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Datasheet for the decision of 8 April 2022

Case Number: T 0424/21 - 3.3.04

Application Number: 12710732.4

Publication Number: 2691417

IPC: C07K16/00, C07K16/28

Language of the proceedings: EN

Title of invention:
Antibody Fc variants

Patent Proprietor:
Roche Glycart AG

Opponent:
Merck Patent GmbH

Headword:
Antibody Fc variants/ROCHE GLYCART

Relevant legal provisions:
EPC Art. 100(a), 100(b), 100(c), 56
RPBA 2020 Art. 13(2)

Keyword:

Amendments - main request, auxiliary requests 1 to 5: added subject-matter (yes) - auxiliary request 6: added subject-matter (no)
Amendment to appeal case - justification by party (yes)
Sufficiency of disclosure - auxiliary request 6 (yes)
Inventive step - auxiliary request 6 (yes)

Decisions cited:

G 0005/83, G 0003/14, J 0014/19, T 0128/82, T 0604/04, T 2222/15, T 1480/16, T 0172/17, T 1569/17, T 0494/18, T 0884/18, T 0914/18, T 0995/18, T 2091/18, T 0482/19, T 1857/19, T 2295/19, T 0317/20

Catchword:

1. If the deletion of dependent claims after notification of a summons to oral proceedings enhances procedural economy by clearly overcoming existing objections without giving rise to any new issues this might constitute cogent reasons justifying exceptional circumstances in the sense of Article 13(2) RPBA 2020.

2. For a first medical use of a substance or composition according to Article 54(4) EPC to be sufficiently disclosed it is not required to show the suitability for each and every disease, but it usually suffices to show that at least one medical use is credibly achieved.

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Case Number: T 0424/21 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 8 April 2022

Appellant: (Opponent)	Merck Patent GmbH Frankfurter Strasse 250 64293 Darmstadt (DE)
Respondent: (Patent Proprietor)	Roche Glycart AG Wagistrasse 18 8952 Schlieren (CH)
Representative:	Mewburn Ellis LLP Aurora Building Counterslip Bristol BS1 6BX (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 24 February 2021 rejecting the opposition filed against European patent No. 2691417 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chair	P. de Heij
Members:	B. Rutz
	O. Lechner

Summary of Facts and Submissions

I. The appeal lodged by the opponent (appellant) lies from the opposition division's decision to reject the opposition against European patent No. 2 691 417. The patent is entitled "*Antibody Fc variants*".

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

III. Claims 1, 4, 5, 7 and 8 of the patent read:

"1. An antibody or an Fc fusion protein comprising an Fc variant of a wild-type human IgG1 Fc region, wherein the Fc variant of the wild-type human IgG1 Fc region contains amino acid substitutions P329G, L234A and L235A, wherein the residues are numbered according to the EU index of Kabat."

"4. The antibody or Fc fusion protein according to any one of claims 1-3, wherein the antibody or Fc fusion protein comprising the wild-type human IgG1 Fc region induces thrombocyte aggregation and wherein the thrombocyte aggregation induced by the antibody or Fc fusion protein comprising the IgG1 Fc variant is reduced compared to the thrombocyte aggregation induced by the antibody or Fc fusion protein comprising the wild-type human IgG1 Fc region."

"5. The antibody or Fc fusion protein according to any one of claims 1-4, wherein the antibody or Fc fusion protein comprising the wild-type human IgG1 Fc region induces CDC and wherein the CDC induced by the antibody or Fc fusion protein comprising the IgG1 Fc variant is

strongly reduced compared to the CDC induced by the antibody or Fc fusion protein comprising the wild-type human IgG1 Fc region."

"7. The antibody or Fc fusion protein according to any one of claims 1-6 for use as a medicament."

"8. The antibody or Fc fusion protein according to any one of claims 1-6, for use in a method for treating a disease in an individual wherein it is favorable that an effector function of the antibody or Fc fusion protein is strongly reduced compared to the effector function induced by the antibody or Fc fusion protein comprising a wild-type human IgG Fc region, the method comprising administering the antibody or Fc fusion protein according to any one of claims 1-6 to the individual."

IV. In the decision under appeal the opposition division decided that none of the grounds for opposition mentioned in Article 100 EPC prejudiced the maintenance of the patent as granted and that therefore the opposition was rejected.

V. With the reply to the statement of grounds of appeal, the patent proprietor (respondent) filed auxiliary requests 1 to 14 (identical to the requests filed during the opposition proceedings).

VI. The board summoned the parties to oral proceedings as requested and informed them of its preliminary opinion in a communication pursuant to Article 15(1) RPBA 2020.

In points 16 and 18 of this communication the board preliminarily noted that claim 1 appeared to fulfil the

requirements of Article 123(2) EPC while claims 4 and 5 did not.

In points 19 to 21 the board further expressed the view that the patent sufficiently disclosed the invention to which the claims of the main request related.

The board informed the parties that it considered document D13, in particular antibody #497, to be the most promising starting point for an inventive step analysis.

VII. In reply to the board's communication the respondent withdrew auxiliary requests 6 to 14 and filed new auxiliary requests 6 to 11, which are identical to the main request and auxiliary requests 1 to 5, respectively, except that claims 4 and 5 of those requests have been deleted.

VIII. Oral proceedings before the board took place on 8 April 2022 in form of a videoconference. At the end of the oral proceedings, the Chair announced the board's decision.

IX. The following documents are cited in the present decision:

D10 WO 2006/076594 A2

D12 Wines et al., Journal of Immunology (2000), vol. 164, 5313-5318

D13 US 2009/0215991 A1

D14 Xu et al., Cellular Immunology (2000), vol. 200, 16-26

X. The appellant's arguments, as far as relevant to the decision, are summarised as follows.

Main request (claims as granted)
Amendments (Article 100(c) EPC) - claims 4 and 5

Original claim 1 could not provide a basis for claim 1 as granted because it included the effects of the polypeptide on the effector functions, namely "*reduced affinity to the human FcγRIIIA and/or FcγRIIA and/or FcγRI compared to a polypeptide comprising the wildtype IgG Fc region, and wherein the ADCC induced by said polypeptide is reduced to at least 20% of the ADCC induced by the polypeptide comprising a wild-type human IgG Fc region*".

Therefore, the reduction of thrombocyte aggregation in granted claim 4 and the reduction of CDC in granted claim 5 had no basis in original claims 8 and 9 either because the functional features of original claim 1 had simultaneously been removed, resulting in an unallowable intermediate generalisation.

The subject-matter of claims 4 and 5 was not disclosed in the passage on page 2, lines 4 to 9 of the application either, since this passage related to separate "embodiments" which were not disclosed in combination with the specific features mentioned in granted claim 1 (e.g. "amino acid substitutions P329G, L234A and L235A").

Auxiliary request 6
Admission into appeal proceedings (Article 13(1) and (2) RPBA 2020)

The filing of a new request represented an amendment to the respondent's appeal case under Article 13(1) and (2) RPBA 2020. It was irrelevant that this amendment concerned only the deletion of two dependent claims. The fact that a response was suitable to address an issue in a straightforward manner did not constitute "*reasons for submitting the amendment at this stage of the appeal proceedings*" as required by Article 13(1) RPBA 2020, which applied to any "*amendment to a party's appeal case*" and therefore had to be complied with. The patentee had not presented any evidence of "*exceptional circumstances, which had been justified with cogent reasons*", as required by Article 13(2) RPBA 2020 (see also decision T 172/17).

Claims 4 and 5 had already been specifically objected to under Article 123(2) EPC in the opponent's notice of opposition (page 16, paragraph 2 to page 17, paragraph 1). The patentee should have submitted its means of defence, including suitable auxiliary requests that rendered the issue moot, in the response to the notice of opposition. Therefore, Article 12(6) RPBA 2020 also applied *mutatis mutandis*.

Moreover, the issue of claims 4 and 5 contravening Article 123(2) EPC was not raised for the first time in the appeal proceedings by the board in its communication. Rather, claims 4 and 5 had already been specifically attacked under Article 123(2) EPC in the opponent's statement of grounds of appeal (page 11, last paragraph to page 12, penultimate paragraph). Accordingly, the appropriate time to file the request

on appeal would have been in the patentee's response to the appeal and not only after the summons to oral proceedings and receiving the communication by the board.

Amendments (Article 100(c) EPC) - claim 1

The skilled person needed to consider different parts of the patent specification and to conclude (i) that the polypeptide was an Fc fusion protein, (ii) which was of the human IgG1 subclass (only disclosed in the context of polypeptides on page 2, lines 1 and 2) and (iii) which carried a P329G, L234A, L234A (PGLALA) triple mutation (only disclosed in the context of antibodies on page 34, lines 6 to 9). This combination was not disclosed in the application.

In particular, upon reading the whole of the application, a skilled person would not be directed specifically to the Fc fusion protein having a human IgG1 Fc region and a PGLALA triple mutation.

The Fc fusion protein of claim 1 also lacked disclosure in the claims as originally filed. If the Fc fusion protein were considered to be included in this claim 1 by means of original claim 7, this would result in an unallowable intermediate generalisation because original claim 1 included the effects of the polypeptide on the effector functions, which were no longer present in claim 1 as granted.

Sufficiency of disclosure (Article 100(b) EPC)

The term "Fc fusion protein" was only mentioned on page 2, lines 2 to 3, page 26, lines 20 to 23, and in claim 7 on page 91 of the application as filed. The

application did not contain any further details about making and using an Fc fusion protein. Thus, an undue burden was placed on the skilled person to figure out what an Fc fusion protein could be in the context of the invention and how to prepare it.

Except for the PGLALA triple mutation in the Fc region, the claimed antibodies or Fc fusion proteins were not defined in terms of chemical structure, composition or other verifiable parameters, but solely by having certain functionalities: reducing ADCC (claim 2), reducing the binding affinity for an Fc receptor (claim 3), being a medicament (claim 5) and treating a disease by reducing an effector function (claim 6). This type of functional definition covered not only the antibodies or Fc fusion proteins already known at the filing date, but also any antibody or Fc fusion protein not yet structurally defined and to be found in future. This kind of claim wording constituted a reach-through definition, which conflicted with sufficient disclosure. On the basis of the disclosure of the application, which was restricted to specific examples (e.g. Examples 2 and 8 applying to an anti-CD9 antibody and Examples 4 to 6 applying to an anti-CD20 antibody), the skilled person was not able to obtain the effects for substantially all the Fc receptor variants falling within the scope of the claims.

The patent did not disclose any experimental data proving treatment effects, nor did it disclose anything about the safety of the therapy if administered according to claims 5 and 6. For the medical use in claims 5 and 6, the skilled person would conclude that the invention did not work in many cases, and that the desired results were not successfully achieved in a reliable way. For want of any selection rule in the

patent, the skilled person had to resort to trial-and-error experimentation on arbitrarily selected (i) antibodies, (ii) Fc fusion proteins and (iii) diseases to establish whether they possessed the capability according to claim 6. This represented an invitation to perform a research programme, based on trial and error, to provide a safe and effective treatment regime, which was an undue burden for the skilled person. Thus, all the relevant molecules were not known, nor was the therapeutic use already well established.

Inventive step (Article 100(a) and Article 56 EPC)

Documents D10 and D13 were considered suitable starting points for analysing inventive step.

Document D10 disclosed an antibody with the sequence of SEQ ID NO: 909, which contained the point mutation P329G in its Fc region.
Document D13 disclosed antibody #479, which likewise contained this point mutation.

The feature distinguishing the claimed subject-matter from these disclosures in documents D10 and D13 was that the Fc region also included the LALA (L234A, L235A) mutations.

The technical effect of these additional mutations was reduced binding to the FcγRI receptor.

The application did not contain any comparative data for binding to other Fc receptors, so other effects could not be taken into account. On the basis of the difference as compared with the subject-matter of claim 1, the objective technical problem was providing

antibodies/Fc fusion proteins with reduced FcγRI receptor binding.

The skilled person aiming to solve this problem would have found a solution in documents D12 and D14, which disclosed the LALA mutations that led to reduced FcγRI receptor binding. The skilled person would have combined the L234A/L235A mutations with the P329G mutation and thus arrived at the claimed subject-matter in an obvious manner.

An alternative approach for analysing inventive step resulted from the interpretation of the term "Fc variant". The meaning of "variant" within the term "Fc variant of a wild-type human IgG1 Fc" in claim 1 was defined by the subsequent feature "wherein the Fc variant of the wild-type human IgG1 Fc region contains amino acid substitutions P329G, L234A and L235A", meaning that the Fc variant of claim 1 differed from the "native" human IgG1 Fc on account of the PGLALA mutations defined in the claim but not any other mutations.

However, if the respondent were to take the far-fetched position that the term "variant" included the PGLALA mutations plus any other number of amino acid changes, this would also encompass Fc variants derived from the IgG1 Fc sequence, which had little resemblance to the "native" human IgG1 Fc sequence (e.g. a sequence in which a significant part of the IgG1 Fc region was replaced with an IgG3 or a human IgG3 Fc region with mutated P329G and L234A/L235A). This would have implications on the formulation of the objective technical problem in the assessment of inventive step as the alleged effect would in that case not be

achieved over the full scope resulting from such a broad interpretation.

XI. The respondent's arguments, as far as relevant to the decision, are summarised as follows.

Main request (claims as granted)
Amendments (Article 100(c) EPC) - claims 4 and 5

The subject-matter of claim 4 was explicitly disclosed on page 2, lines 3 to 6 of the application. Further basis could be found in the disclosure on pages 44 and 45, and in original claim 8.

The subject-matter of claim 5 was explicitly disclosed on page 2, lines 6 to 9 of the application. Further basis could be found in the disclosure on page 15, lines 15 to 20, page 39, lines 27 to 30, and in original claim 9.

The removal in claim 1 as granted of the functional features relating to reduced affinity to human FcγRIIIA and/or FcγRIIA and/or FcγRI and reduced ADCC compared with originally filed claim 1 did not change the subject-matter because these features were inherent to the molecules as a result of the PGLALA mutations. The combination of originally filed claim 1 and originally filed claims 8 and 9 thus equally provided disclosure of the subject-matter of claims 4 and 5, respectively.

Auxiliary request 6
Admission into appeal proceedings (Article 13(2) RPBA 2020)

Auxiliary request 6, filed by letter of 21 February 2022 in response to the board's communication under

Article 15(1) RPBA 2020, corresponded to the main request with dependent claims 4 and 5 deleted. This did not represent an amendment to the respondent's appeal case because the legal and factual circumstances had not changed (in line with decision T 995/18).

Even if this is deemed to be an amendment, it was justified because it was a straightforward and appropriate response to the board's preliminary opinion that did not raise any new issues and rendered the objection moot. It was therefore immediately apparent that the amendment successfully addressed the issue without giving rise to any new ones. This could be considered "exceptional circumstances" as required by Article 13(2) RPBA 2020.

Amendments (Article 100(c) EPC) - claim 1

The core of the invention (the specific triple mutation in the IgG1 context) was clearly disclosed in the application as filed, for example on page 33, lines 7 to 11 and page 34, lines 6 to 9.

Although the passage on page 33, lines 7 to 11 did not explicitly mention substitution with glycine at position 329, glycine was consistently mentioned in the application as the preferred substitution at this position. See for instance page 7, lines 5 to 12, page 31, lines 3 to 6 and original claims 2 and 4, and page 34, lines 6 to 9.

A basis for the polypeptide being an antibody or an Fc fusion protein could be found on page 2, lines 1 to 3. This passage explained the kinds of polypeptides that might be contemplated for the invention, so it would be

read together with the other characteristics of those polypeptides.

The set of PGLALA mutations was disclosed as a preferred embodiment on page 82, for example, which stated, with reference to Figure 1b, that "*the combination of P329G with either LALA or SPLE mutations is much more effective than the P329G mutation or the double mutations LALA or SPLE alone*". This was independent of the antigen specificity of the antibody or Fc fusion protein. Thus, the skilled person would be in no doubt that the triple mutation was specifically contemplated as a preferred combination.

Sufficiency of disclosure (Article 100(b) EPC)

The appellant had not provided evidence of any technical difficulty in applying the Fc mutations of the claimed invention to an Fc fusion molecule. There were therefore no serious doubts, substantiated by verifiable facts, which could form the basis for an objection under Article 83 EPC.

Evidence filed in the first-instance proceedings (e.g. documents D20, D30, D30a and D31 to D33) confirmed that the PGLALA triple mutation could be formed in the Fc region of the IgG1 isotype without altering the binding properties of the antibody, and that a whole array of therapeutic antibodies bearing this triple mutation could be used in a safe and effective way. These results confirmed that the claimed triple mutation could be applied irrespective of the specific identity of the antigen-binding part of the molecule.

There was thus ample evidence to show that the substitutions of the invention were effective in a

range of contexts, and there was no reason to doubt that claim 1 could be worked across its scope.

None of the dependent claims referred to reduced binding to all Fc receptors, or to reduced binding to FcγRIIC or FcγRIIIB. Evidence for reduced binding to substantially all Fc receptors was therefore not required.

The appellant did not provide any technical justification for its assertion that the anti-CD9 antibody in Examples 2 and 8 was unique in terms of reduced FcγRIIA receptor binding and that the anti-CD20 antibody in Examples 4 to 6 was unique in terms of reduced ADCC and CDC activity. These assertions thus did not create any doubt as to sufficiency under Article 83 EPC.

It was entirely normal for a first medical use claim to relate to any first medical use. In the case in hand, the claimed proteins themselves were novel. Accordingly, there was no reason why a first medical use claim should not be allowed.

In relation to claim 6, there was no requirement that all types of diseases should be treatable. The purpose of a medical use meant that ineffectual embodiments (if any existed – which had not been proven) were not covered.

Nor would the skilled person have any difficulty identifying an antibody suitable for a given therapeutic use on the basis of the existing knowledge. The relevant technical effects provided by the invention – reduced Fc receptor affinity and reduced effector function – were useful in a therapeutic

context in which reducing effector function was favourable.

The skilled person could choose to apply the invention (i.e. make the combination of specified amino acid substitutions) in an antibody of their choice for use in a disease in which the antibody was effective. The antibody would continue to treat the disease, and the added use of the invention would provide the additionally beneficial effect arising from the three amino acid substitutions.

The patent contained data showing the effects for a number of molecules, which were defined and clearly suitable for therapeutic use.

The potential side effects alleged by the appellant were entirely speculative and not supported by evidence.

Accordingly, the requirements of Article 83 EPC were met.

Inventive step (Article 100(a) and Article 56 EPC)

Documents D10 and D13 were not suitable as a starting point for assessing inventive step. If document D10 was nonetheless chosen as the starting point for an inventive step analysis, the objective technical problem would be providing a further Fc region with a different spectrum of utility.

The solution in the claims in hand could not be obvious because there was no motivation to (i) select the specific sequence of SEQ ID NO: 909 in document D10 out of the long list of variants it discloses, (ii) select

any other specific document with which to combine it or (iii) select any specific modification for any specific further purpose. There was no realistic chain of considerations giving rise in an obvious way to the claimed subject-matter.

If document D13 was chosen as the starting point, the technical problem to be solved would be generating a highly silenced Fc region, including highly effective reduction in binding to the FcγR1 receptor and C1q.

Document D13 did not contain any pointer to select P329G as a mutation suitable for solving that problem. At best, document D13 suggested a group of 16 positions for reducing Fc ligand binding and/or effector function, with no pointer to any particular position or any particular substitutions from this list. As the problem to be solved related to a reduction in the binding to at least the FcγRI receptor, Figure 41 included many mutations which showed a reduction in binding to said receptor and would therefore have been the skilled person's preferred starting point, not P329G.

The data in Figure 41 showed a substantial increase in C1q binding for the P329G mutation, thus teaching away from this substitution in the context of generating a highly effector-silenced Fc region.

The skilled person would not have been led to select the particular combination of substitutions as claimed here, in the expectation of solving the technical problem.

Furthermore, the appellant had not considered the unexpected and synergistic technical effects brought

about by the combination of P329G and L234A/L235A. For example, the data in the application in hand demonstrated that the P329G/L234A/L235A triple mutant achieved nearly undetectable binding to the FcγRI receptor (Example 2).

Since the claims were to be interpreted by a mind willing to understand (Case Law of the Boards of Appeal, II.A.6.1), the far-fetched interpretation discussed by the appellant should be excluded.

The statement by the Chair of the opposition division that "*the variants still had to be IgG1 and should exhibit the function of IgG1*" (see minutes, page 4, paragraph 4) was endorsed.

XII. The appellant requested that the decision under appeal be set aside and the patent be revoked, and that auxiliary requests 6 to 11, filed on 21 February 2022, not be admitted into the appeal proceedings.

The respondent requested that the appeal be dismissed and maintenance of the patent on the basis of the main request or, alternatively, one of auxiliary requests 1 to 11.

Reasons for the Decision

Main request (claims as granted)
Amendments (Article 100(c) EPC) - claims 4 and 5

1. Claim 4 as granted, which is dependent on claim 1 as granted, further defines the claimed antibody and Fc

fusion protein to the effect that "the thrombocyte aggregation induced by the antibody or Fc fusion protein comprising the IgG1 Fc variant is reduced compared to the thrombocyte aggregation induced by the antibody or Fc fusion protein comprising the wild-type human IgG1 Fc region".

2. The respondent argued that the subject-matter of claim 4 was explicitly disclosed on page 2, lines 3 to 6 of the application, which reads: "*In a further embodiment the thrombocyte aggregation induced by the polypeptide comprising the Fc variant is reduced compared to the thrombocyte aggregation induced by a polypeptide comprising a wild-type human IgG Fc region.*" The board does not agree because this disclosure is not linked to the specific set of P329G, L234A, L235A (PGLALA) mutations as defined in claim 1, but merely defines "*a further embodiment*" independent of any specific mutation. This passage does not refer specifically to an IgG1 Fc variant either.

3. The respondent further cited pages 44 and 45 and original claim 8 as a basis for the subject-matter of claim 4. However, the disclosure on pages 44 and 45 does not refer specifically to an IgG1 Fc variant either. Moreover, it refers to the PGLALA mutations not in general terms but in the context of a specific anti-CD9 antibody.

4. Claim 8 as filed, which refers to thrombocyte aggregation, is dependent on claim 1 as filed, which, apart from generally concerning an IgG Fc variant, also contains further functional requirements. Yet these are not present in claim 1 as granted. In particular, claim 1 as filed requires that "*said polypeptide exhibits a reduced affinity to the human FcγRIIIA and/or FcγRIIA*

and/or FcγRI compared to a polypeptide comprising the wildtype IgG Fc region, and wherein the ADCC induced by said polypeptide is reduced to at least 20% of the ADCC induced by the polypeptide comprising a wild-type human IgG Fc region". The board does not agree with the respondent that the PGLALA mutations inherently imparted the above functional features on any antibody or Fc fusion protein. For the analysis of added subject-matter it cannot simply be assumed that all antibodies or Fc fusion proteins carrying the PGLALA mutations would achieve at least 20% reduced ADCC. Since the correlation is based only on measurements of one particular antibody (anti-CD20 (GA101); see Examples 4 and 5 and Figures 4a and 4b) the board finds that a reduction of ADCC to at least 20% is not directly and unambiguously derivable as an inherent feature of all the antibodies and Fc fusion proteins carrying the triple mutation.

5. Removing this requirement thus enlarges the group of antibodies and Fc fusion proteins falling under the scope of granted claim 1 and thus includes subject-matter which was not part of claim 1 as filed. Claim 8 as filed, which is dependent on claim 1 as filed, therefore does not disclose the subject-matter of claim 4 as granted.

6. Claim 5 as granted, which is dependent on claim 1 as granted, further defines the claimed antibody and Fc fusion protein to the effect that "*CDC induced by the antibody or Fc fusion protein comprising the IgG1 Fc variant is strongly reduced compared to the CDC induced by the antibody or Fc fusion protein comprising the wild-type human IgG1 Fc region*".

7. The respondent argued that the subject-matter of claim 5 was explicitly disclosed on page 2, lines 6 to 9 of the application, which reads: "*In still a further embodiment, the polypeptide according to the invention exhibits a strongly reduced CDC compared to the CDC induced by a polypeptide comprising a wild-type human IgG Fc region.*" This passage does not provide a basis for the subject-matter of the claim, for the reasons set out in point 2.

8. The respondent further cited page 15, lines 15 to 20, page 39, lines 27 to 30 and original claim 9 as a basis. However, the disclosures on pages 15 and 39 do not mention the PGLALA mutations or an IgG1 Fc variant either. Moreover, claim 9 as filed depends on claim 1 as filed, which, as outlined above, contains additional functional features which have been omitted from granted claim 1 on which granted claim 5 is dependent. For the same reasons as outlined above for claim 8 as filed with regard to claim 4 as granted, claim 9 as filed does not disclose the subject-matter of claim 5 as granted.

9. Claims 4 and 5 add subject-matter.

Auxiliary requests 1 to 5
Amendments (Article 100(c) EPC) - claims 4 and 5

10. Claims 4 and 5 of these requests add subject-matter for the same reasons as outlined above for the main request.

Auxiliary request 6
Admission into appeal proceedings
(Article 13(1) and (2) RPBA 2020)

11. Auxiliary request 6 was admitted into the proceedings. The reasons for this decision are as follows.

12. The set of claims in auxiliary request 6, filed by letter of 21 February 2022, i.e. after the notification of the summons to oral proceedings, differs from that in the main request in that dependent claims 4 and 5 have been deleted and claims 6 to 8 renumbered accordingly.

13. Article 13(2) RPBA 2020, which relates to the situation "*after notification of a summons to oral proceedings*", thus applies.

14. In a first step it needs to be assessed whether filing auxiliary request 6 amounts to an "*amendment of the party's appeal case*" within the meaning of Article 13(2) RPBA 2020.

15. A number of decisions have held that deleting a dependent claim that does not represent an amendment to the factual and legal framework of the case is not an amendment within the meaning of Article 13(2) RPBA 2020 (see e.g. T 884/18, Reasons 4; T 914/18, Reasons 4.1; T 995/18, Reasons 2; T 1480/16, Reasons 2.3).

16. In this board's view, however, a party's case should not be confused with the subject-matter that is presented for consideration of patentability. On the contrary, a new claim request normally represents a new line of defence against the opposition, and by adding

this new line of defence to its case the respondent has undoubtedly changed its case.

17. In this respect, the present board agrees with the board in T 494/18, which found: "*According to their wording, Articles 13(1) and 13(2) RPBA 2020 are both applicable to 'any amendment to a party's appeal case'. The provision as such however does not define what is to be regarded as an 'amendment to a party's appeal case', it is thus an undefined legal term. An 'amendment to the party's appeal case' is not identical to an amendment of the patent or of the patent application. Therefore, the provisions and decisions dealing with the latter (see for example G 3/14, OJ 2015, 102) and the definitions given in that context cannot be applied unchanged. However, the question of what can be defined as an 'amendment to a party's appeal case', and with that the question of whether Article 13 RPBA 2020 is applicable, can be answered in the systematic context of the provisions guiding appeal proceedings (see also J 14/19, reasons 1.4). In this context, Article 12(3) RPBA 2020 provides that the statement of grounds of appeal and the reply shall contain a party's complete appeal case. Accordingly, all requests shall be specified expressly at this stage. It follows from this that only those requests that have been filed with a party's statement of grounds of appeal or the reply form part of a party's appeal case.*

Consequently, a new request filed afterwards with a set of claims that is different to that of the previous requests, is usually to be regarded as an 'amendment to a party's appeal case' within the meaning of Article 13 RPBA 2020. Following the systematic context of Articles 12(3) and 13 RPBA, a request in which

claims have been deleted compared to the previous requests is therefore a new request and thus usually amounts to an 'amendment to the party's appeal case' according to Article 13 RPBA 2020." A similar conclusion was reached in decisions T 2091/18, Reasons 4.1 and T 2295/19, Reasons 3.4.5, for example.

18. In a second step, it has to be established whether there are "*exceptional circumstances, which have been justified by cogent reasons*", which allow the request to be admitted into the appeal proceedings.

19. The respondent argued that neither the opposition division's preliminary opinion nor the decision under appeal had addressed the question of added subject-matter with regard to claims 4 and 5. Before receiving the board's communication under Article 15(1) RPBA 2020, which drew attention to this issue, the respondent could therefore not have reasonably expected it to become relevant in the appeal proceedings. It would also not have been procedurally efficient to address all potential objections by filing as early as with the reply to the appeal auxiliary requests with individual dependent claims. The deletion addressed the objections with regard to claims 4 and 5 in full and did not change the assessment of any other issue of the appeal.

20. The appellant countered that the deletion of the claims changed the focus of the appeal and that the late filing of an amended claim request would give the patentee an unfair advantage. It was the purpose of the new RPBA to "front-load" the proceedings in the sense that all means of attack and defence had to be presented at the beginning of the appeal. The late filing was also detrimental to procedural efficiency

because otherwise the appeal could be brought to an end for want of any allowable claim requests. As the objections against claims 4 and 5 had already been present in both the notice of opposition and the statement of grounds of appeal, there could be no "*exceptional circumstances*" justifying the late filing (citing decision T 172/17).

21. The board concluded that although the deletion of dependent claims 4 and 5 constitutes an amendment to the appeal within the meaning of Article 13(2) RPBA 2020 (see above), it did not change the factual and legal framework of the appeal. This distinguishes the case from decision T 172/17, in which auxiliary requests 1 to 3, which were not admitted, contained an amendment to independent claim 1 through the insertion of the subject-matter of former dependent claims.

22. In the case in hand, the deletion of dependent claims 4 and 5 does not affect the objections relating to added subject-matter, sufficiency of disclosure and inventive step for the other claims, all of which had been addressed in the statement of grounds of appeal, the reply and the board's communication under Article 15(1) RPBA 2020. The appellant was therefore not disadvantaged by the admittance of the request. This distinguishes the case from, for example, those underlying decisions T 2222/15 (Reasons 29 and 30), T 1569/17 (Reasons 4.3.4) and T 317/20 (Reasons 28 to 44), where the deletion of claims would have substantially shifted the case, thereby giving rise to new issues to be decided upon.

23. Moreover, the board could not agree with the appellant that the "convergent approach" of the RPBA 2020 (see

"*Table setting out the amendments to the RPBA and explanatory remarks*" accompanying the RPBA 2020), which arguably aims at "front-loading" the appeal proceedings, creates a blanket ban on deleting dependent claims at a later stage of the appeal proceedings. In this respect, the board interprets the wording "*shall, in principle,*" in Article 13(2) RPBA 2020 such that it leaves the board at least some discretion in its assessment of the alleged exceptional circumstances. Sensibly applying this discretion appears to be particularly important in technical fields with patents containing a large number of dependent claims. Generally prohibiting the deletion of dependent claims in reaction to the development of the appeal proceedings would require a huge number of auxiliary requests to be filed at an early stage, i.e. as early as with the statement of grounds of appeal or the reply, covering all combinations and permutations of possible fall-back positions. This would not be in the interest of procedural economy and cannot be deemed to be in line with the "convergent approach" and the aim and purpose of the RPBA 2020.

24. The board concludes that deleting dependent claims 4 and 5 enhances procedural economy as doing so clearly overcomes existing objections without giving rise to any new issues. In the board's opinion these are cogent reasons justifying exceptional circumstances as per Article 13(2) RPBA 2020 (see also T 1857/19, Reasons 1.1, penultimate paragraph).

25. As it deemed the request admissible under the stringent requirements of Article 13(2) RPBA 2020, the board considered it unnecessary to further decide whether the less stringent requirements of Article 13(1) RPBA 2020 were fulfilled.

26. Auxiliary request 6 was admitted into the appeal proceedings.

Amendments (Article 100(c) EPC) - claim 1

27. Page 33, lines 7 to 11 of the application as filed discloses: "*In a specific embodiment the polypeptide comprising an Fc variant of a wildtype human Fc polypeptide comprises a triple mutation: an amino acid substitution at position Pro329, a L234A and a L235A mutation (P329/LALA). In a further specific embodiment the above mentioned polypeptides comprise a human IgG1 region.*"

28. The skilled person will read these two sentences together to mean that the latter embodiment comprises an Fc variant of a human IgG1 region with the specified mutations. As concerns the nature of the polypeptide, the skilled person is instructed on page 2, lines 1 to 3 that one aspect of the invention is that "*the polypeptide is an antibody or an Fc fusion protein*". The skilled person would read this passage as applying in general to all polypeptides carrying Fc variants and mutations disclosed in the application.

29. As concerns the mutation at position Pro329, there is a clear pointer to glycine, which is disclosed as the preferred mutation throughout the application, for example on page 7, lines 5 to 12, which concludes: "[...] *a glycine residue appears to be unexpectedly superior over other amino acid substitutions, like alanine, for example, at position 329 in destroying the proline sandwich in the Fc/Fcγ receptor interface.*" On page 31, lines 3 to 5, the P329G mutation is clearly singled out: "*In another embodiment Pro329 is*

substituted with an amino acid which is either smaller or larger then proline. In still another embodiment the substituted amino acid is Gly, Ala or Arg. In a further aspect of the invention Pro329 of the Fc polypeptide is substituted with glycine." Furthermore, in the experimental section, the following is underlined on page 82: "*P329G, P329A, SPLE and LALA mutations have been introduced ... Thus, the combination of P329G with either LALA of SPLE mutations is much more effective than the P329G mutation or the double mutations LALA or SPLE alone.*"

30. The application thus discloses a polypeptide which is an "*antibody or an Fc fusion protein*" comprising an Fc variant of a wild-type human IgG1 Fc region and the P329/LALA mutations of which P329G, L234A, L235A (PGLALA) is the preferred embodiment.

31. In conclusion, the board finds that the subject-matter of claim 1 does not extend beyond the content of the application as filed (Article 100(c) EPC).

Sufficiency of disclosure (Article 100(b) EPC)
Fc fusion protein - claim 1

32. Fc regions are commonly known and are described in the patent (see e.g. paragraph [0016]). Producing fusion proteins by genetic engineering is also part of the common general knowledge (see e.g. review in document D15, paragraph bridging pages 59 and 60). The appellant did not assert any serious doubts that the skilled person was able to obtain Fc fusion proteins as detailed in claim 1.

Technical effect achievable "over whole range claimed" - claims 2 and 3

33. The antibodies carrying the PGLALA mutations tested in the patent show the effects as mentioned in the claims, i.e. "*ADCC ... reduced to 0-20%*" and "*reduced or ablated affinity for an Fc receptor responsible for an effector function*" (see Examples 2, 4 and 5). The appellant has not provided any evidence that these effects are restricted to the particular antibodies used in the examples and the board sees no reason to assume this to be the case. Moreover, the respondent has provided evidence that the effect can also be achieved for antibodies directed to other targets (see e.g. document D20). Therefore, for want of any serious doubts, it can be accepted that the patent enables the skilled person to obtain antibodies or Fc fusion proteins having the functional features as required by claims 2 and 3, without undue burden.

Medical use - claims 5 and 6

34. Claim 5 is formulated in the form of a first medical use ("*for use as a medicament*") according to Article 54(4) EPC ("*for use in a method referred to in Article 53(c)*"). In view of the above finding with regard to the sufficient disclosure of the antibody and Fc fusion protein as such, it remains to be analysed whether those compounds are suitable for use as a medicament.

35. The patent shows that the PGLALA mutations can be introduced into known therapeutic antibodies having a human IgG1 Fc region and that an antibody of this kind provides relevant medical effects such as reduced Fc receptor affinity and reduced effector function, known

to be useful in several therapeutic contexts (see e.g. paragraphs [0020] and [0021]). It is plausible that this finding also extends to Fc fusion proteins in which the Fc part is fused to a therapeutically effective protein (see e.g. paragraphs [0116] and [0117] of the patent) and that the mutated antibodies or Fc fusion proteins can be used as a medicament in said known therapies without the mutations in the Fc region impairing the therapeutic effect.

The appellant has contested that the examples in the patent show that the mutated antibodies bind to their (antigen) targets and are therapeutically effective. The appellant, however, has not provided any evidence to that effect.

It is common general knowledge that the Fc region and the antigen-binding region of an antibody can be modified independently of each other (see the "Background" section of the patent). This is further supported by later-published data, e.g. document D30, which reports on ongoing clinical trials of PGLALA-mutated therapeutic antibodies (page 458, left-hand column, second-to-last paragraph) and shows retained binding to the antigens (paragraph bridging pages 5 and 6).

Therefore, the only remaining question is whether claim 5 should be restricted to these particular therapies.

36. The case law of the boards of appeal concerning the question of sufficiency of disclosure of a first medical use is not very extensive and generally relates to the situation where, unlike in the case in hand, the substance or composition is part of the state of the

art (in accordance with Article 54(5) EPC 1973 corresponding to Article 54(4) EPC 2000). However, for the question of whether the "medical use" aspect of the claim is sufficiently disclosed, this distinction is irrelevant as the skill required to use a known substance or composition in medicine is the same as that required for a substance or composition provided by the patent for the first time.

37. In decision G 5/83, Reasons 15, the Enlarged Board of Appeal stated: "*Thus the inventor of a 'first medical indication' can obtain purpose-limited product protection for a known substance or composition, without having to restrict himself to the substance or composition when in a form technically adapted to a specified therapeutic purpose. The appropriate protection for him is, therefore, in its broadest form, a purpose-limited product claim. No problem arises over its susceptibility of industrial application, within the meaning of Article 57 EPC.*" The board interprets this statement to mean that the Enlarged Board, although not commenting explicitly on Article 83 EPC, also saw no general issue of sufficiency of disclosure for a broad first medical use claim and did not see the need for the inventor to "*restrict himself ... to a specified therapeutic purpose*".

38. Before decision G 5/83, decision T 128/82 had followed the same line of thinking: "*If an inventor is granted absolute protection in respect of a new chemical compound for use in therapy, the principle of equal treatment would require that an inventor who for the first time makes a known compound available for therapy should be correspondingly rewarded for his service with a purpose-limited substance claim under Article 54(5) EPC to cover the whole field of therapy*" (see Reasons

10). With regard to Article 84 EPC, the decision stated: "*The mere fact that there are not instructions concerning all and any possible specific therapeutic applications does not justify limiting the scope to the therapeutic application actually mentioned. This would not be in accord with the general practice of the European Patent Office concerning therapeutically active compounds*" (see Reasons 12). Thus, although Article 83 EPC is not mentioned, this decision does not require a limitation to a specific therapeutic use either.

39. In decision T 604/04, sufficiency of disclosure of a claim to a monoclonal antibody "*for use in therapy or diagnosis*", i.e. a first medical use, was denied because "*the mere disclosure of a monoclonal antibody against the polypeptides of Figure 4 or 5 without identifying a diseased state caused by the 'misfunctioning' of these polypeptides is not sufficient to acknowledge a use in therapy for the monoclonal antibody*" (see Reasons 25). The case in hand, however, is different from the situation underlying decision T 604/04 because the patent discloses that established therapeutic antibodies and Fc fusion proteins can be modified as claimed in order to reduce the effector function without affecting the therapeutic effect. Common general knowledge about antibodies and Fc fusion proteins and their therapeutic function(s) thus provides the basis for acknowledging a use in therapy.

40. This board cannot derive any requirement from the EPC whereby a patent would have to show that a compound is suitable for each and every disease in order for a first medical use to be sufficiently disclosed. Instead, it is sufficient to show that the compound is

suitable for at least one particular medical use, as is the case in the patent at issue (see point 34. above).

41. Claim 6 defines the disease in functional terms ("*wherein it is favourable that an effector function of the antibody or Fc fusion protein is strongly reduced*"). The patent discusses the physiological background in which the effector function plays a role (see paragraphs [0020] and [0021]). The wording "*in a method for treating a disease ... wherein it is favorable that an effector function ... is strongly reduced*" in the claim presupposes an existing (or future) treatment with an antibody or an Fc fusion protein. To put the invention into practice, it is therefore not necessary to identify a new compound or treatment, but only to establish whether there is a need for reduced effector functions in a known treatment. The appellant has not argued that the latter aspect would be an undue burden. The skilled person is therefore able to identify the appropriate diseases without undue burden.

42. Thus, the invention to which the claims relate is sufficiently disclosed in the patent.

Inventive step (Article 100(a) EPC and Article 56 EPC)
Suitable starting point

43. The parties did not agree on a suitable starting point for an inventive step analysis. The board, however, considers this irrelevant when the subject-matter claimed is not obvious from the state of the art proposed by the opponent (i.e. document D13 or document D10), as in the case in hand (see below).

44. Document D13 discloses the anti-CD20 antibody #497, which carries the P329G mutation in its Fc region. The mutation shows effects on Fc receptor binding and C1q binding compared with the same antibody with a wild-type Fc region as analysed by a high-throughput assay (see Figure 41, #497). The data in document D13 show the following effects on binding: FcγRI unchanged (1.03-fold), C1q increased (4.72-fold), all other Fc receptors (FcγRIIA, FcγRIIB, FcγRIIC, FcγRIIIA, FcRn) reduced.

Difference, effect(s) and objective technical problem

45. It is undisputed that the subject-matter of claim 1 differs from antibody #497 disclosed in document D13 on account of the presence of the L234A and L235A mutations in the Fc region.

46. The effect resulting from this difference, as far as established in the patent, is reduced FcγRI binding to "*nearly undetectable levels*" of the PGLALA triple mutation variant compared with the P329G variant (see Figure 1b and paragraph [0320]).

47. The patent shows that several other characteristics are substantially the same when the PGLALA variant is compared with P329G but are reduced in the PGLALA variant when compared with an antibody having the wild-type Fc region. These effects are:

    1) binding to FcγRIIA (see Figure 1c)
    2) binding to FcγRIIIA (see Figure 1e)
    3) cytolytic activity (see Figure 3a)
    4) ADCC activity (see Figure 4a)
    5) CDC activity (see Figure 5a)

48. The binding of the PGLALA variant to FcγRIIB is reduced compared with wild-type, but no comparison with the P329G variant is carried out (see Figure 1d). The binding of the PGLALA variant to C1q is not analysed (see Figure 2) but it is considered "*very likely* [that] *also the triple mutations comprising the aforementioned single mutations, strongly reduces the above mentioned functions of C1q*" (see paragraph [0325]).

49. The objective technical problem can therefore be formulated as providing antibodies/Fc fusion proteins that show reduced binding to FcγRIIA and FcγRIIIA, reduced cytolytic activity, ADCC activity and CDC activity as compared with wild-type, and reduced binding to FcγRI to "nearly undetectable levels".

Obviousness

50. The skilled person would take document D12 or D14 into account when aiming to solve the above problem because both are concerned with reducing binding to Fcγ receptors. Both documents report reduced FcγRII receptor binding for antibodies with the LALA double mutation in the Fc region (see document D12, Abstract and document D14, Abstract). Document D12 further implies reduced FcγRI binding on the basis of competition experiments but does not directly measure it. Document D14 reports reduced FcγRI and C1q binding for antibodies carrying the LALA mutations (see document D14, Abstract).

51. The question to be answered is therefore whether it was obvious for the skilled person to combine the P329G mutation and the LALA double mutation in the Fc region of an antibody or Fc fusion protein in order to achieve strongly reduced FcγRI binding (to "*nearly undetectable*

levels"), while maintaining reduced binding to FcγRIIA and FcγRIIIA and reduced cytolytic, ADCC and CDC activity.

52. It is undisputed that the high-throughput binding experiments in document D13 provide only low-confidence data. This is evident from the large error margins and diverging results when assays were performed in duplicate (see e.g. #329, #350, #502). Cytolytic activity, ADCC activity and CDC activity were not directly assayed in document D13 but can be inferred indirectly from the binding of the respective receptors, e.g. C1q binding for CDC, FcγRIIIA binding for ADCC. The skilled person therefore would have considered the data in document D13 on Fc receptor binding to be only a first indication of the effects achieved by the P329G mutation which required further experimental confirmation.

53. Document D13 contains no indication to combine mutations in order to achieve greater reduction of binding to particular receptors. Some of the reported examples of combinations of mutations even result in interfering effects, i.e. a combination may cancel out the effects observed for the single mutations (see e.g. #43, #44, #46).

54. The appellant argued during oral proceedings that the double mutations in document D13, which showed a partially cancelling effect, could not be compared with the PGLALA triple mutant as the double mutations reported in document D13 were more closely spaced in the amino acid sequence and thus more likely to interfere with each other.

The board does not agree because the distance in the primary sequence does not necessarily reflect the spatial distance between residues in a folded molecule, such as an antibody. D13 would thus suggest to the skilled person that cancellation of effects was in principle possible.

55. Moreover, documents D12 and D14 do not contain any indication that the LALA mutations could be combined with other mutations in order to achieve a further-silenced Fc region.

56. Even if the skilled person had considered combining the P329G mutation disclosed in document D13 with the LALA mutations disclosed in documents D12 and D14, there would have been no reasonable expectation of success that FcγRI binding could be reduced to "*nearly undetectable levels*" because the P329G mutation showed no effects on FcγRI binding while the LALA mutations showed reduced FcγRI binding but still at detectable levels. A further reduction of FcγRI binding owing to the combination of the three mutations to "*nearly undetectable levels*" was thus unexpected and not obvious.

57. A reduction in C1q binding and CDC activity as compared with wild-type could not be expected from the combination either, since D13 reported an approximately fourfold increase in C1q binding for the P329G variant, suggesting an increased CDC (see document D13, paragraph [0007], "*Fc/C1q binding mediates complement dependent cytotoxicity (CDC)*", and the patent, paragraph [0019], "*Fc binding to C1q mediates a process called complement dependent cytotoxicity (CDC)*"). Although document D14 reports decreased C1q binding for the LALA variant, the skilled person could not

reasonably expect this reduction to be maintained and not cancelled out when combining LALA with P329G.

58. In conclusion, the state of the art does not contain any indication or prompt to add further mutations to the P329G mutation disclosed in document D13 in order to further reduce FcγRI binding, nor did the skilled person have a reasonable expectation of success in combining the three mutations. Starting from the disclosure of antibody #497 in document D13, the skilled person would not have arrived at the subject-matter of claim 1 in an obvious manner.

59. The assessment of inventive step does not change when starting from document D10 because antibody 909 reported in D10, which carries the P329G mutation, is completely uncharacterised, i.e. neither receptor binding nor ADCC nor CDC were tested. In comparison with the subject-matter of claim 1, the same difference, effect and objective technical problem as for document D13 are established (see points 45. to 49. above). As there is no binding data for the P329G mutant, the skilled person starting from the disclosure of document D10 had even less of an expectation of success of arriving at a variant with strongly reduced FcγRI binding and reduced binding to the other Fc receptors, as well as reduced ADCC and CDC.

60. The appellant asserted an additional inventive step objection in the event that the respondent considered claim 1 to mean that, apart from the PGLALA mutations, "*any other number of amino acid changes*" could be present in addition to PGLALA, implying that claim 1 would encompass Fc variants that have little resemblance to the native human IgG1 Fc sequence.

61. However, the respondent agreed that that interpretation would be far-fetched and endorsed the opposition division's interpretation that "*although the variants may have additional mutations in comparison with the wild-type Fc region, these variants must still be human IgG1 Fc regions, and thus, also have the properties of human IgG1 Fc regions*" (see decision, sheet 10; statement of grounds of appeal, page 36, sixth paragraph; reply to the appeal, page 18, point 5.3.3).

62. As the parties seem to agree that the very broad interpretation is incorrect, there is no need to address the appellant's additional inventive step objection.

63. The subject-matter of claim 1 is inventive. As claims 2 to 6 are dependent on claim 1, their subject-matter is inventive as well.

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 claims 1 to 6 of auxiliary request 6, filed with the letter of 21 February 2022, and a description to be adapted thereto.

The Registrar: The Chair:

A. Chavinier-Tomsic P. de Heij

Decision electronically authenticated