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Datasheet for the decision of 23 July 2019

Case Number: T 1872/16 - 3.3.04

Application Number: 11181891.0

Publication Number: 2436697

IPC: C07K16/24, A61P37/02, A61P37/08

Language of the proceedings: EN

Title of invention:
Chimeric and humanised monoclonal antibodies against interleukin-13

Patent Proprietor:
Glaxo Group Limited

Opponents:
Leeming, John Gerard
UCB Biopharma SPRL

Headword:
IL-13 antibodies for the treatment of severe asthma/GLAXO

Relevant legal provisions:
EPC Art. 56, 83

Keyword:
Sufficiency of disclosure of further medical use - main request (no) - auxiliary requests 1, 2, 4, 5 (no)
Inventive step - auxiliary request 3 (no)

Decisions cited:
T 0609/02, T 0895/13, T 0219/01

Catchword:

Europäisches Patentamt
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Beschwerdekammern

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Case Number: T 1872/16 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 23 July 2019

Appellant: (Patent Proprietor)	Glaxo Group Limited 980 Great West Road Brentford, Middlesex TW8 9GS (GB)
Representative:	Chiappinelli, Susan Ann GlaxoSmithKline Global Patents (CN925.1) 980 Great West Road Brentford, Middlesex TW8 9GS (GB)
Respondent I: (Opponent 1)	Leeming, John Gerard J.A. Kemp & Co. 14 South Square Gray's Inn London WC1R 5JJ (GB)
Respondent II: (Opponent 2)	UCB Biopharma SPRL IP Department 60, Allée de la Recherche 1070 Brussels (BE)
Representative:	J A Kemp 14 South Square Gray's Inn London WC1R 5JJ (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 16 June 2016 revoking European patent No. 2436697 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairwoman	G. Alt
Members:	D. Luis Alves
	L. Bühler

Summary of Facts and Submissions

I. The appeal by the patent proprietor (appellant) concerns the decision of the opposition division to revoke European patent No. 2 436 697, entitled "*Chimeric and humanised monoclonal antibodies against interleukin-13*".

II. Two oppositions had been filed. The patent had been opposed as a whole under Article 100(a) EPC on the grounds of lack of novelty and lack of inventive step, and under Article 100(b) and (c) EPC.

III. The decision under appeal dealt with a main claim request (claims as granted) and four auxiliary claim requests (all filed by letter dated 31 March 2016). The opposition division held *inter alia* that none of the claim requests complied with the requirements of Article 56 EPC.

IV. The appellant based its appeal on a main claim request and five auxiliary claim requests. The main claim request and auxiliary claim requests 1, 2, 4 and 5 correspond, respectively, to the main request and auxiliary requests 1 to 4 considered in the decision under appeal. Auxiliary claim request 3 was newly filed with the statement of grounds of appeal, with which the appellant further submitted documents D28 to D35 and arguments. By letter dated 3 July 2017 the appellant submitted document D32a and further arguments.

V. Both opponents (respondent I and respondent II) replied to the statement of grounds of appeal. Respondent I also replied to the board's communication (see below).

VI. The board sent a summons to oral proceedings accompanied by a communication pursuant to Article 15(1) RPBA, in which the board set out its preliminary view on the issues of clarity, claim interpretation, inventive step and sufficiency of disclosure. In particular the communication indicated that, with respect to the subject-matter of claim 1, drafted as a purpose-limited product claim, the board intended to discuss the issue of plausibility of attaining the therapeutic effect as stated in the claim under the requirements of Article 83 EPC.

VII. Oral proceedings were held as scheduled. The appellant did not attend, as announced beforehand.

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

VIII. Claim 1 of the **main request** reads:

"1. A therapeutic antibody or antigen binding fragment thereof which specifically binds the epitope set forth in SEQ ID NO: 84 of SEQ ID NO: 9 and modulates the interaction between hIL-13 and hIL-13R for use in the treatment of a disease or disorder selected from the group consisting of: severe asthma, difficult asthma and idiopathic pulmonary fibrosis."

Claim 1 of **auxiliary request 1** differs from claim 1 of the main request in that it additionally contains the wording:

"wherein when the disease or disorder is severe asthma or difficult asthma, the therapeutic antibody is not

BAK502G9 with a heavy chain having the sequence set out in SEQ ID NO: 111 of W02005/007699 and with a light chain having the sequence set out in SEQ ID NO: 112 of W02005/007699."

Claim 1 of **auxiliary request 2** is directed to an antibody per se, the definition of the antibody differing from that in the main request as shown in the following by the underlined wording. Independent claims 1 and 6 of auxiliary request 2 read as follows:

"1. A therapeutic antibody or antigen binding fragment thereof which specifically binds the epitope set forth in SEQ.I.D. NO:84 of SEQ. I.D. No:9 between residues 103 and 107 inclusively and modulates the interaction between hIL-13 and hIL-13R.

6. A therapeutic antibody or antigen binding fragment thereof according to any one of claims 1 to 4 for use in the treatment of a disease or disorder selected from the group consisting of: Allergic asthma, severe asthma, difficult asthma, brittle asthma, nocturnal asthma, premenstrual asthma, steroid resistant asthma, steroid dependent asthma, aspirin induced asthma, adult-onset asthma, paediatric asthma, atopic dermatitis, allergic rhinitis, Crohn's disease, COPD, fibrotic diseases or disorders such as idiopathic pulmonary fibrosis, progressive systemic sclerosis, hepatic fibrosis, hepatic granulomas, schistosomiasis, leishmaniasis, disease of cell cycle regulation such as Hodgkins disease, B cell chronic lymphocytic leukaemia."

Claim 1 of **auxiliary request 3** is identical to that of auxiliary request 2. However auxiliary request 3 does

not contain any purpose-limited antibody claim, such as claim 6 of auxiliary request 2.

Claim 1 of **auxiliary request 4** and claim 1 of **auxiliary request 5** differ from claim 1 of the main request and auxiliary request 1, respectively, in that they no longer contain the wording:

"or an antigen binding fragment thereof".

IX. The following documents are referred to in the present decision:

D6: WO 2005/007699 A2 (27 January 2005)

D8: Thompson and Debinski, The Journal of Biological Chemistry, 1999, vol. 274, No. 42, 29944-29950.

D9: Madhankumar *et al.*, The Journal of Biological Chemistry, 2002, vol. 277, No. 45, 43194-43205.

D18: https://clinicaltrials.gov/ct2/show/NCT01402986?term=Tralokinumab&rank=4
Clinical trial to evaluate the efficacy of Tralokinumab in adults with uncontrolled, severe asthma.

D23: De Boever *et al.*, J Allergy Clin Immunol, 2014, vol. 133, Issue 4, 898-996 and 996.e1-e4.

D28: Spahn *et al.*, J Allergy Clin Immunol., 1995, 95(1) part 2, abstract 979.

D29: Lukacs *et a*l., J Immunol., 2001, 167: 1060-1065.

D30: Kibe *et al.*, Am J Respir Crit Care Med, 2003, 167: 50-56.

D31: Puddicombel *et al.*, 100th International Conference of the American Thoracic Society, 2004, abstract 2165.

D32: Naseer *et al.*, Am J Respir Crit Care Med, 1997, 135: 845-851.

D32a: List of scientific articles citing D32, as printed on 26 June 2017.

D33: Redacted investigator's brochure for GSK679586A dated 31 July 2006.

D34: Redacted PowerPoint presentation entitled "Alternative indications for Anti-IL-13 Monoclonal Antibody: Idiopathic Pulmonary Fibrosis" dated 7 July 2005.

D35: Fichtner-Feigl *et al.*, Nature Medicine, 2006, 12(2): 99-106 (published online 4 December 2005).

X. The appellant's arguments submitted in writing, in so far as relevant to this decision, may be summarised as follows:

Main request, auxiliary requests 1, 2, 4 and 5 - claim 1
Auxiliary request 3 - claim 6

Sufficiency of disclosure

(a) When examining the requirements of Article 56 EPC, the opposition division had found that, taking into account the teaching in the prior art, the teaching in the patent did not make it plausible that the

antibodies as defined in claim 1 would be suitable as a treatment for the specific medical indications listed in the claim. This question of plausibility should be assessed under the requirements of Article 83 EPC.

(b) According to the case law, clinical trial data was not required to demonstrate the plausibility of a given effect. Also according to the case law, what was required was that the patent contained information establishing a link between the antibody and its target and a link between the target and the medical condition. In the case at hand, the first link was provided in the application, which showed four antibodies falling within the scope of claim 1 that bound to and neutralised IL-13. The second link was provided in the application, in respect of generic asthma conditions, and further provided by documents D28 to D32, all published before the priority date, in respect of the specific conditions severe asthma and difficult asthma. Despite document D33 being dated later than the filing date of the application and not being publicly available on that date, it supported the plausibility of the treatment.

(c) Contrary to respondent I's argument, documents D28 to D33 could be taken into account as evidence of the link between the target and the medical conditions. Reference was made to decision T 734/12, which stated "*It follows from this that either the application must provide suitable evidence for the claimed therapeutic effect or it must be derivable from the prior art.*"

Contrary to respondent II's argument, the link could be established by taking several prior art documents together; there was no basis in the case law for requiring such a link to be established in a single document.

(d) Plausibility should be assessed at the effective date. As a consequence, document D23, which was a post-published clinical trial, could not be used to deny plausibility, otherwise plausibility would change over time, which would be detrimental to legal certainty.

(e) There might be several reasons for the results reported in document D23.

This document noted an inadequate dosing regimen as a possible reason for lack of efficacy (page 994, first full paragraph).

Furthermore, there were several approved drugs which failed to meet their primary end point in at least one clinical trial.

Therefore, the results presented in document D23 did not make it possible to conclude that, if appropriately administered, the antibody would not treat severe asthma.

Other IL-13 antibodies were currently undergoing clinical trials, as exemplified by document D18. This showed that the scientific community had not concluded from document D23 that IL-13 neutralisation was not a promising approach to treating asthma. Even if it were concluded that the antibody tested in document D23 did not treat

severe asthma, this could be considered an isolated failure. The fact that other antibodies falling within the scope of the claim were being studied for the same purpose rather supported this argument.

Auxiliary request 3 - claim 1

Claim construction

(f) Binding outside of residues 103 to 107 was not excluded provided that the core region for binding resided between those residues. Thus, claim 1 encompassed antibodies having the feature that "*the key residues required for binding fall between residues 103 and 107 inclusively, but may differ in which residues are essential*" (see letter dated 3 July 2017, paragraph spanning pages 17 and 18).

Inventive step

(g) Document D6 represented the closest prior art and the objective technical problem could be considered to be the provision of an alternative antibody capable of neutralising hIL-13R. The opposition division considered that the skilled person would arrive at the claimed antibody because they would have modified the epitope to a certain degree but would not have modified the amino acid residues at positions 103 and 107.

Document D6 disclosed an antibody, BAK502G9, which was able to neutralise its target IL-13 and had desirable cross-reactivity, both of which are dependent on the epitope to which the antibody

binds. In view of these advantageous properties the skilled person would not have modified the epitope to which BAK502G9 bound.

(h) The opposition division gave no reason as to why the skilled person would have modified the epitope but would have retained the amino acids in positions 103 and 107. This selection seems to have been made with hindsight because document D6 ranked these residues as being of the same importance as residues 116 and 117 (corresponding to residues 96 and 97 in the patent in suit, respectively). Moreover, this did not reflect how antibodies were developed, which typically involved a selection for functional properties rather than for the epitope.

(i) If the skilled person had nevertheless considered modifying the epitope, they would have preserved not only the positions 103 and 107, but positions 96 and 97 too. In doing so, the skilled person would have arrived at an antibody falling outside the scope of claim 1.

(j) Even if the skilled person had considered changing the epitope altogether, they would have selected an epitope far away from that of the antibody disclosed in document D6, for the following reasons. The skilled person would have known from each of documents D6, D8 and D9 that hIL-13Rα**2** was thought to be a decoy, i.e. non-functional, receptor (document D6, page 2, line 30; document D8, page 29944, column 2, lines 15 to 19; document D9, abstract, lines 7 to 8). It was also known from document D6 that soluble IL-13Rα**2** had been used to antagonise IL-13. The skilled person knew from document D9 that the residues 103, 104 and 107 were

involved in binding with IL-13Rα**2** (numbering as in the patent; in document D9 numbered 105, 106 and 109, respectively). With this in mind, to maximise IL-13 blockade, the skilled person would not have interfered with this interaction. They would rather have looked for an epitope distant from this one, selecting one that prevented the interaction between IL-13 and the functional receptor, IL-13Rα**1**. Documents D8 and D9 each identified residues involved in the interaction with IL-13Rα**1**.

(k) Document D6 did not identify which residues were critical for the neutralisation function of the antibody, so it could not have been predicted that the antibodies as claimed would have the desired function.

XI. Respondent I's arguments, submitted in writing and at the oral proceedings, in so far as relevant to this decision, may be summarised as follows:

Main request, auxiliary requests 1, 2, 4 and 5 - claim 1
Auxiliary request 3 - claim 6

Sufficiency of disclosure

(a) If severe asthma and difficult asthma were considered as specific medical conditions different from the generic condition asthma, it followed that the information required to demonstrate the plausibility of the treatment had to be specific to those medical conditions.

Thus, the patent should provide information supporting the effect of treating severe asthma.

However, the patent did not contain any such information.

Information contained in other documents could not resolve this as it did not change the content of the patent.

(b) Document D33 was published after the effective date of the patent and was not publicly available on that date. Documents D28 to D33 did not demonstrate the plausibility of treating the specific conditions severe asthma and difficult asthma with IL-13 antibodies.

(c) Moreover, in the post-published document D23 it was concluded that the antibody did not result in any improvement of the medical condition severe asthma (abstract, right-hand column).

(d) In the context of Article 83 EPC, an opponent should provide verifiable facts. The evidence an opponent could provide could inevitably only be filed after the effective date of the patent. Such verifiable facts had been provided in the form of document D23 and it was now down to the appellant to address these.

(e) The antibody in document D23 was the same as in the application. The argument that other antibodies falling within the scope of the claim were considered promising and were undergoing clinical trials was not persuasive because the antibodies to which reference was made did not bind to the same epitope, following the appellant's interpretation of the claim. Furthermore, document D23 was

published later than the clinical study disclosed in document D18.

In view of the teaching in document D23, the skilled person relying on the concept of IL-13 neutralisation for the treatment of asthma would have no reason to provide further antibodies binding to the epitope to which the one used in the study disclosed in document D23 bound, i.e. an epitope as defined in claim 1. They would instead provide other IL-13 antibodies for the medical use.

Auxiliary request 3 - claim 1

Claim construction

(f) From the description, in particular the peptide mapping, it was apparent that the claim was not intended to be limited to antibodies binding to the sequence of amino acids 103 to 107 only and to exclude antibodies binding to longer peptides incorporating this sequence. According to the claim wording the antibodies bound within the core region SEQ ID NO 84, but could bind additionally outside this region.

Inventive step

(g) Starting from document D6 as the closest prior art, and faced with the problem of providing an alternative antibody that can be used for neutralising IL-13, the solution provided in the patent did not involve an inventive step because it was a mere alternative to that identified in document D6.

The appellant had not identified any technical effect associated with what the appellant alleged to be a different epitope. No advantageous properties had been identified for antibodies binding to the epitope in the claim over the antibodies disclosed in document D6.

(h) It was evident that in order to provide alternative antibodies to those of the closest prior art the skilled person would use full-length IL-13 or IL-13 peptides for immunisation. If the prior art identified some residues as being critical, as was the case here, the skilled person would be motivated to identify antibodies binding to those residues. Contrary to the appellant's argument, the skilled person had a reason to retain particular residues (103 and 107 in the case at hand) because the prior art identified them as being critical.

XII. Respondent II's arguments, submitted in writing and at the oral proceedings, in so far as relevant to this decision, may be summarised as follows:

Main request, auxiliary requests 1, 2, 4 and 5 - claim 1
Auxiliary request 3 - claim 6

Sufficiency of disclosure

(a) The claims related to the forms of asthma that were the most difficult to treat. The patent did not contain data relating to the treatment of any medical conditions, let alone those referred to in the claim.

(b) Documents D28 to D33 submitted by the appellant did not provide any such evidence, i.e. they did not show any link between IL-13 neutralisation and the specific medical conditions.

(c) The conclusions in document D23 lead to a lack of plausibility for the use of the antibodies in the treatment of severe asthma (document D23, abstract and "Discussion").

(d) No IL-13 antibody was currently being trialled for the treatment of asthma.

(e) The legal test to be applied for sufficiency of disclosure made use of the concept of plausibility in cases in which the patent contained some data and where there was the question of whether or not the effect was rendered plausible. In the case at hand, however, no plausibility was provided on the basis of the patent since it did not contain any data on treatment whatsoever. Thus the skilled person could not carry out the invention, i.e. could not treat patients with severe asthma.

Auxiliary request 3 - Claim 1

Claim construction

(f) Claim 1 as drafted was not limited to antibodies binding only within SEQ ID NO 84.

Inventive step

(g) Document D6 could be taken to represent the closest prior art. It disclosed antibodies binding both

within and beyond SEQ ID NO 84 and disclosed that the residues 103 and 107 were important for binding.

To the extent that a difference could be identified between the epitope in claim 1 and that identified in document D6, the technical effect of the difference seemed to be identical to that achieved in document D6, which already disclosed the use of the antibodies in the treatment of asthma. This document disclosed that specific residues within the claimed binding region of SEQ ID NO 84 were important for modulating the interaction of hIL-13 with hIL-13R. On the other hand, the antibodies claimed in the patent did not show any unexpected properties. Thus, any difference between the claimed antibodies and those in the closest prior art was merely an arbitrary selection without technical effect.

(h) The appellant's argument that the skilled person would not have been motivated to provide antibodies binding to the two residues 103 and 107 in view of two other residues that are identified as being potentially important for binding is not supported by the disclosure of document D6 (page 106, lines 18 to 32). The role of residues 103 and 107 in binding was confirmed by mutational analysis and their importance was not diminished by there being two other residues that were potentially important for binding.

(i) Documents D8 and D9, referred to by the appellant, did not relate to hIL-13 antibodies or to their use in the treatment of disorders.

XIII. The appellant requested in writing that the decision under appeal be set aside and that the patent be maintained on the basis of the claims of the main request filed by letter dated 31 March 2016, or, alternatively, on the basis of the claims of one of auxiliary requests 1 and 2 filed by letter dated 31 March 2016 as auxiliary requests 1A and 2, respectively, and auxiliary requests 3 to 5 filed with the statement of grounds of appeal. The appellant furthermore requested that documents D28 to D35 be admitted into the appeal proceedings.

The respondents requested that the appeal be dismissed. Respondent I further requested that documents D28 to D35 not be admitted into the appeal proceedings.

Reasons for the Decision

1. The duly summoned appellant was not present or represented at the oral proceedings. The board decided to continue the proceedings without the appellant in accordance with Rule 115(2) EPC and treated the appellant as relying on its written case in accordance with Article 15(3) RPBA.

2. No decision needed to be taken as concerns the admissibility of documents D28 to D35, as these did not play a role in the board's decision.

Main request - claim 1

Sufficiency of disclosure - Articles 100(b) and 83 EPC

3. Claim 1 is drafted in the form of a purpose-limited product claim, pursuant to Article 54(5) EPC, and is directed to an IL-13-binding antibody for use in the treatment of severe asthma, difficult asthma and idiopathic pulmonary fibrosis (for the exact claim wording please refer to point VIII. above).

4. In the case law of the boards of appeal of the EPO, where a therapeutic application is claimed in the form according to Article 54(5) EPC, attaining the claimed therapeutic effect is a functional technical feature of the claim. As a consequence, in order to fulfil the requirements of Article 83 EPC, the suitability of the product for the claimed therapeutic application must be derivable from the application, unless this is already known to the skilled person at the priority date (see T 609/02, point 9 of the Reasons and T 895/13, points 3 to 5 of the Reasons).

Thus, in the light of the respondents' arguments, in the case at hand the suitability of an IL-13 antibody as defined in the claim for the treatment of severe asthma, difficult asthma and idiopathic pulmonary fibrosis must be assessed.

This assessment is to be made in the context of the requirement of sufficiency of disclosure. This was not disputed by the parties.

The disclosure in the patent in suit

5. The application does not contain any experiments testing the suitability of the antibodies as defined in the claim for the treatment of any disease. This is not disputed by the parties.

6. As concerns the treatment of severe asthma and difficult asthma, the appellant submitted that, by reference to prior art publications, the application discussed the link between generic asthma and IL-13 as the therapeutic target. Although it did not disclose such a link in respect of the specific conditions severe asthma and difficult asthma, this link was to be found in other publications, as represented by documents D28 to D32 filed with the statement of grounds of appeal, in addition to document D19, which was already part of the opposition proceedings, and the internal and later document D33.

7. It is therefore undisputed that the application does not disclose a link between IL-13 and the specific forms of asthma recited in the claim.

The disclosure in document D23

8. The respondents referred to document D23 to call into question the suitability of the antibodies defined in claim 1 for the treatment of severe asthma.

9. Document D23 reports the results of a clinical trial of IL-13 antibody GSK679586 for severe asthma. It was undisputed that the antibody studied in this clinical trial fell within the scope of claim 1 of the patent in suit.

10. Document D23 was published in 2014, i.e. after the filing date of the application.

10.1 The appellant contested that respondents-opponents could use post-published documents to deny the suitability of a claimed compound for a claimed therapeutic application, submitting that only documents available at the effective date of the patent could be taken into account. Otherwise, the result of the assessment could change over time, which would be detrimental to legal certainty.

This argument was not further substantiated, for example by reference to case law illustrating the appellant's point of view.

10.2 The standard established in the case law of the boards of appeal of the EPO as to what is necessary for an opponent's objection of lack of sufficiency of disclosure to succeed is that serious doubts must be substantiated by verifiable facts. The board considers that opponents are free to use whatever evidence they choose to substantiate the serious doubts. This also applies to the date on which the evidence was generated.

Indeed, a third party is not in a position to dispute the sufficiency of disclosure of claimed subject-matter until after the application has been published. Depending on the circumstances this might, for example, require re-working of the experiments carried out in the patent, i.e. there might be cases where the serious doubts can only be properly substantiated by facts which were obtained after the effective date of the patent. Not allowing those facts would in practice

prevent a third party from making use of the possibility foreseen in Article 100(b) EPC.

10.3 The case underlying decision T 219/01 is an example where, in relation to a medical use claim, there was a finding of a lack of sufficient disclosure on the basis of results from a post-published clinical trial.

10.4 Hence, the respondents can base their arguments on document D23.

11. The clinical trial disclosed in document D23 compared patients receiving the standard treatment for severe asthma with those additionally receiving the IL-13 antibody. The primary end point was the score in the symptom questionnaire. Secondary end points included pulmonary function and number of asthma exacerbations (abstract and page 990, right-hand column, second full paragraph).

The authors of document D23 concluded that "*[...] GSK679586 did not demonstrate clinically meaningful improvements in asthma control, pulmonary function or exacerbations in patients with severe asthma*" (abstract and page 993, last paragraph). No evidence of other significant treatment effects was observed (paragraph spanning the two columns on page 992).

12. The appellant contested that the contents of document D23 were conclusive as to the antibody's unsuitability for the claimed therapeutic application.

12.1 Specifically, as a first argument, it submitted that the lack of efficacy reported in document D23 could have several explanations, such as an inadequate dosing

regimen, as noted in the document itself on page 994, first full paragraph.

The board does not find this argument persuasive because the authors of this document do not seem to adopt that explanation. Instead, after having included it in a list of possible explanations, the authors distance themselves from it. The authors firstly note that the results obtained by them are in contrast to those reported by others, which showed an improvement, albeit with other IL-13-targeting agents and in patients with less severe disease (last full sentence on page 993). Four possible explanations are then listed, including the inadequate dosing regimen (page 994, first full paragraph). As regards this possible explanation the authors state that "*Suboptimal drug potency or an inadequate dosing regimen could be postulated for the lack of efficacy observed in this study ... Given the large intravenous GSK679586 dose (10 mg/kg) used, it would be unlikely that local drug exposures were inadequate to provide sufficient target coverage in the airways ... However, another explanation could be differences in antibody affinity of the various molecules used in clinical studies, and it is possible that the potency of GSK679586 contributed to the lack of efficacy. Indeed ...*" (page 994, second full paragraph, emphasis added by the board).

Elaborating further on possible explanations for the contrasting results with respect to others' studies, it is stated that "*The composition of the study population is a key difference between the current study and other trials of anti-IL-13- or anti-IL-13/IL-4-targeting therapies. Previous studies were conducted primarily in patients with moderate-to-severe asthma* [...] *However,*

our study included only patients with severe asthma who remained symptomatic despite receiving at least 1000 mg/d FPE [fluticasone propionate or equivalent; a corticosteroid drug] [...] *analysis of patients with detectable serum IL-13 levels showed no improvement in efficacy in this subset. Thus, the remaining symptoms, lung function changes, and perhaps exacerbations might not be driven by IL-13 in this severe population.*" (paragraph spanning the columns on page 994, emphasis added by the board).

Thus, the board construes this to mean that, after considering the dosing regimen as a possible explanation, the authors of document D23 disregarded it and questioned the approach of targeting IL-13 in a patient population with severe asthma as well as the adequacy of the specific antibody used.

12.2 As a second argument, the appellant submitted that document D23 had not called into question the concept of IL-13 as a therapeutic target in severe asthma, as evidenced by other IL-13 antibodies currently under development for the same purpose. Document D18 was referred to in this respect.

The board is not persuaded by this argument, instead finding the respondents' arguments convincing. As submitted by the respondents, it is not apparent – and has not been demonstrated – that other IL-13 antibodies generally mentioned by the appellant, and specifically that of document D18, would in fact fall within the scope of claim 1. Respondent I further submitted that if the skilled person were to base the therapy on the concept of IL-13 neutralisation, they would use different antibodies instead.

In this respect, it must also be kept in mind that document D23 suggests differences in antibody affinity as a possible explanation for the observed lack of efficacy.

12.3 Finally, the appellant submitted that the antibody GSK679586 would at most be considered an isolated failure. The board understands the argument to be that, on the basis of the disclosure of the application and also taking account of document D23, the skilled person would understand that other antibodies falling within the scope of the claim achieve the effect of treating severe asthma.

In the present circumstances, however, with the patent not containing any examples of antibodies which have been shown to be suitable for treating severe asthma, the board's view is that it is sufficient for the respondents to show one embodiment which is not suitable.

13. Thus, contrary to the appellant's reasoning, the board is convinced that on the basis of document D23 the skilled person would have had serious doubts that the antibody GSK679586 would be suitable for treating severe asthma.

The disclosure in documents D19 and D28 to D33

14. The appellant submitted that documents D19 and D28 to D33 made plausible the therapeutic application of IL-13 antibodies as defined in claim 1 in the treatment of severe asthma.

However, in view of the fact that none of these documents concerns testing of an IL-13 antibody falling within the scope of the claim, the appellant's argument does not persuade the board.

15. On weighing the evidence before it, i.e. the disclosure in the application, in documents D19, D28 to D33 and document D23, the board comes to the conclusion that, by referring to the disclosure in document D23, the respondents have established that an IL-13 antibody falling under the definition in claim 1 is not suitable for the treatment of a disease referred to in claim 1.

Neither the patent application nor the prior art provided the skilled person with teaching enabling them to provide antibodies that fall within the scope of the claim and achieve the effect of treating severe asthma.

16. Thus, the board comes to the conclusion that the application did not disclose the claimed subject-matter in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. The requirements of Article 83 EPC are not met.

Auxiliary requests 1, 2, 4 and 5

Sufficiency of disclosure - Article 83 EPC

17. As stated for claim 1 of the main request, claim 1 of auxiliary requests 1, 4 and 5 is also drafted in the form of a purpose-limited product claim, pursuant to Article 54(5) EPC, and is directed to an IL-13-binding antibody for use in the treatment of severe asthma, difficult asthma and idiopathic pulmonary fibrosis (for the claim wording see point VIII. above).

As regards auxiliary request 2, the same drafting form is found in claim 6, which is directed to an IL-13-binding antibody for use *inter alia* in the treatment of the medical conditions above.

Therefore, the above conclusion with regard to sufficiency of disclosure applies equally, and auxiliary requests 1, 2, 4 and 5 do not meet the requirements of Article 83 EPC.

Auxiliary request 3

18. Claim 1 of auxiliary request 3 is directed to an antibody, or antigen-binding fragment thereof, defined by two characteristics: (i) the epitope it binds to on hIL-13 and (ii) the ability to modulate the interaction between hIL-13 and its receptor. The epitope is defined as follows: "epitope set forth in SEQ.I.D. NO:84 of SEQ. I.D. No:9 between residues 103 and 107 inclusively".

19. This claim is identical to claim 1 of auxiliary request 2 before the opposition division. In the decision under appeal the opposition division held that this subject-matter did not involve an inventive step having regard to the prior art disclosed in document D6.

This finding is contested by the appellant.

20. There was disagreement between the parties as to the correct claim interpretation, with the parties disputing whether the antibodies disclosed in document D6 fell within the scope of the claim. These questions, however, need not be answered in this decision since,

for the reasons set out below, this request could not be allowed even if the claim were construed as proposed by the appellant.

Inventive step - Article 56 EPC

Closest prior art

21. All parties considered that document D6 could represent the closest prior art.

22. When reading document D6, it should be borne in mind that any reference made to residues 123 and 127, and to 116 and 117, corresponds to residues 103 and 107, and 96 and 97, respectively, in the numbering used in the patent in suit.

Document D6 relates to the preparation of antibodies to hIL-13 that neutralise IL-13 activity, and to their use to treat IL-13-related diseases such as asthma and fibrosis (see first paragraph). A preferred antibody is BAK502G9 (see second paragraph and page 26, fourth paragraph). The effects of IL-13 involve its interaction with a receptor system that includes at least IL-4Rα, IL-13Rα1 and IL-13Rα2. Although IL-13Rα2 shows high affinity for IL-13, cells expressing it are not responsive to the ligand, so it is considered to be a decoy receptor (see page 2, line 30).

The document discloses results of IL-13 neutralisation assays carried out with several antibodies, including the preferred antibody BAK502G9. Experiments to test the neutralising effects of the antibody include testing in mice the efficacy of the antibody on an

asthmatic phenotype that develops when hIL-13 is administered to the lung (example 24).

Epitope mapping of the antibody was carried out involving two sets of experiments (see example 29). From a first set, to identify generally the location of the epitope, the results were reported as follows: "[...] *indicating that helixD within the IL-13 molecule was involved with BAK502G9 epitope binding [...] indicating potential involvement of helixA in the recognition of BAK502G9*" (example 29, page 106, lines 1 to 6).

From a second set of experiments, used for fine-mapping of the epitope within helixD, the results were reported as follows: "*Results show that chimeric constructs 116117TK (where lysine at position 116 was replaced with threonine and the aspartate at position 117 was replaced with lysine), 123KA (where lysine at position 123 was replaced) and 127RA (where arginine at position 127 was replaced) are least able to compete for binding to BAK502G9 (123KA and 127RA do not compete at 1 uM). Other residues implicated in binding to BAK502G9 due to their reduced effectiveness in the competition assay include the helixD residues 124Q (here lysine has been replaced with glutamine) and 120121SY (a leucine histidine pair has been changed to a serine tyrosine pair). Mutation of leucine at position 58L also reduces binding and analysis of the 3D structures revealed that this residue packs against helixD and may either be directly contacted by BAK502G9 or may affect the alignment of helixD. <u>These experiments demonstrate that residues within helixD are critical for the binding of BAK502G9 to IL-13. In particular the lysine at position 123 and the arginine at position 127 are critical for</u>*

this binding as mutation to either abolishes binding of BAK502G9" (emphasis by the board).

A different experimental approach was used to confirm the location of the epitope (see "Epitope Excision", page 107), and from the results it is concluded that "*The experimental sequence as a whole has identified that part of the BAK502G9 epitope on human IL-13 as lying within the twenty-seven C-terminal amino acid residues. These findings corroborate the finding of the molecular approach detailed above.*"

Problem to be solved

23. Despite disagreeing on the interpretation of the claim, the parties were in agreement on the definition of the objective technical problem addressed, namely the provision of an alternative IL-13-neutralising antibody to the antibody disclosed in document D6. This is the case because all parties recognised that, irrespective of which distinguishing features they identified, those features did not bring about any technical effects not already provided by the antibody disclosed in the closest prior art.

Obviousness

24. The question to be addressed in the context of inventive step is then what the skilled person would have done when faced with the problem of providing an alternative IL-13-neutralising antibody.

25. In the board's view, the skilled person would first and foremost have sought to provide an antibody that maintains binding to IL-13. According to document D6, essential residues without which binding is abolished

are those in positions 103 and 107. The skilled person would thus have provided an antibody that ensured binding to these residues. Thus, the skilled person would have provided an antibody which, according to the appellant's proposed claim interpretation (see point X(f)), falls within the definition of claim 1.

26. The appellant submitted that the skilled person would not have considered modifying the epitope, the reason being that the antibody BAK502G9 bound to and neutralised IL-13 and had desirable cross-reactivity.

This argument is not found convincing, as providing an alternative antibody is the problem the skilled person set out to solve.

27. The appellant also reasoned that, when considering modifying the epitope, the skilled person would have also maintained the residues 116 and 117, in addition to 123 and 127 (numbering as in document D6). The resulting antibody would fall outside the scope of claim 1.

As analysed above, the board finds that document D6 identifies the residues in positions 123 and 127, which correspond to positions 103 and 107, respectively, in present claim 1, as being critical for binding. Thus, what claim 1 identifies as the critical region for antibody binding is already identified as being critical in document D6.

The board does not concur with the appellant's interpretation of document D6 as concerns the disclosure of the critical residues. As analysed above, although residues 116, 117, 123 and 127 are identified as affecting the binding, as well as 120, 121 and 124

to a lesser degree, in document D6 the conclusion of the fine-mapping of the epitope is nevertheless that "*These experiments demonstrate that residues within helixD are critical for the binding of BAK502G9 to IL-13. In particular the lysine at position 123 and the arginine at position 127 are critical for this binding as mutation to either abolishes binding of BAK502G9.*"

28. The appellant further reasoned that document D6 did not teach that residues 103 and 107 were critical for the antibody's neutralisation function. As a consequence, it would not have been predictable which antibodies would have the desired neutralisation function.

In the board's view, the skilled person starting from the teaching in document D6 and faced with the problem of providing an alternative antibody likewise had no reason to assume that maintaining the binding to the critical residues would affect neutralisation of the target.

Thus, this argument is not found convincing.

29. Lastly, the appellant reasoned that, were the skilled person to consider modifying the epitope, they would instead provide an antibody binding to IL-13 at an epitope far away from the epitope for BAK502G9. Its reasoning was that the skilled person would have considered IL-13Rα2 to be a decoy receptor, in view of the disclosures in documents D6, D8 and D9, and would therefore have opted not to interfere with this interaction. With a view to increasing IL-13 neutralisation, the skilled person would instead provide an antibody that interferes with IL-13 binding to the receptor at IL-13Rα1. The skilled person would

know from document D9 that the residues 103 and 107 were involved in the binding of the IL-13Rα2.

This line of reasoning seems to assume that the skilled person would seek to improve the neutralisation of IL-13. In view of the effects associated with the antibody as claimed, however, this is not the task the skilled person was faced with, as discussed above under point 23. It is therefore immaterial for this analysis whether the skilled person considered the receptor subunit to be a decoy or functional one, since document D6, which, as stated by the appellant, already provided this information about the receptor, did not express any concerns as to this being a disadvantage for achieving IL-13 neutralisation. Moreover the experiments carried out in this document demonstrated IL-13 neutralisation by the antibody.

30. In light of all the above, the board comes to the conclusion that the subject-matter of claim 1 of auxiliary request 3 does not involve an inventive step and thus is not in compliance with the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chair:

I. Aperribay G. Alt

Decision electronically authenticated