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Datasheet for the decision of 5 June 2024

Case Number: T 1941/21 - 3.3.07

Application Number: 13747521.6

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Language of the proceedings: EN

Title of invention:
TAUROURSODEOXYCHOLIC ACID (TUDCA) FOR USE IN THE TREATMENT OF NEURODEGENERATIVE DISORDERS

Patent Proprietor:
Bruschettini S.r.l.

Opponent:
Ammelburg, Moritz

Headword:
TAUROURSODEOXYCHOLIC ACID (TUDCA) FOR USE IN THE TREATMENT OF NEURODEGENERATIVE DISORDERS/Bruschettini S.r.l.

Relevant legal provisions:
EPC Art. 54, 56
RPBA 2020 Art. 13(2)

Keyword:
Main request - Inventive step (Yes)
Main request and auxiliary request 1 - Novelty (No)
Auxiliary request 2 - Novelty and inventive step (Yes)
Admission of new objections during oral proceedings (No)

Decisions cited:
T 0239/16, T 2506/12, T 0096/20, T 2963/19

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Case Number: T 1941/21 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 5 June 2024

Appellant: (Patent Proprietor)	Bruschettini S.r.l. Via Isonzo, 6 16147 Genova (IT)
Representative:	Dragotti & Associati S.R.L. Via Nino Bixio, 7 20129 Milano (IT)
Respondent: (Opponent)	Ammelburg, Moritz HighLight Business Towers Mies-van-der-Rohe-Strasse 8 80807 München (DE)
Representative:	Fish & Richardson P.C. Highlight Business Towers Mies-van-der-Rohe-Straße 8 80807 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 24 September 2021 revoking European patent No. 3016654 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	M. Steendijk
Members:	D. Boulois
	Y. Podbielski

Summary of Facts and Submissions

I. European patent No. 3 016 654 was granted on the basis of a set of 10 claims.

Independent claim 1 as granted read as follows:

"1. Tauroursodeoxycholic acid or a pharmaceutically acceptable salt thereof for use in the treatment of a neurodegenerative disorder in a mammal, characterized in that said neurodegenerative disorder is amyotrophic lateral sclerosis."

II. An opposition was filed under Article 100 (a) and (b) EPC on the grounds that its subject-matter lacked novelty and inventive step and was not sufficiently disclosed.

III. The appeal lies from the decision of the opposition division to revoke the patent. The decision was based on the claims as granted as the main request, on auxiliary requests 1 and 2 filed on 16 April 2020, auxiliary request 3 (corresponding to auxiliary request 12 as filed on 9 April 2021), auxiliary request 4 (corresponding to auxiliary request 6 as filed on 16 April 2020), auxiliary requests 5 and 6 (corresponding respectively to auxiliary requests 14 and 19 filed on 9 April 2021), auxiliary requests 7-14 (corresponding respectively to auxiliary requests 3, 4, 5, 7, 8, 9, 10 and 11 as filed on 16 April 2020), auxiliary requests 15-19 (corresponding respectively to auxiliary requests 13, 15, 16, 17 and 18 as filed on 9 April 2021), and auxiliary requests 20 and 21 as filed on 9 April 2021.

IV. The documents cited during the opposition proceedings included the following:

D1: WO 2006/050165 A2
D4: Clinical Trials.gov: "Efficacy and Tolerability of Tauroursodeoxycholic Acid in Amyotrophic Lateral Sclerosis (TUDCA-ALS)", 23 March 2012
D8: EP 2 422 787 A1
D9: Maurer M: "Amyotrophic Lateral Sclerosis: An Introduction to Treatment and Trials", Amyotrophic Lateral Sclerosis, Prof. Martin Maurer (Ed.), ISBN: 978-953-307-806-9, InTech, 20, January, 2012
D11: US 2011/0142799 A1
D12: Sung JJ et al.: "Tauroursodeoxycholic acid (TUDCA), a bile acid, inhibits GSNO-induced apoptosis by modulating reactive oxygen species (ROS) production in motor neuronal cells expressing mutant Cu/Zn superoxide dismutase (SOD1)" THEME 4 In vitro Experimental Models, Amyotrophic Lateral Sclerosis, 6:sup1, P81, pages 109-110, published online 10 July 2005
D15: Min J-H et al.: "Oral Solubilized Ursodeoxycholic Acid Therapy in Amyotrophic Lateral Sclerosis: A Randomized Cross-Over Trial", The Journal of Korean Medical Science, vol. 27, no. 2, 27 January 2012
D16: Axcan Pharma US Inc.: "Treatment of Patients With All Stages of Primary Biliary Cirrhosis; URSO (ursodiol) Tablets, 250 mg; Medical Officer's Review; NDA 20-675; 26 March, 1996
D23: ALSUntangled No. 25: Ursodiol., Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2014; 15:475-478
D27: Aldini et al., "Relationship between structure and intestinal absorption of bile acids with a steroid or side-chain modification", Steroids, 1996, vol. 61, October

V. According to the decision under appeal, the main request was sufficiently disclosed.

The claimed subject-matter of the main request was not novel over D1. The claimed subject-matter of auxiliary request 1 was not novel for the same reasons as the main request.

The claimed subject-matter of auxiliary request 2 was novel over D1, D8, D11, D12 and D4.

D4 was the closest prior art for the assessment of inventive step of auxiliary request 2. D4 did not report the effective treatment of ALS in mammals/ humans. The problem was defined as the provision of a treatment for ALS. The claimed solution was not inventive. The remaining auxiliary requests 3-21 were also not inventive over D4.

VI. The patent proprietor (hereinafter the appellant) filed an appeal against said decision. With the statement setting out the grounds of appeal dated 18 January 2022, the appellant filed auxiliary request 1-4 corresponding respectively to auxiliary requests 1, 2, 11 and 20 on file during the opposition proceedings.

Independent claim 1 of auxiliary requests 1 and 2 read as follows, the main differences relating to a comparison with the main request being highlighted:

Auxiliary request 1

"1. Tauroursodeoxycholic acid or a pharmaceutically acceptable salt thereof for use in the treatment of amyotrophic lateral sclerosis **in a human**."

Auxiliary request 2

"1. Tauroursodeoxycholic acid or a pharmaceutically acceptable salt thereof for use in the treatment of amyotrophic lateral sclerosis **in a human, characterized in that it is administered for at least 30 weeks**."

VII. A communication from the Board, dated 26 February 2024, was sent to the parties. In it the Board expressed its preliminary opinion that *inter alia* the claimed subject-matter of the main request was novel as it was not derivable directly and unambiguously from D1, and noticed that the objection of lack of novelty over D8 was maintained by the respondent in its response to the statement of grounds of appeal. The Board also considered that D4 was the closest prior art for the assessment of inventive step of the main request.

VIII. Oral proceedings took place on 5 June 2024.

IX. The arguments of the appellant may be summarised as follows:

Main request - Inventive step

The problem over D4 was the provision of an effective treatment for ALS. The claimed solution, i.e. the use of TUDCA, could not be obvious. In the specific case of ALS, justifying a clinical trial did not correspond to a reasonable expectation of success of the trial itself. D9 listed 89 different drugs which, before the filing date of the opposed patent, had been used in clinical trials for ALS based on allegedly promising preclinical data, among which only riluzole had some efficacy and had received a marketing authorization by

that date and was thus used by patients affected by ALS; the efficacy of riluzole, as confirmed by D4 and D9, was limited to prolonging survival of patients by approximately three months. Consequently, any drug that may give even just a hope to ALS patients, and not a reasonable expectation, that their lives could be prolonged by more than 3 months, did justify a clinical trial. Moreover, some of the drugs disclosed in D9 had the same pharmacological activity as TUDCA, i.e. neuroprotective, antioxidant or anti-apoptosis drugs, but were found inefficient, confirming that the mechanism of action did not provide any expectation of success.

D1 and D15 did not provide any reasonable expectation of success for the trial of D4, since UDCA and TUDCA were different structurally and had different chemical properties. The inefficiency of UDCA for treating ALS was furthermore confirmed by D23. D11 and D12 did not support any relevant expectation in this respect either.

Main request and auxiliary requests 1 and 2 - Novelty

D8 provided experimental data for the treatment of ALS only for diazoxide, but not for TUDCA. Hence, there was no evidence in D8 that TUDCA was efficient for the treatment of ALS. Moreover, TUDCA was disclosed in a list of agents for which efficacy in treatment of ALS was contested in view of D9 and from which a selection was still to be made. Finally, D8 did not disclose a duration of treatment.

Admission of inventive step objections starting from D1 and D12

These objections constituted a new case at a late stage of the appeal proceedings since none of these documents had been mentioned in the written proceedings with regard to inventive step.

X. The arguments of the respondent may be summarised as follows

Main request - Inventive step

The phase II clinical trial disclosed in D4 amounted to a reasonable expectation of success for a skilled person. It appeared illogical to state that a clinical trial was justified, but that there was no reasonable expectation of success. D4 was a well-planned investigation embedded in sound scientific reasoning and known neuroprotective effects of the active ingredient, as also discussed in D9; D4 described, in accordance with D9, that TUDCA had antioxidant, antiapoptotic and neuroprotective activities, and that it could cross the blood brain barrier. The generic notion in D9 that of 89 drugs "only riluzole had received a marketing authorization" did not amount to particular reasons discouraging a skilled person from carrying out the phase II trial of D4 with the reasonable expectation that it will be successful. The skilled person's reasonable expectation of success based on D4's detailed and sound scientific reasoning was further enforced by the efficacy of UDCA in a phase III trial (see D15), and the common general knowledge of the metabolism of these bile salts (see D16, p. 25) as well as by the information from documents D1, D11 and D12.

Main request and auxiliary requests 1 and 2 - Novelty

D8 related to compositions comprising low doses of diazoxide for use in the treatment of a mammal afflicted with ALS. Further, D8 disclosed that diazoxide could be combined with "an additional therapeutic agent useful in the treatment of amyotrophic lateral sclerosis" including TUDCA (see claims 8 and 9) and provided an enabling disclosure for a use of low dose diazoxide in the treatment of ALS. In particular, D8 disclosed in Example 2 that low doses of diazoxide improve survival on transgenic mice models for amyotrophic lateral sclerosis. Accordingly, D8 was also an enabling disclosure for a combination treatment based on diazoxide and TUDCA, the latter of which is known by skilled persons to beneficially act on relevant metabolic mechanisms (cf. D9). A treatment of ALS based on diazoxide and TUDCA anticipated the subject-matter of claim 1.

Admission of inventive step objections starting from D1 and D12

Both documents were suitable starting points for the assessment of inventive step. The problem-solution approach starting from these documents was not an amendment to the case, in particular in view of the Board's statement with regard to D12 in its preliminary opinion.

XI. Requests

The appellant requested that the decision under appeal be set aside and the patent be maintained as granted (main request), or that the patent be maintained on the

basis of one of auxiliary requests 1-4 filed with the statement setting out the grounds of appeal.

The respondent requested that the appeal be dismissed.

Reasons for the Decision

1. Main request - Inventive step

1.1 The object of the claimed invention is the use of TUDCA or a pharmaceutically acceptable salt thereof in the treatment of ALS.

1.2 D4 was considered to represent the closest prior art by the opposition division in its decision, rather than D1 or D12. The respondent developed its objection of lack of inventive step on the basis of D4 as closest state of the art in its reply to the statement of grounds of appeal.

1.2.1 D4 discloses the protocol and design of a clinical trial for evaluating the efficacy and tolerability of TUDCA in the treatment of ALS, wherein TUDCA is administered at 1g b.i.d (2g daily) for a year to 18-75 years old Caucasian male or female ALS patients who had first symptoms of ALS by no more than 1.5 years and were in treatment with a steady regime of riluzole and vitamin E for a minimum of three months (see D4: title; page 6, arms and interventions; page 7, outcome measures; page 7, eligibility). Further, document D4 describes in detail the rational for using TUDCA in these clinical trials. It mentions in particular that TUDCA is endowed with antioxidant, antiapoptotic and neuroprotective activities and describes the detailed pharmacological mechanisms of action for each activity

(see D4, pages 5-6). The results of the trial announced in D4 have not been made available to the public.

1.2.2 The Board agrees with the choice of D4 as closest prior art by the opposition division.

The disclosure of D1 is indeed mainly directed to the use of UDCA for the treatment of ALS and provides experimental results only for UDCA, while mentioning TUDCA as metabolite of UDCA with potential in the treatment of neurodegenerative disease.

The Board considers in particular the teaching of D12 more remote than D4 which envisages a real human treatment with TUDCA. Document D12 provides indeed only some pre-clinical *in vitro* data showing that TUDCA had a protective effect on motor neuron degeneration caused by mutations in SOD1, making it potentially useful as a treatment in patients with some forms of amyotrophic lateral sclerosis through these mechanisms.

1.3 The problem was defined by the opposition division in its decision as the provision of an effective treatment for ALS. This formulation of the objective technical problem is not contested by the appellant or the respondent.

1.4 The problem appears to be solved in view of the examples of the contested patent in paragraphs [0028]-[0038]. The patent shows for instance that the baseline-adjusted absolute ALSFRS-R score was significantly higher in TUDCA-treated than in placebo-treated patients (see par. [0031] of the specification) and that the rate of responder patients was significantly higher under TUDCA (87%) than placebo (43%) (see par. [0032]). Moreover the average survival

time was a bit longer under TUDCA treatment (cf. par. [0034]) and one year of treatment with TUDCA at the prescribed dose was associated with slower deterioration of function in ALS patients (see par. [0036]).

1.5 Clinical trials are usually initiated on the basis of encouraging results from preclinical experiments. Thus, the announcement of a phase II clinical trial protocol for a particular therapeutic agent and a disease may provide the skilled person with a reasonable expectation of success. Such reasonable expectation of success is, however, to be denied in a situation where a skilled person would have been discouraged from carrying out the clinical trials, such as when the state of the art provides the skilled person with reasons for not pursuing the solution envisaged in the clinical trial or provides the skilled person with an expectation of failure. Consequently, "a reasonable expectation of success" is linked with the specific circumstances of the case and requires a case-by-case evaluation of all the facts at hand at the priority date of the contested patent.

In the present case, the Board holds that the state of the art suggested to the skilled person a clear expectation of failure.

1.5.1 The disclosure of document D9 demonstrates indeed that the skilled person could not base any reasonable expectation of success of the use of TUDCA in treatment of ALS on the announcement in document D4 of a phase II clinical trial for the treatment of ALS with TUDCA.

D9 is a scientific article published in 2012 which gives a general review of the treatment of amyotrophic

lateral sclerosis (ALS) at that time. D9 mentions 89 different drugs which, before the filing date of the opposed patent, had been used in clinical trials for ALS based on allegedly promising preclinical data (see page 9, at the top). The document explains the complexity of the disease ALS and mentions all the numerous and possible pathophysiological considerations involved in ALS (see page 7, par. 4.1). It furthermore cites all possible corresponding promising groups of compounds in the planning of ALS treatment strategies, with *inter alia* the anti-oxidants, the neuroprotectants and the anti-apoptotic compounds (see pages 7 and 9 of D9).

Importantly, it discloses that, for all the drugs listed in the document, promising preclinical data, such as biochemical or cellular assays, have been provided, but nevertheless the majority of the clinical trials failed (see D9, page 9 under section 5.1 headed "Programmed failure in clinical trials for AlS?").

Hence, among the tested drugs, **solely** riluzole had received a marketing authorization and was thus used by patients affected by ALS; but the efficacy of riluzole, as confirmed by D4 and D9, is limited to prolonging survival of patients by approximately two to three months (see D9 page 19, "Riluzole"). Other drugs having the same anti-glutamatergic properties as riluzole, such as gabapentin or topiramate, were also tested without however any benefits for patients with ALS (see D9, pages 15 and 21 of D4). **This shows that the choice of compounds on the basis of preclinical data or on the pathophysiological properties of said drugs cannot be seen as an encouraging element in the specific treatment of ALS.**

With regard to TUDCA, D9 mentions simply that the drug was found to be neuroprotective, antioxidative and anti-apoptotic in rat models for diseases such as stroke and Huntington's disease, and that it is currently evaluated in a Phase II study, namely the study of D4 (see page 20).

D9 mentions the trials of many drugs having the same pharmacological properties as TUDCA, i.e. anti-oxidant, neuroprotectant and/or anti-apoptotic properties, all of which having been found to be ineffective. D9 highlights in particular that no evidence of a benefit of an anti-oxidant treatment with regard to survival, neither alone or in combination, has been described (see page 11). More specifically, D9 explains that many antioxidants, such as *inter alia* creatine, lithium or tocopherol, failed in clinical trials on humans. D9 gives the same conclusions with other drugs having anti-apoptotic and/or neuroprotective properties, alone or in combination with other properties. For instance, erythropoietin, which has both neuroprotective and anti-apoptotic properties, did not show any clinical efficacy (see page 14) and sodium valproate, which shows anti-oxidative and anti-apoptotic properties was also not effective with regard to survival and disease progression (see page 20). **This shows that drugs having anti-oxidant, neuroprotectant and/or anti-apoptotic properties have *a priori* no expected efficacy in the treatment of ALS and that a drug having such individual or combined properties, such as TUDCA, would provide the skilled person with at best a "hope of success" for its use in treatment of ALS, but more likely an "expectation of failure".**

Consequently, D9 shows that the selection of a treatment based on existing favourable preclinical data

does not give an expectation of success when the same drug is used in clinical trials for the treatment of ALS and that, in the specific case of drugs having anti-oxidant, anti-apoptotic and/or neuroprotective properties, there is no expectation of success of the treatment.

1.5.2 A reasonable expectation of success from the trial of D4 is furthermore not supported by any potential effective treatment of ALS by an *in vivo* precursor of TUDCA, namely UDCA, as described in documents D1 and D15.

TUDCA is indeed a metabolite of UDCA, more particularly the taurine conjugate of UDCA. Upon entering the hepatocytes, UDCA forms a co-enzyme A derivative and is then amidated with glycine or taurine, to form glyco- or tauro-UDCA while the conjugates are then themselves further metabolized (cf. D16, page 23 or D1, page 15, lines 17-27).

Document D1 discloses a method of treating neurodegenerative diseases, including ALS, wherein said method comprises the oral or parenteral administration of a solution comprising a bile acid, or a derivative or salt thereof (see D1, page 1, lines 2-4; page 2, lines 3-6; page 2, line 21-page 3, line 2).

In example 3, solubilized UDCA was given to transgenic rats expressing a mutated (G93A) human SOD1 gene to evaluate the potential benefits of the product in ALS. D1 concludes that in this animal model for ALS UDCA improved *inter alia* motor performance (see D1: page 35, lines 11-19).

In example 4, an *in vitro* study was performed to evaluate the protective effect of solubilized UDCA on wild type cells containing G93A and A4V mutations in hSOD1. The experimental results in D1 provide evidence that soluble UDCA may protect G93A and A4V cells from NO-mediated apoptosis and may revive apoptosis-mediated damaged cells of ALS, making from UDCA a candidate for treating ALS (see D1: page 40, lines 24 - 27; page 33-35, example 3).

D1 further discloses and claims other bile acids, salts or conjugates, such as TUDCA for the treatment of neurodegenerative disease , without providing any experimental result with regard to the claimed bile acids other than UDCA.

In the Board's view, an extrapolation of the experimental results obtained with UDCA in D1 to the other cited bile acids to suggest efficacy of TUDCA in treatment of ALS, is not realistic or credible for several reasons:

(a) D1 provides only preclinical experimental results for UDCA in its examples.

(b) It is not made credible in D1 that, if UDCA might be useful in the treatment of ALS, this would also apply to TUDCA or any other metabolite or analogue or that the effect relies on one of the metabolites. D1 does not present any evidence that any particular metabolite or analogue could be responsible for the same effect as UCDA. And even if a metabolite of UDCA might be responsible for an effect *in vivo*, there is no evidence that this metabolite would specifically be TUDCA among all other possible alternative metabolites.

(c) UDCA and TUDCA are different from both a chemical and physical point of view. UDCA is a carboxylic

> acid and a weak acid, which is lipophilic and essentially insoluble in water and for this reason may easily cross all cellular membranes (see tables 3 and 4 of D27). To the contrary, TUDCA is a sulphonic acid and a strong acid, which is hydrophilic and water soluble and cannot cross cellular membranes (cf. also D27). In view of these differences and even assuming that D1 made it credible that UDCA is useful in the treatment of ALS, the skilled person would not reasonably expect the same utility in treatment of ALS for TUDCA merely on the basis of a structural similarity or metabolic relationship between UDCA and TUDCA .

The Board does also not see a ground for a reasonable expectation of success from the trial of D4 in the potential effective treatment of ALS by UDCA as presented in the experiments from D15, which were cited by the respondent in support of document D1. The Board has indeed a different reading of this document than the respondent.

D15 is a study from 2012 which evaluates the efficacy and safety of ursodeoxycholic acid (UDCA) with oral solubilized formula in amyotrophic lateral sclerosis (ALS) patients. The study concludes that oral solubilized UDCA seems to be tolerable in ALS patients, and suggests that oral solubilized UDCA may have a beneficial effect on the rate of functional decline in patients with ALS, but **it was not possible to make firm conclusions regarding its efficacy**, particularly due to the high attrition rate in this cross-over trial (see "Abstract" and "Discussion"). D15 mentions that the major problem was the large drop-out rate in this trial, since only one-fourth of the initially randomized patients completed both parts of the study.

It suggests that patients with severe disease at enrolment or progressively more disabled during the trial tended to refuse to visit the clinic for outcome measures. The second problem of this study was the way the data was analyzed, i.e., a "completers-only" analysis, which could not rule out faster declines for patients after their drop-out. This could lead to tiling the results of the study to a positive treatment effect. Consequently, this document is not conclusive and does not appear to confirm the efficiency of UDCA in the treatment of ALS. In any case it does not provide a therapeutic link with a possible efficacy of TUDCA, which makes its disclosure irrelevant. This view of the study is also shared in document D23 (see page 476, "Have there been any trials of ursodiol in PALS?").

1.5.3 The documents D11 and D12, which were also cited by the respondent to support its objection starting from D4, do not provide the skilled person with further reasons for an expectation of success of the clinical trials announced in D4.

D11 discloses in claim 32 a method for treating a subject with a neurodegenerative disease associated with protein aggregation, comprising the administration of an agent that decreases the activity of a molecule selected from the group consisting of XBP-1 , IRE-1 and EDEM, thereby treating a neurodegenerative disease associated with protein aggregation in the subject. The disease can be ALS or Huntington's disease (claims 33 or 34), while the active agent can be either an autophagy activator or a chemical chaperone, the latter being possibly TUDCA among a list of possibilities in claim 35. The disclosure of this document needs therefore several selections of compounds and diseases

to come to the idea to treat ALS with TUDCA. Importantly, the document teaches also a different pharmacological pathway to treat ALS compared to D4, and a link to the disclosure of D4 cannot thus be made. Moreover, D11 does not provide experimental evidence to substantiate effective treatment of neurodegenerative disease with TUDCA, and the argument that this disclosure provides a basis for a skilled person's reasonable expectation of success for the treatment of ALS with TUDCA remains thus purely speculative and therefore not convincing.

D12 discloses in Abstract P81 that TUDCA may contribute to the protection of motor neurons from degeneration caused by SOD 1 mutations through anti-apoptotic and anti-oxidant mechanisms. Therefore, it may provide a potentially useful treatment in patients with some forms of amyotrophic lateral sclerosis. The teaching of this document is based only on preclinical *in vitro* experimentation and provides the skilled person in view of document D9 no reasonable expectation of success for the clinical trial of document D4.

1.6 **Accordingly, the Board concludes that, starting from document D4 and in view of the further cited prior art, the skilled person would not have arrived at the claimed subject-matter in an obvious manner and that the subject-matter of claim 1 of the main request involves an inventive step.**

1.7 Several decisions were cited by the parties during the discussion on inventive step. The Board finds that none of the decisions cited were inconsistent with the present conclusion on inventive step.

1.7.1 According to the respondent, a skilled person would have understood that the phase II clinical trial of D4 constitutes a planned scientific investigation in the sense of T 239/16, in which the benefit will arise with reasonable certainty, i.e. a reasonable expectation of success.

The Board considers that the present situation is different from that in T 239/16.

In T 239/16, the subject of the patent was the therapeutic treatment of conditions of abnormally increased bone turnover, such as osteoporosis, with the bisphosphonate zoledronic acid. The closest prior art was a study to check whether the same specific biphosphonate was an effective product in the prevention of bone loss in patients with post-menopausal osteoporosis. The claimed invention was found to lack inventive step taking *inter alia* account of the known animal models for osteoporosis in which zoledronic acid was preclinically tested and the fact that bisphosphonates represented according to several documents an established class of drugs for the therapeutic treatment of osteoporosis.

In the present case, there are no documents indicating the established efficacy of any class of agents in treatment of ALS. Moreover,as explained in section 1.5.1 above, document D9 calls the relevance of the preclinical results for TUDCA into question.

1.7.2 The present case differs from the case T 2506/12 for the same reason, namely through the absence of any reasonable expectation of success of the announced clinical trial.

In T 2506/12, the claimed subject-matter was indeed found to lack inventive step over two equivalent documents disclosing that the same drug combination was being tested in a clinical phase I study for the treatment of cancer. It was already known from several documents that both drugs had some efficacy in the treatment of some cancers and the Board came to the conclusion that there was no other information on file which would have caused the person skilled in the art to conclude that there was no reasonable expectation of success for the combination treatment.

1.7.3 In the decision T 96/20 also cited by the respondent, the Board held first that actual therapies for treatment represented the closest prior art rather than the clinical trial protocol which was disclosed in the same document and which was considered only for the assessment of obviousness of the solution. The closest prior art was a document relating to the actual treatment of the same disease with alternative drugs.

The Board held furthermore that the announcement of a detailed safety and efficacy clinical trial protocol for a particular therapeutic and disease provided the skilled person with a reasonable expectation of success of this particular therapeutic, unless there was evidence to the contrary in the state of the art.

The case T 96/20 differs however from the present case in that the Board held that no such evidence to the contrary had been brought forward. A decisive point in the case T 96/20 was that a further document relating to the successful treatment of the claimed disease induced in mice with a drug from the same therapeutic category was found to provide an encouragement for

treating the same disease in humans. Hence, the Board concluded that there was a lack of an inventive step.

1.7.4 The decision T 2963/19 has been cited by the appellant to show that inventive step over clinical trials have to be assessed case-by-case, a point with which the Board agrees.

The decision T 2963/15 states that the considerations in T 239/16 regarding the expected success following the approval of a clinical trial were evidently closely linked to the further circumstances of the case decided therein and cannot be extrapolated to the present appeal case T 2963/19. The same applies with respect to similar considerations in T 2506/12 (see point 4.3.1).

2. Main request - Novelty

2.1 D8 relates to compositions comprising low doses of diazoxide for use in the treatment of a mammal afflicted with ALS, in particular a human (see D8, claims 1 and 3). Further, D8 discloses in claim 9 that diazoxide can be combined with "an additional therapeutic agent useful in the treatment of amyotrophic lateral sclerosis" including TUDCA, which constitutes a single selection from a list. Consequently, a composition comprising diazoxide and TUDCA for use in the treatment of a mammal afflicted with ALS is derivable directly and unambiguously from D8.

D8 supports the utility of low dose diazoxide in the treatment of ALS with experimental results, in particular in Example 2. This example shows that low doses of diazoxide improve survival in the SOD1-G93A transgenic mice model for amyotrophic lateral

sclerosis. The utility of diazoxide in treatment of ALS described in D8 has not been disproved.

Accordingly, even if D8 does not provide any *in vitro* or *in vivo* experiments with regard to the efficacy of TUDCA in the treatment of ALS, D8 provides an enabling disclosure for a combination treatment based on diazoxide and TUDCA, in view of the explicit disclosure in D8 of the efficacy of diazoxide.

2.2 As a general rule, a claim to the use of a known compound for a particular purpose or to a product for use in a particular medical purpose, which is aimed at obtaining a technical effect described in the patent, should be interpreted as including that purpose as a functional technical feature, and is accordingly not open to objection under Article 54(1) EPC **provided that such technical feature has not previously been made available to the public**. This functional feature has however been made public in the present case.

In the Board's view, the discovery of a new property of a particular ingredient of a known composition, i.e. here TUDCA in the composition comprising diazoxide and TUDCA, used for a known and identical general purpose, i.e here the treatment of a mammal afflicted with ALS, can indeed not confer novelty to the particular ingredient used for the same general purpose, namely TUDCA for the treatment of ALS. Novelty can only be recognized if this new property is applied in a new use.

Consequently, the disclosure in D8 of treatment of ALS based on diazoxide and TUDCA, wherein the efficacy of diazoxide is supported by experimental data and has not

been disproven, anticipates the subject-matter of claim 1 of the main request.

2.3 Accordingly the main request does not meet the requirements of Article 54 EPC.

3. Auxiliary request 1 - Novelty

Claim 1 of auxiliary request 1 differs from claim 1 of the main request in the specification that the treatment is **"in an human"**. Since D8 is directed to the treatment of a mammal afflicted with ALS, in particular a human, this restriction does not change the conclusion on novelty already reached for the main request. Accordingly, auxiliary request 1 does not meet the requirements of Article 54 EPC.

4. Auxiliary request 2

4.1 Claim 1 of auxiliary request was amended by the addition of the feature **" in a human, characterized in that it is administered for at least 30 weeks"**.

4.2 Since there is no disclosure of any duration of treatment in D8, the subject-matter of claim 1 of auxiliary request 2 is not anticipated, and auxiliary request 2 meets the requirements of Article 54 EPC.

4.3 Claim 1 of this request is more restricted than claim 1 of the main request. Consequently, the conclusions reached above with regard to inventive step apply *mutatis mutandis* also for this request, which meets the requirements of Article 56 EPC.

5. Admission of inventive step objections starting from D1 and D12

5.1 During the oral proceedings before the Board, and after the conclusions on inventive step and novelty over the main request and auxiliary requests 1 and 2 were given by the Board, the respondent raised an objection of lack of inventive step over D1 and D12 against the subject-matter of claim 1 of auxiliary request 2.

The respondent stated that it mentioned the possibility to take D1 as starting point for the assessment of inventive step in its reply to the statement of grounds of appeal. Moreover, the objection over D12 was submitted in response to a comment made by the Board in its preliminary opinion pursuant Article 15(1) RPBA 2020, wherein D12 was mentioned as possible closest prior art.

5.2 The appellant requested that these objections not be admitted into the proceedings.

5.3 The opposition division considered D1 and D12 to be less relevant than D4 with regard to inventive step and took a final decision on the basis of D4 as closest state of the art.

The respondent cited the document D1 in its reply to the statement of grounds of appeal with regard to novelty. It mentioned furthermore in the same letter that "...*we respectfully submit that, in addition to D4, D1 also is a suitable starting point for the assessment of inventive step for the subject-matter of claim 1 as granted. We respectfully reserve the right to present a complete problem-and-solution approach*

starting from D1 should it prove advantageous to do so".

With regard to D12, the respondent did not make any mention of D12 in its reply to the statement of grounds of appeal.

The Board confirmed the choice of D4 as the closest prior art in its preliminary opinion by explaining that it considered the teaching of D12 more remote than D4 and that the assessment of inventive step over D12 may be discussed during oral proceedings. The preliminary opinion of the Board did not comprise an assessment of inventive step over D12 as closest prior art.

5.4 In the present case, Article 13(2) RPBA is relevant with regard to the new submission. That provision indicates that: "Any amendment to a party's appeal case made...after notification of a communication under Article 15, paragraph 1, shall, in principle, not be taken into account unless there are exceptional circumstances, which have been justified with cogent reasons by the party concerned".

An objection of lack of inventive step over D1 or D12 represents clearly an amendment to the respondent's case. A simple statement in the reply to the statement of grounds of appeal with regard to a conditional problem-solution approach starting from D1 against the main request can indeed not be considered as a substantiated objection or reasoning of lack of inventive step, even less against auxiliary request 2. Moreover, D12 was not cited in the reply to the statement of grounds of appeal.

These objections are not only an amendment of the respondent's case at a very late stage of the appeal proceedings. They constitute effectively a new case which would be presented for the first time during the oral proceedings before the Board.

Hence, the Board needs to decide whether there are exceptional circumstances, justified by cogent reasons, why the submission is to be taken into account.

5.4.1 The respondent has not provided any explanation as to what would amount to an exceptional circumstance apart from referring to the Board's communication.

The new objections cannot be seen as a response to the preliminary opinion of the Board, which did not raise any new point in its communication. First, D1 was cited by the Board only in the context of the assessment of novelty and not of inventive step. Then, the statement made by the Board in its communication with regard to D12 related to the main request and to the selection of the closest state of the art and was a confirmation of the decision of the opposition division; it cannot be regarded as an invitation to argue a new inventive step objection based on D12 against auxiliary request 2. The respondent had the possibility to file these objections with its reply to the statement of grounds of appeal.

In the Board's view, there are thus no exceptional circumstances justifying the admission of these new objections.

Consequently, the Board decides not to admit into the proceedings the inventive step objections starting from D1 and D12 against the subject-matter of claim 1 of auxiliary request 2 (Article 13(2) RPBA).

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 in amended form on the basis of auxiliary request 2 filed with the statement setting out the grounds of appeal and a description to be adapted thereto, if necessary.

The Registrar: The Chairman:

B. Atienza Vivancos M. Steendijk

Decision electronically authenticated