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Datasheet for the decision of 26 March 2026

Case Number: T 0593/24 - 3.3.07

Application Number: 15757002.9

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Language of the proceedings: EN

Title of invention:
THERAPEUTIC COMBINATIONS OF A BTK INHIBITOR AND A BCL-2 INHIBITOR

Patent Proprietor:
Acerta Pharma B.V.

Opponent:
STADA Arzneimittel AG

Headword:
Combinations of a BTK inhibitor and a BCL-2 inhibitor/ACERTA

Relevant legal provisions:
RPBA 2020 Art. 13(1)
EPC Art. 83, 56

Keyword:
Admittance of late-filed evidences - (yes)
Sufficiency of disclosure - (yes)
Inventive step - (yes)

Decisions cited:
G 0002/21

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Case Number: T 0593/24 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 26 March 2026

Appellant: (Opponent)	STADA Arzneimittel AG Stadastrasse 2-18 61118 Bad Vilbel (DE)
Representative:	Hamm&Wittkopp Patentanwälte PartmbB Jungfernstieg 38 20354 Hamburg (DE)
Respondent: (Patent Proprietor)	Acerta Pharma B.V. Kloosterstraat 9 5349 AB Oss (NL)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted/ electronically transmitted on 22 February 2024 concerning maintenance of the European Patent No. 3179991 in amended fo rm.**

Composition of the Board:

Chairman	M. Steendijk
Members:	J. Lécaillon
	S. Ruhwinkel

Summary of Facts and Submissions

I. European patent 3 179 991 (hereinafter "the patent") was granted on the basis of 10 claims. The independent claim 1 of the patent as granted related to a pharmaceutical combination comprising (1) a specific B-cell lymphoma 2 (BCL-2) inhibitor or a pharmaceutically acceptable salt thereof, and (2) a specific Bruton's tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer in a human subject.

II. An opposition was filed against the patent on the grounds that its subject-matter lacked inventive step and it was not sufficiently disclosed.

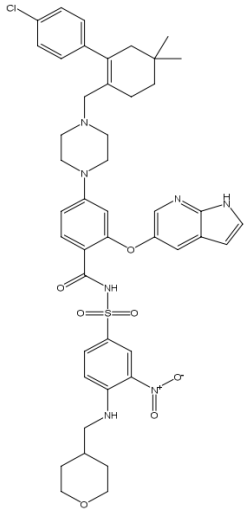
III. The opposition division took the decision that on the basis of the auxiliary request 1, the patent met the requirements of the EPC. This decision was based on an amended main request filed on 22 November 2023 (initially filed as auxiliary request 2 on 30 November 2022) and auxiliary request 1 filed on 22 November 2023 (initially filed as auxiliary request 3 on 30 November 2022).

The independent claims of said auxiliary request 1 can be illustrated as follows:

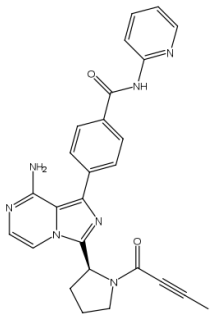
Claim 1 read as follows:

"1. A pharmaceutical combination comprising (1) a B-cell lymphoma 2 (BCL-2) inhibitor or a pharmaceutically acceptable salt thereof, and (2) a Bruton's tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt thereof, for use in the treatment of a B cell

hematological malignancy selected from the group consisting of chronic lymphocytic leukemia (CLL), small lymphocytic leukemia (SLL), non-Hodgkin's lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hodgkin's lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Burkitt's lymphoma, Waldenström's macroglobulinemia (WM), multiple myeloma, and myelofibrosis in a human subject, wherein the BCL-2 inhibitor is a compound of the formula:



and the BTK inhibitor is a compound of the formula:



."

Claim 6 read as follows:

"6. A pharmaceutical composition comprising (1) a BCL-2 inhibitor or a pharmaceutically acceptable salt

thereof; and (2) a BTK inhibitor or a pharmaceutically acceptable salt thereof for use in the treatment of a B cell hematological malignancy selected from the group consisting of chronic lymphocytic leukemia (CLL), small lymphocytic leukemia (SLL), non-Hodgkin's lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hodgkin's lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Burkitt's lymphoma, Waldenström's macroglobulinemia (WM), multiple myeloma, and myelofibrosis in a human subject"
wherein the BCL-2 inhibitor and the BTK inhibitor were defined as in claim 1.

Claim 9 read as follows:

"9. A kit comprising (1) a composition comprising a BCL-2 inhibitor or a pharmaceutically acceptable salt thereof; and (2) a composition comprising a BTK inhibitor or a pharmaceutically acceptable salt thereof, wherein the kit is for co-administration of a BCL-2 inhibitor and a BTK inhibitor, either simultaneously or separately for use in the treatment of a B cell hematological malignancy selected from the group consisting of chronic lymphocytic leukemia (CLL), small lymphocytic leukemia (SLL), non-Hodgkin's lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hodgkin's lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Burkitt's lymphoma, Waldenström's macroglobulinemia (WM), multiple myeloma, and myelofibrosis in a human subject"
wherein the BCL-2 inhibitor and the BTK inhibitor were defined as in claim 1.

In the following, the defined BCL-2 inhibitor is referred to as "venetoclax" and the BTK inhibitor as "acalabrutinib".

IV. The decision of the opposition division, posted on 22 April 2024, cited *inter alia* the following documents:

D1: Axelrod, M. *et al.*, Leukemia, 2014, 28, 407-410, online publication 8 October 2013
D3: Cheah, Chan Yoon *et al.*, Leukemia & Lymphoma, Vol. 54, 9, September 2013, 1859-1861
D4: Cheah, Chan Yoon *et al.*, Future Oncol., Vol. 9, 9, September 2013, 1283-1298
D5: Jones, Jeffrey A. *et al.*, Blood, Vol. 123, 10, 6 March 2014, 1455-1460
D6: WO 2013/010868 A1
D7: Niemann, Cartsen U *et al.*, Poster presentation, Cancer res., Vol. 74, (19_Supplement), 2014, 2624
D9: Tjeerd Barf *et al.*, J Pharmacol Exp Ther, 363, 2017, 240-252
D10: Viralkumar Patel *et al.*, Clin Cancer Res, 23(14), 2017, 1-21
D11: John C. Byrd *et al.*, American Society of Clinical Oncology, 2021, 1-14
D12: Farrukh T. Awan *et al.*, blood advances, 3(9), 2019, 1553-1562
D14: WO 2016/024230 A1 (application as originally filed)
D15: Zhao, Xiaoxian *et al.*, Blood, Vol. 122(21), 2013, 645
D22: Deng, Jing *et al.*, Leukemia, 2017, 31(10), 2075-2084
D23: Kater, Arnon P. *et al.*, NEJM Evid, 2022, 1(7), 1-13

D24: Davids, Matthew S. *et al.*, Lancet Oncol, 2021, 22, 1391-402.

V. The opposition division decided in particular as follows:

(a) The main request contravened Article 123(2) EPC.

(b) Auxiliary request 1 fulfilled the requirements of Article 123(2) EPC.

(c) Auxiliary request 1 met the requirements of Article 83 EPC. The experimental results provided in the patent rendered it credible that acalabrutinib together with venetoclax had some efficacy in the treatment of the claimed B cell hematological malignancies.

(d) Auxiliary request 1 met the requirements of Article 56 EPC. D1, which represented the closest prior art, disclosed a combinatorial screening for drugs to be combined with venetoclax in the treatment of mantle cell lymphoma. The claimed subject-matter differed from the one of D1 in that acalabrutinib was used instead of ibrutinib. This resulted in a reduction of the incidence of diarrhea and skin rash with a synergistic effect. The objective technical problem resided therefore in the provision of an alternative synergistic composition for treating mantle cell lymphoma causing less diarrhea and skin rash. None of the cited prior art documents suggested to replace ibrutinib with acalabrutinib to reduce the incidence of diarrhea or skin rash. A similar approach applied when starting from D3, D4, D5 or D15 as closest prior art documents.

VI. The opponent (appellant) lodged an appeal against the above decision of the opposition division.

VII. With its reply to the appellant's statement setting out the grounds of appeal dated 21 October 2024 the patent proprietor (respondent) defended its case on the basis of a new main request corresponding to the auxiliary request 1 filed on 22 November 2023, and on the basis of auxiliary requests 1 to 5 filed therewith (corresponding to auxiliary requests 2 to 6 filed during the opposition proceedings on 22 November 2023).

The content of the claims of the main request upon which the present decision is based has already been illustrated above (see III.).

VIII. The following items of evidence were filed by the respondent during the appeal proceedings with the letter dated 14 February 2025:

D27: Brown *et al.*,N Engl J Med, Published February 5, 2025, pages 1-15
D28: Supplementary Appendix to Brown *et al.*,N Engl J Med, Published February 5, 2025, pages 1-56

IX. Oral proceedings were held before the Board on 26 March 2026.

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

XI. The respondent requested that the appeal be dismissed, *i.e.* that the patent be maintained based on the main request submitted with the reply to the statement setting out the grounds of appeal, or that the patent

be maintained on the basis of one of the auxiliary requests 1 to 5 submitted with the reply to the statement setting out the grounds of appeal.

The respondent also requested that documents D27 and D28 be admitted into the appeal proceedings. They further requested that the objection of lack of inventive step starting from document D6 not be admitted into the appeal proceedings.

XII. The arguments of the appellant, as far as relevant for the present decision, can be summarised as follows:

(a) The appellant had no objection to the admittance of D27 and D28.

(b) The main request did not meet the requirements of Article 83 EPC. In particular, the data provided in the patent (see table 6) revealed that a synergistic or additive effect was not obtained for all the claimed malignancies. The absence of an additive effect indicated a negative interaction of the active agents. The claimed combination therapy was hence technically meaningless. Furthermore, the claimed therapeutic effect had not been credibly substantiated over the whole breadth of the claims. No experimental data were indeed provided for several claimed B cell malignancies and there was no reason to extrapolate the results provided in the original application or the prior art to said malignancies.

(c) Starting from the closest prior art D1, the distinguishing feature resided in the nature of the BTK inhibitor (acalabrutinib instead of ibrutinib in D1) used in combination with venetoclax. A

synergistic effect had not been substantiated over the whole scope of the claims. Furthermore, to the extent that it had been shown, it was expected. Moreover, the effect of the reduction of the incidence of two particular side effects, namely diarrhea and skin rash, was too specific. The incidence of other relevant adverse events was not reduced. A formulation of the objective technical problem based on the effect on the incidence of diarrhea and skin rash would therefore be unrealistic. During the oral proceedings, the objective technical problem was formulated as the provision of a functioning synergistic combination with improved general safety profile. Replacing ibrutinib in the combination of D1 with acalabrutinib disclosed as a more selective BTK inhibitor in D6 represented an obvious solution to said problem. The reduction of adverse events would be expected in view of the increased selectivity of acalabrutinib and maintenance of synergy was also expected due to a class effect of BTK inhibitors. The subject-matter of claim 1 of the main request did therefore not involve an inventive step.

(d) The claimed subject-matter equally lacked an inventive step starting from D6.

XIII. The arguments of the respondent, as far as relevant for the present decision, can be summarised as follows:

(a) D27 and D28 were to be admitted into the appeal proceedings because they could not have been filed earlier and were relevant evidence in support of the effects of the claimed combination.

(b) The main request met the requirements of Article 83 EPC since the achievement of the claimed treatment was rendered credible by the experimental data of the patent and common general knowledge on the active ingredients.

(c) Starting from the closest prior art D1, the distinguishing feature resided in the nature of the BTK inhibitor (acalabrutinib instead of ibrutinib in D1) used in combination with venetoclax. The associated technical effects compared to the combination of D1 were the maintenance of a synergistic effect and a reduction of the incidence of diarrhea and skin rash. The objective technical problem resided therefore in the provision of an alternative synergistic combination for treating B cell hematological malignancies as defined in claim 1 of the main request and causing less diarrhea and skin rash and having larger therapeutic applicability. The cited prior art, in particular D6, did not suggest to replace ibrutinib in the combination of D1 with acalabrutinib to solve the problem posed. The main request therefore complied with Article 56 EPC.

(d) The objection of lack of inventive step starting from D6 was not to be admitted in the appeal proceedings. This objection had been raised for the first time with the statement of grounds of appeal and the appellant did not provide any reasons justifying this late submission.

Reasons for the Decision

1. Admittance of D27 and D28

1.1 D27 and D28 were filed by the respondent with the letter dated 14 February 2025. As argued by the respondent, these documents were published online on 5 February 2025 and could therefore not have been submitted at an earlier stage. Furthermore, as also stated by the respondent, these documents provide evidence in support of the effects of the claimed combination. They indeed provide results of a clinical study on the administration of the combination of acalabrutinib and venetoclax to patients with untreated chronic lymphocytic leukemia. In particular, data regarding the incidence of diarrhea of grade 3 or more are provided in D28 (see Table S8 on page 37). Notably, the appellant did not object to the admittance of documents D27 and D28.

1.2 Accordingly, D27 and D28 are admitted into the appeal proceedings (Article 13(1) RPBA).

Main request

2. Sufficiency of disclosure

2.1 The claims of the main request relate to a pharmaceutical combination or composition comprising venetoclax and acalabrutinib (or pharmaceutically acceptable salts of these agents) for use in the treatment of a B cell hematological malignancy selected from the specific group of chronic lymphocytic leukemia (CLL), small lymphocytic leukemia (SLL), non-Hodgkin's lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL),

Hodgkin’s lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Burkitt’s lymphoma, Waldenström’s macroglobulinemia (WM), multiple myeloma, and myelofibrosis.

2.2 It is a general principle when assessing compliance with the requirements of Article 83 EPC that, when the therapeutic effect is a functional feature of the claims, the suitability of the claimed product to achieve said effect must be disclosed.

2.3 The experimental data of the patent

2.3.1 As argued by the respondent, table 6 and Figures 95 to 115 of the patent (and of the original application) provide the results of a study assessing the activity of the claimed combination on various malignant cell lines.

2.3.2 The appellant argued that the experimental data provided in said table 6 showed that for many of the tested cell lines no effect beyond the effect already achieved by venetoclax alone was observed at lower concentrations and, for some tested cell lines, no such effect was observed at any of the tested concentrations (results marked with "X" in the table, see in particular the cell lines CA-46, SU-DHL-2 and Raji). These cell lines were representative of non-Hodgkin’s lymphoma, Burkitt’s lymphoma and diffuse large B-cell lymphoma. According to the appellant, this meant that both agents then counteracted. They concluded that the claimed combination therapy would therefore be technically meaningless. During the oral proceedings, the appellant insisted in particular on the fact that there was no evidence that Burkitt's lymphoma could be treated with the claimed combination.

2.3.3 During the oral proceedings, the respondent argued that the absence of effect in Table 6 ("X = no effect") merely meant that the observed effect was below the additive effect but this did not imply a negative interaction. The results shown in Figures 95 to 115, including Figure 103 relating to the cell line CA-46 representative of Burkitt's lymphoma, substantiated that the obtained effect was not below that of venetoclax alone.

2.3.4 The Board shares the view of the opposition division and the respondent that the claimed therapeutic effect is limited to the treatment of B cell hematological malignancies. No additive or synergistic effect is recited in the claims. It follows that, for the purpose of fulfilling the requirement of Article 83 EPC, some level of activity of the claimed combination against said malignancies is sufficient.

The fact that the combination of agents does not lead to an improvement of the response compared to venetoclax alone in some cell lines is therefore irrelevant. Moreover, as underlined by the respondent, a synergistic effect is actually reported at some concentrations for given cell lines of each of the claimed malignancies reported in table 6.

It follows that the data of table 6 of the patent render credible the achievement of the claimed therapeutic effect in the malignancies tested (non-Hodgkin's lymphoma, diffuse large B cell lymphoma (DLBCL), mantle cell lymphoma (MCL) and Burkitt's lymphoma).

2.4 Breadth of the claim

2.4.1 The appellant further contested that the claimed therapeutic effect would be credible over the whole breadth of the claims. No experimental data for cell lines representative of B cell malignancies selected from the group of chronic lymphocytic leukemia, small lymphocytic leukemia, follicular lymphoma, Hodgkin's lymphoma, B-cell acute lymphoblastic leukemia, Waldenström's macroglobulinemia, multiple myeloma, and myelofibrosis were provided. There was furthermore no basis for extrapolating the results provided in the original application or the prior art to these specific malignancies.

2.4.2 The respondent argued that, at the priority date, venetoclax was known to be suitable for the treatment of B cell hematological malignancies, in particular leukemia and lymphoma. Moreover, there was no reason to believe that acalabrutinib would negatively affect this activity, as it was considered to give rise to little drug-drug interactions (see D14, paragraph [01081]).

2.4.3 The Board notes that results have actually been provided in the patent for cell lines representative of follicular lymphoma (see Figure 100 (see Rec-1) and Figure 111 (Pfeiffer)). The above argument of the appellant does therefore not apply to this specific B cell malignancy.

2.4.4 Furthermore, venetoclax is a known BCL-2 inhibitor, which class of compounds is known to be useful in the treatment of B cell hematological malignancies (see *e.g.* D15). The Board also notes that acalabrutinib, a BTK inhibitor, is disclosed as effective in the

treatment of chronic lymphocytic leuklemia (CLL; see D7, D10, D11 and D12).

2.4.5 Moreover, the Board shares the respondent's view that, in view of the results provided in the patent, there is no reason to expect a negative interaction between both active agents to the extent that no effect at all would be achieved (see table 6, Figures 95 to 115 of the patent and paragraph [001081]of the original application, D14).

2.4.6 Finally, the Board observes that, aside from challenging the experimental data provided by the respondent, the appellant has failed to provide any evidence substantiated by verifiable facts that the claimed combination of agents would not exhibit some degree of activity against any remaining malignancy of claim 1.

2.4.7 The Board therefore considers that, in the absence of any evidence of the contrary, the results provided in the patent for some B cell hematological malignancies together with the existing knowledge at the priority date regarding BCL-2 and BTK inhibitors in general, and venetoclax and acalabrutinib in particular (see above 2.4.3 and *e.g.* paragraphs [0009], [0017] of the patent), render the achievement of an effective treatment of the further claimed B cell malignancies credible.

2.5 As a result, the subject-matter of the main request meets the requirements of Article 83 EPC.

3. Inventive step

3.1 Closest prior art and distinguishing feature

3.1.1 D1 was considered a suitable starting point for the assessment of the inventive step by the opposition division and both parties. The Board sees no reason to differ.

3.1.2 D1 discloses a combinatorial screening of drugs combined with the BTK inhibitor ibrutinib in mantle cell lymphoma. The purpose of the authors was to identify drug combinations that block adaptive signaling responses and may provide benefits in cases of acquired BTK mutations (see paragraph bridging pages 407 and 408). Cytotoxic benefits were obtained with agents independent of the B-cell receptor, the target of BTK inhibitors, such as ibrutinib. The BCL-2 inhibitor ABT-199 (which is venetoclax) is listed among the agents which led to synergistic effects in combination with ibrutinib (see page 409, 1st paragraph).

3.1.3 It was undisputed that the claimed subject-matter differs from the one of D1 in that acalabrutinib is used as BTK inhibitor instead of ibrutinib in D1.

3.2 Technical effect and objective technical problem

3.2.1 The respondent argued that the technical effects resulting from this distinguishing feature were *inter alia*:

(i) the maintenance of a synergistic effect (as shown in table 6 of the original

application and further confirmed by the post-published document D22), and

(ii) a reduction of the incidence of diarrhea and skin rash (as substantiated in the original application, see paragraphs [001074] and [001076] and Table 9, Table 14 and paragraph [001113], and further confirmed by the post-published documents D9, D11, D23, D24, D27 and D28).

Effect (i)

3.2.2 During the oral proceedings, the appellant contested that a synergistic effect would be present over the whole scope of the claims.

3.2.3 The Board considers that the effect to be taken into account is the maintenance of a synergistic effect in the treatment of mantle cell lymphoma since the technical effect is to be considered with respect to the closest prior art, *i.e.* D1, which relates to this specific treatment.

3.2.4 The appellant did not dispute the effect of maintenance of a synergistic effect in the treatment of mantle cell lymphoma and rather considered it to be expected due to a class effect.

Effect (ii)

3.2.5 Regarding diarrhea and skin rash, the appellant argued that the assertion that the incidence of these side effects would be linked to the inhibitory activity of the respective BTK inhibitors (ibrutinib or acalabrutinib) on EGFR in original paragraph [001076]

remained unsubstantiated. Furthermore, the data in original table 9 would be limited to ibrutinib and acalabrutinib alone. In the absence of information regarding the potential influence of venetoclax on the occurrence of these side effects, no conclusion could be drawn for the claimed combination (with acalabrutinib) compared to the one of D1 (with ibrutinib).

3.2.6 However, the link between EGFR inhibitory activity and the occurrence of diarrhea and skin rash has been confirmed in D9 (see page 250, left column, second paragraph). Furthermore, the data provided in D11, a clinical study in CLL patients treated with either acalabrutinib or ibrutinib, confirm the reduced incidence of diarrhea of severe grade (grade 3 or higher) for a treatment with acalabrutinib (1,1% of the patients) compared to ibrutinib (4,9% of the patients) (see Table 2 of D11).

Moreover, the data provided in D27 and D28 relating to a clinical study in CLL patients treated with acalabrutinib combined with venetoclax show that diarrhea of grade 3 or more occurs in 1,7% of the patients. In comparison, the data provided in D23, a clinical study in CLL patients treated with ibrutinib combined with venetoclax show that diarrhea of grade 3 or more occurs in 10,4% of the patients. Even if these data are not directly comparable as they originate from different studies, they still confirm that the effect reported in the application and shown in D11 for the individual BTK inhibitors is also observed for combinations of the respective BTK inhibitors with venetoclax. These conclusions are further supported by D24 (see Table 2 page 1399) when taken in comparison with D23.

In this context, the Board agrees with the respondent that the post-published data provided in D11, D24, D27 and D28 may be taken into account in line with G 2/21 since the effect shown was already disclosed and explained for the claimed combination in the original application (D14, see *e.g.* paragraphs [001076], [001112], [001113] and [001139]).

3.2.7 Furthermore, the appellant brought forward that this effect of reduction of the incidence of specific adverse effects was not related to the actual purpose of the invention and was not shown as resulting from the claimed combination. The appellant therefore considered that this effect should not be included in the formulation of the objective technical problem.

This argument is not convincing. The distinguishing feature is the nature of the BTK inhibitor used in the combination therapy, not the combination therapy as such. As detailed above (see 3.2.6, 2nd paragraph), the Board is of the opinion that a reduction of the incidence of diarrhea of grade 3 or more and skin rash has been made credible for this distinguishing feature, including in the context of the combination. Moreover, contrary to the appellant's opinion, the incidence of adverse events induced by a given medical treatment is necessarily directly related to said medical treatment, *i.e.* the purpose of the claimed invention in the present case. According to the problem solution approach, this technical effect is therefore to be taken into account in the formulation of the problem.

3.2.8 The appellant also mentioned that diarrhea, despite having reduced incidence with acalabrutinib, remained a major side-effect of the claimed combination (see D12,

Abstract). This argument does however not undermine the observed effect. As argued by both the respondent and the appellant, diarrhea was the most prominent adverse event in therapies with ibrutinib. A reduction thereof, even if it does not amount to a complete suppression, still represents an advantageous effect.

3.2.9 Finally, during the oral proceedings, the appellant argued that considering only the reduction of the incidence of diarrhea and skin rash without taking into account the occurrence of other known side effects would be too specific and result in the formulation of an unrealistic objective technical problem. According to the appellant, the skilled person would not target specifically only these adverse events but would aim at a reduction of adverse effects in general. The appellant asserted that some other adverse events were actually shown to have increased incidence. They referred to the incidence of headache as well as confusion and fatigue as revealed in D12, page 1557, Figure 2.

The Board considers that not all patients will suffer from all adverse events. Hence, a reduction of even only one particular adverse event represents a benefit for those patients suffering therefrom.

Furthermore, as argued by the respondent, according to Figure 2 of D12, only recurrence of confusion and fatigue that led to ibrutinib intolerance increased from grade 1 to grade 2. Figure 2 of D12 does not show any increase in the incidence of other adverse events. Finally, as also mentioned by the respondent, occurrence of severe headache (*i.e.* Grade 3 or more) remains low in the treatment with the combination of acalabrutinib and venetoclax (see D27, page 7, right

column, first full paragraph, first sentence in combination with Table S8, page 37 of D28). The results referred to by the appellant therefore do not support the conclusion that the replacement of ibrutinib with acalabrutinib would not be advantageous in terms of overall incidence of adverse events.

3.2.10 Accordingly, the Board considers that, starting from the combination of ibrutinib and venetoclax of D1, the objective technical problem may be formulated as the provision of an alternative combination for treating B cell malignancies, including treating mantle cell lymphoma with maintained synergistic effect, and causing less diarrhea and skin rash.

3.3 Non-Obviousness

3.3.1 The appellant considered that the skilled person would have replaced ibrutinib in the combination of D1 with acalabrutinib in view of D6.

3.3.2 The Board observes that D6 discloses among other compounds, acalabrutinib (see example 6). It is reported as being a highly efficacious BTK inhibitor (see table 1 on page 94) with high selectivity over other kinases (see tables 2 to 5 on pages 95-98). However, as argued by the respondent, D6 does not provide any indication regarding the interaction of acalabrutinib with EGFR, let alone the incidence of diarrhea and skin rash upon treatment with acalabrutinib.

3.3.3 The appellant brought forward that D6 generally mentioned the advantage of increasing selectivity over kinases of the Src-family in terms of reduction of severe adverse effects (see page 2 lines 32 to 33).

This does however not provide any direct and clear suggestion that acalabrutinib would reduce specifically the incidence of diarrhea and skin rash compared to ibrutinib, even taking into account the known SRC-dependent phosphorylation of EGFR mentioned by the appellant.

3.3.4 Hence, the reduction of the incidence of diarrhea and skin rash following the replacement of ibrutinib with acalabrutinib in the combination of D1 was not obvious in view of D6.

3.4 Thus, the subject-matter of claim 1 of the main request involves an inventive step starting from document D1.

3.5 Objection starting from D6

3.5.1 In their statement setting out the grounds of appeal, the appellant assessed inventive step from D1 as well as D6 as closest prior art. The respondent requested that the objection starting from D6 not be admitted into the appeal proceedings.

3.5.2 As argued by the respondent, this objection has been raised for the very first time with the statement of grounds of appeal and therefore represents an amendment to the appellant's case (Article 12(4), 1st paragraph, RPBA). As also brought forward by the respondent, the appellant did not provide any reasons in support of this amendment, contrary to the requirements of Article 12(4), 2nd paragraph, RPBA.

3.5.3 Furthermore, this objection does not represent a response to the impugned decision, which only considered D1 as well as D3, D4, D5 and D15 as starting

points for the assessment of inventive step in line with the submissions of the parties during the opposition proceedings. Moreover, D6 was filed by the appellant themselves with their notice of opposition at the outset of the opposition proceedings.

3.5.4 Hence, in its communication pursuant to Article 15(1) RPBA (see sections 3.2 and 3.3), the Board expressed the preliminary opinion that the inventive step attack starting from document D6 should have been raised in the opposition proceedings and that this objection should not be admitted into the appeal proceedings (Article 12(6), 2nd paragraph, RPBA).

3.5.5 In response to the Board's preliminary opinion on the admittance of the objection, the appellant referred during the oral proceedings to its written submission on the issue. The Board therefore confirmed its preliminary opinion.

3.5.6 Thus, the inventive step attack starting from document D6 is not admitted into the appeal proceedings (Article 12(6), 2nd paragraph, RPBA).

3.6 Consequently, the main request complies with the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos M. Steendijk

Decision electronically authenticated