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Datasheet for the decision of 5 September 2023

Case Number: T 1045/21 - 3.3.07

Application Number: 12830484.7

Publication Number: 2754440

IPC: A61K31/4152, A61P25/28, C07D231/26

Language of the proceedings: EN

Title of invention:
MEDICINAL AGENT FOR TREATING AMYOTROPHIC LATERAL SCLEROSIS OR PREVENTING PROGRESSION OF PHASE OF AMYOTROPHIC LATERAL SCLEROSIS

Patent Proprietor:
Mitsubishi Tanabe Pharma Corporation

Opponent:
Maiwald GmbH

Headword:
Edaravone for treating ALS / MITSUBISHI TANABE

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (no)

Decisions cited:
T 0799/16, G 0002/21, T 1437/07, T 0609/02

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Case Number: T 1045/21 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 5 September 2023

Appellant: (Patent Proprietor)	Mitsubishi Tanabe Pharma Corporation 3-2-10, Dosho-machi, Chuo-ku Osaka-shi Osaka 541-8505 (JP)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Respondent: (Opponent)	Maiwald GmbH Elisenhof, Elisenstrasse 3 80335 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 30 April 2021 revoking European patent No. 2754440 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	E. Duval
	L. Basterreix

Summary of Facts and Submissions

I. The appeal was filed by the patent proprietor (appellant) against the decision of the opposition division to revoke the patent in suit (hereinafter "the patent").

The decision was based on a main request and auxiliary requests 1-6, all filed on 21 January 2021.

Claim 1 of the main request read as follows:

"3-methyl-1-phenyl-2-pyrazolin-5-one or a physiologically acceptable salt thereof for use in treating amyotrophic lateral sclerosis or suppressing the disease progress thereof, or treating symptoms caused by amyotrophic lateral sclerosis or suppressing the disease progress thereof,
wherein 3-methyl-1-phenyl-2-pyrazolin-5-one or a physiologically acceptable salt thereof is administered by repeating a 14-day administration period and a 14-day drug holiday period, or by establishing an initial 14-day administration period and an initial 14-day drug holiday period and then repeating an administration period for 10 out of 14 days and a 14-day drug holiday period, and wherein
the 3-methyl-1-phenyl-2-pyrazolin-5-one or the physiologically acceptable salt thereof is administered to a patient with amyotrophic lateral sclerosis, and the amyotrophic lateral sclerosis of the patient administered with 3-methyl-1-phenyl-2-pyrazolin-5-one or the physiologically acceptable salt is amyotrophic lateral sclerosis, which scores two or more points from all items constituting the ALSFRSR and whose %FVC is 80% or more."

II. The following documents are relevant for the present decision:

D1: Amyotrophic Lateral Sclerosis 2006, 7: 247-251
D4: Journal of the Neurological Sciences 169 (1999), 13-21
D5: Neurology, 52 (1999), 1427-1433
D7: Experimental Neurology 213 (2008), 448-455
D14: Extract from Clinical Study Report - pages 1-5, 111 and 112
A015: Expert Opinion Prof. Heneka
A016: Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2017; 18: 11-19
A017: Lancet Neurol, 2017; 16: 505–12
A018: Wikipedia entry on "Post hoc analysis" Submission in opposition proceedings

III. The opposition division decided that none of the requests satisfied the criteria of inventive step.

Starting from D1, in particular the patient scoring 46 in ALSFRS-R, the differentiating feature was the %FVC value as defined in claim 1. Neither an improved effect over D1, nor an unexpected (synergistic) effect could be acknowledged. The technical problem was the provision of an alternative treatment of ALS patients. The claimed solution did not involve an inventive step, in particular because the skilled person would be motivated by D1 to add a further selection step related to the %FVC values as an alternative or even improved method to target patients in early stages of ALS.

IV. With their statement setting out the grounds of appeal, the appellant upheld the main request and auxiliary requests 1-6 underlying the appealed decision.

V. The Board set out its preliminary opinion in a communication pursuant to Article 15(1) RPBA.

VI. Oral proceedings were held before the Board, in the absence, as previously announced, of the opponent (respondent). During the oral proceedings, the appellant withdrew auxiliary requests 1-6.

VII. The parties' requests are the following:

(a) The appellant requests that the decision under appeal be set aside and that the patent be maintained on the basis of the main request.

(b) The respondent requests that the appeal be dismissed.

VIII. The appellant's argument regarding inventive step can be summarized as follows:

The closest prior art D1 reported phase II clinical study data. The subject-matter of claim 1 differed from the teaching of D1 in the specific group of patients to be treated, defined by an ALSFRS-R score of two or more points from all items constituting the ALSFRS-R and a %FVC of 80% or more. In addition, the phase II study of D1 could not establish an expectation of success as regards the successful treatment of ALS with edaravone. In particular, an isolated consideration of selected single patients, such as the patient of D1 scoring 46 in ALSFRS-R, was neither appropriate nor meaningful. If the %FVC was regarded as the sole differentiating feature, a comparison of the respective positive between-group differences for subgroups (3) and (5) of the *post-hoc* analysis (see table 5 of the patent) showed a resulting improvement. The technical problem was the provision of an effective and thus improved

treatment of ALS with edaravone, wherein the improvement resided in the provision of a further (new) treatment option for ALS. The claimed definition of an ALS patient to be successfully treated with edaravone by two or more points from all items constituting the ALSFRSR and a %FVC of 80% or more was not foreseeable for the skilled person. Hence the criteria of inventive step were met.

IX. The respondent's argument regarding inventive step can be summarized as follows:

D1 reported on a phase II study on the safety and efficacy of an edaravone treatment in ALS patients. The treatment regime in D1 was according to claim 1 of the main request. D1 showed that edaravone provided a beneficial therapeutic effect, at least in certain ALS patients, and specifically in patients in the early stage of ALS. One patient in D1 had a total score of 46 immediately prior to treatment start, and hence had at least 2 points in each of the 12 individual ALSFRS-R items. The differentiating feature was at most the %FVC of 80% or more. No technical effect could be ascertained for the claimed subject matter. No comparison could be made between the placebo and the treatment groups studied in the patent, because the data for the subgroups in the patent were based on a *post-hoc* analysis, meaning that no randomization for the individual subgroups took place. The objective technical problem was the provision of an alternative treatment of ALS patients. The skilled person would have been motivated to treat patients in the early stages of the disease, who still had normal or almost normal respiratory function, i.e. with a FVC of at least 80%. Hence the criteria of inventive step were not met.

Reasons for the Decision

1. Main request, lack of inventive step over D1

1.1 Claim 1 of the main (and sole) request pertains to:
- 3-methyl-1-phenyl-2-pyrazolin-5-one, i.e. edaravone, or a physiologically acceptable salt thereof
- for use in treating amyotrophic lateral sclerosis (ALS) or suppressing the disease progress thereof, or treating symptoms caused by ALS or suppressing the disease progress thereof,
- wherein the edaravone administration is defined by a specific administration regimen, and
- wherein the ALS of the patient is characterised by two parameters, namely:
    - a score of two or more points from all items constituting the ALSFRS-R and
    - a %FVC of 80% or more.

1.2 The closest prior art D1 discloses a phase II study to investigate the safety and efficacy of edaravone in ALS patients (see the abstract).

1.2.1 In the study of D1, subjects with ALS received either 30 mg or 60 mg of edaravone via intravenous drip once per day for two weeks of administration, followed by a two-week drug-free period. Following this first cycle, edaravone was again administered for five days a week, for two weeks, followed by a two-week observation period. This second cycle was repeated five times (see page 248, "Patient selection and drug treatment protocol").

This administration regimen is thus according to claim 1 of the main request.

1.2.2 The progression of ALS was monitored in D1 by means of the decline in the revised ALS functional rating scale (ALSFRS-R) score. The ALSFRS-R is a questionnaire-based scale used to monitor and document the progression of ALS in patients. It includes 12 items relating to different aspects of daily activities, including respiratory function, each rated from 0 to 4 points (see Table 1 of D4). The maximum total ALSFRS-R score of 48 (i.e. 4 points in each of the 12 items) corresponds to a patient experiencing no marked impairment in any of the fields covered by the ALSFRS-R, or, in other words, a patient at the beginning of the disease.

One patient in the 60 mg treatment group of D1 has a score of 46 in the revised ALS functional rating scale (ALSFRS-R) at the beginning of the treatment (see fig. 1 of D1, top middle point). This patient of D1 scoring 46 out of 48 necessarily scored two or more points for each of the 12 items constituting the ALSFRS-R, as required by claim 1 of the main request.

1.2.3 A crucial question in the present case is whether the closest prior art D1 discloses the effectiveness of the edaravone in the treatment of ALS, and in particular for the patient scoring 46 in ALSFRS-R, in an enabling manner.

Claim 1 is drafted in the form of a specific medical use-related product claim according to Article 54(5) EPC. An effective treatment of ALS or its symptoms, or suppression of the disease progress, is a functional feature of claim 1 of the main request.

1.2.4 The appellant contends that phase II and phase III data represent different levels of proof, and that the claimed treatment, which is supported by clinical phase III data, cannot be regarded as anticipated by the clinical phase II data disclosed in D1. Accordingly, there would be no enabling disclosure in D1 as regards the efficacy of edaravone in the treatment of ALS so that the claimed treatment cannot be regarded as having been made available to the public in D1.

The Board does not agree with this view.

The relevant disclosure of the closest prior art is determined based on the content of this prior art document, as read by the skilled person, and the differentiating features are established by a comparison with the claimed subject-matter, as defined by the features of claim 1. Whether or not the efficacy of edaravone in the treatment of ALS is disclosed in D1 in an enabling manner is a question of fact that must be assessed on the basis of the content of D1 and calls for a binary response: either D1 discloses this feature, or it does not. There is no place in this assessment for a comparison with any further technical information presented in the patent, and there is no room for a finding that the efficacy of edaravone against ALS is "less" disclosed in D1 than in the patent.

1.2.5 The Board does not agree either with the appellant's view that only where one or more phase III studies have successfully been completed, can efficacy and safety of a new drug or treatment be accepted as proven and thus credible.

The requirement of an enabling disclosure for a prior art document is the same as the requirement of sufficiency of disclosure for a patent: the principles developed by the case law in the framework of the evaluation of the requirements of Article 83 EPC in the case of a medical use - namely that the skilled person should not only be able to carry out the teaching of the prior art document, but it should also be credible that the effect at issue has been achieved – apply equally to a patent or patent application and a prior art disclosure (see Case Law of the Boards of Appeal, 10th edition, 2022, I.C.4.11; T 1437/07, points 25 and 26 of the reasons). In the context of sufficiency of disclosure for a claim comprising a therapeutic application as a functional feature, it is established that an absolute proof that the compound is approved as a drug is not required (see T 609/02, point 9 of the reasons). Results of a phase III study, or the inclusion of a placebo arm in the study, are not always required for a therapeutic effect to be accepted as credible. This is valid for a prior art disclosure just as for a patent.

1.2.6 In the case at hand, for the following reasons, the Board considers the data in D1, discussed below, to be credible evidence of efficacy.

The study in D1 was conducted in an open-trial phase II setting, without placebo arm. The results are reported in figure 1 and 2 and in table II of D1. Table II compares the mean rates of decline in ALSFRS-R score over the 6 months before the start of treatment *versus* the 6 months after the start of treatment, in both the 30 mg and the 60 mg groups. In the 60 mg group in particular, the rate of decline changes from -4.7±2.1 to -2.3±3.6 upon treatment. The authors of D1 mention

that "ALS is a progressive disease, and the ALSFRS-R scores are known to decrease almost linearly throughout the course of the disease", and conclude that "the decrease of the ALSFRS-R score during the six-month edaravone treatment period was significantly smaller than that in the six months prior to the start of treatment. This result suggests that edaravone may delay the progression of functional disturbances in ALS patients" (see page 250, left column). The alleged variability in ALS etiology and subjectivity of the ALSFRS-R test do not invalidate this conclusion, as they are inherent to the field of ALS and well-known to the authors of D1. A randomized, placebo-controlled, double-blind design is stated in D1 to be necessary only to confirm this efficacy and safety (see page 250, right column, 2nd paragraph).

This efficacy of edaravone suggested by the ALSFRS-R data is further supported in D1 by the marked reduction in measured 3NT levels in the cerebrospinal fluid (CSF) of all patients treated in this study (see figure 2 and page 250, left column). The level of CSF 3NT is a marker for oxidative stress in the spinal cord of ALS patients (see page 249 of D1, left column, second paragraph). As explained in D1 (see page 247, left column; page 250, left column), since oxidative stress has been identified as contributing to the pathogenesis of ALS, a reduction of the 3NT levels of patients being treated with edaravone would be consistent with the known radical scavenging activity of edaravone. Contrary to the appellant's view, the observations in the animal model study of the later document D7 neither call into question edaravone's protective effect against neurodegeneration nor disprove that this effect is mediated by its established free radical-scavenging property (see page 454, right column). Likewise, the

fact that the rate of decline in the subjective, questionnaire-based ALSFRS-R score upon edaravone treatment was lowered in most but not all patients, whereas the objective measured 3NT levels were decreased in (almost) all patients (see D1, page 249, left column), cannot be regarded as a divergence which would contradict the conclusions in D1, considering that these markers are independent and that both reflect an overall improvement in the group of patients.

1.2.7 Finally, the results of the phase III study reported in the patent on the full analysis set (FAS) population, i.e. the entire tested treatment and placebo groups (resp. 100 and 99 patients), do not disprove the results of D1. These results show a positive between-group difference of 0.7, i.e. a reduction in the decrease of the ALSFRS-R score in the treatment group in comparison to placebo (see table 5 of the patent; see also the publication A016 pertaining to the same study, abstract). The fact that this phase III trial failed to show sufficient statistical significance for the entire group of patients studied therein is not evidence of a lack of enablement in the study group of D1.

1.2.8 The Board further concludes that the efficacy of the edaravone treatment is disclosed and made credible in D1 not only for the whole group of patients, but also in the case of the patient scoring 46 in ALSFRS-R, which belongs to this group.

In the case of this particular patient of D1, the ALSFRS-R score declined by two points over the 6 months before the start of treatment *versus* one point in the 6 months after the start of treatment. Thus the data show

a slower decline upon edaravone treatment. The Board agrees with the appellant that this single data on one patient could not be regarded as sufficient proof of efficacy in isolation, considering in particular the subjectivity of the ALSFRS-R test. However, for the purpose of establishing whether the effectiveness of the edaravone treatment disclosed in D1 is made credible in this case also, the technical disclosure in the prior art document must be considered as a whole. The data on the patient scoring 46 is consistent with the observations on the whole group, and there is no basis in D1 for suspecting that this patient should actually be a non-responder.

Contrary to the appellant's view, the situation in case T 799/16 is factually different: the prior art in T 799/16 aimed at determining the safety and tolerability of escalating doses and explore efficacy over a broad dose range, but it did not disclose the therapeutic efficacy of the claimed specific 10 mg bid dosage with respect to walking speed (see points 5.5.3 and 5.5.4 of the reasons). In contrast, in the present case, D1 directly and unambiguously discloses the use of edaravone in the treatment of ALS, using the administration regimen as defined in claim 1, in a patient scoring two or more points from all items constituting the ALSFRS-R. For the reasons given above, D1 as a whole makes the effectiveness of the edaravone therapy in this case credible.

In conclusion, D1 discloses the effective use of edaravone, using an administration regimen as defined in claim 1, in the treatment of ALS in a patient scoring two or more points from all items constituting the ALSFRS-R.

1.2.9 D1 does not, explicitly or implicitly, disclose a patient having a percentage predicted forced vital capacity (%FVC) of 80% or more as required by claim 1. The respondent did not established that the patient of D1 scoring 46 in ALSFRS-R must necessarily have a %FVC above 80%. The Board accepts the appellant's argument that the claimed %FVC parameter characterises a new patient population and defines a distinguishing pathological status.

The %FVC of 80% or more is thus the sole feature of claim 1 which differentiates the claimed subject-matter from D1.

1.3 Technical effect and problem

1.3.1 According to the appellant, the objective technical problem is the provision of an effective and thus improved treatment of ALS with edaravone, wherein the improvement resides in the provision of a further (new) treatment option for ALS.

However, the technical problem cannot be formulated in such a way because D1 already describes an effective treatment of ALS with edaravone. The fact that the claimed treatment may be confirmed, in the patent, to be effective in the claimed patient population cannot be regarded as such as an improvement. The alleged confirmation, i.e. by a phase III study as opposed to a phase II study, of the efficacy of edaravone in the treatment of ALS is not a technical effect resulting from the differentiating feature, namely the %FVC of 80% or more.

1.3.2 The appellant further relies on the achievement of an improved efficiency in relation with the selection of

patients having a %FVC of 80% or more, based on the data for subgroups (3) and (5) in table 5 of the patent.

According to established case law, if comparative tests are chosen to demonstrate an inventive step on the basis of an improved effect over a claimed area, the nature of the comparison with the closest state of the art must be such that the alleged advantage or effect is convincingly shown to have its origin in the distinguishing feature of the invention compared with the closest state of the art (Case Law of the Boards of Appeal, 10th edition, 2022, I.D.4.3.2). It rests with the proprietor to properly demonstrate that the purported advantages of the claimed invention have successfully been achieved (see G 2/21, point 26 or the reasons).

1.3.3 The patent presents the results of a first phase III study, conducted on a treatment group (100 patients) and a placebo group (99 patients). As discussed above (see 1.2.7), the results on the full analysis set (FAS) population failed to show sufficient statistical significance.

A *post-hoc* sub-group analysis of this first phase III study was accordingly conducted (see paragraph [0062] and table 5 of the patent; see also A016). A post-hoc analysis does not consist in conducting further clinical studies, but in post-processing the data obtained from the clinical study by means of statistical methods in order to find certain effects for certain subgroups of the original study population (see the Wikipedia entry A018).

(a) The patients of subgroup (3) are characterised by a score of two or more points from all ALSFRS-R items only. This subgroup exhibits a difference of 1.6 between the treated group and placebo group, with a statistical t-test value $p>0.05$.

(b) The patients of subgroup (5) (or EESP in A016) are characterised by a score of two or more points from all ALSFRS-R items and a %FVC of 80% or more. This subgroup exhibits a difference of 2.5 between the treated group and placebo group, with a t-test value of $p=0.0184$.

1.3.4 However, in the Board's opinion, no meaningful conclusion can be drawn from a comparison of these subgroups (3) and (5), because there is no demonstration that these subgroups actually differ only by a %FVC of 80% or more, and that any improvement in the outcome has its origin in this differentiating feature. As argued by the respondent, a randomization was only performed for the initial FAS population but not for the individual subgroups (1)-(7) of table 5. As a result, it cannot be assumed that subgroups (3) and (5) do not differ in other aspects than the %FVC. These subgroups, resulting from a statistical post-processing of the clinical results using additional selection criteria but without randomization between them, may present imbalances e.g. in terms of number of patients and actual ALSFRS-R starting values in the (treated or placebo) groups, certainty of the patients' ALS diagnosis, age, duration of the disease, or simultaneous treatment with riluzole. All of these imbalances may have a large impact on the subsequent rates of decline in ALSFRS-R and observed between-group differences. For instance, the fact that both subgroups (3) and (5) fulfil the condition of a score of two or

more points from all ALSFRS-R items does not exclude the possibility that the subgroups differ significantly in their average ALSFRS-R starting values, which could influence the outcome.

These imbalances between subgroups or between treated and placebo arms are confirmed by A016, which relates to the same clinical results and *post-hoc* data (see table 2 of A016, page 15). The EESP subgroup of A016 (corresponding to subgroup (5) of table 5 of the patent, i.e. the patient population as defined in claim 1) exhibits differences in mean age, diagnostic certainty and use of riluzole, not only between the placebo and edaravone groups but also in comparison with the FAS groups. Furthermore, the characteristics of the comparative subgroup (3) of the patent are not reported in A016. Consequently, it is neither shown nor credible that the characteristics of subgroups (3) and (5) are sufficiently similar to allow a comparison and draw conclusions as to the effect of the sole %FVC feature.

This issue of non comparability of subgroups (3) and (5) is unchanged and cannot be cured by comparing instead the difference between subgroup (3) and FAS *vs* the difference between subgroup (5) and FAS. The appellant further argued that a high number of patients were common to subgroups (3) and (5). However, even if logically all patients meeting the selection criteria of subgroup (5) must also meet those of subgroup (3), the extent to which those patients which are not common to both groups differ from those of subgroup (5) and the resulting impact on the subsequent ALSFRS-R decline rates are anyone's guess.

A second phase III study is reported in D14 and A017. However, A017 or D14 do not contain a comparison supporting any improvement associated with the differentiating feature over D1, namely the %FVC.

1.3.5 It is accordingly concluded that no improvement is convincingly shown to arise over D1, i.e. D1 credibly shows the efficacy of the edaravone treatment, and the selection of the claimed patient population is not associated with any improvement. The technical problem is the provision of an alternative application of edaravone in the context of treating ALS.

1.4 Obviousness

Considering the formulation of the problem as the provision of an alternative, the solution consisting in selecting a subgroup of patients characterised by the claimed %FVC of 80% or more does not involve an inventive step.

The closest prior art D1 focuses on the edaravone treatment of a group of patients having relatively high ALSFRS-R scores, including the patient scoring 46 and taken as starting point, in other words patients in the early stages of the disease (see figure 1 of D1). This is indirectly confirmed by D7, which cites and summarises D1 as reporting that "intravenous edaravone reduced the motor decline of ALS patients in their earlier stages" (see page 454, left-hand column).

Both ALSFRS-R and %FVC are well-known physiological markers and strong predictors of patient survival, and have both been used for the selection of patients in clinical trials (see D4, page 17; page 15, table 2). High FVC values indicate a healthier respiratory system

and in general early stages of disease. Since respiratory impairments tend to develop later than in the gross motor, bulbar and fine motor areas, early stage ALS patients are all the more likely to have high %FVC value (see D4, figure 1).

Accordingly, starting from D1, the further characterisation of the early-stage ALS patient to be treated by a high %FVC value of 80% or more does not, in the absence of associated technical effect, involve an inventive step.

Contrary to the appellant's opinion, document D5 does not teach away from the claimed solution because it does not relate to edaravone but to an unrelated therapeutic agent (BDNF).

Accordingly, the criteria of Article 56 EPC are not met.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated