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Datasheet for the decision of 19 November 2024

Case Number: T 0816/22 - 3.3.04

Application Number: 14809567.2

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Language of the proceedings: EN

Title of invention:
Methods of treating antibody-mediated rejection in organ transplant patients with C1-esterase inhibitor

Patent Proprietor:
Takeda Pharmaceutical Company Limited

Opponent:
CSL Innovation Pty Ltd

Headword:
C1-esterase inhibitor for AMR/TAKEDA

Relevant legal provisions:
EPC Art. 83

Keyword:
Sufficiency of disclosure - reproducibility (no)

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Case Number: T 0816/22 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 19 November 2024

Appellant: (Patent Proprietor)	Takeda Pharmaceutical Company Limited 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi, Osaka (JP)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Appellant: (Opponent)	CSL Innovation Pty Ltd 655 Elizabeth Street Melbourne VIC 3000 (AU)
Representative:	Mewburn Ellis LLP Aurora Building Counterslip Bristol BS1 6BX (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 19 January 2022 concerning maintenance of the European Patent No. 3 071 219 in amended form**

Composition of the Board:

Chairwoman	M. Pregetter
Members:	B. Rutz
	L. Bühler

Summary of Facts and Submissions

I. The appeals by the patent proprietor (appellant I) and the opponent (appellant II) lie from the opposition division's decision that European Patent No. EP 3 071 219 ("the patent"), in amended form based on auxiliary request 4, fulfilled the requirements of the EPC.

II. In this decision appellant I and II are designated by their respective roles in the opposition proceedings (patent proprietor and opponent, respectively).

III. The opposition proceedings were based on the grounds of Article 100(a) EPC, in relation to novelty (Article 54 EPC) and inventive step (Article 56 EPC), and of Article 100(b) and (c) EPC.

IV. In the decision under appeal, the opposition division decided, *inter alia*, that claim 1 of the main request and of auxiliary requests 1 to 3 did not meet the requirements of Article 123(2) EPC.

V. The board adheres to the numbering of the documents as set out in the consolidated list annexed to the decision under appeal (documents D1 to D58, including D1a, D6a and D6b).

VI. With its statement of grounds of appeal the opponent submitted documents D59 to D63.

VII. With its reply to the opponent's appeal, the patent proprietor submitted documents D64 to D66 and sets of claims in auxiliary requests 21 to 28.

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

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

"1. A C1 esterase inhibitor (C1-INH) for use in a method of treating antibody-mediated rejection (AMR) of an organ allograft in a patient in need thereof, wherein the method comprises intravenous administration of the C1-INH at a dose of 5,000 units to 20,000 units given in divided doses over 10 to 20 days, and wherein the organ is kidney."

Claim 1 of auxiliary request 4 reads as follows (amendments underlined by the board):

"1. A C1 esterase inhibitor (C1-INH) for use in a method of treating antibody-mediated rejection (AMR) of an organ allograft in a patient in need thereof, wherein the method comprises a dosage regimen consisting of intravenous administration of the C1-INH at a dose of 5,000 units to 20,000 units given in divided doses over 10 to 20 days, and wherein the organ is kidney."

The text of the sets of claims in auxiliary requests 1 to 3 and 5 to 28 is available in the electronic file.

X. Oral proceedings took place on 19 November 2024. During the oral proceedings the following embodiment of claim 1 of auxiliary request 4 was discussed with regard to sufficiency of disclosure of the invention:

- a C1 esterase inhibitor (C1-INH)

- for use in a method of treating antibody-mediated rejection (AMR) of a kidney allograft in a patient, the method being the
- intravenous administration of the C1-INH at a dose of 5,000 units to 20,000 units given in divided doses over 10 to 20 days,
- no further doses of the C1-INH being administered by other routes of administration.

The proprietor agreed that the dosage regimen considered in relation to auxiliary request 4 was embodied in all of the remaining sets of claim requests and that the board's conclusion for auxiliary request 4 therefore applied to all the requests.

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

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

D15 NCT02547220. A Multicenter Study to Evaluate the Efficacy and Safety of Cinryze® for the Treatment of Acute Antibody-mediated Rejection in Participants With Kidney Transplant, retrieved from ClinicalTrials.com on 14 August 2019

D16 Letter from Takeda, Re: Discontinuation of Cinryze study SHP616-302, dated 30 April 2019

D54 Clinical trial results: A Randomized Double-Blind Placebo-Controlled Study to Evaluate the Efficacy and Safety of CINRYZE (C1 Esterase Inhibitor [Human]) for the Treatment of Acute Antibody-Mediated Rejection in Kidney Transplant Subjects, EU Clinical Trials Register, 14 June 2020

XII. The patent proprietor's submissions are summarised as follows:

Auxiliary request 4 - claim 1
Sufficiency of disclosure (Article 83 EPC)

In document D15, the term "futility" was used in the context of regulatory submissions, which had an entirely separate standard of whether a therapeutic effect is achieved compared with patent law. The standard for regulatory approval was much higher than that set out in Article 83 EPC, and thus it was not necessary for the standard required for regulatory approval to be met in order to satisfy Article 83 EPC.

The phase II clinical trial data reported in the patent were promising enough to warrant a phase III trial (see D15) being conducted.

Document D54 specifically mentioned that the clinical trial was stopped at month 36 due to a "futility issue". This depended on the pre-specified criteria for futility of clinical trials. Accordingly, this conclusion was associated with considerations resulting from setting the parameters forming pre-specified criteria for futility, and thus was not tied specifically to the futility of a technical effect in the sense of Article 83 EPC.

For medical use claims, the patent had to disclose the suitability of the product to be manufactured for the claimed therapeutic application. Clinical trials were not required to establish such suitability. In view of the positive results demonstrated by the data in the patent, and the fact that a link between the observed physiological effects and the disease was established

in the patent, the disclosure of the patent satisfied Article 83 EPC (see decision T 609/02, point 9 of the Reasons).

The main request and auxiliary requests 1 to 3 and 5 to 28 were maintained, but no further comments on the issue of sufficiency of disclosure were made since the dosage regimen considered in relation to auxiliary request 4 was understood to be embodied in all of the remaining sets of claims.

XIII. The opponent's submissions are summarised as follows:

Auxiliary request 4 - claim 1
Sufficiency of disclosure (Article 83 EPC)

None of the data in the patent demonstrated a meaningful difference between the groups in the occurrence of transplant glomerulopathy (TG, or any other parameters) which could be specifically attributed to an intervention. TG occurred in both groups (3/7 vs. 1/7) and no difference between those groups in terms of therapeutic effect had been plausibly established.

Document D54 represented the best available evidence concerning the efficacy of the claimed treatment. It demonstrated a complete failure to provide any therapeutic effect compared with placebo control.

The notion that the termination of the trial meant that the results reported in D54 were merely interim and "*could have been looked upon in a different light had the data for the complete study* [been] *collected, analyzed and reported*" (decision under appeal, page 12, paragraph 6) was pure speculation. There was no

realistic prospect that the fully completed study would have demonstrated a therapeutic effect for the treatment.

Notwithstanding the earlier termination of the trial, the data on the incidence of TG at 6 months for 39 patients did not demonstrate a difference between the treatment and placebo arms. More patients were studied in the phase III trial than in the phase II trial (as reported in the patent) and thus the data was more meaningful, in particular when the earlier phase II trial results undisputedly had no statistical significance.

It could not be expected that an opponent had to conduct even more comprehensive clinical studies than a phase III trial in order to discharge its burden of proof of insufficiency. The disclosure of a patent was insufficient if the invention could not be reproduced across the whole breadth of the claims. Even a plausible disclosure of a therapeutic effect (which was missing in the present case) still had to be subject to refutation by evidence that the therapeutic effect was not in fact attained (which was provided by documents D15, D16 and D54), the standard of proof being "serious doubts, substantiated by verifiable facts".

XIV. Appellant I (patent proprietor) requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the claims of the main request considered by the opposition division and filed on 6 January 2020 with the patent proprietor's observations on the opposition. Alternatively, it requested that the patent be maintained on the basis of one of auxiliary requests 1 to 20, which were filed during the opposition

proceedings, or on the basis of auxiliary requests 21 to 28, which were filed with its reply to the appeal. It further requested that documents D59 to D63 not be admitted and that documents D64 to D66 be admitted into the proceedings.

Appellant II (opponent) requested that the decision under appeal be set aside and that the patent be revoked. It further requested that documents D59 to D63 filed with the statement of grounds of appeal be admitted into the proceedings and that documents D64 to D66 not be admitted. It also requested that auxiliary requests 21 to 28 not be admitted into the proceedings.

Reasons for the Decision

Auxiliary request 4 - claim 1
Sufficiency of disclosure (Article 83 EPC)

1. The parties were not in agreement regarding claim interpretation. The board therefore assesses sufficiency of disclosure of the invention for an embodiment which undisputedly falls under the claim:
   - a C1 esterase inhibitor (C1-INH)
   - for use in a method of treating AMR of a kidney allograft in a patient,

   the method being the
   - intravenous administration of the C1-INH at a dose of 5,000 units to 20,000 units given in divided doses over 10 to 20 days,
   - no further doses of the C1-INH being administered by other routes of administration.

Data in the patent

2. The patent contains data from a randomised, double-blind, placebo-controlled pilot study to evaluate the safety and efficacy of Cinryze (C1 esterase inhibitor [human]) for the treatment of acute antibody-mediated rejection in recipients of donor-sensitised kidney transplants. The study was conducted using plasmapheresis and/or intravenous immunoglobulin (IVIg), if necessary, for desensitisation of donor-specific antibody (DSA) positivity and treatment of acute AMR. The subjects, there being seven in each arm, received a total of seven doses of the study drug (Cinryze or placebo) over a two-week period: an initial intravenous (IV) infusion of 5,000 U Cinryze (not to exceed 100 U/kg) or placebo on day 1, followed by 2,500 U of Cinryze (not to exceed 50 U/kg) or placebo IV on days 3, 5, 7, 9, 11 and 13 (see Figure 2). This amounts to 20,000 units (5,000 U + 6 x 2,500 U) given in divided doses over 13 days, i.e. it corresponds to the dosage regimen defined in the claim and falls within the embodiment described in point 1. above.

3. Chronic glomerulopathy (CG) was analysed as a clinical marker of AMR. According to the patent, transplant glomerulopathy (TG) (a subset of chronic glomerulopathy (CG)) is correlated with impaired graft survival (see paragraphs [0032] and [0033]). In the patients treated with placebo, 3 out of 7 displayed CG, whereas, in the patients treated with Cinryze, 1 out of 7 displayed CG. This is illustrated in Figure 6A, which shows a normal renal tissue slice displaying no CG at six months post-transplant in a patient treated with Cinryze (one of the 6/7 patients) and Figure 6B, which shows a renal tissue slice displaying CG at six months post-transplant in a patient treated with placebo (one of

the 3/7 patients). These tissue studies were confirmed by electron microscopy (EM) of obtained renal tissue (see Figure 7).

4. The decision under appeal in point 16.3.3.4 reasoned that the biochemical data in the patent was confirmed by electron microscopy (EM) in Figures 6 and 7. Figure 6, however, displays exemplary renal tissue slices from two patients from the two arms stained with hematoxylin and eosin (H&E) stain as indicated in the descriptions of the "*Drawings in the patent*", i.e. not EM. According to the patent, "*Figure 7A represents an exemplary normal EM image of a PTC. Figure 7B represents an EM image of a PTC obtained at 6 months post-transplant demonstrating glomerulopathy an patient treated with placebo (one of the 3/7 patients)*". Figures 6 and 7 thus show CG (or its absence) in renal tissue slices of exemplary patients from both study arms using two different imaging methods.

5. Further "biochemical data" reported in the patent and referred to in the decision under appeal is the creatinine clearance in patients during the 13 days of treatment (see Figure 5); however, as pointed out by the opponent and not disputed by the patent proprietor, when the difference in initial creatinine clearance is removed, no meaningful difference between the study arms can be identified.

6. The board therefore concludes that the only relevant data in the patent are finding CG in 1 out of 7 patients in the Cinryze arm compared with 3 out of 7 patients in the placebo arm.

7. In view of the small number of patients, the opponent considered that a treatment effect had not been

demonstrated. The board, however, does not deem it necessary to establish this and instead starts from the assumption that the opposition division was correct in finding that the experimental data provided in the patent (see above), together with the mechanistic explanation provided in paragraphs [0032] to [0039] and Figure 1, made it plausible (or credible) to the skilled person at the time of filing that a therapeutic effect on AMR could be achieved; however, this in itself is not enough to demonstrate that the invention is sufficiently disclosed if the opponent provides evidence which raises serious doubts that the therapeutic effect can indeed be achieved (see below).

Post-published evidence

8. Post-published documents D15, D16 and D54 relate to the phase III clinical trial NCT02547220 (SHP616-302), which was carried out using the same dosage regimen as in the examples of the patent and falling under the terms of the claim: "*5000 Units of CINRYZE (50 millilitre [ml] of CINRYZE/ 50 ml of normal saline) on Day 1 and 2500 Units of CINRYZE (25 ml of CINRYZE/ 75 ml of normal saline) on Day 3, 5, 7, 9, 11, and 13 respectively*" (see document D15, bottom of page 2). The initial number of patients with kidney transplants enrolled was 41 (see document D15, page 2: "*Actual enrollment*"), which was later reduced to 39 (see document D54, page 2: "*Population of trial subjects*"). CINRYZE, a plasma-derived C1-INH (see document D15, page 7, point 14), was administered with plasmapheresis, plasma exchange, or immune adsorption treatments and sucrose-free intravenous immunoglobulin (IVIg) (see document D54, page 2, "*General information about the trial*").

9. According to documents D15, D16 and D54 the study was terminated after 36 months because "[f]*ollowing a prescheduled interim analysis performed by the DMC, it was determined that the study met the pre-specified criteria for futility*" (see document D15, page 1).

10. The only primary endpoint concerned the "*Percentage of Subjects With New or Worsening Transplant Glomerulopathy (TG) at Month 6 Post-Treatment*" and reported 47.5% patients in the placebo group and 50% patients in the CINRYZE group (see document D54, page 7). It was not disputed that this endpoint did not demonstrate a difference between the study arms.

11. Due to the termination of the trial after 36 months, data was not collected, analysed and reported for any of the secondary endpoints related to efficacy (see document D54, pages 8 to 14).

12. The patent proprietor argued that the results obtained as the primary endpoint were only "binary" data, which did not reveal whether, for example, an individual patient had less or more severe CG or whether the CG had occurred faster or slower. Document D54 reported only one aspect, while other important aspects which could have demonstrated a beneficial effect of the treatment had not been analysed due to the early termination of the trial. The termination of the trial was a commercial decision which did not mean that there was no therapeutic effect of any kind.

13. The patent proprietor further argued that beneficial effects of the treatment could have arisen had the clinical trial reported in document D54 been continued until month 48 as planned. The decision under appeal equally considers "*that D54 only shows intermediate*

results which could have been looked upon in a different light had the data for the complete study be collected, analyzed and reported" (see point 16.3.3.5).

14. The board does not agree because the level of efficacy which had been pre-specified for futility is not relevant for the question of sufficiency of disclosure in the present case. What is crucial is that the skilled person, with the teaching of the patent in hand and applying common general knowledge, was able to reproduce the invention, i.e. to achieve a therapeutic effect on kidney transplant AMR when administering C1-INH intravenously using the dosage regimen indicated in the claim and identified in the presently discussed embodiment.

15. The board agrees with the patent proprietor that therapy is not limited to completely curing a disease or condition, but also includes alleviating, removing or lessening the symptoms of any disorder or malfunction of the human or animal body (see Case Law of the Boards of Appeal of the EPO, 10th edition, 2022, I.B.4.5.1 a)).

16. Document D54 shows the complete absence of any therapeutic effect with the claimed dosage regimen. For the very parameter that was considered "*a clinical marker of AMR in a transplant patient*" in the patent (see paragraph [0097]) and assessed in the examples, i.e. CG (or TG) after 6 months, document D54 found no effect for a larger patient cohort (see points 8. to 10. above). The board considers this sufficient to raise serious doubts based on verifiable facts that the claimed treatment achieves a therapeutic effect. In view of this evidence it is not sufficient for the patent proprietor to refer to potential beneficial

effects that might arise when following up with patients for a longer period of time.

17. In conclusion, a phase III clinical trial with the same setup as the examples in the patent and using the dosage regimen which is an embodiment of the claim could not reproduce the claimed subject-matter as exemplified in the embodiment under discussion as it did not exhibit any efficacy after 36 months. The patent proprietor has not dispelled the serious doubts regarding the presence of a treatment effect in view of these data. Therefore, the invention as claimed is not reproducible.

18. The board therefore considers that the patent does not disclose the claimed invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Article 83 EPC).

Main request, auxiliary requests 1 to 3 and 5 to 28
Admission of auxiliary requests 21 to 28

19. In view of its finding on sufficiency of disclosure for auxiliary requests 21 to 28 (see points 20. to 22. below) the board deems it unnecessary to provide reasons for admitting the requests into the appeal proceedings.

Sufficiency of disclosure (Article 83 EPC)

20. Claim 1 of all of the requests encompasses the embodiment outlined in point 1. above. Some auxiliary requests contain additional limiting features: auxiliary requests 1, 5, 9, 12, 15, 19 and 22:

"the method further comprises administration of plasmapheresis and/or intravenous immunoglobulin (IVIg)"

auxiliary requests 2, 6, 16 and 23:

"as an adjunct to plasmapheresis and/or intravenous immunoglobulin (IVIg)"

auxiliary requests 3, 7, 10, 13, 17, 20 and 24:

"(i) the method further comprises subjecting the patient to plasmapheresis;

(ii) the method further comprises administering fresh frozen plasma; and/or

(iii) the method further comprises administering intravenous immunoglobulin"

auxiliary requests 25 to 28:

"the C1-INH is plasma derived"

21. These additional technical features do not change the reasoning provided for auxiliary request 4 in points 1. to 18. above because the clinical trial reported in post-published documents D15, D16 and D54 involved administration of plasma-derived "*CINRYZE with plasmapheresis, plasma exchange, or immune adsorption treatments and sucrose-free intravenous immunoglobulin (IVIg)*" (see document D54, page 2). The patent proprietor has not provided any reasoning to support the sufficiency of disclosure of the invention based on particular additional features present in claim 1 of these requests, either. The same considerations as for auxiliary request 4 are applicable.

22. The patent does not disclose the invention claimed in these requests in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Article 83 EPC).

Admission of documents D64 to D66

23. These documents were cited by the patent proprietor during the appeal proceedings in an attempt to counter statements in document D14 concerning the significance of the reported data. As the board did not take these statements into account for its decision, the documents in rebuttal were not required either, and no decision was taken on their admittance.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairwoman:

I. Aperribay M. Pregetter

Decision electronically authenticated