Internal distribution code:

(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 10 September 2020

Case Number: T 1343/19 - 3.3.04

Application Number: 15171065.4

Publication Number: 2949335

IPC: A61K38/02, A61K38/16, A61P25/28, A61K38/07, A61K9/00, A61K31/785

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)
Synthon B.V.
Alvogen IPCo S.a.r.l.
G. L. Pharma GmbH
Hexal AG
Mylan Teoranta Trading as Mylan Institutional

Headword:
Low frequency glatiramer acetate therapy/YEDA

Relevant legal provisions:
EPC Art. 56

Keyword:
Main (sole) request: inventive step - (no)

Decisions cited:

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 1343/19 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 10 September 2020

Appellant I: (Opponent 1)	Generics [UK] Limited (trading as Mylan) Building 4, Trident Place Mosquito Way, Hatfield GB-Hertfordshire AL 10 9UL (GB)
Representative:	Gill Jennings & Every LLP MXL The Broadgate Tower 20 Primrose Street London EC2A 2ES (GB)
Appellant II: (Opponent 2)	Synthon B.V. Microweg 22 6545 CM Nijmegen (NL)
Representative:	Hamm&Wittkopp Patentanwälte PartmbB Jungfernstieg 38 20354 Hamburg (DE)
Appellant III: (Opponent 3)	Alvogen IPCo S.a.r.l. 5 rue Heienhaff 1736 Senningerberg (LU)
Representative:	Hamm&Wittkopp Patentanwälte PartmbB Jungfernstieg 38 20354 Hamburg (DE)
Appellant IV: (Opponent 4)	G. L. Pharma GmbH Schlossplatz 1 8502 Lannach (AT)
Representative:	Hamm&Wittkopp Patentanwälte PartmbB Jungfernstieg 38 20354 Hamburg (DE)

Appellant V: (Opponent 5)	Hexal AG Industriestrasse 25 83607 Holzkirchen (DE)
Representative:	Breuer, Markus Brienner Straße 1 80333 München (DE)
Respondent: (Patent Proprietor)	YEDA RESEARCH & DEVELOPMENT COMPANY, LTD. P.O. Box 95 76100 Rehovot (IL)
Representative:	D Young & Co LLP 120 Holborn London EC1N 2DY (GB)
Party as of right: (Opponent 6)	Mylan Teoranta Trading as Mylan Institutional Inverin H91 Co. Galway (IE)
Representative:	Gill Jennings & Every LLP APC The Broadgate Tower 20 Primrose Street London EC2A 2ES (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 13 May 2019 concerning maintenance of the European Patent No. 2949335 in amended form**

Composition of the Board:

Chair	G. Alt
Members:	R. Morawetz
	M. Blasi

Summary of Facts and Submissions

I. The appeals by opponents 1, 2, 3, 4 and 5 ("appellants I, II, III, IV and V" or "appellants") lie from the opposition division's interlocutory decision according to which European patent No. 2 949 335 ("the patent") as amended in the form of the main request, and the invention to which it relates, were found to meet the requirements of the EPC.

II. The patent, entitled "*Low frequency glatiramer acetate therapy*", derives from European patent application No. 15 171 065.4 ("application as filed" or "application").

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

D1 WO 2007/081975 (2007)

D2 Flechter S. et al., Journal of the Neurological Sciences (2002), vol. 197, pages 51 to 55

D3 Flechter S. et al., Clinical Neuropharmacology (2002), vol. 25, pages 11 to 15

D4 Khan O. et al., abstract P902, Multiple Sclerosis (2008), vol. 14, page S296

D5 Caon C. et al., abstract P06.141, Neurology (17 March 2009), vol. 72, Suppl 3, page A317

D8 Teva website, FORTE clinical trial press Release (7 July 2008), pages 1 and 2

D19 Comi G. et al., World Congress on Treatment and Research in Multiple Sclerosis (2008), abstract

D19a Comi G. et al., World Congress on Treatment and Research in Multiple Sclerosis (2008), slides 1 to 26

D28 McKeage K., CNS Drugs (2015), pages 1 to 8

D29 Wollinsky J.S. et al., ACTRIMS, ECTRIMS Conference Boston (2014), poster P306

D30 Wollinsky J.S. et al., ACTRIMS, ECTRIMS Conference Boston (2014), abstract P306

D34 FDA, Review and Evaluation of Pharmacology Toxicology Data, Original NDA Review, NDA #: 20-622, pages 1 to 154

D38 Shi L. et al., Expert Rev. Pharmacoeconomics Outcomes Res. (2007), vol. 7, pages 187 to 202

D39 Costello K. et al., Medscape J. Med (2008), vol. 10, page 225

D45 Medication Guide Rebif® (2002), pages 1 to 7

D50 Manfredonia F. et al., (2008), Neuropsychiatric Disease and Treatment, vol. 4, pages 321 to 336

D51 Haas J. and M. Firzlaff, European Journal of Neurology (2005), vol. 12, pages 425 to 431

D66 Treadaway K. et al., J Neurol (27 April 2009), vol. 256, pages 568 to 576

D73 Transcript excerpt from UK High Court Case No HP-2017-000010 (2017), front cover and page 397

D84 Expert Report of Professor Øivind Torkildsen dated 14 December 2018

IV. The following abbreviations are used in the present decision: multiple sclerosis (MS), relapsing-remitting multiple sclerosis (RRMS), 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), GA administered QD at a dose of 20 mg (GA 20 mg QD), GA administered QD at a dose of 40 mg (GA 40 mg QD), GA administered QOD at a dose of 20 mg (GA 20 mg QOD), GA administered QOD at a dose of 40 mg (GA 40 mg QOD).

V. Five oppositions to the patent were filed. The patent was opposed on, *inter alia*, the grounds for opposition set out in Article 100(a) EPC in relation to inventive step (Article 56 EPC) and in Article 100(b) EPC. During the opposition proceedings, an intervention was filed (opponent 6).

VI. In the decision under appeal, the opposition division held, for the assessment of the requirements of Article 83 EPC for the main request, that, at the priority date of the patent in suit, the skilled person would have been aware of documents D2 and D3, which reported on the efficacy of GA 20 mg administered at lower frequency and concluded that "[*i*]*n view of the known efficacy of the 20 mg GA at lower administration frequency, the opposition division considers the efficacy of the defined TIW administration of 40 mg GA as described in the patent plausible*" (see point 4.3).

For assessing inventive step, the opposition division held that the GA 40 mg QOD schedule disclosed in document D1 could not be considered "*a feasible or realistic starting point for the development of a dosage regimen aimed at optimizing tolerance of treatment*" and the "*conventional 20 mg GA QD as described in reports from the FORTE trial, in particular documents D19/D19a*" was taken as representing the closest prior art (see point 6.3). The claimed subject-matter was held to meet the requirements of Article 56 EPC.

VII. In their statements of grounds of appeal, the appellants submitted arguments to the effect that, *inter alia*, the claimed invention was not sufficiently disclosed by the patent and lacked an inventive step.

VIII. In addition, appellants I to IV requested that the appeal proceedings be accelerated in view of ongoing European national litigation in relation to the patent in suit.

IX. The board summoned the parties to oral proceedings, as requested by the appellants, and issued a communication pursuant to Article 15(1) RPBA 2007 in which it indicated that it had decided to grant the request for acceleration of the proceedings. Guidance pertaining to the management of the case was provided.

X. In reply to the statements of grounds of appeal, the respondent provided their counter-arguments and submitted sets of claims of a main request and auxiliary requests 1 to 5. The main request was identical to the main request underlying the decision under appeal.

Claim 1 of the main request reads as follows:

"1. Glatiramer acetate for use in a regimen of three subcutaneous injections of a 40mg dose of glatiramer acetate every seven days with at least one day between each subcutaneous injection for use in treating a patient who is suffering from relapsing-remitting multiple sclerosis or who has experienced a first clinical episode and is at high risk of developing clinically definite multiple sclerosis and wherein the pharmaceutical composition further comprises mannitol."

XI. With a letter dated 3 April 2020, appellant I provided their response to the respondent's reply, as did appellants II, III and IV with letters dated 30 April 2020.

XII. With letters of 28 April 2020 and 4 May 2020, the respondent provided their counter-arguments to appellant I, II, III and IV's previous submissions.

With a letter of 12 May 2020, appellant II replied to the respondent's submissions.

XIII. The board issued a communication under Article 15(1) RPBA dated 23 April 2020, providing further procedural guidance with respect to, *inter alia*, the conduct of the oral proceedings.

XIV. In a further communication pursuant to Article 15(1) RPBA dated 18 May 2020 sent to all parties by email on 14 May 2020, the board indicated, *inter alia*, its preliminary view with respect to the construction of claim 1 of the main request, sufficiency of disclosure and inventive step.

Procedural guidance with respect to the scheduled oral proceedings was given.

XV. In a letter dated 15 May 2020, the respondent provided their comments on the board's preliminary view with respect to the starting point for the assessment of inventive step, to which appellant I provided their comments in a letter of 20 May 2020.

XVI. With a letter of 7 July 2020, the respondent filed sets of claims of auxiliary requests 6 to 11.

Oral proceedings

XVII. With a letter dated 13 March 2020, appellant I requested that the hearing dates set for 9 and 10 June 2020 be maintained and that if due to the Sars-CoV-2 outbreak the hearing could not be conducted in person, they requested that a videoconferencing alternative on the same dates be organised.

In reply, with a letter dated 20 April 2020, the respondent submitted that the EPO had announced a pilot scheme for conducting oral proceedings by videoconference and that it would be wholly inappropriate for a complex, multiparty appeal hearing to form part of a pilot scheme.

XVIII. With a letter of 14 May 2020, the respondent requested a postponement of the oral proceedings.

With a letter of 15 May 2020, appellant I requested that the oral proceedings scheduled for 9 and 10 June 2020 not be postponed.

In further submissions, the respondent reiterated their request for postponement of the oral proceedings, while appellant I requested that the oral proceedings went ahead as scheduled.

XIX. In a communication dated 27 May 2020 sent to all parties by email on 20 May 2020, the board indicated that, at present, it saw no need to postpone the oral proceedings.

XX. With a letter of 28 May 2020, the respondent provided further arguments supporting their request for postponement of the oral proceedings.

XXI. In a further communication dated 3 June 2020, the board informed the parties that it had decided to postpone the oral proceedings to 10 September 2020.

XXII. With a letter of 10 August 2020, the respondent inquired if it was possible to arrange a video or audio transmission of the oral proceedings to a limited group of people.

In a communication dated 18 August 2020, the board informed the parties, *inter alia*, that it did not intend to arrange for a video or audio transmission of the oral proceedings.

XXIII. In a letter dated 28 August 2020, the respondent inquired whether the board was agreeable to the respondent's transmission of the proceedings via phone or equivalent means to those unable to travel.

In a communication dated 3 September, the board rejected the respondent's request.

XXIV. Oral proceedings before the board took place on 10 September 2020. During the oral proceedings, the respondent withdrew auxiliary requests 1 to 11.

XXV. At the end of the oral proceedings, the Chair announced the board's decision.

XXVI. The arguments of appellants I, II, III, IV and V, submitted in writing and during the oral proceedings, are summarised as follows.

Main (sole) request - claim 1

Claim construction

The claim construction set out in the board's communication pursuant to Article 15(1) RPBA was accepted.

Inventive step (Article 56 EPC)

Purpose of the claimed invention and possible starting points for the assessment of inventive step

The closest prior art had to be determined in view of the claimed invention. The opposition division's rejection of document D1 as the closest prior art was based on a wrong understanding of how the purpose of the claimed invention was to be determined.

The opposition division considered that the opposed patent was concerned with "*optimizing tolerance of treatment*". Based on document D19, it disqualified all approaches starting with the dose of 40 mg GA as unrealistic and not feasible starting points.

However, the purpose indicated in the claim was treating a patient suffering from RRMS. All prior art documents describing dosage regimens of GA for treating RRMS, i.e. 20 mg QD, 40 mg QD, 20 mg QOD and 40 mg QOD, shared this purpose and were realistic and promising starting points for an analysis of inventive step.

Document D1 and its disclosure of a GA 40 mg QOD dosage regimen for alleviating a symptom in a patient suffering from RRMS, see claims 1 to 4, page 8, lines 10 to 13, shared the same purpose as the claimed invention.

Document D1 had to be seen in light of the skilled person's common general knowledge. The skilled person's common general knowledge would have been the same when reading the patent in suit and document D1. It would have belonged to the skilled person's common general knowledge that low frequency administration of GA was effective, see documents D2 to D5; the decision under appeal, point 4.3; and the respondent's reply to the statement of grounds of appeal, paragraph B.35.

The 40 mg QD treatment described in document D1 was effective and safe, see page 4, lines 10 to 14; page 20, lines 1 to 8; and page 19, lines 8 to 14, and document D1 also described the 40 mg QOD dosage regimen as an effective use of GA in the treatment of RRMS.

The structural similarity of the prior art with the claimed subject-matter was a second critical consideration in the determination of the closest prior art.

The 40 mg QOD dosage regimen of document D1 shared the most features with the claimed dosage regimen,

i.e. same dose and reduced frequency of administration. It represented the structurally most similar prior art disclosure.

The respondent had not applied the problem and solution approach correctly. In the correct application of the problem and solution approach, the possible starting points were identified along the general "purpose or effect" or "purpose or objective" of the claimed subject-matter. This "effect" was not the effect determined as being caused by the feature distinguishing the claimed subject-matter from the closest prior art.

Even when later clinical trial data relating to the GA 40 mg QD dosage regimen were taken into account, the regimen only failed to meet its primary end point of improved efficacy, see document D19. It did, however, prove to have similar efficacy to the GA 20 mg QD dosage regimen.

"Realistic" was not a separate criterion but was reflected in the criterion of whether a particular disclosure served the same purpose.

The disclosure of document D1 was the more realistic starting point than the approved dosage regimen. Document D1 provided a "bridgehead" position because it already indicated how the GA 20 mg QD dosage regimen could be modified by changing the dose and/or the frequency of administration. In document D1, GA 40 mg QOD was a possible starting point.

As to a real-world approach, anything that could have been on the skilled person's desk had to be considered a realistic starting point. In reality, by the priority

date of the patent in suit, the GA 20 mg QD dosage regimen would not have been the only GA dosage regimen known to the skilled person.

Even if the purpose formulated by the respondent was accepted, the GA 20 mg QD dosage regimen could not be the closest prior art since it did not share the purpose of improving its own tolerability.

If different approaches could be followed in the analysis of inventive step, and one of these approaches led to the conclusion that the claimed subject-matter would have been reached in an obvious manner, the subject-matter was not inventive.

Objective technical problem

The only difference between a 40 mg TIW GA dosage regimen and a 40 mg QOD dosage regimen was the frequency of administration.

No particular effect of the GA 40 mg TIW dosage regimen and, in particular, no improvement over the GA 40 mg QOD dosage regimen was shown in the patent.

There was also no comparative data which made a direct comparison of the claimed invention with the GA 40 mg QOD dosage regimen of document D1.

The two dosage regimens differed by one administration every two weeks or two injections per month.

The respondent's own experts regarded the two dosage regimens as "*materially identical*", see document D73, page 397, lines 7 to 17, and document D84, paragraph 33.

The objective technical problem to be solved was the provision of an alternative dosage regimen of GA to be administered to RRMS patients.

Obviousness of the claimed solution

The skilled person would have been looking for an alternative; not an improvement.

The person skilled in the art would have been generally motivated to improve patient compliance. Maintaining long-term treatment adherence in patients with MS was known to be a problem, see document D39, page 1, first paragraph.

The skilled person would have been acquainted with the side effects that the use of immuno-modulatory drugs caused and would have considered patient non-compliance, due to side effects caused by injections, a problem.

It was known that a reduction in frequency would likely lead to an improvement in compliance, see document D38, page 187, abstract; and page 188, left-hand column, first paragraph, final two sentences.

Whether GA was taken had no immediate impact on the patient's perceived state of health. The skilled person would therefore have aimed at improving patient compliance by reducing the frequency of administration in view of the known, injection-related side effects.

Document D34 had raised the question whether daily injections which subjected the patient to an excessive amount of discomfort were really necessary and

specifically suggested that more infrequent, intermittent administration be evaluated, see page 121, last section.

Lowering the frequency of injections would obviously lower the frequency of injection-associated adverse events.

The skilled person would have been familiar with the immuno-modulatory medicines available for the treatment of RRMS before the priority date and known that there were various dosing regimens.

TIW administration was known in the prior art for the same patient group from treatment with Rebif®, see document D45, page 2; and document D50, abstract. The skilled person would have been familiar with the benefits of the TIW regimen, such as patient convenience of fixed weekday injections. Having the same administration scheme every week was easier to adhere to.

The skilled person would have expected a GA 40 mg TIW dosage regimen to work since low frequency administration of GA 20 mg was known to be effective, see documents D2 to D5.

The various discontinuation rates of document D51 were related to the different drugs' side effects and not the different dosage regimens. Document D66 did not teach away from TIW.

It would have been obvious for the skilled person to reduce the frequency of 40 mg GA from QOD to TIW.

XXVII. The arguments of the respondent, submitted in writing and during the oral proceedings, are summarised as follows.

Main (sole) request - claim 1

Claim construction

In the context of RRMS, "*treating*" and "*alleviating symptoms*" were synonymous. The claim did not relate to a curative therapy. The claim related to continuous treatment because RRMS is a chronic condition.

Inventive step (Article 56 EPC)

Purpose of the claimed invention and possible starting points for the assessment of inventive step

The skilled person reading the patent would have understood that the "purpose" of the invention was to improve the tolerability of GA, particularly compared to the only approved dosage of 20 mg QD, see paragraph [0052].

The opposition division was correct to take the improved tolerability into account for determining the closest prior art.

The person skilled in the art seeking, at the priority date, a starting point directed to the purpose of the invention - an optimal balance between efficacy and side effects (i.e. tolerability) - would have found no evidence that anything other than the GA 20 mg QD dosage regimen was capable of providing such a balance.

The objective "purpose and effect" underlying the disclosure in document D1 was to increase the dose of GA to improve efficacy. Unlike the patent, document D1 did not seek to improve the side effect profile of GA.

Document D1 thus failed the initial test of being directed to the same purpose as the invention.

Document D1 did not disclose that the GA 40 mg QOD dosage regimen had actually been tested. This dosage regimen was a hypothetical suggestion made on the basis of the main exemplified disclosure of document D1, the GA 40 mg QD dosage regimen.

The closest prior art had to be one which the skilled person would have realistically taken as a starting point under the circumstances of the case.

Document D1 failed the test of being a realistic starting point due to subsequent developments concerning the GA 40 mg QD dosage regimen published before the priority date, see document D19, abstract and slides. The FORTE clinical trial had confirmed that the "*40 mg dose did not demonstrate increased efficacy in reducing the relapse rate*", see document D8, first paragraph; and it had more severe side effects than the GA 20 mg QD dosage regimen, see document D19.

Thus, by the priority date of the patent in suit, neither the GA 40 mg QD nor the GA 40 mg QOD dosage regimen disclosed in document D1 would have been seen as a promising springboard for finding an effective dosing regimen having a favourable side effect profile.

The assessment of inventive step should start from a situation as close as possible to that encountered by

the inventor in reality. The real-world circumstances had to be taken into account, see also decisions T 1760/11, T 1149/09 and T 1666/16.

As GA 20 mg QD remained "*the optimal treatment dose*" of GA at the priority date, see document D8, a document disclosing this dosage such as document D19 represented the closest prior art.

Objective technical problem

The skilled person reading the patent would have considered it plausible/credible that the therapeutic effect and improved tolerability would be achieved by the GA 40 mg TIW dosage regimen. "*Such a reading of the patent would be supported by the general knowledge of GA e.g. the evidence of some level of continued efficacy when attempting 20 QOD [GA] and expectation of improved tolerability when decreasing frequency (see D2 and D3)*" (see reply, page 33, last paragraph).

The (post-published) GLACIER trial data confirmed a significant benefit with regard to the frequency and severity of ISRs and IPIRs of the GA 40 mg TIW dosage regimen compared to the GA 20 mg QD dosage regimen, see documents D28, D29 and D30.

While the claimed regimen was not an improvement over the GA 40 mg QOD dosage regimen, the achievements of the inventors should be honoured by granting a patent in view of the improvements over the GA 20 mg QD dosage regimen.

The objective technical problem was to be seen as providing a therapy that achieved similar efficacy and improved tolerability with respect to frequency and

severity of side effects as compared with the GA 20 mg QD dosing regimen.

Obviousness of the claimed solution

The appellants had not pointed to any particular reference showing that the TIW regimen was better.

The documents relied upon by the appellants were extremely general, unrelated to GA and not about a TIW treatment. Document D45 related to a distinct drug, Rebif®. The appellants had not explained why the skilled person would have turned to the Rebif® dosage regimen. There was no pointer in the prior art towards the claimed invention.

No connection between frequency of administration and patient compliance could be made, see documents D51 and D66. In document D51, GA given daily, had the lowest discontinuation rate, see Figure 1. In document D66, the number of missed injections no longer correlated with injection frequency, see page 573, left hand column, second full paragraph.

Starting from the GA treatment with a 40 mg QOD dosage regimen, the improvement over the known GA 20 mg QD dosage regimen was an element of surprise which justified granting a patent in the current circumstances.

XXVIII. Opponent 6, party as of right to the appeal proceedings, did not submit any arguments or requests during the appeal proceedings.

XXIX. The appellants requested that the decision under appeal be set aside and that the patent be revoked.

XXX. The respondent requested that the appeals be dismissed, implying that the patent be maintained in amended form on the basis of the main request as considered allowable by the opposition division.

Reasons for the Decision

1. The appeals comply with Articles 106 to 108 and Rule 99 EPC and are admissible.

Respondent's request for transmission of the oral proceedings via phone or equivalent means to those unable to travel

2. The oral proceedings in the current case were scheduled to take place in the physical presence of the parties and the public, having regard to general travel restrictions including obligations to self-isolate being absent and not to be expected around the date of the oral proceedings.

When the board decided on the respondent's request for video or audio transmission of the oral proceedings, it was not foreseen that, where oral proceedings took place in the physical presence of the parties, persons, be it persons accompanying one of the parties or members of the public, could attend other than in person, for example, by electronic means, regardless of whether transmission by such means was officially or "privately" organised (see the communication of the Boards of Appeal dated 29 July 2020, published on the web section of the Boards of Appeal). The board did not consider it appropriate, nor necessary, to deviate from

the publicly announced measures for the conduct of oral proceedings before the boards in this case.

When taking the decision about the respondent's request, the board also considered that the parties would be duly represented by professional representatives at the oral proceedings and that if a representative attending the oral proceedings considered it necessary to seek information or instructions from a person unable to attend, they could always request, during the oral proceedings, a short break for such purposes.

3. Therefore, the respondent's request was rejected.

Introduction

4. The invention concerns a low frequency dosage regimen of GA for treating patients suffering from RRMS, a particular form of MS. MS is a chronic disease of the central nervous system, and patients require treatment on a long-term basis. Patients suffering from RRMS, one of the five main forms of MS, experience sporadic exacerbations or relapses, as well as periods of remission.

5. GA, a mixture of polypeptides, is also referred to in the art as Copolymer 1 or Copaxone®. Before the priority date of the patent in suit, GA 20 mg QD was the recommended dosage regimen of GA for the treatment of patients with RRMS. GA is self-administered by SC injection.

Main (sole) request - claim 1

6. The set of claims of this request is identical to the set of claims of the main request in the proceedings before the opposition division. The opposition division held that this request met the requirements of the EPC (see section VI. above).

Claim construction

7. The claim is drafted as a second medical use claim pursuant to Article 54(5) EPC and is directed to a GA 40 mg TIW dosage regimen administered by SC injection for treating a patient suffering from RRMS or who has experienced a first clinical episode and is at high risk of developing clinically definite MS, with the pharmaceutical composition further comprising mannitol.

8. Thus, one embodiment of claim 1 is the use of a GA 40 mg TIW dosage regimen for treating a patient suffering from RRMS in which the pharmaceutical composition further comprises mannitol. This is the embodiment considered in this decision.

9. In view of paragraph [0016] of the patent and in line with the decision under appeal (see points 3.1 and 4.1) and the respondent's arguments on appeal, the board considers that the term "*treating*" in claim 1 is to be understood to mean "*alleviating a symptom*" of RRMS but not to mean "*curative treatment*". The claimed therapeutic effect is thus the alleviation of a symptom of RRMS in a patient suffering from RRMS.

10. The board agrees with the respondent that the person skilled in the art can be taken as being a team

comprising at least a physician involved in the diagnosis and treatment of patients suffering from or suspected to be suffering from MS and a statistician with experience in planning and interpreting clinical trials.

11. The board also agrees with the respondent that the skilled person would have understood the claim to relate to a continuous treatment because RRMS is a chronic condition demanding continuous therapy.

Inventive step (Article 56 EPC)

Purpose of the claimed invention and possible starting points for the assessment of inventive step

12. The opposition division held that the conventional GA 20 mg QD dosage regimen as described in documents D19/D19a represented the closest prior art, while the GA 40 mg QOD dosage regimen disclosed in document D1 was considered not to be a "*realistic*" starting point for the assessment of inventive step.

13. The appellants maintained that the GA 40 mg QOD dosage regimen disclosed in document D1 was, in accordance with the relevant case law of the boards of appeal, a "*possible*" starting point for the assessment of inventive step in accordance with the problem and solution approach.

14. The first question in this case is thus whether the disclosure of the GA 40 mg QOD dosage regimen in document D1 is a possible starting point or, in the words of the opposition division, a "*realistic*" starting point for the assessment of inventive step pursuant to the problem and solution approach.

15. In accordance with the established case law of the boards, the closest prior art for assessing inventive step is normally a prior art disclosing subject-matter conceived for the same purpose or having the same objective as the claimed invention and having the most relevant technical features in common, i.e. requiring the minimum of structural modifications (see also Case Law of the Boards of Appeal of the European Patent Office, "CLBA", 9th edition 2019, section I.D.3.1).

16. Thus, the primary consideration for the selection of the closest prior art is that it has the same purpose or objective as the claimed invention. A disclosure can be considered a "realistic" or "possible" starting point (hereinafter "possible") if it aims at the same purpose or objective as the claimed invention.

17. The purpose or objective of a purpose-limited product claim under Article 54(5) EPC is, generally, the therapeutic indication recited in the claim. In the case at hand, this is the treatment of RRMS, i.e. alleviating a symptom of it (see points 7. and 9. above). This is the purpose of the claimed invention.

18. In the decision under appeal, the opposition division held that the patent explicitly taught that the GA 40 mg TIW dosage regime "*maintains efficacy and increases tolerability*" with respect to the conventional GA 20 mg QD dosage regimen. The opposition division further noted that the patent provided a protocol for a clinical trial but no results. However, in view of "*reports concerning reduced side effects from 20 mg GA at reduced administration frequency in the prior art (D2-D5, D55, D59)*", the reduction of side effects from the TIW administration in the patent could, according to the opposition division, "*not be*

qualified as prima facie implausible". Accordingly, the "*optimization of the tolerability of treatment*" was taken into account for the determination of the closest prior art.

The opposition division noted that the GA 40 mg QD dosage regimen exemplified in document D1 was found in later studies to be accompanied by increased adverse reactions (i.e. it was less tolerable) while not having an improved efficacy.

It was on the basis of these considerations that the opposition division concluded that the GA 40 mg QOD dosage regimen described in document D1 was not a "*realistic*" starting point for the development of a dosage regimen aimed at optimising tolerance of treatment (see decision under appeal, points 6.1 to 6.3).

19. It is evident from the preceding point that the opposition division based the selection of the closest prior art on the effect stated in the patent as being achieved in the light of the starting point described in the patent, the GA 20 mg QD dosage regimen.

20. However, as stated above in point 16., the purpose to be used for selecting the possible starting point is that of the claimed invention. While the description is sometimes resorted to for determining the purpose of claimed compounds, this is not necessary when the purpose is stated in the claim, as in the case of purpose-limited product claims under Article 54(5) EPC.

21. Hence, in the current circumstances, the purpose to be used for selecting the closest prior art, as established by the case law of the boards in the

context of the problem and solution approach, is the one stated in the claim.

22. Turning to the question of which prior art disclosures fulfil the criterion of having the same purpose as the claimed invention, i.e. which are for use in the treatment of RRMS, the board agrees with the appellants that these are any GA dosage regimens disclosed in the prior art for use in the treatment of RRMS. Any of these can be considered to represent a possible starting point for the assessment of inventive step (see point 16. above).

23. While the GA 20 mg QD dosage regimen was the recommended dosage regimen before the effective date of the patent in suit, various other GA dosage regimens using higher doses or lower frequencies had been proposed or tested in the prior art, as described in the following points.

24. Thus, in document D1, the safety and efficacy of a GA 40 mg QD dosage regimen in RRMS patients was compared to that of a GA 20 mg QD dosage regimen (see Example 1). Based on the data after 9 months, it is concluded that "*The 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 doubling of the administered dose*" (see page 19, last paragraph).

Document D1 also discloses the use of the higher dose, 40 mg, at a lower frequency, every other day, i.e. a GA 40 mg QOD dosage regimen, for alleviating a symptom

in a patient suffering from RRMS wherein GA is administered to the patients by subcutaneous injection in a composition which also comprises mannitol (see page 8, lines 1 to 13, and claims 1 to 4).

25. In documents D2, D3, D4 and D5, the GA 20 mg QD dosage regimen was compared with a dosage regimen using the same dose at a lower frequency, a GA 20 mg QOD dosage regimen, in RRMS patients. Despite the limitations of these open-label studies (in documents D2 and D3) or "rater-blinded" studies (in documents D3 and D4), of which the authors are aware (see document D2, abstract), the authors conclude that the studies suggest that the two compared dosage regimens are equally effective in RRMS (see the abstracts of documents D2, D3, D4 and D5).

26. Documents D19 (abstract) and D19a (slides), collectively referred to as document D19, provide results from the FORTE clinical trial, a phase III, randomised, double-blind study with RRMS patients comparing the GA 20 mg QD dosage regimen with a dosage regimen using a higher dose at the same frequency, the GA 40 mg QD dosage regimen. The authors note that the GA 40 mg QD dosage regimen has a "[*g*]*ood safety and tolerability profile*" and that "*no unexpected adverse effect with the higher dose*" was observed (see slide 26). Only marginally differences in "*Serious Adverse Events*", namely 4.3% for GA 20 mg versus 4.2% for GA 40 mg, and "*Injection Site Reactions*", namely 55.6% for GA 20 mg versus 58% for GA 40 mg, were reported (see slide 25). The authors conclude that in RRMS patients, both dosage regimens were "*safe and well tolerated, and were equally effective in reducing clinical relapses and MRI activity*" (see document D19, abstract).

27. A further, secondary, criterion in establishing the closest prior art for the assessment of inventive step among the possible starting points is the similarity of the most relevant technical features between the selected prior art and the claimed invention (see point 15. above).

28. As set out in points 23. to 26. above, various GA dosage regimens had been disclosed in the prior art for use in the treatment of RRMS. The GA 40 mg QOD dosage regimen disclosed in document D1, advanced by the appellants as representing the closest prior art, uses the same dose as the claimed dosage regimen. Like the claimed dosage regimen, it uses less than daily administration, i.e. a reduced frequency of administration. It thus represents a starting point which shares the same purpose as the claimed invention and also has technical features - in terms of dose and frequency of administration - most similar to the claimed dosage regimen. Other dosage regimens disclosed in the prior art addressing the same purpose, including the GA 20 mg QD dosage regimen disclosed in document D19 and advanced by the respondent as closest prior art, have technical features which are less similar to those of the claimed invention.

29. While there is no disclosure in document D1 that the GA 40 mg QOD dosage regimen had actually been tested, the board has not seen evidence that the skilled person would have had concerns that this regimen would not have been suitable for the treatment of RRMS.

On the contrary, the efficacy of low frequency administration of GA in patients suffering from RRMS had been established in the art before the priority date of the patent in suit (see documents D2 to D5 and

point 25. above). Indeed, the respondent held that "*the evidence of some level of continued efficacy when attempting 20 QOD and expectation of improved tolerability when decreasing frequency (see D2 and D3)*" would have belonged to the "*general knowledge of GA*" of the skilled person when reading the patent in suit. Of course, the skilled person's common general knowledge would have been the same when reading the patent in suit and when reading document D1 at the day before the effective date of the claimed invention (see also CLBA, section I.D.3.1).

30. The board concludes from the above that document D1 and its disclosure of the GA 40 mg QOD dosage regimen is a possible starting point for the assessment of inventive step in accordance with the problem and solution approach, and is in fact the closest prior art.

31. The respondent's main line of argument in support of choosing a different starting point for the assessment of inventive step may be summarised as follows. The "purpose" of the invention was, according to the patent, to improve the tolerability of GA compared to the GA 20 mg QD dosage regimen. Since the objective "*purpose and effect*" of the disclosure of document D1 was to increase the dose of GA to improve efficacy, it failed the initial test of being directed to the same purpose as the invention.

32. This line of argument fails because the purpose of the claimed invention is the treatment of RRMS (see point 17. above), and the GA 40 mg QOD dosage regimen disclosed in document D1 is used for this purpose (see point 24. above).

33. In a further line of argument, the respondent held that the "untested" GA 40 mg QOD dosage regimen of document D1 failed the test of being a possible starting point in the light of the subsequently published "*failure*" of document D1's exemplified GA 40 mg QD dosage regimen.

34. The board agrees with the respondent that the skilled person's view on the day before the effective date of the claimed invention (see also above, point 29.) is relevant for determining the disclosure content of the prior art for evaluating inventive step. With respect to the GA 40 mg QD dosage regimen, it was known on that date that "]*t*]*he 40mg dose did not demonstrate increased efficacy in reducing relapse rate; however, the higher dose maintained the favorable safety and tolerability profile of COPAXONE® 20mg*" (see document D8, page 1, first paragraph).

35. The clinical trial data relating to the GA 40 mg QD dosage regimen available before the effective date of the claimed invention (see point 34. above) thus merely showed that it failed to meet the primary end point of "*improved efficacy*". This was contrary to what the initial results reported in document D1 suggested. The GA 40 mg QD dosage regimen did, however, have similar efficacy to the GA 20 mg QD dosage regimen and the same favourable safety and tolerability profile (see also document D19 and point 24. above).

36. The board can therefore see no reason why this knowledge about the GA 40 mg QD dosage regimen would have deterred the skilled person from considering the

GA 40 mg QOD dosage regimen as a possible starting point for finding a dosage regimen effective in the treatment of RRMS.

37. In a yet further line of argument, the respondent submitted that real-world circumstances had to be taken into account for choosing the proper starting point for the problem and solution approach and that these real-world circumstances were that GA 20 mg QD remained "*the optimal treatment dose*" of GA at the priority date.

38. This line of argument is not found persuasive either. The "optimal dose" of GA was, in fact, unknown at the priority date, and there was considerable interest in alternate dosing regimens of GA in RRMS in the field. The skilled person would have been aware of this (see document D4, abstract, lines 1 to 4; document D5, abstract, lines 3 to 5; and points 24. to 26. above).

39. Finally, again with respect to the respondent's position that the GA 20 mg QD dosage regimen disclosed in document D19 was the closest prior art, the board observes that while it may seem convenient to assess inventive step according to a single problem and solution approach starting from one disclosure, there is no reason to limit the assessment to one starting point. Pursuant to Article 56 EPC, the claimed invention must not be obvious to the person skilled in the art having regard to any prior art, subject to Article 56, second sentence, EPC. Accordingly, the claimed subject-matter lacks an inventive step if it is found to be obvious as a result of one of these approaches. In the case at issue, the claimed subject-matter is found to lack an inventive step when starting from the GA 40 mg QOD dosage regimen disclosed in document D1 (see point 60. below). Hence, there is no

need to consider other starting points, such as the GA 20 mg QD dosage regimen, before concluding that an inventive step is lacking.

Difference and its effect(s)

40. The parties were in agreement that the sole difference between the claimed subject-matter and the GA 40 mg QOD dosage regimen disclosed in document D1 was the lower frequency of administration, namely three times a week versus every other day. In practice, this difference amounts to one injection less of GA every two weeks.

41. As regards the effect(s) linked to this difference, the respondent did not dispute that there was no evidence on file comparing the two dosage regimens directly with regard to any effect.

42. The respondent pointed to post-published evidence in the form of the GLACIER clinical trial (see documents D28, D29 and D30) comparing the claimed regimen with the approved GA 20 mg QD dosage regimen. They argued that the improvement of the claimed regimen over this regimen, as demonstrated by the clinical trial, should be taken into account for the formulation of the objective technical problem to honour the achievement of the inventors.

43. Leaving aside the question whether post-published evidence can be used as the only evidence for proving an effect of the claimed subject-matter with regard to the prior art used as the starting point for the assessment of inventive step according to the problem and solution approach, it is the established case law of the boards in the context of the problem and solution approach that the only effects taken into

account for the formulation of the problem are those demonstrated to be caused by features by which the claimed invention and the prior art, which is used as the starting point in accordance with the problem and solution approach, differ (see also CLBA, section I.D.2). Hence, since the current analysis starts with the dosage regimen of GA 40 mg QOD, evidence comparing the claimed dosage regimen with regimens other than this dosage regimen is not relevant.

44. The effect of improving the tolerability of the treatment is an effect envisaged in the patent - yet with regard to the GA 20 mg QD dosing regimen. This effect cannot be acknowledged with regard to the prior art dosage regimen taken as the starting point for the assessment of inventive step here in the absence of any evidence to that effect.

45. As pointed out by the appellants, the claimed dosage regimen and the GA 40 mg QOD dosage regimen can be considered to be materially identical (see document D73, page 397, lines 7 to 17; and document D84, paragraph 33).

Objective technical problem to be solved

46. Therefore, based on the GA 40 mg QOD dosage regimen as a starting point and the effects of the differing features as defined in point 40. above, the board agrees with the appellants that the objective technical problem to be solved by the claimed subject-matter is the provision of an alternative GA dosage regimen for administration to RRMS patients.

Obviousness of the claimed solution

47. It was commonly known that RRMS is a chronic disease which requires long-term therapy (see also point 11. above) and that patient compliance is one of the most challenging issues in treating patients with chronic diseases (see document D38, a review article, abstract, lines 1 to 3). Indeed, it is evident from document D39 (see page 1, first paragraph) that long-term adherence to disease-modifying therapy - the benefit of which is not immediately apparent in terms of perceived improvement of health state - was known to be a challenge for patients with MS.

48. It was also well known in the art that SC injection of GA is uncomfortable (see document D34, page 121, last paragraph), challenging for long-term patient compliance (see document D4, abstract, lines 1 to 4) and associated with injection-related adverse events such as ISRs (see document D19, slide 25).

49. It was also generally known that reducing the number of injections may have a more pronounced effect on compliance than, for example, reducing the number of pills a patient needs to take (see document D38, page 188, left-hand column, last two lines of the first paragraph).

50. In the board's view, it is an evident consequence of lowering the frequency of injections that the frequency of injection-associated adverse events such as ISRs and the patient's discomfort caused by having to inject the drug will be lowered as well (see also document D34, page 121, last paragraph).

51. In the board's judgement, the skilled person, when faced with the objective technical problem formulated above, would thus have been motivated to modify the GA 40 mg QOD dosage regimen by reducing the frequency of administration in the expectation of improving patient compliance and discomfort.

52. The board considers that the skilled person would have been familiar with other medicines available for the treatment of RRMS at the priority date and their dosage regimens and would have taken these dosage regimens into account, especially those with a reduced frequency of administration, for solving the problem.

53. Thus, one such dosage regimen the person skilled in the field of RRMS would have been familiar with is the dosage regimen for SC administration of interferon β-1a (Rebif®) to RRMS patients, namely three times per week, preferably on the same three days each week (see document D45, page 2; and document D50, abstract).

54. In the board's opinion, the skilled person would have realised that such an administration scheme was simple and easy to adhere to and thus likely to increase patient compliance also for this reason.

55. The skilled person would also have had reasons to expect that a GA 40 mg TIW regimen was efficacious because, first, the weekly amount of GA administered would only have been slightly reduced in comparison to a 40 mg QOD regimen. Second, the skilled person would have been aware that the 20 mg QOD dosage regimen - having an even lower cumulative weekly dose - was efficacious (see point 29. above).

56. The respondent's criticism that the documents relied upon by the appellants as evidence that the skilled person would have been motivated to change the frequency of administration from QOD to TIW were extremely general and unrelated to GA is not tenable. With the exception of document D38, a review article relating to the impact of dose frequency on compliance and health outcomes, all the other documents relied on by the appellants relate to the treatment of MS or RRMS with GA or other disease-modifying therapies, such as Rebif®.

57. With respect to the alleged absence of a "pointer" to the TIW dosage regimen, the board notes that the skilled person would have been aiming at providing an alternative GA dosage regimen for administration to RRMS patients. In these circumstances, any suitable dosage regimen would have been an equally obvious solution to the problem and, therefore, choosing one of these would have been obvious, too. Nevertheless, in the case at hand, the board considers that the skilled person would have indeed had good reasons to select the TIW regimen (see point 54. above).

58. The respondent's line of argument that no connection between frequency of administration and patient compliance could be made based on documents D51 and D66 is also not persuasive. In document D66, four different dosage regimens involving four different drugs were compared with regard to injection frequency and number of missed injections (see page 573, left-hand column, second full paragraph). In the board's view, no conclusions can be drawn from this comparison for altering the frequency of administration of the same drug and patient compliance. Similar considerations apply to document D51, which compared discontinuation

rates for four different drugs and not discontinuation rates for the same drug administered with different frequencies (see Figure 1).

59. The respondent's argument as to an element of surprise in the claimed regimen over the GA 20 mg QD dosing regimen cannot succeed as it runs counter the problem and solution approach as set out above. The closest prior art is the GA 40 mg QOD dosage regimen, and no technical effect achieved over it had been demonstrated (see points 41. to 44. above).

60. The board concludes that the skilled person faced with the objective technical problem of providing an alternative GA dosage regimen for administration to RRMS patients would have replaced the QOD administration scheme of the GA 40 mg QOD dosage regimen with a TIW administration scheme and would thus have arrived in an obvious manner at an embodiment of claim 1.

Conclusion

61. The main (sole) claim request in the appeal proceedings does not meet the requirements of Article 56 EPC. Accordingly, the patent cannot be maintained in amended form on the basis of this request and, in the absence of another, allowable claim request, the patent has to be revoked.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chair:

L. Malécot-Grob G. Alt

Decision electronically authenticated