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Datasheet for the decision of 10 October 2024

Case Number: T 1048/21 - 3.3.04

Application Number: 12708029.9

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Language of the proceedings: EN

Title of invention:
Use of low dose IL-2 for treating type 1 diabetes

Patent Proprietors:
Assistance Publique - Hôpitaux de Paris
Sorbonne Université
INSERM (Institut National de la Santé et de la Recherche Médicale)

Opponent:
Strawman Limited

Relevant legal provisions:
EPC Art. 54(2), 56, 83, 123(2)
RPBA 2020 Art. 12(4)

Keyword:
Auxiliary request 8 - allowable

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Case Number: T 1048/21 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 10 October 2024

Appellant: (Opponent)	Strawman Limited Orchard Lea Horns Lane Combe, Witney Oxfordshire OX29 8NH (GB)
Representative:	Mewburn Ellis LLP Aurora Building Counterslip Bristol BS1 6BX (GB)
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Representative:	Cabinet Becker et Associés 25, rue Louis le Grand 75002 Paris (FR)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 28 April 2021 concerning maintenance of the European Patent No. 2683395 in amended form.**

Composition of the Board:

Chairwoman	M. Pregetter
Members:	R. Hauss
	L. Bühler

Summary of Facts and Submissions

I. European patent No. **2 683 395** (patent in suit) was opposed under Article 100(a), (b) and (c) EPC on the grounds that the claimed subject-matter lacked novelty and inventive step, was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, and extended beyond the content of the application as filed.

II. The documents cited in the proceedings included the following:

D1: JEM 207, 1871-1878 (30 August 2010)

D1a: History of changes for study: NCT00525889, Proleukin and Rapamune in Type 1 Diabetes, ClinicalTrials.gov archive (6 February 2017, published study status of December 2010)

D4: WO 2007/084651 A2

D5: EP 0262802 A2

D7: Journal of Translational Medicine 8.113, 1-12 (2010)

D8: Lancet Diabetes Endocrinol 1, 295-305 (2013)

D9: Diabetes, 59, 407-415 (February 2010)

D13: Immunity 28, 687-697 with Supplemental Data 1-6 (May 2008)

D17: WO 99/26660 A2

D26: N Engl J Med 365:22, 2067-2077 (1 December 2011)

D28: Nature Reviews Immunology, D. Klatzmann, A.K. Abbas: The promise of low-dose interleukin-2 therapy for autoimmune and inflammatory diseases, 12 pages (published online 17 April 2015)

D43: History of changes for study: NCT01353833, Dose-Effect Relationship of Low-dose IL-2 versus Placebo in Type 1 Diabetes (DF-IL2) ClinicalTrials.gov archive (13 May 2011)

III. The following abbreviations are used in the text below:

T1D: type 1 diabetes

IU: International Units

MIU: million International Units

IL-2: Interleukin-2 (see claim 1 above and paragraph [0002] of the patent in suit)

IL-2R: IL-2 receptor (see paragraph [0005])

Treg: regulatory T cell/lymphocyte (see paragraphs [0004] and [0009])

Teff: effector T cell/lymphocyte (see paragraphs [0005] and [0009])

NOD mice: nonobese diabetic mice (see document D1: abstract)

IV. The decision under appeal is the opposition division's interlocutory decision rejecting the patent proprietors' main request and auxiliary requests 1 to 7 and finding that the patent as amended in the form of auxiliary request 8 meets the requirements of the EPC.

V. Claim 1 of auxiliary request 8, which is the only independent claim of that request, reads as follows:

> *1. Interleukin-2 (IL-2) for use in treating type I diabetes in a human subject, wherein IL-2 is to be administered at a dose of less than 3.5 MIU/day, wherein said Il-2* [sic] *is human IL-2 or aldesleukin.*

VI. The decision under appeal included the following findings:

The claims of the main request and of auxiliary requests 1 to 7 were not allowable.

The subject-matter claimed in auxiliary request 8 did not extend beyond the disclosure of the application as filed (Article 123(2) EPC), met the requirement of sufficiency of disclosure (Article 83 EPC) and was also novel over the disclosure of documents D1a, D4 and further documents (Articles 52(1) and 54 EPC).

The claimed invention was disclosed in an enabling manner in the priority documents EP 11305269 and US 61/451,663. The claims of auxiliary request 8 were thus entitled to priority, and the intermediate documents cited, which included D26 and D43, were not part of the state of the art.

Documents D1 and D13 represented the closest prior art. They disclosed preclinical data on the efficacy of IL-2 against type 1 diabetes (T1D) in a mouse model. The objective technical problem was the provision of an effective treatment in humans. The prior art did not provide any pointer to the low-dose treatment of T1D in humans with IL-2 at dosages lower than 3.5 MIU/day. Since the person skilled in the art would not have had a reasonable expectation of success for this dosage range, the subject-matter of auxiliary request 8 involved an inventive step (Articles 52(1) and 56 EPC).

VII. Both the opponent and the patent proprietors appealed against this decision.

VIII. With their grounds of appeal, the patent proprietors submitted the sets of claims of a main request and eleven auxiliary requests. The claims of auxiliary

request 8 are identical to the claims that were upheld with the decision under appeal (for the wording of claim 1, see point V. above).

IX. With its grounds of appeal, the opponent submitted new documents D46 to D53, as identified in point 2.1 of the opponent's letter.

X. With a submission replying to the opponent's reply to their appeal, the patent proprietors filed document D54 (Exhibit A: Declaration by D. Klatzmann).

XI. The board issued a summons to oral proceedings.

XII. The opponent announced that it would not be attending the oral proceedings and would not be filing any further submissions.

XIII. Oral proceedings before the board were held on 10 October 2024, in the opponent's absence (Rule 115(2) EPC, Article 15(3) RPBA). The board decided against the admittance of documents D46 to D54. The patent proprietors withdrew their appeal. As a consequence, the main request and auxiliary requests 1 to 7 were no longer to be considered. The board found the claims of auxiliary request 8 allowable. At the end of the oral proceedings, the board announced its decision dismissing the opponent's appeal.

XIV. The opponent's pertinent arguments (as presented in writing) may be summarised as follows.

Admittance of evidence filed upon appeal

Documents D46 to D53 were filed as a response to positions taken by the opposition division in the decision under appeal.

Amendments (Article 123(2) EPC)

In claim 1 of auxiliary request 8, the combination of the feature "to be administered at a dose of less than 3.5 MIU per day" with the therapeutic indication "type 1 diabetes" went beyond the content of the application as filed, all the more so when combined with the further feature "human IL-2 or aldesleukin".

The combination of the features of claim 1 with the dosage regimens in claims 5 to 7 also gave rise to added subject-matter.

Sufficiency of disclosure

The patent in suit did not disclose the suitability of low-dose IL-2 for the claimed therapeutic application (i.e. the treatment and prevention of T1D).

The patent provided data relating to two different clinical trials.

The first (Example 1) related to a study carried out with patients suffering from HCV-related vasculitis and did not disclose a therapeutic effect in T1D patients. The induction of regulatory T cells (Tregs) and clinical improvement in HCV-related vasculitis observed in this trial could not be considered proof of therapeutic efficacy in type 1 diabetes, either.

As also acknowledged in the patent in suit (see paragraph [0172]), it had been a concern of the inventors that T1D patients could have alterations in the IL-2/IL-2R activation pathway making Treg induction less effective. Aberrant IL-2R signalling in Treg cells of subjects having T1D had indeed been known from document D9, which thus provided proof of a prejudice in the art that called the hypothesis behind the technical effect (increase of Treg cells) into question. Already for this reason, the data observed

for HCV-related vasculitis could not be considered "proof of concept" applicable to T1D.

In Example 2, the application as filed disclosed interim data obtained from a clinical trial designed to define the lowest active dose of IL-2 that could safely induce Treg cells in adult T1D patients. While the data showed that Treg cells were induced also in these patients, this did not amount to evidence of clinical improvement in patients with T1D, or to evidence of a preventive effect.

Validity of the priority claim (Article 87 EPC)

The descriptions of the two priority documents corresponded to the description of the application as filed, except that they did not include Example 2.

The suitability of low-dose IL-2 for use in treating T1D was not disclosed in the priority documents in an enabling manner, for the same reasons as given regarding the issue of sufficiency of disclosure in relation to Example 1.

Even if the board were to consider Example 2 of the application as filed as evidence of the desired clinical benefit of low-dose IL-2 in type 1 diabetes, this Example was missing and could not be relied on for enablement in the case of the priority documents.

Novelty

The subject-matter of at least claim 1 of auxiliary request 8 lacked novelty over the disclosure of documents D1a and D4.

While D1a disclosed a trial protocol without any data, the claimed therapeutic effect had not been shown and, therefore, it could not be relied on to establish novelty.

D4 disclosed the dose amount of 1 MIU, to be administered once or twice per day (see page 9, lines 11 to 17, 23 to 25 and page 12, lines 12 to 19).

Inventive step

Inventive step should be assessed starting from the disclosure of documents D1 or D13, both relating to preclinical studies in NOD mice. The same reasoning applied starting from either document.

The features distinguishing the claimed subject-matter from the disclosure of D1/D13 were (i) therapy in human patients, (ii) the dose of less than 3.5 MIU/day.

As stated by the opposition division in the decision under appeal, the objective technical problem was the provision of an effective treatment in humans.

The question to be answered was, therefore, whether the person skilled in the art would have carried out the IL-2 treatment on human patients with T1D at the claimed dosage with a reasonable expectation of success.

This would indeed have been obvious based on the teaching of D1/D13 taken alone, but also in view of the teaching of supplementary documents D5 and/or D1a. D17 taught the administration of ultra-low doses of IL-2 to treat auto-immune diseases.

Since document D9 had been considered irrelevant by the opposition division in its reasoning relating to the issue of sufficiency of disclosure, this document could not now be relied on as removing the skilled person's expectation of success.

XV. The patent proprietors' arguments may be summarised as follows.

Admittance of evidence filed upon appeal

It was not apparent that the opponent's filing of documents D46 to D53 had been occasioned by any new argument made by the opposition division. These documents were not only irrelevant but they were cited in support of objections newly raised by the opponent. Thus, they should have been filed in the proceedings before the opposition division.

Document D54 was filed to rebut the opponent's comments regarding document D44, presented for the first time in its reply to the patent proprietors' appeal (page 14, last paragraph, to page 16, second paragraph).

Amendments (Article 123(2) EPC)

The combination of the features of treating T1D and administering less than 3.5 MIU/day of IL-2 was supported by the direct combination of claims 3 and 22 as filed. Moreover, the dose of less than 3.5 MIU/day was generally disclosed in the description for any autoimmune disease (page 4, line 4; page 16, lines 1 to 4), T1D being a preferred example. Support for human IL-2 and aldesleukin in the form of general disclosures could be found on page 10, lines 31 to 32, and page 11, third paragraph of the application as filed. Aldesleukin was also the active ingredient in Proleukin®, which was used in the Examples (see Example 2, page 40, line 7). The preferred administration protocol as set out in claims 5 to 7 found support on page 4, lines 10 to 12 and in claim 9 of the application as filed.

Sufficiency of disclosure (Article 83 EPC)

It was known before the priority date that HCV-related vasculitis and T1D were pathologies that were both characterised by a Treg insufficiency. Example 1 in the application as filed provided proof of concept, namely that low-dose IL-2 could tip the Treg/Teff balance and induce a selective increase of Tregs in patients who showed a Treg insufficiency. The extrapolation from the vasculitis data of the effect on Tregs in patients with T1D would have been credible because it was based on the same mechanism of action. The clinical improvement that was observed in HCV-related vasculitis, and which was a secondary end point in the trial reported in Example 1, supported the causal link between this preferential Treg stimulation and the therapeutic effect in an autoimmune disease.

Example 2 (with Figures 8 and 9) confirmed that the same increase of the Treg/Teff ratio was observed in T1D patients. It also provided preliminary data of clinical improvement that supported the expected efficacy in the treatment of T1D.

In its grounds of appeal, the opponent contended that the credibility of the claimed treatment's efficacy in T1D could only rely on data from Example 2, which, however, was insufficient. This was a new line of argument that should not be admitted.

The opponent's further concerns regarding an alleged lack of disclosure of the prevention of T1D remained unsubstantiated.

Validity of the priority claim (Article 87 EPC)

The results observed in patients with HCV-related vasculitis (Example 1) provided proof of concept supporting the claimed invention in its full scope in any pathology with Treg insufficiency, including T1D.

The priority documents also taught translating from vasculitis to T1D on the basis of the same mechanism of action, namely a preferential stimulation of Treg cells.

Novelty

D1a was the announcement of a phase 1 clinical study which proposed to administer a combination of IL-2 with sirolimus (rapamycin). This disclosure could not anticipate the claimed subject-matter because D1a did not disclose any results observed in the study. Moreover, the dosage regimen of D1a (administration of IL-2 at a dose of 4.5 MIU/day, three times weekly for 28 days) was not covered by the current claims.

D4 did not provide direct and unambiguous disclosure of treating a patient with T1D with a maximum dose of IL-2 of 3.5 MIU/day.

Inventive step

The disclosure of document D1 (published two years later than D13) represented the closest prior art. The content of D1 and D13 was similar. Two different experimental set-ups were described in both documents. One used recombinant mouse IL-2 and was not relevant to the current claims. The other used human IL-2 at a dosage of 25000 IU. This dosage in mice was equivalent to 7 MIU in humans. Thus, neither document disclosed the administration of low-dose IL-2 according to claim 1.

Starting from the disclosure of either D1 or D13, the objective technical problem was the provision of an effective treatment of T1D in humans.

At the effective date, the person skilled in the art could not have known whether there was any dose that could be useful in humans.

Document D5, relied on by the opponent, related to different medical conditions, namely rheumatoid arthritis and systemic lupus erythematosus. Its relevance was thus doubtful. Document D1a provided a trial protocol without any experimental results and disclosed a higher dosage of 4.5 MIU/day even in the scenario of the envisaged combination treatment. The known treatments of cancer in which IL-2 had previously been used involved higher dosages and were based on a different mechanism.

D9 could have been the basis for certain concerns regarding reduced responsiveness in T1D patients.

Thus, at the priority date the person skilled in the art would not have been faced with a straightforward route to the claimed invention and, in particular, would not have derived any pointer from the prior art towards exploring the dosage range below 3.5 MIU/day. Thus, the inventors' contribution went beyond mere routine dose-finding experimentation.

XVI. The patent proprietors (respondents) requested that the opponent's appeal be dismissed and the patent be maintained on the basis of the claims of auxiliary request 8 (filed with the statement setting out the grounds of appeal and identical to the claims held allowable in the decision under appeal),

or in the alternative, that the patent be maintained on the basis of the claims of one of auxiliary requests 9 to 11 (all filed with the statement setting out the grounds of appeal).

The patent proprietors also requested that documents D46 to D53 and the opponent's arguments based on these documents not be admitted.

XVII. The opponent (appellant) requested that the decision under appeal be set aside and that the patent be revoked.

Reasons for the Decision

1. Oral proceedings, absence of the opponent

1.1 The opponent was duly summoned and, in reply, advised the board that it would not be attending the oral proceedings (see point XII. above). Thus, the opponent chose not to avail itself of the opportunity to present its comments at the oral proceedings (Article 113(1) EPC).

1.2 In conformity with Article 15(3) RPBA and Rule 115(2) EPC, the oral proceedings before the board took place in the opponent's absence, and the opponent was treated as relying on its written submissions.

2. Scope of the appeal proceedings

2.1 Since the patent proprietors withdrew their appeal (see point XIII. above), their main request and auxiliary requests 1 to 7 are no longer relevant, and the opponent remains as the sole appellant.

2.2 The opponent's objections in the proceedings before the opposition division are detailed in points XVIII.a to XVIII.d, Reasons 3.1, 3.2, and Reasons 5, 5.1 and 5.2 of the decision under appeal. These objections are addressed in the decision under appeal, in particular also where relevant to auxiliary request 8. The opponent did not argue that there were any procedural errors by the opposition division on this account (i.e. that it failed to address the opponent's submissions).

2.3 Article 12(2) RPBA requires that, in view of the primary object of the appeal proceedings to review the decision under appeal in a judicial manner, a party's appeal case shall be directed to the requests, facts, objections, arguments and evidence on which the decision under appeal was based.

Insofar as the opponent raised further objections or lines of argument in its written appeal submissions without demonstrating that these were admissibly raised and maintained in the proceedings before the opposition division, such further objections or lines of argument (e.g. objections against further dependent claims or based on further documents) were not admitted under Article 12(4) RPBA and are not taken into consideration below.

Article 12(4) RPBA requires parties to clearly identify each amendment to their case and to provide reasons for submitting it in the appeal proceedings, as the board cannot be reasonably expected to conduct its own investigations in this regard.

The board exercised its discretion taking into account

- the absence, in the opponent's appeal submissions, of such clear identification of the amendments and reasons for submitting them and
- the need for procedural economy, especially in view of the appellant's absence at the oral proceedings.

3. Admittance of evidence filed on appeal

Documents D46 to D53

3.1 With its statement setting out the grounds of appeal, the opponent submitted, for the first time, documents D46 to D53 (see point IX. above). This is an amendment to the opponent's case under Article 12(4) RPBA.

3.2 As mentioned in point 2.3 above, Article 12(4) RPBA requires parties to clearly identify each such amendment and provide reasons for submitting it in the appeal proceedings.

3.3 The passage in the appellant's letter entitled "2.2 Admissibility of Documents" contains no more than the general statement that the new documents were filed

> *"directly in response to positions taken by the OD* [sic] *in their decision regarding the teaching of the opposed patent and the common general knowledge of the skilled person at the effective filing date".*

3.4 As this statement is not substantiated with regard to any of the individual documents, the board was left in the dark as to why, in the opponent's view, each of these documents, filed only at the appeal stage, should nevertheless be admitted. Since the criterion set out in Article 12(4) RPBA was not met, the board decided not to admit any of documents D46 to D53.

Document D54

3.5 The filing of D54 (see point X. above) is an amendment to the patent proprietors' case under Article 13(1) RPBA. Article 13(1) RPBA states that "Article 12, paragraphs 4 to 6, shall apply *mutatis mutandis*". The board decided not to admit D54 pursuant to Articles 13(1) and 12(6) RPBA because this document, as its content touched upon the core of the debate in the proceedings before the opposition division, should have been filed at an earlier stage, and the circumstances of the appeal case did not justify its admittance.

3.6 A reasoned decision on the non-admittance of D54 is not required since it was filed in the context of the discussion on sufficiency of disclosure of the main request and auxiliary requests 1 to 7, which is not relevant for the present decision.

4. Claim construction

4.1 Claim 1 of auxiliary request 8 is directed to a further medical use and is drafted in the claim format provided by Article 54(5) EPC.

4.2 According to the established jurisprudence of the EPO, where a therapeutic application is claimed in the format according to Article 54(5) EPC, attaining the claimed therapeutic effect is regarded as a functional technical feature of the claim that may establish novelty (see Case Law of the Boards of Appeal of the European Patent Office, 10th edn. 2022, I.C.7.2.1; G 2/08, OJ 2010, 456, Reasons 5.10.9). It also has to be taken into account in the assessment of sufficiency of disclosure (see G 1/03, OJ EPO 2004, 413, Reasons 2.5.2).

4.3 According to claim 1, IL-2, which may be either human IL-2 or aldesleukin, is the active agent responsible for the therapeutic effect of treating type 1 diabetes in a human subject.

4.4 Dependent claim 8 specifies that the treatment is therapeutic, whereas dependent claim 9 specifies that the treatment is preventive. Thus, the feature "treating type 1 diabetes" in claim 1 is understood to encompass both curative and preventive treatment.

5. Amendments (Article 123(2) EPC)

5.1 The opponent's objection under Article 123(2) EPC to claim 1 of auxiliary request 8 concerned the combination of the specific therapeutic indication of "treating type 1 diabetes" with the dose of "less than 3.5 MIU/day", and also the combination of both these features with the feature specifying that the IL-2 is either human IL-2 or aldesleukin.

5.2 This objection was not found convincing for the following reasons.

5.2.1 The question to be decided under Article 123(2) EPC is whether the application as filed discloses the technical features of the amended claim in combination, directly and unambiguously. According to the established jurisprudence of the EPO, a general disclosure in the description or the disclosure of a preferred feature may be combined with claimed embodiments.

5.2.2 Claim 3 as filed relates to IL-2 for use in treating an autoimmune, an immune-related or an inflammatory disorder according to claim 1 (i.e. in a human subject), wherein the IL-2 is to be administered at a dose of less than 3.5 MIU/day. The dose of less than 3.5 MIU/day is thus disclosed in claim 3 as filed for any of the conditions to be treated. The same general disclosure is also found in the description as filed (see page 4, lines 1 to 4), where the dosage in question is moreover disclosed in the section on IL-2 dosage as typical for the invention (see page 16, lines 1 to 4).

5.2.3 T1D as a preferred example of conditions to be treated is individualised in claim 22 (which refers back to claim 3) and on page 9 (lines 12 to 14), and is also

presented in the form of a general disclosure in the description (see page 5, lines 16 to 19; page 26, lines 22 to 24 as filed).

5.2.4 The application as filed teaches that the invention resides in a treatment that stimulates regulatory T lymphocytes (Tregs) without substantially inducing effector T lymphocytes (Teffs) in a human subject (see page 5, lines 9 to 12). Since the desired balancing between Tregs and Teffs is not dependent on the specific immune disorder to be treated, the person skilled in the art, when reading the application as filed, would consider the generally disclosed IL-2 dose of less than 3.5 MIU/day (with 3.5 MIU/day being the highest upper limit mentioned in the text) applicable to all the conditions to be treated, also including the treatment of T1D.

The fact that, in other passages, a smaller range of equal or below 3 MIU/day is mentioned in the context of treating T1D (see page 18, lines 19 to 22) does not change this, since this can be considered a specific embodiment of the general disclosure of less than 3.5 MIU/day.

5.2.5 Support for the IL-2 being human IL-2 or aldesleukin is provided in the form of general disclosures on page 10, lines 30 to 31 ("The invention more preferably uses a human IL-2"), and page 11, third paragraph of the application as filed (disclosing Aldesleukin® as a suitable commercial form for use in human patients).

5.2.6 Thus, the combination of features as defined in claim 1 derives directly and unambiguously from the content of the application as filed.

5.3 As to dependent claims 5 to 7, the board agrees with the opposition division's finding in the decision under appeal (Reasons 5 and 3.1.3) that the application as filed (page 4, lines 10 to 14; page 19, lines 1 to 20) provides general disclosure of a preferred dosage "once per day during at least three consecutive days", more preferred during 3 to 7 consecutive days. Claim 9 as filed recites a maintenance dose given after 1 to 4 weeks.

5.4 For the reasons set out above, the combination of technical features defined in claims 1 and 5 to 7 does not extend beyond the content of the application as filed.

5.5 The claims of auxiliary request 8 *prima facie* meet the requirements of Article 123(2) EPC. With regard to any additional objections raised by the opponent on appeal, reference is made to point 2.3 above.

6. Sufficiency of disclosure (Article 83 EPC)

6.1 As mentioned above (see point 4.2), attaining the claimed therapeutic effect is regarded as a functional technical feature of claim 1.

6.2 For the requirement of sufficiency of disclosure to be met, the claimed therapeutic efficacy has to be credible on the basis of the information provided in the patent application together with the common general knowledge then available to the skilled person.

6.3 The opponent objected that this was not the case as the opposed patent did not render the suitability of low-dose IL-2 for treating T1D credible.

In this regard, the opponent argued that the clinical study described in Example 1 could not prove efficacy

in the claimed therapeutic indication since the patients involved in this study did not have T1D. Example 1 could not provide a more general proof of concept, either, the reason being that document D9 showed a prejudice in the art that called the hypothesis behind the alleged mechanism (increase of Treg cells) into question. While Example 2 showed that Treg cells were induced also in T1D patients, this did not amount to evidence of clinical improvement in patients with T1D.

6.4 These arguments were not found convincing for the following reasons.

6.4.1 The application as filed (page 1, line 17 to page 2, line 26) and the corresponding passages of the patent in suit set out that IL-2 had been used in the clinic for boosting effector immune responses in cancers and infectious diseases, but had been found to also play a major role in the survival and function of regulatory T cells (Tregs), which were known to suppress anti-tumour effector responses.

In the particular situation of an autoimmune disease, the effector T cells (Teffs) include the T cell population responsible for or involved in the disease (see page 12, lines 17 to 18). Thus, the capacity of IL-2 to stimulate Teffs carries the risk of activating the cells that mediate the disease, and thus of aggravating the disease (page 2, lines 11 to 13).

The invention seeks to reduce or prevent an undesirable immune response in a human subject by administering an amount of IL-2 effective to stimulate Tregs without substantially inducing Teffs. The invention thereby makes it possible to increase the Treg/Teff ratio.

According to the application as filed, the invention can be used for the treatment or prevention of autoimmune conditions or any condition associated with or caused by an undesirable immune response and is particularly suited for, among other conditions, HCV-related vasculitis and T1D (see the application as filed, page 5, lines 9 to 12 and 16 to 22).

Thus, a common mechanism, namely the selective amplification of Treg cells, is identified as the basis for the efficacy of IL-2 in the pathologies to be treated.

6.4.2 The passages describing the Examples (Examples 1 and 2) in the application as filed have the same content as the corresponding passages in the patent as granted.

6.4.3 Example 1 presents data from a prospective phase I/II clinical study in patients having HCV-related vasculitis, who received 1.5 MIU/day or 3 MIU/day of IL-2. Low-dose IL-2 was found to be well-tolerated. It led to a marked increase in Tregs and Treg/Teff ratio as well as clinical improvement in parameters of the vasculitis.

6.4.4 Thus, Example 1 shows that IL-2 at a dose of below 3.5 MIU/day induces Tregs without inducing Teffs, thereby providing the skilled person with proof of concept and a way of putting the claimed invention into practice for the treatment of the targeted auto-immune related pathologies based on the same mechanism, including the treatment of T1D.

6.4.5 While HCV-related vasculitis and T1D are different pathologies, they have Treg insufficiency as an underlying cause in common, and the opponent did not provide conclusive evidence that could call the mechanism of selectively increasing the level of Treg

cells to treat T1D into question (regarding the mechanism in T1D, see also the pre-published review article D7: page 4, right-hand column, "Collectively, these studies suggest that T1D onset is associated with a loss of Treg cells numbers or/and function").

The opponent asserted that document D9 showed a prejudice in the art concerning the effective treatment of T1D in humans (without, however, indicating any supporting passages in D9).

The board notes that D9 is a scientific journal article. As such it does not represent common general knowledge and its disclosure cannot be considered evidence of a prejudice in the art. Nor did the opponent point out any specific passage in D9 that could be understood as referring to a pre-existing general prejudice in the art.

D9 describes experiments that suggest that, in T1D patients with aberrant IL-2R signalling, responsiveness to IL-2 may be decreased in comparison with control subjects. However, the authors of D9 do not draw any conclusion from this that could be taken to clearly suggest that the mechanism shown in the application as filed would not work for treating T1D. Instead, they state that many questions remain to be answered and further investigation is needed (see D9: page 412, left-hand column, Discussion). Thus, the teaching of D9, if taken into consideration, does not appear sufficient to substantiate a serious doubt.

6.4.6 The comment in the second paragraph on page 18 of the description:

> *"However, the occurrence of new onset of T1D has been described in patients with cancer treated with low dose of IL-2. Therefore the treatment of human patients with T1D is not straightforward (...) "*

remains unspecific and does not provide a verifiable basis for doubting the conclusions based on the data in Example 1 and on the reported outcome in mouse models of T1D. Consequently, this passage cannot tip the balance of the available evidence against enablement.

6.4.7 In conclusion, the content of Example 1 alone, in light of Treg insufficiency occurring in both pathologies as a mechanistic explanation, renders the claimed therapeutic efficacy credible not only for HCV-related vasculitis, but also for T1D. Absolute proof of clinical efficacy in T1D is not required.

6.4.8 In addition, the application as filed mentions earlier findings (see page 17, line 30 to page 18 line 2; corresponding to paragraph [0090] of the patent in suit) that it was known that IL-2 can prevent the onset of T1D in mouse models (NOD mice) and, given very early after onset, can reverse diabetes.

6.4.9 Example 2 reporting on interim results observed in a dose-finding clinical study in T1D patients confirms that low-dose IL-2 (0.3, 1 and 3 MIU/day) provided as Proleukin® (aldesleukin) is safe and can induce Tregs in T1D patients. This is corroborated by the post-published results in D8.

6.4.10 From the opponent's appeal submissions it is not evident that former objections regarding insufficient disclosure of the treatment's suitability specifically for preventing T1D or the suitability of dosages higher than 3 MIU/day were maintained.

For the sake of completeness, the board notes that these objections were not substantiated by conclusive verifiable facts (see also the decision under appeal, Reasons 3.2.1 and 3.2.2). The fact that non-serious

adverse events occurred in the 3 MIU/day group of the T1D study (see the application as filed, page 40, lines 19 to 21 and D8: Abstract) does not necessarily mean that dosages between 3.0 and 3.5 MIU are unsuitable.

6.5 For these reasons, the claimed subject-matter meets the requirement of sufficiency of disclosure (Article 83 EPC).

7. Validity of the priority claim (Article 87 EPC)

7.1 The patent in suit claims priority from two earlier applications filed on the same day. As the content of these earlier applications is identical, reference is made only to US 61/451,663.

7.2 The opponent's objection was that the priority application was not enabling for the subject-matter of claim 1 of auxiliary request 8 due to the lack of experimental data on T1D.

7.3 Like the application as filed, the priority application mentions (see page 16, lines 20 to 25) that it was known that IL-2 can prevent the onset of T1D in mouse models (NOD mice). It includes Example 1 (page 25, line 21 to page 34, line 5 and page 2, lines 18 to 28) and the accompanying figures and tables, as present identically in the application as filed and in the patent in suit. The priority application also teaches translating from vasculitis to T1D on the basis of the same mechanism of action, namely a preferential stimulation of Tregs (see page 2, lines 18 to 28; page 4, lines 26 to 30 and the paragraph bridging pages 5 and 6). The priority application does not include Example 2.

7.4 The board concludes that the claimed subject-matter is enabled in the priority application by the same elements (the corresponding passages being present in the priority application) and for the same reasons as set out in points 6.4.3 to 6.4.8 above.

7.5 For these reasons, the subject-matter according to claim 1 of auxiliary request 8 is entitled to the claimed priority.

7.6 Concerning additional objections relating to the dependent claims, reference is made to point 2.3 above.

7.7 As the priority was found valid, documents D26, D28 and D43 are not part of the state of the art. Accordingly, the opponent's arguments regarding sufficiency of disclosure, novelty and inventive step that relied on any of these documents could not be taken into account.

8. Novelty (Articles 100(a), 52(1) and 54 EPC)

Document D1a

8.1 The opponent contended that the disclosure of document D1a (see pages 3 to 5), which describes the setup and protocol for a phase 1 clinical study on combination treatment with proleukin and rapamune in T1D, anticipated the claimed subject-matter.

8.2 This objection fails because D1a does not include any result, and therefore does not disclose the therapeutic efficacy of the combination treatment (see point 4.2 above). Data obtained in a one-arm study for a combination treatment (see D1a: page 4, Study Design) would, moreover, not be conclusive regarding the therapeutic efficacy of IL-2 (see point 4.3 above).

8.3 The opponent's argument that, in its view, the patent in suit does not disclose the claimed therapeutic benefit, either, is not relevant in this context.

According to the terms of claim 1, the therapeutic effect is attained. This is a limiting feature of the claim (see point 4.2 above).

What has to be established in assessing novelty is whether the combination of technical features of the claim in question, including in the case in hand the feature of attaining the therapeutic effect, can be derived directly and unambiguously from the prior-art document cited against it.

This is different from the assessment of sufficiency of disclosure, where it has to be established whether a technical effect which is a feature of the claim in question has been rendered credible in the application as filed. This issue is addressed in section 6. above, with the result that the claimed subject-matter meets the requirement of sufficiency of disclosure.

8.4 A further distinction is that the dosage of 4.5 MIU proleukin administered three times a week as specified in D1a (see page 5: "Assigned interventions") is not in conformity with the terms of claim 1, because on any day that the drug is administered, the dosage is 4.5 MIU, which is more than 3.5 MIU/day.

Document D4

8.5 Document D4 relates to a treatment that combines an IL-2 receptor agonist with a proteasome inhibitor for the treatment of immune conditions in mammals, in general humans (see D4: page 1, lines 21 to 26 and 32). The immune condition may be T1D (see page 1, first paragraph; paragraph bridging pages 4 and 5). The IL-2 receptor agonist may be Proleukin (i.e. aldesleukin;

see page 2, last paragraph and claim 14). The dosage ranges disclosed in D4 for mammals are less than 20 MIU, less than 7 MIU and 1 to 10 MIU of the IL-2 receptor agonist (see page 2, lines 29 to 31; page 5, lines 23 to 27; page 9, lines 15 to 16; claims 15 and 16). The dosage ranges are not disclosed as dosages to be administered per day and are mentioned separately from dosage frequency, which may be daily dosing (see page 9, lines 11 to 14), twice daily intravenous administration (see page 9, lines 23 to 24) or administration on days 1, 5, 9 and 13 of a 21-day cycle (see claim 20).

8.6 The board agrees with the opposition division's conclusion that document D4 does not provide specific disclosure of the combination of features defined in claim 1 of auxiliary request 8 (see the decision under appeal, Reasons 5.1.2). In particular, the dosage of 1 MIU is not specifically disclosed in D4 for human IL-2 or aldesleukin, for administration at less than 3.5 MIU/day (such as daily or twice daily administration of 1 MIU), and for T1D.

Conclusion on novelty

8.7 For these reasons, the subject-matter of claim 1 is novel over the disclosure of D1a and D4 (Articles 52(1) and 54 EPC).

9. Inventive step (Articles 100(a), 52(1) and 56 EPC)

Patent in suit

9.1 The patent in suit aims to provide IL-2-based therapies of diseases caused by an undesirable immune response in human subjects, without inducing IL-2 associated side effects. More specifically, the invention relates

to low-dose IL-2 therapy of T1D in human subjects (see paragraphs [0001] and [0009] of the patent in suit).

9.2 What is claimed is IL-2, selected from human IL-2 or aldesleukin, for use in treating T1D in human subjects in a low-dose treatment of less than 3.5 MIU/day (see the wording of claim 1 rendered in point V. above).

Starting point in the prior art

9.3 It was common ground that inventive step should be assessed starting from the disclosure of documents D1 and D13.

9.4 Both documents relate to preclinical data observed in NOD mice, a mouse model of T1D, showing that low-dose IL-2 increases the number of Treg cells.

Both describe two different experimental setups. One of these used recombinant human IL-2 at a dosage of 25000 IU daily (D1) or 25000 IU three times per week (D13). The second setup is further removed from the subject-matter of current claim 1 as it used recombinant mouse IL-2.

D1 (Figure 1 and page 1877, section "Materials and methods: IL-2 treatment") shows that a daily dose of 25000 IU of recombinant human IL-2 given for five days reverses established T1D in NOD mice.

D13 discloses that 25000 IU human recombinant IL-2 given three times a week protects NOD mice from developing diabetes (see D13: Summary; Figure 7; page 692, left-hand column and page 695, section "Experimental procedures - Treatment with IL-2").

Objective technical problem and solution

9.5 It was not in dispute that the subject-matter of claim 1 differs from the disclosure in documents D1 and D13 by two distinguishing technical features:

(i) the therapy is carried out in human subjects

(ii) the dosage to be administered is less than 3.5 MIU/day

9.6 Thus, starting from the disclosure of D1 or D13, the objective technical problem is to provide an effective treatment of T1D by IL-2 administration in human subjects.

9.7 As set out in the section relating to the issue of sufficiency of disclosure, it is acknowledged that achieving the claimed therapeutic efficacy of low-dose IL-2 in T1D in human subjects is a credible technical effect based on mechanistic considerations involving the preferential stimulation of Tregs without substantial stimulation of Teffs, and the observed clinical response in HCV-associated vasculitis. It was also shown that the administration of IL-2 at a dosage below 3.5 MIU/day, such as 1 MIU/day, induces Tregs in T1D patients and is well tolerated (see the patent in suit, Example 2, paragraph [0169], Figure 8).

The study results post-published in D8 confirm that IL-2 was well-tolerated in T1D patients and that it induced a dose-dependent increase in the proportion of Treg cells, significant at all doses (0.33 MIU/d, 1 MIU/d, 3 MIU/d) compared with placebo (see D8 Summary/ Findings and page 302: Discussion).

In the decision under appeal (Reasons 5.2.1 and 3.2.2), it was acknowledged that, in view of the known data, the upper limit of the dosage range of 3.5 MIU/day was

appropriate for delimiting the range permitting the desired selective amplification of Tregs. The opponent did not contest this any longer on appeal.

Obviousness of the solution

9.8 The link between IL-2 deficiency, loss of Treg cells and T1D as well as the interest to use IL-2 modulatory strategies for treating T1D was known in the art, not only from D1 and D13 but also from the review article D7 (see page 9, section "Conclusion").

9.9 Both D1 and D13 propose the use of "low-dose" IL-2 for inducing Treg cells in human T1D patients without an undesirable effect on other cells, such as Teff cells (see D1: paragraph bridging the columns on page 1877; D13: paragraph bridging pages 694 and 695).

9.10 Neither document suggests a particular dose or dosage regimen. D1 and D13 do not provide clinical evidence of a therapeutic effect of low-dose IL-2 in human T1D patients, nor was this known from D7.

9.11 What has to be established is whether the person skilled in the art would have translated the positive results obtained in the NOD mouse model into an effective treatment of human patients at a dose of less than 3.5 MIU/day with a reasonable expectation of success.

9.12 The opponent argued that dosage determination of IL-2 for a new therapeutic indication (in the case in hand, T1D) by way of clinical dose-ranging studies would have been a routine activity that did not require inventive skill. Based on the knowledge from D13 alone or in combination with D1a and D5, it would have been likely that a dose below 3.5 MIU/day would have been tested,

which would inevitably have led to the claimed invention.

9.13 The board does not agree with the opponent's conclusion because, firstly, only preclinical data in rodents were known, and secondly, dose-finding would not have been obvious.

9.13.1 As pointed out by the patent proprietors, it would not have been straightforward to establish a suitable dosage regimen for humans starting from a situation in which no dose had been proposed to treat T1D in human patients. This is different from trying to reduce a dose known to be effective, as it was not clear that a safe and effective dose existed for these patients.

9.13.2 In contrast to the assessment of obviousness, the assessment of sufficiency of disclosure as set out in section 6. above is based on the data provided in the patent in suit, according to which it was shown that a dose of below 3.5 MIU/day IL-2 could achieve a preferential amplification of Tregs in human patients. This was however not known to the skilled person at the relevant date.

9.13.3 The dose of 25000 IU in mice is what the authors of D13 and D1 call a low dose. As set out by the patent proprietors (undisputed by the opponent), this corresponds to a dose of 7 MIU in humans (see the patent proprietors' statement setting out the grounds of appeal, footnote 11 on page 30). This is considerably higher than the claimed dose of less than 3.5 MIU/day. Neither document contains a suggestion for dosage translation for use in human patients, and neither document points to dosages of below 3.5 MIU/day.

9.13.4 The skilled person would not have been certain that the preclinical results disclosed in D1 and D13 could be reproduced in human T1D patients to provide a useful Treg/Teff ratio, seeing that pathogenic Teff cells (which may be activated by IL-2) in diabetes exacerbate the disease and T1D patients may show decreased IL-2 responsiveness in Tregs, as disclosed in D9. This could have been the basis for certain concerns regarding reduced responsiveness in T1D patients.

9.13.5 D13 acknowledges that the in vivo effect of IL-2 can vary widely depending on the dosing regimen, the amount of endogenous IL-2 and the numbers of various relevant activated cell types in the host. Thus, an optimal IL-2 treatment regimen could be difficult to predict (see D13, page 694, paragraph bridging the columns).

9.13.6 These circumstances (points 9.13.2 to 9.13.5) taken together do not establish a reasonable expectation of success specifically for dosages below 3.5 MIU/day, i.e. less than half the human equivalent dose based on D1 and D13 (see point 9.13.3 above), and it is not certain that such dosages would inevitably have been tested by the person skilled in the art seeking to solve the objective technical problem.

9.14 The opponent also argued that the disclosure of D1 and D13, when combined with the teaching of D5 and D1a, would have led the skilled person to the claimed invention. D17 was also mentioned as teaching the use of ultra-low doses of IL-2 to treat autoimmune diseases.

9.14.1 As discussed in more detail above, D1a merely discloses the protocol of a clinical phase I study, without revealing any results observed in such a study. The disclosure of the study protocol, in the case in hand

for a combination treatment (4.5 MIU of IL-2 three times weekly combined with sirolimus) rather than for IL-2 monotherapy, does not translate into a reasonable expectation of success for low-dose IL-2 monotherapy with less than 3.5 MIU/day.

9.14.2 The European patent application D5 relates to treatment of rheumatoid arthritis or systemic lupus erythematosus using 35 to 2000 U/day of IL-2 (see D5: claim 6). The document, which was published in 1987, does not provide any rationale with regard to Tregs. As pointed out by the patent proprietors, the dose in D5 is not indicated in IU (i.e. international units established by the WHO) but in units used internally by the applicant company for which it is not indicated how they can be converted into IU. Thus, even if it had been consulted, D5 does not contribute any decisive piece of information that would have led the person skilled in the art to the claimed invention.

9.14.3 D17 relates to the use of proliferatively active compounds, especially cytokines or growth factors, as active vectors for pharmacologically active compounds, for example conventional drugs or genes (see D17: page 1, lines 4 to 6). No detailed arguments on D17 in relation to the expectation of success for the subject-matter of claim 1 were provided. D17 is silent as to the impact of IL-2 on the Treg/Teff balance, let alone possible doses that would have a positive effect on this balance. In view of the different treatment concept and the absence of any data in D17, this document could not have provided a reasonable expectation of success.

9.14.4 In conclusion, the person skilled in the art would not have seen a straightforward route to the claimed invention and would not have been pointed by the

prior art towards exploring the dosage range below 3.5 MIU/day. Thus, the inventors' contribution went beyond mere routine dose-finding experimentation.

9.15 For these reasons, the subject-matter of claim 1 of auxiliary request 8 involves an inventive step within the meaning of Article 56 EPC. The same conclusion applies to the dependent claims.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

A. Wille M. Pregetter

Decision electronically authenticated