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Datasheet for the decision of 23 May 2022

Case Number: T 0784/19 - 3.3.04

Application Number: 12723733.7

Publication Number: 2705057

IPC: C07K16/22, C07K16/46

Language of the proceedings: EN

Title of invention:
Therapeutic canine immunoglobulins and methods of using the same

Patent Proprietor:
Zoetis Services LLC

Opponent:
MorphoSys AG

Headword:
Canine immunoglobulins/ZOETIS

Relevant legal provisions:
EPC Art. 56, 123(2), 123(3)
RPBA Art. 12(2), 12(4)

Keyword:
Sole request - Amendments - allowable (yes)
Inventive step - (yes)
Statement of grounds of appeal - party's complete case
Late-filed evidence - no reasons for submitting with the statement of grounds of appeal

Decisions cited:

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Case Number: T 0784/19 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 23 May 2022

Appellant I: (Patent Proprietor)	Zoetis Services LLC 10 Sylvan Way Parsippany, NJ 07054 (US)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Appellant II: (Opponent)	MorphoSys AG Semmelweisstrasse 7 82152 Martinsried/Planegg (DE)
Representative:	Geissler, Andreas Windeckstraße 66A 81375 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 8 January 2019 concerning maintenance of the European Patent No. 2705057 in amended form.**

Composition of the Board:

Chairwoman	M. Pregetter
Members:	D. Luis Alves
	L. Bühler

Summary of Facts and Submissions

I. European patent No. 2 705 057, entitled "*Therapeutic canine immunoglobulins and methods of using the same*", was granted on European patent application No. 12 723 733.7, filed as an international application published as WO 2012/153126 ("application as filed").

II. The patent was granted with 13 claims. The two independent claims read as follows:

"1. An antibody, fusion protein or a binding fragment thereof for use in the therapeutic treatment of a canine where target neutralisation is desired in the absence of undesirable effector function, wherein said antibody, fusion protein or binding fragment has a heavy chain constant domain comprising the amino acid sequence of SEQ ID NO:8, SEQ ID NO:11 or SEQ ID NO:13, wherein the amino acid sequence of the heavy chain minimises the activation of downstream immune system effector functions when the antibody, fusion protein or binding fragment is bound to its target antigen."

"8. An antibody or a fusion protein or a binding fragment thereof for use in the therapeutic treatment of a canine where target destruction is desired, wherein said antibody, fusion protein or binding fragment has a heavy chain constant domain comprising the amino acid sequence of SEQ ID NO:9, SEQ ID NO:10, or SEQ ID NO:14 wherein the amino acid sequence of the heavy chain mediates the activation of downstream immune system effector functions when the antibody, fusion protein or binding fragment is bound to its target antigen."

III. The patent was opposed on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC), under Article 100(a) EPC, and on the grounds under Article 100(b) and (c) EPC.

IV. The opposition division decided that, account being taken of the amendments in the form of auxiliary request 1, the patent and the invention to which it related met the requirements of the EPC.

With respect to the patent as granted (main request) the opposition division held, *inter alia*, that the subject-matter of claim 1 lacked novelty in view of the disclosure in document D8.

V. Both the patent proprietor (appellant I) and the opponent (appellant II) filed appeals against this decision.

VI. With the statement setting out the grounds of appeal, appellant I filed sets of claims of a main request, identical to the claims as granted, and of auxiliary requests 1 and 2. They submitted arguments to the effect that claim 1 of the main request met the requirements of Articles 54 and 56 EPC.

VII. With the statement setting out the grounds of appeal, appellant II submitted documents D21 to D25 and arguments to the effect that priority was not validly claimed, the subject-matter in claims 1 and 8 did not involve an inventive step, and the subject-matter of claim 1 extended beyond the content of the application as filed. Reference was made to the opposition proceedings in respect of submissions on Articles 54, 83 and 123(2) EPC.

VIII. Appellant I submitted a reply to appellant II's statement of grounds of appeal, together with sets of claims of auxiliary requests 2a and 3 to 56.

IX. The board appointed oral proceedings and in a communication pursuant to Article 15(1) RPBA informed the parties of its preliminary opinion that, *inter alia*, documents D21 to D25 were not to be admitted into the appeal proceedings and that appellant II's case was not substantiated for the objections under Articles 54 and 83 EPC or under Article 123(2) EPC for claims 8 to 13, and accordingly the board saw no reason to consider these issues in the appeal. Furthermore, inventive step and priority right were also addressed.

X. Appellant I subsequently submitted a claim set of auxiliary request 2'.

XI. Appellant II, by letter dated 3 May 2022, informed the board that they would not attend the oral proceedings. Furthermore, they submitted arguments on admittance of document D23 into the appeal proceedings.

XII. The oral proceedings took place in the absence of appellant II.

At the oral proceedings, appellant I filed a set of claims of a main request and withdrew all other requests.

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

XIII. The two independent claims of the main request read as follows (differences to independent claims 1 and 8 as granted are highlighted by the board):

"1. An antibody, fusion protein or a binding fragment thereof for use in the therapeutic treatment of a canine where target neutralisation is desired in the absence of undesirable complement activity ~~effector function~~, wherein said antibody, fusion protein or binding fragment has a heavy chain constant domain comprising the amino acid sequence of ~~SEQ ID NO:8,~~ SEQ ID NO:11 or SEQ ID NO:13, wherein the amino acid sequence of the heavy chain minimises the activation of downstream immune system effector functions when the antibody, fusion protein or binding fragment is bound to its target antigen."

"8. An antibody or a fusion protein or a binding fragment thereof for use in the therapeutic treatment of a canine where target destruction is desired, wherein said antibody, fusion protein or binding fragment has a heavy chain constant domain comprising the amino acid sequence of SEQ ID NO:9, ~~SEQ ID NO:10, or SEQ ID NO:14~~ wherein the amino acid sequence of the heavy chain mediates the activation of downstream immune system effector functions when the antibody, fusion protein or binding fragment is bound to its target antigen."

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

D1: WO 2010/117448

D3: WO 2010/110838

D4: L. Tang *et al.*, Veterinary Immunology and Immunopathology 80, 2001, 259-70

D5: US 5,852,183

D9: D.T. Chao *et al.*, Immunological Investigations 38, 2009, 76-92

D10: K.A. Jeglum, Cancer Therapy 7, 2009, 59-62

D14: L.M. Begeron *et al.*, Veterinary Immunology and Immunopathology 157, 2014, 31-41

D16: WO 2010/027488

D17: W.R. Strohl, Current Opinion in Biotechnology 20, 2009, 685-91

D21: PCT request form of application PCT/GB2012/051008

D22: S.L. Sazinsky *et al.*, PNAS 105(51), 2008, 20167-72, and "Supporting Information", 1-8

D23: Declaration of Dr Markus Waldhuber

D24: T.S. Raju *et al.*, Glycobiology 10(5), 2000, 477-86

D25: B.J. Sutton and D.C. Phillips, Biochemical Society Transactions, 1983, 130

XV. Appellant I's arguments relevant to this decision may be summarised as follows.

Admittance into the appeal proceedings of objections under Articles 123(2), 83 and 54 EPC (Article 12(2) RPBA 2007)

As regards Articles 83 and 54 EPC, appellant II's statement of grounds of appeal did not go beyond a mere reference to their submissions in opposition proceedings. The same applied to Article 123(2) EPC for claim 8. Therefore, no objections under these grounds should be admitted into the appeal proceedings.

Admittance into the appeal proceedings of documents D21 to D25 (Article 12(2) RPBA 2007)

No reasons had been submitted for filing these documents only at the appeal stage. Therefore, they should not be admitted into the appeal proceedings.

Main request

Amendments - extension beyond the content of the application as filed (Article 123(2) EPC)

The subject-matter of claim 1 was disclosed in the application as filed in claim 1 in combination with page 24, lines 26 to 29.

Amendments - extension of protection conferred by the patent (Article 123(3) EPC)

The amendment in claim 1 from "absence of undesirable effector function" to "absence of undesirable complement activity" restricted the scope of claim 1 as granted, which included both the absence of all effector functions as well as the absence of only one effector function.

Inventive step (Article 56 EPC)

Claim 1 - SEQ ID NO:11

Document D5 disclosed dog-mouse chimeric antibodies comprising canine heavy chain constant domains (title and column 3, lines 17 to 39). The focus of this document was on the treatment of canine viral diseases (column 1, lines 14 to 17 and column 2, lines 8 to 24). There was no teaching of effector functions of the heavy chain constant domains in general or specifically of those having the sequence of SEQ ID NO:17.

There were two differences between the claimed subject-matter and this disclosure: the amino acid sequence and the medical use, i.e. the treatment of a canine disease where target neutralisation is desired in the absence of complement activity.

The objective technical problem was the provision of an improved therapeutic for dogs where target neutralisation is desired.

Document D5 had no teaching on effector functions of canine heavy chain constant domains or the benefits of the absence of effector functions in dog therapy where

target neutralisation was desired. Thus, from this document, no motivation was derivable leading the skilled person to provide the solution as claimed.

The objective technical problem as formulated by appellant II referred to the therapy of diseases "where target neutralisation is required but immune effector function is not desired". This formulation was the result of hindsight as it contained a pointer to the claimed solution.

The patent provided experimental data demonstrating that antibodies comprising SEQ ID NO:11 did not elicit effector functions (Example 4) and demonstrating their clinical efficacy *in vivo* in the treatment of inflammatory pain in dogs (Example 8), as confirmed by post-published document D14.

Document D22 did not address effector function of canine immunoglobulin heavy chains or the therapy of dogs where target neutralisation is desired.

Claim 1 - SEQ ID NO:13

There were two differences between the claimed subject-matter and the disclosure in each of documents D3 and D16: the amino acid sequence and the medical use, i.e. the treatment of a canine where target neutralisation is desirable in the absence of undesirable complement activity.

The technical effect of the difference in amino acid sequence was the abrogation of effector function.

The objective technical problem could be formulated as the provision of an improved therapeutic for dogs where

target neutralisation is desired. By referring to "reduced effector function", the objective technical problem as formulated by appellant II contained a pointer to the solution.

The disclosure in document D16 provided the skilled person with no motivation to look at document D17, in particular since it disclosed that effector function was desirable (document D16, paragraph 20 and embodiments 1.2 and 2.5 to 2.6, on pages 28 and 29, respectively). Document D17 pertained to human antibodies and contained no disclosure on canine antibodies. In view of this, combining the disclosure in these two documents would not lead the skilled person to the claimed solution. Moreover, with respect to human antibodies, this document taught that not all aglycosyl-IgG mutants lacked effector function (document D17, page 687, right-hand column, fourth paragraph and page 688, left-hand column, second paragraph). Also when starting from the disclosure in document D3 and taking into account the disclosure in document D17, the skilled person would not have arrived at the claimed solution for the same reason as above for document D16.

Under established case law, for a finding of obviousness, it was necessary to show that the skilled person would have arrived at the claimed subject-matter due to a prompt in the prior art and not merely that they could do so. No such prompt existed in the current case.

Claim 8 - SEQ ID NO:9

Documents D3 and D16 as representing the closest prior art

SEQ ID NO:9 differed from SEQ ID NO:4 of document D3 (also designated VET 203 in this document) by two amino acid substitutions.

The objective technical problem was the provision of an alternative method of treating dogs that causes target neutralisation and effector function.

The skilled person would not have provided an antibody with these substitutions for the following reasons. Different variants of the sequence SEQ ID NO:4 differed in their effector activities (document D3, Example 4, Table 4 and paragraph 135). Moreover, the skilled person would not perform modifications in very conserved domains of the molecule, as was the case here (document D3, Table 2). The skilled person had a conservative attitude. Furthermore, the prior art was silent on the effect of modifications in these domains, with the exception of document D1. This document disclosed a constant domain of canine IgG subtype B (SEQ ID NO:17) which lacked effector function (Example 7, paragraph bridging pages 43 and 44, and page 56). Like SEQ ID NO:9, the sequence disclosed in document D1 comprised the substitution to glutamic acid in position 327. The same applied when starting from SEQ ID NO:54 in document D16.

Consequently, the claimed subject-matter involved an inventive step.

Document D10 as representing the closest prior art

Document D10 disclosed that murine antibody MAb231 was capable of inducing effector function in dogs and was used in the treatment of canine lymphoma.

The claimed subject-matter differed from this disclosure in the use of a canine instead of a murine constant domain. The patent showed that the claimed antibody with a constant domain having the sequence SEQ ID NO:9 was able to bind complement (see Example 2 and Figure 3).

The objective technical problem was the provision of an alternative method of treating dogs that causes target neutralisation and effector function.

The claimed solution was not obvious. Document D10 did not disclose sequences of canine constant domains. It moreover did not provide any motivation for modifying antibody MAb231 with canine constant domains, as known from document D4, because this antibody already presented complement-dependent cytotoxicity activity (document D10, page 60, left-hand column, last full paragraph). Furthermore, according to this document, there was no need to provide caninised MAb231 antibodies (document D10, page 60, right-hand column, last full paragraph), and instead completely different problems should be addressed (page 61, last paragraph).

The claimed solution was also not obvious to the skilled person in light of the disclosure in documents D3 and D16 for the reasons presented above for these documents as representing the closest prior art.

XVI. Appellant II's arguments, submitted in writing for the claim request held allowable by the opposition division, relevant to this decision may be summarised as follows.

Admittance into the appeal proceedings of documents D21 to D25 (Article 12(2) RPBA 2007)

Document D23 was *prima facie* relevant because it provided evidence that no technical effect could be attributed to the mutations Y259F and E327K in SEQ ID NO:13.

This document was filed in reaction to the reasoning of the opposition division in the decision under appeal that the technical effect of a lack of effector function resulted from the three mutations N297A, Y259F and E327K (see decision page 14, seventh and eighth paragraphs). This was a surprising development in the proceedings because previously no arguments had been submitted in this regard on the two mutations Y259F and E327K.

Inventive step (Article 56 EPC)

Claim 1 - SEQ ID NO:11

Document D5 represented the closest prior art. It disclosed mouse-dog chimeric antibodies having neutralising activity against the target antigen. The antibodies were useful in the treatment of dogs (abstract, page 1, lines 14 to 16 and page 2, lines 59 to 63). In one embodiment, the constant domain of the canine immunoglobulin had the amino acid sequence of SEQ ID NO:17, corresponding to canine subtype IgG-D. SEQ ID NO:11 differed from SEQ ID NO:17 disclosed in

document D5 in five amino acids, there being 95.8% shared identity between these sequences.

The claimed subject-matter differed from this disclosure in the use of an IgG-D subtype variant of SEQ ID NO:17 for the therapeutic treatment of a canine where target neutralisation was desired. The patent demonstrated that the variant having SEQ ID NO:11 did not mediate immune effector functions.

The objective technical problem could be formulated as the provision of an IgG-D variant for the treatment of dogs suffering from diseases where neutralisation is required but immune effector function is not desired.

The solution was obvious since it was known that only four canine IgG subtypes existed. In view of the common general knowledge that not all IgG subtypes in a given species mediated immune effector functions, when selecting SEQ ID NO:17, the skilled person had a reasonable expectation of providing an antibody suitable for target neutralisation and lacking effector function.

Furthermore, the patent did not show any technical effect that could be attributed to the five-amino-acid difference between SEQ ID NO:11 and SEQ ID NO:17, so this difference could not contribute to inventive step.

Claim 1 - SEQ ID NO:13

The closest prior art was represented by the disclosure in any of documents D3 and D16. Document D3 disclosed a heavy chain constant domain having the amino acid sequence of SEQ ID NO:4, whereas document D16 disclosed an identical sequence as SEQ ID NO:54. These

corresponded to canine IgG isotype B and shared 99.6% identity with current SEQ ID NO:13. The IgG-B isotype mediated the activation of immune effector functions. The immunoglobulins were to be used in the treatment of dogs.

The claimed subject-matter differed from this disclosure in that the antibody did not mediate effector functions and had a different amino acid sequence. SEQ ID NO:13 and SEQ ID NO:54 differed in three amino acids, corresponding to the following substitutions: N297A, Y259F and E327K.

The objective technical problem could be formulated as the provision of a modified canine constant domain isotype with reduced effector function.

The claimed antibody did not involve an inventive step because each of the three mutations was obvious to the skilled person.

As concerns the mutation N297A, document D17 disclosed aglycosylated mutant IgGs having such a mutation and which did not bind well to Fcγ receptors (document D17, page 687, right-hand column, fourth paragraph). Thus, this document disclosed a mechanism to silence the function of the Fc domain. Furthermore, at least one therapeutic candidate antibody was known carrying such a mutation so as to silence antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (document D17, page 688, Table 2, top item). Moreover, the N297 residue was conserved in canine IgGs (document D4, Figures 1 and 2) as well as in mammals in general. Therefore, the skilled person expected this residue to be involved in Fcγ receptor binding and its mutation to reduce immune effector

function. Indeed, such a reduction had been observed in humans and mice (document D9, page 78, "Materials and Methods"). Such an expectation also existed because it was known that N297 was present in canine IgGs and that canine IgGs were glycosylated.

Document D4, which disclosed the sequences of constant domains of canine immunoglobulins, referred to an N-glycosylation site at this position as "putative". However, this did not allow concluding that the effect of a mutation at this site was not predictable. Instead, the term "putative" merely reflected that the document did not include experimental evidence of glycosylation at this position.

As concerns the two other mutations relative to SEQ ID NO:54, no technical effects had been demonstrated. To the contrary, document D23 contained experimental evidence demonstrating the absence of an effect of these two mutations on effector functions and an effect only of the mutation N297A.

The same line of argument applied when considering the disclosure of SEQ ID NO:4 in document D3 as the closest prior art.

Claim 8 - SEQ ID NO:9

Each of documents D3, D16 and D10 could be considered to represent the closest prior art.

Documents D3 and D16 as representing the closest prior art

Document D3 disclosed a heavy chain constant domain having the amino acid sequence of SEQ ID NO:4, whereas

document D16 disclosed an identical sequence as SEQ ID NO:54. This sequence corresponded to canine IgG isotype B and shared 99.4% identity with current SEQ ID NO:9. Both documents disclosed the use of the antibodies in the treatment of dogs and that the antibodies mediated the activation of immune effector functions.

The claimed subject-matter differed from this disclosure in the amino acid sequence. Specifically, SEQ ID NO:9 differed from the prior-art sequence in two amino acids, corresponding to the following substitutions: Y259F and E327K.

No technical effect of this difference had been demonstrated. Moreover, the experimental results in document D23 confirmed the absence of a technical effect.

The objective technical problem could thus be formulated as the provision of an alternative canine IgG-B constant domain that mediates the activation of downstream effector functions.

As acknowledged by the opposition division, document D1 could not be considered to establish a technical prejudice. The finding of non-obviousness by the opposition division relied on a lack of predictability of the technical effects that could result from the two amino acid substitutions. However, in view of the absence of any technical effect that could be attributed to these substitutions, the claimed antibody based on SEQ ID NO:9 did not involve an inventive step.

Document D10 as representing the closest prior art

The claimed subject-matter differed from the disclosure in document D10 in the use of canine-derived instead of murine-derived antibodies.

In view of this difference, the objective technical problem could be formulated as the provision of an improved treatment for dogs wherein target destruction is desired.

Document D10 already identified the issue of a canine anti-mouse antibody response in reaction to therapy with the murine MAb 231. It was in any case part of the common general knowledge that proteins from one species induced immune responses in a host from another species. The skilled person was thus prompted to provide a canine-derived antibody, and the claimed subject-matter did not involve an inventive step.

The solution was also obvious in view of the disclosure in document D16 or alternatively in view of the disclosure in document D3. Document D16 disclosed canine antibodies which elicited a reduced immune response (see page 5). Therefore, the skilled person would use the antibodies disclosed in this document. Although there were differences between SEQ ID NO:9 and the amino acid sequence disclosed in document D16, these were not associated with any technical effect, and therefore no inventive step was involved in arriving at the claimed solution, for the reasons put forward for document D16 as the closest prior art.

The same conclusion, for the same reasons, applied in view of the disclosure in document D3 of canine constant domains mediating immune effector functions

(see Tables 4 and 5). Sequence Vet203, which was one of the most frequently occurring canine constant domain sequences, differed from SEQ ID NO:9 in two amino acids only (see Example 2, III).

Thus, the claimed subject-matter did not involve an inventive step.

XVII. Appellant I's final requests at the oral proceedings were that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the main request filed during the oral proceedings on 23 May 2022.

Appellant II requested in writing that the decision under appeal be set aside and that the patent be revoked in its entirety.

Reasons for the Decision

Party not attending the oral proceedings

1. Appellant II was duly summoned but did not attend the oral proceedings, as announced beforehand. The proceedings were held in the absence of this party, which was considered as relying on its written case, in accordance with Rule 115(2) EPC and Article 15(3) RPBA 2020.

Admittance into the appeal proceedings of objections under Articles 123(2), 83 and 54 EPC (Article 12(2) RPBA 2007)

2. Article 12(2) RPBA 2007 stipulates that the statement of grounds of appeal must contain an appellant's

complete case. Accordingly, it must set out clearly and concisely the reasons why it is requested that the decision under appeal be reversed.

3. Appellant II, in their submissions for Articles 83 and 54 EPC, merely referred to "*the Notice of Opposition submitted 3.5.2017 and his submissions of 14.9.2018 in response to the summons*" (see points 6 and 7 of the statement of grounds of appeal). The same applies to appellant II's submissions under Article 123(2) EPC referring to claims other than claims 1 to 7 (see point 5, last paragraph of the statement of grounds of appeal).

4. On these issues, the board agrees with appellant I that appellant II has not substantiated their case and, accordingly, the board sees no reason to consider these issues in the appeal.

Admittance of documents D21 to D25 into the appeal proceedings

5. Documents D21 to D25 were submitted with appellant II's statement of grounds of appeal. However, with the exception of document D23, no reasons were provided why these documents could not have been filed in opposition proceedings. Hence, the board maintains the view expressed in its preliminary opinion and decides to hold inadmissible documents D21, D22, D24 and D25.

6. As concerns document D23, appellant II argued, in reply to the board's preliminary opinion, that it should be admitted into the appeal proceedings because it was filed in reaction to reasoning in the decision under appeal on inventive step of the embodiment relating to SEQ ID NO:13. Although admittance of this document was contested by appellant I, no reasoning needs to be

given on this issue since, as set out below, its contents do not change the outcome of the appeal.

Main (sole) request

7. *Admittance into the appeal proceedings (Article 13(2) RPBA)*

7.1 This claim request was filed at the oral proceedings before the board. Compared to auxiliary request 1 filed with the statement of grounds of appeal, the embodiments relating to SEQ ID NOs:8, 10 and 14 have been deleted.

7.2 The deletion of the above embodiments remains within the framework of facts, evidence and arguments submitted in a timely fashion in the written proceedings. It cannot be seen as a surprising turn in appellant I's appeal case, nor does it give rise to new issues or discussions. The board considers that there is no amendment of the appeal case. In any event, taking into account that the claims according to the main request overcome all pending objections (see below), and compromise neither the procedural rights of appellant II, not procedural economy, the board considers that exceptional circumstance are present and decided to admit it into the appeal proceedings.

8. *Amendments - extension beyond the content of the application as filed (Article 123(2) EPC)*

8.1 No objections were brought forward in appeal proceedings against claim 8 in the current request or in the claim request held allowable by the opposition division. Claim 8 differs from claim 8 in the request held allowable by the opposition division on account of

the deletion of SEQ ID NOs:10 and 14. This amendment amounts to a deletion of alternatives in a way that does not introduce subject-matter not present in the claim before the amendment. Therefore, the amendment does not result in subject-matter extending beyond the content of the application as filed.

8.2 Claim 1 is drafted as a purpose-limited product claim in accordance with Article 54(5) EPC. It is directed to an antibody "*for use in the therapeutic treatment of a canine where target neutralisation is desired in the absence of undesirable complement activity*".

8.3 Claim 1 in the application as filed is the same as claim 1 of the sole request before the board, apart from the following features: (i) "where target neutralisation is desired" and (ii) "in the absence of undesirable complement activity". The application as filed discloses that certain isotypes of canine IgG immunoglobulins "*are active in terms of activating immune effector functions, while other IgG antibody isotypes do not activate immune effector functions*", and that "*heavy chain constant domains from two (calgG-B and calgG-C) of the four canine heavy chain immunoglobulins* [...] *surprisingly bind complement, whereas the other two (calG-A and calgG-D) do not*." (see paragraph bridging pages 3 and 4). The former or latter isotypes will be selected for the therapeutic use, depending on whether such use is "*for purposes where the intended target is selected for immune mediated destruction through complement mediated cytotoxicity (CDC; e.g. for killing canine tumours in vivo) or where the target is selected simply for neutralisation in the absence of undesirable immune mediated destruction* [...]" (see page 4, third paragraph). This correspondence between the properties

of the immunoglobulin in effecting (or not) complement-mediated cytotoxicity and its use in therapy with the purpose of target destruction (or neutralisation) is disclosed also on page 24, last two paragraphs. Therefore, the application as filed discloses features (i) and (ii) in combination with all the features in claim 1.

8.4 It follows from the above considerations that the requirements of Article 123(2) EPC are fulfilled.

9. *Amendments - extension of protection conferred by the patent (Article 123(3) EPC)*

9.1 Claim 1 as granted included the feature "*in the absence of undesirable effector function*". In the board's view, due to the use of the term "undesirable", the feature is to be understood as relating both to the absence of every effector function as well as the absence of only one, "undesirable", effector function.

9.2 Claim 1 of the main request before the board includes instead the feature "*in absence of undesirable complement activity*". It is thus directed to one of the alternatives already falling within the scope of claim 1 as granted, namely the one in which only one effector function was excluded.

9.3 Claim 1 further differs from claim 1 as granted on account of the deletion of SEQ ID NO:8. Claim 8 differs from claim 8 as granted on account of the deletion of SEQ ID NOs:10 and 14. These deletions result in a restriction of the scope of the claims.

9.4 In conclusion, the requirements of Article 123(3) EPC are met.

10. Inventive step (Article 56 EPC)

10.1 Claims 1 and 8 are drafted as purpose-limited product claims in accordance with Article 54(5) EPC. Claim 1 relates to a product for use in canine therapy in which "*target neutralisation is desired in the absence of undesirable complement activity*". The product is an antibody, fusion protein or binding fragment defined by a heavy chain constant domain which comprises the amino acid sequence represented by either SEQ ID NO:11 or SEQ ID NO:13, both of which minimise the activation of downstream effector functions upon binding to a target. By contrast, claim 8 relates to a product for use in canine therapy in which "*target destruction is desired*". The antibody, fusion protein or binding fragment is defined by a heavy chain constant domain which comprises the amino acid sequence represented by SEQ ID NO:9, which mediates the activation of downstream effector functions upon binding to a target. Each of these three embodiments requires a separate assessment of inventive step.

10.2 Claim 1 - SEQ ID NO:11

Closest prior art

10.2.1 According to appellant II, the disclosure in document D5 represents the closest prior art to this claimed subject-matter.

10.2.2 This document is concerned with providing constant domains of canine antibodies, such as those having the amino acid sequence of SEQ ID NO:17, and their uses in the preparation of dog-mouse chimeric antibodies for use in canine treatment. The treatment of infectious

diseases is addressed. The variable domains of the antibodies should be such that the antibodies achieve neutralisation of the virus causing the infection (see column 2, lines 59 to 63). Effector functions mediated by the antibody constant domains are not addressed.

Objective technical problem

10.2.3 The claimed subject-matter differs from the disclosure in document D5 in the purpose, i.e. therapy where target neutralisation is desired in the absence of complement activity, and in the amino acid sequence of the antibody constant domain. This has not been disputed by the parties.

10.2.4 The technical effect resulting from the first of these differences is that a treatment is provided for conditions where target neutralisation is desired in the absence of complement activity.

10.2.5 Irrespective of any technical effect that may be attributed to the difference in the amino acid sequence of the constant domain, in view of the above technical effect the objective technical problem may be formulated as the provision of further uses of antibodies of canine IgG-D subtype in canine therapy.

10.2.6 For the claim request found allowable by the opposition division, appellant II submitted the following formulation of the objective technical problem: "*the provision of an IgG-D variant for the treatment of dogs suffering from diseases where target neutralisation is desired but immune effector function is not desired*".

10.2.7 The board considers this formulation of the problem to result from an impermissible inclusion of elements of

the solution for the following reasons. The difference between the claimed subject-matter and the disclosure in document D5 lies both in the antibody and in the conditions to be treated (see point 10.2.3 above). Consequently, the problem as formulated by appellant II, by including these same conditions, i.e. "*where target neutralisation is desired but immune effector function is not desired*", partly anticipates the solution (see also decisions in Case Law of the Boards of Appeal of the European Patent Office, 9th edn. 2019, I.D.4.3.1.).

Obviousness

10.2.8 The board agrees with the opposition division that, in the absence of any mention of effector functions in the documents relied upon by appellant II in this context, the skilled person would not have arrived in an obvious way at an antibody for use in a therapy where the absence of immune effector function, complement activity in current claim 1, is desired.

10.2.9 Furthermore, SEQ ID NO:11 is not disclosed in document D5. As acknowledged by appellant II, this sequence is a variant of SEQ ID NO:17 disclosed in that document. However, starting from this disclosure and seeking to solve the posed problem, the skilled person would have had no motivation to provide a variant which does not mediate complement activity, as claimed. In other words, the solution defined by SEQ ID NO:11 is not a mere variant but has the functionality required by the claim.

10.2.10 Therefore, having regard to the cited prior art, the subject-matter of claim 1 is not obvious to a skilled person.

10.2.11 Appellant II argued that the skilled person had a reasonable expectation of providing a canine constant domain lacking immune effector function when providing a variant of SEQ ID NO:17. This line of argument is not persuasive because it exclusively addresses the obviousness of providing an immunoglobulin constant domain which does not mediate effector functions, failing to reason why the skilled person would have been prompted to provide constant domains with this characteristic. Appellant II has not pointed the board to any document prompting the skilled person to do this. Documents disclosing four canine IgG subtypes cannot be considered to provide such a prompt if they do not address the therapeutic advantage of using antibodies with constant domains that do not mediate effector functions, especially complement activity.

10.3 *Claim 1 - SEQ ID NO:13*

Closest prior art

10.3.1 Appellant II considered the disclosure in each of document D3 and document D16 to represent equivalent starting points for the assessment of inventive step of the claimed subject-matter. Indeed, it has not been argued that the relevant disclosure in these documents differs. In the following, document D16 is analysed since it was the one discussed in more detail by appellant II. The assessment below applies *mutatis mutandis* when starting from the disclosure in document D3 as the closest prior art.

10.3.2 Document D16 discloses chimeric antibodies directed among others to canine, feline and equine antigens and their uses in therapy. In one embodiment, the antibody

has a constant canine heavy chain domain having the amino acid sequence of SEQ ID No:54. Some antibodies are disclosed as mediating effector functions (document D16, paragraphs [0020] and points 1.2, 2.5 and 2.6 in pages 28 and 29).

Objective technical problem

10.3.3 The claimed subject-matter differs from the disclosure in document D16 in the purpose, i.e. therapy where target neutralisation is desired in the absence of complement activity. Furthermore, there are three amino acid differences in the antibody heavy chain constant domain. This has not been disputed by the parties.

10.3.4 The technical effect resulting from the first of these differences is that a treatment is provided for conditions where target neutralisation is desired in the absence of complement activity.

10.3.5 As to the technical effect of the three-amino-acid difference, the parties were in disagreement. Appellant I considered this to be the abrogation of immune effector function, whereas appellant II submitted that such a technical effect was attributable to only one of the amino acid differences.

10.3.6 Taking into account solely the technical effect associated with the purpose of the therapy, the objective technical problem may be formulated, in the least ambitious case, as the provision of further uses of antibodies of the canine IgG-B subtype in canine therapy.

10.3.7 For the claim request found allowable by the opposition division, Appellant II submitted a different

formulation of the objective technical problem: "*the provision of a modified canine constant region isotype with reduced effector function*".

10.3.8 As noted above for SEQ ID NO:11, the formulation of the problem should not include elements of the solution (see point 10.2.7). The difference between the claimed subject-matter and the disclosure in document D16 lies both in the antibody and in the conditions to be treated (see point 10.3.3 above). Consequently, the problem as formulated by appellant II, by including features of the antibody which are not disclosed in the closest prior art and are part of the solution claimed, i.e. "with reduced effector function", anticipates the solution (see also decisions in Case Law of the Boards of Appeal of the European Patent Office, 9th edn. 2019, I.D.4.3.1.).

Obviousness

10.3.9 In the absence of any mention of reduced effector functions in the documents relied upon by appellant II in this context, the board finds that the skilled person would not have arrived in an obvious way at an antibody for use in a therapy where the absence of complement activity is desired.

10.3.10 Furthermore, SEQ ID NO:13 is not disclosed in document D16. Instead, as acknowledged by appellant II, a variant, SEQ ID NO:54, is disclosed in that document. However, when starting from that document, the skilled person would have had no motivation to provide a variant which does not mediate effector functions. In other words, the variant defined by SEQ ID NO:13 is not a mere variant but one with the functionality required by the claim.

10.3.11 Therefore, this embodiment of claim 1 is not obvious from the cited prior art.

10.3.12 On obviousness of the claimed solution, appellant II argued that the skilled person had a reasonable expectation of providing a canine constant domain lacking immune effector function when providing a variant of SEQ ID NO:54 modified at the predicted glycosylation site. The board does not find this line of argument persuasive, the reasons provided for SEQ ID NO:11 applying equally here (see point 10.2.11). Indeed, appellant II has not pointed the board to any document prompting the skilled person to provide constant domains which do not mediate effector functions and to provide a therapy where effector function is not desired. Documents disclosing four canine IgG subtypes cannot be considered to provide such a prompt if they do not address the therapeutic advantage of using antibodies with constant domains that do not mediate effector functions.

10.4 Claim 8

10.4.1 Documents D3, D16 and D10 have been relied upon by appellant II as representing the closest prior art to this subject-matter.

Documents D3 and D16 as representing the closest prior art

10.4.2 Documents D3 and D16 were considered to represent equivalent starting points. As summarised above (see point 10.3.2), these documents disclose antibodies for use in canine therapy in which effector function is desirable. Both documents disclose a canine heavy chain constant domain having an amino acid sequence which has

99.4% shared identity with SEQ ID NO:9 (document D16, SEQ ID NO:54 and document D3, SEQ ID NO:4).

Objective technical problem

10.4.3 The amino acid sequence of SEQ ID NO:9 differs from the sequence disclosed in the prior art in that it contains tyrosine in position 259 and glutamic acid in position 327. In the decision under appeal, these were denoted as substitutions Y259F and E327K, respectively. The board adheres to this annotation.

10.4.4 No technical effect beyond that disclosed in the closest prior art has been attributed to these substitutions. Accordingly, in agreement with appellant II, the objective technical problem may be formulated as the provision of an alternative canine IgG-B constant domain that mediates the activation of downstream effector functions for use in canine therapy where target destruction is desired.

Obviousness

10.4.5 To determine whether the claimed solution was obvious, the question is whether the skilled person, in the expectation of solving the above-posed problem, would have modified the teaching in the closest prior art in light of other teachings to arrive at the claimed invention, i.e. in the case at hand, the treatment based on SEQ ID NO:9. Accordingly, what the skilled person would or would not have done depends not solely on the disclosure in the closest prior-art document but also on the state of the art in the relevant technical field.

10.4.6 In the board's judgement, the skilled person faced with the problem as stated above would be able to provide alternative amino acid sequences by applying routine experimentation. However, the board is not convinced that the skilled person would have pursued as an alternative an amino acid sequence with the substitution E327K, as claimed.

10.4.7 Document D1, which is also concerned with chimeric antibodies for use in canine therapy, aims at providing antibodies with improved Fc-receptor binding and improved effector functions (see abstract and pages 3 and 4). It discloses sequences of canine constant domains of several IgG isotypes, including a sequence of canine IgG-B isotype reported to lack antibody-dependent cellular cytotoxic activity (ADCC) (see Example 7, referring to SEQ ID NO:17, on page 44, second paragraph). It was common ground that SEQ ID NO:17 includes, as does SEQ ID NO:9 in claim 8, the amino acid glutamic acid in position 327.

10.4.8 In agreement with the opposition division, the board considers that the disclosure in document D1 of a variant constant domain of the IgG-B subtype having the E327 substitution and lacking the desired activity would demotivate the skilled person from providing a sequence with glutamic acid in this position as a solution to the problem of providing an alternative which mediates immune effector functions. Thus, the claimed solution is not obvious when starting from the disclosure of document D3 or document D16 in light of the relevant prior art.

10.4.9 Appellant II argued that document D1 cannot be considered to provide a technical prejudice against the use of the sequence SEQ ID NO:17 for mediating immune

effector functions. However, the board's finding does not rely on a technical prejudice. Instead, the relevance of document D1 is in defining which alternatives were available to the skilled person. Indeed, while the skilled person would have considered any functionally equivalent alternatives when solving the above-formulated problem, they would not have considered a sequence comprising the substitution in question since there was reason to expect it would not be functionally equivalent (see point 10.4.7 above).

10.4.10 Appellant II further submitted that in the absence of a technical effect associated with the two amino acid substitutions, as demonstrated by the experimental evidence submitted with document D23, the antibody comprising SEQ ID NO:9 did not involve an inventive step. The board points out that in formulating the objective technical problem, it did not take into account any technical effect beyond that present in the closest prior art. Therefore, the contents of document D23 cannot alter the objective technical problem as formulated above.

Document D10 as representing the closest prior art

10.4.11 Document D10 reviews the development of anti-canine monoclonal antibody MAb 231 and its use in veterinary medicine. This murine-derived antibody mediates cytotoxicity and was used to treat tumours in dogs (see Summary and page 60, left-hand column, last full paragraph). The impact of canine anti-mouse antibodies to MAb231 in the therapy is addressed. It is concluded that there were no "*clinical ill effects observed in dogs treated with murine mAb231*" (see page 60, right-hand column, last full paragraph).

10.4.12 The claimed subject-matter differs from this disclosure in the constant domains of the antibodies, which are of canine instead of murine origin.

10.4.13 The parties have adopted different formulations of the objective technical problem but in essence were in agreement as to it involving the provision of an improved treatment compared to that disclosed in document D10. In view of an expected reduction in immunogenicity when using antibodies having at least in part sequences from the same species, the board considers, in agreement with the parties, that the objective technical problem may be formulated as the provision of an improved canine therapy where target destruction is desired.

10.4.14 The proposed solution consists of using an antibody with a canine constant domain having SEQ ID NO:9.

10.4.15 The board agrees with appellant II that the use of antibodies with canine constant domains was obvious in light of the prior art. However, it remains to be assessed whether the skilled person would have provided antibodies for the claimed use which have the sequence of SEQ ID NO:9, as claimed.

10.4.16 The board is not convinced that the skilled person would have provided antibodies having constant domains of such a sequence, essentially for the same reasons as above (see points 10.4.8 and 10.4.9).

10.4.17 In one line of argument, appellant II referred to prompts in document D10 to provide antibodies with canine sequences. However, this line of argument does not address how the skilled person would have arrived at the particular sequence claimed. In a further line

of argument, the appellant referred to the sequences known from documents D16 and D3. Thus, this line of argument relies on the arguments put forward for the disclosure in documents D3 and D16 as the starting point for the assessment of inventive step. This line of argument is not persuasive for the reasons given above (see points 10.4.8 and 10.4.9).

10.5 It follows from the above considerations that the subject-matter of claims 1 and 8 of the sole request 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 with the following claims and a description and drawings to be adapted thereto:
claims 1 to 13 of the main request filed during the oral proceedings on 23 May 2022.

The Registrar: The Chairwoman:

I. Aperribay M. Pregetter

Decision electronically authenticated