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Datasheet for the decision of 4 September 2019

Case Number: T 0799/16 - 3.3.01

Application Number: 11160247.0

Publication Number: 2377536

IPC: A61K31/44

Language of the proceedings: EN

Title of invention:
Methods of Using Sustained Release Aminopyridine Compositions

Patent Proprietor:
Acorda Therapeutics, Inc.

Opponents:
Actavis Group PTC ehf
Synthon B.V.
neuraxpharm Arzneimittel GmbH

Relevant legal provisions:
EPC Art. 123(2), 123(3), 83, 54, 56

Keyword:
Amendments - allowable (yes)
Sufficiency of disclosure - (yes)
Novelty - (yes)
Inventive step - (yes)

Decisions cited:
T 1212/97

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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 0799/16 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 4 September 2019

Appellant: (Patent Proprietor)	Acorda Therapeutics, Inc. 420 Saw Mill River Road Ardsley, NY 10502 (US)
Representative:	Oates, Edward Christopher Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Respondent: (Opponent 1)	Actavis Group PTC ehf Reykjavikurvegi 76-78 220 Hafnarfjördur (IS)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Respondent: (Opponent 2)	Synthon B.V. Microweg 22 6545 CM Nijmegen (NL)
Representative:	Prins, Hendrik Willem Arnold & Siedsma Bezuidenhoutseweg 57 2594 AC The Hague (NL)
Respondent: (Opponent 3)	neuraxpharm Arzneimittel GmbH Elisabeth-Selbert-Str. 23 40764 Langenfeld (DE)
Representative:	Königer, Karsten Harmsen Utescher Rechtsanwalts- und Patentanwaltspartnerschaft mbB Neuer Wall 80 20354 Hamburg (DE)

Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 6 April 2016 revoking European patent No. 2377536 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman A. Lindner
Members: R. Hauss
R. Romandini

Summary of Facts and Submissions

I. European patent No. 2377536 (patent in suit) derives from European patent application No. 11160247.0, which is a divisional of European patent application No. 05732613.4 (published as international application WO 2005/099701). The patent in suit was granted with a set of 20 claims.

II. Three notices of opposition were filed, opposing the patent in suit under Article 100(a), (b) and (c) EPC on the grounds that the claimed subject-matter lacked novelty and inventive step, was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art and extended beyond the content of the application as filed.

III. The documents cited in the opposition proceedings included the following:

C3: Neurology 48, 817-821 (1997)

C10: Neurology 60 (Suppl 1), A167, S21.001 (2003)

C20: Declaration of Dr Ron Cohen (1 January 2013)

C21-Annex C: Lancet 373, 732-738 (2009)

C21-Annex D: Ann Neurol 68, 494-502 (2010)

C27: SEC Form S-1, Acorda Therapeutics, Inc. (September 2003)

C30: Goodman et al., Poster

C30A: List of references cited by applicant for US application 11/102,559

C31: Goodman et al., Slideshow

C32: Neurology, 46(4), 907-911 (1996)

C33: Declaration Dr Andrew Blight (15 September 2014)

C36: McAlpine's Multiple Sclerosis 3rd edn., 31-32, Churchill Livingstone, London 1998

C43: Prescribing Information for Ampyra™, revised 2010

C45: Ann Neurol 27, 186-192 (1990)

IV. The decision under appeal is the decision of the opposition division revoking the patent, announced on 24 February 2016 and posted on 6 April 2016.

The decision is based on an amended main request and seven auxiliary requests filed by the patent proprietor.

The opposition division found none of these requests allowable and, *inter alia*, decided that the disclosure of document C30 formed part of the state of the art pursuant to Article 54(2) EPC and anticipated the subject-matter of claim 1 of auxiliary request 3.

V. The patent proprietor (appellant) filed an appeal against this decision.

VI. With the statement setting out the grounds of appeal, the appellant submitted two sets of claims labelled "Main Request - August 2016" and "Auxiliary Request - August 2016". The claims of the main request are identical to those of former auxiliary request 3 presented before the opposition division.

The independent claims of the **main request** read as follows:

> "*1. A sustained release 4-aminopyridine composition for use in a method of increasing walking speed of a patient with multiple sclerosis, wherein said composition is administered twice daily in a dose of 10 milligrams of 4-aminopyridine.*

5. Use of 4-aminopyridine in the manufacture of a sustained release composition for increasing walking speed in a patient with multiple sclerosis, wherein said composition is administered twice daily in a dose of 10 milligrams of 4-aminopyridine."

With the statement setting out the grounds of appeal, the appellant also submitted further evidence, including the following document:

C30B: Supplemental Information Disclosure Statement (26 July 2012)

VII. By letter dated 23 November 2018 the board summoned the appellant and the respondents (opponents 1, 2 and 3) to oral proceedings.

VIII. With a further submission dated 8 March 2019, the appellant filed new auxiliary requests 1 to 5. With a submission dated 28 August 2019, the appellant filed auxiliary requests 6 to 11.

IX. Oral proceedings were held on 4 September 2019, in the absence of respondent-opponent 2 and respondent-opponent 3, which, in accordance with Article 15(3) RPBA and Rule 115(2) EPC, were treated as relying only on their written case.

X. The arguments presented by the respondents may be summarised as follows.

Amendments

Claim 1 of the main request extended the scope of the claims as granted because of the feature "increasing walking speed in a patient with multiple sclerosis", which covered increasing walking speed outside a method of treating multiple sclerosis (Article 123(3) EPC).

Furthermore, such treatment outside a method of treating multiple sclerosis (MS) was not disclosed in the application as filed (Article 123(2) EPC).

Sufficiency of disclosure

The appellant's own data suggested that the desired therapeutic benefit was only attained in a sub-population of responders rather than in all MS patients. Assuming (as argued by the appellant) that the "responder analysis" method was critical to identifying the patients to be treated, the claimed subject-matter was insufficiently disclosed because the claims were not restricted to such responder patients.

Public availability of evidence

C30 and C31 were copies of a poster and slides which had been presented by the appellant at a public conference. According to respondent-opponent 1, the correct standard of proof to be applied with regard to the issue of public availability before the effective date of the patent was the balance of probabilities. According to respondent-opponent 2 and respondent-opponent 3, the burden of proof was on the appellant to substantiate, beyond reasonable doubt, its allegation that the content of C30 and C31 was not identical to what had actually been presented to the public.

Novelty

The disclosure of documents C10 and C30 anticipated the claimed subject-matter. The statements made in both documents regarding efficacy in a dosage range of 20 to 40 (or 50) mg daily included the lowest dosage (corresponding to 10 mg bid). Treatment was plausibly disclosed in the prior-art documents because there existed a clear and accepted relationship between the pharmacological properties of 4-aminopyridine and the

treatment of symptoms of MS, including walking speed, and according to C10 and C30, the claimed dosage of 10 mg bid was administered to MS patients over a period of one week for the purpose of improving walking speed. Additionally, the dose-response curve shown in C30 demonstrated the efficacy of the 10 mg bid dosage regime. While the study providing the reported data would not have been adequate for obtaining marketing approval, the person skilled in the art would still have regarded these data as clincally meaningful.

Inventive step

Either document C30 or C27 could be regarded as the closest prior art, assuming that the distinguishing feature was the confirmation that the 10 mg bid dosage had a therapeutic effect in improving walking speed.

Starting from the technical teaching of document C30, the objective technical problem was the confirmation that the 10 mg bid dosage, already disclosed in C30, had a therapeutic effect (respondent-opponent 1).

Starting from the technical teaching of document C27, the objective technical problem was the set-up of a clinical trial carrying out a comparison between the 10 mg bid, 15 mg bid and 20 mg bid dosages, and thus the selection of the optimum dose for efficacy and safety (respondent-opponent 2, respondent-opponent 3).

Setting up a clinical trial powered to confirm the skilled person's expectation that the 10 mg bid dosage regime would show therapeutic utility was routine work which would not have required inventive skill, and on this basis, the selection of the 10 mg bid dosage regime would have been straightforward. It was incorrect to assume that the efficacy of the 10 mg bid dosage could only have been confirmed by the appellant's specific statistical method (the "responder

analysis"). Furthermore, the claims covered the treatment of a single patient and did not define a minimum level of improvement in walking speed to be attained. The therapeutic effect for a single patient could be determined simply by administering 4-aminopyridine and then measuring the patient's walking speed.

An assessment of inventive step starting from the technical teaching of document C3 should also be taken into consideration.

XI. The arguments presented by the appellant may be summarised as follows.

Amendments

Reading the claims of the main request, it was evident that increasing the walking speed in a patient with multiple sclerosis could only refer to the therapeutic treatment of such a patient and, thus, the treatment of multiple sclerosis. Therefore, the premise of the respondents' objections under Article 123(2) and (3) EPC was flawed.

Sufficiency of disclosure

The data presented in Example 5 of the patent in suit and its associated figures showed that the claimed dosage regime was effective and safe. Specifically, the responder analysis developed and carried out post hoc by the inventors, which was based on consistency rather than on magnitude of response, revealed a significantly higher number of responders in the group treated with 4-aminopyridine than in the placebo group, without a difference in efficacy between the three dosages tested. These results also had been confirmed by subsequent phase 3 clinical studies.

Subpopulations of non-responders were a common phenomenon to many treatments. Medical uses were nonetheless patentable, as the technical contribution resided in the therapeutic benefit for a substantial proportion of the treated population. It was also appropriate and usual to claim the treatment of an individual patient, while the efficacy of a treatment could only be demonstrated in a population of patients.

Public availability of evidence

The burden of proof was on the respondents to establish beyond reasonable doubt that documents C30 and C31, both relating to disclosures allegedly presented at a public conference, had actually been publicly displayed. However, there was reasonable doubt that the content of these documents was identical to what had been presented. The appearance and inaccurate content of documents C30 and C31 suggested that they were unlikely to be copies of any visual aids actually used at the conference. There was no evidence on file of what the audience understood from the presentations, and no record of what the presenter(s) had said.

Novelty

Documents C10 and C30 cited by the respondents against novelty did not specifically disclose the efficacy of 4-aminopyridine, when administered twice daily in a dose of 10 mg, in increasing walking speed. If the treatment was inherently present in the prior-art teaching but had not been recognised and disclosed, there was no lack of novelty. Saying that a particular dose of a drug provided "treatment" involved demonstrating that that dose had statistically improved efficacy relative to placebo, which in this case had not been shown in the prior art. Furthermore, the person skilled in the art would have realised that the

dose-escalation study reported in C10 and C30 had not been powered to allow the efficacy of each separate dose of 4-aminopyridine to be assessed.

Inventive step

Neither document C27 nor C30 cited by the respondents against inventive step disclosed drug efficacy for a dosage of 10 mg bid, the lowest dosage mentioned in these documents. Nor did they suggest that the therapeutic benefit of the 10 mg bid dosage was comparable to that achieved with higher dosages while the incidence of adverse effects was lower.

The technical problem to be solved was thus to provide an improved therapy for MS patients.

The person skilled in the art would not have expected the dosage of 10 mg bid to be effective. Additionally, it had not been a simple matter of routine to confirm the efficacy of this dosage. Rather, the inventors had designed a parallel-arm study and had only been able to ascertain the optimum dose by employing a novel statistical methodology based on the consistency of the subjects' response to the drug rather than the magnitude of response. As the inventors' study design and subsequent analysis had been non-obvious measures, their result was not obvious either.

The new line of argument proposed by respondent-opponent 1, assessing inventive step starting from the disclosure of document C3, should not be admitted into the proceedings as it amounted to a last-minute change of its case on the day of the oral proceedings before the board.

XII. The appellant requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the claims of the main request labelled "Main Request - August 2016" enclosed with the statement setting out the grounds of appeal, or in the alternative, on the basis of the claims of one of the following auxiliary requests:

- auxiliary requests 1 to 5 filed with the letter dated 8 March 2019

- auxiliary requests 6 to 11 filed with the letter dated 28 August 2019.

XIII. The respondents requested that the appeal be dismissed.

Reasons for the Decision

1. Admissibility of the appeal

The appeal complies with Articles 106 to 108 EPC and Rule 99 EPC and is therefore admissible.

2. Amendments

2.1 According to the respondents, claim 1 of the main request contained added subject-matter and extended the scope of protection as compared to the claims as granted.

2.2 Added subject-matter

2.2.1 The subject-matter of independent claim 1 of the main request finds support in lines 1 to 7 on page 49 and paragraph [0010], third sentence, of the application as filed (Article 123(2) EPC), and in claim 3 and paragraph [0010], third sentence, of the parent application as filed (Article 76(1) EPC). These

passages disclose a method of increasing walking speed comprising administering to a patient with multiple sclerosis an effective amount of a sustained-release aminopyridine composition twice daily, wherein this effective amount may be (about) 10 mg. Furthermore, the most preferred aminopyridine is 4-aminopyridine.

2.2.2 In claim 1 of the current main request, this same subject-matter is drafted as a further medical use in the format provided in Article 54(5) EPC. Redrafting as a further medical use does not give rise to added subject-matter (nor was this argument made by the respondents).

2.2.3 Hence, claim 1 of the main request meets the requirements of Articles 76(1) and 123(2) EPC.

2.3 Extension of scope

2.3.1 While the claims of the patent as granted refer to

> "*treating multiple sclerosis* (claim 1)
> *... wherein the method of treating multiple sclerosis is increasing walking speed in a patient with multiple sclerosis*" (dependent claim 5),

and

> "*treating multiple sclerosis* (claim 12)
> *... wherein the treating is increasing walking speed in a patient with multiple sclerosis*" (dependent claim 16),

claim 1 of the main request refers to

> "*increasing walking speed in a patient with multiple sclerosis*".

The respondents argued that the deletion of the explicit reference to treating multiple sclerosis had the effect of extending the scope of protection to

cover an increase in walking speed "outside" the treatment of multiple sclerosis.

2.3.2 This argument cannot succeed, since it will be inferred from the wording of claim 1 of the main request that increasing walking speed specifically in a patient with multiple sclerosis must refer to the treatment of a symptom of multiple sclerosis - all the more so since the drug to be administered is a medicament which acts against symptoms occurring in multiple sclerosis (see the patent in suit, paragraphs 3 and 4, mentioning that 4-aminopyridine is a potassium channel blocker which restores conduction in blocked and demyelinated nerves).

2.3.3 Hence, claim 1 of the main request does not extend the scope of protection of the claims as granted (Article 123(3) EPC).

3. Sufficiency of disclosure

3.1 The patent in suit seeks to provide a sustained-release oral dosage form of an aminopyridine, most preferably 4-aminopyridine (also called fampridine), with utility in the treatment of patients suffering from multiple sclerosis (MS) (see paragraphs [0001] and [0009] of the patent in suit and paragraphs [0002] and [0010] of the application as filed).

3.2 The independent claims of the main request (claims 1 and 5) specify a dosage regime involving twice-daily treatment with 10 mg of sustained-release 4-aminopyridine for increasing walking speed.

3.3 These claims relate to a further medical use. According to the case law of the boards of appeal, attaining the claimed therapeutic effect is regarded as a functional technical feature of such claims.

In order to meet the requirement of sufficiency of disclosure of Article 83 EPC, the therapeutic efficacy of the composition and, in this case, the 10 mg bid dosage for the claimed therapeutic indication must therefore be credible.

3.4 It was not in dispute that the person skilled in the art is capable of preparing sustained-release dosage forms of 4-aminopyridine. The objections raised by the respondents with regard to sufficiency concerned the credibility of the alleged therapeutic efficacy across the scope claimed, the argument being that the claims of the main request did not exclude the treatment of non-responders.

Non-responders

3.5 As acknowledged in the application as filed (see paragraph [0079]), it was known that only a proportion of patients, estimated to be about one third, responded to treatment with 4-aminopyridine. The existence of a population of non-responders was also confirmed by the inventors' own results reported in Example 5.

Aminopyridines are potassium channel blockers whose proposed mechanism of action is the restoration of conduction in demyelinated axons. Given the highly variable pathology of MS, only a proportion of MS patients would be expected to possess axons of appropriate functional relevance susceptible to this mechanism of action, which would explain the occurrence of non-responders (see the application as filed, paragraphs [0005] and [0079]).

Contrary to the respondents' view, the existence of non-responders is not a reason to deny sufficiency of disclosure, and the treatment of non-responders does not have to be excluded or disclaimed.

The existence of a substantial proportion of patients who are non-responders is a common phenomenon observed with drugs in many treatment areas, such as diabetes, migraine or cancer. It is common practice to treat patients with a drug and change their medication should it turn out that they do not respond to the treatment.

If it can be shown that a relevant proportion of patients benefits from a treatment and that it has acceptable safety, the criterion of sufficiency of disclosure is met, since the person skilled in the art has the necessary technical information to perform the treatment.

Therapeutic utility of 10 mg bid 4-aminopyridine

3.6 In view of the data presented in Example 5 of the patent in suit and the application as filed, the board is satisfied that the efficacy of the 10 mg bid dosage regime was rendered credible in the application as filed.

3.7 Example 5 (see the application as filed, paragraphs [0101] to [0133], and the associated figures) relates to a phase 2, 20-week, double-blind, placebo-controlled treatment study in 206 subjects diagnosed with MS, designed to investigate the safety and efficacy of three dose levels of sustained-release 4-aminopyridine. The dosages administered in this study during a 12-week stable-dose treatment period were 10 mg bid, 15 mg bid and 20 mg bid. The primary efficacy endpoint was an increase, relative to base line, in walking speed on the "Timed 25-Foot Walk".

3.8 As explained in the statement setting out the grounds of appeal (section 2) and in documents C32 (figures) and C36 (Figure 1.23), multiple sclerosis is a disease that is characterised by unusual variability in the

occurrence of symptoms, frequent episodes of relapse and remission being common. Progression of disability may occur, at variable rates, from onset or from a later stage, with or without plateau or remission phases. As a result of the fluctuating nature of MS symptoms, recognising the clinical benefit of therapies is particularly difficult. This is acknowledged in the application as filed (paragraph [0081]), which states:

> "*Given the often large variations in function experienced by people with MS, it is difficult for the subject or a trained observer to separate a treatment-related improvement from a disease-related improvement without the element of consistency over time. Consistency of benefit might therefore be expected to be a more selective measure of true treatment effect than magnitude of change*".

3.9 According to the appellant, presumably due to these fluctuations, the pre-planned first analysis of the data obtained in the clinical trial of Example 5 for the primary efficacy endpoint (per cent change in average walking speed during the 12-week stable-dose period relative to baseline) did not show statistically significant differences between any of the 4-aminopyridine groups and the placebo group (see paragraphs [0103], [0114] and Figure 3 of the application).

This was also the case for a second approach (the "protocol-specified responder analysis"), which identified successful response for each subject as improvement in walking speed (percent change from baseline) of at least 20% (see paragraphs [0104], [0115] and Figure 4 of the application).

3.10 To overcome this difficulty, and following the rationale explained in point 3.8 above, the inventors introduced an adapted evaluation method which focused on the consistency rather than the intensity (or magnitude) of response to the drug - the "responder analysis", which was carried out post hoc.

This post hoc analysis identified likely responders as subjects showing a faster walking speed for at least three of five assessment visits during the double-blind stable-dose treatment period as compared to the maximum value observed among a set of five non-treatment visits - four before treatment and one after discontinuation of treatment (see paragraph [0105] of the application). Furthermore, the proportions of subjects meeting this criterion in the pooled 4-aminopyridine groups and in the placebo group were compared.

3.11 This analysis revealed the existence of a subset of subjects who responded to the drug with clinical meaningfulness (see paragraph [0120] of the application). The number of subjects who met the post hoc responder criterion in the pooled 4-aminopyridine-treated group was 58 (36.7%) compared to 4 (8.5%) seeming "responders" in the placebo-treated group, and this difference was statistically significant ($p<0.001$) (see paragraph [0122] and Figure 8). The post hoc responder rates based on consistency of improved walking speed were significantly higher in all three active dose groups (35%, 36% and 39%) compared to placebo (9%; $p<0006$ for each dose group, adjusting for multiple comparisons) (see paragraph [0121] and Figure 7). The mean improvement in walking speed for the 4-aminopyridine responders was more than 24% (paragraph [0126] and Figure 10). No notable differences in efficacy were found between 15 mg bid and 10 mg bid among responders (see paragraph [0132]).

It is also reported that serious adverse effects did not occur in the 10 mg bid group (paragraph [0133]).

3.12 The board considers that the explanation for the initial finding of lacking statistical significance, the rationale given for the post hoc methodology, and the respective results presented in Example 5 of the application (see points 3.10 and 3.11 above) are convincing and also sufficient to have rendered the alleged therapeutic efficacy and safety of 10 mg bid 4-aminopyridine credible at the effective date of the patent.

3.13 In view of these considerations, the subject-matter of independent claims 1 and 5 is disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Article 83 EPC).

4. Public availability of documents C30 and C31

4.1 Relying, *inter alia*, on document C30A, the respondents contended that the poster C30 and the slide presentation C31 (both undated) had been presented to the public at the 7th Annual Meeting of the Americas Committee for Treatment and Research in Multiple Sclerosis and 18th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS/ECTRIMS), which took place in Baltimore, Maryland (USA), 18-21 September 2002, i.e. before the effective date of the patent in suit.

4.2 C30 and C31 are identical to references CC15 and CC16 listed in document C30A ("List of References cited by Applicant"), which mentions that these were presented at the ACTRIMS/ECTRIMS conference in September 2002. The appellant itself filed both documents at the US Patent and Trademark Office (USPTO) in 2012, with the document list C30A, as part of an

Information Disclosure Statement (IDS) for the case file of related US application No. 11/102,559 (see C30B and the statement setting out the grounds of appeal, point 3.7). They were obtained by the respondents from the USPTO's online register (PAIR).

4.3 In these appeal proceedings, the appellant disputed, however, that the content of C30 and C31 was identical to what had been presented at the ACTRIMS/ECTRIMS conference.

According to the appellant, these documents had been filed with the USPTO years after the conference in question. At that point in time, it was not known beyond reasonable doubt to the US attorney who wrote C30B (the accompanying letter submitted to the USPTO together with C30A, C30 and C31) whether C30 and C31 really had been presented at the conference of 2002.

As explicitly stated in document C30B, identification of the references in C30A was not meant to be construed as an admission that they were prior art.

Furthermore, C30B included the following statement:

> "*On information and belief, after reasonable inquiry, the poster and slide presentation listed as References CC15 and CC16, respectively, in the attached List of References Cited, were presented at the ACTRIMS 7th Annual Conference and ECTRIMS 18th Congress on September 18-21, 2002. Applicants reserve the right to correct this information should further information show such correction is warranted.*"

If there had been absolute certainty, the appellant would not have reserved the right to correct the information. The appellant also argued that, while there was no evidence from the respondents to show that

C30 and C31 were an accurate description of what was disclosed at the ACTRIMS/ECTRIMS conference, the appearance and inaccurate content of C30 and C31 suggested that they were not the visual aids actually used at the conference.

Furthermore, the appellant contended that the presentation of slides or a poster in both cases also involved an aural element. What an audience would have understood from any oral discussion with the presenter could not be established in either case.

4.4 It was a disputed subject among the parties which standard of proof was required regarding the public availability of documents C30 and C31.

4.5 According to the case law of the boards of appeal, the usual standard of proof is the overall balance of probabilities.

4.6 The stricter standard of proof "beyond all reasonable doubt" applies, exceptionally only, in cases of public prior use where all the supporting evidence lies within the power and knowledge of the opponent (see decisions cited in "Case Law of the Boards of Appeal of the European Patent Office", 9th edn. 2019, III.G.4.3.2). The issue of public prior presentation of posters or slides has, as a rule, been assessed in line with the requirements for public prior use.

In these appeal proceedings, that condition is not fulfilled, since C30 and C31, alleged to be public prior disclosures, are the patent proprietor's (appellant's) own documents.

4.7 The appellant also argued that both C30 and C31 involved "ephemeral" oral presentations and, therefore, that the standard of proof for ascertaining the content

of the oral disclosure must be higher (see decision T 1212/97, Reasons 2).

The board considers that at least in the case of the poster C30, this argument is not convincing, since the disclosure relied on by the respondents is the printed and therefore "fixed" content of the poster displayed, whereas T 1212/97 cited by the appellant deals with the alleged information content of an orally delivered lecture (without a written complement in the form of a script, handout or later publication being available).

4.8 The question whether citing a reference in an IDS is, as a matter of principle, an acknowledgement that it is prior art is irrelevant to the issue under discussion. What is more relevant is that the appellant explicitly stated in C30B that to its best knowledge ("on information and belief and after reasonable inquiry"), C30 and C31 (designated "CC15" and "CC16" in C30A) were presented at the ACTRIMS/ECTRIMS conference of 2002.

4.9 In the case of the poster C30, the appellant's own statement in C30B leaves little room for doubt that this poster was indeed displayed, whereby the entirety of the information printed on the poster was disclosed to the public. In this situation, it was for the appellant to show that this was not the case.

4.9.1 The appellant did not provide any first-hand evidence from witnesses, in particular the presenters themselves, regarding the actual printed content of the poster presented at the ACTRIMS/ECTRIMS conference. Rather, the appellant's argument is based on circumstantial evidence. Pointing out certain errors in the technical content of document C30 as well as typographical and formatting errors, the appellant contended that such errors were not expected to occur in a presentation by professional scientists and that

the poster therefore could not have been presented in the version of C30. C30, retrieved only at a later point in time for filing with the IDS, might simply have been a draft.

4.9.2 This argument is based on speculation and is thus not persuasive in discharging the appellant's burden of proof. As a consequence, on the overall balance of probabilities, the poster C30 is considered to form part of the prior art.

4.10 It is different with C31, due to its nature as a slide presentation. Slides are typically used as the basis of an oral presentation. No evidence is on file from which it may be inferred that the slides of C31 were handed out in printed form at the conference, or that all of the slides were shown to an audience. There is no evidence available regarding the manner or speed of the oral presentation. The printed content of the slides alone is insufficient for establishing what precisely the members of the audience would have understood, and retained, from an oral presentation at the ACTRIMS/ECTRIMS conference during which all or some of the slides of C31 may have been shown. Hence, and irrespective of the standard of proof applied, the content of C31 cannot be considered as prior art.

5. Novelty

5.1 Since the therapeutic efficacy of sustained-release 4-aminopyridine administered at 10 mg bid is a functional technical feature of claims 1 and 5 of the main request (see point 3.3 above), this feature must be taken into account in the assessment of novelty and inventive step.

5.2 This means that a prior-art disclosure can only be novelty-destroying if it discloses this therapeutic efficacy.

It is not sufficient in this case that 4-aminopyridine may have been known to have a therapeutic benefit for improving walking speed and that a prior-art document discloses its administration as a sustained-release dosage form at 10 mg bid in a clinical study.
The issue is rather whether the therapeutic efficacy of the 10 mg bid dosage is specifically disclosed in the prior art.

5.3 During the development of the treatment which is the subject of the claims of the main request, the appellant carried out the following two clinical studies (as set out in the declaration C20 filed by the appellant and as mentioned in C27, pages 45 and 46).

- "MS-F201" (completed in 2001): a double-blind phase 2 clinical trial of sustained-release 4-aminopyridine designed to assess safety and determine favourable dose levels and involving a total of 36 subjects and dosages from 10 mg bid to 40 mg bid;
- "MS-F202" (initiated in 2003, completed in 2004): a late phase 2 clinical trial assessing the efficacy and safety of three doses of sustained-release 4-aminopyridine (10, 15 and 20 mg bid). This is the parallel-arm trial with 206 subjects discussed in Example 5 of the patent in suit.

Documents C10, C27 and C30 cited in this appeal case all relate to data obtained in the MS-F201 trial.
C27 also mentions the MS-F202 trial, without however providing any data obtained from that later trial.

5.4 C10 is a conference abstract reporting on the MS-F201 trial. This was an escalating-dose study of a sustained-release formulation of 4-aminopyridine, starting from 20 mg/day (10 mg bid), increased in weekly increments of 10 mg/day to 80 mg/day and administered orally to 25 multiple sclerosis patients. 11 patients received placebo treatment. The results relating to therapeutic efficacy are described as follows:

> "*The fampridine-SR group showed statistically significant improvement from baseline compared to placebo in functional measures of mobility (timed 25 walking speed; p = 0.04) and lower extremity strength (manual muscle testing; p= 0.01). Dose response curves showed increasing benefit in both measures in the 20 to 50 mg/day range.*"

5.4.1 It cannot be inferred from this statement in a direct and unambiguous manner that a statistically significant therapeutic benefit for walking speed was attained, specifically, with the (lowest) dosage of 20 mg/day (10 mg bid). The first sentence does not refer to dosage at all. The second sentence is also consistent, for instance, with a situation where there is no improvement in efficacy relative to placebo at 20 mg/day but increasing improvement from 30 to 50 mg/day. C10 does not contain any statement from which it might be conclusively inferred that the efficacy of each dosage was assessed separately.

5.4.2 Referring to paragraph [0004] of the patent in suit and to documents C3 and C45, respondent-opponent 1 contended that the standard of disclosure for novelty did not require results from clinical studies, and that the efficacy of the sustained-release 10 mg bid dosage regime disclosed in C10 was nevertheless sufficiently plausible on the basis of a clear and accepted

relationship between the properties of 4-aminopyridine and this therapeutic use which could be derived from common general knowledge.

5.4.3 The board does not reach the same conclusion.

The passage in paragraph [0004] of the patent in suit relates in a general way to 4-aminopyridine and its known utility in restoring conduction in blocked and demyelinated nerves, whereas individual dosages and their effect on walking speed are not mentioned.

The issue relevant for novelty, however, is the prior disclosure of efficacy of the 10 mg bid dosage regime with regard to walking speed.

Documents C3 and C45 are scientific articles and, as such, they are not considered part of the common general knowledge of the skilled person.

Moreover, these documents do not disclose or render plausible the efficacy of 10 mg bid 4-aminopyridine in improving walking speed. C3 describes a small study with ten patients who received 17.5 mg bid of sustained-release 4-aminopyridine. It does not disclose or discuss a 10 mg bid dosage regime. C45 relates to a study involving the administration of single doses of immediate-release 4-aminopyridine. This document mentions "motor function" and "gait" but does not refer to walking speed at all (see C45: abstract, Table 1).

The passage and documents cited by the respondent (see point 5.4.2 above) are thus not pertinent to the issue of novelty over C10.

5.4.4 For these reasons, the disclosure of C10 does not anticipate the subject-matter of claims 1 and 5 (Articles 52(1) and 54(1) and (2) EPC).

5.5 Document C30, the poster which was displayed at the 2002 ACTRIMS/ECTRIMS conference, also presents data from the MS-F201 trial.

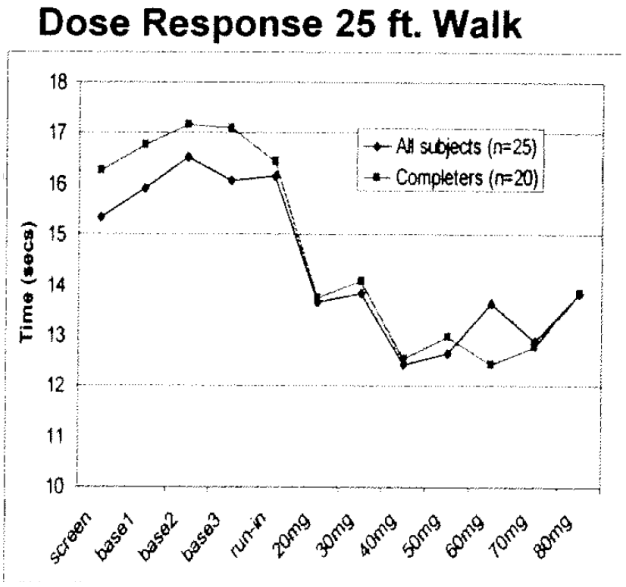
5.5.1 The abstract section of C30 is largely identical to the text of C10, including the inconclusive statement that dose-response curves showed increasing benefit in the 20 to 50 mg/day range (see points 5.4 and 5.4.1 above). The section "Conclusions" states in a similar manner that there was "evidence of dose-response in 20-40 mg/day range". This statement alone does not imply that therapeutic efficacy was actually shown individually at the lowest dosage of 10 mg/bid.

5.5.2 The histogram figure "25 Foot Walk-Change in Speed" presents the individual subjects' results for improvement in walking speed (%).

The per cent values indicated in this figure represent the averaged response of each subject over the first four treatment weeks. During this time, each subject receiving 4-aminopyridine was treated with escalating doses from 10 to 25 mg bid (20 to 50 mg/day). As only the aggregated value across several dosages is shown,

this figure does not provide any response data which can be attributed specifically to the 10 mg bid dosage. (The figure also appears to be erroneous in that it shows, contrary to the cohort sizes indicated in the section "Demographics", 26 rather than 25 values for the aggregated (20-50 mg/day) 4-aminopyridine group and 12 rather than 11 values for the placebo group.)

5.5.3 A further figure in C30 is entitled "Dose Response 25 ft. Walk".



This graph contains only data from patients administered the drug and not those given placebo. The walking time in seconds indicated in this curve is the mean value of all participants receiving 4-aminopyridine treatment.

The respondents argued that the drop from about 16 seconds to about 13.5 seconds between run-in and 20 mg disclosed treatment efficacy at 20 mg/day (10 mg bid). While the respondents did not demonstrate why this drop would be regarded as statistically significant, they contended that the skilled person had no reason, nevertheless, to question the meaningfulness of the data presented in C30. Also, the claims covered the

treatment of a single patient and any increase in walking speed, even a small increase. Therapeutic benefit in a single patient could simply be shown by observing that patient.

In fact, as also pointed out by the appellant, there are several serious reasons to doubt the significance of the drop depicted in the dose-response curve.

In particular, the skilled person studying C30 would be well aware of the fluctuations in the occurrence and severity of symptoms that are characteristic of MS (see point 3.8 above) and of the limited number of participants in the trial in question, which was designed merely as a preliminary dose-ranging study (see C30: Methods). Accordingly, the abstract section of C30 notes that the primary object of the study was to determine the safety and tolerability of escalating doses, while the secondary aim was to explore efficacy over a broad dose range. Thus, it is not credible that the study with only 36 participants, 25 of whom received drug, was powered to enable conclusions about the efficacy of individual doses to be drawn.

If the study had been intended to compare the efficacy of individual dosages, it would not have been designed as a dose-escalation study with only a short period of time on any one dose. The skilled person would be aware that, in general, one week on a dose may not be enough to evaluate drug effects, and there may also be effects resulting from the length of time on a particular drug rather than from dosage level.

The small sample size would increase the risk that the data would be distorted by noise, in particular since only one measurement per dose was taken. Furthermore, potential placebo effect, known to be prominent in MS,

was not eliminated by comparison with a placebo control group.

The dose-response curve itself shows fluctuations in the baseline average (see the first five values determined before the start of the drug administration) of up to 1-1.5 seconds, which would be attributed to "noise".

While the absolute values in seconds observed in the placebo group are not indicated, C30 discloses that relative changes of up to 18% increase in walking speed were observed in the placebo group during the initial low-dose treatment period (see C30: Results Summary and "25 Foot Walk - Change in Speed" histogram), which further corroborates the existence of fluctuations in the individuals' symptoms which are unrelated to treatment.

Only the mean values of all treated subjects are shown in the dose-response curve of C30; no information about the variability of individual measurements is provided.

It can also be inferred from the values shown in the histogram figure for the relative change in speed ("25 Foot Walk-Change in Speed") that there was a large degree of inter-patient variability.

The dose-response curve is about a different parameter as it indicates the absolute improvement in walking speed; this would have a different relative impact depending on the baseline walking speed of each subject. Without knowledge of each subject's individual measurements, it is not possible to know how the absolute and relative changes compare.

In view of these considerations, in particular the low number of trial participants and the manner in which the data presented lacks pertinent information (such as a comparison with the placebo group), the

board is not convinced that the drop between run-in and 20 mg/day shown in the dose-response curve can unambiguously be attributed to the administration of 4-aminopyridine.

The respondents' argument that according to the claims only a single patient may be treated is not pertinent in this context, since the issue here is proof of efficacy of a specific dosage regime, which can only be provided by statistical methods with a sufficient sample size.

5.5.4 In conclusion, the efficacy of the 10 mg bid dosage regime of sustained-release 4-aminopyridine, and thus the subject-matter of claims 1 and 5, cannot be directly and unambiguously derived from the disclosure of C30 (Articles 52(1) and 54(1) and (2) EPC).

6. Inventive step

Starting point in the prior art

6.1 Inventive step has been assessed starting from the disclosure of document C27 (for alternative starting points, see points 6.10 and 6.11 below).

6.2 C27 reports on the appellant's MS-F201 trial (see point 5.3 above) which was designed as a preliminary study with 36 subjects to explore the safety and efficacy of escalating doses of sustained-release 4-aminopyridine from 10 mg bid to 40 mg bid. C27 (see page 46 and the paragraph bridging pages 45 and 46) reports that the 4-aminopyridine-treated group as a whole showed improvement in walking speed, including statistically significant improvement in the lower dosage range from 10 mg bid to 25 mg bid; however, no separate individual analysis is provided on how each

dose of drug affected walking speed from baseline compared to placebo.

C27 further mentions that, after extensive consultation with a panel of expert MS neurologists and with the FDA (the US regulatory agency for pharmaceutical drugs), a larger clinical trial (the MS-F202 trial) had been initiated which was designed to compare three doses of 10, 15 and 20 mg bid and to assess their relative safety and efficacy over a treatment period of 12 weeks, with regard to an improvement in average walking speed (see C27: page 45).

Technical problem to be solved and solution

6.3 Claims 1 and 5 of the main request require therapeutic efficacy of the 10 mg bid dosage regime for increasing the walking speed of MS patients, whereas document C27 does not disclose whether this specific dosage regime has therapeutic efficacy.

6.4 On the basis of the data analysis of the MS-F202 study presented in Example 5 of the patent in suit, the board is satisfied that the technical effect of applying the 10 mg bid dosage regime is acceptable efficacy combined with a favourable safety profile.

6.5 The technical problem to be solved was thus the identification of an advantageous dosage regime for 4-aminopyridine for increasing the walking speed of a patient with multiple sclerosis.

6.6 The solution to this problem is defined in claims 1 and 5 of the main request.

Obviousness of the solution

6.7 The respondents contended that determining the appropriate dosage of a known drug, let alone merely

confirming the efficacy of the 10 mg bid dosage regime envisaged in C27, would not have required inventive skill, for the following reasons (points 6.7.1 to 6.7.4).

6.7.1 The person skilled in the art would have routinely sought to identify the lowest effective dose in order to minimise the risk of adverse effects.

Since document C27 mentioned that a dose-finding trial designed to compare the three doses of 10 mg bid, 15 mg bid and 20 mg bid was underway (see C27: page 45, discussing the MS-F202 study), the person skilled in the art would have had a reasonable expectation of success also with regard to the lowest dosage of 10 mg bid included in that trial. C27 furthermore envisaged phase 3 trials to supplement the data from the phase 2 trial (see C27, page 45, fourth paragraph).

6.7.2 It would have been routine work for the person skilled in the art to follow this teaching and set up a clinical trial powered to confirm the expectation that the 10 mg bid dosage regime would show the desired therapeutic efficacy.

6.7.3 The responder analysis developed by the appellant was not mandatory for showing therapeutic efficacy. The data from phase 3 trials shown in Figures 1 and 2 of document C43 (the prescribing information for the appellant's sustained-release 4-aminopyridine (10 mg) tablets Ampyra^{TM}) confirmed that a significantly greater proportion of patients taking 10 mg bid of the drug had shown increases in walking speed of at least 10%, 20% and 30% from baseline compared to placebo.

6.7.4 Nor was it even necessary to conduct a large-scale trial. The appellant's own publications (C10, C27,

and C30) measured treatment, at least over the whole dose range, without using the responder analysis.

6.8 The board does not come to the same conclusion, for the following reasons.

6.8.1 On the basis of the information presented in C27, it would have appeared realistic to the skilled person to investigate the dosages of 10, 15 and 20 mg bid, with the primary endpoint being an improvement in average walking speed, since this was known to have been recommended by a panel of expert MS neurologists and a relevant regulatory authority (the FDA), and these dosages had been found to be of interest in a preliminary study (the MS-F201 study).

6.8.2 However, presumably due to the high intra-patient and inter-patient variability of disease symptoms (here walking speed) in the case of MS and the relatively high proportion of non-responders to 4-aminopyridine, it actually turned out to be exceptionally difficult in this case to provide the required proof of efficacy - as shown in Example 5 of the patent, which presents data obtained in the MS-F202 study, and as discussed in the appellant's declaration C20 (on this subject, see also points 3.1 to 3.12 above). The MS-F202 study provides experimental evidence of this difficulty.

(a) The MS-F202 trial was designed as a parallel-arm study to investigate three doses of sustained-release 4-aminopyridine which had been found to be below the threshold for increased adverse effects.

The primary efficacy variable in the MS-F202 study was percent change in average walking speed during stable-dose treatment relative to baseline (placebo run-in) using the Timed 25-Foot Walk test.

(b) It was recognised in the art that, due to the variability in MS, only a change of at least 20% in walking time reliably indicated a change in true function. 206 patients were randomised to the MS-F202 study. As explained by the appellant (see C33: point 14), the MS-F202 study was adequately powered to determine the efficacy of each dosage, since the sample size was designed to have >80% power to detect a 20% or greater improvement in mean walking speed with an active treatment arm compared with placebo, at the 5% significance level, at each of the three doses.

(c) Nevertheless, the pre-planned statistical analysis did not, after all, provide the desired evidence of statistically significant differences in the primary efficacy variable between the groups receiving the drug and the placebo group. Nor did the "protocol-specified responder analysis", which still identified responders according to the magnitude of response (see point 3.9 above, Figures 3 and 4 of the patent in suit).

(d) According to the appellant (see C33: point 14), even if the results from each of the three treatment groups of the MS-F202 study were pooled (sample size = 152 subjects), the change in walking speed would still not be found to be significantly increased over placebo.

(e) These data support the appellant's argument that it was not straightforward, even with data obtained in an adequately powered dose-finding study, to demonstrate and compare the efficacy of the three dosage regimes. Using conventional methods, the person skilled in the art would have thus failed

to appreciate the utility of the 10 mg bid dosage regime.

(f) In contrast, it is speculative to assume (as argued by the respondents) that the person skilled in the art carrying out a dose-finding study as suggested in C27, and relying on the magnitude of response for its analysis, would not have encountered similar difficulties as the appellant. Further, the respondents did not provide any evidence of their assertion that it would have been possible to demonstrate efficacy at the claimed dose on the basis of small-scale studies and without having recourse to the appellant's responder analysis.

6.8.3 Failure of a phase 2 trial such as MS-F202 would not have caused the person skilled in the art to simply set up, in spite of this result, a larger-scaled trial with the same outcome variables, nor is this suggested in C27. Such an approach would be contrary to both ethical and cost considerations.

6.8.4 Only by developing, post hoc, a new statistical technique (the "responder analysis") which focused on the consistency of response over several assessment visits rather than the intensity of response was the appellant able to prove that the 10 mg bid dosage regime has efficacy in increasing walking speed. The responder analysis is suitable for identifying response when a subsection of the treated group is not actually responding, and it eliminates background noise resulting from the fluctuating nature of MS symptoms. The analysis of the data with this tool also led to the conclusion that there are no notable differences in efficacy between 10 mg bid and the higher dosages. Also, the mean improvement in walking speed for the 4-aminopyridine responder group ranged from 24.6% to 29%, although responders were identified according

to consistency and not magnitude of response (see paragraph [0125], Table 12 and Figure 10 of the patent in suit). Given that 10 mg bid demonstrated the most favourable safety profile, it was identified as being superior to higher doses.

The respondents did not argue that the "responder analysis" methodology would have been obvious to the person skilled in the art and did not present any prior art using this methodology.

6.8.5 The appellant also used the more reliable variable of consistency of response according to the new "responder analysis" as the primary outcome variable in the subsequent phase 3 trials MS-F203 (C21-Annex C) and MS-F204 (C21-Annex D), which confirmed its utility as well as the results on efficacy obtained in the MS-F202 trial.

6.8.6 Thus, the respondents' arguments failed to convince the board that the person skilled in the art would have been able, without difficulty and without resorting to the novel responder analysis based on consistency of response, to confirm the efficacy of the 10 mg bid dosage regime.

6.9 As a consequence, the subject-matter of independent claims 1 and 5 would not have been obvious starting from the disclosure of document C27.

Further possible starting points

6.10 Apart from document C27, the respondents also regarded document C30 as a suitable starting point for the assessment of inventive step.

6.10.1 As already mentioned (see point 5.3 above), C27 and C30 both relate to the same study, namely the appellant's MS-F201 study. These documents predate the completion

of the MS-F202 study, which for the first time provided evidence of the efficacy of the 10 mg bid dosage.

6.10.2 The board considers that the disclosure of C30 is not more relevant than that of C27 and does not represent a more promising starting point for the assessment of inventive step (see also points 5.5 and 6.2 above for a discussion of the disclosure of both documents). Since the dose-response curve presented in C30 is inconclusive regarding the efficacy of the 10 mg bid dosage regime (see point 5.5.3 above), C30 does not add any relevant information regarding the MS-F201 trial beyond the content of document C27.

6.10.3 In fact, C27 may even be regarded as more relevant on account of its description of the general set-up and purpose of the MS-F202 trial, which confirms that the 10 mg bid dosage regime was about to be investigated for its therapeutic efficacy (see point 6.2 above).

6.10.4 Thus, the board's conclusion acknowledging an inventive step would not be any different if the assessment started from C30 instead of C27. As a consequence, a separate discussion of the approach starting from C30 is not required.

6.11 In their written submissions in these appeal proceedings, the respondents consistently argued that document C3 was a less promising starting point than C30 or C27, while the appellant preferred C3 as a possible starting point.

In its letter dated 1 August 2019 (see paragraphs (60) to (63)), respondent-opponent 1 conceded that C3 could be considered a realistic starting point for inventive step, but did not provide an inventive-step analysis starting from C3.

During the oral proceedings before the board, respondent-opponent 1 stated that it now wished to present an approach to the assessment of inventive step with C3 as the starting point.

The mere statement that a document may be considered a realistic starting point for the assessment of inventive step does not imply the conclusion that inventive step must be denied on that basis. Even if the appellant argued that the claimed subject-matter was inventive starting from the teaching of document C3, the respondent's line of reasoning against inventive step could not necessarily have been predicted.

Since the respondent's new inventive-step approach amounted to an unexpected change of its case at a late stage of the appeal proceedings, the board did not admit this line of argument into the proceedings (Article 13(1) and (3) RPBA).

Conclusion on inventive step

6.12 For these reasons, the subject-matter of independent claims 1 and 5 and of the dependent claims of the main request involves an inventive step within the meaning of Article 56 EPC.

7. Admission of documents

7.1 The respondents requested that certain documents filed by the appellant not be admitted into the proceedings. During the oral proceedings before the board, the board admitted several of these documents (the documents designated C55A-F, C56, C57 and C58).

7.2 Since, however, these documents were ultimately not pertinent to the board's assessment and the outcome of

the case in the appellants' favour, there is no need to provide a reasoning on the issue of admission.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside

2. The case is remitted to the opposition division with the order to maintain the patent on the basis of the set of claims labelled "main request - August 2016" enclosed with the statement setting out the grounds of appeal and a description to be adapted thereto.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated