PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

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/EP2022/077817	06.10.2022	08.10.2021

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

Applicant
GENMAB A/S

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 P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	see form PCT/ISA/210	Valcárcel, Rafael Telephone No. +31 70 340-0

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 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.

   b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.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. 49-57

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. 49-57

☐ 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. 1-48, 58-60

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	1-48, 58-60
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-48, 58-60
Industrial applicability (IA)	Yes:	Claims	1-48, 58-60
	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

Cited documents

1 Reference is made to the following documents:

D1 WO 2008/119567 A2 (MICROMET AG [DE]; EBERT EVELYN [DE] ET AL.) 9 October 2008 (2008-10-09)cited in the application

D2 US 2019/284278 A1 (RADEMAKER RIK [NL] ET AL) 19 September 2019 (2019-09-19)

D3 US 2020/239579 A1 (ALTINTAS ISIL [DK] ET AL) 30 July 2020 (2020-07-30)

D4 WO 2020/068774 A1 (MEDICAL COLLEGE WISCONSIN INC [US] ET AL.) 2 April 2020 (2020-04-02)

D5 OLDHAM ROBYN A A ET AL: "T Cells Armed with Novel Anti-CD30/Anti-CD3 Bispecific Antibodies for Immunotherapy of CD30+Malignancies", MOLECULAR THERAPY,
vol. 27, no. 4, Suppl. 1, 22 April 2019 (2019-04-22), page 387, XP009536442,
& 22ND ANNUAL MEETING OF THE AMERICAN-SOCIETY-OF-GENE-AND-CELL-THERAPY (ASGCT); WASHINGTON, DC, USA; APRIL 29 - MAY 02, 2019

D6 SCHWARTZ C L ET AL: "Development of an A-CD30 bispecific antibody immunotherapy for Hodgkin lymphoma",
HEMASPHERE 20181001 EMBASE CONFERENCE ABSTRACTS NLD,
vol. 2, no. Supplement 1, 1 October 2018 (2018-10-01), XP009536443,
ISSN: 2572-9241

D7 US 2017/073421 A1 (KJAERGAARD KRISTIAN [DK] ET AL) 16 March 2017 (2017-03-16)

D8 US 2021/163594 A1 (BAILEY LUCAS [CN] ET AL) 3 June 2021 (2021-06-03)

D9 WO 2006/105062 A2 (DIVERSA CORP [US]; HANSEN GENEVIEVE [US]; NESLUND GERALD [US]) 5 October 2006 (2006-10-05)

D10 WO 2014/006217 A1 (GENMAB BV [NL]) 9 January 2014 (2014-01-09)

D11 US 2021/009718 A1 (AMBROGELLY ALEXANDRE [US] ET AL) 14 January 2021 (2021-01-14)

D12 WO 2019/025545 A1 (GENMAB AS [DK]; BIONTECH AG [DE]) 7 February 2019 (2019-02-07)

D13 CHRISTIAN KLEIN ET AL: "Progress in overcoming the chain association issue in bispecific heterodimeric IgG antibodies", MABS, vol. 4, no. 6, 1 November 2012 (2012-11-01), pages 653-663, XP55106060, ISSN: 1942-0862, DOI: 10.4161/mabs.21379

D14 DENNIS R. GOULET ET AL: "Kinetic mechanism of controlled Fab-arm exchange for the formation of bispecific immunoglobulin G1 antibodies", JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 293, no. 2, 17 November 2017 (2017-11-17), pages 651-661, XP055549625,US ISSN: 0021-9258, DOI: 10.1074/jbc.RA117.000303

Re Item IV

Lack of unity of invention

2 The application lacks unity contravening the requirements of Rule 13 PCT. This Authority considers that the application does not meet the requirements of unity of invention and that there are 3 inventions covered by the claims indicated as follows:

1. claims: 1-48, 58-60

A multispecific antibody as defined in claim 1. A nucleic acid construct or a combination of nucleic acid constructs encoding said multispecific antibody. Expression vector, delivery vehicle, recombinant host cell, composition as defined in claims 28-36. The multispecific antibody for the uses as defined in claims 37-43. The above products that have been administered as defined in claim 44. Methods for producing the multispecific antibody as defined in claims 45, 46, 58 and 59. Kits and diagnostic compositions as defined in claims 47 and 48. A multispecific antibody obtained by the method as described in claims 58 or 59.

2. claims: 49-51

   An antibody a defined in claim 49.

3. claims: 52-57

   An antibody as defined in claim 52.

3 The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows.

4 Rule 13.1 PCT states that for unity of invention to be present, all subject-matter should be linked by a single general inventive concept. Rule 13.2 PCT stipulates that where a group of inventions is claimed the requirement of unity shall be fulfilled only where there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. "Special" technical features are those features that define a contribution which each of the inventions makes over the prior art.

5 The common matter linking together the bispecific antibody of claim 1 and the monospecific antibodies of independent claims 49 and 52 is the concept of antibodies binding cluster of differentiation proteins present on lymphocytes which can be used as tumor markers.

Said common matter is however not novel since antibodies specific for CD30 and antibodies specific for CD3 were known in the art, even having the exact particular CDRs listed in present claims 49 and 52, which are the CDRs listed in the bispecific antibody of claim 1.

6 As acknowledged in the present application, **the individual antibodies specific for CD30 and CD3 were known** but not the particular combination of the two specific antibodies in a bispecific antibody.

7 For example, D1 (cited e.g. on page 2 of the present application) discloses in SEQ ID NO: 1113 an identical sequence to SEQ ID NO: 13 of the present application (the VH of the anti-CD30 antibody) and in SEQ ID NO: 1118 an identical sequence to SEQ ID NO: 14 of the present application (the VH of the anti-CD30 antibody).

Example 29 of D1 starting on page 176 and finishing on page 183 discloses the generation and functional characterization of a particular bispecific antibody CD30-CD3 as single chain molecules, see Figures 46 and 47 for the experimental data.

8 D2 discloses two antibodies binding CD3 comprising the first one:

as VH CDR1 SEQ ID NO: 1, being identical to SEQ ID NO: 7 of the present application;

as VH CDR2 SEQ ID NO: 2, being identical to SEQ ID NO: 8 of the present application;

as VH CDR3 SEQ ID NO: 3, being identical to SEQ ID NO: 9 of the present application, wherein position 3 of the CDR3 (i.e. position X) is a H;

comprising the second antibody binding CD3 wherein

as VH CDR1 SEQ ID NO: 1, being identical to SEQ ID NO: 7 of the present application;

as VH CDR2 SEQ ID NO: 2, being identical to SEQ ID NO: 8 of the present application;

as VH CDR3 SEQ ID NO: 176, being identical to SEQ ID NO: 9 of the present application, wherein position 3 of the CDR3 (i.e. position X) is a G (designated HC-H101G);

The VL CDRs of the huCD3-L1-T41K antibody are identical to the VL CDRs of the CD3 antibody of claim 1 of the present application:

SEQ ID NO: 6 of D2 is identical to SEQ ID NO: 10 of the present application;

the VL CDR2 being GTN of SEQ ID NO: 11 of the present application is also the CDR2 disclosed in Table 1 for the VL-huCDR2-L1-T41K of D2;

SEQ ID NO: 7 of D2 is identical to SEQ ID NO: 12 of the present application.

D2 also discloses bispecific antibodies, see e.g. paragraphs 846 to 855, 859 and 861.

The introduction of the mutations L234F and L235F mutations in the Fc region are also disclosed in D2, see paragraph 715 (and are well known in the art of bispecific antibodies). Also known is the mutation at G236 to minimize the interaction of the Fc region with the Fc gamma receptor, see paragraph 716.

It is noted that D2 is a family member of WO2017009442 (cited in e.g. page 51 of the present application, line 24 as disclosing the IgG1-huCD3-H1L1-H101G). However, D2 is cited instead since it has paragraph numbering which makes easier the discussion about the subject-matter disclosed.

9 D3 also discloses two antibodies binding CD3 comprising the first one:

as VH CDR1 SEQ ID NO: 26, being identical to SEQ ID NO: 7 of the present application;

as VH CDR2 SEQ ID NO: 27, being identical to SEQ ID NO: 8 of the present application;

as VH CDR3 SEQ ID NO: 28, being identical to SEQ ID NO: 9 of the present application, wherein position 3 of the CDR3 (i.e. position X) is a H;

comprising the second antibody binding CD3:

as VH CDR1 SEQ ID NO: 26, being identical to SEQ ID NO: 7 of the present application;

as VH CDR2 SEQ ID NO: 27, being identical to SEQ ID NO: 8 of the present application;

as VH CDR3 SEQ ID NO: 45, being identical to SEQ ID NO: 9 of the present application, wherein position 3 of the CDR3 (i.e. position X) is a G (designated HC-huCD3-H1-H101G).

The VL CDRs of the huCD3-L1 antibody of D3 are identical to the VL CDRs of the CD3 antibody of claim 1 of the present application:

SEQ ID NO: 30 of D3 is identical to SEQ ID NO: 10 of the present application;

the VL CDR2 being GTN of SEQ ID NO: 11 of the present application is also the CDR2 disclosed in the sequence listing of D3 for the CDR2 of the VL-huCD3-L1 of D2;

SEQ ID NO: 31 of D3 is identical to SEQ ID NO: 12 of the present application.

Methods of preparing bispecific antibodies are disclosed in e.g. paragraphs 239 to 256. Particular examples are disclosed in e.g. Examples 3 and 12 of a CD3XPD-L1 bispecific antibody.

The introduction of the mutations L234F and L235E mutations in the Fc region are also disclosed in D2, see e.g. claim 29(e) or paragraph 715, **rendering present claim 49 not even novel**. Furthermore the L234F and L235E mutations in the Fc region are well known in the art of bispecific antibodies. Also known is the mutation at G236 to minimize the interaction of the Fc region with the Fc gamma receptor, see paragraph 291.

10 D4 (see e.g. Example 2), D5 (see abstract) and D6(see abstract) disclose the use of bispecific anti CD3-CD30 antibodies to treat human Hodgkin lymphoma.

11 **Furthermore there is no technical relationship between the "not common" technical features of the different groups of inventions, i.e. there are not common structural elements other than being an antibody binding a cluster of differentiation protein that can be used as a tumor cell marker.**

The antibody sequences defined in claims 49 and 52 provide the technical effect of binding CD30 and CD3 respectively and **solve the objective technical problem of providing alternative antibodies against cluster of differentiation proteins present on lymphocytes that can be used as tumor cell markers. The "alternative" is just stated here to define the technical problem, but as discussed above and as acknowledged in the present application, the individual antibodies to CD30 and CD3 were not even novel.** In any case, the just defined technical problem is known from the prior art and solutions have been disclosed in the prior art as discussed above.

Also, examining the possible correspondence by technical effect, one finds that the technical effect of the different inventions is the same, an antibody binding a cluster of differentiation protein present on lymphocytes that can be used as tumor cell marker, but there is no evidence of any further technical effect that could link them: the individual antibodies against CD30 and CD3 are not even novel, and the Fc modifications listed are standard in the art, in particular in the case of bispecific antibodies.

Hence, the claims comprise neither the same, nor corresponding special technical features, so the technical relationship between the subject matter of the claims required by Rule 13.2 PCT is lacking and the claims are not so linked as to form a single general inventive concept as required by Rule 13.1 PCT. Hence, the above listed 6 separate inventions or groups of inventions are not so linked as to form a single general inventive concept.

Consequently the application does not meet the requirement for unity of invention.

12 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).

INVENTION 1

Re Item V

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

Lack of inventive step

13 The present application does not meet the criteria of Article 33(1) PCT, because **the subject-matter of claims 1-48 and 58-60 does not involve an inventive step** in the sense of Article 33(3) PCT.

14 As acknowledged in the present application, **the individual antibodies specific for CD30 and CD3 were known** but not the particular combination of the two specific antibodies in a bispecific antibody.

15 For example, D1 (cited e.g. on page 2 of the present application) discloses in SEQ ID NO: 1113 an identical sequence to SEQ ID NO: 13 of the present application (the VH of the anti-CD30 antibody) and in SEQ ID NO: 1118 an identical sequence to SEQ ID NO: 14 of the present application (the VH of the anti-CD30 antibody).

Example 29 of D1 starting on page 176 and finishing on page 183 discloses the generation and functional characterization of a particular bispecific antibody CD30-CD3 as single chain molecules, see Figures 46 and 47 for the experimental data.

16 D2 discloses two antibodies binding CD3 comprising the first one:

as VH CDR1 SEQ ID NO: 1, being identical to SEQ ID NO: 7 of the present application;

as VH CDR2 SEQ ID NO: 2, being identical to SEQ ID NO: 8 of the present application;

as VH CDR3 SEQ ID NO: 3, being identical to SEQ ID NO: 9 of the present application, wherein position 3 of the CDR3 (i.e. position X) is a H;

comprising the second antibody binding CD3 wherein

as VH CDR1 SEQ ID NO: 1, being identical to SEQ ID NO: 7 of the present application;

as VH CDR2 SEQ ID NO: 2, being identical to SEQ ID NO: 8 of the present application;

as VH CDR3 SEQ ID NO: 176, being identical to SEQ ID NO: 9 of the present application, wherein position 3 of the CDR3 (i.e. position X) is a G (designated HC-H101G);

The VL CDRs of the huCD3-L1-T41K antibody are identical to the VL CDRs of the CD3 antibody of claim 1 of the present application:

SEQ ID NO: 6 of D2 is identical to SEQ ID NO: 10 of the present application;

the VL CDR2 being GTN of SEQ ID NO: 11 of the present application is also the CDR2 disclosed in Table 1 for the VL-huCDR2-L1-T41K of D2;

SEQ ID NO: 7 of D2 is identical to SEQ ID NO: 12 of the present application.

D2 also discloses bispecific antibodies, see e.g. paragraphs 846 to 855, 859 and 861.

The introduction of the mutations L234F and L235E mutations in the Fc region are also disclosed in D2, see paragraph 715 and claim 29(e). Both mutations are are well known in the art of bispecific antibodies. Also known is the mutation at G236 to minimize the interaction of the Fc region with the Fc gamma receptor, see paragraph 716.

It is noted that D2 is a family member of WO2017009442 (cited in e.g. page 51 of the present application, line 24 as disclosing the IgG1-huCD3-H1L1-H101G). However, D2 is cited instead since it has paragraph numbering which makes easier the discussion about the subject-matter disclosed

17 D3 also discloses two antibodies binding CD3 comprising the first one:

as VH CDR1 SEQ ID NO: 26, being identical to SEQ ID NO: 7 of the present application;

as VH CDR2 SEQ ID NO: 27, being identical to SEQ ID NO: 8 of the present application;

as VH CDR3 SEQ ID NO: 28, being identical to SEQ ID NO: 9 of the present application, wherein position 3 of the CDR3 (i.e. position X) is a H;

comprising the second antibody binding CD3:

as VH CDR1 SEQ ID NO: 26, being identical to SEQ ID NO: 7 of the present application;

as VH CDR2 SEQ ID NO: 27, being identical to SEQ ID NO: 8 of the present application;

as VH CDR3 SEQ ID NO: 45, being identical to SEQ ID NO: 9 of the present application, wherein position 3 of the CDR3 (i.e. position X) is a G (designated HC-huCD3-H1-H101G).

The VL CDRs of the huCD3-L1 antibody of D3 are identical to the VL CDRs of the CD3 antibody of claim 1 of the present application:

SEQ ID NO: 30 of D3 is identical to SEQ ID NO: 10 of the present application;

the VL CDR2 being GTN of SEQ ID NO: 11 of the present application is also the CDR2 disclosed in the sequence listing of D3 for the CDR2 of the VL-huCD3-L1 of D2;

SEQ ID NO: 31 of D3 is identical to SEQ ID NO: 12 of the present application.

18 D9 discloses in Figure 1 the amino acid sequence of the heavy chain of the human anti-CD30 antibody designated 5F11 gamma 1 . Said sequence is almost identical with SEQ ID NO: 17 of the present application having only 4 differences: these differences being the known Fc modifications: L234**F**, L235**E**, G236**R** and K409**R**, these 4 mutations being abbreviated in the present application as FERR (using the same nomenclature as in the prior art). These mutations, some of them even in combination were known as discussed in detail below.

19 Methods of preparing bispecific antibodies are disclosed in D3 in e.g. paragraphs 239 to 256. Particular examples are disclosed in e.g. Examples 3 and 12 of a CD3XPD-L1 bispecific antibody.

The introduction of the mutations L234F and L235F mutations in the Fc region are also disclosed in D2, see claim 29(e) and paragraph 715 (and are well known in the art of bispecific antibodies). Also known is the mutation at G236 to minimize the interaction of the Fc region with the Fc gamma receptor, see paragraph 291.

20 D4 (see e.g. Example 2), D5 (see abstract) and D6(see abstract) disclose the use of bispecific anti CD3-CD30 antibodies to treat human Hodgkin lymphoma.

21 The present application discloses that particular combinations of antibody sequences comprising particular mutations in the constant regions result in improved effects compared to other constructs. However there are no claims restricted only to entire chain sequences comprising the Fc mutations that would provide an unexpected effect. Some of the differences in activity in e.g. examples 8-18 are no so significant and even assuming they were significant: **only claims restricted to entire chains consisting on the exemplified improved combinations could be considered inventive**.

22 For example in claim 20 the first Fc polypeptide comprises L234F, L235E and G236R (the so called FER) and the second Fc polypeptide comprises the substitutions L234F, L235E and D265A (FEA).

However, as above discussed L234F and L235E is a known combination to abrogate binding to Fc gamma receptors see e.g. D1 and D2 discussed above and also see D10, page 43, lines 7 and 8 and page 43, 7th paragraph, that discloses the combination of L234F and L235E and D265A (FEA) which results in inert Fc domains.

23 These mutations that abrogate the effector function of the Fc domain were also known from FLT3L-Fc fusions as e.g. L234F + L235E + D265A + F405L designated FEAL and also the further combinations abbreviated "FEALLS" , "FEARLS" and FEA, see e.g. paragraph 106 of D11.

24 Also D12 discloses in e.g. Example 13 the FEAL and FEAR variants having knobs-into-holes. The concept of knob-into-holes is also disclosed in e.g. Figures 2 and 5 of D13, and in Figure 5 in combination with the K409R mutation in IgG2.

25 D14 discloses that the Fc mutant K409R in the CH3 is advantageous to generate bispecific antibodies (see e.g. the abstract).

26 There is no unexpected technical effect associated to the particular bispecific antibodies over the used in the present application. Starting from one of D4, D5 or D6 as closest prior art the technical problem would have been to provide an **alternative bispecific antibody** against CD3-CD30 suitable for use in the treatment of cancer, e.g. in the treatment of human Hodgkin lymphoma.

The solution of claim 1 is to use an antibody defined by 12 CDRs, taking into account that SEQ ID NO: 9 has two alternatives.

In the absence of an unexpected effect, said solution is not considered inventive because it is a mere alternative to the ones of e.g. D4, D5 or D6.

27 Furthermore, since the individual antibodies against CD3 and CD30 were known (see above) and were studied in depth, the skilled person would have been motivated to combine both antibodies in a bispecific antibody following the teachings of D4, D5 and D6 and would have arrived at precisely the solution claimed.

28 The addition of known mutations L234F, L235E, position G236A and even K409R is standard in the art of bispecific antibodies as discussed above in relation to D1-D3 and D8-D14 and therefore can not render the claims inventive either since the skilled person would have tried these known Fc mutations that were already used in the field of bispecific antibodies.

29 The particular mutation G236R in order to decrease the effector function due to Fc modification was also known in the prior art from e.g. D7 (see paragraph 187 section (e)) even in conjunction with mutations at L234 and L235, being the disclosed triple combination L234A/L235E/G236R. It is noted that G236R is only an optional feature of e.g. present claim 15, being the only requirement to mutate G236, a feature disclosed already in D2 and D3 (as discussed above).

30 The mutations listed in present claim 18 are also disclosed in e.g. D8, see e.g. Examples 1-5 on pages 39-41 in bispecific antibodies.

31 As discussed above, the combination of known features cannot justify the involvement of inventive step unless an unexpected effect would be achieved by said combination of features. However, decreased effector function due to Fc modification was a known feature and the effect achieved by said modifications was also well known so that no inventive step can be acknowledged.

32 The same reasoning would apply to the individual antibodies of claims 49 and 52. The antibodies were known from D1, D2 and D3 as discussed above. The combination of these antibodies with L234, L235 and G236 mutations was also known from D1, D2 and D3, although there is apparently no unambiguous disclosure of the simultaneous combination of L234F, L235F and G236 mutations. As above discussed, even a new combination of mutations can only be considered inventive if there is an unexpected effect. No unexpected effect is evident at present from the application documents. However in the case of independent claims 49 and 52 in view of the lack of unity objection (see item IV above) no further examination is required.

Remark on medical uses

33 Claims 37-44 relate to an antibody for medical use. 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 37-44 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

Re Item VIII

Certain observations on the international application

Lack of clarity

34 **Claim 60 is unclear**, contravening the requirements of Article 6 PCT, since the antibody is defined by the method of manufacture. However, the antibody can be defined by its particular sequence, rendering claim 60 unclear.