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Datasheet for the decision of 7 February 2024

Case Number: T 0853/22 - 3.3.04

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Language of the proceedings: EN

Title of invention:
Low Frequency Glatiramer Acetate Therapy

Patent Proprietor:
YEDA RESEARCH & DEVELOPMENT COMPANY, LTD.

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

Headword:
GA dosage regimen for MS 2/YEDA

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

Keyword:

Grounds for opposition - main request - added subject-matter (yes)
Inventive step - auxiliary request NAR1a (no)
Sufficiency of disclosure - auxiliary request NAR2a (no)

Decisions cited:

G 0002/21, T 0609/02, T 1437/07, T 1859/08, T 2255/10, T 1087/15, T 0728/21

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Case Number: T 0853/22 - 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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Representative:	Hamm&Wittkopp Patentanwälte PartmbB Jungfernstieg 38 20354 Hamburg (DE)

Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 4 February 2022 revoking European patent No. 2 630 962 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. 2 630 962 (the patent), which is based upon European patent application No. 13 166 080.5, which was filed as 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 5 withdrew its opposition during the opposition proceedings.

III. In the decision under appeal, the opposition division decided, for the main request (patent as granted), that claim 1 did not comply with Article 123(2) EPC and Article 76(1) EPC. On auxiliary request 1a (NAR1a), it decided, *inter alia*, that the subject-matter of claim 1 was not inventive over the disclosure of document D1 in combination with common general knowledge and other state of the art (documents D51 and D64). On auxiliary request 2a (NAR2a), it decided, *inter alia*, that the invention to which it related was sufficiently disclosed (Article 83 EPC) but that the subject-matter of claim 1 was not inventive over the disclosure of document D1 in combination with common general knowledge and other prior art (documents D51 and D64).

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 NAR1a and NAR2a, which are identical to the requests with the same names on which the decision under appeal was based.

V. 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 2020.

VI. In this communication, the board indicated that it agreed with the findings of the opposition division on the main request and auxiliary request NAR1a and that it found the invention of claim 1 of auxiliary request NAR2a to lack sufficient disclosure.

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

"Glatiramer acetate in the form of a pharmaceutical composition for use in treating a human patient suffering from a relapsing form of multiple sclerosis in a regimen of three subcutaneous injections of a 40 mg dose of glatiramer acetate every week with at least one day between every subcutaneous injection and wherein the pharmaceutical composition further comprises mannitol and has a pH in the range of 5.5 to 7.0."

Claim 1 of auxiliary request NAR1a differs from claim 1 of the main request in that glatiramer acetate is "in the form of a pharmaceutical composition" and the human patients suffer from "relapsing-remitting multiple sclerosis".

Claim 1 of auxiliary request NAR2a differs from claim 1 of auxiliary request NAR1a in that the use "reduces brain atrophy".

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

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

D1 US 2007/0161566 A1

D2 S. Flechter 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

D7 D. Simpson et al., "*Glatiramer Acetate A Review of its Use in Relapsing-Remitting Multiple Sclerosis*", CNS Drugs, 16(12), 2002, 825-50

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, front cover and page 397

D47 "*High-dosage Copaxone trial results are bad news for Teva*", PharmaTimes, 2008

D51 Product leaflet of the Rebif® product

D56 Rebif® (interferon beta-1a), 2002

D57 J.J. Jessop, "*Copolymer-1 for treatment of relapsing-remitting multiple sclerosis*", Review and Evaluation of Pharmacology Toxicology Data, Original NDA Review, NDA, 20-622, 1996

D86 Y. Ge et al., "*Glatiramer acetate (Copaxone) treatment in relapsing-remitting MS*" Neurology 54, 2000, 813-7

D87 M. Rovaris et al., "*Short-term brain volume change in relapsing-remitting*

multiple sclerosis", Brain, 124, 2001, 1803-12

D88 O. Khan et al., "*Efficacy and safety of a three-times-weekly dosing regimen of glatiramer acetate in relapsing-remitting multiple sclerosis patients: 3-year results of the Glatiramer Acetate Low-Frequency Administration open-label extension study*", Multiple Sclerosis Journal, 23(6), 2017, 818-29

D92 G. Francis, "*Benefit-risk assessment of interferon-β therapy for relapsing multiple sclerosis*", Expert Opin. Drug Saf., 3(4), 2004, 289-303

D95 Expert report of Prof. Brück, dated 12 June 2022

X. 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)
glatiramer acetate (GA)
every day (QD)
every other day (QOD)
three times in a week (TIW)
injection site reactions (ISRs)
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)

XI. 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).

An 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 40TIW regimen (e.g. paragraphs [0054] and [0056]). 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 NAR1a - 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. 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 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 D47 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 compared 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 polymers 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 40TIW was therefore inventive.

Auxiliary request NAR2a - claim 1
Disclosure (Article 83 EPC)

The rate of brain atrophy had been shown to be decreased after treatment with GA 20QD (see documents D86 and D87). This effect was therefore included in the Example 1 protocol for GA 40TIW as a credible effect to be observed. The skilled person would have been aware of the results of the FORTE Phase III study comparing treatment with GA 40QD vs GA 20QD in RRMS patients, which had been reported in documents D34 and D34a. At the conclusion of the 12-month comparison of GA 40QD with GA 20QD, the skilled person would have noted (D34a

slide 21) that the effect on brain atrophy in the GA 40QD cohort (–0.53% brain volume change from baseline to month 12) was similar to that observed in the GA 20QD cohort (–0.58%). However, the skilled person would also have been aware that a 12-month observation period was comparatively short in the context of brain atrophy and that a period of at least two years would be required to draw any firm conclusions.

The skilled person reading the application in light of their knowledge of previous trials of GA would have considered the effect on brain atrophy credible. As noted above, although the brain atrophy endpoint referred to an effect after 12 months, an open-label continuation was anticipated (page 20, lines 19 to 27 of the earlier application), which the skilled person would have known, from their common general knowledge, to be necessary to observe an effect vs placebo.

As the brain atrophy effect described in the application was credible, post-published documents could be referred to. The data in document D88 confirmed that GA 40TIW was effective in reducing brain atrophy relative to placebo (as measured by grey matter volume changes).

XII. Summary of the submissions of respondents I to IV

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 application as filed. There was only basis for RRMS. Other forms of relapsing MS existed, such as SPMS and

PRMS, (paragraph [0010] of the application as filed). Paragraph [0100] of the application as filed, however, 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 had to amount to a generalisation, for which there was no basis in the application as filed.

Auxiliary request NAR1a - claim 1
Inventive step (Article 56 EPC)

The GA 40QOD regimen was no less enabled than that of the patent in suit. Neither the patent nor document D1 contained any data on the GA 40QOD or GA 40TIW regimens, 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 lower frequency dosing were known from the prior art (see documents D51, D56 and D92), the invention was obvious.

Auxiliary request NAR2a - claim 1
Disclosure (Article 83 EPC)

Neither the application as filed nor the common general knowledge provided any support for the reduction in brain atrophy when given at a low frequency, i.e. TIW, and a high dose, i.e. 40 mg.
Documents D86 and D87, which were neither text book references nor reviews of the art, did not represent common general knowledge, so the appellant could not rely on the teachings of these documents to support the sufficient disclosure of the invention claimed. In any case, at least document D87 provided doubts about the effect of GA on brain atrophy in RRMS patients (see, for example, page 1809, left column, penultimate paragraph).

Document D87 concluded on page 1810, left column, second paragraph that "*immunomodulating and immunosuppressive treatments that reduce multiple*

sclerosis inflammatory activity and lesion accumulation may not be translated into a similar effect on progressive tissue loss, either in RR or progressive multiple sclerosis patients". Even if document D88, which is post-published, were taken into account, the clinical trial in D88 was a comparison of 40TIW administration with placebo (D88, page 819, left column, second, fourth and fifth paragraphs) and thus did not involve a comparison with the closest prior art.

The appellant's expert in document D95 also expressed doubts about the claimed effect in considering that brain atrophy was only weakly correlated with relapse rate (see points 13, 19, 22 and 44).

Therefore, there were serious doubts substantiated by verifiable facts that brain atrophy could not be reduced by the dosage regimen required in the claim. The claimed invention was not sufficiently disclosed.

XIII. The appellant requests 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, on the set of claims of auxiliary request NAR1a or NAR2a (dealt with in the decision under appeal).

The respondents request that the appeal be dismissed and the decision to revoke the patent be upheld.

Reasons for the Decision

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

1. 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).

2. 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.

3. 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).

4. 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 40TIW is thus not disclosed in the (earlier) application as filed in combination with "*a relapsing form of multiple sclerosis*".

5. 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.

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

Auxiliary request NAR1a - claim 1
Inventive step (Article 56 EPC)
Closest prior art

7. 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 D47). 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.

8. 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.

9. 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).

10. Document D1 finds, in addition to what is discussed under point 7. 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.

11. 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

12. 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.

13. 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

14. 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 D51, page 2; document D56, page 17; document D92, abstract, 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*".

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

Auxiliary request NAR2a - claim 1
Sufficiency of disclosure (Article 83 EPC)
Claim construction

16. Claim 1 of NAR2a differs from claim 1 of NAR1a in that GA is "in the form of a pharmaceutical composition ... which reduces brain atrophy". It is established case law that attaining the therapeutic effect indicated in a purpose-limited product claim in accordance with Article 54(5) EPC is a technical feature of the claim. The claim does not define a treatment or situation compared to which brain atrophy is reduced. Also, the description of the earlier application as filed (identical to the application as filed) does not indicate such a comparison (see page 9, lines 5 to 6; page 27, lines 28 to 29; page 28, lines 23 to 26; page 31, lines 4 to 5).

17. The board interprets the claim wording in the broadest technically meaningful sense as a reduction of brain atrophy compared to patients treated with placebo (see e.g. D7, page 839). A comparison to baseline, i.e. the start of the treatment, is not a technically meaningful comparison because it is common general knowledge that for neurodegenerative diseases, there is no cure available capable of reversing brain atrophy. The skilled person would therefore interpret "reduces" as slowing down brain atrophy and not as reversing it. For the requirement of Article 83 EPC to be fulfilled, it therefore has to be established whether reducing brain atrophy with the indicated dosage regimen of GA (compared to placebo) was credibly achieved at the relevant date.

18. The earlier application as filed does not contain any evidence on the effect of the proposed dosage regimen

on brain atrophy because the results of the proposed clinical trial are not reported. In the absence of data in the patent, it must be established whether the skilled person with their common general knowledge would consider that the effect of "reducing brain atrophy" was credibly achieved at the relevant date of the patent or, in the wording of decision G 2/21, whether "*the patent at the date of its filing renders it credible that the known therapeutic agent, i.e. the product, is suitable for the claimed therapeutic application*" (Reasons 74).

19. The respondents cited the appellant's expert, Prof. Brück, who stated in the context of inventive step "*that brain atrophy was only weakly correlated with relapse rate. There would therefore have been uncertainty in the mind of the Skilled Person as to the effect of reducing administration frequency (from QD to TIW) on brain atrophy, particularly in circumstances where there was no data on the effect of less-than-daily administration of GA on brain atrophy. There was also no data on less-than-daily administration of GA 40 mg on <u>any</u> parameter (relapse rate or brain atrophy) in August 2009*" (see D95, page 15, point 44; see also points 13, 19 and 22 where similar statements are made).

20. The board concludes from this statement that even if a therapeutic effect in RRMS patients was credibly achieved at the relevant date, for example, a reduced relapse rate, the skilled person would have had serious doubts about the effect on brain atrophy.

21. The appellant's argument that the statement of Prof. Brück was only made for inventive step and could not be relied on for the issue of sufficient disclosure is not

considered convincing by the board. Under the EPC, the skilled person for determining inventive step (Article 56 EPC) and sufficiency of disclosure (Article 83 EPC) is the same. It is also established case law that the common general knowledge in a technical field at a given time point is the same for all requirements of the EPC. The only difference in the mind of the skilled person mentioned in Article 83 compared to the one mentioned in Article 56 is their knowledge about the teaching of the patent application (Case Law of the Boards of Appeal, 10th edition 2022, I.D.8.3).

22. The board also does not agree with the appellant that the detailed clinical trial proposal in the application as filed would indicate to the skilled person that achieving the indicated endpoints was credible. It is established case law that the report of the start of a clinical study does not implicitly disclose achieving the therapeutic effect which represents the final result of the study (see Case Law of the Boards of Appeal, 10th edition 2022, I.C.4.1 and decision T 1859/08 cited there). Moreover, the disclosure of the application for sufficiency (Article 83 EPC) has to be determined according to the same standards as the disclosure of a document of the state of the art (see e.g. decision T 1437/07, Reasons 25).

23. As the earlier application contains no data on the effect of the claimed dosage regimen on brain atrophy but only a proposal to measure this parameter in a clinical trial (see point 18. above), the skilled person in fact did not learn anything in this respect from the patent application. The board agrees with the appellant that decision G 2/21 in its *obiter dictum* on sufficiency of disclosure, in particular with regard to further medical use claims, did not consider

experimental evidence mandatory. However, it stated in Reasons 77 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*" and that "[a] *lack in this respect cannot be remedied by post-published evidence*". The board interprets this statement by the Enlarged Board as meaning that if there is no experimental data in the application as filed (as in the case in hand), a different proof of the claimed therapeutic effect has to be provided in the application as filed, e.g. by way of a theoretical or mechanistic explanation or by relying on common general knowledge.

24. Since the earlier application as filed provides no theoretical or mechanistic explanation as to why the proposed dosage regimen would reduce brain atrophy, it has to be determined whether the skilled person, based on their common general knowledge, would have considered it credible that a reduction of brain atrophy in RRMS patients was achieved by "three subcutaneous injections of a 40 mg dose of glatiramer acetate every week with at least one day between every subcutaneous injection".

25. The documents cited by the parties on this point are D7, a review article on GA use in RRMS which refers to documents D86 and D87, and documents D2 to D5. It is undisputed that documents D2 to D5 relate to clinical trials of GA 20QD or 20QOD and can be considered common general knowledge at the relevant date because the underlying clinical studies were widely known and recognised. It is also undisputed that documents D2 to D5 do not mention brain atrophy. The board therefore

considers the statements in document D7 as particularly relevant for the common general knowledge on brain atrophy and GA treatment of RRMS.

26. The review article D7 reports two clinical trials in which brain atrophy was assessed (see paragraph bridging columns on page 839 and references 80 and 81 there, corresponding to D86 and D87, respectively). In both studies, GA 20QD was tested (see Abstract in D86 and D87). Document D7 reports from a study involving one centre and lasting two years that "*the annual reduction in brain volume [...] was significantly less in glatiramer recipients than in placebo recipients*" (referring to document D86) and from another study which lasted 18 months that "*no differences in brain volume changes between glatiramer acetate and placebo-treated patients in the first 9 months of the study and no significant change over the whole study period*" while "*in patients who had received only glatiramer acetate, there was a 50% greater reduction in the rate of brain volume loss during the second 9 months compared with the first phase, whereas patients randomised to placebo before active treatment was initiated had similar decreases in brain volume in each phase*" (referring to document D87). Document D87 itself cautions that "[i]*n conclusion, we were unable to find a significant effect of GA on reducing the brain tissue loss that occurs in RR multiple sclerosis over 9 months*" and that "*these results strengthen recent evidence that immunomodulating and immunosuppressive treatments that reduce multiple sclerosis inflammatory activity and lesion accumulation may not be translated into a similar effect on progressive tissue loss, either in RR or progressive multiple sclerosis patients*" (see page 1810).

27. Therefore, from document D7 (and documents D86 and D87 cited in it), it can be concluded that a reduction of brain atrophy for GA 20QD could only be seen after a longer study period of 18 to 24 months, while after 9 months no effect was detectable. From the reports in documents D86 and D87, it is not apparent whether the reduction of brain atrophy is linear. At least the absence of an effect in the first nine months speaks against this and instead seems to suggest that a reduction of brain atrophy occurs only in the later stages of treatment.

28. The claim, in contrast, relates to a different dosage regimen (GA 40TIW) than the studies cited in document D7. The skilled person could not simply expect that a reduction in brain atrophy which is only weakly correlated with the occurrence of relapses (see points 19. and 20. above) would be achieved with a different dosage regimen. Moreover, the claim does not prescribe the time in which the reduction in brain atrophy is to be achieved. At least for the early stages of treatment, a reduction of brain atrophy is not credible based on the teaching of the earlier application as filed taking into account common general knowledge.

29. Thus, even accepting the appellant's argument that in a case such as this one where the technology is relatively new, the credibility of the effect could be established by relying on prior art, irrespective of whether it represented common general knowledge (see e.g. T 609/02, Reasons 9 and T 728/21, Reasons 3.3), the board does not find any support in the cited prior art which renders the claimed effect of reducing brain atrophy credible.

30. The effect was thus not credibly disclosed to be achievable at the relevant date. In line with decision G 2/21, this cannot be remedied by post-published evidence (e.g. document D88).

31. The invention to which claim 1 relates is not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Article 83 EPC).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

I. Aperribay M. Pregetter

Decision electronically authenticated