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Datasheet for the decision of 8 February 2022

Case Number: T 0108/21 - 3.3.01

Application Number: 15177166.4

Publication Number: 2959894

IPC: A61K31/137, A61P37/06, A61K31/397

Language of the proceedings: EN

Title of invention:
S1P RECEPTOR MODULATORS FOR TREATING MULTIPLE SCLEROSIS

Applicant:
Novartis AG

Headword:
Treatment of multiple sclerosis/NOVARTIS

Relevant legal provisions:
EPC Art. 83, 54, 56

Keyword:
Main request - sufficiency of disclosure (yes)
Main request - novelty (yes)
Main request - inventive step (yes)

Decisions cited:
T 0609/02

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Case Number: T 0108/21 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 8 February 2022

Appellant: (Applicant)	Novartis AG Lichtstrasse 35 4056 Basel (CH)
Representative:	Ter Meer Steinmeister & Partner Patentanwälte mbB Nymphenburger Straße 4 80335 München (DE)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 19 November 2020 refusing European patent application No. 15177166.4 pursuant to Article 97(2) EPC**

Composition of the Board:

Chairwoman	M. Pregetter
Members:	S. Albrecht
	M. Blasi

Summary of Facts and Submissions

I. The appeal of the applicant ("the appellant") lies from the decision of the examining division refusing European patent application No. 15 177 166.4 ("the application") entitled "S1P receptor modulators for treating multiple sclerosis". This application is a divisional application of earlier European patent application 13 186 359.9. This earlier application is itself a divisional application of European patent application 07 764 828.5.

II. The decision of the examining division was based on a main request and two auxiliary requests. The single claim of the main request was filed on 18 November 2019 and reads as follows.

"A S1P receptor modulator for use in the treatment of relapsing-remitting multiple sclerosis, at a daily dosage of 0.5 mg p.o., wherein said S1P receptor modulator is 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol in free form or in a pharmaceutically acceptable salt form."

This compound is also known by the international nonproprietary name "fingolimod" and by the term "FTY720".

III. The documents cited during the examination proceedings include the following:

D4: US 2006/0046979 A1
D10: Novartis media release, "Phase II data for FTY720 shows sustained efficacy and good tolerability over 18

months in patients with relapsing multiple sclerosis (MS)", 6 April 2006
D11: J. A. Cohen et al., "Oral Fingolimod or Intramuscular Interferon for Relapsing Multiple Sclerosis", The New England Journal of Medicine 362(5), February 2010, 402-15
D14: K. Chiba et al., "Role of Sphingosine 1-Phosphate Receptor Type 1 in Lymphocyte Egress from Secondary Lymphoid Tissues and Thymus", Cellular & Molecular Immunology 3(1), February 2006, 11-19
D23: A. Thomson, "FTY720 in multiple sclerosis: the emerging evidence of its therapeutic value", Core Evidence 1(3), 2006, 157-67
D26: S. I. Park et al., "Pharmacokinetic/ pharmacodynamic relationships of FTY720 in kidney transplant recipients", Brazilian Journal of Medical and Biological Research 38, 2005, 683-94
D27: B. D. Kahan et al., "PHARMACODYNAMICS, PHARMACOKINETICS, AND SAFETY OF MULTIPLE DOSES OF FTY720 IN STABLE RENAL TRANSPLANT PATIENTS: A MULTICENTER, RANDOMIZED, PLACEBO-CONTROLLED, PHASE I STUDY", TRANSPLANTATION 76(7), 15 October 2003, 1079-84
D28: M. Webb et al., "Sphingosine 1-phosphate receptor agonists attenuate relapsing-remitting experimental autoimmune encephalitis in SJL mice", Journal of Neuroimmunology 153, 2004, 108-21

IV. In the appealed decision, the examining division concluded, *inter alia*, that the subject-matter of the single claim of the main request lacked novelty over document Dl0.

V. With the statement setting out the grounds of appeal, the appellant requested as the main request that the decision under appeal be set aside and that a patent be granted on the basis of the single claim of the main

request underlying the impugned decision and resubmitted with the statement of grounds of appeal or, as an auxiliary measure, on the basis of the single claim of one of auxiliary requests 1 and 2 underlying the impugned decision and resubmitted with the same statement.

VI. Third-party observations were received on 27 April 2021.

VII. In a communication under Article 15(1) RPBA issued on 8 October 2021, the board drew the appellant's attention to the points to be discussed during the oral proceedings and provided a preliminary opinion acknowledging novelty of the single claim of the main request.

VIII. Further third-party observations were received on 2 November 2021, 17 November 2021, 9 December 2021, 23 December 2021 and 18 January 2022.

IX. By letter dated 7 January 2022, the appellant submitted, *inter alia*, the following documents:

D43: Declaration of Professor Pieter van der Graaf dated 28 April 2021
D44: K. Gijbels et al., "EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS: AN ANIMAL MODEL FOR MULTIPLE SCLEROSIS", NEUROSCIENCE RESEARCH COMMUNICATIONS 26(3), 2000, 193-206

X. Oral proceedings were held by videoconference on 8 February 2022 in the presence of the appellant. At the end of the oral proceedings, the Chairwoman announced the board's decision.

XI. The appellant's submissions on the main request relevant to the present decision can be summarised as follows.

Sufficiency of disclosure

The claimed medical use was sufficiently disclosed. The application contained *in-vivo* data on fingolimod obtained in one of the most widely used animal models of multiple sclerosis ("MS"), i.e. a rodent model of experimental autoimmune encephalomyelitis ("EAE"). These data together with the application's disclosure of a prophetic human clinical trial involving the use of an oral daily dose of 0.5 mg fingolimod in patients with relapsing-remitting multiple sclerosis ("RRMS") made it credible that an oral daily dose of 0.5 mg fingolimod would block disease-associated angiogenesis and inhibit relapses in such patients. This finding was confirmed by several experts, including Professor van der Graaf in his declaration D43, and corroborated, *inter alia*, by post-published data disclosed in document D11.

Novelty

Document D10 did not directly and unambiguously disclose that a therapeutic effect or clinical benefit in the treatment of RRMS was obtained in humans by administration of an oral daily dose of 0.5 mg fingolimod.

Inventive step

Document D10's disclosure of a successful phase II study establishing the therapeutic efficacy of an oral daily fingolimod dose of 1.25 mg in patients with RRMS

constituted the closest prior art. The claimed subject-matter differed from this disclosure in that the oral daily dose of fingolimod was 0.5 mg. The objective technical problem was to be seen as the provision of an oral treatment of RRMS that was at least as effective as the closest prior art. The solution proposed by the claimed subject-matter was not rendered obvious by the prior art. At the priority date of the application, it was believed that the underlying mode of action of fingolimod was suppression of lymphocyte circulation. In that context, a threshold of lymphocyte reduction of at least 70% was believed to be required for treating RRMS. Since the prior art taught that an oral daily dose of 0.5 mg fingolimod did not achieve this threshold, the skilled person did not have any expectation of success that such a dose would provide an effective therapeutic treatment of RRMS. This lack of expectation of success was not removed by document D10's announcement of an exploratory dosage arm of 0.5 mg fingolimod in the confirmatory phase III trial of the 1.25 mg fingolimod dose.

The same conclusions applied if the disclosure of this announcement or document D4 was taken as the closest prior art.

XII. The appellant's final requests relevant to the present decision were as follows.

The appellant requested that the decision under appeal be set aside and that the case be remitted to the examining division with an order to grant a patent on the basis of the single claim of the main request underlying the impugned decision and a corresponding description of 15 pages filed on 7 January 2022.

The appellant further requested that

(a) appellant's submissions dated 7 January 2022 and documents D43 and D44 filed therewith be admitted into the proceedings,

(b) the third-party observations filed on 27 April 2021, 2 November 2021, 17 November 2021, 9 December 2021 and 23 December 2021 not be admitted into the proceedings.

Reasons for the Decision

1. The appeal is admissible.

Procedural issues

2. Admittance of documents D43, D44 and appellant's submissions, all filed on 7 January 2022, into the appeal proceedings (Article 13(2) RPBA 2020)

2.1 These documents and submissions were filed by the appellant after notification of the summons to oral proceedings.

2.2 In accordance with Article 13(2) RPBA 2020, such an amendment to the appellant's appeal case shall, in principle, not be taken into account unless there are exceptional circumstances, which have been justified with cogent reasons by the appellant.

2.3 The appellant argued that documents D43 and D44 and its submissions dated 7 January 2022 had been filed to resolve the issue of plausibility of the claimed

medical use which had been raised by the board for the first time in its communication dated 8 October 2021.

2.4 The board accepts the appellant's arguments as cogent reasons justifying exceptional circumstances within the meaning of Article 13(2) RPBA 2020. As a consequence, the board decided to admit documents D43, D44 and the appellant's submissions dated 7 January 2022 into the proceedings.

3. Admittance of the third-party observations received on 27 April 2021, 2 November 2021, 17 November 2021, 9 December 2021, 23 December 2021 and 18 January 2022 within the meaning of Article 115 EPC

3.1 All of these submissions have been received after the filing of the statement of grounds of appeal.

3.2 With this statement, the appellant had requested as the main request that the decision under appeal be set aside and that a patent be granted on the basis of the single claim of the main request underlying the impugned decision.

3.3 The board notes that this claim request had already been filed on 18 November 2019, i.e. almost one year before oral proceedings took place before the examining division.

3.4 In view of the foregoing, the board considers that the third-party observations received on 27 April 2021, 2 November 2021, 17 November 2021, 9 December 2021, 23 December 2021 and 18 January 2022 could and should have been filed during the examination proceedings. As a consequence, the board decided not to take these observations into account.

Substantive issues - Main request

4. Background of the claimed invention

4.1 MS is a human, immune-mediated disease of the central nervous system with chronic inflammatory demyelination leading to progressive decline of motor and sensory functions and permanent disability (see application, page 10, penultimate paragraph). The relapsing-remitting course is the most common form of the disease. Patients suffer acute self-limiting attacks (relapses) of neurological dysfunction followed by complete or incomplete remission in function (see document D10, page 2, last paragraph).

4.2 Various therapeutic options have been studied in the art for the treatment of patients with RRMS, among which fingolimod. Specifically, D10 (see page 1, second and fifth paragraphs) reveals data from a clinical phase II study on RRMS patients treated with fingolimod. Patients taking fingolimod orally at daily doses of 1.25 mg and 5 mg, respectively, experienced more than a 50% reduction in their annualised relapse rate during the study's first six months compared to patients taking placebo, and maintained this low relapse rate during the subsequent twelve-month extension phase of the study.

4.3 Concerning the underlying mechanism of action of fingolimod, document D10 explains on page 2, penultimate paragraph, that fingolimod binds to the sphingosine 1-phosphate receptor-1 ("S1P1") on a proportion of circulating lymphocytes and reversibly traps them in the lymph nodes. As a result, fingolimod lowers the number of activated T-cells circulating to

the blood stream and central nervous system. This reduces neuroinflammation and myelin damage in the brain and spinal cord. This mode of action of fingolimod is also referred to in the art as lymphocyte depletion (see document D28, paragraph bridging pages 118 and 119) or lymphocyte sequestration (see document D14, abstract, penultimate sentence).

5. Sufficiency of disclosure of the claimed invention (Article 83 EPC)

5.1 The single claim of the main request ("claim 1") is drawn up as a purpose-related product claim in accordance with Article 54(5) EPC. It is directed to the S1P receptor modulator fingolimod in free form or in a pharmaceutically acceptable salt form ("fingolimod (salt)") for use in the treatment of RRMS at a daily dosage of 0.5 mg *per os* (see point II. above).

5.2 In accordance with the settled case law of the boards, attaining the claimed therapeutic effect is a functional technical feature of claims directed to medical uses (see for example T 609/02 of 17 October 2005, Reasons: 9).

5.3 As a consequence, under Article 83 EPC, unless already known to the skilled person at the filing date, the application as filed must disclose the suitability of fingolimod (salt) at an oral daily dose of 0.5 mg for the claimed therapeutic application. Post-published evidence may be taken into account but only to back up the findings in the application as filed and not to establish sufficiency of disclosure on its own.

Fingolimod in the context of MS

5.4 In the case at hand, the appellant submitted that the following findings on fingolimod were disclosed in the prior art.

(a) The lowest effective dose of fingolimod reported in animal models of EAE was 0.1 mg/kg/day p.o. (see document D14, page 17, left-hand column, last paragraph, first sentence).

(b) From these models, a threshold of about 70% depletion of peripheral lymphocytes was believed to be required to see any efficacy (see document D28, paragraph bridging pages 118 and 119).

(c) The claimed dose of 0.5 mg of fingolimod had been shown not to meet this threshold in stable transplant patients (see document D27, Figure 1) and acute transplant patients (see document D26, Figure 7A)

(d) Pharmacokinetic and pharmacodynamic outcomes following single- or multiple-dose administration of fingolimod in transplantation patients could be extrapolated to patients with MS (see document D23, page 162, right-hand column, second full paragraph).

5.5 On the basis of these facts, the board concludes that the prior art does not support the suitability of the claimed dosage regimen for the claimed therapeutic application.

The disclosure of the application

5.6 However, in the case at hand the information presented in the application as filed is sufficient by itself to support the suitability of the claimed dosage regimen of fingolimod for the claimed therapeutic application under the aspect of sufficiency of disclosure. In other words, the information provided in the application as filed makes it at least plausible that the dosage regimen of fingolimod (salt) recited in claim 1 constitutes an effective therapy of RRMS. As a consequence, the outcome of referral G 2/21, currently pending before the Enlarged Board of Appeal (see also OJ EPO 2021, A102), is not decisive for the decision in the present case. The board was thus able to decide the present case without having to wait for the outcome of this referral first.

5.7 The reasons for acknowledging initial plausibility of the claimed medical use are as follows.

5.8 The appellant relied on the animal study disclosed in the application as filed (see page 12, last paragraph to page 13, second paragraph) to support its case.

5.9 This study ("EAE study") aims at determining the effects of "Compound A, in the hydrochloride salt form" (i.e. fingolimod hydrochloride; see page 9, last paragraph of the application), on neo-angiogenesis associated with relapsing EAE in rats. To this end, female Lewis rats were immunised with guinea pig spinal cord tissue emulsified in complete Freund's adjuvant. This immunisation caused an acute disease within 11 days, followed by an almost complete remission around day 16 and a relapse at around day 26 (see page 12, last paragraph).

5.10 The results of the EAE study are disclosed on page 13, second paragraph of the application. This passage reads as follows.

"In this assay, a S1P1 receptor modulator, e.g. Compound A significantly blocks disease associated neo-angiogenesis when administered to the animals at a dose of from 0.1 to 20 mg/kg p.o. For example, Compound A, in the hydrochloride salt form, fully blocks disease associated angiogenesis and completely inhibits the relapse phases when administered daily at a dose of 0.3 mg/kg p.o. The same effect is obtained when Compound A, in the hydrochloride salt form, is administered p.o. at 0.3 mg/kg every 2nd or 3rd day or once a week."

5.11 In the appellant's view, the study's finding that the administration of a weekly oral dose of 0.3 mg/kg of fingolimod hydrochloride to rats with EAE fully blocks disease-associated angiogenesis and completely inhibits the relapse phases translates into the suitability of the claimed dosage regimen of fingolimod (salt) for the therapeutic treatment of RRMS in humans.

5.12 Upon comparing the subject-matter of claim 1 with the aforementioned finding of the EAE study, the board notes two significant differences, namely:

(a) the disease, i.e. RRMS versus EAE in Female Lewis rats ("point 1")

(b) the dosage regimen of fingolimod (salt), i.e. 0.5 mg daily *per os* versus 0.3 mg/kg weekly *per os* ("point 2")

5.13 The board agrees with the appellant that, despite these differences, the results of the EAE study, based on a weekly oral dose of 0.3 mg/kg of fingolimod hydrochloride, make it plausible that an oral daily dose of 0.5 mg fingolimod (salt) provides the claimed therapeutic activity in human RRMS patients.

5.14 The reasons are as follows.

With regard to point 1 - Suitability of the rodent model used in the EAE study as an animal model for RRMS

5.15 As correctly observed by the appellant, the EAE model is a well-known and widely used animal model of MS in the prior art (see document D23, page 162, right-hand column, first full paragraph, second sentence and document D44, page 203, first full paragraph, first sentence). Figure 1 of document D44 depicts the different phases in the development of EAE as follows.

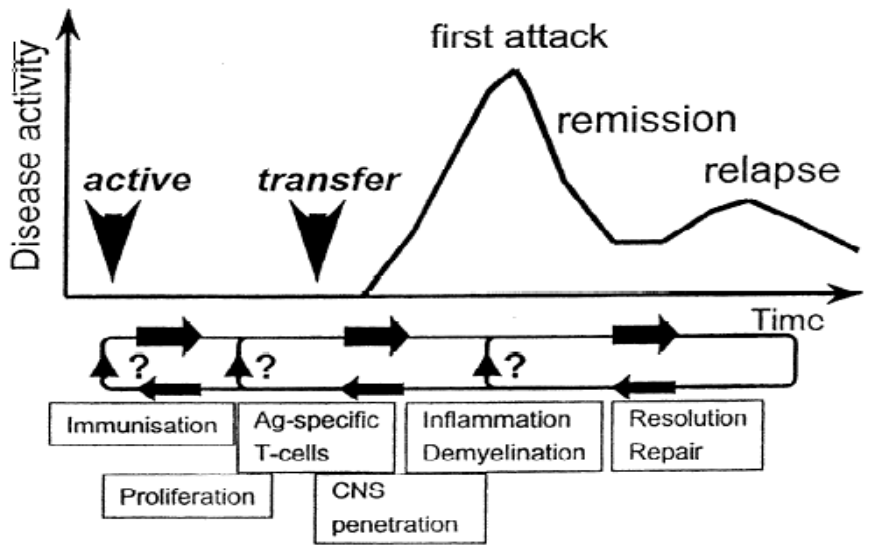

Figure 1. Schematic representation of the different phases in the development of EAE and their relation to the pathophysiological mechanisms.

5.16 Hence, like the EAE model disclosed in the application (see point 5.9 above), the EAE model reported in document D44 includes a first attack, followed by remission and a relapsing phase. This latter phase exhibits lower disease activity than the preceding first attack (see Figure 1 above). However, in the absence of any evidence to the contrary, the board is satisfied that the EAE model is suitable for testing therapies targeting both the phase of first attack and the relapsing phase.

5.17 As regards the correlation between the different phases in EAE development and MS, document D44 (see page 203, first full paragraph, lines 12 to 13) teaches that most probably the MS patient was in the stage after the first attack in the EAE model.

5.18 As a consequence, the board is satisfied that the EAE model used in the EAE study is suitable for studying the therapeutic benefit of fingolimod in human patients with RRMS.

With regard to point 2 - Plausibility of attaining a therapeutic benefit in RRMS patients with the claimed dosage regimen of fingolimod (salt) on the basis of the technical effects observed in the EAE rat study with a weekly oral dose of 0.3 mg/kg fingolimod hydrochloride

5.19 In this respect, the appellant essentially argued as follows.

(a) The technical effects of full blocking of disease-associated neo-angiogenesis and complete inhibition of the relapse phases observed in the EAE study with a weekly oral fingolimod dose of

0.3 mg/kg translated to a seven-fold lower daily dose of fingolimod hydrochloride, i.e. about 0.042 mg/kg ("point 2.1").

(b) This daily dose, in turn, was 58% lower than the lowest daily dose previously reported for providing clinical benefit in rat EAE studies of 0.1 mg/kg. Likewise, a daily dosage of 0.5 mg in humans was 60% lower than the lowest human dosage which had been shown to be therapeutically effective in the treatment of RRMS before the priority date of the application, i.e. 1.25 mg/day. In view of this same proportional reduction of the known effective doses in EAE rats and RRMS patients, it was plausible that a 0.5 mg daily dosage in humans would block RRMS-associated angiogenesis and inhibit relapses to the same degree as higher doses ("point 2.2").

5.20 On the basis of the facts on file, the board accepts the appellant's position. The reasons are as follows.

With regard to point 2.1 - Translation of the technical effects reported in the application with a weekly oral dose of 0.3 mg/kg of fingolimod hydrochloride to a seven-fold lower daily dose (i.e. about 0.042 mg/kg) of fingolimod hydrochloride

5.21 This issue is addressed in detail in declaration D43 by Professor van der Graaf. In paragraphs 34 to 36 of this document, Professor van der Graaf discusses the pharmacokinetic data disclosed in document D23 (see table 3), pointing in particular to the following findings reported in D23.

(a) The pharmacokinetic characteristics Cmax and AUC of fingolimod exhibit dose-proportionality over the

dose ranges of 0.25 to 3.5 mg both in healthy subjects and transplant patients.

(b) The pharmacokinetic outcomes measured are not affected by disease status and may therefore be extrapolated to the MS patient population.

5.22 In view of the foregoing, it is plausible that:

(a) an oral daily dose of about 0.042 mg/kg of fingolimod hydrochloride will produce the same overall body exposure to the drug (expressed as AUC) as a seven-fold higher oral weekly dose of 0.3 mg/kg of fingolimod hydrochloride

(b) the Cmax of a daily dose of about 0.042 mg/kg of fingolimod hydrochloride will be proportionally lower than the Cmax of the seven-fold higher weekly dose of 0.3 mg/kg of fingolimod hydrochloride

5.23 In the oral proceedings, the appellant alleged that the AUC was decisive for obtaining full blocking of disease-associated neo-angiogenesis and complete inhibition of the relapse phases, and not the Cmax. To support its case, the appellant relied, *inter alia*, on paragraph 52 of document D43. This paragraph includes the following passage.

"The skilled person would expect the therapeutic effects of FTY720 to be more closely linked with AUC, based on the relevant biological pathways for this drug, i.e., exposure over time is likely to be the most relevant factor for these effects. In relation to lymphocyte homing and circulation, and neoangiogenesis (the pathways that the Patent Application explains are targeted by FTY720) it is unlikely that the relevant

effects would be lost when switching from a 7- fold higher weekly dose to a lower, equivalent, daily dose. There is a time period associated with sequestration of lymphocytes into the lymph nodes following dosing with FTY720. The reverse process, release of lymphocytes back into circulation, will not take place instantly. Similarly for angiogenesis, when sufficient levels of FTY720 are present, the biological signals leading to angiogenesis will be blocked. Then, when FTY720 levels eventually drop, there will be a delay until a signal triggers angiogenesis and the process of forming new blood vessels itself will take some time."

5.24 The board does not have any reason to doubt Professor van der Graaf's explanations. The board therefore accepts as plausible that a daily oral dose of about 0.042 mg/kg of fingolimod hydrochloride will give rise to the same technical effects as those reported in the application with a weekly oral dose of 0.3 mg/kg of fingolimod hydrochloride, i.e. full blocking of disease-associated neo-angiogenesis and complete inhibition of the relapse phases.

With regard to point 2.2 - Transferability of the technical effects of full blocking of disease-associated neo-angiogenesis and complete inhibition of the relapse phases observed in the EAE study to a 0.5 mg oral daily dose of fingolimod (salt) administered to human patients with RRMS

5.25 The appellant bases its argument in support of plausibility of the therapeutic activity of the claimed dosage regimen in human RRMS patients on the observation that the claimed oral daily dose of 0.5 mg of fingolimod (salt) represents the same proportional reduction from the lowest oral fingolimod dose previously reported to provide clinical benefit in this

patient group as the aforementioned oral daily dose of 0.042 mg/kg in EAE rats does in respect of the lowest known efficacious oral dose of fingolimod in this species (i.e. a proportional reduction of 60% and 58% respectively, see point 5.19 above).

5.26 The board finds the appellant's line of reasoning convincing.

5.26.1 As set out in point 4.2 above, document D10 discloses the therapeutic efficacy of fingolimod at a daily oral dose of 1.25 mg in human patients with RRMS. Document D14 (see page 17, left-hand column, last paragraph, first sentence), in turn, teaches that fingolimod at 0.1 mg/kg p.o. or higher doses almost completely prevented paralysis in Lewis rats afflicted with EAE.

5.26.2 The board is not aware of any prior-art teaching that oral doses of fingolimod lower than 1.25 mg/day and lower than 0.1 mg/kg/day are beneficial in treating RRMS patients and EAE rats respectively. In the absence of such teaching, the board accepts the appellant's submission that the aforementioned fingolimod doses of 1.25 mg/day and 0.1 mg/kg/day are species equivalents in terms of their technical effects of blocking disease-associated neo-angiogenesis and inhibiting the relapse phases. In light of this equivalence, the board's positive finding on plausibility set out in point 5.24 above in respect of a 58% lower EAE rat dose of about 0.042 mg/kg of fingolimod equally applies to a 60% lower dose of 0.5 mg/day in human RRMS patients.

5.27 As a consequence, the board judges the experimental data reported in the application in the context of the EAE study to be sufficient for establishing the initial plausibility of the therapeutic benefit of the claimed

dosage regimen in human RRMS patients. Initial plausibility being given, the outcome of referral G 2/21, currently pending before the Enlarged Board of Appeal, is not decisive for the decision in the present case (see point 5.6 above).

5.28 Under these circumstances, post-published evidence may be taken into account (see point 5.3 above). In this context, the appellant referred, *inter alia*, to document D11. This document discloses the results of a clinical study in 1153 patients with RRMS who had a recent history of at least one relapse. Patients received either oral fingolimod at a daily dose of either 1.25 mg or 0.5 mg or intramuscular interferon beta-1a (an established therapy for MS) at a weekly dose of 30 µg. Figure 2A illustrates a significantly greater reduction in the annualised relapse rates in both fingolimod groups than in the interferon group, confirming the results of the EAE study reported in the application.

5.29 In view of the preceding considerations, the board is satisfied that the subject-matter of claim 1 is disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art within the meaning of Article 83 EPC.

6. Novelty (Article 54 EPC)

6.1 In the decision under appeal, the examining division concluded that the subject-matter of claim 1 lacked novelty over document D10.

6.2 Document D10 includes the following two technical teachings.

(a) Results from a clinical phase II study showing sustained efficacy and good tolerability over 18 months in RRMS patients treated with an oral daily dose of 1.25 mg fingolimod (see point 4.2 above), immediately followed by

(b) the announcement of a clinical phase III study including more than 1000 patients with RRMS to be equally randomised to receive either 1.25 mg or 0.5 mg of oral fingolimod or placebo once daily for up to 24 months (see page 2, third to fifth full paragraphs).

6.3 The examining division considered (see point 16.2.11 of the impugned decision) that any prior art describing the therapeutic effect of an oral daily dose of 1.25 mg of fingolimod in the treatment of RRMS and then explicitly disclosing the use of an oral daily dose of 0.5 mg of fingolimod (albeit without data) anticipated the subject-matter of a claim directed to a therapeutic treatment of RRMS using an oral daily dose of 0.5 mg of fingolimod. In the examining division's view, the 1.25 mg dose of fingolimod was directly and unambiguously disclosed in document D10 and was further "deemed to be fully enabling" given the positive outcome of the phase II study. The further mention of the 0.5 mg dose of fingolimod in the phase III trial was thus also deemed to be directly and unambiguously disclosed in document D10 in an enabling manner.

6.4 The board does not agree.

6.4.1 In accordance with the settled case law of the boards, for prior art to anticipate the subject-matter of a claim, it must, as a first requirement, disclose directly and unambiguously all the technical features

of this claim in combination. As a further requirement, this disclosure must be enabling, in the sense that the skilled person must be able to carry out this disclosure on the basis of the information provided in this prior art, if required, by using common general knowledge, at the date of public availability of this prior art.

6.4.2 In the case at hand, document D10 does not anticipate the subject-matter of claim 1 for failure to meet the first requirement. As set out in point 6.2 above, document D10 discloses the claimed dosage regimen in the context of a phase III study involving the therapeutic treatment of RRMS patients with the claimed fingolimod dosage regimen. Page 2, fourth full paragraph of document D10 states that this study "has begun enrolling patients in several European countries". No further details are provided in this regard. In particular, no mention is made of the therapeutic efficacy of this dosage regimen in the treatment of RRMS.

6.4.3 In view of the foregoing, the board concludes that document D10 does not directly and unambiguously disclose the effective therapeutic treatment of RRMS using the claimed dosage regimen. The subject-matter of claim 1 is thus novel pursuant to Article 54 EPC over this document.

7. Inventive step (Article 56 EPC)

The closest prior art

7.1 In agreement with the appellant, the board considers document D10's disclosure concerning the successful phase II trial on RRMS patients treated with fingolimod

at an oral daily dose of 1.25 mg (see point 6.2(a) above) to be a suitable starting point for assessing inventive step of the claimed subject-matter.

7.2 The subject-matter of claim 1 differs from this disclosure in that fingolimod is administered at an oral daily dose of 0.5 mg.

Objective technical problem and solution

7.3 To formulate the objective technical problem, it is necessary to establish the technical effect(s) achieved by the aforementioned distinguishing feature.

7.4 For the reasons given above regarding sufficiency of disclosure, the board is satisfied that the claimed fingolimod dosage regimen provides an effective therapeutic treatment of RRMS.

7.5 Hence, starting from the closest prior art defined above, the objective technical problem is the provision of further means to effectively treat RRMS.

7.6 The proposed solution to this problem is the fingolimod dosage regimen recited in claim 1.

7.7 The appellant defined the objective technical problem differently (see point XI. above, under the heading "Inventive step"). However, in view of the outcome of these proceedings, this point does not need further consideration.

Obviousness

7.8 As set out in point 6.2 above, document D10's disclosure of the successful phase II trial with an

oral daily dose of 1.25 mg fingolimod is immediately followed by the announcement of a phase III study using oral daily dose of 0.5 mg and 1.25 mg of fingolimod.

7.9 In the board's judgement, this announcement would have provided the skilled person with a reasonable expectation of solving the objective technical problem with fingolimod at an oral daily dose of 0.5 mg, unless a teaching in the prior art would have dissuaded the skilled person from considering this dosage regimen as a solution to the technical problem posed.

7.10 In the case at hand, the board is satisfied that the prior art teaches away from the claimed invention. As set out in point 5.4(b) above, the skilled person would have inferred from document D28 that a threshold of lymphocyte reduction of at least 70% was required for a therapeutic treatment of RRMS. Moreover, the board agrees with the appellant's position that the teachings of documents D26 and D27 taken in combination with the teaching of document D23 would have led the skilled person to conclude that an oral daily dose of 0.5 mg fingolimod would be insufficient for reaching this threshold and hence would not be therapeutically effective in the treatment of RRMS (see points 5.4(c) and 5.4(d) above).

7.11 In light of these particular circumstances, the board finds that the announcement of the phase III trial in document D10 would have given the skilled person hope of success but not a reasonable expectation of it.

7.12 A mere hope of success does not suffice as motivation to render the claimed subject-matter obvious. As a consequence, the subject-matter of claim 1 involves an inventive step starting from D10's disclosure of the

successful phase II trial with an oral daily dose of 1.25 mg fingolimod.

7.13 For the sake of completeness, the board observes that the same considerations apply when starting the assessment of inventive step from the announcement of the phase III trial in document D10 taken as the closest prior art (see point 6.2 above).

7.14 As regards document D4, cited by the examining division as the closest prior art in its communication annexed to the summons to oral proceedings, the following is observed.

7.14.1 In its communication, the examining division considered that the claimed fingolimod dose of 0.5 mg fell within the range of dosages provided for in document D4, paragraph [0142].

7.14.2 However, as correctly noted by the appellant, the range disclosed in paragraph [0142] (i.e. about 0.03 to 2.5 mg/kg per day) lies outside the claimed daily dose of fingolimod.

7.14.3 It follows that the teaching of this document is more remote than the subject-matter of claim 1 than document D10 and can therefore not render the claimed subject-matter obvious either.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the examining division with the order to grant a patent on the basis of the single claim of the main request filed on 18 November 2019 underlying the impugned decision and resubmitted with the statement of grounds of appeal, and a description to be adapted thereto.

The Registrar: The Chairwoman:

M. Schalow M. Pregetter

Decision electronically authenticated