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Datasheet for the decision of 10 October 2024

Case Number: T 1601/22 - 3.3.04

Application Number: 18179669.9

Publication Number: 3443979

IPC: A61K38/20, A61K38/12, A61P3/10

Language of the proceedings: EN

Title of invention:
IL-2 dosage regimen for treating systemic lupus erythematosus

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, 87, 123(2), 76(1)
RPBA Art. 12(4)

Keyword:
Auxiliary request 4 - allowable

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Case Number: T 1601/22 - 3.3.04

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

Appellant: (Patent Proprietor 1)	ASSISTANCE PUBLIQUE - HÔPITAUX DE PARIS 3, avenue Victoria 75004 Paris (FR)
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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)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 28 April 2022 concerning maintenance of the European Patent No. 3443979 in amended form.**

Composition of the Board:

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

Summary of Facts and Submissions

I. European Patent No. 3 443 979 (patent in suit) derives from European patent application No. 18179669.9, which is a divisional of European patent application No. 12708029.9 (the earlier application, published as international application No. WO 2012/123381).

II. The 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 and of the parent application.

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

SLE: systemic lupus erythematosus

IU: International Units

MIU: million International Units

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

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

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

IV. The documents cited in the proceedings before the opposition division included the following

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 0 262 802 A2

D7: WO 2012/065212 A1

D9: Declaration D. Klatzmann (26 June 2019)

D11: Journal of Autoimmunity 21, 273-276 (2003)

D12: The Journal of Immunology, 175, 8392-8400 (2005)

D13: Immunology 117, 280-286 (2006)

D21: N Engl J Med 365:22, 2067-2077 (1 December 2011)

D26: History of changes for study: NCT01353833, Dose-Effect Relationship of Low-dose IL-2 versus Placebo in Type 1 Diabetes (DF-IL2), version of 13 May 2011, ClinicalTrials.gov archive

D28: WO 2010/085495 A1

D40: Proleukin® Package Insert - Reference ID 3165255

D53: Journal of Autoimmunity 58, 48-58 (2015)

V. In the proceedings before the opposition division, the patent proprietors submitted an amended main request and twelve auxiliary requests.

VI. The decision under appeal is the opposition division's interlocutory decision, announced in oral proceedings on 28 March 2022 and posted on 28 April 2022, rejecting the patent proprietors' main request and auxiliary requests 1 to 4 and finding that the patent as amended in the form of auxiliary request 5 (filed at the oral proceedings of 28 March 2022) met the requirements of the EPC.

VII. Claim 1 of auxiliary request 5, which is the only independent claim of this request, reads as follows:

1. Interleukin-2 (IL-2) for use in treating systemic lupus erythematosus 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 is human IL-2 or aldesleukin, and wherein said IL-2 is to be

administered at a dose of between 1 MIU/day and 3 MIU/day.

VIII. According to the decision under appeal, the subject-matter of claim 1 of auxiliary request 5 did not extend beyond the disclosure of the application and the patent application as filed (Articles 123(2) and 76(1) EPC).

The claimed subject-matter met the requirement of sufficiency of disclosure (Article 83 EPC) and was also novel over the disclosure of document D7 (Articles 52(1) and 54 EPC).

The claimed invention was disclosed in an enabling manner in the priority applications EP 11305269 and US 61/451,663. The claims of auxiliary request 5 were thus entitled to priority (Article 87 EPC). As a consequence, intermediate documents D21 and D26 cited by the opponent were not part of the state of the art.

Inventive step was assessed starting from the disclosure of document D5. The objective technical problem was to provide a treatment of systemic lupus erythematosus that ensured a reproducible therapeutic effect. Having regard to the state of the art, in particular D5 itself and supplementary documents D4 and D28 relied on by the opponent, the claimed subject-matter would not have been considered an obvious solution to this technical problem (Articles 52(1) and 56 EPC).

IX. Both the opponent and the patent proprietors appealed against this decision. Since both parties filed an appeal, they are referred to in this decision as the opponent and the patent proprietors for better ease of reading.

X. With their grounds of appeal, the patent proprietors filed the sets of claims of a main request and eleven auxiliary requests.

XI. The claims of current auxiliary request 4 are identical to those of former auxiliary request 5 held allowable by the opposition division (see point VII. above for the wording of claim 1), except that the claim dependencies in claim 10 were amended to read "according to any of claims 1 to 8" in current auxiliary request 4 instead of "according to any of claims 1 to 9" as in former auxiliary request 5.

XII. With its grounds of appeal, the opponent filed new documents D56 to D67, as set out in point 2.1 of the opponent's submission.

XIII. The board issued a summons to oral proceedings.

XIV. The opponent advised the board that it would not be attending the oral proceedings and would not be filing any further written submissions.

XV. Oral proceedings before the board were held on 10 October 2024, in the opponent's absence.

The board decided against the admittance of any of documents D56 to D67.

The patent proprietors withdrew their appeal, which meant that the main request and auxiliary requests 1 to 3 were no longer to be considered.

The board found the claims of auxiliary request 4 allowable. The patent proprietors confirmed that auxiliary request 4 also encompassed the description and drawings as amended before the opposition division

for former auxiliary request 5 that was held allowable in the decision under appeal.

XVI. The opponent's pertinent arguments as presented in writing may be summarised as follows.

Admittance of evidence filed upon appeal

Documents D56 to D65 were filed in response to positions taken by the opposition division regarding the teaching of the opposed patent and common general knowledge at the effective date. Documents D66 and D67 were relevant for the interpretation of D5, also in response to the opposition division's views on this.

Amendments (Articles 76(1) and 123(2) EPC)

The dosage ranges of between 1 MIU/day and 3 MIU/day in claim 1 and between 1 MIU/day and 2 MIU/day in claim 3 did not find the required support in the application as filed.

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 systemic lupus erythematosus (SLE), because it did not provide any data or technical reasoning in respect of the treatment of SLE.

Instead, the patent in suit and the application as filed 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 SLE.

The second (Example 2) provided interim data from a clinical study in patients with type 1 diabetes on the induction of regulatory T cells (Tregs).

Treg induction and clinical improvement in HCV-related vasculitis observed according to Example 1 could not be considered proof of therapeutic efficacy in SLE.

It was contested that it was common general knowledge at the effective date of the patent in suit that patients with SLE, like those with HCV-related vasculitis, were characterised by a significantly decreased number of Treg cells and the presence of autoantibodies.

The teaching of D21 and D53 showed that there were reasons not to accept the experimental data in the application as filed as proof of concept for SLE. For instance, the authors of D21, a post-published report of the HCV-related vasculitis trial, stated that further studies were needed to determine whether this invention (i.e. treatment with IL-2) would also be effective in the treatment of other inflammatory and autoimmune diseases, such as atherosclerosis and type 1 diabetes.

Validity of the priority claim (Article 87 EPC)

The suitability of low-dose IL-2 for use in treating SLE was not disclosed in the priority applications in an enabling manner.

Furthermore, the claimed dosage ranges of between 1 and 3 MIU/day and between 1 and 2 MIU/day could not be derived directly and unambiguously from the priority applications.

Novelty

Document D7 was citable against novelty of the claimed subject-matter under Article 54(3) EPC.

The subject-matter of at least claim 1 of auxiliary request 4 lacked novelty over the disclosure of documents D7 (claim 10 in combination with page 14).

Inventive step

The claims of auxiliary request 4 also lacked an inventive step, starting from the disclosure of document D5, taken alone or in combination with supplementary documents D4 or D1a.

D5 disclosed the treatment of SLE in human patients using human IL-2 and demonstrated a therapeutic benefit. The claimed subject-matter differed from the disclosure of D5 only by the dosage range of between 1 and 3 MIU/day as D5 used a lower dosage. The objective technical problem should be defined as the need for an alternative IL-2 treatment regimen for SLE. Since the claimed dosage range of 1-3 MIU/day was arbitrary, the claimed subject-matter did not involve an inventive step.

Document D4 disclosed the use of human IL-2 (Proleukin) and also mentioned SLE (page 1, lines 7 to 9). In view of the teaching in D4 that IL-2 could be administered safely at doses of less than 20 MIU/day, the skilled person would have been motivated to increase the dosage used in D5.

XVII. The patent proprietors' pertinent arguments may be summarised as follows.

Admittance of evidence filed upon appeal

Documents D56 to D67 had been cited by the opponent in relation to questions which had been part of the discussion well before the date of the oral proceedings before the opposition division. Hence, the opponent should have filed these documents at first instance, and they should, therefore, be held inadmissible in the

appeal proceedings. The documents also lacked relevance.

Amendments (Articles 76(1) and 123(2) EPC)

The dosage ranges of between 1 MIU/day and 3 MIU/day in claim 1 and between 1 MIU/day and 2 MIU/day in claim 3 were supported by page 4, lines 1 to 4 and 6 to 8 and page 16, lines 1 to 4 of the (earlier) application as filed. The (earlier) application also made it clear that such dosages were contemplated in the curative or preventive treatment of all disorders listed in the patent. The section at page 16, lines 10 to 22 also provided preferred dosages falling within the claimed ranges, and the examples clearly pointed the skilled person to working within the claimed ranges.

Sufficiency of disclosure

Both patients with HCV-related vasculitis and those with SLE were characterised by a significantly decreased number of Treg cells and the presence of autoantibodies. Example 1 of the application as filed showed that low-dose IL-2 increased Tregs in patients with HCV-related vasculitis. The clinical improvement which was observed, and which was a secondary endpoint of the study reported in Example 1, supported the causal link between this preferential Treg stimulation and the therapeutic effect. Extrapolation to SLE was credible as it was based on the same mechanism of action. Thus, Example 1 provided proof of concept for the medical use defined in claim 1.

Example 2 confirmed that the same increase in Treg/Teff ratio was also seen in patients with type 1 diabetes, and provided preliminary data of clinical improvement. This further confirmed the proof of concept provided

with Example 1, as type 1 diabetes was also known as a pathology presenting a deficiency in Tregs.

The opponent had not substantiated its alleged doubt regarding sufficiency of disclosure with verifiable facts. D53 (mentioned by the opponent) related to type 1 diabetes, and its content was not relevant to the suitability of low-dose IL-2 for the treatment of SLE. Documents D11 to D13 confirmed that it was known at the relevant date that SLE was characterised by a deficiency in Tregs.

Validity of the priority claim (Article 87 EPC)

The dosage range of claim 1 found direct and unambiguous support in various passages of the priority applications.

The priority applications related to the same invention as currently claimed. Proof of concept was provided by Example 1 showing the preferential stimulation of Tregs over Teffs in HCV-related vasculitis. Extrapolation to SLE was appropriate as both pathologies, mediated by auto-antibodies, were characterised by a deficiency in Tregs.

Novelty

D7 disclosed a broad range of doses for any interleukin, and SLE was one in a list of inflammatory conditions to be treated. D7 also taught that the daily dose administered to a patient depended on the nature and severity of the inflammatory condition to be treated (see D7: page 14, line 25 to page 15, line 2). Thus, D7 did not provide direct and unambiguous disclosure of treating a patient with SLE with a dose of IL-2 of between 1 and 3 MIU/day.

Inventive step

Document D5 disclosed a general dosage range for IL-2 of 35 to 2000 units per day (column 6, line 40 to 56) and two case reports disclosing the intravenous administration of 500 units of IL-2.

D5 provided no rationale supporting a particular dosage range. Tregs were not known at the filing date of D5.

Moreover, the actual dosage amounts used according to D5 were not clear because D5 did not indicate the dosage in International Units. The assumptions underlying the opponent's calculation, intended to establish a correspondence with International Units, were not correct. The activity of the molecule varied from one preparation to another, and the preparation used in D5 was not characterised sufficiently. In fact, it was not possible to derive from the information in D5 how the (undefined) units of IL-2 activity applied in D5 might be converted into standard International Units as determined by the WHO (World Health Organization). The International Units, which were based on a standardised preparation of IL-2, had only been established after the priority date of D5 and were not mentioned in D5.

Starting from the teaching of D5, the objective technical problem was to find the appropriate dose to treat SLE in a reproducible manner.

This problem was credibly solved by providing a dose between 1 and 3 MIU/day which, in humans affected with a Treg deficiency, achieved a preferential stimulation of the Tregs, without substantial stimulation of the Teffs. This would not have been obvious based on the teaching of D5, which did not establish any link between the dose and an immunoregulatory effect.

The supplementary document D4 disclosed a broad range of IL-2 dosages of up to 7 MIU/day (claim 16) or even 20 MIU/day (claim 15). D4 was interested in IL-2 for its ability to stimulate Teffs and did not point to a dose of 1-3 MIU for stimulating Tregs over Teffs. The experimental results provided in D4 concerned a combination treatment and were not relevant to SLE.

The combination of D5 with D1a, also invoked by the opponent, was a new line of argument that should not be admitted on appeal.

XVIII. The opponent requested that the decision under appeal be set aside and that the patent be revoked.

XIX. The patent proprietors requested that the patent be maintained on the basis of the claims of one of auxiliary requests 4 to 11, all filed with the statement setting out the grounds of appeal.

The patent proprietors also requested that documents D56 to D67 not be admitted.

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 XIV. 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 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 XV. above), their main request and auxiliary requests 1 to 3 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 12.1.1, 12.2.1, 12.3.1, 12.4.1 and 12.5.1 of the decision under appeal. These objections are addressed in the decision under appeal, in particular also where relevant to current auxiliary request 4 (which corresponds to former auxiliary request 5 and, but for the deletion of claim 9, to former auxiliary request 4; see the decision under appeal, reasons VII.b to VII.g, VI.a to VI.e and II.b - ad (ii)).

The opponent did not argue that there were any procedural errors by the opposition division in this regard (in particular, that it failed to take the opponent's submissions into account).

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, accordingly, 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 opponent's absence at the oral proceedings.

3. Admittance of evidence filed on appeal

3.1 With its statement setting out the grounds of appeal, the opponent submitted, for the first time, documents D56 to D67 (see point XII. above). This is an amendment to the opponent's case under Article 12(4) RPBA.

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

3.3 The passage in the opponent's statement of grounds of appeal entitled "2.2 Admissibility of Documents" contains the following statements:

- that D56 was filed to illustrate the skilled person's common general knowledge at the effective date, in response to the opposition division's position that the skilled person would be aware that both HCV-related vasculitis and systemic lupus

erythematosus were diseases characterised by a deficiency in Treg cells

- that D57 to D65, all referenced in D56, were filed in case D56 was disregarded on account of being post-published
- that D66 and D67 were filed for details used in D5 to assess IL-2 units of activity, and D66 was cited also in response to the opposition division's view that the IL-2 molecule in D5 could have been glycosylated

3.4 The opponent's explanation fails to set out, however, why the timing, i.e. the filing of these documents only at the appeal stage, might be justified.

3.5 The issue of the relevance of the data on HCV-related vasculitis as a proof of concept applying by extrapolation also to the treatment of SLE was known and had been discussed at first instance (see the patent proprietors' reply to the opposition, page 4, first paragraph and the opposition division's communication dated 23 September 2021, page 13, first paragraph). In its communication dated 23 September 2021, the opposition division mentioned (see page 12, third paragraph) that it was "not apparent that the doses disclosed in D5 were established according to the WHO standard for IU". Thus, this issue was also known and was not mentioned for the first time in the decision under appeal. The issue of glycosylation in D5 is irrelevant against this background.

3.6 Hence, the board did not admit documents D56 to D67 under Article 12(6) RPBA since these documents should have been filed at first instance.

4. Claim construction

4.1 Claim 1 of auxiliary request 4 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 systemic lupus erythematosus in a human subject.

5. Amendments (Articles 76(1) and 123(2) EPC)

5.1 The description of the application as filed is identical to the description and claims of the earlier application. The claims of the earlier application are listed as "items" in the application as filed. The application as filed additionally includes its own set of claims. In the following assessment (points 5.2 to 5.5), reference is made only to the earlier application.

5.2 The earlier application states on page 16 that the dosage according to the invention is typically below 3.5 MIU/day, more preferably below 3.0, 2.5 or below 2.0 MIU/day. A list of preferred dosages includes 3.0,

2.5, 2.0, 1.5 and 1.0 MIU/day and further dosages below 1 MIU/day (see page 16, lines 2 to 22). The passage on page 4, lines 6 to 8 additionally states that in a preferred embodiment, IL-2 is administered at a dose of about 3 MIU/day or less than about 2 MIU/day, preferably between about 0.1 MIU/day and about 2 MIU/day, preferably between about 0.3 and about 1 MIU/day. In the examples, dosages of 1.5, 1 and 3 MIU/day were used.

5.3 On this basis, as the endpoints of the claimed ranges are disclosed, and the claimed dosage ranges are within the general range of below 3.5 MIU/day, the claimed ranges of 1 to 3 MIU/day (claim 1) and 1 to 2 MIU/day (claim 4), although not recited as such, are covered implicitly and do not extend beyond the content of the application as filed.

5.4 The board thus agrees with the reasoning provided in the decision under appeal, reasons II.a.

5.5 Decisions T 2/81, T 925/98 and T 249/12 mentioned by the opponent do not support the opponent's case as the circumstances with regard to the disclosed and claimed endpoints and ranges were different from those in the case in hand. The opponent's argument that the person skilled in the art would not contemplate working within the claimed ranges because a lower dosage was exemplified (in particular, 0.3 MIU/day in Example 2) is not plausible, seeing that values within the claimed dosage ranges are clearly envisaged, applied in the Examples, and disclosed as preferred dosages (see point 5.2 above).

5.6 For these reasons, the subject-matter of claims 1 and 4 of auxiliary request 4 meets the requirements of Articles 76(1) and 123(2) EPC.

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 SLE credible.

In this regard, the opponent argued that the clinical studies described in Examples 1 and 2 could not prove efficacy in the claimed therapeutic indication since the patients involved in these studies did not have SLE. The examples could not provide a more general proof of concept based on mechanism, either, the reason being that it was not generally known at the relevant date that SLE was a pathology characterised by a deficiency in Tregs (in other words, that it could be treated by the same underlying mechanism). Also, the teaching of D21 and D53 showed that there were reasons not to accept the experimental data in the application as filed as proof of concept for SLE.

6.4 These arguments were not found convincing for, *inter alia*, the same reasons as set out in the decision under appeal, reasons II.b - ad (ii).

6.5 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, type 1 diabetes and SLE (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.

6.6 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.

6.6.1 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.

6.6.2 Example 2 reporting on interim results observed in a dose-finding clinical study in patients with type 1 diabetes confirms that low-dose IL-2 (0.3, 1 and 3 MIU/day) provided as Proleukin® (aldesleukin) is safe and can induce Tregs in these patients.

6.7 Thus, the application as filed mentions that a Treg defect has been reported in various autoimmune human diseases and the invention is particularly suited for treating inflammatory or autoimmune diseases, including SLE (page 26, lines 22 to 25).

6.8 The application identifies a common mechanism, namely the selective amplification of Treg cells, as the basis for the efficacy of IL-2 in the pathologies to be treated. This mechanism is demonstrated in patients with HCV-related vasculitis and with type 1 diabetes.

6.9 The application refers to a previous publication which reports that Tregs are significantly reduced in HCV patients (see page 27, lines 1 to 16).

6.10 The patent proprietors furthermore provided a declaration by one of the inventors which confirms that it was known at the effective date that SLE is a disease showing Treg insufficiency (see D9: point 7). The references D11, D12 and D13 mentioned in D9 all relate to Treg deficiency in SLE. All of these references are articles in scientific journals (not reviews that would be considered evidence of common general knowledge). Taken together, they nevertheless show that this knowledge was published by different

research teams before the priority date of the patent in suit and that the subject of Treg deficiency was widely known as a subject of research in the field.

6.11 In contrast, the opponent did not provide timely and adequate substantiation for its allegation that it was not part of the common general knowledge that SLE was a pathology characterised by Treg deficiency. As mentioned above (see point 3.6), documents D56 to D65 were not admitted as they should have been filed at an earlier stage.

6.12 In support of its assertion of a disincentive or technical prejudice, the opponent relied on D21 and D53 (both published after the priority date). Neither document provides information relating to SLE. This line of argument cannot, therefore, substantiate serious doubt regarding the application of the invention to the treatment of SLE (for more detail, see the decision under appeal, reasons II.b, page 13, fifth and sixth paragraphs).

6.13 In conclusion, the experimental results provided in the examples are acknowledged as proof of concept that is also valid in the case of SLE. In this regard, Example 1 is enough to support the finding that 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. For the purpose of this assessment, it is enough to refer only to US 61/451,663.

7.2 As set out in the decision under appeal (reasons VI.c, first six paragraphs, and reasons VII.d), the claimed dosage ranges of 1 to 3 MIU/day (claim 1) and 1 to 2 MIU/day (claim 4) find a basis also in the priority application as filed, see page 15, lines 10 to 17 and page 15, line 25 to page 16, line 8 of US 61/451,663. These passages recite the typical dosage of below 3.5 MIU/day, more preferably below 3.0, 2.5 or below 2.0 MIU/day, and exemplary dosages including 3.0, 2.5, 2.0, 1.5 and 1.0 MIU/day. Claims 9 and 10 disclose administration of less than 2 and less than 1 MIU/day. In Example 1, 1.5 MIU/day is exemplified.

7.3 The opponent's further objection of lack of enablement cannot succeed. Since the priority application contains Example 1 and the further relevant passages discussed above (with the exception of Example 2), the reasoning provided in the section on sufficiency of disclosure also applies here (see points 6.4, 6.5, 6.6.1, 6.7 to 6.9, 6.11 to 6.13 above).

7.4 For these reasons, the subject-matter claimed in auxiliary request 4 is entitled to the claimed priority.

7.5 As a consequence, document D21, which was published after the priority date, is not part of the state of the art.

8. Novelty (Articles 100(a), 52(1) and 54(3) EPC)

8.1 The opponent argued that the International patent application D7 was prior art under Article 54(3) EPC, since its priority was validly claimed and it had entered the regional phase before the EPO.

8.2 Irrespective of whether these conditions are met, the disclosure of D7 does not anticipate the subject-matter of claim 1 for the following reasons.

8.2.1 D7 (see claim 1 and page 1, first paragraph) relates to the treatment of an inflammatory condition by mucosal, e.g. sublingual, administration of an interleukin or a fragment or derivative thereof. The interleukin may be IL-2, such as recombinant human IL-2 (page 3, lines 10 to 11). Among other options, the condition to be treated may be SLE (page 3, lines 16 to 21 and claim 10).

8.2.2 However, the proposed dose covers a broad range "in the order of" from 1 IU to 3 MIU/day and doses below and above this range, typically between 1 IU and 100000 IU (see D7: page 14, lines 17 to 19, lines 27 to 29). D7 also states that the therapeutically effective dose level will depend upon the type and stage of the inflammatory condition to be treated and the activity of the active agent (page 14, lines 5 to 11).

8.3 Consequently, the dose of 3 MIU/day, or any particular dose within the claimed dosage range, is not directly and unambiguously linked in D7 with the therapeutic indication SLE and with the administration of human IL-2 or aldesleukin.

8.4 In conclusion, the novelty of the claimed subject-matter is acknowledged.

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 SLE in human subjects (see paragraphs [0001] and [0008] of the patent in suit).

9.2 What is claimed in claim 1 of auxiliary request 4 is IL-2, selected from human IL-2 or aldesleukin, for use in treating SLE in human subjects in a low-dose treatment with doses of between 1 MIU/day and 3 MIU/day (see the wording of claim 1 rendered in point VII. above).

Starting point in the prior art

9.3 It was common ground that inventive step should be assessed starting from the disclosure of document D5.

9.4 D5 relates to the treatment of SLE or rheumatoid arthritis with an "interleukin-2 active substance" which may be human IL-2 (see D5: claim 1).

9.5 D5 discloses two case studies reporting a therapeutic effect of IL-2 administered intravenously at a dose of "500 U" for 14 days in the treatment of SLE (see D5: Clinical Cases 9 and 10). Figure 1 shows the amino acid sequence of the recombinant IL-2 used in the clinical cases (see D5: column 7, lines 26 to 28).

9.6 In view of the early filing date in 1987, it cannot be confirmed that the doses disclosed in D5 were established according to the WHO standard for IU.

9.6.1 The board agrees with the position of the patent proprietors and the opposition division that it cannot be derived from D5 what the actual dosage was (see the patent proprietors' reply to the statement setting out the grounds of appeal, section 7, pages 17 to 18 and the decision under appeal, reasons VI.e, page 20). This includes the additional uncertainty that it is not

apparent from the wording in D5 whether 500 U was a daily dose or, possibly, the cumulative dose.

9.6.2 The opponent wished to rely on D66 and D67 as evidence for the dosage in D5. As mentioned above, these documents were not admitted as they should have been presented at an earlier stage.

Objective technical problem and solution

9.7 The subject-matter of claim 1 differs from the disclosure in document D5 in the dosage of between 1 and 3 MIU/day of IL-2, which is not derivable from D5.

9.8 As set out in the section on sufficiency of disclosure, it is credible that the envisaged dosages provide the desired mechanistic effect of selective Treg amplification without proliferation of Teff cells. The examples illustrate dosages of 1, 1.5 and 3 MIU/day. Example 1 demonstrates (in patients with HCV-associated vasculitis) that treatment with 5 days of a daily dose of 1.5 MIU IL-2 followed by three further treatment cycles at daily doses of 3 MIU increased the number of Tregs and the Treg/Teff ratio (see Example 1, Figures 2A and 2B).

9.9 The claimed dosage range of between 1 and 3 MIU/day provides dosages below 3 MIU/day. This range is not selected arbitrarily, because the administration of higher IL-2 doses (not excluded by the teaching of D5) also stimulates Teffs, which is an undesirable effect (see the application as filed, page 1, lines 16 to 17; page 2, lines 8 to 13 and D40: sections "Clinical Pharmacology" and "Clinical Studies").

9.10 Starting from the disclosure of D5, the objective technical problem as formulated by the opposition division, i.e. to provide a treatment of SLE that ensures a reproducible therapeutic effect, can be adopted.

9.11 This problem is solved by the subject-matter defined in claim 1 of auxiliary request 4.

Obviousness of the solution

9.12 While D5 provides isolated case studies of the treatment of two patients having SLE with IL-2, these do not prove statistical significance, and furthermore, the dosage used is not apparent from the information provided in D5.

9.13 Moreover, D5 does not provide any rationale that might guide the person skilled in the art in selecting a suitable dosage. The general range of 35 to 2000 units proposed in D5 (column 6, lines 40 to 56) is very broad. The use of un-standardised "units" and the vague description of the dosage regimen applied in the reported clinical cases does not permit any conclusions with regard to the dosage levels proposed, or the actual dosages used in the clinical cases. No theoretical link between a selected dose and an immunoregulatory effect is provided. Hence, the information in D5 itself would not have suggested the solution of using low-dose IL-2 in the claimed dosage range to the person skilled in the art.

9.14 D4 cannot provide the necessary incentive for the claimed dosage range, either. D4 is about a combination therapy, and IL-2 serves to enhance the effect of the second component, a proteasome inhibitor (see D4: page 11, line 28 to page 12, line 26). The experimental data provided in D4 concern the combination treatment

and are also not relevant to SLE. D4 discloses a broad range of IL-2 dosages of up to 7 MIU/day (claim 16) or even 20 MIU/day (claim 15). It does not point to a dose of 1-3 MIU for stimulating Tregs over Teffs as a monotherapy with IL-2.

9.15 The combination of D5 with D1a, also invoked by the opponent, was a new line of argument that was not admitted (see point 2.3 above).

9.16 For these reasons, the subject-matter of claim 1 of auxiliary request 4 would not have been obvious to a person skilled in the art and involves an inventive step within the meaning of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent as amended in the following version:

Claims:
No. 1 to 13 according to auxiliary request 4 filed with the patent proprietors' statement of grounds of appeal.

Description:
Paragraphs [0001] to [0007], [0009] to [0038], [0043], [0045] to [0096], and [0098] to [0178] of the patent specification,
paragraphs [0008], [0039], [0044] and [0097] as filed during the oral proceedings before the opposition division on 28 March 2022.

Drawings:
Figures 1 to 9 of the patent specification.

The Registrar: The Chairwoman:

A. Wille M. Pregetter

Decision electronically authenticated