7 May 2015 (P-doc) (2015-05-07)
- D9 EP 2 522 724 A1 (CHUGAI PHARMACEUTICAL CO LTD [JP]) 14 November 2012 (2012-11-14)
- D10 WO 2012/131555 A2 (GLENMARK PHARMACEUTICALS SA [CH]; BLEIN STANISLAS [CH]; SKEGRO DARKO []) 4 October 2012 (2012-10-04)
- D11 ROSEN P W ET AL: "VH3 family antibodies bind domain D of staphylococcal protein A", THE JOURNAL OF IMMUNOLOGY, vol. 154, no. 12, 15 June 1995 (1995-06-15), pages 6437-6445, XP002508063

- D12 POTTER K N ET AL: "Staphylococcal protein A binding to VH3 encoded immunoglobulins", INTERNATIONAL REVIEWS OF IMMUNOLOGY, vol. 14, no. 4, 1 January 1997 (1997-01-01), pages 291-308, XP008116757
- D13 GRAILLE M ET AL: "Crystal structure of a Staphylococcus aureus protein A domain complexed with the Fab fragment of a human IgM antibody: Structural basis for recognition of B-cell receptors and superantigen activity", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, vol. 97, no. 10, 9 May 2000 (2000-05-09), pages 5399-5404, XP002284947
- D14 ALMAGRO J C ET AL: "Humanization of antibodies", FRONTIERS IN BIOSCIENCE, vol. 13, 1 January 2008 (2008-01-01), pages 1619-1633, XP009126790
- D15 WO 2010/151792 A1 (REGENERON PHARMA [US]; DAVIS SAMUEL [US]; SMITH ERIC [US]; MACDONALD D) 29 December 2010 (2010-12-29)
- D16 WO 2014/049003 A1 (GLENMARK PHARMACEUTICALS SA [CH]) 3 April 2014 (2014-04-03)
- D17 LUM L G ET AL: "Development and prospects for bispecific antibody-based therapeutics in cancer and other applications", EXPERT OPINION ON DRUG DISCOVERY, vol. 3, no. 9, September 2008 (2008-09), pages 1081-1097

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

V.2.1 Prior art documents

Document D1 describes antibodies directed against human CD38 designated 025, 026, 028, 049 and 056 (p. 97-107, Examples 1-8). The sequences of said antibodies are disclosed on p. 5-10 (SEQ ID NO. 1-50). Furthermore, bispecific antibodies directed against CD3 and CD38 are suggested (p. 73 1st paragraph).

Document D2 describes the anti-CD38 antibody designated AT13/5 used for the treatment of multiple myeloma (abstract). The sequences of said antibody are disclosed in Figure 3.

Document D3 describes the anti-CD38 antibody designated MOR202 (Figure 1, CDRs are referred to as SEQ ID NO. 1, 14, 2-6). Said antibody is labeled with a radionuclide (abstract).

Document D4 describes the anti-CD38 antibody designated SAR650984 (isatuximab, hu38SB19) demonstrating antitumor activity in multiple myeloma (abstract). D4 describes the 3D structure of the huCD38/SAR650984-Fab complex. The epitope is reported to include a continuous segment from Met110 to Cys119 (p. 4578 left-hand col. 3rd paragraph - right-hand col. 2nd paragraph).

Document D5 describes several anti-CD38 antibodies, one anti-CD38 antibody is designated SAR650984 (38SB19, hu38SB19) (p. 4 l. 1 - p. 7 l. 29). It appears that said antibody has a CDRL2 sequence comprising the sequence SAS referred to as SEQ ID NO. 29 of the present application (SEQ ID NO. 42). SAR650984 is a chimeric IgG1-kappa antibody. Conjugates comprising the anti-CD38 antibody conjugated to a cytotoxic agent is described (claims 52-56).

Document D6 describes the use anti-CD38 antibody Daratumumab (HuMax-CD38) in treating multiple myeloma (abstract).

Document D7 describes anti-CD38 antibodies designated AB79 and AB19. Furthermore, D7 discloses the sequences of anti-CD38 antibodies designated HuMax-CD38 (Daratumumab) (SEQ ID NO. 24/25, Benchmark 1)) and SAR650984 (38SB19) (SEQ ID NO. 26/27, Benchmark 2). The CDRs of AB79 are referred to as SEQ ID NO. 3-8. The CDRs of AB19 are referred to as SEQ ID NO. 13-18. A treatment of autoimmune diseases is claimed (claim 19).

Intermediate document D8 describes the anti-CD38 antibody designated 9G7 (SEQ ID NO. 122-134) being identical to the antibody of the present application. Furthermore, said document describes bispecific antibodies directed against CD38 and CD3 (SEQ ID NO. 167-179, p. 114-115).

Document D9 describes a method for purifying bispecific antibodies through differential binding to protein A. Mutations of certain amino acid positions in the CH1, CH2, CH3 domains are described (paragraph 12, 14). The protein A binding ability is altered by mutating certain amino acids in the CH2 or CH3 region, e.g. residue at position 435 (EU numbering). Furthermore, D1 describes the modification of at least one amino acid residue in the amino acid sequences of FR1, CDR2 and FR3 of the antibody heavy-chain variable region (paragraph [15] item 10, item 28, item 42). The alteration of protein A binding ability may be a reduction or an increase of binding ability (paragraph [16] item 22, paragraph [73]-[74]). D1 describes modifications of the antibody heavy chain variable region, i.e. positions H15-H23, H56-H59, H63-H72 and H79-H83 (EU numbering). Furthermore, D1 states that "the heavy chain variable region of the VH3 subclass has protein A-binding activity. Thus, to increase the protein A-binding ability, the amino acid sequences at the above modification sites are preferably identical to those of the heavy chain variable region of the VH3 subclass. To reduce the protein A-binding ability, the amino acid sequences are preferably

identical to those of the heavy chain variable region of another subclass" (emphasis added (paragraph [75])). D1 describes further a GC33-IgG1-CD3-scFv molecule which divalently binds to cancer specific antigen glypican-3 (GPC3) and monovalently binds to T cell antigen CD3 (Figure 4 and Example 8).

Document D10 describes hetero-dimeric immunoglobulins comprising various substitutions in the CH2, CH3, and CH4 domains (p. 6 l. 15 - p. 11 l. 16).

Document D11 describes interaction of domain D of SpA with VH3-Fab (abstract).

Document D12 describes that residues in FR1, CDR2 and FR3 are involved in the interaction between VH3 encoded antibodies and SpA. All three regions are simultaneously required for SpA binding to occur and when any one of the three regions was altered, SpA binding was severely disrupted (abstract).

Document D13 describes crystal structure of a complex comprising SpA domain and Fab fragment of a human IgM antibody (abstract, Figure 1, Table 1).

Document D14 describes the method of humanizing antibodies using fixed framework strategy in which back mutations are necessary in order to retain or restore affinity (p. 1624 right-hand col. 3rd paragraph - p. 1625 right-hand col. 2nd paragraph).

Document D15 describes the production of heterodimeric immunoglobulins wherein one CH3 heavy chain constant domain sequence comprises a modification that reduces or eliminates binding to protein A (paragraph [24]). Said modification is 95R (IMGT, 435R by EU), 96F (IMGT, 436F by EU) (paragraph [25]). Said CH3 is from a modified human IgG1 comprising a further modification, i.e. D16E, L18M, N44S, K52N, V57M, or V82I (IMGT) (paragraph [26]). Further modifications of IgG2 or IgG4 are mentioned (paragraphs [27] and [28]). Protein A separation of differentially modified hIgG1 CD3xCD20 was performed wherein a pH of 4.2 eluted bispecific CD3xCD20 IgG1 (Example 7 paragraph [165]).

Document D16 describes a heterodimeric immunoglobulin comprising a first polypeptide that binds to protein A comprising an epitope binding region and an Ig constant region; and a second polypeptide that does not bind to protein A or has a reduced binding to protein A comprising an epitope binding region having at least a VH3 region comprising a modification that reduces or eliminates binding of the second polypeptide to protein A (p. 9 l. 1-13, p. 11 l. 27 - p. 12 l. 29, p. 66 l. 15 - p. 69 l. 33, claims 55-63, 67-69).

Document D17 describes the anti-CD3 antibody OKT3 and its therapeutic effects. Furthermore, D17 describes bispecific antibodies comprising the binding specificity of OKT3 (p. 1088 left-hand col. 2nd paragraph).

V.2.2 With respect to claims 1, 2, 5, 10-15

The antibody designated SAR650984 (isatuximab, hu38SB19) disclosed in D4 is considered novelty destroying for the subject-matter of claims 1, 2, 5, 10, 11, 12, 14, 15. Furthermore, the disclosure of D5 is novelty destroying for the subject-matter of claims 1, 2, 5, 10, 12, 13, 14, 15. Therefore, claims 1, 2, 5, 10-15 do not meet the requirements of Article 33(2) PCT.

V.2.3 With respect to claims 3, 4, 6-9

None of the documents cited describes the subject-matter of claims 3, 4, and 6-9. Therefore, claims 3, 4, and 6-9 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 3 and 4

The subject-matter of claims 3 and 4 refers to an anti-CD38 antibody defined by one CDR (selected from those defined in claim 1, e.g. VLCDR2: SAS) and a sequence 80% identical to the non-CDR region of SEQ ID NO. 55, 59, and 61 (VL) (or of SEQ ID NO. 74, 77, 146, 148 and 150 (LC)). The subject-matter of claims 3 and 4 differs from the closest prior art documents D4/D5 in that the non-CDR region is 80% identical to the listed VL or CL. The technical effect based on this difference is not apparent from the application as originally filed.

The technical problem to be solved may be formulated as providing an alternative anti-CD38 antibody. The skilled person is aware of all methods necessary for producing alternative antibodies. Therefore, the subject-matter of claims 3 and 4 is not considered inventive in the sense of Article 33(3) PCT.

V.3.2 With respect to claims 6-9

The subject-matter of claims 6-9 refers to bispecific antibodies comprising an anti-CD38 antibody (defined by one CDR of claim 1, e.g. the antibody designated SAR650984) and an anti-CD3 antibody (e.g. with the CDRs of SEQ ID NO. 3-12 or 163-168). CDRs referred to as SEQ ID NO. 3-8 are the CDRs of mouse SP34 antibody, SEQ ID NO. 9-12 are humanized SP34 CDRs. SEQ ID NO. 163-168 are the CDRs of mouse OKT3 antibody (muromonab). Therefore, it appears that these CDRs are derived from widely known anti-CD3 antibodies.

The subject-matter of claims 6-7 differs from D1 in that the CD38 binding antibody of the bispecific antibody comprises the LCDR2 sequence of SAR650984. The technical effect based on this difference is not apparent from the application. Therefore, the technical problem to be solved may be regarded as providing an alternative bispecific antibody targeting CD38 (and CD3). The antibody designated SAR650984 is known in the art showing promising therapeutic effects (see D4). Therefore, the skilled person

searching for alternative bispecific antibodies would clearly introduce SAR650984 into such bispecific antibodies without inventive skills. Therefore, the subject-matter of claims 6-7 is not considered inventive (Article 33(3) PCT).

The subject-matter of claims 8 and 9 differs from D1 additionally that the second binding part of a bispecific antibody is derived from an anti-CD3 antibody, i.e. the antibodies designated SP34 or OKT3. D1 suggested to combine binding specificities against CD3 and CD38. Furthermore, both anti-CD3 antibodies are generally known in the field. The technical problem to be solved is regarded as providing alternative bispecific antibodies. The combination of SAR650984 with one of the antibodies SP34 and OKT3 falls under the daily routine of the skilled person, since all antibodies used are known in the field, wherein their therapeutic effects are also known (see D4 and D17). Therefore, the subject-matter of claims 8 and 9 is not considered inventive in the sense of Article 33(3) PCT.

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

V.4.1 With respect to claims 1-15

The subject-matter of claims 1-15 appears to be susceptible of industrial application.

V.5 Further remarks

V.5.1 With respect to claims 1-15

The subject-matter of claim 1 refers to an anti-human CD38 antibody defined by only one CDR sequence. The subject-matter of claims 3 and 4 refers to an anti-human CD38 antibody wherein the antibody comprises a sequence at least 80% identical to the non-CDR region of either of VH sequences SEQ ID NO. 52, 58, 60. Claims 3 and 4 require additionally, due to the dependency on claim 1, that one of the CDR sequences of claim 1 is present. The wording of claims 3 and 4 do not require that the six CDRs of the sequences referred to as SEQ ID NO. 52, 58, 60, 55, 59, 61, 73, 75, 76, 145, 147, 149, 74, 77, 146, 148, and 150 are present.

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.

Item VI

VI.1 With respect to document D8

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 document D8 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 document D8 could be relevant to the question of novelty.