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Datasheet for the decision of 1 October 2024

Case Number: T 0979/23 - 3.3.04

Application Number: 18152406.7

Publication Number: 3329909

IPC: A61K31/137, A61P25/08

Language of the proceedings: EN

Title of invention:
Fenfluramine for use in the treatment of Dravet syndrome

Patent Proprietors:
Katholieke Universiteit Leuven
University Hospital Antwerp

Opponents:
Kraus & Lederer PartGmbB
Teva Pharmaceutical Industries, Ltd.

Headword:
Dravet syndrome II/KATHOLIEKE UNIVERSITEIT LEUVEN

Relevant legal provisions:
RPBA 2020 Art. 13(2)
EPC Art. 100(b)

Keyword:
Late-filed document - justification for late filing (no)
Sufficiency of disclosure - (no)

Decisions cited:
G 0001/03, G 0002/21, T 0609/02, T 0754/11, T 0887/14, T 1779/21

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Case Number: T 0979/23 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 1 October 2024

Appellant I: (Opponent 1)	Kraus & Lederer PartGmbB Thomas-Wimmer-Ring 15 80539 München (DE)
Representative:	Kraus & Lederer PartGmbB Thomas-Wimmer-Ring 15 80539 München (DE)
Appellant II: (Opponent 2)	Teva Pharmaceutical Industrieds, Ltd. 124 Dvora HaNevi'a St. 6944020 Tel Aviv (IL)
Representative:	Hamm&Wittkopp Patentanwälte PartmbB Jungfernstieg 38 20354 Hamburg (DE)
Respondents: (Patent Proprietors)	Katholieke Universiteit Leuven KU Leuven Research & Development Waaistraat 6 Box 5105 3000 Leuven (BE) and University Hospital Antwerp Wilrijkstraat 10 2650 Edegem (BE)
Representative:	Leonard, Thomas Charles Kilburn & Strode LLP Lacon London 84 Theobalds Road London WC1X 8NL (GB)

Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 15 March 2023 rejecting the oppositions filed against European patent No. 3 329 909 pursuant to Article 101(2) EPC**

Composition of the Board:

Chairwoman M. Pregetter
Members: B. Rutz
M. Blasi

Summary of Facts and Submissions

I. The appeals by the opponents (appellant I and II) lie from the opposition division's decision to reject the oppositions against European patent No. 3 329 909 (the patent), entitled "*Fenfluramine for use in the treatment of Dravet syndrome*", which was granted on European patent application No. 18 152 406.7, which is a divisional application of European patent application No. 14 724 037.8 (the parent application).

II. The opposition proceedings were based on Article 100(a) EPC, in relation to inventive step (Article 56 EPC), and Article 100(b) EPC.

III. With its statement of grounds of appeal, appellant II filed document D35 (Communication of the Board of Appeal in case T 1779/21).

IV. In their reply to the appeals, the patent proprietors (respondents) relied on the patent as granted.

V. Claim 1 reads as follows.

"1. A formulation comprising fenfluramine or a pharmaceutically acceptable salt thereof for use in the treatment of Dravet syndrome, wherein said treatment comprises administration of fenfluramine as a monotherapy."

VI. The board summoned the parties to oral proceedings, as requested, and informed them of its preliminary opinion in a communication under Article 15(1) RPBA dated 6 June 2024.

VII. Appellant II provided further arguments in a letter dated 13 March 2024. With their letter dated 22 July 2024, the respondents requested that the oral proceedings be held by videoconference. The appellants did not object to this request. With their letter dated 25 July 2024, the respondents filed further arguments and submitted a declaration by Dr Sullivan (renumbered to D36 during oral proceedings before the board).

VIII. At the end of the oral proceedings, which were held by videoconference, the chairwoman announced the board's decision.

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

D2 B. Ceulemans et al., "*Successful use of fenfluramine as an add-on treatment for Dravet syndrome*", Epilepsia 53(7), 2012, 1131-9

D3 Annex 1 attached to the respondents' response of 25 May 2017, in the parent application

D4 J. Aicardi et al., "*Treatment of self-induced photosensitive epilepsy with fenfluramine*", NEJM 313(22), 1985, 1419

D5 J. Aicardi et al., "*Syncopal Attacks Compulsively Self-induced by Valsalva's Maneuver Associated with Typical Absence Seizures*", Arch. Neurol. 45, 1988, 923-5

D6 B. Clemens, "*Dopamine agonist treatment of self-induced pattern-sensitive epilepsy. A case report*", Epilepsy Res. 2, 1988, 340-3

D7 M. Boel and P. Casaer, "*Add-On Therapy of Fenfluramine in Intractable Self-Induced Epilepsy*", Neuropaediatrics 27(4), 1996, 171-3

D8 P. Casaer and M. Boel, "*Fenfluramine as a Potential Antiepileptic Drug*", Epilepsia 43(2), 2002, 205-6

D11 S. Grosso, et al., "*Dexfenfluramine effective in drug-resistant temporal lobe epilepsy*", Neurology 57, 2001, 1139-40

D17 B. Ceulemans et al., "*Successful use of Fenfluramine as add-on treatment in Dravet syndrome: a two year prospective follow up*", Eur. J. Paediatr. Neurol. 178, 2013, S4, O11-1866

D18 C. Dravet, "*Dravet syndrome history*", Dev. Med. Child. Neurol. 53(Suppl. 2), 2011, 1-6

D19 K. Gentsch et al., "*Fenfluramine Blocks Low-Mg^{2+}-Induced Epileptiform Activity in Rat Entorhinal Cortex*", Epilepsia 41(8), 2000, 925-8

D25 Declaration by Dr Sullivan, dated 26 May 2022, with accompanying CV

D27 Treatment algorithm from C. Dravet and R. Guerrini, "*Dravet Syndrome*", 2011

D32 M. Wolff et al. "*Severe Myoclonic Epilepsy of Infants (Dravet Syndrome): Natural History and Neuropsychological Findings*", Epilepsia 47(Suppl. 2), 2006, 45-8

D35 Communication of the Board of Appeal pursuant to Article 15(1) RPBA in case T 1779/21 (23 June 2023)

D36 Second declaration by Dr Sullivan, dated 22 July 2024

X. The appellants' submissions are summarised as follows.

Admission of document D36 (Article 13(2) RPBA)

The respondents had not provided sufficient reasoning as to why the document was filed late. The decision in the parent case was handed down in December 2023 and the written reasoned decision was issued in February 2024, but the document was not filed until July 2024. An expert declaration should not take more

than 1 or 2 months to prepare and other experts on the topic must have been available. The arguments to which the document allegedly responded were already on file (see e.g. paragraph bridging pages 6 and 7 of opponent 2 's submission dated 20 December 2023 citing "*'potentially devastating consequences' that had to be expected from using fenfluramine as the only active ingredient*"). The respondents' argument that the document did not contain new knowledge was not relevant when deciding on admission of a document in appeal.

Disclosure (Article 100(b) EPC)

The teaching of the patent was limited to the use of fenfluramine in combination with further active agents. All the documents cited in the patent (paragraphs [0002] to [0004], documents D4 to D8 in the present proceedings) described treating different forms of epilepsy (not including Dravet syndrome) by using combinations of fenfluramine with several further agents. The patent's experimental part was limited to a "*Comparative Example*" that was a summary of prior-art document D2. The patent did not comprise any new data; in particular, it did not comprise any experimental results or any additional teaching regarding the use of fenfluramine in a monotherapy.

The person skilled in the art would have serious doubts about the efficacy of fenfluramine as a monotherapy for Dravet syndrome. The respondents themselves argued extensively that the person skilled in the art "knew" that treatment of the highly complex Dravet syndrome required a combination therapy involving different agents acting via multiple mechanisms, and that there was an established "bias" against the use of fenfluramine as a monotherapy for Dravet syndrome. In

order to provide a clear and complete disclosure of the claimed invention within the meaning of Article 100(b) EPC, the information provided by the patent would have had to dispel these doubts.

Decision T 1779/21 (parent case)

The reasoning in this decision was legally and factually correct and should be applied to the present case. Claim 1 differed from claim 1 of the patent as granted on the parent application ("parent patent") only in that it did not require the treatment to occur by oral administration. The claim was therefore broader and the reasoning of the board in the parent case equally applied to the current one.

Since the grounds that led to the revocation of European patent 2 991 637 were fully applicable to the opposition against the present patent, the matter (at least, with respect to the issue of sufficiency of disclosure) had been ultimately settled by a court of competent jurisdiction, i.e. it was *res judicata*.

XI. The respondents' submissions are summarised as follows.

Admission of document D36 (Article 13(2) RPBA)

Dr Sullivan's declaration (D36) was filed in direct response to the communication of the board providing its preliminary opinion. The board referred in this communication to the parent case decision T 1779/21 and the reasoning therein with regard to sufficiency of disclosure. The decision, however, contained technical and legal errors and used arguments which had not been raised during the proceedings, but which the respondents were confronted with for the first time in

the written decision (see points 12 and 15). Since the summons for the present oral proceedings were issued shortly after the decision in the parent case was issued, there was no time to respond before the summons. Furthermore, Dr Sullivan was not available immediately and consultation with him and the clients needed time. The new objections raised for the first time in the written reasoned decision presented new and unforeseen, thus exceptional, circumstances. Moreover, the document did not contain substantially new matter and was not complex. It should therefore be admitted.

Disclosure (Article 100(b) EPC)

The inventors of the patent in suit recognised the potential for fenfluramine to have a clinically significant effect when administered as a monotherapy, and indicated a mechanism of action for this effect (see page 7, lines 1 to 5 of the application as filed). This was confirmed by document D2 (see page 1137, right-hand column, last paragraph). In view of the stated mechanism of action, it would have been plausible to the skilled person that fenfluramine had anti-convulsive effects, and therefore could be used as a monotherapy in the treatment of Dravet syndrome.

The exact scope of the supporting data in the application as filed did not alter the fact that a fenfluramine monotherapy was clearly envisaged and was explicitly disclosed in the application as filed as a mode of administration.

Fenfluramine as a monotherapy had subsequently been shown to have a significant clinical effect in the treatment of Dravet syndrome (see document D3).

The skilled person could carry out the invention across the scope of the claims without any undue burden, following the teaching in the patent, since it merely required the administration of a compound that was already known to the skilled person as a treatment for the same disease, albeit in a combination therapy in the prior art.

Decision T 1779/21 (parent case)

There were three major legal and technical errors in the decision.

1. The board applied a level of proof that required the skilled person to "assume" that the treatment could be successful (see point 12 of the Reasons). However, for the claimed invention to be sufficiently disclosed it was merely required that achieving the therapeutic effect was credible to the skilled person from the application as filed and on the basis of their common general knowledge. Such a decision had to be based on the "overall balance of probabilities", as distinct from "beyond all reasonable doubt" or "absolute conviction" (see Case Law of the Board of Appeal, 10th Edition, III.G.4.3.1).

2. The board implied that the efficacy of fenfluramine as a monotherapy should be assessed against valproate as a standard treatment (see point 15 of the Reasons). There was no evidence on file that suggested potential treatments for Dravet syndrome should be assessed against valproate.

3. The board considered that the treatment should provide an equivalent or better level of seizure control. This was incorrect because a treatment did not

need to be better than, or equivalent to, existing therapies for the attainment of a therapeutic effect to be credible. What was required to establish sufficiency of disclosure was that any therapeutic effect falling within the scope of the claims was made credible.

Furthermore, there was no scientific basis for the board to conclude that fenfluramine was "*only acting in support of valproate, i.e. potentiating the effect of this established anti-convulsant*".

The reasoning of decision T 1779/21 should therefore not be applied to the present case.

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

The respondents requested that the appeal be dismissed and that the patent be maintained as granted.

Reasons for the Decision

Admission of document D36 (Article 13(2) RPBA)

1. Document D36 was filed by the respondents with their letter dated 25 July 2024, i.e. after issuance of the board's communication pursuant to Article 15(1) RPBA, which was dated 6 June 2024. Admittance of the document is therefore subject to the provisions in Article 13(2) RPBA as in force since 1 January 2024. The respondents argued that the document was filed due to exceptional circumstances, namely the board's reference in its communication setting out its preliminary opinion to the reasoning given in the parent case (see decision T 1779/21). The respondents

furthermore argued that obtaining declaration D36 from Dr Sullivan had required some time, i.e. the document was filed in a timely manner.

2. The board does not agree. The oral proceedings in which decision T 1779/21 was taken took place on 19 December 2023. The written reasoned decision was issued on 20 February 2024. Given the very similar wording of the claims of the granted parent patent and the present patent, the respondents must have been aware that the issues to be dealt with in the present case were very similar if not identical to the ones in the parent case. The respondents therefore could not be taken by surprise by decision T 1779/21 and the reasoning therein being considered relevant by the board in its preliminary opinion. In this regard, the board also notes that appellant II referred to the preliminary opinion of the board in case T 1779/21 (submitted as D35) in its statement of grounds of appeal and to written reasoned decision T 1779/21 in its letter dated 13 March 2024. If they considered it necessary, the respondents could therefore have responded to issuance of that decision in a timely manner.

3. The respondents' argument that the declaration did not introduce substantially new matter and was not detrimental to procedural efficiency because it was not complex is not relevant because Article 13(2) RPBA first and foremost requires there to be exceptional circumstances for a document to be admitted at such a late stage in the proceedings. The additional criteria of procedural efficiency and complexity as also mentioned in Article 13(1) RPBA may also be considered in the context of Article 13(2) RPBA, but, in the

board's view, come into play only once the presence of exceptional circumstances has been acknowledged.

4. The board also disagrees with the respondents' further argument that, by referring to decision T 1779/21, the board's communication introduced new arguments which had not been raised before by any party in the proceedings.

5. The question of whether it was credible that a therapeutic effect was obtained by fenfluramine as a monotherapy had already been central to the discussion in the current case in the proceedings before the opposition division (see notices of opposition) and had also been reiterated by the appellants in their statements of grounds of appeal (see e.g. statement of grounds of appeal by appellant I, points 4.3 and 4.4 and statement of grounds of appeal by appellant II, point 1.2). The same applies to the discussion of the experiments in the patent and the relevance of the combination treatments reported therein.

6. The fact that the board in points 12 and 15 of the Reasons for decision T 1779/21 used wording which had not been used *expressis verbis* before in the proceedings does not change this.

7. Equally, alleged technical or legal errors in the written reasons for decision T 1779/21 cannot change the situation described in point 5. above (see also points 29. to 34. below).

8. In light of the above, document D36 was not admitted into the proceedings.

Disclosure (Article 100(b) EPC)

9. Present claim 1 differs from claim 1 in the parent patent only in that it does not require "oral administration" and in that it does not state "as the sole therapeutic agent". These features were, however, not crucial in decision T 1779/21 and the parties have also not provided arguments relating to a possible difference in the meaning of the term "monotherapy" in the absence of the phrase "as the sole therapeutic agent" or to the relevance of administration routes. The board's reasoning regarding the current case is thus similar to the reasoning of decision T 1779/21.

Decisions G 2/21 and G 1/03

10. Claim 1 is formulated as a purpose-limited product claim according to Article 54(5) EPC.

11. Point 74 of the Reasons for decision G 2/21 (OJ EPO 2023, A85) confirmed the relevant case law that "*a technical effect, which in the case of for example a second medical use claim is usually a therapeutic effect, is a feature of the claim, so that the issue of whether it has been shown that this effect is achieved is a question of sufficiency of disclosure under Article 83 EPC*" and that "*it is necessary that the patent at the date of its filing renders it credible that the known therapeutic agent, i.e. the product, is suitable for the claimed therapeutic application*".

12. It therefore had to be decided whether fenfluramine as a monotherapy, i.e. as the sole therapeutic agent, could be considered suitable for the treatment of Dravet syndrome at the relevant date. As decision G 2/21 further explains, in point 77 of the Reasons:

"[i]*n order to meet the requirement that the disclosure of the invention be sufficiently clear and complete for it to be carried out by the person skilled in the art, the proof of a claimed therapeutic effect has to be provided in the application as filed, in particular if, in the absence of experimental data in the application as filed, it would not be credible to the skilled person that the therapeutic effect is achieved. A lack in this respect cannot be remedied by post-published evidence*."

13. The Enlarged Board of Appeal endorsed the conclusions in decision T 609/02 (see G 2/21, point 75 of the Reasons) and decisions T 754/11 and T 887/14 (see point 76 of the Reasons). The expression "*proof of a claimed therapeutic effect*" in point 77 of the Reasons cannot therefore be interpreted as a deviation from the established case law in the context of second medical uses: it does not apply a stricter requirement than the established case law prior to decision G 2/21. Rather, by referring in the same sentence to a particular situation in which "*in the absence of experimental data in the application as filed, it would not be credible to the skilled person that the therapeutic effect is achieved*", the Enlarged Board confirmed that means other than experimental data in the application as filed can establish proof of a claimed therapeutic effect.

14. What is required, however, in the absence of experimental evidence, is for the patent or the application as filed to provide some information demonstrating that the claimed compound has a direct effect on a metabolic mechanism specifically involved in the disease, this mechanism being either known from

the prior art or demonstrated in the patent itself (see T 609/02, points 5 to 9 of the Reasons).

15. Decision G 1/03 (OJ EPO 2004, 413) notes in this regard, in point 2.5.3 of the Reasons, that "[w]*hen an application for a patent is filed, the process of making the invention has to be completed. The requirement of sufficiency of disclosure ensures that a patent is only granted if there is a corresponding contribution to the state of the art. Such a contribution is not present as long as the person skilled in the art is not able to carry out the invention. Therefore, the decisive date for fulfilling the requirement has to be the date of filing or priority, as the case may be. Deficiencies in this respect cannot be remedied during the proceedings before the EPO.*"

16. The board concludes that a contribution to the state of the art which enables the skilled person to carry out the invention has to be present in the application as filed.

The teaching of the patent

17. The patent relates to the treatment of Dravet syndrome with fenfluramine. Dravet syndrome is a rare and catastrophic form of intractable epilepsy that begins in infancy. Children with Dravet syndrome are particularly susceptible to episodes of *status epilepticus*. This severe and intractable condition is categorised as a medical emergency requiring immediate medical intervention, typically involving hospitalisation. *Status epilepticus* can be fatal. It can also be associated with cerebral hypoxia, possibly leading to damage to brain tissue.

18. It was undisputed that the only example in the application as filed, "Comparative Example 1", does not relate to fenfluramine monotherapy, but reports administration together with valproate, a known anti-convulsant (see table 3). This combination treatment resulted in a seizure-free condition in 66.6% of test subjects, and in a slightly improved reduction in seizures (75%) as compared to the reduction in seizures in patients treated with valproate and stiripentol for two months (69.7%).

19. In the absence of experimental data for fenfluramine monotherapy in the application as filed, the board considered whether achieving the claimed therapeutic effect was made credible in the application as filed in any other way (see points 12. and 13. above). "*Monotherapy*" is explicitly mentioned in the application as filed on page 8, lines 11 to 13 and in claim 9, in both cases as an alternative to combination therapy. However, this mere statement is not in itself sufficient to provide any "proof" within the meaning of decision G 2/21. The application as filed furthermore states that "[f]*enfluramine has been known to inhibit serotonin reuptake and to trigger the release of serotonin in the brain due to disruption of its vesicular storage. However, until the present invention was made, it was not known that fenfluramine's mechanism of action made it suitable for the treatment of Dravet Syndrome*" (see page 7, first paragraph). The board notes that treatment by therapy does not *per se* require the disease to be completely cured or even that its cause be addressed, but does encompass the alleviation of symptoms (see also Case Law of the Boards of Appeal, 10th edition 2022, I.B.4.5.1).

Level of proof required

20. Although the skilled person could conclude, from the data in the patent or the application as filed, that fenfluramine in combination with valproate alleviated some symptoms of Dravet syndrome, it was not clear whether this also applied in the case of a monotherapy. In view of the serious nature of the disease, additional circumstances have to be borne in mind when deciding whether "*proof of a claimed therapeutic effect*" is provided in the application as filed. As noted in document D2: "*Dravet syndrome is a truly catastrophic therapy-resistant epilepsy syndrome, and families faced with this disorder are required to cope with special circumstances*" (see page 1136, left-hand column, penultimate paragraph). Discontinuation of treatment can lead to a greater number of seizures, potentially with adverse effects on mental development (see for example the case reported in document D17, right-hand column, lines 2 to 4 and D32, page 47, right-hand column, second full paragraph). According to several prior-art documents, including reviews authored by Charlotte Dravet, the physician after whom the disease is named, the standard first-line therapy for Dravet syndrome was valproate, a known anticonvulsant (see for example the upper part of the flowchart in D27). Depending on the response of the individual patient, this treatment was supplemented by additional medicaments (e.g. clobazam and stiripentol or topiramate, see the middle part of D27), while maintaining valproate as the basic medicament. Anti-epileptic drugs that target the sodium channel (e.g. carbamazepine, oxcarbazepine, phenytoin, lamotrigine) had to be avoided, because they were known to aggravate the condition, which could be associated with mutations

in the sodium channel gene *SCN1A* (see D18, paragraph bridging columns on page 2 and paragraph bridging pages 3 and 4). The expert declaration submitted by the respondents (D25) states in point 13 that "*removal of potentially efficacious compounds from a drug regimen is done with extreme caution and only with a rationale justifying the removal*".

21. In this particular case, namely a very serious disease for which an established, albeit sub-optimal, therapy exists (only 16% of patients remained seizure-free, see D2, Summary) and where an incorrect therapeutic decision could lead to irreversible damage, the level of proof required has to be at least such that the skilled person has reason to assume that the standard valproate treatment could be discontinued and replaced by fenfluramine without worsening the patient's condition.

Mechanism of action

22. In the absence of experimental or clinical data in the application as filed that would indicate that fenfluramine monotherapy had a therapeutic effect, the board further considered whether the application as filed or the prior art established that fenfluramine had a direct effect on a metabolic mechanism specifically involved in the disease. The respondents argued that the inhibition of serotonin reuptake and triggering of the release of serotonin in the brain due to disruption of its vesicular storage, as reported in the application as filed (see page 7, first paragraph), was such a metabolic mechanism. The board does not agree, for the following reasons.

23. Document D2, published shortly before the priority date of the patent, refers to earlier *in vitro* studies (D19) which indicate that "*serotonin-releasing drugs (like fenfluramine) could have an effect on the epileptic activity*" (see page 1137, right-hand column, first full paragraph). However, D2 concludes that "*although it is known that fenfluramine increases synaptic serotonin concentration, which has potential anticonvulsive effects, it is unclear whether the serotonin effects explain our favorable results*". In summary, it was far from established at the filing date whether the greater number of seizure-free patients with Dravet syndrome who were treated with fenfluramine as an add-on therapy resulted from increased serotonin levels.

24. Furthermore, and importantly, the skilled person could not derive from the experimental data in the patent or the application as filed whether fenfluramine was able to exert its beneficial effect alone, or whether it was only acting in support of valproate, i.e. potentiating the effect of this established anti-convulsant.

The teaching of the prior art

25. Since "*proof of a claimed therapeutic effect*" is not provided in the application as filed, the board also considered whether the teaching of the prior art provided the skilled person with any indication of a therapeutic effect of fenfluramine as a monotherapy for Dravet syndrome.

26. Most of the documents cited relate to combination treatments (see for example D4 and D6 to D8). It was undisputed that the only prior-art documents which relate to monotherapy with fenfluramine, D5 and D11, concern distantly related epileptic diseases. Document

D5 refers to a single case in which fenfluramine was given - as a monotherapy - to treat self-induced apnoeic syncopes and true epileptic absence seizures. The patient "*responded favorably to treatment with fenfluramine hydrochloride, as already reported in cases of compulsively self-induced syncopes*" (see page 923, left-hand column). In document D11, a single patient with temporal lobe epilepsy was treated with fenfluramine monotherapy. The document also refers to experimental data in rats and mice as a possible mechanistic explanation for the effect of fenfluramine (see paragraph bridging pages 1139 and 1140 and references cited therein). However, the conclusion in document D11 of an "*involvement of serotoninergic circuits in some forms of drug-resistant temporal lobe epilepsy*" limits the teaching concerning fenfluramine to these particular conditions (page 1140, last paragraph).

27. In view of the established use of fenfluramine in combination with other anti-convulsive medicaments, and the very different nature and isolated cases of the two epileptic diseases for which monotherapy with fenfluramine was reported, the skilled person could not draw any conclusions as to the effectiveness of fenfluramine as a monotherapy for Dravet syndrome.

Decision T 1779/21 (parent case)

28. The facts of the present case differ from the case decided in T 1779/21. In particular, claim 1 in case T 1779/21 contained the features: "wherein the formulation is for oral administration" and "as the sole therapeutic agent" which are not present in claim 1 of the present patent. Thus, the principle of *res judicata* does not apply.

29. The respondents considered that legal and technical errors in decision T 1779/21 would prevent the application of similar reasoning to the present case. The first alleged legal error was that the board set a higher standard of proof than the established case law of the Boards of Appeal of the EPO by stating that "*the level of proof required has to be at least such that the skilled person has reason to assume that the standard valproate treatment could be discontinued and replaced by fenfluramine without worsening the condition of the patient*" (see decision T 1779/21, point 12 of the Reasons).

30. Decision G 2/21 states in point 77 of the Reasons, in respect of sufficiency of disclosure of second medical use claims, that "*the proof of a claimed therapeutic effect has to be provided in the application as filed, in particular if, in the absence of experimental data in the application as filed, it would not be credible to the skilled person that the therapeutic effect is achieved. A lack in this respect cannot be remedied by post-published evidence.*" The case dealt with in decision T 1779/21 relates to a situation where experimental data for the therapeutic effect of fenfluramine monotherapy of Dravet syndrome, i.e. the treatment in the claim, is absent from the application as filed. As set out in detail in that decision, it was also not credible from common general knowledge or the prior art that a therapeutic effect could be achieved (see decision T 1779/21, points 16 to 18 of the Reasons). Therefore, according to decision G 2/21, "*proof of a claimed therapeutic effect has to be provided in the application as filed*" and a "*lack in this respect cannot be remedied by post-published evidence*".

31. To express this requirement, decision T 1779/21 uses a formulation ("*reason to assume ... without worsening the condition of the patient*") which is adapted to the specific case in hand and thus does not introduce a different legal standard. To assess whether the skilled person had "*reason to assume*" does not require proof "*beyond all reasonable doubt*" or "*absolute conviction*" as alleged by the respondents, but rather the establishment of proof based on "*the overall balance of probabilities*" as can been seen from the detailed reasoning in decision T 1779/21 (see points 13. to 18. of the Reasons therein).

32. The respondents further alleged that a technical error had been made in decision T 1779/21 by referring to "*standard valproate treatment*" for Dravet syndrome and considering whether the skilled person would have replaced such treatment with fenfluramine monotherapy (see point 12 of the Reasons). The board does not agree because evidence on file in both the parent and the present case refers to this medicament as a first line treatment (see e.g. D2, D25, D27). The respondents' expert Dr Sullivan in document D25 states with regard to document D27 that valproate was "*a typical treatment pathway taken by the majority of clinicians before the priority date of the patent. Here we can see that patients would be placed on valproate (VPA) monotherapy following the clinical symptoms of Dravet syndrome. In some cases, the first line therapy may be topiramate.*" It is self-evident that fenfluramine monotherapy requires any other treatment to be discontinued or that fenfluramine be started before any other treatment.

33. The respondents further alleged that the board incorrectly took the severity of the disease into

account, which implied a higher standard. The board does not agree because what was assessed in decision T 1779/21 is whether it was credible that fenfluramine monotherapy could achieve a therapeutic effect in Dravet syndrome. Achieving a therapeutic effect means that the therapeutic treatment results at least in an amelioration of the patient's condition in some way. This is in particular the case if not treating the disease has irreversible consequences. If, however, it is not credible that fenfluramine monotherapy lowers the number of epileptic seizures (or other potentially catastrophic events, such as life threatening status epilepticus) in comparison to other established treatments, a relative worsening of the patient's condition has to be expected, since monotherapy means that no additional treatment is permitted.

34. The board therefore cannot recognise any legal or technical errors in decision T 1779/21.

Conclusion

35. From the technical teaching of the application as filed, even taking into account the prior art, it was not credible that fenfluramine achieved a therapeutic effect in Dravet syndrome patients when given as a monotherapy. In line with decision G 2/21, the board has not taken the post-published data (document D3) into account (see point 77 of the Reasons).

36. The claimed invention is not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. The ground of opposition under Article 100(b) EPC therefore prejudices maintenance of the patent.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairwoman:

C. Spira M. Pregetter

Decision electronically authenticated