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Datasheet for the decision of 26 February 2021

Case Number: T 0707/18 - 3.3.04

Application Number: 07802348.8

Publication Number: 2066352

IPC: A61K39/395, C07K16/28, A61P25/00

Language of the proceedings: EN

Title of invention:
Treatment of multiple sclerosis (MS) with Campath-1H

Patent Proprietors:
Alcafleu Management GmbH & Co. KG
Genzyme Corporation

Opponent:
Furo Ventures B.V.

Headword:
Campath-1H/ALCAFLEU

Relevant legal provisions:
EPC Art. 83, 100(b), 111(1)
RPBA 2020 Art. 11

Keyword:
Sufficiency of disclosure - main request (yes)
Remittal - special reasons for remittal

Decisions cited:
T 0609/02

Catchword:
-

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Case Number: T 0707/18 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 26 February 2021

Appellants: (Patent Proprietors)	Alcafleu Management GmbH & Co. KG Lilienthalstrasse 4 12529 Schönefeld OT Waltersdorf (DE)
	Genzyme Corporation 50 Binney Street Cambridge, MA 02142 (US)
Representative:	Mathys & Squire The Shard 32 London Bridge Street London SE1 9SG (GB)
Respondent: (Opponent)	Furo Ventures B.V. Willemsplein 2 5211 AK s'Hertogenbosch (NL)
Representative:	Breuer, Markus Brienner Straße 1 80333 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 8 January 2018 revoking European patent No. 2 066 352 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	B. Claes
Members:	D. Luis Alves
	M. Blasi

Summary of Facts and Submissions

I. The patent proprietors (appellants) filed an appeal against the decision of the opposition division to revoke European patent No. 2 066 352, entitled "*Treatment of multiple sclerosis (MS) with Campath-1H*".

II. The patent had been opposed on the grounds in Article 100(a) EPC, in this case lack of inventive step (Article 56 EPC), and Article 100(b) EPC. The opposition division decided that the patent failed to disclose the invention as defined in claim 1 in a manner sufficiently clear and complete for it to be carried out by a skilled person.

Claim 1 of the patent as granted reads:

"1. Use of Campath-1 H for the production of a medicament for reducing the risk of relapse in a patient having a relapsing form of multiple sclerosis (MS) who has received prior therapy for MS, wherein the treatment with Campath-1 H comprises a first treatment cycle of Campath-1 H followed by at least one further treatment cycle of Campath-1H, in which each treatment cycle comprises 1-5 daily doses which are applied on consecutive days, wherein the daily dose is >0 and ≤12 mg, and wherein each treatment cycle is separated from the next treatment cycle by at least 1-24 months, wherein said first treatment cycle of Campath-1 H is administered at a dose of 12 mg/day for five days and wherein said patient is retreated at 12 months after said first treatment cycle with a further treatment cycle of Campath-1 H at a dose of 12 mg/day for three days."

III. With their statement setting out the grounds of appeal the appellants submitted arguments in support of sufficiency of disclosure.

IV. With their reply to the statement setting out the grounds of appeal the opponent (respondent) submitted arguments addressing the requirements of sufficiency of disclosure and inventive step.

V. The board summoned the parties to oral proceedings in line with the parties' requests. In a subsequent communication pursuant to Article 15(1) RPBA the board informed them of its preliminary opinion on various matters concerning the appeal.

VI. By letter dated 17 June 2020 the appellants submitted sets of claims of three auxiliary requests, document D17, arguments addressing *inter alia* sufficiency of disclosure and inventive step, and reasons why the case should be remitted to the opposition division for inventive step to be assessed.

VII. The respondent submitted further arguments *inter alia* against remitting the case to the opposition division.

VIII. The appellants submitted further arguments in support of remitting the case to the opposition division.

IX. With both parties' agreement, the oral proceedings were held by Zoom videoconference. At the end of the oral proceedings the chair announced the board's decision.

X. The following document is mentioned in this decision:

D3: Coles, A.J. et al., J. Neurol., 253, 2006, pages 98-108

XI. The appellants' arguments relevant to this decision may be summarised as follows:

Main request - claim 1
Sufficiency of disclosure (Article 100(b) EPC)

The requirement for sufficient disclosure was fulfilled if the patent disclosed a plausible technical concept underlying the claimed use (see T 898/05). The standard for plausibility amounted to an educated guess.

The patent disclosed (paragraph [0058]) that an analysis was performed on the basis of the data obtained in the clinical trial CAMMS223 referred to in paragraph [0012]. The analysis used pharmacodynamic and pharmacokinetic models to test eight dosage regimens, as listed in paragraph [0059], and thus included the one in claim 1. The result of this modelling was disclosed in Figures 1 to 3 and discussed in paragraph [0060] of the patent, which stated that even dosages lower than those specified in the claim resulted in lymphocyte depletion. As stated in the same paragraph, lines 37 to 41, lymphocyte depletion correlated with the therapeutic effect.

Neither the model(s) used nor the data entered into the model needed to be disclosed in the patent. The skilled person was able to carry out the claimed invention by administering the substance in the dosage specified in the claim.

The case in hand differed from that in decision T 1592/12 in that no serious doubts

substantiated by verifiable facts were presented. It was down to the respondent to substantiate such serious doubts.

In paragraph [0047], the patent provided the teaching that the dosage regimens were applicable to patients who had received prior therapy for MS.

The mechanism of action of Campath-1H differed from that of other substances used in MS therapy. It could thus not be assumed that patients who had received prior MS therapy with other substances would not respond to therapy with Campath-1H.

The disclosure in document D3 did not give rise to serious doubts that patients who had received prior therapy for MS would respond to therapy with Campath-1H because it failed to show that the invention did not work. Not only did it contain no reference to the daily dose of 12 mg required by claim 1, it also disclosed that the same therapeutic effect was observed in both treatment-naive patients and those who had received prior treatment (see page 6, lines 14 to 16).

Remittal of the case to the opposition division for further prosecution

The opposition division did not take a decision on the issue of inventive step, so the board could not review any decision in that respect. The case should be remitted to the opposition division in line with decisions T 2017/16, T 516/18, T 1616/18, T 1621/17 and T 2092/18.

The issue of inventive step was not confined to considerations relating to document D3. Documents D15

and D16, which the respondent considered to be highly relevant in respect of inventive step, were filed at a late stage of the opposition proceedings with the consequence that they were not considered in the opposition division's communication accompanying the summons to oral proceedings. The board would thus be the first deciding body to consider the content of these documents.

Remittal provided an opportunity to have document D17 and the auxiliary requests, which addressed the issue of inventive step, considered by the opposition division.

The respondent did not present evidence of any alleged commercial interest in relation to the validity of the patent, so prolonged uncertainty arising from a remittal of the case to the opposition division was not an issue.

XII. The respondent's arguments relevant to this decision may be summarised as follows:

Main request - claim 1
Sufficiency of disclosure (Article 100(b) EPC)

Beyond mere statements, the patent did not disclose that the substance was suitable for the claimed therapeutic application. The examples in the patent were hypothetical. Moreover, the patent did not contain details of the clinical trial. Paragraph [0012] did not contain the protocol of the CAMMS223 clinical trial referred to. The skilled person could not reproduce the results of the pharmacokinetic and pharmacodynamic modelling at the core of the claimed dosage regimen

without undue burden, as the patent disclosed neither the model used nor the data entered into the model.

The facts in this case were similar to those underlying decision T 1592/12, in which the board held that when the claimed therapeutic application differed from the known therapeutic application merely on account of the dosage regimen, the patent should disclose the suitability of the substance when used in that dosage regimen.

The CAMMS223 clinical trial enrolled treatment-naive MS patients (see document D3), and information derived from this clinical trial could not be extrapolated to patients who had received prior therapy for MS. The skilled person would assume that such patients would require higher doses of Campath-1H than treatment-naive patients; in the appeal proceedings the appellants themselves had argued that such patients were more difficult to treat. Hence, information specific to patients who had received prior MS therapy was required and lacking in the patent. Therefore, on the basis of the information in the patent a therapeutic effect on patients who had received prior therapy was not plausible.

Remittal of the case to the opposition division for further prosecution

There was no general right for a party to have an issue considered at two instances; Article 11 RPBA 2020 foresaw remittal only in special circumstances.

In the case in hand, the issue ruled on by the opposition division - sufficiency of disclosure - was closely related to that yet to be decided - inventive

step. Both issues focused on the lack of information in the patent and on the discussion of document D3, which represented the closest prior art for the assessment of inventive step.

In the appeal proceedings both parties had been given and had made use of the opportunity to address the issue of inventive step starting from the disclosure of document D3.

A divisional application claiming overlapping subject-matter was pending, and the outcome of these appeal proceedings was relevant for that application. A final decision on the patentability of the invention claimed in the patent in this case was also in the public interest.

Remitting the case would lead to prolonged commercial uncertainty as the patent might end up in appeal for a second time.

XIII. The appellants requested that the decision under appeal be set aside and, as the main procedural request, that the case be remitted to the opposition division for further prosecution, or alternatively, i.e. if the case not be remitted, that the opposition be rejected, implying that the patent be maintained as granted, or further alternatively, that the patent be maintained in amended form on the basis of one of the sets of claims of auxiliary requests 1 to 3 filed with the letter dated 17 June 2020. They requested that document D17 be admitted into the appeal proceedings in the event that the case not be remitted.

The respondent requested that the appeal be dismissed, the case not be remitted to the opposition division for

further prosecution and the patent be revoked. They further requested that auxiliary requests 1 to 3 and document D17, filed with the letter dated 17 June 2020, not be admitted into the appeal proceedings.

Reasons for the Decision

1. The appeal complies with the requirements of Articles 106 to 108 EPC and the further provisions referred to in Rule 101(1) EPC and is admissible.

Main request - claim 1
Sufficiency of disclosure (Article 100(b) EPC)

2. The claim relates to a therapeutic application of the monoclonal antibody Campath-1H in the treatment of a patient having a relapsing form of multiple sclerosis (MS). This therapeutic application is further defined by a dosage regimen, involving the administration of Campath-1H in a specified daily dose of 12 mg, and the patient is stated as having received prior therapy for MS.

3. The patent refers both to "Campath-1H" and "Campath-1 H". In this decision the board uses the former expression except, as the case may be, in quoted text.

4. According to established case law of the boards of appeal of the EPO, where a therapeutic application is claimed in the form of the use of a substance or composition for the manufacture of a medicament for a defined therapeutic application, attaining the claimed

therapeutic effect is a functional technical feature of the claim. As a consequence, unless this is already known to the skilled person at the priority date, in order to fulfil the requirements of sufficiency of disclosure the patent must disclose the suitability of the product for the claimed therapeutic application (see also decision T 609/02, point 9 of the reasons and the further decisions cited in Case Law of the Boards of Appeal of the European Patent Office, 9th edition 2019, "CLBA", II.C.7.2). Although it has been accepted in the case law that for sufficient disclosure of a therapeutic application it is not always necessary that results of applying the claimed composition in clinical trials, or at least to animals, are reported, this does not mean that a simple verbal statement that the substance may be used to treat the disease is enough to ensure sufficiency of disclosure (*Ibid.*).

5. Nonetheless, it is established in the case law of the boards of appeal that a finding of lack of sufficient disclosure presupposes serious doubts, substantiated by verifiable facts (see CLBA, II.C.9.).

6. In the case in hand, it was undisputed that the use of Campath-1H for the treatment of patients with relapsing forms of MS was known to the skilled person. Rather, the key points in dispute in relation to sufficiency of disclosure related to the 12-mg dose and to patients who had received prior therapy for MS.

Disclosure in the patent

7. The patent is directed to the provision of therapies for MS with Campath-1H, which result in "*significant efficacy and a favourable safety profile which offers an acceptable benefit/risk ratio*" (see paragraph

[0001]). It discloses that the therapies are applicable both to relapsing and progressive forms of the disease (see paragraph [0046]) irrespective of whether the patients have received prior therapy for MS (see paragraph [0047]). Eight dosage regimens were analysed with pharmacokinetic and pharmacodynamic modelling based on data collected with the "CAMMS223 clinical trial" on patients suffering from relapsing-remitting multiple sclerosis (RRMS; see paragraphs [0012] and [0058]). One of those dosage regimens involves administering Campath-1H at a daily dose of 12 mg as claimed (see paragraphs [0056] and [0059]). The simulated result of the modelling, in terms of lymphocyte count, is depicted in Figures 1 to 3 (see paragraphs [0059] and [0026]).

8. Paragraph [0060] discloses that "*pharmacokinetic and pharmacodynamic modelling showed that Campath-1 H is an extremely potent depleter of lymphocytes*" and that "*the modelling showed that increasing dose resulted in greater lymphocyte depletion, with almost complete lymphocyte depletion seen with the 5 x 12 mg treatment group. One specific result of this analysis is the recognition that Campath-1 H treatment delivered in a cycle of 10 mg/day for two days with re-treatment at 12 months with 10 mg/day for 2 days (i.e., the 20/20 mg regimen) is predicted to lead to a sustained lymphocyte depletion that is only modestly less than with higher doses*". In the same paragraph a link is established between the mechanism of action of Campath-1H, associated with immune suppression, and the observed lymphocyte depletion and treatment efficacy: "*Given that the mechanism of action of Campath-1 H is presumed to be due to immune suppression, it is anticipated that a modest reduction in lymphopenia will only be*

associated with a comparably modest reduction in efficacy".

9. Paragraphs [0012] and [0013] give information on the interim results of the CAMMS223 clinical trial, based on a dosage regimen of 12 or 24 mg daily over five consecutive days followed one year later by the same dose over three consecutive days, i.e. the same dosage regimen as in the claim is disclosed in paragraph [0013]. The treatment was efficacious (75% reduction in risk of relapse and 60% reduction in disease progression relative to the reference IFN-β-1a treatment) and there were three cases of severe side effects in the group of patients treated with Campath-1H.

10. On the basis of the disclosure referred to above, the board is satisfied that the patent establishes a link between the mechanism of action of Campath-1H (lymphocyte depletion) and a therapeutic effect on MS. Moreover, the patent discloses a link between the Campath-1H dosage and the extent of lymphocyte depletion, observing that the claimed dosage results in almost complete lymphocyte depletion and that even a lower dosage is expected to result in only moderately less lymphocyte depletion. The board is thus satisfied that on the basis of the disclosure in the patent the skilled person had no reason to doubt that Campath-1H at the daily dose of 12 mg administered at the frequency specified in the claim would reduce the relapse rate in patients suffering from a relapsing form of MS.

11. In a first line of reasoning, the respondent held that because the patent failed to disclose both the details of the pharmacokinetic and pharmacodynamic model and

the particulars of the data applied in the model on which the results in paragraph [0060] are based, the skilled person was not in a position to reproduce the modelling to confirm the simulated dose-effect at the core of the claimed dosage regimen.

12. A lack of sufficiency of disclosure presupposes serious doubts substantiated by verifiable facts. However, the respondent's argument is not based on verifiable facts and thus fails to discredit the modelling results disclosed in the patent. Merely contesting the completeness of the information given in the patent cannot succeed in challenging the suitability of the dosage regimen for the treatment specified in the claim.

13. The respondent's parallel with decision T 1592/12 cannot persuade the board either. The respondent argued that the claim related to a therapeutic application which differed from the known therapeutic application on account of the dosage regimen and so, in line with the findings in that decision, the patent should disclose the suitability of Campath-1H for treatment when used in this dosage regimen.

14. However, the case underlying that decision is fundamentally different to the case in hand. In that decision the board acknowledged that there were serious doubts that the therapeutic effect could be attained, and substantiated them on the basis of the common general knowledge relating to the half-life of the substance to be administered. For the skilled person, the half-life and the frequency of administration specified in the claim were not compatible with maintaining the serum concentration required for treatment efficacy. This was why the board in that case

held that the requirements of sufficiency of disclosure were not met.

15. In a second line of reasoning, the respondent, like the opposition division, referred to an argument that the appellants have relied on in the context of inventive step in view of the disclosure in document D3, in which they reason that the skilled person would have considered it more challenging to treat patients who had received prior therapy.

16. However, when assessing sufficiency of disclosure it is irrelevant whether the information disclosed in document D3 would have prompted the skilled person to treat patients who had received prior therapy or discouraged the skilled person from doing so. What is relevant in this context is whether the skilled person expected those patients not to respond to treatment with the dosage regimen as specified in the claim.

17. In the opposition division's view, the disclosure in document D3 confirmed that such patients were more resilient to treatment than treatment-naive patients in view of the expressions "*early in the disease*" and "*drug naive*" used in the document.

18. However, in the board's view the disclosure in document D3 does not substantiate serious doubts that Campath-1H administered according to the dosage regimen specified in the claim would reduce the relapse rate in these patients.

19. Document D3 reports on treatment of MS patients (including patients with relapsing or progressive forms of MS) with Campath-1H. It discloses treating patients with a relapsing form of the disease, including 5 out

of 22 patients for which treatment with IFN-β had not been successful. The patients were administered a daily dose of 20 mg for 5 consecutive days and after 12 months the daily dose was repeated for 3 days (see abstract, page 99, right-hand column, second paragraph and page 100, left-hand column, second paragraph). The authors conclude that the timing of the treatment is a determining factor for an effect on long-lasting disability (see title, page 104, left-hand column, first paragraph and paragraph bridging the two columns on page 106). This document does not disclose either treatment outcomes with the daily dose of 12 mg or an expectation of treatment inefficacy for patients who had had prior treatment for MS. The opposition division relied on statements in document D3 to the effect that Campath-1H was to be administered to patients "early in the disease" and "drug-naive". While this document does state that the clinical trial CAMMS223 enrolled treatment-naive patients with early active RRMS (see page 106, last paragraph), it does not state that this is the case because of an expectation that the treatment would otherwise be unsuccessful. In fact the document reports the authors' observation that the reduction in relapse rate when treating RRMS patients with Campath-1H did not differ between the two patient groups, i.e. those who had received prior therapy with IFN-β versus those who were treatment-naive (see page 103, left-hand column, lines 14 to 16).

20. The board is instead convinced by the appellants' argument that a lack of treatment efficacy with one substance, such as IFN-β, does not imply a lack of efficacy with another substance (in this case Campath-1H) when the underlying mechanisms of action differ. As disclosed in document D3 (see page 99, second paragraph, first sentence) Campath-1H leads to

depletion of lymphocytes, which as is known to the skilled person is not the mechanism of action of IFN-β.

21. In conclusion, the arguments put forward by the respondent and those in the decision under appeal do not raise serious doubts that Campath-1H in the claimed dosage would reduce the relapse rate in patients suffering from a relapsing form of MS who had received prior therapy.

22. Therefore, the ground of opposition under Article 100(b) EPC does not prejudice the maintenance of the patent as granted.

Remittal of the case to the opposition division for further prosecution

23. The decision under appeal dealt solely with the question of sufficiency of disclosure, the ground for opposition under Article 100(b) EPC. As set out above, the board concludes that this ground for opposition does not prejudice the maintenance of the patent as granted. The appeal is thus allowable and the decision under appeal is to be set aside.

24. Under Article 111(1) EPC, following the examination as to the allowability of the appeal, the board shall decide on the appeal. It may either exercise any power within the competence of the department which was responsible for the decision appealed or remit the case to that department for further prosecution. Under Article 11 RPBA 2020 the board shall not remit a case for further prosecution to the department whose decision was appealed unless special reasons present themselves for doing so.

25. The appellants requested that the board remit the case for further prosecution whereas the respondent requested the board not to.

26. The decision under appeal does not deal with the ground for opposition of lack of inventive step. The opposition division addressed the issue of inventive step in its communication accompanying the summons to oral proceedings. However, various documents, including D15 and D16, were subsequently filed on opposition in support of further objections of lack of inventive step. The documents were admitted into the proceedings by the opposition division, but not assessed in substance. The parties consider these documents, as well as document D17 submitted on appeal, to be very relevant for the issue of inventive step, and auxiliary requests were submitted to address the inventive-step objections. Accordingly, the board would be the first and final instance to decide on the question of inventive step in relation to the patent as granted and, as the case may be, as amended according to the auxiliary requests. The board acknowledges that remitting the case to the opposition division entails a certain extension of the period of legal uncertainty in relation to the validity of the patent or any amended version of it. However, since the respondent has no particular interest beyond a party's general interest in obtaining legal certainty, and since the primary object of the appeal proceedings is to review the decision under appeal in a judicial manner as expressed in Article 12(2) RPBA 2020, the board decides to remit the case to the opposition division for further prosecution.

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 for further prosecution.

The Registrar: The Chair:

A. Chavinier Tomsic B. Claes

Decision electronically authenticated