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Datasheet for the decision of 20 January 2026

Case Number: T 0655/24 - 3.3.04

Application Number: 14700200.0

Publication Number: 2943507

IPC: C07K16/00, C07K16/10, C07K16/28, C07K16/32

Language of the proceedings: EN

Title of invention:
Inert format

Patent Proprietor:
Genmab A/S

Opponents:
Ampersand Partnerschaft von Rechanwälten mbB

Headword:
Inert Fc region/GENMAB

Relevant legal provisions:
EPC Art. 123(2), 84, 83, 54, 56

Keyword:

Amendments - added subject-matter (no)
Claims - clarity (yes)
Sufficiency of disclosure - (yes)
Novelty - (yes)
Inventive step - (yes)

Decisions cited:

G 0001/03, G 0002/10, G 0002/21, T 1791/11, T 0787/14, T 1322/17, T 1989/19, T 2716/19, T 0314/20, T 0364/20, T 1913/21, T 0446/22, T 0840/22, T 1135/22

Catchword:

Considerations in view of G 2/21 on taking an improvement of a technical effect into account for assessing inventive step (points 58 to 72 of the Reasons)

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Case Number: T 0655/24 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 20 January 2026

Appellant: (Opponent 2)	Ampersand Partnerschaft von Rechanwälten mbB Widenmayerstraße 4 80538 München (DE)
Representative:	Schiweck Weinzierl Koch Patentanwälte Partnerschaft mbB Ganghoferstraße 68 B 80339 München (DE)
Respondent: (Patent Proprietor)	Genmab A/S Carl Jacobsens Vej 30 2500 Valby (DK)
Representative:	J A Kemp LLP 80 Turnmill Street London EC1M 5QU (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 12 March 2024 concerning maintenance of the European Patent No. 2 943 507 in amended form**

Composition of the Board:

Chair	A. Chakravarty
Members:	B. Rutz
	R. Romandini

Summary of Facts and Submissions

I. Opponent 2 (appellant) filed an appeal against the decision of the opposition division that European Patent No. 2 943 507, as amended based on the main request and the invention to which it relates, fulfilled the requirements of the EPC.

II. The patent had been opposed on the grounds of Article 100(a) EPC, in relation to novelty (Article 54 EPC) and inventive step (Article 56 EPC), and of Article 100(b) and (c) EPC.

III. With its reply to the appeal, the respondent filed auxiliary requests 1 to 7. Auxiliary requests 1 to 3 are identical to auxiliary requests 3, 2 and 11, respectively, filed during the opposition proceedings. Auxiliary requests 4 to 7 are newly filed in appeal and correspond to the main request and auxiliary requests 1 to 3, respectively, except that the final two claims have been deleted.

IV. Opponent 1 withdrew its opposition during the opposition proceedings and is no longer a party to the proceedings.

V. The board summoned the parties to oral proceedings, as they had requested, and informed them of its preliminary opinion in a communication under Article 15(1) RPBA.

VI. Oral proceedings were held on 20 January 2026. At the end of the oral proceedings, the respondent made former auxiliary request 6 its main request and renumbered the

former main request and auxiliary requests 1 to 5 as auxiliary requests 1 to 6, respectively.

VII. Claim 1 of the main request reads as follows:

"1. A protein having an Fc region comprising a first polypeptide and a second polypeptide, wherein said first and second polypeptide each comprises in the direction from the N- to C-terminal at least a hinge region, a CH2 region and a CH3 region of a human IgG1 immunoglobulin heavy chain, wherein in both said first and second polypeptide the amino acids at positions L234, L235, D265, N297 and P331 of the human IgG1 heavy chain, are F, E, A, N and P, respectively, wherein the amino acid positions are numbered according to the EU-index of numbering; wherein said Fc region does not bind to any Fcγ receptors, and wherein said protein has a plasma clearance rate (ml/day/kg) which deviates from a wild-type protein by no more than 10%, such as no more than 8%, no more than 7%, no more than 5%, no more than 3%, no more than 1%, and no more than 0% wherein the plasma clearance rate is calculated by the dose (pg/kg) administered to a subject divided by the area under the curve (AUC), wherein the AUC value is determined from concentration-time curves, wherein said wild-type protein is identical to said protein except that in both first and second polypeptides the amino acids at positions L234, L235 and D265 of the human IgG1 heavy chain, are L, L, and D, respectively."

VIII. At the end of the oral proceedings the Chair announced the board's decision.

IX. The following documents are referred to in this decision:

D1 WO2012/143524 A2

D3 V. Oganesyan et al.,"*Structural characterization of a human Fc fragment engineered for lack of effector functions*", Acta Crystallographica D64, 2008, 700-704.

D6 R. L. Shields et al., "*High Resolution Mapping of the Binding Site on Human IgG1 for FcγRI, FcγRII, FcγRIII, and FcRn and Design of IgG1 Variants with Improved Binding to the FcγR*", The Journal of Biological Chemistry 276(9), 2001, 6591-6604.

D8 S. M. Canfield and S. L. Morrison, "*The Binding Affinity of Human IgG for its High Affinity Fc Receptor Is Determined by Multiple Amino Acids in the C_H2 Domain and Is Modulated by the Hinge Region*", J. Exp. Med. 173, 1991, 1483-1491.

D10 WO2011/085343 A1

D15 R. A. Clynes et al., "*Inhibitory Fc receptors modulate in vivo cytoxicity against tumor targets*", Nature Medicine 6(4), 443-446.

D19 W. Wang et al., "*Monoclonal Antibody Pharmacokinetics and Pharmacodynamics*", Nature 84(5), 2008, 548-558.

D21 WO2009/100309 A2

D23 L. Baudino et al.,"*Crucial Role of Aspartic Acid at Position 265 in the CH2 Domain for Murine IgG2a and IgG2b Fc-Associated Effector Functions*", The Journal of Immunology 181, 2008, 6664-6669.

D24 E. A. Kabat et al., "*SEQUENCES OF PROTEINS OF IMMUNOLOGICAL INTEREST*", Fifth Edition, 1991, pages 1, 680 and 718.

D25 Declaration of Dr Aran F. Labrijn and CV

D26 P. J. Engelberts et al., "*DuoBody-CD3xCD20 induces potent T-cell-mediated killing of malignant B cells in preclinical models and provides opportunities for subcutaneous dosing*", EBioMedicine 52(102625), 2020, 1-13.

D34 G. M. Edelman et al., "*The covalent structure of an entire γG immunoglobulin molecule*", PNAS 63(1), 1969, 78-85.

D35 J. W. Ellison et al., "*The nucleotide sequence of a human immunoglobulin Cγ1 gene*", Nucleic Acids Research 10(13), 1982, 4071-4079.

D36 R. A. Dwek et al., "*Glycobiology: 'The function of sugar in the IgG molecule'*", Journal of Anatomy 187, 1995, 279-292.

D37 S. Bolt et al., "*The generation of a humanized, non-mitogenic CDS monoclonal antibody which retains in vitro immunosuppressive properties*", European Journal of Immunology 23, 1993, 403-411.

X. The appellant's submissions are summarised as follows:

Admittance (Article 12(4) RPBA)

The main request (filed as auxiliary request 6) should not be admitted because it lacked convergence with claim 1 as maintained by the opposition division. It comprised the subject-matter of granted claim 2, which had been deleted in the claims as maintained. For this reason the request would not have been admitted by the opposition division.

The request should have been filed during opposition proceedings because the objections against the medical use claims deleted in this request had been already present at that stage.

Amendments (Article 123(2) EPC)

The application as filed disclosed that the amino acid at the position 297 was the same as the naturally occurring amino acid in a human IgG1 heavy chain – said naturally occurring amino acid was however "B" and not the now claimed "N" (see paragraph bridging pages 12 and 13 and document D24).

The hinge, CH2 and CH3 regions of a human IgG1 heavy chain were only disclosed in conjunction with the precise position of said regions in said heavy chain (see page 10 of the application as filed).

The omission of the clear reference to Kabat et al., Sequences of Proteins of immunological interest, 5th Edition, amounted to a problem under Article 123(2) EPC, since the claim did not specify which EU numbering was meant.

Introduction of the feature "*does not bind to any Fcγ receptor*" added subject-matter because the relevant passage on page 14 of the application as filed contained further mandatory features which had been omitted.

The combination of features in claim 1 was not disclosed in the application as filed.

Clarity (Article 84 EPC)

The wording "*a protein having an Fc region comprising a first polypeptide and a second polypeptide*" was ambiguous and could be understood as referring to a protein comprising two polypeptides each comprising a

hinge region, a CH2 region and a CH3 and wherein the protein comprised an additional Fc region.

The type of Fcγ receptor and the method of measuring the plasma clearance rate was not defined in the claim. This rendered the claim unclear.

Sufficiency of disclosure (Article 83 EPC)

The claimed invention was not sufficiently disclosed over the whole breadth of the claim because "Fc region" according to the patent differed from what was commonly understood in the art. According to paragraph [0025] it encompassed a single unpaired hinge-CH2-CH3 element. Further, defining the orientation of the elements hinge, CH2 and CH3 did not suffice, as the open-ended language of the claims allowed the presence of an unlimited number of mutations, including a number of mutations, which were known to prevent homodimerisation. There was no feature recited in claim 1, which explicitly or implicitly defined that the protein comprised a dimeric Fc region.

Novelty (Article 54 EPC)

The numbering "234", "235", "265", "297", "331" was meaningless even if it was according to the EU-index of numbering, since it was impossible to start counting numbers, because hinge, CH2 and CH3 region could be anywhere in the claimed protein. Accordingly, the claimed protein encompassed a protein which comprised anywhere in its sequence a hinge, CH2 and CH3 region of an IgG1 subclass. Any antibody comprising an F, E, A, N, and P residue at any position anticipated the protein of claim 1.

The claimed subject-matter was not novel over document D1.

Inventive step (Article 56 EPC)

Documents D10 or D21 were equally suitable as closest prior art. Document D10 disclosed the Fc variants FE (L234F, L235E), FES (L234F, L235E, P331S) and FEAS (L234F, L235E, D256A, P331S). Document D21 disclosed the Fc variants FE (L234F, L235E) and FES (L234F, L235E, P331S).

There was no technical effect resulting from the difference between the FEA Fc variant claimed and the Fc variants in the prior art so that the objective technical problem had to be defined as the provision of an alternative Fc variant that modulates unwanted Fc-receptor interactions.

The claimed subject-matter was obvious over the disclosure of D10 or D21 alone or in combination with D6, D15 or D23.

Even if the problem was formulated as the provision of an improved Fc variant, the claimed subject-matter lacked an inventive step. The skilled person would combine the mutation D265A with the mutations FE which were both disclosed in D10 as having "*reduced or no effector function*" with a reasonable expectation of success when seeking to further reduce Fc effector functions.

XI. The respondent's submissions are summarised as follows:

Admittance (Article 12(4) RPBA)

The claims were identical to claims 1 to 16 of auxiliary request 2 which had been filed during opposition proceedings. The medical use claims 17 and 18 of that request were deleted although the opposition division had had no issues with regard to sufficiency of disclosure of these claims.

The request was therefore in parts admissibly raised and maintained during the opposition proceedings.

Added subject-matter (Article 123(2) EPC)

The opposition division arrived at the correct conclusion, for the reasons stated in the appealed decision.

The skilled person would clearly and unambiguously know the identity of the naturally occurring (and thus "unsubstituted") amino acid at position 297 of the human IgG1 heavy chain, i.e. asparagine (N). Similarly, the skilled person would clearly and unambiguously know the identity of the naturally occurring (and thus "unsubstituted") amino acid at position 331 of the human IgG1 heavy chain, i.e. proline (P) (see paragraphs 38 to 49 of declaration D25).

Clarity (Article 84 EPC)

In the phrase "A protein having an Fc region" in claim 1 the verb "having" established a possessive or characteristic relationship between "A protein" and "an Fc region". In this context, "having" implied that the

protein included or contained an Fc region as part of its structure. The phrase illustrated that this protein was defined or characterized by having an Fc region, which was a specific domain that some proteins, such as antibodies, possessed for functions such as binding to cell receptors. It was apparent that the protein of claim 1 had an Fc region. The claim was also unambiguous in specifying that the Fc region itself comprised two polypeptides and that each of the two polypeptides comprised (in the direction from the N- to C-terminal) at least: a hinge region, a CH2 region, and a CH3 region.

Claim 1 was clear in its own right, independently of the description. The skilled person would have no difficulty in understanding that the protein of claim 1 comprised a standard-format Fc region. The term Fc region would be given its normal meaning in the art by a skilled person. The patent specification was entirely consistent in this respect.

Only a finite number of Fcγ receptors were commonly known. The skilled person would compare the effects of Fc variants only within one species. The skilled person would understand that the plasma clearance rate was measured against a defined wild-type protein.

Sufficiency of disclosure (Article 83 EPC)

No new or additional facts, objections, arguments or evidence had been provided by the appellant to explain why the decision under appeal was wrong in this respect.

The arguments advanced under Article 83 EPC were identical to the arguments advanced under Article 84 EPC.

In any case, the skilled person would be able to carry out the invention by the preparation of embodiments such as those described in the examples of the patent.

Novelty (Article 54 EPC)

The skilled person would adopt a technically sensible interpretation of claim 1. Consequently, the claim could not be anticipated by "any antibody" as proposed by the appellant. Document D1 did not disclose a protein having a first polypeptide and a second polypeptide, wherein said first and second polypeptides each comprised (in the direction N-terminal to C-terminal) at least a hinge region, a CH2 region and a CH3 region of a human IgG1 immunoglobulin heavy chain, and wherein both said first and second polypeptides had the FEA mutations combined with the naturally-occurring N at position 297 and the naturally-occurring P at position 331.

Inventive step (Article 56 EPC)

Documents D10 or D21 might be considered as closest prior art. However, whilst the passage on page 44, lines 23 to 27, in D10 stated having "*one, two, or three of the following substitutions: L234F, L235E, or P331S*", the skilled person was aware that the relevant functional effects had been determined for the triple mutant, as evidenced in D3 which was cited in D10. The skilled person, reading D10, would thus not be motivated to deviate from the triple mutant FES disclosed therein and move to FE, given that the

relevant functional activity and crystal structure had been demonstrated for the triple mutant, and for no other variants.

There was no suggestion or teaching in D10 that would lead the skilled person to combine D265A with other mutations. The D265A substitution was disclosed in D10 as a stand-alone embodiment compared to FES.

The FES mutation was also a preferred embodiment of document D21 (see various passages and the examples) while the FE mutant was only mentioned in embodiment 5 without further data. There was no reason why the skilled person would intentionally choose a starting point without an associated effect over the FES variant for which the effects were established.

It had been established in the examples of the patent that the claimed FEA variant lacked Fcγ receptor binding activity (see CD69 expression assays), and in this respect showed an improved profile compared to the closest prior art embodiment FES. For the claimed FEA variant antibodies, the plasma concentration over the time course was equivalent to the wild-type counterpart control antibodies.

The problem was thus the provision of an improved Fc mutant that abolished T cell activation (T cell expression of CD69) and retained a plasma clearance comparable to the wild type. The solution to this problem as claimed was not obvious over either one of D10 or D21.

At the very least the claimed FEA variant represented an alternative solution to a known problem. Also this alternative solution was not obvious from the prior art

because achieving the effect of no binding to any FcγR receptor while maintaining a plasma clearance rate comparable to wild-type could not be predicted for the FEA variant.

XII. The appellant requested that the decision under appeal be set aside and the patent be revoked. The appellant further requested that the main request (former auxiliary request 6) and auxiliary requests 2 to 7 (former auxiliary requests 1 to 5 and 7) be not admitted.

The respondent requested that the patent be maintained on the basis of the main request, originally filed as auxiliary request 6 with the reply to the statement of grounds of appeal, or alternatively on the basis of the other requests as renumbered.

Reasons for the Decision

Main request (filed as auxiliary request 6)
Admittance (Article 12(4) RPBA)

1. The set of claims was newly filed with the reply to the statement of grounds of appeal. The provisions of Article 12(4) RPBA therefore apply.

2. The main request is identical to auxiliary request 2 filed during the opposition proceedings on 23 November 2023 and refiled with the reply to the statement of grounds of appeal, except that claims 17 and 18 have been deleted.

3. During the oral proceedings in appeal, the board concluded that the then pending auxiliary request 2 was to be considered part of the appeal proceedings.

4. In coming to this conclusion, the board recalled that claim requests which had been filed during the opposition proceedings, but which were not discussed or decided upon in the decision under appeal, are automatically part of the appeal proceedings only where they "were admissible raised and maintained" in the sense of Rule 12(4) RPBA (see e.g. T 1135/22, Reasons 4). Whether this is the case depends on whether the department of first instance would have had to admit them, if a decision on admittance had been required (see e.g. decisions T 1913/21, T 446/22 and T 364/20). The board could not identify any reasons why the opposition division would not have admitted auxiliary request 2. Indeed, the request was filed within the time limit set out under Rule 116(1) EPC. Furthermore, it was a response to an objection of lack of inventive step by the opposition division in its preliminary opinion annexed to the summons to oral proceedings (see point 8.2.7 therein).

5. The main request no longer contains claims 17 and 18 which related to the claimed protein for medical use. The board exercised its discretion to admit this request because it solved the issue under Article 83 EPC of sufficient disclosure for the invention to which claims 17 and 18 relate, did not introduce new issues and enhanced procedural efficiency (Article 12(4) RPBA).

Claim interpretation
Fc region

6. The parties differed in their interpretation of the claim wording *"A protein having an Fc region comprising*

a first polypeptide and a second polypeptide". The two interpretations put forward were:

(a) a protein which has an Fc region, wherein the Fc region comprises a first and a second polypeptide

(b) a protein which has an Fc region and (in addition) comprises a first and a second polypeptide

7. The board finds that the skilled person when reading the claim would consider the word "comprising" to relate to the entity mentioned immediately preceding it, i.e. "Fc region", and not to the entity mentioned earlier in the claim, i.e. "protein". The skilled person would further know from their common general knowledge that an Fc region is composed of two polypeptide chains usually held together by disulfide bonds which form a functional entity and are often also referred to as such. An Fc region is commonly known to comprise a hinge region, a CH2 region and a CH3 region. The board therefore concludes that interpretation (a) above is the only technical sensible interpretation for a skilled person.

8. The appellant argued that this interpretation was contrary to the definition of an Fc region in paragraph [0025] of the patent which states: "*'Fc region' as used herein, is intended to refer to a region comprising, in the direction from the N- to C-terminal, at least a hinge region, a CH2 region and a CH3 region*".

9. The board does not agree with this view because the skilled person would read the definition in the patent as relating to an Fc region as commonly known in the art (see above). In many scientific articles a corresponding wording can be found, i.e. "CH2 region" or "CH3 region" in the singular referring to a dimeric region (see e.g. D8, legend to Figure 5: "*Graphic*

representation of the Fc region of IgG. C_H2 is shown in yellow, C_H3 and the C_H2-linked carbohydrate are in white"; D19, Figure 1 and legend to Figure 1; "*the Fc portion of the antibody includes CH2 and CH3*"; D34, Figure 1).

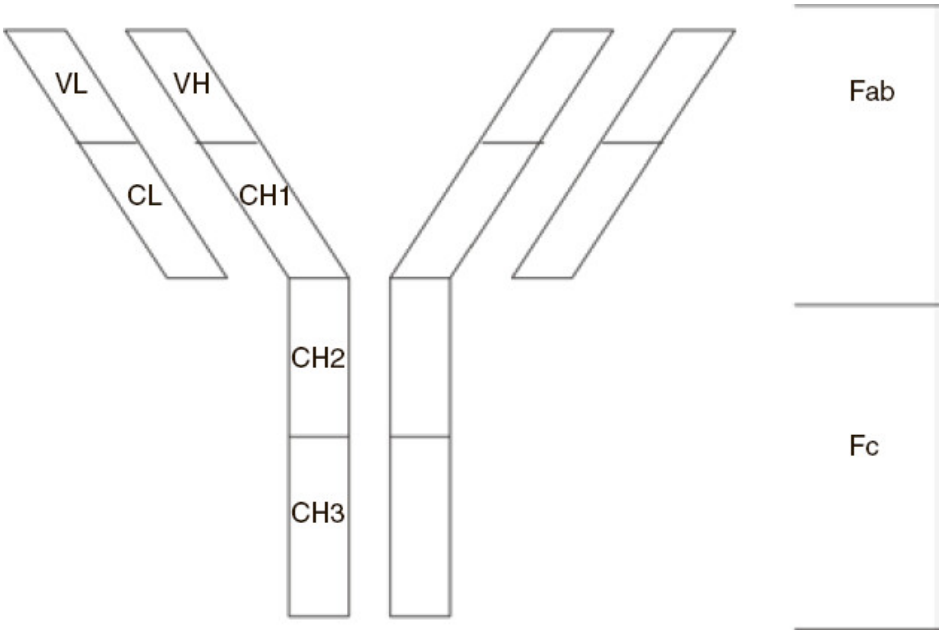

Figure 1 of D19

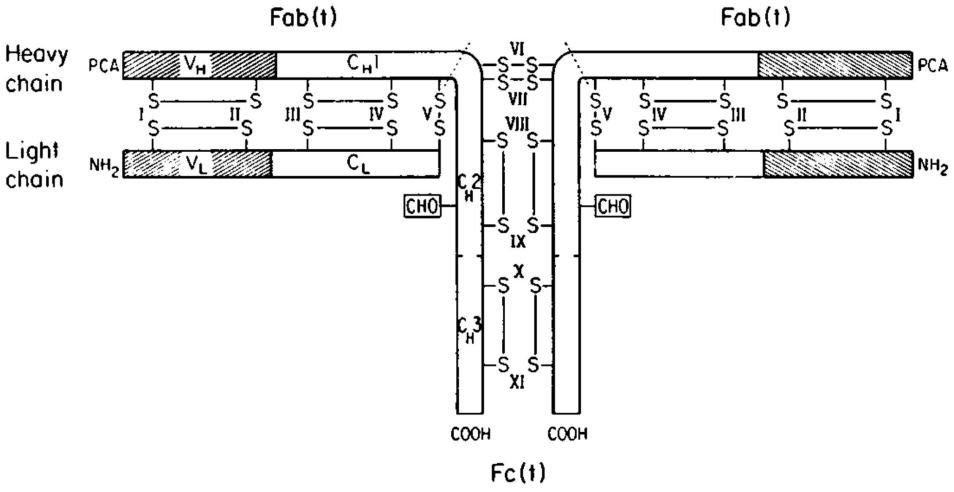

Figure 1 of D34

10. This reading is further supported by the disclosure of the patent seen as a whole including the examples which

all relate to antibodies with complete Fc regions composed of two polypeptide chains (see Example 1).

L234, L235, D265, N297 and P331

11. The appellant further argued that "*the numbering '234', '235', '265', '297', '331', even if this numbering may be according to EU-index of numbering, is meaningless, since it is impossible to start counting numbers, because hinge, CH2 and CH3 region can be anywhere in the claimed protein*".

12. The board does not agree. The skilled person would be able to identify the positions by comparison with the known human IgG1 heavy chain sequence even if the hinge, CH2, CH3 regions were not immediately adjacent to each other, but separated by spacers, or if the protein contained further regions or additional mutations (as, for example, in claim 11 of the main request). Moreover, the claim defines the order and direction of the hinge, CH2 and CH3 regions, namely "*in the direction from the N- to C-terminal*". The hypothetical possibility to modify an Fc region in a way that its sequence would no longer be recognisable and comparable to a human IgG1 heavy chain sequence is not relevant because such a molecule would no longer be considered an Fc region by the skilled person. The positions recited in the claim therefore relate to precise positions within an Fc region as commonly understood by the skilled person.

Amendments (Article 123(2) EPC)

13. In view of the claim interpretation above, the board sees no reason to address objections which stem from the reading of the claim as relating to a protein

having an Fc region and (additionally) a first and a second polypeptide as defined in the claim (see points 6. to 10. above).

N297 and P331 are N and P

14. The appellant argued that the amino acid at position N297 was not clearly and unambiguously defined as N in the application as filed because the relevant passage (paragraph bridging pages 12 and 13) referred to document D24 which listed "ASX" at this position, i.e. either aspartate (D) or asparagine (N), for the heavy chain of a human IgG1 molecule according to the EU-index numbering.

15. The board agrees with the decision under appeal (see point 5.2.3 therein) that at the priority date it was common general knowledge that position N297 was indeed N. Document D25 provides several references (D6 and D35 to D37) which reflect the common general knowledge at the priority date for the correct sequence. In contrast, D24 represents an outdated reference, which reflects the technical limitations at an earlier point in time.

16. The appellant also argued that the wording "*amino acids in the positions corresponding to positions N297 and P331 in a human IgGl heavy chain have not been substituted*" on page 12, last paragraph, in the application as filed meant that the amino acids in these positions were essentially undefined because any amino acid could be present in a "corresponding" position, not necessarily N and P.

17. The board does not agree because the following sentence in the same paragraph states: "*Thus, a 'have not been*

substituted' amino acid in a position corresponding to the position in a human IgG1 heavy chain means the amino acid at the particular position is the ***same as the naturally occurring amino acid*** *in a human IgG1 heavy chain*" (highlighting added by the board).

18. The board therefore concludes that the passage on pages 12 to 13 of the application as filed defines the naturally occurring, i.e. unsubstituted, amino acid for positions 297 and 331 according to EU-index numbering of a human IgG1 heavy chain, i.e. N297 and P331 (see also documents D6 and D35 to D37).

Combination of L234F, L235E, D265A with N297 and P331

19. Basis for the combination FEA in "*both said first and second polypeptides*" can be found in claims 1, 15 and 18 as filed which are dependent on each other. The unsubstituted, i.e. wild-type or naturally occurring, positions N297 and P331 are disclosed in the paragraph bridging pages 12 and 13 of the application as filed, albeit without explicit reference to both polypeptides ("*in at least one of the polypeptides*") and with reference to the broader embodiment of L234F, L235E and D265A being not L, L, D, i.e. being mutated to something else than the wild-type or naturally occurring residue.

20. However, the skilled person reading the application as a whole and taking into account common general knowledge would recognise that the preferred combination of mutations in positions L234, L235, and D265 is FEA. The following passages in the application as filed are relevant in this regard:

page 28, second paragraph: "*In one embodiment, in both said first and second polypeptides the amino*

acids in the positions corresponding to position L234, L235, and D265 in a human IgG1 heavy chain are F, E, and A, respectively."
claim 15: "*The protein according to any of the preceding claims, wherein in at least one of said first and second polypeptides the amino acids corresponding to positions L234, L235 and D265 in a human IgG1 heavy chain are F, E, and A, respectively.*"

21. While another combination of mutations at the positions L234, L235 and D265, namely AAA (see page 28, third and fourth paragraph) is mentioned in the description, the combination FEA is the only one which is singled out in an individual claim (see above) and represented as an individual sequence in the sequence listings (SEQ ID NO: 20, see table on page 52).

22. Moreover, several passages in the description point to the particular advantageous features of the FEA variant:
page 13, middle of page: "*An antibody of the present invention has been proven to be completely inert when tested in several different assays, i.e. see Examples 3 to 9 and 11 to 13. The CD3 antibody comprising the amino acid substitutions L234F, L235E, and D265A* **[FEA]**, *as described in the Examples, showed abrogation of Fc-mediated T-cell proliferation, Fc-mediated CD69 expression on T-cells, unspecific killing and cytokine release in a cytotoxicity assay, as well as in vitro C1q binding. Similarly, the antibody comprising the amino acid substitutions L234F, L235E, and N297Q* **[FEQ]** *showed comparable results.*"
page 22, last paragraph, to page 23, first paragraph: "*The invention provides an antibody*

comprising the amino acid substitutions L234F, L235E, and D265A **[FEA]**, *which results in absolutely no proliferation of T-cells, indicating that the protein according to the invention does not enable Fcγ Receptor binding, as described in Example 4 and 12.*
Furthermore, an antibody according to the invention, i.e. an antibody comprising the amino acid substitutions L234F, L235E, and D265A **[FEA]**, *has been shown to retain its ability to kill tumor cells.*"
page 56, with reference to Figure 3: "I*ncubation of PBMCs with IgG1-CD3 Fab, IgG1-b12, IgG1-CD3-LFLEDA* **[FEA]**, *IgG1CD3-LFLENQ* **[FEQ]**, *IgG1-CD3-DANQ and IgG1-CD3-LFLEDANQPS antibodies did not induce any expression of CD69 on T-cells.*"
page 61, with reference to Figure 10A: "*The human IgG concentrations in plasma for antibody variants LFLEDA* **[FEA]** *and LALA were similar to those of wild-type antibodies.*" (abbreviations in square brackets and highlighting added by the board)

23. While the variant L234F, L235E, and N297Q (FEQ) showed a similar inert character as the FEA variant (see page 13, cited above), it was less stable as evident from the plasma clearance assay (see Figure 10A and page 61 cited above).

24. The skilled person would therefore have recognised FEA as the most preferred variant and would have considered it to be disclosed in combination with the unsubstituted amino acids N297 and P331 disclosed on page 12 and 13 as also used in the examples.

A hinge region, a CH2 region and a CH3 region of a human IgG1 immunoglobulin heavy chain

25. The appellant considered the addition of "*human IgG1*" to the wording of claim 1 as filed to add subject-matter because this feature was only disclosed together with the precise position of said region within the heavy chain (see page 10 of the application as filed).

26. The board disagrees because the passages on page 10 list the amino acid positions only as "for example". The skilled person would therefore understand that the hinge, CH2 and CH3 regions of a human IgG1 immunoglobulin heavy chain are disclosed in general and not limited to precise amino acid positions.

EU-index of numbering

27. The appellant alleged that the omission from the claim of the reference "*Kabat et al., Sequences of Proteins of immunological interest, 5th Edition*" which was cited in the application as filed with regard to the EU-index of numbering would add subject-matter.

28. The board agrees with the decision under appeal that the EU-index of numbering is common general knowledge and can be understood without specific reference to Kabat *et al*. (see decision under appeal, point 5.4.2).

Does not bind to any Fcγ receptor

29. The appellant objected that the subject-matter of claim 1 extended beyond the content of the application as filed because the feature "does *not bind to any Fcγ receptor*" had been extracted from page 14, third paragraph, of the application as filed while omitting

several additional conditions which were linked to this feature, namely "*which does not enable Fc mediated T-cell activation, does not induce the complement system, does not bind Fcγ Receptors, but at the same time have a plasma clearance rate which is comparable to the plasma clearance rate of a wild-type protein*".

30. The board does not agree. Several other passages in the application as filed show that the feature "*does not bind to any Fcγ receptor*" is one of several alternatives. Page 13, penultimate paragraph, refers to

> "*an Fc region which is at least not able to bind any Fcγ Receptors, induce Fc-mediated cross-linking of FcRs, **or** induce FcR-mediated cross-linking of target antigens via two Fc regions of individual proteins, such as antibodies, **or** is not able to bind C1q*" (highlighting added by the board).

31. Further passages indicate that this feature is particularly relevant. Page 21, second paragraph, states that:

> "*The present invention provides a protein, which does not result in CD69 expression on T-cells indicating that the protein according to the invention does not enable Fcγ Receptor binding.*"

and page 22, last paragraph, states that:

> "*the protein according to the invention does not enable Fcγ Receptor binding*".

32. The board therefore concludes that "*does not bind to any Fcγ receptor*" is disclosed as a functional feature of the protein which is not inextricably linked with the other features listed on page 14.

Combination of features

33. The appellant also objected that the combination of features in claim 1 was not disclosed in the application as filed because the different mutations and the functional requirements, i.e. no Fcγ receptor binding and no substantial deviation in plasma clearance rate were all disclosed in separate parts of the application.

34. The board does not agree because the claimed subject-matter is directly and unambiguously derivable from the application as a whole taking common general knowledge into account (see above). The relevant passages are claims 1, 2, 3, 15 and 18 as filed and the above cited passages on pages 10, 12, 13, 16, 21 and 22 of the application as filed.

35. Claims 1, 2 and 3 which are linked by dependencies disclose "[a] *protein comprising a first polypeptide and a second polypeptide, wherein said first and second polypeptide each comprises at least a hinge region, a CH2 region and a CH3 region of an immunoglobulin heavy chain*", "*wherein in at least one of said first and second polypeptides the amino acid in the positions corresponding to positions L234, L235 and D265 in a human IgG1 heavy chain, are not L, L, and D, respectively, and wherein the amino acids in the positions corresponding to positions N297 and P331 in a human IgG1 heavy chain are not Q and S, respectively*" and "*wherein said protein has a plasma clearance rate (mL/day/kg) which deviates from a wild-type protein by no more than 10%, such as no more than 8%, no more than 7%, no more than 5%, no more than 3%, no more than 1%, and no more than 0% wherein the plasma clearance rate is calculated by the dose (pg/kg) administered to a*

subject divided by the area under the curve (AUC), wherein the AUC value is determined from concentration-time curves".

36. As discussed above, the more limited combination L234F, L235E, D265A, N297 and P331 is disclosed in claim 15 (dependent on any preceding claim) as filed and in the paragraph spanning pages 12 and 13. "Both said first and second polypeptides" are disclosed in claim 18 (dependent on any preceding claim) as filed. The reference to the EU-index of numbering is disclosed on page 10, fifth paragraph, and the non-binding to any Fcγ receptor is disclosed on page 22, last paragraph. The definition of the "wild-type protein" is disclosed on page 16, third paragraph.

37. In conclusion, the claims do not infringe Article 123(2) EPC.

Clarity (Article 84 EPC)

38. In view of the claim interpretation above, the board sees no reason to address objections based on a reading of the claim as relating to a protein having an Fc region and (additionally) a first and a second polypeptide as defined in the claim (see points 6. to 10. above).

39. The appellant further argued that the amendment "wherein said Fc region does not bind to any Fcγ receptors" was unclear, because it was not defined which Fcγ receptors (species, subtypes) were meant and how the non-binding and the plasma clearance rate should be measured.

40. The board does not agree because Fcγ receptors are well known in the art (see D3, D6, D23). The fact that different types and subtypes exist and that Fcγ receptors occur in different species does not render the claim unclear. The same applies to the argument that the measurement method was not defined in the claim. The skilled person is aware of different binding measurement methods, some of which have been used in the patent (see examples), and would choose an appropriate method.

41. The claim also provides a method for determining the clearance rate ("*dose (pg/kg) administered to a subject divided by the area under the curve (AUC), wherein the AUC value is determined from concentration-time curves*"). The appellant alleged that this method would not be applicable because the clearance rate changed over time (see Figure 10 in the patent). The board does not agree because the skilled person would know that the same time frame had to be chosen when comparing the claimed protein with the corresponding wild-type protein.

Sufficiency of disclosure (Article 83 EPC)

42. The appellant argued that the subject-matter of claim 2 as granted, which had been incorporated into claim 1, was not sufficiently disclosed (see opponent 2's submission of 26 November 2020 (section VI.) and opponent 1's submission of 25 November 2020 (section 8), refiled with the statement of grounds of appeal as Annex I).

43. In particular, the appellant argued that the plasma clearance rate of a given antibody depended, *inter alia*, on the species in which it was measured. The

plasma clearance rate of a given antibody further depended on the dosing range. Antibody clearance was affected by numerous factors other than FcRn binding. In the non-linear range, little difference might be seen between wild type and variant antibodies. The parameter defined in the claim could thus be measured in different ways which would give different results. The skilled person was therefore unable to identify the particular antibody which fulfilled the requirements of the claim which meant that the skilled person was unable to make a meaningful selection of any antibody using this parameter.

44. The board disagrees because the claim requires a relative plasma clearance rate compared to wild type ("*deviates from a wild-type protein by no more than 10%*"). Variations related to the species or the dosing are irrelevant for carrying out the invention as claimed.

45. The invention to which the claims relate is sufficiently disclosed (Article 83 EPC).

Novelty (Article 54 EPC)

46. In view of the claim interpretation above the board does not agree with the appellant that "*the recited positions are meaningless*" and "*any antibody comprising an F, E, A, N, and P residue at any position anticipates the protein of claim 1*". The prior art cited in this regard, document D1, does not disclose IgG1 heavy chain constant regions which comprise the combination of mutations L234F, L235E, D265A in the context of N297 and P331.

Inventive step (Article 56 EPC)
Closest prior art D10 or D21

47. The decision under appeal analyses inventive step starting from the disclosure in documents D10 or D21. The parties agreed with this choice. The board also considers documents D10 and D21 to represent valid starting points for assessing inventive step. It is, however, important to note that present claim 1 differs from the claim considered in the decision under appeal in that it contains additional functional features, namely "*wherein said Fc region does not bind to any Fcγ receptors, and wherein said protein has a plasma clearance rate (ml/day/kg) which deviates from a wild-type protein by no more than 10%* [...]". These functional features may result in further differences between the claimed subject-matter and the prior art.

Starting from document D10

48. In document D10 human IgG1 antibodies are disclosed in which "*the variant constant region having reduced or no effector function comprises one, two, or three of the following substitutions: L234F, L235E, or P331S*" (page 44, lines 23 to 27). In addition, document D10 discloses the modification D265A as a separate embodiment (see page 44, lines 20 to 23). N297 and P331 are implicitly disclosed in D10 because they correspond to the wild-type residues at the indicated positions, which were well known at the publication date of document D10 (see document D25, points 38 to 49). Although document D25 is a post-published expert declaration the references cited therein (D35, D36, D37 and D6) reflect the common general knowledge at the priority date and before the publication date of D10.

49. The appellant considered each of the combinations FE (L234F, L235E), FES (L234F, L235E, P331S) and FEAS (L234F, L235E, D265A, P331S) to be disclosed in document D10 and thus to represent suitable starting points for the assessment of inventive step.

50. The respondent considered that only the combination FES was disclosed in D10 because the list of substitutions on page 44 was followed by a reference to a scientific article (D3 in this appeal) which related to the crystal structure and functional analysis of only the triple mutation FES. The skilled person would therefore consider that only FES was "*shown to reduce substantially ADCC and CDC activity of variant constant regions*", i.e. "*having reduced or no effector function*" (D10, page 44, lines 23 to 27).

51. The board agrees with the appellant that an FE variant of the Fc region is disclosed in D10 because it is one of only seven possibilities arising from "*one, two, or three of the following substitutions: L234F, L235E, or P331S*": i.e. F, E, S, FE, FS, ES and FES. The skilled person had no reason to assume that a variant FE as disclosed in D10 could not be obtained. Whether the skilled person would have reasonably expected the FE variant to have the function "*to reduce substantially ADCC and CDC activity of variant constant regions*" as assigned to all variants as disclosed in D10 is a different question which will be addressed under the heading of obviousness below.

52. An FEAS variant is however, not disclosed in D10 because the combination of FES with the additional substitution D265A is not directly and unambiguously derivable from this document. The passage on page 44 in D10 discloses the D265A variant and the variants L234F,

L235E and P331S variants as separate embodiments ("*In some embodiments*"). The passage provides no indication that those embodiments should be combined.

Starting from D21

53. Document D21 discloses IgG1 antibodies which "*comprise the addition, substitution or deletion of at least one amino acid residue selected from the group consisting of: L234F, L235E, and P331S*" (FES, paragraph [00112]). D21 further discloses in its claim 5: "*The antibody of claim 3, wherein said antibody comprises the amino acid substitutions: L234F and L235E*". Claim 5 is dependent on claim 1 via claims 3 and 2. Claim 1 reads: "*A modified IgG class monoclonal antibody specific for IFNAR1, wherein said antibody comprises in the Fc region at least one amino acid substitution selected from the group consisting of L234F, L235E, and P331S, as numbered by the EU index as set forth in Kabat and wherein said antibody exhibits reduced affinity for at least one Fc ligand compared to an unmodified antibody*".

54. The board therefore concludes that document D21 discloses an antibody having an Fc region which has the FE or FES combinations of mutations.

Difference and effect

55. The board considers the variant FE disclosed in both D10 and D21 to differ the least from the claimed subject matter. It therefore represents the most appropriate starting point. The difference between the said FE variant and the claimed variant is that the latter includes an additional modification of D265A.

56. The appellant argued that this difference did not result in a technical effect because the comparison in Figure 3A of the application as filed showed only a marginal difference in CD69 expression which could not be considered significant (compare variants "*LFLE*", representing FE, and "*LFLEDA*", representing FEA). Furthermore, Figure 13A showed that at least some embodiments with FEA mutations also showed low CD69 expression comparable to the level of the FE variant in Figure 3A. This raised serious doubts whether the effect of reduced CD69 expression was achieved over the whole breadth of the claim.

57. The respondent, also referring to Figure 3A, considered that the difference resulted in reduced CD69 expression, which was an improvement compared to the FE variant and showed that the FEA variant Fc region induced less effector function. It also referred to additional data provided in post-published documents D25 and D26 as evidence that the effect of further reduced effector function was achieved by essentially all claimed subject-matter. The board, however, notes that such evidence (data) can only be taken into account when the technical effect that it is purported to show is already credible from the disclosure in the application as filed itself. On whether evidence which was not public before the filing date of the patent in suit and was filed after that date to prove a technical effect can be relied upon for acknowledgement of inventive step, the Enlarged Board of Appeal in decision G 2/21 held that: "*A patent applicant or proprietor may rely upon a technical effect for inventive step if the skilled person, having the common general knowledge in mind, and based on the application as originally filed, would derive said effect as being*

encompassed by the technical teaching and embodied by the same originally disclosed invention."

58. Applying the principles of G 2/21, the board does not consider that an improvement of an effect, here further reduced effector functions mediated by the Fc region, is encompassed by the technical teaching and embodied by the same originally disclosed invention merely because the effect itself (but not the improvement), was shown to be achieved in the application as filed (see G 2/21, Headnote, Reasons 67 and 72).

59. The board is aware that a different approach to this issue was taken in decisions T 1989/19, T 2716/19 and T 840/22 and makes the following observations.

60. Decision T 1989/19 provided the following reasoning for taking into account post-published evidence to show an improved effect:

> "*In the board's view, once the above-mentioned criterion of the derivability of a technical effect is met, this applies equally to the improvement of this effect. Specifically, the skilled person, even if he has no inventive skills, will strive for further developments or technical improvements in every area of technology. Thus, if a certain technical effect, such as storage stability in the present case, is derivable for the skilled person within the meaning of the order, point 2 of decision G 2/21, from the originally filed application, its improvement is also to be regarded as implicitly derivable.*" (Reasons, 3.3.16, translation by the board).

61. Decision T 2716/19 reasoned similarly:

"*The skilled person would thus derive from the application as filed a focus on the two specific alkoxides to which claim 1 of the current main request is restricted. Furthermore, the skilled person would have immediately recognised an improvement in the yield of the desired product, here PMPA, as a fundamental objective of the disclosed method. […] Therefore, the improvement of the PMPA yield in a reaction starting from HPA by using the alkoxides defined in the current main request relied on by the respondent was encompassed by the technical teaching and embodied by the invention originally disclosed in the application as filed.*" (Reasons, 8.3.2)

62. Decision T 840/22 referred to earlier decision T 1989/19 and stated:

"*..., the technical effect of corrosion resistance is derivable from the application as filed for the subject-matter of claim 1 (this being equivalent to saying that the technical effect of corrosion resistance meets the requirements of order No. 2 of G 2/21 when relied on for inventive step for the subject-matter of claim 1). This being the case, it must be possible - contrary to the views of the appellant and the opposition division - for the respondent to rely on an improvement in the derivable effect, at least in the case of an improvement over a piece of prior art such as D2 in the present case. In this respect, the board agrees with T 1989/19 (point 3.3.16 of the Reasons). The fact to which the appellant took offence, namely that one of several embodiments disclosed in the application as filed turns out to be better after the effective date with respect to the*

technical effect set out in the application as filed than the other embodiments disclosed in the application as filed, does not change this conclusion. The board points out that this scenario is precisely what regularly occurs in patents/ patent applications in the field of chemistry, where claimed subject-matter must be limited at the expense of subject-matter disclosed in the application as filed as part of the invention, because the effect relied on for inventive step over the closest prior art is not achieved across the entire breadth of the claimed subject-matter." (Reasons, 15.2)

63. In each of the three above mentioned cases, the improved effect was decisive for the competent board to conclude that the claimed subject-matter was inventive. However, this board is of the view that an improved effect that has not been credibly achieved at the filing (or priority) date cannot be considered as "*encompassed by the technical teaching and embodied by the same originally disclosed invention*". In other words, if acknowledging inventive step requires taking an improved effect into account, the invention must be considered to have been made at the filing (or priority) date. Thus, this board is of the view that assessment of inventive step can only take effects into account which were achieved at the effective date.

64. This board also notes that none of the three decisions referred to above give any explanation why they depart from the basic legal principle that an invention must have been made at the effective date of the patent or patent application. This principle was confirmed in decision G 2/10 (OJ EPO 2012, 296), point 4.6: "*It is vital that a uniform concept of disclosure is applied*

in all these respects and that the rights of an applicant are uniformly determined in all these contexts as extending to but at the same time as being limited to the disclosure made at the relevant point in time."

65. Reference is also made to decision G 1/03 (OJ EPO 2004, 413) which states in Reasons, 2.5.3: "*The same* [as for inventive step] *must apply if sufficiency of disclosure is at stake. When an application for a patent is filed, the process of making the invention has to be completed.* [...] *Therefore, the decisive date for fulfilling the requirement has to be the date of filing or priority, as the case may be. Deficiencies in this respect cannot be remedied during the proceedings before the EPO.*"

66. Decision G 2/21 (OJ 2023, A85) itself, in point 67 of the Reasons, cites a number of decisions which confirm that an improved effect has to be credible from the disclosure in the application as filed, see e.g. decisions T 787/14, T 1791/11, T 1322/17.

67. In decision T 787/14 the board concluded that "*the problem to be solved cannot be defined as put forward by the appellant, namely as the provision of an improved composition, which induces a better immune response to each of the serogroups*" because from the clinical trial reported in the patent it was not conclusive whether the relevant subgroup of patients had been treated.

68. The claim dealt with in decision T 1791/11 related to variants of the BLSAVI subtilase enzyme. The patent proprietor formulated the technical problem as providing a variant with "*improved wash performance*

compared to BLSAVI". The board found that the patent "*aims at providing subtilase variants with improved properties, in particular with improved wash performance, and that it discloses a number of selected 'interesting' variants which are however still to be tested for their performance*" and that "[t]*here is however no data in the patent application or elsewhere on file which allows the performance of the claimed variants to be compared with that of the variants of D1*". An improvement had thus not been disclosed in the application as filed, but only shown by post-published evidence. The variant was considered as a mere alternative and not inventive.

69. In case T 1322/17 the respondent invoked the effect of "*fracture reduction benefits*", i.e. a reduced incidence rate of bone fractures. The board, however, found that although reduced fracture was mentioned as an aim of the invention in the application as filed, "*the unexpected fracture reduction benefits are neither supported by experimental evidence nor by a theoretical, possibly mechanistic, explanation*". The "*technical effect related to higher fracture reduction has not been made plausible for the specific dose of 150 mg ibandronic acid administered in any dosing interval in the application as filed*" and "*post-published evidence, in the present case document (22), cannot be taken into consideration*".

70. G 2/21 further states in point 72 of the Reasons: "*Applying this understanding to the aforementioned decisions, not in reviewing them but in an attempt to test the Enlarged Board's understanding, the Enlarged Board is satisfied that the outcome in each particular case would not have been different from the actual finding of the respective board of appeal. Irrespective*

of the use of the terminological notion of plausibility, the cited decisions appear to show that the particular board of appeal focussed on the question whether or not the technical effect relied upon by the patent applicant or proprietor was derivable for the person skilled in the art from the technical teaching of the application documents."

71. Had the respective boards in the above mentioned cases, cited in G 2/21, considered that an improvement was generally implicit when the effect itself was credible from the disclosure of the application as filed the outcome would indeed have been different, contrary to the clear statement in G 2/21. This board therefore takes from decision G 2/21 that an improvement of an effect cannot be taken into account in the assessment of inventive step merely because the effect itself can be derived by the skilled person from the application as originally filed.

72. Furthermore, the approach taken in decisions T 1989/19, T 2716/19 and T 840/22 would allow an applicant to solely rely on post-published evidence to establish inventive step by filing an application disclosing an effect that was already known from the prior art or formed part of common general knowledge and subsequently invoking an improvement of said effect as "implicitly derivable" from the application as filed. This scenario goes against the principle that patents should not be granted for subject-matter whose inventive contribution is identified only after their effective date. Such an outcome directly contradicts the "first to file" principle enshrined in the EPC and confirmed in decisions G 1/03 and G 2/10. It is also in evident tension with the framework established by

decision G 2/21 (see also decision T 314/20, points 6.13.3 and 6.14 of the Reasons).

73. The board therefore must turn to the disclosure in the application as filed to determine if the evidence for a further reduced effector function of the FEA variant compared to the FE variant reported in post-published documents D25 and D26 can be taken into account.

74. Figure 3A is the only figure representing an example in which the FE ("*IgG1-CD3-LFLE*") and FES ("*IgG1-CD3-LFLEPS*") variants of the prior art are directly compared to the claimed FEA variant ("*IgG1-CD3-LFLEDA*"). As disclosed in the corresponding Example 3 on page 56 of the application as filed, a dose response series of IgG1-CD3 antibody variants, a negative control (IgG1-CD3 Fab) and a positive control (IgE-CD3) were prepared in culture medium (ranging from 1 to 1000 ng/mL in 3-fold dilutions) and added to the wells of a 96-well round bottom plate containing the PBMCs. CD69 expression on CD28 positive cells was measured by FACS. The application concludes that "*incubation with IgG1-CD3-LFLE* **[FE]** *and IgG1-CD3-LFLEPS* **[FES]** *induced CD69 to a lesser extent*" while "[i]*ncubation of PBMCs with IgG1-CD3 Fab, IgG1-b12, IgG1-CD3-LFLEDA* **[FEA]**, *IgG1CD3-LFLENQ, IgG1-CD3-DANQ and IgG1-CD3-LFLEDANQPS antibodies did not induce any expression of CD69 on T-cells*" (highlighted text in square brackets added by the board). The board notes that a consistent difference between the FE (or FES) and the FEA variant over a large concentration range is apparent from Figure 3A, i.e. most pronounced at about 12 and 36 ng/ml, but also evident at about 1, 4, 100, 360 and 1000 ng/ml. The board considers that the differences over such a large concentration range render it credible that reduced effector function, as reflected

by decreased CD69 release, was achieved by the FEA variant compared to FE or FES.

75. With regard to Example 11 and Figure 13A in which the FEA variant induced low levels of CD69 expression, the board notes that this example does not include a comparison with the FE or FES variants and lacks a proper negative control, i.e. an antibody without an Fc region (e.g. IgG1-CD3 Fab as in Figure 3A). Example 11 and Figure 13A are therefore not sufficient to raise serious doubts about the FEA variant's improved effect. Moreover, the two figures (3A and 13A) were obtained with variants of two different CD3 antibody clones and are likely to have involved PBMCs from different donors (see point 35. of document D25 and Examples 3 and 11 in the application as filed). It is therefore not possible to directly compare the data in figures 3A and 13A.

76. The board also considers it credible from the evidence in the application as filed that the effect of a decreased CD69 expression is achieved over the whole scope of the claim, i.e. also with the Fc region in the context of other molecules than antibodies or for antibodies with other binding specificities. It is common general knowledge that the activities of the Fc region are largely independent of the binding specificity of the respective antibody or even of other protein moieties fused to it. The appellant has also not provided evidence of embodiments lacking the improved effect of the FEA variant compared to the FE variant.

77. The appellant also argued that the claimed protein could include further mutations in the Fc region which might abolish the advantageous behaviour of the FEA variant. The board notes that an FEA variant which did

not fulfil the functional requirements in the claim, i.e. "*not bind to any Fcγ receptors, and wherein said protein has a plasma clearance rate (ml/day/kg) which deviates from a wild-type protein by no more than 10%*", would not be covered by the claim. More importantly, the skilled person would have been aware of the potentially negative effects of further mutations and knew how to test them to avoid effects which were contrary to the purpose of the invention.

78. In conclusion, the board considers the improved effect of decreased CD69 release of the FEA variant compared to the FEFE variant to have been credibly disclosed in the application as filed. Thus, while it is not strictly necessary to consult the evidence in documents D25 and D26, it can be noted that their disclosure supports the improved effect shown in the application as filed. In particular, Supplementary Figure 1B of D26 (reproduced as Figure 5 in D25) shows a statistically significant decrease in T-cell activation, as judged by CD69 expression, of the FEA variant compared to the FES variant. The board considers that the FEA variant also shows decreased T-cell activation compared to the FE variant. Supplementary Figure 1C of D26 shows a reduced T-cell proliferation of FEA compared to FE. Post-published document D26 concludes that "[t]*he combination of three mutations L234F, L235E and D265A (FEA) provided the most favourable characteristics* in vitro *and* in vivo" (D26, page 5, left-hand column).

Objective technical problem - improvement

79. The board therefore formulates the objective technical problem as the provision of a protein having an improved Fc region that reduces T cell activation as measured by CD69 expression and retains plasma

clearance comparable to a protein with the corresponding wild type Fc region. The opposition division formulated a similar objective problem in point 15.3 of their decision: "*provision of an improved Fc mutant, i.e. that abolishes T cell activation (T cell expression of CD69) and retains plasma clearance comparable to the wild type*" (underlining in the decision).

Obviousness - improvement

80. The appellant argued that from document D10 alone, the skilled person would conclude that the combination of the D265A mutation and the FE mutation would result in an improved effect, i.e. less T cell activation as measured by CD69 expression.

81. The board disagrees. While the D265A mutation is disclosed in D10 as advantageous, the FE mutation was not tested. Rather, the reference to D3 on page 44 of D10 would have indicated to the skilled person that all three mutations, i.e. FES, were required to achieve "*reduced or no effector function*". It was therefore far from clear to the skilled person whether the combined FE mutations abolished the effector function of the Fc region and even less clear how this untested combination would behave in combination with the D265A mutation which was described in D10 as "*having reduced or no effector function*" with reference to D23. The same considerations apply when starting from the FES variant disclosed in D10, which was known from D3 to have reduced or no effector function. The skilled person would have been cautious about replacing the P331S mutation in FES with a D265A mutation because this combination had never been tested and the combined effect was not predictable (see also D25, points 21. to

31.). In view of the above, the skilled person would not have had a reasonable expectation of success that the combination of the FE variant with D265A would result in an improvement.

82. Similar considerations apply if the inventive step is assessed starting from document D21. This document does not mention the D265A mutation, but only discloses position 265 in a list of further modifications to "*decrease the ability of the antibody to mediate antibody dependent cellular cytotoxicity (ADCC) and/or to decrease the affinity of the antibody for an Fcγ receptor*" (D21, paragraph [00192]). Moreover, also D21 contains functional data for the Fcγ receptor binding activity of the FES variant, but not of the FE variant (see Examples 20 to 22 and 26). The skilled person seeking a solution to the objective technical problem would not have modified an untested FE variant with a further modification in position 265 (D265A), which was not even disclosed in D21, and expected that the resulting Fc region could not bind to any Fcγ receptor but would retain a plasma clearance rate more or less unaffected compared to the wild type Fc region.

83. The additional cited documents, D6, D15 and D23, which disclose D265A as an advantageous mutation for reducing the effector function of the Fc region do not provide the skilled person with any guidance how this mutation would behave in combination with other mutations, such as L234F and L235E.

Objective technical problem - alternative

84. There follows an assessment of inventive step when adopting the less ambitious objective technical problem of provision of an alternative protein having an Fc

region, i.e. no improvement over the FE or FES variants disclosed in prior art D10 or D21. This is in the appellant's favour and was also a line of argument submitted by the respondent (see reply to the appeal, points 6.45 to 6.50).

Obviousness - alternative

85. In keeping with the functional features of the claim the alternative protein sought must "*not bind to any Fcγ receptor*" and must have "*a plasma clearance rate (ml/day/kg) which deviates from a wild-type protein by no more than 10%*".

86. Although document D10 discloses mutations which are said to achieve "*reduced or no effector function*", i.e. D265A and FES (L234F, L235E, P331S) it does not disclose how the combination FEA (L234F, L235E, D265A) would perform with regard to Fcγ receptor binding and plasma clearance rate. It is common general knowledge that minimal modifications in an Fc region can affect its structure and function in an unpredictable manner (see D25, points 29. to 35.). The skilled person aiming to provide an alternative Fc variant which had similar functionality as the known and tested variants (D265A or FES) could therefore not have had reasonable expectation that the advantageous features, i.e. reduced or no effector function, of these variants would be maintained when they were combined in a single Fc region.

87. Similar considerations apply when starting the assessment from document D21 which does not disclose D265A and does not provide functional data for the FE variant.

88. The board therefore concludes that the skilled person would not have arrived at the claimed subject-matter even if only seeking to provide an alternative to the Fc variants disclosed in D10 or D21.

89. The claimed subject-matter therefore involves an inventive step (Article 56 EPC).

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent on the basis of the set of claims of the main request, originally filed as auxiliary request 6 with the reply to the statement of grounds of appeal, and a description and drawings to be adapted as necessary.

The Registrar: The Chair:

I. Aperribay A. Chakravarty

Decision electronically authenticated