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Datasheet for the decision of 7 December 2023

Case Number: T 0569/21 - 3.3.04

Application Number: 15721912.2

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Language of the proceedings: EN

Title of invention:

PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR MEDIATED DISEASES

Patent Proprietor:

Vertex Pharmaceuticals Incorporated

Opponent:

Generics (U.K.) Limited

Headword:

Combination treatment for cystic fibrosis / VERTEX

Relevant legal provisions:
EPC Art. 54, 56, 83, 123(2), 123(3)
RPBA 2020 Art. 12(3), 12(5), 13(2)

Keyword:
Main request - amendments - added subject-matter (no)
Main request - sufficiency of disclosure (yes)
Main request - novelty (yes)
Inventive step - (yes) - unexpected improvement shown
Objection of lack of inventive step - not substantiated - admitted (no)
Late-filed request - circumstances of appeal case justify admittance (yes)

Decisions cited:
T 0305/87, G 0002/21

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Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0

Case Number: T 0569/21 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 7 December 2023

Appellant: (Opponent)	Generics (U.K.) Limited Building 4, Trident Place Mosquito Way Hatfield Herts AL 10 9UL (GB)
Representative:	Ter Meer Steinmeister & Partner Patentanwälte mbB Nymphenburger Straße 4 80335 München (DE)
Respondent: (Patent Proprietor)	Vertex Pharmaceuticals Incorporated 50 Northern Avenue Boston, MA 02210 (US)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 10 March 2021 concerning maintenance of the European Patent No. 3131582 in amended form**

Composition of the Board:

Chair	M. Pregetter
Members:	S. Albrecht
	R. Romandini

Summary of Facts and Submissions

I. European patent No. 3 131 582 ("the patent") was granted with 22 claims. It is based on European patent application 15721912.2 ("application").

II. Opposition proceedings were based on the grounds for opposition under Article 100(a) EPC for lack of novelty and lack of inventive step and under Article 100(b) and (c) EPC.

III. The documents filed during the opposition and appeal proceedings include the following:

D1: KALYDECO™ (ivacaftor) Tablets US Prescribing Information, August 2012, 1-13

D2 WO 2013/185112 A1

D3 WO 2014/014841 A1

D6 "Remington, The Science and Practice of Pharmacy", 20th edn., A. R. Gennaro et al. (eds.), 2000, 1970

D13 Compilation of nine decisions of the German Federal Court of Justice

D17 R. Rogge, "Gedanken zum Neuheitsbegriff nach geltendem Patentrecht", GRUR, 1996, 931-40

IV. The opposition division decided that the patent as amended according to the patent proprietor's main request, the claims of which had been filed on 16 July 2019, and the invention to which it related met the requirements of the EPC.

Claim 1 of this request reads:

"1. A pharmaceutical composition comprising:
a first spray dried dispersion and a second spray dried dispersion,
wherein the first spray dried dispersion comprises 70 wt% to about 90 wt% of an amorphous form of (R)-1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-N-(1-(2,3-dihydroxypropyl)-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl)cyclopropanecarboxamide (Compound 1) and from about 10 wt% to about 30 wt% of a polymer, wherein the polymer comprises hydroxypropyl methylcellulose, and
wherein the second spray dried dispersion comprises an amorphous form of N-[2,4-bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide (Compound 2);
wherein the pharmaceutical composition is a tablet which comprises about 25 mg to 125 mg of Compound 1 and about 100 mg to 200 mg of Compound 2."

V. In the following, Compound 1 is referred to by its international non-proprietary name "tezacaftor", and Compound 2 is referred to by its international non-proprietary name "ivacaftor".

VI. The opponent ("appellant") lodged an appeal against the opposition division's decision.

VII. The parties were summoned to oral proceedings at the premises of the boards.

VIII. In a communication under Article 15(1) RPBA, the Board drew the parties' attention to the points to be discussed during the oral proceedings.

IX. Subsequently, the Board changed the format of the oral proceedings to a videoconference in accordance with the respondent's request submitted on 12 April 2023.

X. Oral proceedings took place on 7 December 2023 in the presence of both parties. In the course of these proceedings, the patent proprietor ("respondent") filed a further claim request as "new auxiliary request 1". Subsequently, the respondent made this request its main request ("main request") and withdrew the previous main request, i.e. the main request underlying the decision under appeal. At the end of the oral proceedings, the Chair announced the Board's decision.

XI. The set of claims of the main request comprises two independent claims, i.e. claims 1 and 16.

The subject-matter of claim 1 of the main request is identical to the subject-matter of claim 1 of the main request underlying the decision under appeal (see point IV. above) except that the first spray dried dispersion comprising tezacaftor and the second spray dried dispersion comprising ivacaftor must be present in the claimed pharmaceutical composition in the form of a mixture.

Claim 16 of the main request, in turn, reads:

"16. A pharmaceutical composition of any preceding claim for use in a method of treating cystic fibrosis in a patient."

Claim 17 of the main request is worded as a dependent claim of claim 16, and further specifies that the method comprises orally administering the pharmaceutical composition to the patient.

Claim 18 of the main request is worded as a dependent claim of claims 16 and 17, and further specifies that the method comprises administering one tablet once daily.

Claim 19 of the main request is worded as a dependent claim of claims 16 to 18, and further specifies that the method comprises administering one tablet once daily followed by the administration of 150 mg of ivacaftor once daily.

Claims 20 and 21 of the main request are worded as dependent claims of claims 16 to 19, and further specify the patient to be homozygous in the Δ508 CFTR mutation and heterozygous in the Δ508 CFTR mutation, respectively.

XII. The appellant's written and oral submissions relevant to the present decision may be summarised as follows.

(a) Sufficiency of disclosure of the medical uses recited in claims 16 to 21

As submitted by the respondent itself (see paragraphs 8.25 and 8.27 of the reply to the notice of opposition), the skilled person would have expected the ivacaftor-containing spray dried dispersion ("SDD") of the tablets recited in claims 16 to 21 to cause the amorphous tezacaftor contained in these tablets to transition into its less bioavailable, crystalline form. This increase in crystalline tezacaftor created the risk that patients taking the tablets would be exposed to low and ultimately ineffective doses of tezacaftor.

Hence, the respondent itself proved that serious doubts about the suitability of the claimed pharmaceutical composition for the intended medical use (treatment of cystic fibrosis) must have existed at the effective date of the patent.

As a consequence, the invention defined in claims 16 to 21 was not sufficiently disclosed.

(b) Novelty

When concluding that document D2 did not disclose the technical features recited in claim 1 in combination, the opposition division failed to comply with the principles established in the case law of the boards.

In accordance with these principles (see Case Law of the Boards of Appeal of the EPO, 10th edn. 2022, I.C.4.1; decision T 305/87 cited in the EPO Guidelines G-VI, 1), the technical disclosure in a prior-art document must be considered as a whole. The individual sections of a document cannot be considered in isolation from the others but must be seen in their overall context. Hence, pieces of information contained in individual sections of a prior-art document could be combined, provided they were disclosed in the same technical context.

Applying these principles to the case at issue, document D2 disclosed all the technical features of claim 1 in combination and therefore deprived the claimed subject-matter of novelty.

(c) Admittance of the appellant's inventive-step attack starting from document D2

The statement of grounds of appeal contained a very detailed analysis of the disclosure of document D2, albeit for novelty only. No such detailed analysis had been provided for inventive step starting from this same document because it was difficult to provide an analysis of lack of inventive step for a document believed to be novelty-destroying. Moreover, in the absence of any explanation by the Board on why it acknowledged the novelty of the subject-matter of claim 1 over document D2, the Board's reasons for coming to this conclusion could only be speculated on.

(d) Inventive step starting from document D3

Starting from document D3, in particular paragraphs [0023] and [0024], the subject-matter of claim 1 differed from this closest prior art solely in that the SDDs of amorphous tezacaftor and amorphous ivacaftor where formulated into a single tablet.

As explained in the statement of grounds of appeal (see pages 19 and 20, in particular Tables 1 and 2), claim 1 comprised embodiments which did not give rise to the increase in physical stability postulated by the respondent. In consequence, this technical effect could not be taken into account for the formulation of the objective technical problem posed. The latter was therefore to be worded as how to provide an alternative pharmaceutical composition containing tezacaftor and ivacaftor.

The solution to this problem proposed in claim 1 would have been obvious in view of the closest prior art

taken in combination with document D2 and common general knowledge reflected in document D6.

XIII. The respondent's written and oral submissions relevant to the decision may be summarised as follows.

(a) Sufficiency of disclosure of the medical uses recited in claims 16 to 21

The respondent's statements referred to by the appellant did not substantiate that serious doubts existed as to whether the combination of ivacaftor and tezacaftor was suitable for treating cystic fibrosis.

Moreover, even if the disclosure of the prior art would have led the skilled person to have doubts about the biological compatibility of tezacaftor and ivacaftor in combination (which was not conceded), these doubts would vanish when the skilled person took into account the disclosure of the application as filed, particularly the data in the application as filed, which they were permitted to consider in the assessment of sufficiency of disclosure.

(b) Novelty

Document D2 failed to disclose a pharmaceutical composition in the form of a tablet which comprised both the first dried dispersion and the second dried dispersion set out in claim 1. The appellant's line of reasoning amounted to treating document D2 as a reservoir from which features pertaining to different embodiments had been cherry-picked and combined in the absence of any sort of pointer towards such a combination.

(c) Inventive step - admittance of the appellant's inventive-step attack starting from document D2

This attack should not be admitted into the proceedings for lack of substantiation.

Document D2 was very long. Rather than adopting the problem-solution approach and specifying the starting point in this document, the appellant devoted over ten pages of its statement of grounds of appeal to a range of arguments about the validity of the problem-solution approach and why it believed that the opposition division should have allowed the appellant in opposition proceedings to argue inventive step starting from document D2.

(d) Inventive step starting from document D3

The so-called embodiments relied on by the appellant in support of its case that the increase in tezacaftor stability demonstrated in the patent had not been shown over the entire breadth of claim 1 were hypothetical tablet scenarios which upon proper interpretation of this claim would not fall under its scope.

But even if these tablets were deemed to be within the scope of claim 1, there would still be a non-zero stabilising interaction between the tezacaftor and the small amount of ivacaftor present in the layer of the tablet comprising the tezacaftor-containing SDD. The appellant had not provided any evidence or convincing argument which called this stabilising interaction into question.

As a consequence, starting from document D3, the objective technical problem was to provide a tezacaftor

dosage form which had improved stability, was bioavailable, and was able to safely and efficaciously treat cystic fibrosis.

The solution proposed in claim 1 would not have been obvious having regard to the prior art relied on by the appellant.

XIV. The parties' final requests relevant to the decision were as follows.

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

The respondent requested as its main request that the appeal be dismissed and the patent be maintained on the basis of the claims of the main request filed as new auxiliary request 1 during the oral proceedings.

As an auxiliary measure, the respondent requested that the patent be maintained in amended form on the basis of one of the sets of claims of auxiliary requests 1 to 7, all filed on 16 July 2019 or, alternatively, on the basis of one of the sets of claims of auxiliary requests 8 to 15, all filed with the reply to the statement of grounds of appeal.

Reasons for the Decision

1. The appeal is admissible.

Main request filed as new auxiliary request 1 during the oral proceedings before the Board
Admittance (Article 13(2) RPBA)

2. The respondent filed this claim request at the oral proceedings before the Board after the Chair had announced the Board's conclusion that the subject-matter of claim 1 of the previous main request (filed on 16 July 2019) lacked an inventive step.

3. In coming to this conclusion, the Board adopted a claim construction introduced by the appellant for the first time at the oral proceedings.

4. The Board considers these circumstances to constitute exceptional circumstances under Article 13(2) RPBA, justifying the admittance of the main request - which the appellant had not objected to - into the proceedings.

Amendments (Articles 123(2) and (3) EPC)

5. The subject-matter of claim 1 of the main request differs from that of claim 1 of the previous main request in that the first spray dried dispersion ("SDD") and the second SDD must be present in the form of a mixture.

6. As a basis for the amendment made, the respondent referred to paragraphs [0284] and [0293] of the application as filed.

7. The appellant did not raise any objections against the main request under Article 123(2) and (3) EPC.

8. The Board is equally satisfied that the main request fulfils the requirements of Article 123(2) and (3) EPC.

Sufficiency of disclosure of the medical uses recited in claims 16 to 21

9. Claims 16 to 21 are purpose-limited product claims drawn up in accordance with Article 54(5) EPC.

10. They are directed to a pharmaceutical composition in the form of a tablet for use in a method of treating cystic fibrosis in a patient.

10.1 This tablet comprises a mixture of:

(a) a first SDD comprising 70 to about 90 wt% of an amorphous form of tezacaftor and from about 10 to about 30 wt% of a polymer, where the polymer comprises hydroxypropyl methylcellulose ("first SDD")

(b) a second SDD comprising an amorphous form of ivacaftor ("second SDD")

10.2 Claims 16 to 21 further require that this tablet comprise about 25 to 125 mg of ivacaftor and about 100 to 200 mg of tezacaftor.

11. In accordance with the case law of the boards (see Case Law of the Boards of Appeal of the EPO, 10th edn. 2022, in the following "Case Law of the Boards of Appeal", II.C.7.2.1), when assessing claims pertaining to a therapeutic use such as purpose-limited product claims in accordance with Article 54(5) EPC, attaining the claimed therapeutic effect is a functional technical feature of the claims. As a consequence, for the

requirement of sufficiency of disclosure, unless this effect is already known to the skilled person at the effective date of the patent, the patent must disclose the suitability of the claimed product for the claimed therapeutic use.

12. In the case at hand, it was not in dispute that the following facts formed part of the skilled person's knowledge at the earliest priority date of the patent.

(a) Tablets containing 150 mg of ivacaftor are therapeutically effective in the treatment of cystic fibrosis (see document D1, page 1).

(b) Tezacaftor has shown activity against the cystic fibrosis transmembrane conductance regulator *in vitro* (see document D3, page 124).

13. Moreover, as submitted in writing by the respondent (see reply to the statement of grounds of appeal, paragraph 5.14 in conjunction with paragraphs 7.26 to 7.30), the patent contains experimental data showing that at a temperature of 70°C and 75% relative humidity, less than 10% of the amorphous tezacaftor present in a tablet comprising a mixture according to claim 16 transitions to its less bioavailable, crystalline form after more than 80 days (see triangles in Figure 13).

14. In view of these facts and data, the Board is satisfied that the medical uses defined in claims 16 to 21 are sufficiently disclosed.

15. At the oral proceedings, the appellant stated that it maintained its objection of lack of sufficiency of

disclosure raised against the previous main request and did not make any oral submissions on this issue.

16. In writing (see the statement of grounds of appeal, point 2), the appellant referred to statements made by the respondent in the reply to the notice of opposition as proof of the existence of serious doubts concerning the suitability of the tablet claimed in the previous main request for the treatment of cystic fibrosis.

17. The Board does not concur.

17.1 A successful objection based on insufficient disclosure presupposes that there are serious doubts, substantiated by verifiable facts, that the invention is disclosed in a sufficiently clear and complete manner for it to be carried out by a person skilled in the art (see Case Law of the Boards of Appeal, II.C.9).

17.2 In the case at issue, the respondent's statements relied on by the appellant to support its case (see point XII.(a) above) do not include any verifiable facts in support of the appellant's allegation that serious doubts must have existed at the effective date of the patent about the suitability of a pharmaceutical composition according to claims 16 to 21 for the claimed therapeutic application (cystic fibrosis).

17.3 Furthermore, even if, for the sake of argument, the alleged serious doubts did exist in the art at the effective date of the patent, these would have been dispelled by the patent's experimental data discussed in point 13. above.

18. In view of the foregoing considerations, the Board concludes that the appellant's objection of

insufficiency of disclosure does not prejudice the maintenance of the patent as amended according to the main request.

Novelty (Article 54 EPC)

19. In line with the consistent view in the case law of the boards, for an invention to lack novelty, its subject-matter must be directly and unambiguously derivable from the prior art (see Case Law of the Boards of Appeal, I.C.4.1, fourth paragraph).

20. In the case at hand, it was not in dispute that the disclosures of document D2 relied on by the appellant in support of its novelty objection (see statement of grounds of appeal, point 3.1) stem from numerous, separate sections across the entire description of this document. For example, paragraphs [00419], [00595], [001080], [001252], [001261], [001262] and [001346] of document D2 may be cited. Moreover, paragraph [001346] itself discloses a list of distinct embodiments in the context of a pharmaceutical composition comprising "Compound 1" in combination with "Compound 3". Compound 1 is ivacaftor (see paragraph [0002]) of document D2). Compound 3 is defined in document D2 at the same time as the R-enantiomer and the S-enantiomer of 1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-N-(1-(2,3-dihydroxypropyl)-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl)cyclopropanecarboxamide (see chemical structure on the right-hand side of page 119 and paragraph [00595] of document D2 for the R-enantiomer and paragraph [0002] of this document for the S-enantiomer). The aforementioned R-enantiomer ("Compound 3 in the R-configuration") is tezacaftor.

21. In support of its argument that the different disclosures of document D2 relied on could nevertheless be combined, the appellant referred to section I.C.4.1 of Case Law of the Boards of Appeal and decision T 305/87 (see point XII.(b) above).

22. The Board does not concur.

22.1 Section I.C.4.1 of Case Law of the Boards of Appeal outlines the general rules of interpretation of the information content of a prior-art document. It is not concerned with combinations of technical disclosures contained in separate sections of a prior-art document.

22.2 Combinations of this kind are addressed in the next section of Case Law of the Boards of Appeal, i.e. section I.C.4.2.

22.3 This section cites, *inter alia*, the decision referred to by the appellant, i.e. decision T 305/87 (published in OJ EPO 1991, 429). This decision (see point 5.3 of the Reasons) states that when contesting the novelty of a claim comprising combinations of features, it is not permissible to combine separate items belonging to different embodiments described in the same document unless such a combination has been suggested in that document. In other words, when the content of a single prior-art document is considered in isolation when contesting the novelty of a claim, the content must not be treated as a reservoir from which it is permissible to draw features from separate embodiments to artificially create an embodiment which destroys novelty unless the document itself suggests such a combination of features.

22.4 In the case at issue, the appellant has not pointed to any passage in document D2 that suggests combining the multiple disclosures of this document cited by the appellant in support of its novelty objection.

22.5 In the absence of any such suggestion in document D2, the Board concludes that the disclosures of document D2 relied on by the appellant do not directly and unambiguously disclose the technical features of claim 1 in combination.

23. It follows that the appellant's objection under Article 54 EPC does not prejudice the maintenance of the patent on the basis of the set of claims of the main request.

24. For the sake of completeness, the Board notes that the appellant additionally referred to document D13's disclosure relating to the Olanzapin decision of the German Federal Court of Justice (BGH X ZR 65/18) and to document D17 in support of its objection of lack of novelty.

25. However, when asked about these references at the oral proceedings, the appellant stated that it did not require the Board to discuss the aforementioned decision BGH X ZR 65/18 in detail in its written decision. The appellant furthermore expressed its agreement that the Board should follow the established case law of the boards on novelty (see point 19. above). For completeness, the Board emphasises that it is bound to follow the case law of the Boards of Appeal and cannot deviate from it based on the case law of an individual EPC member state.

26. As a consequence, there was no need for the Board to decide on the admittance of documents D13 and D17.

Admittance of the appellant's inventive-step attack starting from document D2

27. Under Article 12(3) RPBA, the statement of grounds of appeal and the reply must contain a party's complete appeal case. Accordingly, they must set out clearly and concisely the reasons why it is requested that the decision under appeal be reversed, amended or upheld, and should expressly specify all the requests, facts, objections, arguments and evidence relied on. Under Article 12(5) RPBA, the boards have discretion not to admit any part of a submission by a party which does not meet the requirements of Article 12(3) RPBA.

28. In the statement of grounds of appeal, the appellant addressed in detail the criteria for the selection of the closest prior art and elaborated on the validity of the problem-solution approach.

29. However, the appellant did not substantiate its inventive-step attack starting from document D2 ("appellant's objection") - neither in writing nor orally - by means of a comprehensible approach. In particular, the appellant's submissions lack a comprehensible problem-solution approach but also do not include any other comprehensible approach either.

29.1 As set out in decision G 2/21 of the Enlarged Board of Appeal (see OJ EPO 2023, 85, point 24 of the Reasons), the boards and the administrative departments of the EPO regularly apply the problem-solution approach in deciding whether a claimed subject-matter involves an inventive step and fulfils the requirements of Article 56 EPC. This approach consists essentially of the

following methodological steps:

"(a) identifying the 'closest prior art';
(b) comparing the subject-matter of the claim at issue with the disclosure of the closest prior art and identifying the difference(s) between both ['step (b)'];
(c) determining the technical effect(s) or result(s) achieved by and linked to these difference(s);
(d) defining the technical problem to be solved as the object of the invention to achieve these effect(s) or result(s); and
(e) examining whether or not a skilled person, having regard to the state of the art within the meaning of Article 54(2) EPC, would have suggested the claimed technical features in order to obtain the results achieved by the claimed invention."

29.2 In the case at issue, the appellant selected document D2 as the closest prior art.

29.3 As submitted by the respondent at the oral proceedings, this is a very long document, with 295 pages of description divided into 1 549 paragraphs. It describes a significant number of different technical teachings and hence many possible points to start from within document D2 for the assessment of inventive step.

29.4 In such a case, step (b) of the problem-solution approach (see point 29.1 above) requires identifying a starting point within document D2. Otherwise, no comparison of the subject-matter of the claim at issue with the disclosure of the closest prior art can be made, and hence no difference(s) between both can be identified ("distinguishing feature(s)").

29.5 In the statement of grounds of appeal, the appellant did not define any such starting point within document D2. Instead, the appellant merely stated that "*[s]tarting from D2, the problem is to provide an alternative treatment for CTFR-related conditions*".

29.6 At the oral proceedings, the appellant stated that all features of claim 1 of the main request were disclosed in document D2 with the exception of tezacaftor, i.e. Compound 3 in the R-configuration. In support of its statement, the appellant relied on its written submissions on novelty of the claimed subject-matter of the previous main request.

29.7 However, as explained in point 20. above, the disclosures of document D2 relied on by the appellant in support of its novelty objection stem from numerous, separate sections across the entire description of this document, one of these sections disclosing a list of distinct embodiments. In such a case, it is incumbent on the appellant to identify a technical teaching or embodiment as the starting point within document D2. However, the appellant did not do so, leaving the respondent and the Board to guess the starting point within document D2 on the basis of which the appellant argued lack of inventive step of the subject-matter of claim 1 of the main request.

29.8 Consequently, the appellant's problem-solution approach is not comprehensible.

29.9 Furthermore, the Board is unable to recognise any other comprehensible approach in the appellant's submissions which could serve as the required substantiation for the appellant's objection.

29.10 As a consequence, the appellant's objection lacks substantiation, contrary to the requirements of Article 12(3) RPBA.

30. The appellant's arguments to justify the aforementioned lack of substantiation (see point XII.(c) above) are not convincing.

30.1 An opponent must always be prepared that an objection made by it may be found unconvincing.

30.2 In the case at hand, the appellant's objection of lack of inventive step based on document D2 served as its fallback position if the opposition division found its novelty objection based on this same document unsuccessful (see point 5 of the decision under appeal).

30.3 This turning out to be the case, the appellant should have argued its entire case on inventive step starting from document D2 at the outset of the appeal proceedings, as stipulated by Article 12(3) RPBA. Hence, the appellant should have identified a starting point in document D2 in the statement of grounds of appeal. However, the appellant failed to do so.

31. Under these circumstances, the Board decided, in the exercise of its discretion under Article 12(5) RPBA, not to admit the appellant's objection into the proceedings.

Inventive step starting from document D3 (Article 56 EPC) as the closest prior art
Starting point(s) within document D3 and difference(s) between the claimed subject-matter and this/these starting point(s)

32. The appellant defined several alternative starting points in document D3, i.e.:

(a) the disclosure in paragraphs [0022] to [0024] of a tablet comprising an SDD comprising tezacaftor in amorphous form and HPMC

(b) tablets exemplified in paragraphs [0026] to [0030] and [0047] to [0051] which each comprise an SDD comprising tezacaftor in amorphous form and HPMCAS

33. It is uncontested that none of the aforementioned tablets referred to as a starting point by the appellant contain an SDD comprising amorphous ivacaftor.

34. Hence, the tablets recited in claim 1 differ from each of these starting points at least in that they include an SDD comprising amorphous ivacaftor. Moreover, this SDD ("ivacaftor-SDD") must take the form of a mixture with the SDD containing amorphous tezacaftor ("tezacaftor-SDD"). This was not contested by the appellant.

Objective technical problem and solution

35. To formulate the objective technical problem effectively solved by the claimed subject-matter over the closest prior art, the technical effect(s) associated with the distinguishing feature(s) need to be identified.

36. The respondent submitted that the distinguishing feature (see point 34. above) increases the physical stability of the amorphous tezacaftor (with respect to crystallisation) contained in the tablets of the closest prior art. In support of its case, the respondent referred to the experimental data in Figures 12 to 14 of the patent and the disclosure in paragraphs [0282] and [0283] of the patent.

37. In the Board's judgement, the experimental data relied on by the respondent credibly show that the distinguishing feature gives rise to the purported increase in physical stability of amorphous tezacaftor.

38. As a consequence, the objective technical problem to be solved by the claimed invention is to increase the physical stability of amorphous tezacaftor (with respect to crystallisation) in the SDD of the tablets of the closest prior art.

39. The proposed solution to this problem is to provide a mixture of this tezacaftor-SDD with an ivacaftor-SDD according to claim 1.

40. The appellant did not dispute the validity of the experimental data disclosed in Figures 12 to 14 of the patent but argued that claim 1 comprised embodiments for which the purported increase in physical stability had not been shown for the distinguishing feature identified in point 34. above.

41. As an example for such embodiments, the appellant referred to tablets in which the ivacaftor-SDD consists of amorphous ivacaftor and a polymer (HPMC or HPMCAS) in a ratio of 1:99, the amount of amorphous ivacaftor

contained in this SDD representing only a small part of the overall amount of ivacaftor present in the tablet (see Table 1 on page 19 of the statement of grounds of appeal; in the following, "tablets according to the Table 1 embodiment").

42. In the appellant's view, if a stabilising effect on amorphous tezacaftor were indeed observed for tablets according to the Table 1 embodiment comprising HPMC in the ivacaftor-SDD, this effect would be caused exclusively or almost exclusively by this HPMC. Moreover, in tablets according to the Table 1 embodiment comprising HPMCAS in the ivacaftor-SDD, this HPMCAS would destabilise the amorphous tezacaftor in the tezacaftor-SDD.

43. The Board does not concur.

43.1 Even if the appellant were correct and claim 1 did include tablets of the aforementioned Table 1 embodiment, claim 1 requires these tablets to contain the ivacaftor-SDD in admixture with the tezacaftor-SDD.

43.2 In consequence, it is credible that the amount of ivacaftor contained in the ivacaftor-SDD, even if small compared to the overall amount present in these tablets, will interact with at least some of the amorphous tezacaftor in the tezacaftor-SDD and stabilise it.

43.3 The mere fact that the high amount of HPMC in the ivacaftor-SDD may stabilise the amorphous tezacaftor in the tezacaftor-SDD to a significantly larger extent than ivacaftor does not, in the absence of any evidence

to the contrary, allow concluding that ivacaftor does not contribute to this stabilisation at all.

43.4 As regards the alleged destabilisation of amorphous tezacaftor in the tezacaftor-SDD owing to the high amount of HPMCAS in the ivacaftor-SDD (see point 42. above), the appellant did not provide any technical facts or evidence to support this claim. Moreover, there is no proof on file that such destabilisation, if any, would make the overall physical stability of amorphous tezacaftor in the tablet equal to or worse than in the closest prior art. Without such evidence, the appellant's argument fails.

44. In a further line of argument, the appellant submitted that when adding the amounts of tezacaftor and the overall amount of HPMC used in a tablet according to the Table 1 embodiment comprising HPMC in the ivacaftor-SDD, the ratio between the amount of amorphous tezacaftor and the overall amount of HPMC in this tablet would be nearly 1:1. Formulation C in Table 1 of page 31 of the reply to the statement of grounds of appeal exhibited almost the same amorphous tezacaftor/HPMC ratio. As shown in this table, formulation C was as stable or as unstable as the formulations disclosed in document D3 comprising a 1:1 mixture of amorphous tezacaftor with HPMC.

45. This line of argument cannot succeed either. Formulation C comprises two SDDs in total, i.e. one SDD consisting of 50 wt% amorphous tezacaftor and 50 wt% HPMC and one SDD comprising ivacaftor (see Table 1 and paragraph 7.19 of the reply to the statement of grounds of appeal). The ratio between amorphous tezacaftor and HPMC in the tezacaftor-containing SDD of this formulation is thus 1:1. By contrast, the ratio

between the amount of amorphous tezacaftor and the amount of HPMC in the tezacaftor-containing SDD of the tablet according to the Table 1 embodiment relied on by the appellant is 9:1 (see Table 2 on page 20 of the statement of grounds of appeal). The ratio of nearly 1:1 referred to by the appellant (see point 44. above) concerns the amount of amorphous tezacaftor and the overall amount of HPMC in the tablet. In view of these discrepancies, the appellant's argument that the tablet according to the Table 1 embodiment relied on by it was as stable or as unstable as the formulations disclosed in document D3 comprising a 1:1 mixture of amorphous tezacaftor with HPMC falls short.

46. Consequently, the objective technical problem (see point 38. above) is considered solved by the solution proposed in claim 1.

Obviousness of the proposed solution

47. The solution proposed in claim 1 would not have been obvious having regard to the state of the art relied on by the appellant.

47.1 As correctly observed by the appellant, document D3 discloses tezacaftor-containing tablets according to the invention described in this document which comprise an additional therapeutic agent. In one embodiment, this additional therapeutic agent is ivacaftor (see paragraph [0033], first and last sentences).

47.2 Document D2 (see paragraph [0002]) describes pharmaceutical compositions of ivacaftor. In one embodiment (see paragraph [001080]), these compositions take the form of a tablet comprising a solid dispersion of amorphous ivacaftor (100 mg). In a further

embodiment (see paragraph [00419] and claim 31 as a dependent claim of claim 21 of document D2), ivacaftor is co-formulated with Compound 3 (see point 20. above), in a single tablet. In paragraph [00419] and claim 21, Compound 3 is represented by a structural formula depicting the S-enantiomer of this compound. However, to the appellant's advantage, the Board will assume that the skilled person would understand the term "Compound 3" in paragraph [00419] and claim 31 to include Compound 3 in the R-configuration, i.e. tezacaftor.

47.3 Document D6 reports the common general knowledge that reducing the number of tablets improves patient compliance.

47.4 However, it remains that the appellant has not pointed to any disclosure in any of the aforementioned prior art from which the skilled person would have inferred that the amorphous ivacaftor-containing SDD disclosed in document D2 could increase the physical stability of amorphous tezacaftor in the tablets of the closest prior art. In the absence of any such disclosure, the skilled person would not have been led to select the ivacaftor-containing SDD disclosed in document D2 and include it in the tablets forming the closest prior art to solve the objective technical problem posed.

48. For these reasons, the Board concludes that the claimed subject-matter involves an inventive step.

Overall conclusion

49. None of the grounds for opposition invoked by the appellant prejudices the maintenance of the patent on the basis of the set of claims of the main request.

50. Accordingly, there is no need for the Board to consider the respondent's lower-ranking auxiliary requests 1 to 15.

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 based on the following documents:

   claims 1 to 21 of the main request submitted during the oral proceedings as new auxiliary request 1; the description and drawings possibly to be adapted thereto.

The Registrar: The Chair:

A. Vottner M. Pregetter

Decision electronically authenticated