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Datasheet for the decision of 7 July 2020

Case Number: T 0099/19 - 3.3.01

Application Number: 04819152.2

Publication Number: 1708690

IPC: A61P3/00, A61K31/519, C07D475/04

Language of the proceedings: EN

Title of invention:
TREATMENT OF PHENYLKETONURIA WITH BH4

Patent Proprietor:
BioMarin Pharmaceutical Inc.

Opponents:
Alfred E. Tiefenbacher (GmbH & Co. KG)
DIPHARMA S.A.
Teva Pharmaceutical Industries Ltd

Headword:
BH4 for Phenylketonuria / BIOMARIN

Relevant legal provisions:
EPC Art. 56
RPBA Art. 12(4)

Keyword:
Inventive step - all requests (no) - technical prejudice or disincentive in the art (no)

Decisions cited:
G 0002/88, G 0006/88, T 0609/02, T 0895/13

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Case Number: T 0099/19 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 7 July 2020

Appellant: (Patent Proprietor)	BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949 (US)
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Respondent: (Opponent 1)	Alfred E. Tiefenbacher (GmbH & Co. KG) Van-der-Smissen-Straße 1 22767 Hamburg (DE)
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Respondent: (Opponent 2)	DIPHARMA S.A. Piazza Col. C Bernasconi 5 6830 Chiasso (CH)
Respondent: (Opponent 3)	Teva Pharmaceutical Industries Ltd 5 Basel Street P.O. Box 3190 49131 Petah Tiqva (IL)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 12 November 2018 revoking European patent No. 1708690 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman A. Lindner
Members: S. Albrecht
R. Romandini

Summary of Facts and Submissions

I. European patent No. 1 708 690 ("the patent") was granted on the basis of a set of ten claims.

Claim 1 as granted reads as follows:

"1. Tetrahydrobiopterin (BH4), or optionally a salt form thereof, for use in the treatment of a subject with phenylketonuria (PKU), wherein the BH4 is to be administered orally once daily at a daily dose of 5 mg/kg to 30 mg/kg, and wherein the BH4 is to be administered in combination with a protein restricted diet."

II. Three oppositions were filed against the patent, the opponents requesting revocation of the patent in its entirety on the grounds of lack of novelty and inventive step (Articles 54 and 56 EPC and Article 100(a) EPC), lack of sufficiency of disclosure (Article 100(b) EPC) and added subject-matter (Article 100(c) EPC).

III. The evidence filed during the opposition proceedings included the following:

D2: Blau et al., Chapter 78 "Disorders of Tetrahydrobiopterin and Related Biogenic Amines", 2001, pages 1725 to 1776
D3: Declaration of Dr Emil Kakkis dated 25 July 2008
D7: Steinfeld et al., Amino Acids, 2003, vol. 25, pages 63 to 68
D8: Hennermann et al., J. Inherit. Metab. Dis., 2002, vol. 25, Suppl.1, abstract 041-P
D10: Package insert, Biopten® Granules 2.5% Sapropterin

hydrochloride, 2003

D17: Kure et al., J Pediatr 1999, vol.135, pages 375 to 378

D21: Spaapen et al., Molecular Genetics and Metabolism, vol. 78, 2003, pages 93 to 99

D22: Spaapen et al., J. Inherit. Metab. Dis., vol. 24, 2001, pages 352 to 358

D32: Cerone et al., Molecular Genetics and Metabolism, vol. 81, 2004, pages 137 to 139

D40: Niederwieser et al., Eur J Pediatr, 1982, vol. 38, pages 110 to 112

D42: Ponzone et al., Eur J Pediatr, 1993, vol. 152, pages 655 to 661

D44: Declaration of Dr Cederbaum dated 18 December 2018 with Exhibits A to C

D45: Declaration of Dr Levy dated 18 December 2008 with Exhibits A to C

D48: Schircks Laboratories, Summary of Product Characteristics "Tetrahydrobiopterin 10 mg /50 mg tablets", 7 January 2004, 17 pages

D49: Declaration of Dr Barbara Burton dated 29 August 2017

D51: Blau et al., chapter 1, Disorders of Phenylalanine and Tetrahydrobiopterin Metabolism, 15 August 2002, pages 89 to 106

IV. The opposition division's decision to revoke the patent was based on the patent as granted as the main request and 12 sets of claims filed as the first to twelfth auxiliary requests in the course of the opposition proceedings.

V. The patent proprietor ("the appellant") lodged an appeal against the opposition division's decision. With its statement setting out the grounds of appeal, the appellant requested that the decision under appeal be

set aside and that the case be remitted to the opposition division for further prosecution on the basis of a set of claims of a main request, i.e. the set of claims of auxiliary request 1 underlying the impugned decision or, alternatively, on the basis of one of the following auxiliary requests:

(a) the first auxiliary request ("auxiliary request 1"), based on the set of claims of the main request and description pages 3 to 31 filed with the statement setting out the grounds of appeal

(b) the set of claims of the second auxiliary request which corresponds to the set of claims of auxiliary request 2 underlying the impugned decision ("auxiliary request 2")

(c) the set of claims of the third auxiliary request filed with the statement setting out the grounds of appeal ("auxiliary request 3")

(d) the set of claims of the fourth auxiliary request filed with the statement setting out the grounds of appeal ("auxiliary request 4")

Claim 1 of the main request and auxiliary request 1 is identical to claim 1 as granted (see point I above).

Claim 1 of auxiliary request 2 reads as follows:

"1. Tetrahydrobiopterin (BH4), or optionally a salt form thereof, for use in the treatment of a subject with BH4-responsive phenylketonuria (PKU), wherein the BH4 is to be administered orally once daily at a daily dose of 5 mg/kg to 30 mg/kg, and wherein the BH4 is to

be administered in combination with a protein restricted diet."

Claim 1 of the auxiliary request 3 reads as follows:

"1. Tetrahydrobiopterin (BH4), or optionally a salt form thereof, for use in the treatment of a subject with phenylketonuria (PKU), wherein the subject has been identified as being responsive to BH4 by a BH4 loading test, wherein the BH4 is to be administered orally once daily at a daily dose of 5 mg/kg to 30 mg/kg, and wherein the BH4 is to be administered in combination with a protein restricted diet."

Claim 1 of auxiliary request 4 reads as follows:

"1. Tetrahydrobiopterin (BH4), or optionally a salt form thereof, for use in the treatment of a subject with classic severe phenylketonuria (PKU), wherein the BH4 is to be administered orally in a single daily dose at a daily dose of 5 mg/kg to 30 mg/kg, and wherein the BH4 is to be administered in combination with a protein-restricted diet, and wherein the combined administration of the protein-restricted diet and BH4 is effective to lower the phenylalanine concentration in the plasma of said subject as compared to said concentration in the absence of said combined administration."

VI. With their replies to the statement setting out the grounds of appeal, opponents 2 and 3 ("respondents 2 and 3") requested that the appeal be dismissed.

Opponent 1 ("respondent 1") did not file a reply to the statement setting out the grounds of appeal.

VII. The parties were summoned to oral proceedings to be held on 7 July 2020 at the premises of the boards of appeal.

VIII. In a communication pursuant to Article 15(1) RPBA 2020 sent on 18 May 2020, the board drew the parties' attention to the points to be discussed during the oral proceedings, addressing, *inter alia,* in point 3.6, the issue of inventive step.

IX. With a letter dated 11 June 2020, respondent 1 informed the board that it would not attend the oral proceedings.

X. Consequently, the oral proceedings were - with the appellant's and respondent 2 and 3's consent - converted into videoconference-based oral proceedings.

XI. Oral proceedings were held by videoconference on 7 July 2020 in the presence of the appellant and respondents 2 and 3. In these proceedings, the appellant stated that it did not have any objections against discussing inventive step of the requests on file. At the end of the oral proceedings, the chairman announced the board's decision.

XII. The appellant's arguments in relation to inventive step and relevant for the present decision can be summarised as follows.

Claim 1 of all requests differed from the closest prior art, D21, in that BH4 was administered once daily to the PKU patient. Based on the experimental data disclosed in example 3 of the patent in suit and D3, the objective technical problem to be solved by the

claimed invention was the provision of a dosage regimen of BH4 for the treatment of PKU that resulted in improved patient compliance without compromising efficacy. The proposed solution - once-daily dosing of BH4 - was not rendered obvious by the cited prior art. In particular, because of the short serum half-life of orally administered BH4 in humans, a prejudice existed in the art against oral once-daily dosing of BH4 in the treatment of PKU. Further disincentives against the claimed dosage regimen in the treatment of PKU were found in prior art documents D7, D17, D21 and D22. As for the remaining documents cited by respondents 2 and 3 in the context of obviousness, these did not contain any pointer towards oral once-daily dosing of BH4 in the treatment of PKU and could therefore not prejudice inventive step of the claimed subject-matter either.

XIII. Respondent 2 and 3's arguments in relation to inventive step and relevant for the present decision can be summarised as follows.

Claim 1 of the main request and auxiliary requests 1 to 3

Claim 1 of these requests differed from the closest prior art, D21, in that BH4 was administered once daily to the PKU patient. In the absence of any comparative data on file vis-à-vis the closest prior art, i.e. other forms of oral daily dosing of BH4, no particular technical effect could be attributed to the distinguishing feature apart from the well-known advantage of providing improved patient convenience. Accordingly, the objective technical problem was to be worded as the provision of a dosage regimen of BH4 for the treatment of PKU that improved patient compliance. The solution proposed in claim 1 would have been obvious since it was common general knowledge that oral

once-daily administration of a medicament improved patient convenience. Contrary to the appellant's allegation, there was neither a prejudice nor a disincentive in the art against oral once-daily dosing of BH4 in the treatment of PKU. Rather, the closest prior art D21 itself but also D7, D17 and D22 showed that the effects of a single dose of BH4 lasted well beyond the serum half-life of orally administered BH4, and hence clearly pointed to the efficacy of oral once-daily dosing of BH4 in the treatment of PKU. Documents D2, D10, D40, D42 and D51 would also have prompted the skilled person to use the claimed dosage regimen of BH4.

Claim 1 of auxiliary request 4

The amendments made to claim 1 of auxiliary request 4 were not suitable to overcome the lack of inventive step observed for claim 1 of the preceding requests in view of the fact that D21 explicitly acknowledged the responsiveness of patients with classic severe PKU to BH4 after an oral single-dose BH4 loading test.

XIV. The parties' final requests as far as relevant for the present decision were as follows.

The appellant requested that the decision under appeal be set aside and that the case be remitted to the opposition division for further prosecution on the basis of the set of claims of the main request or, alternatively, on the basis of auxiliary request 1 or one of the sets of claims of auxiliary requests 2 to 4.

Respondents 2 and 3 requested that the appeal be dismissed.

Respondent 1 did not file any requests in the appeal proceedings.

Reasons for the Decision

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

2. Absence of respondent 1 at the oral proceedings

2.1 As announced in its letter dated 11 June 2020, respondent 1 did not attend the oral proceedings.

2.2 In accordance with Rule 115(2) EPC and Article 15(3) RPBA 2020, the oral proceedings were held without respondent 1. By its decision not to attend the oral proceedings, respondent 1 has chosen not to make any submissions during such proceedings.

The duly summoned respondent 1 has thus to be treated as relying only on its written case.

3. Background to the invention

3.1 Claim 1 of the main request is a purpose-limited product claim drawn up in accordance with Article 54(5) EPC. It relates to tetrahydrobiopterin (BH4) or optionally a salt thereof for use in the treatment of a subject with PKU, wherein the BH4 is to be administered at a specific dosage regimen in combination with a protein-restricted diet.

3.2 PKU is an inherited metabolic disorder that can be subdivided in the following two categories:

(a) mild or moderate PKU, characterised by plasma phenylalanine (Phe) concentrations of 600-1200 µmol/L

(b) classical or severe PKU, manifesting itself in plasma Phe concentrations greater than 1200 µmol/L (see paragraphs [0003] and [0006] of the patent in suit)

3.3 PKU is caused by a deficiency in the liver enzyme phenylalanine hydroxylase (PAH) (see paragraph [0005] of the patent in suit). PAH is the rate-controlling enzyme of Phe homeostasis. In normal, non-PKU subjects, Phe is converted to tyrosine in the liver by PAH requiring BH4 as cofactor (see D21, page 93, left-hand column). This keeps the plasma Phe concentrations low.

3.4 In PKU patients, the situation is different. The following two patient groups can be distinguished.

(a) Patients afflicted with a BH4-responsive form of PKU

These patients possess residual PAH activity. When subjected to a loading dose of BH4, this patient group will respond by a lowering of its blood Phe levels.

(b) Patients suffering from a BH4-non-responsive form of PKU

These patients carry specific mutations in their PAH gene leading to a loss of function of the corresponding enzyme. Accordingly, this latter patient group does not exhibit any residual PAH

activity and therefore will not respond to BH4 by a decrease of their blood Phe levels.

4. Main request - inventive step of claim 1

In view of the fact that the appellant did not have any objections against discussing inventive step of the requests on file (see point XI above), the board saw no reason to remit the case to the opposition division for further prosecution.

Claim construction

4.1 At the oral proceedings, the appellant and respondents 2 and 3 had diverging views on how to interpret the claimed feature "treatment of a subject with phenylketonuria (PKU)". In the appellant's opinion, the subject-matter of claim 1 was limited to the treatment of BH4-responsive PKU patients. Respondents 2 and 3, on the other hand, contended that the claimed patient group also encompassed BH4-non-responsive PKU patients (see item 3.4 above). Therefore, the board has to determine how the feature "treatment of a subject with phenylketonuria (PKU)" must be construed to determine the technical features of the claimed subject-matter for the examination of inventive step.

4.2 According to the case law of the boards of appeal, when assessing claims pertaining to a therapeutic use such as purpose-limited product claims in accordance with Article 54(4) and 54(5) EPC or claims drafted in accordance with the "Swiss-type format", attaining the claimed therapeutic effect is a functional technical feature of the claims (see e.g. decision T 609/02, point 9 of the Reasons and T 895/13, point 5 of the

Reasons in conjunction with G 0002/88 and G 0006/88, Headnote III and points 9 and 9.1 of the Reasons).

4.3 Respondents 2 and 3 had not questioned the validity of the considerations set out in G 2/88 and G 6/88 as such. However, they submitted that each single claim was a new issue of interpretation and, therefore, had to be read in light of the teaching of the patent and the common general knowledge. In the case at hand, the following facts had to be taken into account for determining the meaning of the term "treatment of a subject with phenylketonuria (PKU)":

(a) The lack of efficacy of BH4 observed in some PKU patients was of a fundamental nature in that it was not merely linked to issues such as degree of treatment or patient compliance but instead involved variables inherent to the illness itself (see point 3.4 above).

(b) As explained in paragraph [0222] of the patent, the claimed invention specifically targeted PKU patients who were not responsive to a BH4 loading test of the prior art.

In view of these facts, claim 1 had to be construed as being directed to any type of PKU patient, including BH4-non-responsive PKU patients.

4.4 The board does not agree with the proposed interpretation.

4.4.1 Point 9 of the Reasons of G 2/88 contains the following passage:

"In relation to a claim whose wording clearly defines a new use of a known compound, depending upon its particular wording in the context of the remainder of the patent, the proper interpretation of the claim will normally be such that the attaining of a new technical effect which underlies the new use is a technical feature of the claimed invention. In this connection, and with reference to the discussion in paragraphs 2.1 and 2.2 above, it is necessary to bear in mind the Protocol to Article 69 EPC, as discussed in paragraph 4 above. Thus with such a claim, ***where a particular technical effect which underlies such use is described in the patent, having regard to the Protocol, the proper interpretation of the claim will require that a functional feature should be implied into the claim, as a technical feature****; for example, that the compound actually achieves the particular effect."*

4.4.2 In the next paragraph, the following is, *inter alia*, noted (see 9.1 of the Reasons):

"In other words, when following the method of interpretation of claims set out in the Protocol, what is required in the context of a claim to the "use of a compound A for purpose B" is that such a claim should not be interpreted literally, as only including by way of technical features "the compound" and "the means of realisation of purpose B"; ***it should be interpreted (in appropriate cases) as also including as a technical feature the function of achieving purpose B, (because this is the technical result)****. Such a method of interpretation, in the view of the Enlarged Board, is in accordance with the object and intention of the Protocol to Article 69 EPC."*

4.4.3 At the oral proceedings, respondents 2 and 3 explicitly acknowledged novelty of claim 1 on the basis of the claimed use. According to the patent, the technical effect underlying this use is a beneficial decrease of the patients' plasma Phe levels (see example 1, in particular paragraphs [0200] and [0201]). This effect is further supported by the experimental data of example 3, as evidenced by paragraph [0220] with regard to a single-dose loading test and paragraph [0222] with regard to a seven-day loading test. In both of these tests, a beneficial reduction in the patients' blood Phe levels is observed. Accordingly, these patients are afflicted with a BH4-responsive form of PKU (see point 3.4 above). This does not contradict paragraph [0222] of the patent referred to by respondents 2 and 3 since BH4-responsiveness is defined in this paragraph in a more restrictive manner as a reduction in blood Phe levels of 30% or more.

4.4.4 Against this background, the board concludes that the claimed feature "treatment of a subject with phenylketonuria (PKU)" is to be construed as being limited to PKU patients in whom the claimed therapeutic effect is achieved, that is, BH4-responsive PKU patients, with the terms "responsive" and "responsiveness" being understood to have their broadest reasonable meanings.

The closest prior art

4.5 In agreement with the appellant, the board considers that the oral use of 12 to 15 mg BH4/kg/day divided in three doses for the treatment of PKU constitutes the closest prior art (e.g. page 98, left-hand column, lines 6 to 9 of D21).

4.6 The subject-matter of claim 1 differs from the closest prior art in that BH4 is to be administered once daily. This was not disputed by the appellant.

Objective technical problem and solution

4.7 To formulate the objective technical problem effectively solved by the claimed subject-matter over the closest prior art, the technical effects associated with the distinguishing feature need to be identified.

4.8 The appellant submitted that the claimed dosage regimen of BH4 provided for an effective treatment of PKU over a prolonged period of time, as demonstrated in example 3 of the patent (see paragraphs [0221] and [0222]) and confirmed by D3. The experimental data of D3 clearly showed that no loss of efficacy or other disadvantage was associated with the claimed dosage regimen. Accordingly, the objective technical problem to be solved by the claimed invention was the provision of a dosage regimen of BH4 for the treatment of PKU that resulted in improved patient compliance without compromising efficacy.

4.9 Respondents 2 and 3, on the other hand, argued that there was no evidence on file to support the alleged avoidance of efficacy loss.

4.10 In the board's judgement, the experimental data relied upon by the appellant credibly show that the claimed dosage regimen of BH4 provides for a level of efficacy sufficient to bring about the claimed therapeutic effect in PKU patients. However, it does not support the appellant's contention that this dosage regimen maintains the same level of efficacy as the BH4 dosage regimen of the closest prior art. As correctly argued

by respondents 2 and 3, example 3 of the patent does not contain any comparative data. D3 solely compares the oral once-daily dosing of BH4 with placebo. Accordingly, in the absence of any evidence confirming the alleged avoidance of efficacy loss invoked by the appellant, such an effect remains unsubstantiated and cannot be taken into account for the formulation of the objective technical problem. The latter can only be seen in the provision of a dosage regimen of BH4 in the treatment of PKU that leads to improved patient compliance.

4.11 The proposed solution to this problem is a dosage regimen of BH4 as defined in claim 1, i.e. the once-daily oral administration of BH4 at a daily dose of 5 mg/kg to 30 mg/kg.

Obviousness

4.12 It remains to be established whether the subject-matter of claim 1 is obvious in light of the relevant prior art.

4.13 In this regard, the board observes the following.

At the relevant date of the patent, it was a commonly known general principle that once-daily administration of a drug provides for improved patient compliance compared to multiple daily doses. Accordingly, the skilled person would have applied such a dosage regimen to BH4 in an obvious manner, unless there existed particular reasons leading them to conclude that oral once-daily dosing of BH4 would not be appropriate for achieving the claimed purpose, i.e. the effective treatment of a subject with PKU.

4.14 The appellant contended that a prejudice existed in the art against once-daily oral dosing of BH4 in the treatment of PKU. In particular, it argued that it was generally held and well accepted in the art that, because of its short half-life in humans after oral administration, BH4 had to be administered to PKU patients in more than one dose per day to ensure a sufficient concentration of BH4 in the plasma. In support of the alleged prejudice, the appellant referred to following documents:

(a) expert declarations D3 (see paragraph 7), D44 (see paragraph 5), D45 (see paragraph 5), and D49 (see paragraph 10)

(b) documents D17, D32 and D48

4.15 According to the case law of the boards of appeal, a prejudice in any particular field relates to an opinion or preconceived idea widely or universally held by experts in that field. The existence of such prejudice is normally demonstrated by reference to the literature or encyclopedias published before the priority date. The prejudice must have existed at the priority date; any prejudice which might have developed later is of no concern in the judgement of inventive step (Case Law of the Boards of Appeal", 9th edition 2019, I.D.10.2).

4.16 In the case at hand, the board finds that the expert declarations D3, D44, D45 and D49 relied upon by the appellant merely reflect individual views held by some researchers in the field (including, *inter alia*, one of the inventors, Mr E. Kakkis). Therefore, they are insufficient to demonstrate the existence of a general prejudice as defined above (see point 4.15).

4.17 Documents D32 and D48 cannot serve as evidence for the alleged prejudice at the priority date of the patent either because these disclosures were made available to the public after the priority date of the patent in suit.

4.18 Document D17 is a pre-published scientific article. It contains, *inter alia*, the following sentence (see page 376, middle-column, first full paragraph):

"*Because the half-life of orally administered BH4 in serum was 1.1 and 3.5 hours in rats*[9] *and humans (Suntory Co Ltd, unpublished data), respectively, BH4 was administered again at 24 hours (10 mg/kg body weight) and at 36 and 48 hours (5 mg/kg body weight) to maintain high plasma BH4 levels during the loading test.*"

The results of this administration are reported in figure B of D17 as follows:

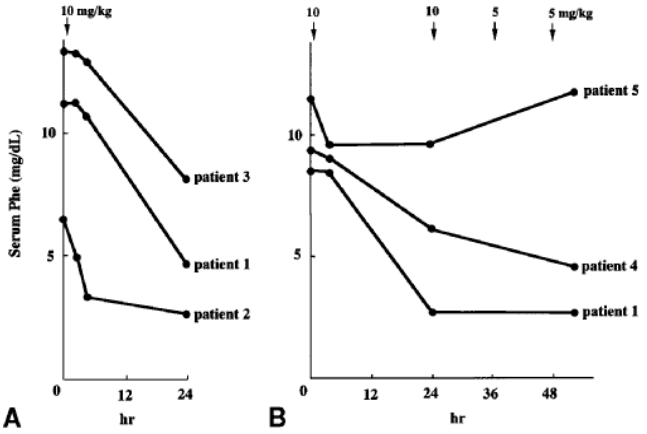

Figure. BH4 loading test in patients with PAH deficiency. **A,** Conventional protocol. *Arrow* indicates time of oral BH4 administration (10 mg/kg body weight). Blood samples were collected to determine serum Phe concentrations at 0, 2, 4, and 24 hours after initiation of loading. Results are for patients 1, 2, and 3 during infancy. **B,** Modified protocol. BH4 was administered orally 4 times. *Arrows* indicate times of BH4 administration at 0 (10 mg/kg), 24 (10 mg/kg), 36 (5 mg/kg), and 48 hours (5 mg/kg). Blood samples were obtained at 0, 4, 24, and 52 hours. These tests were performed in patients 1, 4, and 5 at 1.3, 13, and 8 years of age, respectively.

4.19 In the appellant's opinion, the skilled person would not immediately have concluded from these disclosures that maintained treatment of PAH deficiencies with a once-daily regime (i.e. one administration every 24 hours) of BH4 would suffice (see page 12 of appellant's letter dated 2 April 2020).

4.20 The board does not endorse this view. The aforementioned sentence of D17 cites the short half-life of orally administered BH4 as the reason for administering BH4 twice daily at 36 and 48 hours, respectively. The purpose of this twice-daily dosing of BH4 is to "maintain high plasma BH4 levels during the loading test" (see point 4.18 above), i.e. to achieve a **significant** decrease of serum Phe concentrations in the patients tested. In view of these teachings, the skilled person would have expected once-daily administration of BH4 to result in a lesser decrease of serum Phe concentrations than BH4 administered at two doses per day. However, neither the aforementioned sentence of D17 nor the data reported in figure B of D17 contain any indication which would have led the skilled person to conclude that oral once-daily dosing of BH4 would not be sufficient to treat PAH deficiencies (see point 4.19 above). The data reported in figure B rather demonstrate the opposite. In particular, as pointed out by respondents 2 and 3 in paragraphs (66) and (68) of their letters dated 23 December 2019, an oral loading dose of 10 mg/kg BH4 administered at 0 hours to patients 1 and 4 provides for a significant reduction of their serum Phe levels at 24 hours. The board does not deny that BH4 may take several hours to become effective and that the intermediate administration of 5 mg/kg BH4 at 36 hours may have additional positive effects such as for instance reducing the patients' serum Phe levels even

further. However, in the absence in D17 of any pointer towards the lack of therapeutic benefit of oral once-daily dosing of BH4 in patients with PAH deficiencies, the appellant's argument cannot succeed.

4.21 The board therefore concludes that the alleged prejudice has not been conclusively proven by any of the evidence relied on by the appellant. It follows that the appellant's arguments on this issue must fail.

4.22 In a further line of attack, the appellant submitted that documents D7, D21 and D22 provided a disincentive against oral once-daily dosing of BH4 in the treatment of PKU.

4.23 However, this argument is not convincing either for the following reasons.

With regard to D7

4.24 This document pertains to a study in children with BH4-responsive PAH deficiency. Two of these children (i.e. patients "BS" and "LW") suffered from a mild form of PKU (see page 64, right-hand column, third full paragraph). As a first step, BH4-responsiveness of several patients including patients BS and LW was demonstrated by an oral BH4-loading test (see figure 1). Subsequently, patients BS and LW were subjected to a BH4-optimisation assay consisting of supplementing these patients with 5 or 10 mg/kg of oral BH4 per day in six single doses (see page 64, right-hand column, first full paragraph and figure 2). In this assay, the authors of D7 observed, *inter alia*, a delayed rise in patient BS's blood Phe levels after discontinuing BH4 supplementation (see page 65, right-hand column, the first two lines). Subsequently, patient BS was

successfully treated over a period of seven months with 10 mg/kg of oral BH4 per day administered in three single doses (see figure 3).

4.25 The appellant held that D7, like D17, was mostly concerned with a BH4 loading test; not BH4 therapy. Furthermore, the fact that the authors of this document decided to treat patient BS with three single doses of BH4 per day, despite having observed a 18- to 24-hour delayed rise in blood Phe levels after discontinuing BH4 supplementation in the BH4-optimisation assay, constituted a teaching away from the claimed invention.

4.26 The board does not agree.

4.26.1 As set out in point 4.10 above, the objective that the skilled person would have sought to attain in the case at hand was to provide a dosage regimen of BH4 in the treatment of PKU that leads to improved patient compliance, whilst at the same time retaining a level of efficacy sufficient to bring about the claimed therapeutic benefit in PKU patients.

4.26.2 Neither the aforementioned disclosure of D7 nor any other part of it would have taught or suggested to the skilled person that oral once-daily dosing of BH4 would not be effective in the treatment of PKU. On the contrary, as demonstrated in figure 1, a single oral dose of 20 mg/kg of BH4 gives rise to a significant decrease of serum Phe levels in several patients including patient BS within 8 hours, although orally administered BH4 exhibits a serum half-life of only 3.5 hours in humans (see point 4.18 above). Furthermore, as argued by respondents 2 and 3, loading experiments are clearly aimed at being transposed to treatment regimens (see paragraph (72) and (81) of respondents 2 and 3's

letters of 23 December 2019 as well as D49, paragraph 18). Whilst it is true that figure 1 does not contain any data on the serum Phe levels of patient BS after the initial 8-hour period, this does not allow the conclusion that these values will be above the therapeutic threshold at 24 hours post-administration of BH4.

4.26.3 As regard figure 3 of D7, the data reported demonstrates that an oral three-time-daily dosage regimen of BH4 effectively treats PKU in patient BS. However, it cannot be inferred from this disclosure or any other part of D7 that oral once-daily dosing of BH4 would not be effective at all.

4.26.4 Accordingly, in the absence of substantiating facts in support of the alleged disincentive against once-daily dosing of BH4 in the treatment of PKU, the appellant's argument is unconvincing.

With regard to D21

4.27 D21 discusses the state of the art on BH4-responsive PAH deficiency, including its clinical relevance (see title and chapter "BH4-responsiveness and clinical relevance" on pages 97 to 98). Figure 1 of this document shows the time courses of the plasma Phe concentrations of four patients with mild hyperphenylalanemia in combined Phe/BH4 loading tests up to 21 hours post BH4 load.

4.28 As correctly noted by the appellant, the plasma Phe levels of some of the tested patients increase between 8 and 21 hours post BH4 load. Furthermore, figure 1 does not contain any data on the plasma Phe concentrations beyond the 21-hour time point.

4.29 However, contrary to the appellant's contention, this teaching would not have discouraged the skilled person from trying oral once-daily dosing of BH4 to solve the technical problem as posed. D21 does not contain any information on the basis of which the skilled person would have assumed these patients' plasma Phe concentrations to be above the therapeutic threshold at 24 hours after administration of the BH4 loading dose. D21 rather points to the opposite in that it qualifies all tested patients as complete responders (see page 94, paragraph bridging the left and right-hand column).

4.30 The appellant further argued that D21 was totally silent with respect to any treatment of a BH4-responsive patient. In addition, the following teaching of D21 indicated that no conclusion could be drawn from the disclosure of D21 with regard to the treatment of PKU patients:

"*However, Weglage et al. [27] reported three patients who were responsive after a loading test with BH4 but who did not respond on ongoing BH4 treatment.*"

(See page 98, left-hand column, sentence preceding the first full paragraph.)

4.31 The board does not find these arguments convincing. As pointed out by respondents 2 and 3, D21 discloses (page 97, right-hand column, first full paragraph) that BH4-responsive PKU patients are treatable with BH4 with concomitant relief or withdrawal of the burdensome PKU diet. Various successful treatments of these patients with BH4 are reported in the paragraph bridging pages 97 and 98.

4.32 The sentence referred to by the appellant (see point 4.30 above) would appear to suggest the opposite. However, the negative finding reported concerns only three patients. Furthermore, in the paragraph immediately following this statement, the authors of D21 conclude that "the presented observations **compel** to further clinical studies to assess efficacy, optimal dosage and safety of BH4 supplementation in this group of patients", that is, BH4-responsive PKU patients (see page 98, left-hand column, last sentence; emphasis added by the board). For these reasons, the board considers that no disincentive is given by the aforementioned sentence of D21.

With regard to D22

4.33 D22 reports on four neonates with a BH4-responsive PAH deficiency (see title). Figure 2 shows the courses of the plasma Phe concentrations of three patients (i.e. patients 2 to 4) during a combined Phe/BH4 loading test up to 21 hours after a single oral loading dose of BH4 (i.e. 20 mg/kg, see abstract).

4.34 As pointed out by the appellant, the plasma Phe levels of patients 3 and 4 increase between 8 and 21 hours post BH4 load. Furthermore, figure 2 pertains to a loading test and does not contain any data on the plasma Phe concentrations beyond the 21-hour time point.

4.35 However, the skilled person would not have inferred from this finding that once-daily BH4 dosing would not be effective in the treatment of PKU. As submitted by respondents 2 and 3, the plasma Phe concentration of patients 3 and 4 at 21 hours post BH4 load remains below 100 µmol/l. Hence, a single oral loading dose of

20 mg/kg of BH4 is able to maintain low levels of plasma Phe concentrations over a time period of 21 hours. Furthermore, the board fails to see in the fact that figure 2 does not disclose the plasma Phe concentrations beyond the 21-hour time point any suggestion that once-daily BH4 dosing may not be effective in the treatment of PKU. As pointed out by respondents 2 and 3, D22 rather concludes that the PAH deficiency of patients 2 to 4 is treatable with BH4. In particular, the following is stated in the final paragraph of D22:

"In patients 2 and 4, plasma Phe levels remain well controlled (<350 µmol/L) on protein restriction and a PKU formula. Without protein restriction, Phe concentrations in patient 3 remain mostly below 250 µmol/L. In principle this form of PAH deficiency is treatable with BH4."

Hence, contrary to the appellant's contention, the board is unable to identify any teaching in D22 which would constitute a disincentive against oral once-daily dosing of BH4 in the treatment of PKU.

4.36 Lastly, the appellant's argument that none of the prior art referred to by respondents 2 and 3 in the context of obviousness (i.e. D2, D7, D10, D17, D21, D22, D40, D42 and D51) contained a pointer towards the claimed solution cannot succeed either. For the reasons set out in point 4.13 above, no specific incentive is required to establish obviousness of the claimed subject-matter.

4.37 In conclusion, the board finds that there is no prejudice in the art against oral once-daily dosing of BH4 in the treatment of PKU, nor do any of the prior art documents invoked by the appellant contain a

teaching on the basis of which the skilled person would have been dissuaded from trying oral once-daily dosing of BH4 to solve the technical problem posed. In the absence of such prejudice or disincentive, it would have been obvious for the skilled person in view of their common general knowledge (see point 4.13 above) to select oral once-daily dosing of BH4 to solve the objective technical problem.

4.38 Consequently, the subject-matter of claim 1 of the main request does not involve an inventive step within the meaning of Article 56 EPC.

5. Auxiliary request 1 - inventive step of claim 1

5.1 Claim 1 according to this request is identical to claim 1 of the main request.

5.2 It follows that auxiliary request 1 is not allowable for lack of inventive step pursuant to Article 56 EPC either.

6. Auxiliary request 2 - inventive step of claim 1

6.1 Claim 1 of this request differs from claim 1 of the main request only in that the phenylketonuria is specified to be BH4-responsive.

6.2 However, the board has already interpreted claim 1 of the main request in this way (see point 4.4.4 above). Therefore, the subject-matter of claim 1 of this request also does not involve an inventive step pursuant to Article 56 EPC.

7. Auxiliary request 3

7.1 Admission of this request - Article 12(4) RPBA 2007

7.1.1 The appellant filed this request together with its statement setting out the grounds of appeal.

7.1.2 In the oral proceedings, the board decided to admit this request into the proceedings.

7.1.3 In view of the outcome of the appeal proceedings, a detailed reasoning on the admission of this request is not necessary.

7.2 Inventive step of claim 1 of auxiliary request 3

7.2.1 Claim 1 of this request differs from claim 1 of the main request by inserting the wording "wherein the subject has been identified as being responsive to BH4 by a BH4 loading test," after the term "(PKU),".

7.2.2 As conceded by the appellant in the oral proceedings, this amendment does not have any bearing on the assessment of inventive step given above for the subject-matter of claim 1 of the main request.

7.2.3 Therefore, for the same reasons as set out for claim 1 of the main request, claim 1 of auxiliary request 3 does not meet the requirements of Article 56 EPC and is thus not allowable.

8. Auxiliary request 4 - inventive step of claim 1

8.1 Claim 1 of this request differs from claim 1 of the main request in that:

(a) the PKU is defined as classic severe phenylketonuria

(b) BH4 is administered orally in a single daily dose (instead of orally once daily)

(c) the combined administration of the protein-restricted diet and BH4 is effective to lower the phenylalanine concentration in the plasma of the subject as compared to said concentration in the absence of said combined administration.

8.2 As submitted by respondents 2 and 3 and further noted in point 3.6.1 of the board's communication dated 18 May 2020, table 2 of document D21 reports, *inter alia*, on a treatment trial with BH4 at a daily dose of 20 mg/kg in patients with classic severe PKU (see the last two lines of this table, in particular reference [15] which corresponds to document D8).

8.3 The subject-matter of claim 1 of auxiliary request 4 differs from this disclosure solely in that BH4 is administered in a single daily dose.

8.4 This was not disputed by the appellant. In its view, this difference gave rise to the surprising technical effect of maintaining constant blood Phe levels in the claimed patient group, as demonstrated in figure 1 of D3.

8.5 However, as stated in point 4.10 above, D3 solely compares the once-daily dosing of BH4 with placebo and can therefore not serve to support any particular technical effect over the closest prior art. Consequently, the objective technical problem to be solved by the claimed invention over the closest prior

art is the same as for claim 1 of the main request, that is, the provision of a dosage regimen of BH4 in the treatment of PKU that leads to improved patient compliance.

8.6 In terms of obviousness, the appellant relied on its arguments previously presented with regard to claim 1 of the main request.

8.7 However, as explained above with respect to claim 1 of the main request, there is no general prejudice or disincentive in the art against oral once-daily dosing of BH4 in the treatment of PKU. The same holds true for classic severe PKU. As submitted by respondents 2 and 3, D21 explicitly identifies patients with classic severe PKU as BH4-responsive after an oral single-dose BH4 loading test (see table 2, the three first lines referring to classic PKU, page 97, right-hand column, the bottom half of the first full paragraph).

8.8 It follows that claim 1 of auxiliary request 4 does not involve an inventive step within the meaning of Article 56 EPC either.

9. Since none of the claim requests is allowable, the appeal is to be dismissed.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated