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Datasheet for the decision of 7 February 2024

Case Number: T 0843/22 - 3.3.04

Application Number: 17157735.6

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Language of the proceedings: EN

Title of invention:
Dosing regimen for multiple sclerosis

Patent Proprietor:
Yeda Research and Development Co., Ltd.

Opponents:
Generics [UK] Limited (trading as Mylan)
Synthon B.V.
G. L. Pharma GmbH
Alvogen IPCo S.a.r.l.

Headword:
GA dosage regimen for MS 1/YEDA

Relevant legal provisions:
EPC Art. 100(c), 83, 56

Keyword:

Grounds for opposition - main request - added subject-matter (yes)
Inventive step - auxiliary requests 1 and 5 (no)
Sufficiency of disclosure - auxiliary requests 2 to 4 (no)

Decisions cited:

G 0002/21, T 1437/07, T 2255/10, T 1087/15

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Case Number: T 0843/22 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 7 February 2024

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 27 January 2022 revoking European patent No. 3 199 172 pursuant to Article 101(3)(b) EPC**

Composition of the Board:

Chairwoman M. Pregetter
Members: B. Rutz
A. Bacchin

Summary of Facts and Submissions

I. The appeal by the patent proprietor (appellant) lies from the decision of an opposition division to revoke European patent No. 3 199 172 (the patent), which is based upon European patent application No. 17 157 735.6, which was filed as a divisional application of European patent application No. 17 153 450.6 (not published). The latter is a divisional application of European patent application No. 13 166 080.5, which is a divisional application of European patent application No. 10 810 282.3 published under the PCT as international application WO 2011/022063 (the earlier application).

II. The patent had been opposed on the grounds of Article 100(a) EPC, in relation to novelty (Article 54 EPC) and inventive step (Article 56 EPC), and Article 100(b) and (c) EPC. Oppositions were filed by opponents 1 to 5. Opponent 2 withdrew its opposition during the opposition proceedings.

III. In the decision under appeal, the opposition division decided that claim 1 of the main request (patent as granted) did not comply with Article 123(2) EPC and Article 76(1) EPC. On auxiliary request 1, the opposition division decided that the invention to which claim 4 related was not sufficiently disclosed. The same reasoning applied to claim 1 of auxiliary request 2, claim 2 of auxiliary request 3 and claim 1 of auxiliary request 4. The opposition division decided that auxiliary request 5 lacked an inventive step over the disclosure of document D1.

IV. With its statement of grounds of appeal, the appellant stated that it continued to request rejection of the oppositions (main request) and filed sets of claims of auxiliary requests 1 to 5 (identical to the requests on which the decision under appeal was based, identified as NAR1 to NAR5, the same designation used in appeal). The appellant further submitted its reply to the opposition as Annex A and its submission to the opposition division under Rule 116 EPC as Annex B and document D97.

V. Opponents 1, 3, 4 and 5 (respondents I, III, IV and V) replied to the appeal.

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

VII. In this communication, the board indicated that it agreed with the findings of the opposition division on the main request and that it considered the subject-matter of claim 1 of auxiliary requests 1 to 5 to lack an inventive step.

VIII. Claim 1 of the main request (as granted) reads as follows:

"Glatiramer acetate for use in treating a human patient suffering from a relapsing form of multiple sclerosis or who has experienced a first clinical episode and is determined to be at high risk of developing clinically definite multiple sclerosis, comprising administering to the human patient three subcutaneous injections of 40mg glatiramer acetate for every seven days with at least one day between every subcutaneous injection, wherein the glatiramer acetate is present in a

pharmaceutical composition having a pH in the range of 5.5 to 7.0."

Claim 1 of auxiliary request 1 differs from claim 1 of the main request in that "a relapsing form of multiple sclerosis" was replaced by "relapsing-remitting multiple sclerosis".

Claim 1 of auxiliary request 2 differs from claim 1 of auxiliary request 1 in that the use is further specified by the addition of the wording "to increase the tolerability of glatiramer acetate in the human patient".

Claim 1 of auxiliary request 3 differs from claim 1 of auxiliary request 1 in that "relapsing-remitting multiple sclerosis" was deleted from the claim. Dependent claim 2 of auxiliary request 2 specifies that the use includes "to increase the tolerability of glatiramer acetate in the human patient".

Claim 1 of auxiliary request 4 differs from claim 1 of auxiliary request 2 in that "relapsing-remitting multiple sclerosis" was deleted from the claim.

Auxiliary request 5 differs from auxiliary request 3 in that dependent claim 2 was deleted.

IX. Oral proceedings took place on 6 and 7 February 2024. At the end of the oral proceedings, the Chairwoman announced the board's decision.

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

D1 US 2007/0161566 A1

D2 S. Flecther et al., "*Comparison of glatiramer acetate (Copaxone®) and interferon β-1b (Betaferon®) in multiple sclerosis patients: an open-label 2-year follow-up*", Journal of the Neurological Sciences, 197, 2002, 51-5

D3 S. Flechter et al., "*Copolymer 1 (Glatiramer Acetate) in Relapsing Forms of Multiple Sclerosis: Open Multicenter Study of Alternate-Day Administration*" Clinical Neuropharmacology, 25(1), 2002, 11-5

D4 O. Khan et al., "*Randomized, prospective, rater-blinded, four-year, pilot study to compare the effect of daily versus every-other-day glatiramer acetate 20 mg subcutaneous injections in relapsing-remitting multiple sclerosis*", Multiple Sclerosis, 14, 2008, S296, P902

D5 C. Caon et al., "*Randomized, Prospective, Rater-Blinded, Four Year Pilot Study To Compare the Effect of Daily Versus Every Other Day Glatiramer Acetate 20 mg Subcutaneous Injections in RRMS*", Neurology, 72(11), Suppl. 3, 2009, P06.141

D8 Excerpt from Summary of Product Characteristics of the Copaxone 20 mg/ml product, text revised on 3 February 2009 and last updated on 17 April 2009

D11 "*Doubling the Dose of Glatiramer Acetate Does Not Increase Efficacy*", MedScape, 22 September 2008

D34 Abstract presented at the World Congress on Treatment and Research in Multiple Sclerosis: 2008 Joint Meeting of the American, European, and Latin America Committees on Treatment and Research in Multiple Sclerosis (ACTRIMS, ECTRIMS, LACTRIMS)

D34a Slides presented at the World Congress on Treatment and Research in Multiple Sclerosis, 2008

D43 Transcript excerpt from UK High Court Case No. HP-2017-000010, font cover and page 397

D46 Rebif® (interferon beta-1a), 20 pages

D52 "*High-dosage Copaxone trial results are bad news for Teva*", PharmaTimes, 2008

D57 Medication Guide Rebif® product, 2002, 7 pages

D70 Prof. Brück, witness statement on EP 29 493 335 dated 15 February 2019

D89 O. Khan et al., "*A phase 3 trial to assess the efficacy and safety of glatiramer acetate injections 40mg administered 3 times a week compared to placebo*", Abstract presented at the 28th Congress of the European Committee for treatment and research in multiple sclerosis, 13 October 2012

D92 K. McKeage, "*Glatiramer Acetate 40 mg/mL in Relapsing-Remitting Multiple Sclerosis: A Review*", CNS Drugs, ADIS Drug Evaluation April 2015, 8 pages

D93 J. S. Wolinski et al., "*Reduced Frequency and Severity of Injection-site Reactions With Glatiramer Acetate 40 m/ml Three-*

times Weekly Dosing", poster P306, ACTRIMS/ ECTRIMS Conference, 10-13 September 2014

D94 J. S. Wolinski et al., "*Reduced frequency and severity of injection site reactions with glatiramer acetate 40mg/ml three times weekly dosing*", abstract P306, ACTRIMS/ECTRIMS Conference, 10-13 September 2014

XI. The following abbreviations are used in this decision:

multiple sclerosis (MS)
relapsing form of multiple sclerosis (RMS)
relapsing-remitting multiple sclerosis (RRMS)
secondary progressive multiple sclerosis (SPMS)
progressive-relapsing multiple sclerosis (PRMS)
clinically definite multiple sclerosis (CDMS)
clinically isolated syndrome (CIS)
glatiramer acetate (GA)
every day (QD)
every other day (QOD)
three times in a week (TIW)
subcutaneous (SC)
injection site reactions (ISRs)
immediate post-injection reactions (IPIRs)
adverse side effects (ASEs)
QD at a dose of 20 mg (20QD)
QD at a dose of 40 mg (40QD)
QOD at a dose of 20 mg (20QOD)
QOD at a dose of 40 mg (40QOD)
TIW at a dose of 40 mg (40TIW)

XII. Summary of the appellant's submissions

Main request - claim 1
Extension beyond the content of the (earlier) application as filed (Article 100(c) EPC)

The concept of intermediate generalisation invoked in the decision under appeal only arose when an example in the specification had been generalised to an extent between the specific example and the most general part of the description. This was not the case with claim 1 of the main request. However, even if such an intermediate generalisation or restriction arose in an amended claim, the question of added matter remained (see, for example, section 2.3 of T 461/05).

The term "a relapsing form of multiple sclerosis" (RMS) was used in the specification both generally (e.g. paragraphs [0017] and [0119] of the application as filed) and specifically in conjunction with the benefit derived from the GA 40TIW regimen (e.g. paragraphs [0054] and [0056]). The same passages were present in the earlier application. It was therefore clear to the skilled person that the embodiments of the invention were equally relevant to RMS and RRMS.

The (earlier) application as a whole therefore disclosed the claimed subject-matter.

Auxiliary request 1 - claim 1
Inventive step (Article 56 EPC)

Document D1 was not a suitable starting point because it contained no data on the GA 40QOD regimen in the treatment of RRMS. Furthermore, it was concerned with improving efficacy while the focus of the invention was

on the balance between efficacy and tolerability. In contrast, document D1 also showed that side effects were more severe for GA 40QD (see Table 4). Data from a later phase III trial showed that increasing the dose did not improve efficacy but led to a higher number of withdrawals from the trial (see slide 14 of document D34a). Documents D11 and D52 also showed that doubling the dose did not improve efficacy.

The approved GA 20QD regimen, as disclosed for instance in D2 to D5, was a realistic starting point as it represented the optimal balance at the priority date. The prior art contained no pointer to reduce the frequency of injection. The effect of the difference to the closest prior art was improved tolerability while maintaining efficacy, i.e. an improved patient experience. The objective technical problem was the provision of a GA dosage regimen which improved patient experience. There was no indication in the prior art that GA 40TIW could solve the problem. GA consisted of random peptides of four amino acids for which no regular pharmacodynamics applied. Therefore, it was also not comparable to other drugs, such as interferon β-1a (Rebif®). The dosage regimen GA 40TIW was therefore inventive.

Auxiliary request 2 - claim 1, auxiliary request 3 - claim 2, auxiliary request 4 - claim 1
Sufficiency of disclosure (Article 83 EPC)

The claimed regimen required two effects - that 40TIW was (a) efficacious and (b) provided improved tolerability compared to the GA 20QD regimen. Both aspects were described in the application as filed. Tolerability was described as the beneficial effect arising from the GA 40TIW regimen in paragraphs [0019],

[0023], [0024], [0026], [0053], [0054], [0056] (with the aspects of tolerability described in [0057] and [0058]), [0065], [0066] and [0068] and clauses 22 to 26 and 29 to 30 of the application as filed. The application as filed included the protocol for what became known as the GALA trial where the claimed regimen was compared to placebo. Tolerability and safety were clear objectives of the trial (see paragraphs [0084], [0089], [0105] and [0106]). The disclosure of a clinical trial protocol "*cannot be disregarded as void of technical significance*" (T 239/16).

The improvement in tolerability was a central effect of the novel dosing regimen. The skilled person reading the specification with their common general knowledge would have no doubt as to the credibility that at least one effect to be attained by changing the GA 20QD regimen to GA 40TIW would be an improvement in tolerability as assessed by the decreased frequency and severity of ISRs and IPIRs (see also the final paragraph of document D2 and points 255 to 257 of Prof. Brück's declaration D70).

The disclosure in the specification when read with the common general knowledge met the criteria of both "ab initio plausible" and "not ab initio implausible". Consequently, the post-filing GALA and GLACIER clinical trials could be taken into consideration. The claimed regimen (GA 40TIW) was first tested against placebo in the GALA trial (essentially using the protocol in the patent specification), the initial results of which were reported in document D89 and subsequently in a head-to-head comparison with GA 20QD in the GLACIER trial reported in documents D92, D93 and D94.

The opponents failed to identify and substantiate any serious doubts substantiated by verifiable facts.

Auxiliary request 5 - claim 1
Inventive step (Article 56 EPC)

Claim 1 of auxiliary request 5 limited the patient group to "a human patient who has experienced a first clinical episode and is determined to be at high risk of developing clinically definite multiple sclerosis". Such patients were generally referred to as displaying "clinically isolated syndrome" or CIS (see pages 17 to 18 of the earlier application) and were distinct from RRMS patients. This was also apparent from the need for separate clinical trials in document D8. Only 43% of placebo-treated CIS patients converted to RRMS (see document D8, point 5.1).

The closest prior art was a document describing the treatment of CIS patients with GA, e.g. document D8 disclosing the administration of GA 20QD to CIS patients. The difference to the closest prior art was the change in dosing regimen to GA 40TIW. The effect arising from the difference was a more convenient treatment with reduced ISRs and IPIRs (improved tolerability). This was not obvious from the closest prior art because there was no motivation in the closest prior art or any other document on the treatment of CIS patients to increase the dosing amount while decreasing the frequency of administration.

XIII. Summary of the submissions of respondents I, III, IV and V

Main request - claim 1
Extension beyond the content of the (earlier) application as filed (Article 100(c) EPC)

The term "relapsing" constituted an intermediate generalisation in view of the content of the (earlier) application as filed. There was only basis for RRMS. Other forms of relapsing MS existed, such as SPMS and PRMS, (paragraph 10 of the application as filed). Paragraph [0100] of the application as filed excluded progressive forms of MS from the application of the invention.

RRMS was a subset of RMS. Therefore, any broadening of the term RRMS to RMS amounted to a generalisation, for which there was no basis in the application as filed.

Auxiliary request 1 - claim 1
Inventive step (Article 56 EPC)

The GA 40QOD regimen in document D1 was no less enabled than that of the patent in suit. Neither the patent nor document D1 contained any data relating to the GA 40QOD or GA 40TIW regimen, respectively. Thus, if document D1 was non-enabled, the technical effect of the patent was implausible. While experimental data were not always required, if the invention relied on a technical effect that was "not self-evident nor predictable or based on a conclusive theoretical concept", some evidence had to be provided at the filing date to show that a technical problem has been solved. A "mere verbal statement" was not sufficient (see T 488/16). As pointed out by the

board in decision T 184/10 (Reasons 3.2), even in the absence of experimental evidence, if speculation was reasonably based on data available at the time, the skilled person would not dismiss statements made in the prior art as speculative.

The adverse events that did take place with GA administration were well known to be associated with administration frequency. To reduce injection-related adverse events, such as ISRs, the skilled person would be motivated to reduce the frequency of the injections.

There was no evidence in the patent that an improvement had been made over the objectively structurally closest known dosage regimen of GA 40QOD in document D1. Indeed, the TIW and QOD Copaxone® administration regimens had to be considered "*materially identical in terms of equivalence*" (see document D43, page 397, lines 7 to 17). Thus, the only technical difference between a TIW and QOD administration regimen was the frequency, not the efficacy. The problem to be solved was an alternative dosage regimen of GA. Given that the advantages of convenience and compliance associated with TIW dosing were already known from the prior art (see e.g. documents D46 and D57), the invention was obvious.

Auxiliary request 2 - claim 1, auxiliary request 3 - claim 2, auxiliary request 4 - claim 1
Sufficiency of disclosure (Article 83 EPC)

The appellant had stated that the improvement in tolerability was relative to the GA 20QD administration. However, there was no such point of reference in the claim. Moreover, the patent did not present the skilled person with any evidence or

rationale for the tolerability of the claimed regimen, per se or relative to any particular prior-art regimen.

The appellant had advanced evidence which showed that a 40 mg dose led to higher adverse events. In the absence of contrary evidence in the patent, it had to be assumed that all 40 mg doses shared such an adverse event profile. Therefore, taking into account the lack of teaching in the common general knowledge, the lack of evidence in the patent and the contradictory evidence given by the appellant's experts, the opposition division was correct to conclude that it was not plausible that the GA 40TIW regimen would be more tolerable than any other regimen, let alone the GA 20QD regimen. As argued by the appellant's experts, the outcome of increasing dosage while decreasing frequency was not predictable without carrying out a clinical trial (paragraph 171 of document D70). Therefore, in the absence of any such trial, something that is unpredictable cannot be plausible. The invention to which the claims relate was not sufficiently disclosed.

Auxiliary request 5 - claim 1
Inventive step (Article 56 EPC)

The definition of CIS was found on page 17, second paragraph of the earlier application. This defined CIS as (1) a single clinical attack suggestive of MS and 2) at least one lesion suggestive of MS. In the paragraph bridging pages 17 and 18, CDMS was defined as "[t]*wo attacks and clinical evidence of two separate lesions or* [t]*wo attacks; clinical evidence of one lesion and paraclinical evidence of another separate lesion*". In other words, this appeared to define CIS as simply the first attack having MS symptoms.

The skilled person understood CIS to be symptomatically identical to MS but not having reached the frequency threshold to be formally diagnosed as CDMS.

In document D1 (paragraph [0059]), the MS subjects had to have "at least one lesion" to fulfil the inclusion criteria. This meant that the patient group could include CIS patients. In addition, document D8 also disclosed that CIS patients were treated in the same manner as other MS patients and further taught that Copaxone® delayed the progression from the first clinical event to further episodes (paragraph 5.1 on page 5 of D8). In this regard, if document D8 was considered to be common general knowledge, it taught that there was effectively no difference in the therapeutic management of CIS patients compared to other MS patients.

Copaxone® was not a cure for CIS but only delayed the time until the second attack, by which time it could be classified as CDMS. It then worked in the same way to delay subsequent attacks.

The post-published GALA or GLACIER trials (documents D92 to D94) did not disclose any results in CIS patients and only related to RRMS. Therefore, even if taken into account, these trials still proved nothing about the efficacy of the claimed regimen for such patients.

Document D1 was the closest prior art, and the technical problem to be solved was merely an alternative dosing regimen for administration to patients suffering from MS symptoms. As the problem to be solved was a mere alterative, the solution was obvious for analogous reasons to auxiliary request 1.

XIV. The appellant requested that the decision under appeal be set aside and the patent be maintained based on the claims of the main request (claims as granted) or, alternatively, one of the sets of claims of auxiliary requests 1 to 5 (dealt with in the decision under appeal).

The respondents requested that the appeal be dismissed and the decision to revoke the patent be upheld. They further requested that documents D92 to D94 and D97 not be admitted into the proceedings.

Reasons for the Decision

Admission of documents D92 to D94 and D97

1. As these documents were not required for the decision, the board sees no reason to discuss their admission.

Main request - claim 1
Extension beyond the content of the earlier application as filed (Article 100(c) EPC)

2. The board, in agreement with the decision under appeal, considers that the subject-matter of claim 1 extends beyond the content of the (earlier) application as filed because the dosage regimen "*three subcutaneous injections of 40mg glatiramer acetate for every seven days with at least one day between every subcutaneous injection*" is only disclosed for "*relapsing remitting multiple sclerosis*" (RRMS) in the earlier application as filed (see e.g. page 5, lines 2 to 12 and page 8, lines 2 to 12) and not for "*a relapsing form of multiple sclerosis*" (RMS).

3. The appellant referred to the earlier application as filed, which disclosed at the end of the "*Background*" section on page 4, lines 21 to 25 and at the end of the "*Experimental details*" section on page 37, lines 8 to 10 "*an effective low frequency dosage regimen of GA administration to patients suffering from a relapsing form of multiple sclerosis*". Since the only dosage regimen disclosed was the one specified in the claim, it was clear from these passages that this dosage regimen also applied to RMS. A pointer from the examples was therefore not required.

4. The board does not agree because all parts of the (earlier) application as filed which describe and define the invention, i.e. Summary, Detailed Description and Claims, relate to RRMS (see "SUMMARY OF THE INVENTION" section, pages 4 to 7; "DETAILED DESCRIPTION OF THE INVENTION" section, pages 8 to 15; "Experimental Details" section, pages 20 to 36; claims 1 to 32).

5. In the "Background" section of the (earlier) application as filed, several forms of MS are mentioned and characterised as "*relapsing*" (see list on pages 1 to 3: Relapsing-Remitting Multiple Sclerosis (RRMS), Secondary Progressive Multiple Sclerosis (SPMS), Primary Progressive Multiple Sclerosis (PRMS)). The passages on page 4, lines 21 to 25 and on page 37, lines 8 to 10, which relate to "*a relapsing form of multiple sclerosis*" (underlining by the board), however, do not specify whether each of these known relapsing forms is meant by the formulation "*a relapsing form*" or only one of them. The disclosed clinical trial proposal also explicitly excludes progressive forms, such as SPMS and PRMS (see page 26,

lines 1 to 2). The dosage regimen of GA 40TIWA is thus not disclosed in the (earlier) application as filed in combination with "*a relapsing form of multiple sclerosis*".

6. Moreover, the only other passages in the earlier application as filed which mention "*a relapsing form of multiple sclerosis*" do so only in the context of "*increasing the tolerability*" and refer in general to "*reducing the frequency of an immediate post injection reaction*" (see page 11, lines 24 to 27) or "*reducing the frequency of an injection site reaction*" (see page 12, lines 14 to 17) without mentioning the dosage regimen required in the claim. Thus, a direct and unambiguous disclosure of the combination of the latter with RMS is missing. From the earlier application as a whole, the skilled person would thus conclude that the dosage regimen required in the claim applies only to RRMS.

7. The subject-matter of claim 1 extends beyond the content of the earlier application as filed (Article 100(c) EPC).

Auxiliary request 1 - claim 1
Inventive step (Article 56 EPC)
Closest prior art

8. Document D1 discloses the treatment of RRMS with GA 40QOD injected subcutaneously (see claim 3 in document D1, which is dependent on claim 1). The appellant questioned whether this embodiment was a suitable starting point for the analysis of inventive step because the only experiments in document D1 related to the treatment of MS with GA 20QD and GA 40QD (see Example 1, paragraph [0056]). The appellant further

considered that from Table 4 in this document it was apparent that the 40QD injection was associated with increased adverse effects. Also, other prior art showed that increasing the dose did not improve efficacy (see documents D11, D34a and D52). The skilled person would therefore have chosen 20QD and not 40QOD in document D1 as a realistic starting point. The appellant further opined that the purpose of document D1 was different because the claimed invention aimed at improving patient experience, i.e. finding the correct balance between efficacy and tolerability. In contrast, document D1 was mainly concerned with efficacy and did not provide data on improved tolerability. Therefore, its choice would have been possible only with hindsight.

9. The board does not agree that document D1 is not a suitable starting point because Article 56 EPC requires the invention to be not obvious over any state of the art. State-of-the-art disclosure can only be excluded as a starting point for an inventive-step analysis if it is clearly defective when trying to reproduce its disclosure or if it relates to a remote technical field which the skilled person would usually not consider (see Case Law of the Boards of Appeal, 10th edition 2022, I.D.3.1., 3.5.1 and 6, and decision T 1087/15 cited there). None of this has been argued by the appellant for document D1 and the embodiments disclosed in it. By the same token, any consideration of "how close" the prior-art starting document is judged to be to the claimed invention is not something which should exclude it from being the closest prior art.

10. Document D1 also has the same general purpose as the claimed invention, namely the treatment of RRMS. The appellant invoked the purpose of "*finding a balance*

between efficacy and tolerability". However, merely setting out a purpose, related to the general purpose as defined in or derivable from the claimed subject-matter, cannot lead to the exclusion of disclosure in the state of the art as a starting point for an inventive-step analysis (see e.g. T 2255/10, Reasons 2.2.4).

11. Document D1 finds, in addition to what is discussed under point 8. above, that "[t]*he increased efficacy observed with 40 mg/day GA in reducing MRI-measured disease activity and relapse rate indicates that it is well tolerated and can improve the treatment of RRMS patients. The improvement in efficacy, however, is not accompanied by a corresponding increase of adverse reactions which would be expected upon a doubling of the administered dose*" (see paragraph [0070]). Based on this finding, document D1 further proposes GA 40QOD (see claims 1 and 3). 40QOD corresponds to the same absolute amount of GA over a period of two days as 20QD, which in document D1 is disclosed as effective (see Tables 1 to 3). Moreover, documents D2 to D5, which all parties considered part of the common general knowledge, disclose that also a dose of 20QOD is effective in treating RRMS (see D2 to D5, Abstracts). The skilled person therefore knew from D1 that 20QD and 40QD were effective and from the common general knowledge that 20QOD was effective. The board has also seen no evidence that the dosage regimen of 40QOD would not have been considered suitable by the skilled person.

12. In conclusion, the skilled person would have considered it credible that RRMS patients could be treated with 40QOD. No hindsight would have been required to reach this conclusion. This embodiment in document D1

therefore represents a suitable starting point for an inventive-step analysis.

Difference, effect and objective technical problem

13. The difference compared to the disclosure of document D1 of an injection "*every other day*" (QOD; see claim 3) is the dosage regimen of "*three subcutaneous injections [...] for every seven days with at least one day between every subcutaneous injection*" (TIW). In absolute terms, this difference amounts to one dose less over two weeks (seven for QOD, six for TIW). In view of this minor difference in dosage and in the absence of comparative data, no effect of the claimed dosage regimen compared to the dosage regimen disclosed in document D1 can be recognised.

14. The objective technical problem can be formulated as the provision of an alternative GA dosage regimen for administration to a patient suffering from RRMS.

Obviousness

15. The board agrees with the finding of the opposition division that the solution is obvious. The skilled person was aware that different dosage regimens existed (see e.g. document D46, page 17 and document D57, page 2, for the treatment of RRMS with Rebif®, i.e. interferon β-1a). Since there is no effect associated with the difference, the appellant's argument on the different mechanism of action of Rebif® compared to GA is irrelevant. It is further common general knowledge that a dosage regimen of TIW allows for the medication to be given on the same day every week and to exclude the weekend. The associated advantages for the patient and the health system in general are equally common

general knowledge. The skilled person in search of an alternative dosage regimen to the one proposed in document D1 would therefore have come in an obvious manner to the dosage regimen of 40 mg GA "*every seven days with at least one day between every subcutaneous injection*".

16. The subject-matter of claim 1 lacks an inventive step over the disclosure of document D1 in combination with common general knowledge.

Auxiliary request 2 - claim 1, auxiliary request 3 - claim 2, auxiliary request 4 - claim 1
Sufficiency of disclosure (Article 83 EPC)
Claim construction

17. Claim 1 of auxiliary request 2, claim 2 of auxiliary request 3 and claim 1 of auxiliary request 4 contain the feature "to increase the tolerability of glatiramer acetate treatment in the human patient". The requirement to "*increase the tolerability*" is not further defined in terms of its meaning or with regard to a reference treatment. The board therefore interprets the claim in its broadest technically meaningful sense taking into account the application as a whole. It is undisputed that the disclosure on "tolerability" is identical in the earlier application.

18. Page 16, lines 9 to 13 in the earlier application defines tolerability as "*the level of discomfort associated with GA treatment*" and states that tolerability is "*associated with the frequency and severity of post injection reactions and injection site reactions*" (underlining by the board). It was undisputed that tolerability involves both frequency and severity of post-injection reactions, including

IPIRs, and ISRs, both these aspects of tolerability contributing to the "*level of discomfort associated with GA treatment*".

19. The appellant argued that the reference treatment was the established and approved treatment with 20QD (see the earlier application as filed, page 3, lines 21 to 26 and page 36, lines 5 to 15). The respondents argued that since a reference treatment was not provided in the claim, any other dosage regimen or even placebo could serve as a comparison. An increase of tolerability over placebo or a treatment of 20QOD as used in the prior art (see documents D2 to D5) was, however, not credibly achieved by the teaching of the earlier application as filed.

20. The board agrees with the appellant that it would be nonsensical to compare the tolerability of a medicament known to lead to adverse reactions to the tolerability of placebo. This, however, does not mean that the increase in tolerability required in the claim has to be interpreted relative to the only prior art dosage regimen which had received regulatory approval at the time of filing, i.e. 20QD. The clinical trials reported in documents D2 to D5, which are common general knowledge,represent equally valid comparative dosage regimens. It is therefore crucial whether an improvement of tolerability was credibly achieved compared to the dosage regimen disclosed, i.e. 20QOD.

21. As noted above and not disputed, "frequency" is one aspect of tolerability. The TIW dosage regimen, which amounts to one injection less over two weeks compared to QOD, credibly reduces, albeit only marginally, patient discomfort by reducing the frequency of

injections. This aspect of tolerability is therefore fulfilled by the TIW dosage regimen.

22. The skilled person, however, was also aware of the potentially stronger ASEs of a higher dose of 40 mg (see Table 4 and paragraph [0070] of document D1). This was acknowledged by the appellant, albeit in the context of inventive step (see statement of grounds of appeal, page 20, last paragraph: "*The board did not consider* [sic] *fact that 40QD had more severe ASEs than 20QD (Table 4 of D1, slide 14 of D34)*"). The skilled person would have weighed these ASEs against a slightly reduced frequency of injections.

23. The appellant referred to document D70 in which the appellant's expert, Prof. Brück, stated in point 242 that "*it was plausible or credible to the skilled person, just looking at the 335 Patent and taking into account their CGK, that the 40 mg TIW dosage regimen contained in the 335 Patent would be as effective as a 20 mg QD dose, but with improved tolerability. In my opinion, it would be credible for the skilled person to look at the patent and to think that a 40 mg TIW regimen could be as effective as a 20 mg QD regimen with improved tolerability. For example, if the skilled person had been asked to take part in a clinical trial to investigate whether a 40 mg TIW regimen versus a 20 mg QD regimen would be as effective but with improved tolerability, they would agree to participate in such a clinical trial and they would think that such a clinical trial would be worthwhile to pursue because it would be a credible thing to investigate*".

24. The board notes that the expert's statement is not supported by any facts or evidence. It remains therefore unclear why the skilled person should assume

that a 40TIW regimen would be more tolerable than a 20QOD (or even 20QD) regimen, in particular with regard to the severity of post-injection reactions, including IPIRs, or ISRs.

25. Moreover, in point 226 of the same expert report, cited by the appellant itself, Prof. Brück states that "*it was part of the skilled person's CGK that 40mg QD was no more efficacious than 20mg QD but led to more IPIRs and ISRs. The skilled person in 2009 would therefore not have thought that pursuing the 40mg dosage regimens would have been desirable. The increase in IPIRs and ISRs seen at the 40mg dose would have pushed the skilled person away from the 40mg dose (and indeed doses greater than 20mg). In addition, in August 2009 the skilled person would not have known what the overall effect on adverse events would be when increasing the GA dose from 20mg to 40mg and simultaneously decreasing the injection frequency from QD to TIW. Based on Pinchasi and the CGK, it was not possible for the skilled person to predict what the outcome would be*".

26. The appellant repeatedly stated that the expert's statements on inventive step should not be applied to sufficiency of disclosure. The board notes, however, that the disclosure of the application for sufficiency (Article 83 EPC) has to be determined using the same standards as for the disclosure of a document of the state of the art (see e.g. decision T 1437/07, Reasons 25), or, in other words, the knowledge of the skilled person and their common general knowledge at the relevant date are the same. The only difference is the teaching of the application, which the skilled person knows for sufficiency of disclosure but does not know for inventive step. If, however, as in the current

case, the application does not make any contribution to the state of the art other than verbal statements based on mere speculation, there is in fact no difference in the knowledge of the skilled person at the relevant date.

27. The (earlier) application as filed also does not provide any data or mechanistic explanation on the second aspect of tolerability, namely "*severity of post injection reactions and injection site reactions*" (see page 16, lines 9 to 13). The board recalls point 77 of decision G 2/21, which states for sufficiency of disclosure of medical use claims that "*the proof of a claimed therapeutic effect has to be provided in the application as filed, in particular if, in the absence of experimental data in the application as filed, it would not be credible to the skilled person that the therapeutic effect is achieved. A lack in this respect cannot be remedied by post-published evidence*".

28. There is also no evidence on file that from their common general knowledge the skilled person could assume that a dosage regimen of 40TIW would increase tolerability compared to 20QOD or even 20QD.

29. It is therefore not credible from the teaching of the (earlier) application as filed that the dosage regimen defined in the claim would increase tolerability of the treatment. This cannot be remedied by post-published evidence (e.g. document D89).

30. The invention as claimed is not disclosed in a manner sufficiently clear and complete for it to be carried out by the skilled person (Article 83 EPC).

Auxiliary request 5 - claim 1
Inventive step (Article 56 EPC)
Closest prior art

31. Document D1 and its embodiment of a treatment of RRMS with GA 40QOD represents a possible starting point for the analysis of inventive step (see points 8. to 12. above on inventive step of claim 1 of auxiliary request 1).

32. Claim 1 defines "*a patient who has experienced a first clinical episode and is determined to be at high risk of developing clinically definite multiple sclerosis* [CDMS]". This definition implies that because of the "high risk", the patient will in most cases develop MS.

33. The RRMS patients in document D1 (paragraph [0061]) are characterised as having "*at least one Gd-enhancing lesion at screening (month -1)*" (paragraph [0059]). This indicator is also used in the (earlier) application for the characterisation of patients (see page 13, lines 6 to 8: "*prior to administration the patient has at least 1 cerebral lesion detectable by an MRI scan and suggestive of multiple sclerosis*"), including patients with CIS (see page 17, lines 4 to 13 and page 37, lines 8 to 22). The appellant also referred to the evolving criteria for classifying patients as having CDMS (see e.g. D6, page 940, left-hand column, first full paragraph and reference 10; D18b, Table 4), this strengthening the view that a clear distinction between CIS and CDMS is difficult. There exists, therefore, at least an overlap between the patients of document D1 and the group of patients defined in the claim, but the patient groups are not identical.

Difference, effect and objective technical problem

34. It is undisputed that the difference between the subject-matter of claim 1 and the disclosure of D1 is the dosage regimen of "*three subcutaneous injections [...] for every seven days with at least one day between every subcutaneous injection*"; in D1, the injection is given "*every other day*" (see e.g. claim 3). In the absence of comparative data, no effect of the claimed dosage regimen is apparent to the board (see also point 13. above on inventive step of claim 1 of auxiliary request 1).

35. The patient group defined in the claim represents a further distinguishing feature over the disclosure of document D1. The effect of this difference is the treatment of an alternative patient group. Because of the likelihood for CIS patients to progress to CDMS and the overlap in symptoms, the board considers it credible that the dosage regimen in the claim is effective also for CIS.

36. The objective technical problem can thus be defined as the provision of an alternative GA dosage regimen for administration to an alternative patient group.

Obviousness

37. The skilled person was aware that a GA 20QD dosage regimen had been approved for RRMS and CIS (see document D8, points 4.1 and 5.1), this indicating that these two closely related conditions could be treated in the same manner. The application confirms this view of the skilled person at the relevant date by stating on page 37, lines 13 to 22, that "[b]*ased on the performance of the dosage regimen in these studies, the*

administration of three s.c. injections over a period of seven days with at least one day between every injection is also expected to work in the treatment of patients who have experienced a clinically isolated syndrome (CIS). This is based on the fact that the 20mg daily s.c. injection has been shown to work in PCT International Application No. PCT/US2008/013146 (see International Publication No. WO 2009/070298 and also U.S. Patent Application Publication No. US 2009-0149541 A1)". The earlier application as filed also does not include CIS patients in the proposed clinical trial (see page 20, lines 29 to 30: *"Study Population: Subjects with RRMS*"; page 24, lines 28 to 32).

38. The board interprets this to mean that the skilled person at the relevant date would have considered a dosage regimen effective in RRMS patients to be equally applicable to CIS patients and to patients who have experienced a first clinical episode and are determined to be at high risk of developing CDMS as defined in the claim. However, since this extrapolation from RRMS to CIS is entirely based on the results of prior-art studies, the same studies would be considered by the skilled person when aiming to identify alternative patient groups.

39. The skilled person would therefore have considered the dosage regimen disclosed for RRMS in document D1 to be also applicable to a patient who has experienced a first clinical episode and is determined to be at high risk of developing CDMS. The minor adaption of the dosage regimen from QOD to TIW (one additional day of interruption per week) is an alternative with no other effect than the obvious advantage of allowing the same schedule every week and/or to exclude the weekend and

can therefore not contribute an inventive step either (see point 15. above).

40. The subject-matter of claim 1 lacks an inventive step (Article 56 EPC).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

I. Aperribay M. Pregetter

Decision electronically authenticated