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Datasheet for the decision of 22 January 2026

Case Number: T 0432/24 - 3.3.07

Application Number: 11740764.3

Publication Number: 2593090

IPC: A61K9/20, A61K9/28, A61K31/47

Language of the proceedings: EN

Title of invention:
C-MET MODULATOR PHARMACEUTICAL COMPOSITIONS

Patent Proprietor:
Exelixis, Inc.

Opponents:
STADA Arzneimittel AG
Teva Pharmaceutical Industries Ltd
Generics (U.K.) Limited

Headword:
C-Met modulator / EXELIXIS

Relevant legal provisions:
RPBA 2020 Art. 12(4), 12(3)
EPC Art. 123(2), 83, 56

Keyword:
Admittance of late-filed items of evidence - yes
Amendments - allowable (yes)
Statement of grounds of appeal - reasons set out clearly and concisely (no)
Sufficiency of disclosure - (yes)
Inventive step - (yes)

Decisions cited:
G 0002/10, G 0002/21, T 1121/17, T 0116/18, T 2046/21

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Case Number: T 0432/24 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 22 January 2026

Appellant: (Opponent 1)	STADA Arzneimittel AG Stadastrasse 2-18 61118 Bad Vilbel (DE)
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Appellant: (Opponent 2)	Teva Pharmaceutical Industries Ltd 124 Dvora HaNevi'a St. 6944020 Tel Aviv (IL)
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Appellant: (Opponent 3)	Generics (U.K.) Limited Building 4, Trident Place Mosquito Way Hatfield Hertfordshire AL10 9UL (GB)
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Respondent: (Patent Proprietor)	Exelixis, Inc. 1851 Harbor Bay Parkway Alameda, CA 94502 (US)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)

Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 1 February 2024 rejecting the opposition filed against European patent No. 2593090 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman A. Usuelli
Members: J. Lécaillon
A. Jimenez

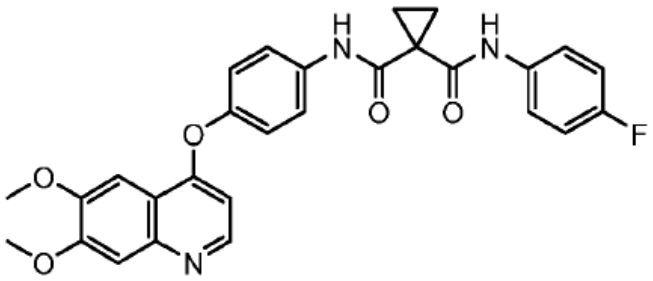
Summary of Facts and Submissions

I. European patent 2 593 090 (hereinafter "the patent") was granted on the basis of 13 claims. The independent product claim of the patent as granted read as follows:

"1. A tablet pharmaceutical composition comprising:

30-32 percent by weight of Compound I, malate salt;
38-40 percent by weight of microcrystalline cellulose;
18-22 percent by weight of lactose;
2-4 percent by weight of hydroxypropyl cellulose;
4-8 percent by weight of croscarmellose sodium;
0.2-0.6 percent by weight of colloidal silicon dioxide; and
0.5-1 percent by weight of magnesium stearate;

wherein Compound I is:



."

II. Three oppositions were filed against the patent on the grounds that its subject-matter lacked inventive step, it was not sufficiently disclosed and it extended beyond the content of the application as originally filed.

III. The opposition division took the decision to reject the oppositions.

IV. The decision of the opposition division, posted on 1 February 2024, cited *inter alia* the following documents:

D2: WO 2010/083414 A1
D8: ClinicalTrials. gov archive, History of changes for Study: NCT00704730 (view May 28th, 2010)
D9: ClinicalTrials. gov archive, History of changes for Study: NCT00704288 (view April 7th, 2010)
D12a: Ritschel, W.A. und Bauer-Brandl, A., "Die Tablette - Handbuch der Entwicklung, Herstellung und Qualitätssicherung", 2nd Edition, Volume 7, Chapter 2, pages 67-77, 85-07, 115-130, 143-160
D13a: Handbook of Pharmaceutical Excipients, 2009, 6th Edition, pages 129-133, 185-188, 206-208, 317-322, 359-361, 404-407
D16: Encyclopedia of Pharmaceutical Technology, Third Edition, Volume 1, 2007, edited by James Swarbrick, pages 3641-3672
D18: Pharmaceutics - The Science of Dosage Form Design, Second Edition, 2006, edited by M. E. Aulton, Chapter 27, pages 398-410
D19: Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products, https://www.fda.gov/media/71707/download
D20: Pharmaceutics - The Science of Dosage Form Design, Second Edition, 2006, edited by M. E. Aulton, Chapter 8, pages 116-141
D25: Submission dated 12 January 2018 during examination proceedings of EP 3 692 983
D29: Experimental report from Exelixis "Document D30"
D30: Experimental report from Exelixis "Document D31"

D31: Pharmazeutische Technologie, Kurt H. Bauer, Karl-Heinz Frömming, Clau Führer, 5th Edition, 1997, pages 437-439
D32: Declaration of Khalid Shah dated 1 August 2016

V. The opposition division decided in particular as follows:

(a) The subject-matter of the granted claims met the requirement of Article 123(2) EPC. In particular the subject-matter of granted claim 1 was disclosed in original claim 4 and the original description.

(b) The granted subject-matter was sufficiently disclosed.

(c) None of the priority dates was validly claimed. As a consequence, D2 formed part of the prior art relevant for the assessment of inventive step.

(d) The subject-matter of the granted claims involved an inventive step starting from D2 as well as D8 or D9 as closest prior art documents.

VI. The opponents 1 to 3 (appellants 1 to 3) lodged an appeal against the above decision of the opposition division.

VII. With their reply to the appellants' statements of grounds of appeal the patent proprietor (respondent) defended their case on the basis of the patent as granted as the main request, and on the basis of auxiliary requests 1 to 50 filed with the reply to the statements of grounds of appeal (hereinafter "reply to the appeals").

The content of the claims upon which the present decision is based can be illustrated as follows:

Granted claim 1 was already recited above (see I.).

Granted claims 6 and 7 read as follows:
"6. The tablet pharmaceutical composition of claim 5, wherein the film coating comprises hypromellose, titanium oxide, triacetin, and iron oxide yellow."
"7. The tablet pharmaceutical composition of any of claims 1-6, wherein the composition contains from 20 to 100 mg of Compound I."

Granted claims 2 to 5 and 8 to 13 are either dependent product claims (claims 2 to 5 and 8) or medical use and Swiss-type claims (claims 9 to 13) all referring to the product of claim 1.

VIII. The following items of evidence were filed by appellant 1 (HW17 renumbered D36) and appellant 3 (D34-D35) with their respective statements of grounds of appeal:

D34: Remington, The Science and Practice of Pharmacy, 20th Edition, (2000), 858-893
D35: Bacher *et al.*, International Journal of Pharmaceutics, 358, (2008), 69-74
D36: Developing Solid Oral Dosage Forms: Pharmaceutical Theory and Practice, (2009), Chapter 6: Excipient Compatibility, 125-145

IX. With the letter dated 12 December 2025, appellant 1 withdrew their request for oral proceedings and indicated that they would not attend the oral proceedings.

X. Oral proceedings were held before the Board on 22 January 2026.

XI. All the appellants requested that the decision under appeal be set aside and the patent be revoked. Appellant 3 further requested that documents D34 and D35 be admitted into the appeal proceedings.

XII. The respondent requested that the appeals be dismissed, *i.e.* that the patent be maintained as granted (main request), or that the patent be maintained on the basis of one of auxiliary requests 1 to 50 filed with the reply to the statements setting out the grounds of appeal.

They further requested that documents D34 to D36 and the arguments based thereupon not be admitted into the appeal proceedings.

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

(a) Admittance of items of evidence and related arguments

D34 to D36 were to be admitted into the appeal proceedings. They were filed with the statements of grounds of appeal in direct response to the impugned decision.

(b) Amendments

Granted claim 1 did not meet the requirements of Article 123(2) EPC because:
- the claimed features were not originally disclosed in combination,

- the absence of the reference to the directly compressible formulation for the definition of the relative amounts of ingredients resulted in the inclusion of subject-matter not originally disclosed, and
- the omission of the function of each excipient, in particular of microcrystalline cellulose (MCC), broadened the claimed subject-matter compared to the original disclosure.

Granted claims 6 and 7 infringed Article 123(2) EPC due to their dependency on granted claim 1 and because:

- original paragraph [0061] did not disclose the subject-matter of claim 6, and
- a selection within a list from original paragraph [0066] had to be performed to arrive at the subject-matter of claim 7.

Granted claims 3 to 5 and 8 to 13 did not fulfil the requirements of Article 123(2) EPC in view of their reference to granted claim 1.

(c) Sufficiency of disclosure

According to appellant 3, it was not credible that cabozantinib was effective in the treatment of each and every type of cancer, in particular cancers known to be difficult to treat such as pancreatic cancer and non small-cell lung cancer (granted claims 9 to 13). Moreover, no safe treatment would be ensured over the whole scope of the claims due to the lack of definition of cabozantinib dose. Accordingly, the subject-matter of the granted claims was not sufficiently disclosed.

(d) Inventive step

D2 represented a suitable starting point for the assessment of inventive step. The claimed subject-matter differed from D2 in (i) the nature and specific combination of excipients and (ii) the specific relative amounts of active ingredient and excipients. The alleged technical effect of desirable long-term storage stability substantiated by the post-published data provided in D25/D29 and D30 was not to be taken into account according to G 2/21. This technical effect was neither encompassed nor embodied by the original application. Furthermore, even if it would be taken into account, the experimental data provided in D25/D29 and D30 did not appropriately substantiate that the technical effect was achieved by the distinguishing feature, let alone over the whole scope claimed. The objective technical problem resided therefore in the provision of an alternative or suitable pharmaceutical composition comprising cabozantinib malate. The selection of commonly known excipients for the preparation of tablets represented an obvious solution thereto. Even if the objective technical problem would be formulated in a more ambitious way taking into account the technical effect alleged by the respondent, the skilled person would still have arrived at the present solution by performing routine excipients compatibility studies (as disclosed in D16, D20 and D19). Accordingly, the subject-matter of granted claim 1 did not involve an inventive step starting from D2. According to appellant 3, the same conclusion applied starting from D8 or D9 as closest prior art documents.

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

(a) Admittance of items of evidence and related arguments

D34 to D36 were not to be admitted into the appeal proceedings since they should have already been filed during the opposition proceedings.

(b) Amendments

The granted claims met the requirements of Article 123(2) EPC. The subject-matter of granted claim 1 was disclosed in claim 4 and paragraph [0063] of the original application together with original claims 7, 12 and 22 and original paragraphs [0008], [0026], [0051], [0053], [0055], [0056] and [0060]. Furthermore, original claim 1 provided a pointer to the combination of the claimed features. The subject-matter of claims 2 to 13 was also disclosed in the original application.

(c) Sufficiency of disclosure

The subject-matter of the granted claims was sufficiently disclosed. In particular, the known activity of cabozantinib on protein kinases pathway rendered an activity against cancer credible.

(d) Inventive step

D2 represented the closest prior art. The claimed subject-matter differed from D2 in (i) the nature and specific combination of excipients and (ii) the specific relative amounts of active ingredient and excipients. The specific combination of excipients

claimed resulted in the achievement of a desirable long-term storage stability, as substantiated by the post-published data provided in D25/D29 and D30. This technical effect was to be taken into account according to G 2/21. The objective technical problem resided therefore in the provision of a pharmaceutical composition of cabozantinib malate which exhibited desirable long-term storage stability. None of the cited prior art provided any indication that the selection of the present excipients in the claimed amounts would allow to solve the problem posed. Accordingly, the subject-matter of the granted claims involved an inventive step.

Reasons for the Decision

1. Admittance of items of evidence and related arguments

1.1 D34 to D36 were filed by appellant 1 (D36) and appellant 3 (D34-D35) with their respective statements of grounds of appeal. The respondent requested that D34 to D36 and the related arguments not be admitted into the appeal proceedings because they should already have been filed during the opposition proceedings (Article 12(6) RPBA).

1.2 The Board observes that D34 to D36 correspond to excerpts of text books (D34 and D36) and a review (D35) on the preparation of pharmaceutical formulations (preparation of tablets, D34 and D35, and selection of excipients, D36). These documents therefore represent evidence of common general knowledge in the field of the invention.

1.3 Moreover, D34 and D35 were filed by appellant 3 to support the argument that the properties of tablets obtained by wet or dry granulations or direct compression may differ, so that the resolution of the objective technical problem over the whole scope was further questionable. D36 was filed by appellant 1 to support their arguments that (i) excipients compatibility studies are routine measures in the development of pharmaceutical formulations and that (ii) povidone, crospovidone and stearic acid were known to promote hydrolysis of moisture sensitive drugs, so that the skilled person would have expected the advantageous effect of replacing these excipients by the claimed ones as in D30.

1.4 While the issue of resolution of the technical problem over the whole scope and of the predictability of the degradation of cabozantinib due to hydrolysis had already been discussed in the opposition proceedings (see decision of the opposition division, points 7.3.3.2.4, 7.3.4.2 and 7.3.3.2.2), the Board considers that the specific arguments supported by D34 to D36 were provided in response to the impugned decision and represent further developments of lines of argument already generally raised in the opposition proceedings.

1.5 As a result, D34 to D36 and the related arguments are admitted into the appeal proceedings (Article 12(4) RPBA).

Main request - patent as granted

2. Amendment

2.1 Claim 1

2.1.1 As stated in the impugned decision and argued by the respondent, the Board observes that the various features of granted claim 1 are disclosed in the original application as follows:

(a) a tablet pharmaceutical composition comprising:
30-32 percent by weight of compound I in at least one of the forms disclosed in the original application;
50-70 percent by weight of a filler;
2-4 percent by weight of a binder;
4-8 percent by weight of a disintegrant;
0.2-0.6 percent by weight of a glidant; and
0.5-1 percent by weight of a lubricant
in claims 4 and 22 as well as paragraph [0063],

(b) the formula of compound I in original paragraph [0008],

(c) the compound I being in the form of the malate salt in claim 7 as well as in paragraphs [0023] and [0025]- [0026],

(d) the filler being preferably a mixture of lactose and microcrystalline cellulose (MCC) in claim 12 and paragraph [0050], wherein lactose is present in an amount of 18-22 percent by weight and MCC in an amount of 38-40 percent by weight in paragraph [0051],

(e) the binder being preferably hydroxypropyl cellulose (HPC) in an amount of 2-4 percent in paragraph [0053],

(f) the disintegrant being preferably croscarmellose sodium in an amount of 4-8 percent by weight in paragraph [0055],

(g) the glidant being preferably colloidal silicon dioxide in claim 17 and paragraph [0056] and being preferably present in an amount of 0.2-0.6 percent by weight in paragraph [0057],

(h) the lubricant being preferably magnesium stearate in an amount of 0.5-1.0 percent by weight in paragraph [0060].

Combination of features

2.1.2 In the written proceedings, appellant 2 contested that the subject-matter of original paragraph [0063] could be combined with other separate embodiments and that the claimed combination of said features was originally disclosed in the absence of a pointer thereto.

2.1.3 Contrary to the view of appellant 2, the embodiment disclosed in paragraph [0063] does not define a stand-alone composition which cannot be further defined by combining this embodiment with other ones defining preferred features thereof. Paragraph [0063], while being worded as "in one embodiment", still defines a tablet composition in generic terms covering a bunch of alternative compositions ("compound I in at least one of the forms disclosed herein", and excipients defined merely by their functional class "a filler", "a binder", "a disintegrant", "a glidant", "a lubricant").

The skilled person would therefore directly and unambiguously understand that this embodiment can be further defined more specifically using the various embodiments regarding the form of compound I and the various classes of excipients as specified in the following paragraphs.

Furthermore, the generic tablet composition disclosed in original claims 4 and 22 or original paragraph [0063] already defines the combination of compound I with various classes of excipients. Further restricting the form of compound I and each class of excipients to their respective preferred embodiments does not result in the singling out of a subject-matter not originally disclosed. Furthermore, if any pointer to the present combination of features would be required, the specific composition of original claim 1 contains the combination of specific excipients of granted claim 1 and confirms that the combination of each individually preferred specific excipient represents the preferred combination according to the invention.

2.1.4 The argument of appellant 3 that original claims 7, 12 and 17 were only dependent on claim 4 and could not therefore provide a basis for the combinations of features disclosed therein is not convincing for the same reasons.

Definition in terms of relative amounts

2.1.5 Appellant 2 disputed that a tablet composition with the claimed relative amounts of excipients (expressed in "percent by weight") was originally disclosed because the claimed amounts would originally be defined either (i) by reference to the "direct compressible

formulation" (*i.e.* not to a compressed tablet as in granted claim 1) or (ii) without any clear reference.

2.1.6 It was undisputed that the "percent by weight" values before and immediately after compression were the same. According to appellant 2, the skilled person would however consider a directly compressible composition and a compressed tablet as two different entities. Appellant 2 hence concluded that, according to G 2/10 and the gold standard defined therein, granted claim 1 would not be allowable because it would relate to an entirely new and undisclosed product even if it had the same constituents as the originally disclosed direct compressible formulation.

2.1.7 This argument is not convincing in the present case since the original application directly and unambiguously discloses a tablet composition obtained from said direct compressible formulation (see e.g. original paragraphs [0069] to [0071]) as well as final tablets with the claimed amounts of each class of excipients (see paragraph [0063]).

2.1.8 In this context, during the oral proceedings, appellant 2 argued that further steps may be involved in the provision of the final tablet according to the invention, such as a coating step (see granted claim 5 and original paragraph [0061]). The addition of a coating would modify the weight of the final composition compared to the direct compressible composition. In such a case, amounts defined in percentage by weight would hence vary depending on the reference composition.

2.1.9 The respondent requested that this newly raised argument not be admitted into the appeal proceedings (Article 13(2) RPBA).

2.1.10 The Board observes that this issue regarding the optional coating of the claimed tablet and the potentially associated shift in the definition of the percentage by weight of ingredients represented an amendment to the case of appellant 2. The passage of their statement of grounds of appeal cited by appellant 2 (paragraphs 4.11 to 4.21) did indeed not refer to any shifting of the definition of the weight percentages due to the optional coating step. This argument was hence raised for the first time during the oral proceedings.

Furthermore, appellant 2 did not provide any exceptional circumstances, supported by cogent reasons, that would justify admitting this new argument at such a late stage of the proceedings.

Accordingly, appellant 2's argument related to the consequence of the presence of a coating on the calculation of the weight percentages of the components is not admitted into the proceedings.

Omission of the function of microcrystalline cellulose (MCC)

2.1.11 Both appellants 2 and 3 contended that the omission of the function of MCC in granted claim 1 infringed Article 123(2) EPC. In their view, since MCC could also be used as disintegrant (see original paragraph [0054]) and the original amount of 38-40 percent by weight was defined for a filler, there would be no basis in the original application for a composition containing 38-40

percent by weight of MCC acting as both filler and disintegrant.

2.1.12 The Board disagrees.

As detailed above (see 2.1.1 and 2.1.3), the original application discloses a composition containing *inter alia* 38-40 percent by weight of MCC (which is a filler) and 4-8 percent by weight of croscarmellose sodium (which is a disintegrant), *i.e.* the subject-matter of granted claim 1 is originally disclosed. The fact that excipients may have more than one function, and that MCC is also listed as suitable disintegrant in the present application, does not change this original disclosure. Whether MCC may in practice also act as disintegrant is irrelevant in the context of assessing whether the claimed subject-matter is originally disclosed or not.

2.1.13 During the oral proceedings, appellant 2 further argued that a final tablet in which MCC would be used as a filler would not be structurally identical to one in which MCC would be used as a disintegrant. According to original paragraph [0070], the filler would be entirely contained in the intra-granular portion of the tablet while a disintegrant would be present in both the intra- and extra-granular portions thereof. Since in present claim 1 MCC was not limited to its function as filler, claim 1 encompassed tablets wherein MCC was present as disintegrant and hence in both intra- and extra-granular portion of the tablet.

2.1.14 This argument is not convincing. There is no disclosure in the original application that the filler must always be only in the intra-granular portion of the tablet, nor that the disintegrant has necessarily to be present

in both intra- and extra-granular portion. The disclosure of paragraph [0070] cited by appellant 2 is that of a very specific process for the preparation of one type of composition according to the claims, namely a film coated tablet obtained by wet granulation. It represents only one example of a preparation process of compositions according to the invention and has no limiting effect.

Omission of the function of each excipient

2.1.15 Finally, appellants 2 and 3 objected that the original disclosure (claim 4 and paragraph [0063]) limited the amount of each class of excipients while granted claim 1 only limited the amount of specific excipients. Since granted claim 1 was worded with an open language ("comprising"), the scope of granted claim 1 had been broadened compared to original claim 4 and paragraph [0063].

2.1.16 The Board observes that, as stated in T 1121/17 already referred to by the opposition division, the relevant question for the purpose of Article 123(2) EPC is whether the amendments remained within the limits of what a skilled person would derive directly and unambiguously, using common general knowledge, from the whole of the application as filed ("gold standard" of G 2/10, OJ 2012, 376). An amendment having the effect of broadening the scope of protection of a claim as originally filed does not infringe Article 123(2) EPC if the amended subject-matter derives directly and unambiguously from the whole of the application as filed.

2.1.17 In the present case, the original application provides a general disclosure of "a tablet comprising compound I

and excipients selected from the group consisting of a filler, a binder, a disintegrant, a glidant and a lubricant" without any limitation regarding the amounts of each class of excipients (see *e.g.* original paragraph [0019]). As detailed above (see 2.1.1), each of the specific excipient in the amount claimed in present claim 1 is subsequently disclosed as preferred for each of the corresponding above classes of excipient. Should any basis for the disclosure of an alleged broader subject-matter be required, it is hence provided in the original application, so that Article 123(2) EPC is complied with.

2.1.18 During the oral proceedings, appellants 2 and 3 contested that there was an unambiguous basis for a broader subject-matter in the original application. According to them, the skilled person reading the original application would indeed understand that the general disclosure of paragraph [0019] would be of introductory nature and would have to be understood as further restricted by the subsequent paragraphs, which limit the amounts of each excipients class before specifying specific excipients and their amounts. This would be confirmed by original paragraph [0018] specifying after having listed the various classes of excipients that "each of which are described in greater detail in the following paragraphs".

2.1.19 This argument is not convincing. As argued by the respondent, paragraph [0019] is an independent paragraph provided below its own heading "Compound I Pharmaceutical Composition", which is not necessarily limited by any other specific paragraph of the original description.

2.1.20 Accordingly, the subject-matter of granted claim 1 does not extend beyond the content of the original application.

2.2 Claims 6 and 7

2.2.1 Regarding claims 6 and 7 of the main request, the opposition division considered that:

- the subject-matter of claim 6 was disclosed in original claim 21 in combination with the final sentence of original paragraph [0070], and

- the subject-matter of claim 7 was based on original paragraph [0066] which disclosed the claimed range as the more restricted one amongst converging alternatives.

2.2.2 In their statements setting out the grounds of appeal, appellant 3 objected to claims 6 and 7 merely due to their dependency on claim 1 and appellant 2 repeated their arguments already provided in the opposition proceedings and dealt with in the impugned decision. Appellant 2 considered that paragraph [0061] did not disclose the subject-matter of claim 6 and that the selection of the range of claim 7 was a selection from a list of equal alternatives in paragraph [0066]. These arguments do not address the reasoning provided by the opposition division in the impugned decision (different passage cited for claim 6, argument of converging ranges for claim 7 not responded to).

2.2.3 It follows that, contrary to the requirement of Article 12(3) RPBA, the appellants did not set out clearly and concisely the reasons why the decision of the

opposition division regarding claims 6 and 7 should be reversed.

2.2.4 The function of the Boards of Appeal is not to re-examine the opposition procedure but to review the decision taken by the opposition division. In the absence of arguments against the reasoning of the opposition division with respect to claims 6 and 7, which appears reasonable, the Board considers that the subject-matter of granted claims 6 and 7 fulfils the requirement of Article 123(2) EPC.

2.3 Claims 3 to 5 and 8 to 13

The Board observes that the objection of appellant 3 against claims 3 to 5 and 8 to 13 is only based on their reference to claim 1, so that said objection can be considered as implicitly covered by the one against claim 1 (see Case Law of the Boards of Appeal, 11th Edition, 2025, V.A.3.2.3.d)). Since claim 1 fulfils the requirement of Article 123(2) EPC, the objection of appellant 3 against claims 3 to 5 and 8 to 13 is moot.

2.4 The Board observes that subject-matter of the remaining dependent claim 2 is based on original claim 1 and Table 1 on original page 4. During the oral proceedings, appellant 2 withdrew their objections of added subject-matter for this claim.

2.5 As a result, the ground of opposition under Article 100(c) EPC does not prejudice the maintenance of the patent.

3. Sufficiency of disclosure

3.1 In their statement of grounds of appeal, appellant 3 maintained their objection of lack of sufficiency of disclosure of claims 9 to 13.

3.2 According to appellant 3, the known ability of cabozantinib to regulate the signal transduction pathway of protein kinases would not be sufficient to render credible that cabozantinib would be effective in the treatment of each and every type of cancer (claims 9 to 12). The effectiveness would be particularly doubtful in case of cancers known to be difficult to treat such as pancreatic cancer and non small-cell lung cancer, which are part of the list of claim 13.

3.3 The Board observes that claims 9 to 12 are directed to the treatment of cancer as a general condition. As stated by the opposition division and the respondent, the known activity of cabozantinib on protein kinases pathway renders an activity against cancer credible.

Furthermore, the appellant did not provide any evidence in support of their allegation that this would not apply to some of the cancers claimed in claim 13 such as pancreatic cancer and non small-cell lung cancer.

3.4 Appellant 3 further repeated the argument already provided in the opposition proceedings that no safe treatment would be ensured over the whole scope of the claims. According to appellant 3, since no cabozantinib dose was specified in the claims, doses beyond the maximum tolerated dose of 175 mg daily were covered by the claims.

3.5 The Board notes that the present claims are standard medical use claims and do not define a dosage regimen. Administration of cabozantinib in an ineffective or unsafe manner would not be considered as encompassed by the scope of such claims, which are limited to an effective and safe treatment. Moreover, as argued by appellant 3 himself, the maximum tolerated dose of cabozantinib was known, so that the skilled person would have known from common general knowledge that the administered dose had to be maintained below.

3.6 Consequently, the ground of opposition under Article 100(b) EPC does not prejudice the maintenance of the patent.

4. Inventive step

4.1 Closest prior art

4.1.1 The finding of the opposition division that the priority dates were not validly claimed was not disputed by the respondent. Hence it was undisputed that D2 forms part of the prior art relevant for the assessment of the issue of inventive step. In line with the impugned decision, all the parties considered that D2 represented a suitable starting point for the assessment of inventive step. Appellant 3 further considered that D8 and D9 also represented suitable starting points.

4.1.2 D2 discloses various forms of cabozantinib malate salt and generally discloses pharmaceutical compositions comprising cabozantinib malate as well as the treatment of cancer (see *e.g.* claims 11 to 13 and paragraphs [0004] and [0013]). Suitable excipients for the preparation of solid dosage forms, including tablets

(see list in paragraph [0087]), are disclosed in paragraph [0082] and include *inter alia* lactose, cellulose derivatives, croscarmellose sodium and magnesium stearate. Finally paragraph [0078] indicates that the active ingredient can be present in the composition in an amount of 1 to 99 percent by weight.

4.2 Distinguishing features

4.2.1 In line with the impugned decision, all the parties agree that the claimed tablet differs from the one generally disclosed in D2 in:

- the nature (MCC, hydroxypropyl cellulose and colloidal silicon dioxide are not disclosed in D2) and specific combination of excipients, and
- the specific relative amounts of active ingredient and excipients (not defined in D2).

4.3 Associated technical effect

4.3.1 The respondent considered that the specific combination of excipients provided desirable long-term storage stability of the composition by minimizing the formation of the newly identified degradation product, 6,7-dimethoxy-quinoline-4-ol. The respondent relied on the post-published documents D25/D29 and D30 to substantiate this effect and the fact that it resulted from the specific combination of excipients claimed.

Reliance on post-published experimental data

4.3.2 The appellants contested that the respondent could rely on said effect and the post-published data provided in D25/D29 and D30 to substantiate it, in accordance with G 2/21.

4.3.3 G 2/21 states that "a patent applicant or proprietor may rely upon a technical effect for inventive step if the skilled person, having the common general knowledge in mind, and based on the application as originally filed, would derive said effect as being encompassed by the technical teaching and embodied by the same originally disclosed invention", see headnote 2.

Criteria of the effect being encompassed by the technical teaching of the original invention

4.3.4 As argued by the respondent, the skilled person would have understood desirable long-term stability to be one of the advantageous properties aimed at for the disclosed compositions in the original application. It was undisputed that storage stability is generally a desired property when preparing pharmaceutical compositions. Moreover, paragraph [0010] of the original application mentioned storage stability within a list of desirable properties for pharmaceutical formulations and paragraph [0011] of the original application referred to these properties in the context of "the present disclosure". The Board is therefore of the opinion that technical effect of desirable long-term storage stability is encompassed by the teaching of the original application.

4.3.5 Appellants 2 and 3 argued that paragraphs [0010] and [0011] were not appropriate to consider that the alleged technical effect was encompassed by the technical teaching of the original application. They argued that the last sentence of paragraph [0010] mentioning "some or all of these desired properties" suggested that storage stability was not a feature common to all the disclosed compositions. Furthermore,

according to appellant 2, paragraph [0011] would be limited to the specific composition of table 1.

However, in the Board's view, the skilled person would consider that some degree of generalisation to the compositions as claimed applies. Moreover, the fact that storage stability is mentioned amongst further desirable properties does not necessarily mean that it was not encompassed by the technical teaching of the invention. There is no requirement in G 2/21 for a technical effect to be necessarily individualised in the original application.

4.3.6 Appellant l further considered that the technical effect relied upon by the respondent in view of D30 would be in contradiction with the technical teaching of the original application, so that it could not be encompassed thereby. This would be because D30 provided a comparison of the storage stability with respect to compositions containing povidone (PVP) and crospovidone (PVPP), while these excipients were mentioned as suitable excipients in the original application (see paragraphs [0052] and [0054]).

This argument is not convincing. The original application discloses a clear preference for the claimed combination of excipients (each one being the preferred embodiment in the corresponding class and the examples of preferred composition all containing this combination). The fact that the original application indeed discloses further excipients as suitable ones for the preparation of solid dosage forms does therefore not appear to be in contradiction with the argument of the respondent that a particularly good long-term storage stability is obtained with the preferred combination of excipients.

4.3.7 Furthermore, appellants 2 and 3 referred to the fact that both D2 (see paragraph [0052]) and the original application (see paragraphs [0026] and [0037]) disclose that carbozantinib malate shows good stability. There would therefore be no issue of storage stability.

This argument is also not compelling because it forms part of common general knowledge that stability of the active ingredient *per se* does not necessarily imply good storage stability of the solid pharmaceutical formulation. This is one of the reasons why excipient compatibility studies are performed during the development of pharmaceutical dosage forms.

4.3.8 Moreover, appellant 2 explained that the effect actually shown by the post-published experimental data was only the reduction of the formation of the impurity, 6,7-dimethoxy-quinoline-4-ol. Appellant 2 was therefore of the opinion that this was the effect that had to fulfil the requirements of G 2/21. According to appellant 2, this effect was not mentioned at all in the original application.

The Board disagrees with this approach. The reduction of the formation of an undesired degradation product upon storage inevitably results in an improvement of the stability of the active ingredient, which represents the primary aspect of stability upon storage. In the Board's view, referring to a desirable long-term storage stability is hence appropriate.

Criteria of the effect being embodied by the same originally disclosed invention

4.3.9 Appellants 2 and 3 considered that there would be no indication that the long-term storage stability observed in D25/D29 and D30 would be due to the combination of excipients claimed, *i.e.* that the second criteria of G 2/21 was fulfilled.

4.3.10 The Board observes that, independently of the interpretation of G 2/21 provided in T 116/18 and relied upon in the impugned decision and by appellant 2, G 2/21 states that the main issue is "what the skilled person, with the common general knowledge in mind, would understand at the filing date from the application as originally filed as the technical teaching of the claimed invention" (see paragraph 93).

4.3.11 In the present case, the composition as originally claimed was already very specific (see original claim 4) and the presently claimed combination of excipients was clearly disclosed as preferred in the original application (see above 4.3.6, 2nd paragraph). The purported effect of desirable long-term storage stability for tablets containing the claimed specific combination of excipients does thus not change the nature of the claimed invention, as defined in G 2/21 (see last sentence of paragraph 93), so that it is embodied by the same originally disclosed invention in the sense of G 2/21. Contrary to the opinion of appellants 2 and 3, an explicit indication in the original application that the preference for the claimed excipients would be linked to the obtention of a desirable storage stability is not required.

4.3.12 In this context, the reference of appellant 2 to T 2046/21 is not relevant, since the facts underlying this earlier case and the present one differ substantially. In said earlier case the technical

effect of lowering intra-ocular pressure (IOP) in general was expected from common general knowledge and post-published data supporting this general effect were taken into consideration in line with G 2/21. However an additional effect of IOP lowering occurring only in a subpopulation of patients which actually resulted in a modification of the medical use underlying the invention (treatment of a subpopulation of patients), *i.e.* a modification of the nature of the invention, was not taken into account in line with G 2/21. In the present case, for the reasons detailed above (see 4.3.10), there is no such modification of the nature of the invention.

4.3.13 Hence, the Board considers that the technical effect in terms of desirable long-term stability relied upon by the respondent and the post-published data provided in D25/D29 and D30 to substantiate it, can be taken into account in accordance with G 2/21.

Suitability of the post-published data to substantiate the presence of the alleged effect

4.3.14 The respondent explained that D25/D29 substantiated that a composition according to present claim 1 (specific composition of claim 2) showed desirable long-term storage stability, since the formation of the degradation product 6,7-dimethoxy-quinoline-4-ol was kept low. Furthermore, D30 substantiated that the long-term storage stability was linked to the specific combination of excipients claimed.

4.3.15 The appellants considered that the provided post-published data D25/D29 and D30 did not appropriately substantiate that the alleged technical effect was

directly linked to the distinguishing features and obtained over the whole scope of the claims.

They brought forward that cabozantinib is a phenol ether known to be prone to hydrolysis and hence degradation (see D31). It followed that the presence of water might play a role in the formation of the degradation product 6,7-dimethoxy-quinoline-4-ol. As a consequence, the results obtained in D25/D29 for dried compositions (see D32, paragraph 18.) containing anhydrous lactose (see claim 2 of the patent) could not be extrapolated to composition with a higher degree of residual water and/or with hydrated lactose. Appellants 2 and 3 also stated that the compositions of D25/D29 were prepared by wet granulation, so that the results could not be extrapolated to compositions obtained by a different preparation method (such as dry granulation or direct compression), since this was known to have an impact on the final properties of the tablets (see D34, page 865 and following and page 869 and following and D35, page 69 under "1. Introduction").

The appellants further disputed that D30 convincingly supported the claimed effect, for the following main reasons:

- the results were obtained for homogenous mixtures and could therefore not be extrapolated to tablets since the tabletting method may also influence storage stability,
- the ratios of the components in sample 4 would not be according to present claim 1, so that no conclusion could be drawn for the claimed tablets,
- lactose monohydrate was used in sample 3 while anhydrous lactose was used in sample 4, so that the reduced storage stability of sample 3 was to be expected.

Finally, the appellants argued that there would be no comparison with the closest prior art, so that the claimed effect could not be used in the formulation of the technical problem.

4.3.16 These arguments are not persuasive in the present case.

Regarding the lack of comparison with the closest prior art D2, the Board observes that since no specific tablet composition is disclosed in D2, a specific comparison thereto is not possible.

Furthermore, as stated by the opposition division, the post-published data have to be considered in their entirety.

D25/D29 indeed show that a composition according to present claim 2 have desirable long-term storage stability. The additional data provided in D30 substantiate that, for homogenous mixtures (*i.e.* not yet processed to tablets by any type of method), the combination of present specific excipients provides better long-term storage stability than other combinations. This was furthermore the case for both dried mixtures and wet mixtures containing 20 % water. Hence, the effect due to the nature of the excipients appears to occur independently of the amount of water present. The fact that residual water or the degree of hydration of lactose may also have some impact, does not undermine the effect of the choice of excipients. The same applies to the type of tabletting method used.

In the absence of any evidence of the contrary, it can therefore be considered credible that the effect observed on physical mixtures due to the choice of

excipients will also be observed on corresponding tablet compositions obtained by a given tabletting method at least to some extent, as it is the case for exemplary tablets according to the invention in D25/D29.

Moreover, the Board observes that the ratios of components in the composition are identical in samples 3 and 4 in D30. Hence the comparison of these samples is suitable to show an effect of the nature of the excipients shown. There is no reason to doubt that this effect would not also occur, at least to some extent, when applying the ratio of present claim 1.

Concerning the argument raised by appellants 1 and 3 regarding the extent of the comparison performed in D30 (the comparison in D30 concerns only two different excipients, namely HPC (according to the claims) *versus* povidone (comparative) and croscarmellose sodium *versus* crospovidone (comparative)), the Board observes that the technical teaching of the patent has to be considered in relation with the teaching of the prior art. In the present case, none of the cited prior art discloses any specific tablet formulation of cabozantinib malate. It cannot therefore be expected that an effect is shown over any other possible combination of known excipients.

Finally, the appellants did not provide any counter-evidence that the alleged effect would not be observed for the claimed tablets.

4.3.17 The Board therefore considers that the data of D25/D29 and D30 taken in combination renders credible that the specific choice of excipients provides desirable long-

term storage stability and that said long-term stability is conserved in tablet compositions.

4.4 Objective technical problem

It follows that, starting from D2, the objective technical problem resides in the provision of a pharmaceutical composition of cabozantinib malate which exhibits desirable long-term storage stability.

4.5 Non-obviousness

4.5.1 None of the cited prior art documents suggests that the claimed combination of specific excipients would lead to a composition having desirable long-term storage stability.

4.5.2 Appellant 3 contented that the claimed excipients were frequently used in pharmaceutical compositions and that the claimed amounts were standard (see D12a, page 68, left column, Table 2/4 and right column, 3rd paragraph and Table 2/6, page 87, Table 2/11, page 125, Table 2/21 and page 146, left hand column 2nd full paragraph; D13a, page 131, Table 1, page 318, Table 1, page 206, Table 1, page 186, Table 1 and page 404, section 7; D16, page 3647 under "Excipients", page 3656, Table 1, page 3655, right hand column, 2nd full paragraph, page 3658, Table 2, page 3661, under "The disintegrating agent", page 3659, under "The glidant" and "The lubricant" and Table 3, page 3662, Table 5 and page 3660, Table 4; D18, page 405, right hand column, 2nd and last paragraphs, page 406, right hand column, 4th paragraph, page 408, left hand column, under "The Glidant" and page 409, left hand column, 1st paragraph).

This argument is not compelling. While the skilled person could indeed have chosen the present excipients, there is still no direct and clear hint in the cited prior art that the present combination would provide long-term storage stability with a reasonable expectation of success.

4.5.3 Appellants 1 and 3 further asserted that the skilled person would have recognised that cabozantinib, being a phenol ether, would be prone to hydrolysis. The skilled person would therefore have performed excipient compatibility studies known from common general knowledge illustrated by D16, D20, D19 or D36 (see D16, page 3642 under "Preformulation" and page 3645 under "Formulation Design"; D20, page 114 Table 8.2 and pages 129 to 132; D19, page 3 under "2. Stress Testing (2.1.2)"; D36, page 125, left column, 2nd paragraph, lines 2 to 7, page 125, right column, 1st and 2nd paragraphs, page 128, right column, 3rd entry, page 134, paragraph bridging both columns and page 135, right column, 2nd paragraph) and consequently selected the present excipients.

As explained by the respondent, this argument is based on hindsight knowledge of the invention and hence not convincing.

4.5.4 Accordingly, the subject-matter of granted claim 1 is not obvious in light of the cited documents. The same applies to granted claims 2 to 13 since they refer to claim 1.

4.6 As a consequence, the subject-matter of the claims of the main request meets the requirement of Article 56 EPC starting from document D2 as closest prior art. It

was undisputed that this conclusion equally applies starting from documents D8 or D9 as closest prior art.

4.7 Hence, the ground of opposition under Article 100(a) EPC in combination with Article 56 EPC does not prejudice the maintenance of the patent.

Order

For these reasons it is decided that:

The appeals are dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated