

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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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/EP2023/061909	International filing date (day/month/year) 05.05.2023	Priority date (day/month/year) 06.05.2022
International Patent Classification (IPC) or both national classification and IPC INV. C07K16/28 A61P35/00 A61K39/00 A61P33/00		
Applicant ICHNOS SCIENCES SA		

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 Mattugini, Nicola Telephone No. -0	
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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.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13ter.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. 17-21

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. 17-21

☐ 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. 1-16

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>2-12</u> |
| | No: Claims | <u>1, 13-16</u> |
| Inventive step (IS) | Yes: Claims | |
| | No: Claims | <u>1-16</u> |
| Industrial applicability (IA) | Yes: Claims | <u>1-16</u> |
| | No: Claims | |
2. Citations and explanations
- see separate sheet**

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)
and / or
2. Non-written disclosures (Rules 43*bis*.1 and 70.9)
see form 210

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 IV

1 Lack of unity of invention

The application lacks unity.

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

1. claims: 1-16

A trispecific antibody or antibody fragment thereof comprising at least three binding portions, at least one of which binds to human CD3, at least one which binds to human BCMA and at least one of which binds to human CD38.

2. claim: 17

An antibody or antibody fragment thereof or antigen-binding fragment which binds to the same epitope on human CD3 as a reference antibody or antibody fragment thereof comprising the at least one binding portion which binds to human CD3, one binding portion which binds to BCMA, and one binding portion which binds to CD38 according to claim 9.

3. claim: 18

An epitope on the human CD38 extracellular domain which is bound by the antibody or antibody fragment thereof of any one of the preceding claims and comprising the residues Glu103, Gln107, Thr114, Thr116, Arg194, Arg195, Glu198, Ala199, Asp202, Ser224, His228, Asn229, Gln231, Pro232, Glu233, Lys234, Val235, Gln236, Ile265, Ser267, Lys268, Arg269 and Asn270, as detected by X-ray crystallography.

4. claim: 19

An antibody or antibody fragment thereof that binds to human CD3, comprising a heavy chain CDR set comprising an amino acid sequence selected from the group comprising: SEQ ID NO: 181, SEQ ID NO: 307, and SEQ ID NO: 433; SEQ ID NO: 184, SEQ ID NO: 310, and SEQ ID NO: 436; SEQ ID NO: 186, SEQ ID NO: 312, and SEQ ID NO: 438; SEQ ID NO: 188, SEQ ID NO: 314, and SEQ ID NO: 440; SEQ ID NO: 192, SEQ ID NO

318, and SEQ ID NO: 444, and a light chain CDR set comprising the amino acid sequences of SEQ ID NO: 721, SEQ ID NO: 722 and SEQ ID NO: 723.

5. claim: 20

An antibody or antibody fragment thereof that binds to human BCMA, comprising a heavy chain CDR set comprising an amino acid sequence selected from the group comprising: SEQ ID NO: 234, SEQ ID NO: 360, and SEQ ID NO: 486; SEQ ID NO: 219, SEQ ID NO: 345, and SEQ ID NO: 471; SEQ ID NO: 227, SEQ ID NO: 353, and SEQ ID NO: 479; SEQ ID NO: 231, SEQ ID NO: 357, and SEQ ID NO: 483, and a light chain CDR set comprising the amino acid sequences of SEQ ID NO: 721, SEQ ID NO: 722 and SEQ ID NO: 723.

6. claim: 21

A trispecific hetero-dimeric antibody or antibody fragment thereof comprising a first and a second engineered CH3 domain, wherein said first engineered CH3 domain comprises the substitutions of the group comprising: Q347A, S364K, T366V, K370T, K392Y, F405S, Y407V, K409W, T411N (EU numbering), and said second engineered CH3 domain comprises the substitutions of the group comprising: Q347E, Y349A, L351F, S364T, T366V, K370T, T394D, V397L, D399E, F405A, Y407S, K409R, T411R (EU numbering), and wherein said trispecific hetero-dimeric immunoglobulin or hetero-dimeric fragment heterodimerize through said first and second engineered CH3 domains, characterized in that said trispecific hetero-dimeric antibody or antibody fragment thereof comprises at least three binding portions each binding portion which binds to a different antigen.

The reasons are as follows:

- 1.1 There is no common matter in the claims which links **invention 3** with the other potential **inventions 1-2 and 4-6** (beside being a peptide, and peptides are known in the art). In the absence of common matter, there is no single general inventive concept linking the claims.

- 1.1.1 Furthermore, the subject matter of **claim 18** encompasses compounds, i.e. epitopes defined only by their desired technical function, contrary to the requirements of clarity **Article 6 PCT**, because the results to be achieved type of definition does not allow the scope of the claim to be ascertained.

Furthermore, the epitope seems to be a conformational epitope, which is formed by non-adjacent residues (as shown in **example 26** of the current application). Therefore, it is unclear how the invention of **claim 18** can be carried out by a person skilled in the art without undue burden under the provision of **Article 5 PCT**.

- 1.2 The common matter linking **groups 1-2 and 4-6** of potential inventions is the feature of being an antibody.

This common matter (antibodies) is known in the art (see any **D1-D7**), including trispecific antibodies against CD3, CD38 and BCMA (see **D2** or **D3**).

The common matter therefore cannot constitute a single general inventive concept linking the independent claims.

Potential **invention 1** comprises the additional features:

of being a trispecific antibody binding to human CD3, CD38 and BCMA

Potential **invention 2** comprises the additional features:

of being an antibody binding to an epitope as an antibody binding to human CD3 having the sequences as recited in the claim

Potential **invention 4** comprises the additional features:

of being an antibody binding to human CD3 having the sequences as recited in the claim

Potential **invention 5** comprises the additional features:

of being an antibody binding to human BCMA having the sequences as recited in the claim

Potential **invention 6** comprises the additional features:

of being a trispecific antibody having engineered CH3 domains as recited in the claim

It follows that the features of potential inventions **1-2 and 4-6** which make a technical contribution over the common matter are different.

- 1.3 The technical effect of the additional features of potential **invention 1** is binding to human CD3, CD38 and BCMA. The problem solved by these technical features can be regarded as: the provision of a trispecific antibody binding to human CD3, CD38 and BCMA.

The technical effect of the additional features of potential **invention 2** is binding to the epitope on the human CD3. The problem solved by these technical features can be regarded as: as the provision of an antibody binding to the human CD3.

The technical effect of the additional features of potential **invention 4** is binding to human CD3. The problem solved by these technical features can be regarded as: the provision of an antibody binding to the human CD3.

The technical effect of the additional features of potential **invention 5** is binding to human BCMA. The problem solved by these technical features can be regarded as: the provision of an antibody binding to the human BCMA.

The technical effect of the additional features of potential **invention 6** is a modulation of the Fc domain properties. The problem solved by these technical features can be regarded as: as the provision of a further Fc domain.

- 1.4 As the technical problems are different, the additional technical features cannot be considered to be corresponding special technical features.

- 1.5 Additionally potential **inventions 2 and 4** are not so linked as to form a single general inventive concept as required by **Rule 13.1 PCT**.

The common matter linking these groups of potential **inventions 2 and 4** is an antibody binding to human CD3.

This common matter is already known because **D1** already discloses an antibody against human CD3.

The common matter therefore cannot constitute a single general inventive concept linking the independent **claims 17 and 19**.

The remaining features of potential **inventions 2 and 4** are the structurally different sequences.

Each of said sequences solves the technical problem of providing an antibody binding to human CD3. However, the sequences do not share a significant common structural element leading to a common technical effect upon which a common inventive concept can be based.

Since this objective technical problem is known from the prior art (see above), the provision of further compounds cannot be considered to constitute a corresponding special technical feature making a contribution over the prior art.

As the claims do not comprise the same or corresponding special technical features, they lack the technical relationship between their subject-matter required by **Rule 13.2 PCT** and are not so linked as to form a single general inventive concept.

The application therefore does not fulfil the requirement for unity of invention within the meaning of **Rule 13 PCT**.

1.6 The International Search Authority has carried out a search on the first invention mentioned in the claims, i.e **claims 1-16**.

1.7 As note, the subject matter of **claim 17** is not fully searchable for the following reasons:

Claim 17 does not have the sequence of the epitope where the antibody of **claim 17** should bind, and in the description the epitope YVCYPRGSKPEDANFY, is identified as the main epitope to which the clone anti-CD3-CI-D6 binds (**Example 4 pages 77-78**). Thus, it is unclear if such sequence is the exact sequence, or it is only a part of a larger epitope.

Furthermore, the prior art can disclose antibodies against the antigens recited in the claim, but the epitope where the CD3 binding portion is not determined.

Therefore, it is not possible to make a meaningful comparison with the antibodies of the prior art in case the applicant will pay an additional search fee to search **invention 2**.

1.8 The same above applies to **invention 3** which has an unclear subject matter (see above).

1.9 To note that the application relates to a plurality of inventions, or groups of inventions, in the sense of **Rule 13.1 PCT**. They have been divided as defined above. If the applicant pays additional fees for one (or more) not yet searched group(s) of invention(s), then the further search(es) may reveal further prior art that gives evidence of a further lack of unity 'a posteriori' within one (or more) of the not yet searched group(s). In such a case only the first invention in this (each of these) group(s) of inventions, which is considered to lack unity of invention, will be the subject of a search. No further invitation to pay further additional fees will be issued. This is because **Article 17(3)(a) PCT** stipulates that the ISA shall establish the International Search Report on those parts of the international application which relate to the invention first mentioned in the

claims ('main invention') and for those parts which relate to inventions in respect of which the additional fees were paid. Neither the PCT nor the PCT Guidelines provide a legal basis for further invitations to pay further additional search fees (W17/00, point 11 and W1/97, points 11-16). In such a case the non-searched claims may be the subject of one or more divisional applications after the application has entered the regional phase before the EPO (see W18/07, point 26).

Re Item V

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

2 Documents

Reference is made to the following documents:

- D1 CA 3 133 624 A1 (MERUS NV [NL]) 8 October 2020 (2020-10-08)
- D2 US 10 882 922 B2 (SANOFI SA [FR]) 5 January 2021 (2021-01-05)
- D3 US 2021/163620 A1 (GRANDA BRIAN [US] ET AL) 3 June 2021 (2021-06-03)
- D4 WO 2022/058539 A1 (ICHNOS SCIENCES SA [CH]) 24 March 2022 (2022-03-24)
- D5 US 11 124 577 B2 (ENGMAB SARL [CH]) 21 September 2021 (2021-09-21)
- D6 GARFALL ALFRED L ET AL: "Trispecific antibodies offer a third way forward for anticancer immunotherapy",
NATURE, NATURE PUBLISHING GROUP UK, LONDON,
vol. 575, no. 7783, 1 November 2019 (2019-11-01), pages 450-451,
XP036928494,
ISSN: 0028-0836, DOI: 10.1038/D41586-019-03495-3
[retrieved on 2019-11-18]
- D7 LANCMAN GUIDO ET AL: "Bispecifics, trispecifics, and other novel immune treatments in myeloma",
HEMATOLOGY
,
vol. 2020, no. 1 4 December 2020 (2020-12-04), pages 264-271,
XP055964173,

DOI: 10.1182/hematology.2020000110

Retrieved from the Internet:

URL: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7727546/pdf/bloodbook-2020-264.pdf>

- D8 Perro Mario: "ISB 2001, A FIRST FIRST-IN -CLASS TRISPECIFIC BCMA AND CD38 T CELL ENGAGER DESIGNED TO OVERCOME MECHANISMS OF ESCAPE FROM TREATMENTS FOR MULTIPLE MYELOMA BY TARGETING TWO ANTIGENS",
, 10 December 2022 (2022-12-10), XP93070280,
Retrieved from the Internet:
URL: <https://www.ichnoscience.com/wp-content/uploads/ISB-2001-a-First-in-Class-Trispecific-BCMA-and-CD38-T-Cell-Engager-Designed-to-Overcome-Mechanisms-of-Escape-from-Treatments-for-Multiple-Myeloma-by-Targeting-Two-Antigens-Perro-M-1.pdf>
- D9 Pihlgren Maria: "ISB 2001, a First-in-Class Trispecific BCMA and CD38 T Cell Engager Designed to Overcome Mechanisms of Escape from Treatments for Multiple Myeloma By Targeting Two Antigens | Blood | American Society of Hematology",
, 15 November 2022 (2022-11-15), XP93070548,
Retrieved from the Internet:
URL: <https://ashpublications.org/blood/article/140/Supplement%201/858/491649/ISB-2001-a-First-in-Class-Trispecific-BCMA-and>
[retrieved on 2023-08-04]

D1 discloses an antibody against human CD3 and a bispecific antibody comprising CD3 and a tumor-antigen such as human BCMA, CD38 etc (**claims 1, 20, 21 and 22**).

D2 discloses a trispecific binding protein comprising four polypeptide chains that form three antigen binding sites that specifically bind one or more targets (**claim 1**). The trispecific binding protein specifically binds three targets that correspond to two target proteins on T cells and to one tumor target protein (**claim 5**). The trispecific protein can also bind to a list of different antigens including CD3, BCMA and CD38 (**claim 9**). **D2** also discloses a pharmaceutical composition comprising the trispecific protein and a method for preventing cancer (including leukemia) using such composition (**claims 39-40 and page 78**). The method is applied to human patients and the trispecific protein can bind to CD3, BCMA

and CD38 (**claims 46, 47**). **D2** discloses a trispecific antibody capable of binding to human CD3, CD38 and BCMA (**page 2**). **Example 2** shows an overview of the trispecific binding proteins.

D3 discloses a multispecific binding molecule (MBM), comprising: (a) an antigen-binding module 1 (ABM1) that binds specifically to a first human tumor-associated antigen that is expressed on cancerous B cells (TAA 1); b) an antigen-binding module 2 (ABM2) that binds specifically to a second human tumor-associated antigen that is expressed on cancerous B cells (TAA 2), and (c) an antigen-binding module 3 (ABM3) that binds specifically to a component of a human T-cell receptor (TCR) complex (**claim 1**). TAA1 and TAA2 can be any antigen of the list of **claim 9** including CD38 and BCMA and the antigen that binds to the T-cell is CD3 (**claim 22**). **D3** provides the principles of providing multispecific binding molecules ("MBMs") that engage at least two tumor-associated antigens that are expressed on cancer cells (e.g., cancerous B cells) ("TAAs") in addition to CD3 or other component of a TCR complex on T-cells (**paragraph 0006**). Such approach aims to improve the clinical outcomes of RTCC therapy of cancer, e.g., B cell malignancies by targeting a greater number of cancerous B cells than using bispecific engagers that target only a single TAA and a TCR complex component (**paragraph 0007**). **D3** also discloses a multispecific binding molecule that binds to (1) a first tumor-associated antigen that is expressed on cancerous B cells ("TAA 1"), (2) a second tumor-associated antigen that is expressed on cancerous B cells ("TAA 2"), and (3) CD3 or others component of a TCR complex (**paragraph 0008**). The MBM comprises an altered Fc domain (**claim 36**). The MBM can be a trispecific binding molecule (**claim 43**). **Claims 46 and 49** disclose a method of treating B cell malignancy such as Non-Hodgkin's lymphoma. **Example 2** shows the production and characterization of anti-CD19-BCMA-CD3 Human IgG1 bi- and tri-specific binding molecules in knobs-into-holes format.

D4 discloses a bispecific antibody comprising at least two binding portions, at least one of which binds to human CD38 and at least one of which binds to human CD47 (**claim 1**). **D4** already discloses **SEQs. ID NOs: 1, 110, 111, 122, 236, 362, 712, 237, 363, 700, 248, 374 and 500** of the current application.

D5 discloses a method of treatment comprising a bispecific antibody comprising a first binding part specifically binding to human B cell maturation antigen (BCMA) and a second binding part specifically binding to human CD3E (CD3); and, b) an immunotherapeutic drug selected from the group consisting of thalidomide or an immunotherapeutic derivative thereof, an anti-CD38 antibody,

an anti-PD-1 antibody and an anti-PD-L1 antibody (**claim 1**). **Example 21** shows the combined use of anti-BCMA/Anti-CD3 T Cell bispecific antibody with an immunotherapeutic drug such as an antibody against CD38 (daratumumab).

D6 discloses a trispecific antibody against CD3, CD38 and CD28 (**whole document**).

D7 discloses different formats of bispecific and trispecific antibodies. In figure 4 two formats are shown, one where the trispecific antibody targets two antigens on the T-cells and one antigen on the myeloma cells, and the other format targets two antigens on the cancer cells and one on NK-cell (**whole document**).

D8 is an intermediate document from the applicant of the current application. **D8** discloses the subject matter of the current application. **D8** will be relevant in case of invalid priority (**whole document**).

D9 is an intermediate document from the applicant of the current application. **D9** discloses the subject matter of the current application. **D9** will be relevant in case of invalid priority (**whole document**).

3 **Novelty Article 33(2) PCT**

3.1 **Claim 1** relates to " a trispecific antibody or antibody fragment thereof comprising at least three binding portions, at least one of which binds to human CD3, at least one which binds to human BCMA and at least one of which binds to human CD38".

However, **D2** already discloses a trispecific binding protein against CD3, CD38 and BCMA which is used to treat cancer in human patients, thus such protein is able to bind to human CD3 and to human CD38. Hence, **claim 1** is not novel over **D2** under the provision of **Article 33(2) PCT**.

3.2 **Claims 14-16** are not novel over **D2** under the provision of **Article 33(2) PCT** because it already discloses a method of treatment against cancer using a trispecific binding protein against CD3, CD38 and BCMA.

3.3 All the remaining **claims 2-13** are novel over **D2** under the provision of **Article 33(2) PCT** because **D2** does not disclose a trispecific antibody against CD3, CD38 and BCMA with a common light chain, a specific format and the SEQs. ID NOs: reported in the claims.

3.4 **D3** discloses a multispecific binding molecule against human BCMA, CD38 and CD3. Thus **claim 1** is not novel over **D3** under the provision of **Article 33(2) PCT**.

- 3.5 **Claim 13** is not novel over **D3** because it discloses a MBM with an altered (non-naturally occurring) Fc-domain.
- 3.6 **Claims 14-16** are not novel over **D3** because it discloses a method of treatment against B cell malignancy such as Non-Hodgkin's lymphoma.
- 3.7 All the remaining **claims 2-12** are novel over **D3** because it does not disclose a trispecific antibody against CD3, CD38 and BCMA with a common light chain, a specific format and the SEQs. ID NOs: reported in the claims.

4 **Inventive step Article 33(3) PCT**

- 4.1 **Claim 3** refers to "The trispecific antibody or antibody fragment thereof according to any one of the preceding claims, wherein said at least one binding portion which binds to human CD3 comprises a heavy chain CDR set comprising an amino acid sequence selected from the group comprising: SEQ ID NO: 181, SEQ ID NO: 307, and SEQ ID NO: 433; SEQ ID NO: 184, SEQ ID NO: 310, and SEQ ID NO: 436; SEQ ID NO: 186, SEQ ID NO: 312, and SEQ ID NO: 438; SEQ ID NO: 188, SEQ ID NO: 314, and SEQ ID NO: 440; SEQ ID NO: 192, SEQ ID NO: 318, and SEQ ID NO: 444".

D3 can be considered the closest prior art to assess the inventive step of **claim 3**. Indeed, **D3** already discloses a trispecific antibody against CD3, CD38 and BCMA, then it is from the same technical field and directed to the same purpose: binding two antigens on the tumor and one on the T-cells to target more tumors markers and improve patients clinical outcome compared to bispecific antibodies (**0007 of D3 and at page 3** of the current application).

The distinguishing features are the sequences of the CDRs against CD3.

There is no technical effect arising from the distinguishing features.

The objective technical problem can be formulated as the provision of an alternative trispecific antibody against CD3, CD38 and BCMA.

The solution is the trispecific antibody of **claim 3**. However, the proposed solution is not inventive under the provision of **Article 33(3) PCT** for the following reasons.

Claim 3 allows the formation of 5 different trispecific antibodies which seem to have same HCDRs 1/3, different HCDRs 2 and they bind to CD38 and BCMA. The application shows 11 different trispecific antibodies (CD3-CD38-BCMA) (**table 9**) which comprise the HCDRs of claim 3. However, the antibodies of table 9 are different between each other. They have different CDRs sequences and different formats.

For example, antibody 43 (SEQs. ID NOs: 522, 523) has a BO format meaning CD38 binding domain in one arm and CD3 and BCMA binding domains are located on the other arm of the BEAT antibody, whereby the CD3 binding domain is in the Fc distal position, and the BCMA binding domain of high affinity is in the Fc proximal position.

Antibody 86 (SEQs. ID NOs: 530, 531) has the C format wherein a CD3 binding domain is in one arm and a CD38 binding domain is fused to the C-terminus of a first BCMA-binding domain of a second arm.

Clone 118 (SEQs. ID NOs: 546, 547) has the BO configuration as the antibody 43 but the CDRs of the CD3 binding portion are different.

From the examples, it appears that not only the sequences have a different technical effect but also that the format of the trispecific antibody plays a role. **Example 13** shows that the BO format impacts positively the tumor cell lines killing, demonstrating an increase of potency (antibody 118 is better than antibody 115). Moreover, there is a difference between different formats on binding affinity as well (**table 18**).

Any surprising or unexpected technical effect of one of the exemplified antibodies in **table 9** cannot provide an inventive step to the whole scope of **claim 3**. Indeed, **claim 3** does not restrict the subject matter to a specific antibody with a specific set of six CDRs and a specific format but it allows several combinations and formats.

In conclusion the antibodies of **claim 3** are seen as alternative antibodies over the antibody of **D3** and the solution to the problem posed is not inventive under the provision of **Article 33(3) PCT**.

Indeed, a person skilled in the art would be motivated and would have a reasonable expectation of success in the provision of a trispecific antibody against CD3, CD38 and BCMA by applying techniques known in the art.

- 4.2 The same reasoning as above applies to **claims 4-8** which have a broader scope compared to the exemplified antibodies of table 9. Moreover, some of the sequences are already known in the prior art (see **D4**). Thus, **claims 4-8** are not inventive over **D3** under the provision of **Article 33(3) PCT**.
- 4.3 **Claim 9** refers to "The trispecific antibody or antibody fragment thereof according to any one of the preceding claims, wherein said at least one binding portion which binds to human CD3 comprises a heavy chain CDR set comprising an amino acid sequence of SEQ ID NO: 181, SEQ ID NO: 307, and SEQ ID NO: 433, and a light chain CDR set comprising an amino acid

sequence of SEQ ID NO: 721, SEQ ID NO: 722 and SEQ ID NO: 723; said at least one binding portion which binds to human BCMA comprises a heavy chain CDR set comprising an amino acid sequence of SEQ ID NO: 234, SEQ ID NO: 360, and SEQ ID NO: 486, and a light chain CDR set comprising an amino acid sequence of SEQ ID NO: 721, SEQ ID NO: 722 and SEQ ID NO: 723; and said at least one binding portion which binds to human CD38 comprises a heavy chain CDR set comprising an amino acid sequence of SEQ ID NO: 239, SEQ ID NO: 365, and SEQ ID NO: 491, and a light chain CDR set comprising an amino acid sequence of SEQ ID NO: 721, SEQ ID NO: 722 and SEQ ID NO: 723".

The antibodies **118 (figure 9A)** and **170 (figure 49)** of table 9 and example 25 respectively comprise those sequences.

The distinguishing features of the antibody of **claim 9** and the antibody of **D3** are the CDRs sequences.

There is no technical effect arising from those differences.

The objective technical problem can be formulated as a provision of an alternative trispecific antibody against CD3, CD38 and BCMA.

The solution is the subject matter of **claim 9**. Such solution is not inventive over **D3** under the provision of **Article 33(3) PCT** for the following reason.

The particular format (BO format) of the trispecific antibodies 118 and 170 is not reflected in the subject matter of **claim 9**. Thus, (as mentioned above) the surprising or unexpected technical effect associated with one of the exemplified antibodies cannot provide an inventive step to the whole scope of the claim. Thus, arriving to the solution of the problem posed is obvious for a person skilled in the art and **claim 9** is not inventive over **D3** under the provision of **Article 33(3) PCT**.

The applicant is also informed that if a surprising technical effect involves the binding affinity, the structural requirements for conventional antibodies inherently reflecting this affinity must comprise the required CDRs and the framework regions because the framework regions also can influence the affinity.

- 4.4 **Claim 10** is directed to " The trispecific antibody or antibody fragment thereof according to claim 9, comprising three amino acid chains having amino acid sequences of SEQ ID NO: 546, SEQ ID NO: 547 and SEQ ID NO: 1".

The antibody **118** of table 9 comprises those sequences.

The distinguishing features of the antibody of **claim 10** and the antibody of **D3** are the sequences of the antibody.

There is no technical effect arising from those differences.

The objective technical problem can be formulated as a provision of a further trispecific antibody against CD3, CD38 and BCMA.

The solution is the antibody of **claim 10**. Such solution is not inventive over **D3** under the provision of **Article 33(3) PCT** for the following reason.

Indeed, the particular format (BO format) of the trispecific antibody 118 of the current application is not reflected in the subject matter of **claim 10**. Indeed, according to **figure 9A** of the current application the trispecific antibody of **figure 9A (BO format)** has two heavy chains and three common light chain. Said feature is not reflected in the subject matter of **claim 10**. Thus, (as mentioned above) the surprising or unexpected technical effect associated with such particular antibody cannot provide an inventive step to the whole scope of the claim. Thus, arriving to the solution of the problem posed is obvious for a person skilled in the art and **claim 10** is not inventive over **D3** under the provision of **Article 33(3) PCT**.

4.5 **Claims 2 and 11-12** 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 but they rather relate to obvious modifications and applications of the product to which they refer.

4.6 **D2** discloses a trispecific binding molecule which binds to human CD3, CD38 and BCMA.

D2 can be considered the closest prior art in order to assess inventive step of the remaining claims because it is from the same field and directed to a similar purpose.

As already mentioned before any technical effect associated with one particular exemplified antibody cannot confer an inventive step to the whole scope of the claims. Thus, **claims 2-12** are seen as merely alternative antibodies over the antibody of **D2**. Indeed, a person skilled in the art would be motivated and would have a reasonable expectation of success in the provision of a trispecific antibody against CD3, CD38 and BCMA by applying techniques known in the art. Thus, **claims 2-12** are not inventive over **D2** under the provision of **Article 33(3) PCT**.

Re Item VI

5 Certain documents cited

Reference is made to the following documents:

- D8 Perro Mario: "ISB 2001, A FIRST FIRST-IN -CLASS TRISPECIFIC BCMA AND CD38 T CELL ENGAGER DESIGNED TO OVERCOME MECHANISMS OF ESCAPE FROM TREATMENTS FOR MULTIPLE MYELOMA BY TARGETING TWO ANTIGENS",
, 10 December 2022 (2022-12-10), XP93070280,
Retrieved from the Internet:
URL:<https://www.ichnossiences.com/wp-content/uploads/ISB-2001-a-First-in-Class-Trispecific-BCMA-and-CD38-T-Cell-Engager-Designed-to-Overcome-Mechanisms-of-Escape-from-Treatments-for-Multiple-Myeloma-by-Targeting-Two-Antigens-Perro-M-1.pdf>
- D9 Pihlgren Maria: "ISB 2001, a First-in-Class Trispecific BCMA and CD38 T Cell Engager Designed to Overcome Mechanisms of Escape from Treatments for Multiple Myeloma By Targeting Two Antigens | Blood | American Society of Hematology",
, 15 November 2022 (2022-11-15), XP93070548,
Retrieved from the Internet:
URL:<https://ashpublications.org/blood/article/140/Supplement%201/858/491649/ISB-2001-a-First-in-Class-Trispecific-BCMA-and>
[retrieved on 2023-08-04]

D8 is an intermediate document from the applicant of the current application. **D8** discloses the subject matter of the current application. **D8** is a power point presentation available from the website of the applicant where the first page mentions that said presentation was made available to the public on the 10 of December 2022 at the 64TH AMERICAN SOCIETY OF HEMATOLOGY ANNUAL MEET MEETING; therefore, **D8** will be relevant in case of invalid priority (**whole document**).

D9 is an intermediate document from the applicant of the current application. **D9** is an abstract of the program of the 64TH AMERICAN SOCIETY OF HEMATOLOGY ANNUAL MEET MEETING available online in November 2022. **D9** will be relevant in case of invalid priority (**whole document**).

Re Item VIII

6 Certain observations on the international application

- 6.1 **Claims 3, 4 and 5** refer to an antibody with only three CDRs. If an IgG is defined by fewer than the six sequences of its CDRs it lacks an essential technical feature. Thus, **claims 3, 4 and 5** lack clarity under the provision of **Article 6 PCT**.
- 6.2 **Claims 6-8** refer to about 95%, 96%, 97%, 98%, 99% of sequences. The word about introduces ambiguity because it does not properly restrict the subject matter of the claim and prevent a person skilled in the art to know if it is working or not under the scope of the claim. Thus, **claims 6-8** lack clarity under the provision of **Article 6 PCT**.