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Datasheet for the decision of 27 November 2023

Case Number: T 0852/20 - 3.3.02

Application Number: 15171526.5

Publication Number: 2955180

IPC: C07D471/04, A61P35/00, A61K31/437

Language of the proceedings: EN

Title of invention:

PROPANE-I-SULFONIC ACID {3- [5- (4- CHLORO-PHENYL) -1H-PYRROLO [2, 3-B} PYRIDINE-3-CARBONYL] -2, 4-DIFLUORO-PHENYL} -AMIDE COMPOSITIONS AND USES THEREOF

Patent Proprietor:

F. Hoffmann-La Roche AG
Plexxikon Inc.

Opponent:

Generics (UK) Ltd

Headword:

Relevant legal provisions:

EPC Art. 56
RPBA 2020 Art. 13(1), 13(2)

Keyword:
Inventive step - obvious alternative
Amendment to appeal case
Amendment after summons

Decisions cited:
G 0002/21

Catchword:
Purported technical effect not derivable from the application as filed in the sense of G 2/21 (points 3.5 to 3.5.3 of the Reasons)

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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
Fax +49 (0)89 2399-4465

Case Number: T 0852/20 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 27 November 2023

Appellant: (Opponent)	Generics (UK) Ltd Station Close Potters Bar Hertfordshire EN6 1TL (GB)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Respondent: (Patent Proprietor 1)	F. Hoffmann-La Roche AG Grenzacherstrasse 124 4070 Basel (CH)
Respondent: (Patent Proprietor 2)	Plexxikon Inc. 211 Mount Airy Road Basking Ridge, New Jersey 07920 (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 14 February 2020 rejecting the opposition filed against European patent No. 2955180 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	M. O. Müller
Members:	S. Bertrand
	L. Bühler

Summary of Facts and Submissions

I. The appeal by the opponent ("appellant") lies from the opposition division's decision to reject the opposition filed against European patent No. 2 955 180.

II. Claim 1 of the patent relates to a crystalline polymorph Form 1 of compound I.

Compound I is propane-1-sulfonic acid {3-[5-(4-chloro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide.

III. The following documents are referred to in the present decision:

D1 WO 2007/002325 A2

D2 M. R. Caira, Topics in Current Chemistry, Vol. 198, Crystalline Polymorphism of Organic Compounds, Springer Verlag Berlin Heidelberg, 1998, 163-208

D4 S. Bym *et al.*, Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations, Pharmaceutical Research, July 1995, 12(7), 945-984

IV. In the impugned decision, the opposition division's conclusions included the fact that the subject-matter of the claims according to the main request involved an inventive step in view of D1 as the closest prior art (Article 56 EPC). In arriving at this conclusion, the opposition division took into account an effect evidenced by post-published data.

V. In the statement of grounds of appeal and in a further letter, the appellant contested the opposition division's reasoning regarding the inventive step of the subject-matter of claim 1 of the main request. It disputed that the patent proprietor could rely on an effect evidenced in post-published data since the effect on the basis of which the objective technical problem was formulated in the impugned decision was not plausible.

VI. In the reply to the grounds of appeal and in a further letter, the patent proprietor ("respondent") provided counter-arguments to the submissions provided by the appellant regarding inventive step of the subject-matter of claim 1 of the main request.

VII. The board summoned the parties to attend oral proceedings on 9 February 2023.

VIII. In a communication, the board informed the parties that the oral proceedings scheduled for 9 February 2023 had been cancelled since the Enlarged Board of Appeal's decision in G 2/21 (plausibility) had not been issued and it could not be ruled out that the outcome of the present case would hinge on G 2/21.

IX. The board subsequently summoned the parties to attend oral proceedings on 27 November 2023 and issued a communication under Article 15(1) RPBA 2020.

X. Oral proceedings before the board were held by videoconference on 27 November 2023 in the presence of both parties.

XI. The parties' requests, where relevant to the decision, were as follows:

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

The respondent requested that the appeal be dismissed.

XII. The appellant's case and the respondent's case are summarised in the Reasons below.

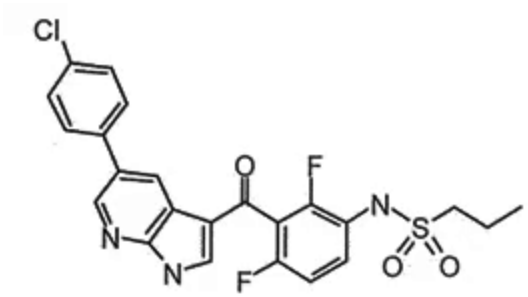
Reasons for the Decision

Main request (patent as granted)

1. The main request is the sole claim request.

2. As set out above, claim 1 of the patent relates to a crystalline polymorph Form 1 of compound I. Form 2, referred to in the patent and by the parties, is a further polymorph of compound I.

Compound I has the following chemical formula and will be referred to hereinafter as vemurafenib:



Compound I

3. Inventive step (Article 56 EPC)

3.1 In the impugned decision, with regard to the assessment of inventive step (point 2) b) of the Reasons), the opposition division referred to "post-published

experimental data" filed by the respondent during the examination phase with the letter of 11 October 2016. The opposition division relied on these data for formulating the objective technical problem, namely that of providing an improved form of vemurafenib with the aim of overcoming known solubility issues. According to the opposition division, the post-published experimental data were "*meaningful, since they represent experimental evidence in support of an alleged improved solubility already mentioned in the application.*"

The post-published experimental data in the respondent's letter of 11 October 2016 comprise two tables. The first table contains amounts of Form 1 and Form 2 of vemurafenib dissolved in water per unit of time and demonstrates that Form 1 of vemurafenib exhibits increased water solubility in comparison with Form 2. The second table in the respondent's letter of 11 October 2016 is a table on the bioavailability of Forms 1 and 2 of vemurafenib. This second table demonstrates increased bioavailability of Form 1 in comparison with Form 2.

3.2 The appellant did not dispute that the experimental data demonstrated increased water solubility and bioavailability achieved by Form 1 of vemurafenib compared with Form 2; however, it contested that the post-published experimental data could be used as the sole basis to demonstrate this effect, since this effect was not derivable from the application as filed.

This was a matter of dispute between the parties.

3.3 This question has been dealt with in decision G 2/21 by the Enlarged Board of Appeal. Before addressing whether

the effect demonstrated by the post-published experimental data can be taken into account in view of this decision, the admittance of a new submission made by the respondent during the oral proceedings needs to be discussed.

3.4 Admittance of the respondent's new submission

3.4.1 During the oral proceedings before the board and in the context of the discussion of whether the increased water solubility and bioavailability of Form 1 of vemurafenib in comparison with Form 2 was derivable from the application as filed in the sense of G 2/21, the respondent relied on paragraph [0168] of the application as filed in combination with D2. It submitted that the skilled person would infer from this passage of the application as filed that Form 1 was thermodynamically less stable than Form 2 at physiological temperature and that, based on the teaching of D2, which represented common general knowledge, water solubility and bioavailability of Form 1 of vemurafenib would be inversely related to thermodynamic stability, such that they would be increased in comparison with Form 2. The increased water solubility and bioavailability of Form 1 of vemurafenib could thus be derived from the application as filed.

Paragraph [0168] of the application as filed discloses the differential scanning calorimetry (DSC) data of Form 1 and Form 2 of vemurafenib. It is stated that the DSC thermogram for Form I shows an exothermic shift at approximately 152-164°C and an endothermic peak at 268.0°C and that the DSC thermogram for Form 2 shows an endothermic peak at 271.2°C.

According to D2, page 191, second full paragraph, "*For a given drug, metastable polymorphs tend to have higher solubilities and faster dissolution rates than the stable polymorph. When metastable forms are employed in solid dosage forms (tablets, capsules), they generally yield higher and earlier blood serum levels*".

3.4.2 The appellant submitted that the respondent's submission that the skilled person would infer from the application as filed that Form 1 was thermodynamically less stable than Form 2 at physiological temperature represented a new allegation of fact. The appellant requested that this new allegation of fact not be admitted into the appeal proceedings.

3.4.3 The board concurs with the appellant that the respondent's submission is not just an argument but a factual allegation, namely that Form 1 of vemurafenib is thermodynamically less stable than Form 2 at physiological temperature. The first question to be discussed in relation to admittance is whether this allegation of fact represents an amendment to the respondent's appeal case.

3.4.4 The respondent did not contest that this allegation of fact was made for the first time during the oral proceedings before the board. It was, however, of the view that its allegation did not change the factual evidence provided in the application as filed that Form 1 of vemurafenib was less stable than Form 2 at physiological temperature. Furthermore, the respondent argued that it merely accepted the appellant's submissions in paragraph (101) of the statement of grounds of appeal. The allegation of fact was thus not an amendment to the respondent's appeal case.

The board disagrees. As submitted by the appellant, on page 11 of the reply to the grounds of appeal the respondent stated that "*Form 1 is stable (see DSC data in [0165]), indicating a polymorphic change only at 152-164°C*". A similar statement was made in paragraph x) on pages 6 and 7 of the respondent's letter of 18 November 2020: "*As disclosed in [0165] Form 1 shows an exothermic DSC shift only at 152° - 164°C. In other words, up to this temperature Form 1 and Form 2 are* ***equally stable****. Appellant's allegation of an inverse relationship of stability and solubility -if at all correct- therefore does not give rise to any expectation, especially in respect of bioavailability under physiological conditions, namely at temperatures that are some 110°C lower*" (emphasis added by the board). The respondent's position during the written appeal proceedings was thus that Form 1 of vemurafenib was as stable as Form 2 at physiological temperature. This is in clear contradiction to the respondent's allegation of fact submitted during the oral proceedings, namely that Form 1 of vemurafenib is less stable than Form 2 at physiological temperature. The allegation of fact made during the oral proceedings is thus an amendment to the respondent's appeal case (and even a "*venire contra factum proprium*", as it goes against the respondent's initial interpretation of the data in paragraph [0168]).

This conclusion is not changed by the respondent's argument that its allegation did not change the factual evidence provided in the application as filed that Form 1 of vemurafenib was less stable than Form 2 at physiological temperature. What matters is whether the respondent's allegation of fact is an amendment to its appeal case compared with its earlier submissions on appeal rather than compared with the application as

filed. Irrespective of this, it is noted that nowhere in the application as filed is it stated that Form 1 is thermodynamically less stable than Form 2 at physiological temperature. In any case, the respondent's altered interpretation of the DSC data presented in paragraph [0168] of the application was based on alleged knowledge of the skilled person which had not been previously relied upon during the appeal proceedings.

The respondent's further argument that it merely accepted the appellant's submission in paragraph (101) of the statement of grounds of appeal that "*for crystalline forms, stability is generally inversely correlated with solubility*" is not relevant, even if it is correct. What is to be decided is not the admittance of any assertion of such an inverse correlation, but the respondent's allegation that the skilled person would infer from the application as filed that Form 1 of vemurafenib is thermodynamically less stable than Form 2 at physiological temperature.

The board thus remains of the view that the allegation of fact that the skilled person would infer from the application as filed that Form 1 of vemurafenib is thermodynamically less stable than Form 2 at physiological temperature represents an amendment to the respondent's appeal case.

Since this amendment was filed only during the oral proceedings before the board, its admittance is governed by Article 13(1) and (2) RPBA 2020. According to Article 13(1) RPBA 2020, any amendment to a party's appeal case after it has filed its grounds of appeal or reply is subject to the party's justification for its amendment and may be admitted only at the discretion of

the board. The board will exercise its discretion in view of, *inter alia*, the current state of the proceedings and whether the amendment is detrimental to procedural economy.

According to Article 13(2) RPBA 2020, any amendment to a party's appeal case made after notification of a summons to oral proceedings will, in principle, not be taken into account unless there are exceptional circumstances, which have been justified with cogent reasons by the party concerned.

3.4.5 The respondent submitted that G 2/21 was issued after the summons to the oral proceedings and that this represented exceptional circumstances, which justified admittance of its submission.

The board does not agree.

First, the respondent did not identify the part of G 2/21 which could be regarded as a reason for the respondent to change its appeal case, and the board could not find any part that provided a reason, either. In fact, whether or not the effect shown by the post-published data could be relied upon was a matter of dispute between the parties right from the start of the appeal proceedings.

3.4.6 The respondent further submitted that the allegation of fact was made in response to the appellant's submission regarding the stability of Form 1 at physiological temperature made during the oral proceedings.

The board disagrees. As argued by the appellant, the submission on the stability of Form 1 of vemurafenib at physiological temperature was not discussed for the

first time during the oral proceedings. This submission was already made by the respondent itself in point x) on pages 6 and 7 of its letter of 18 November 2020, as set out above (3.4.4, *supra*). Furthermore, the board does not see any reason, and none was cited by the respondent, why the reference to a physiological temperature could have triggered the respondent's new allegation of fact. Therefore, the reference to a physiological temperature cannot represent a cogent reason justifying exceptional circumstances for the submission of the allegation of fact made during the oral proceedings.

3.4.7 Therefore, no cogent reasons which would justify exceptional circumstances can be recognised. The respondent's new submission thus cannot be admitted in view of Article 13(2) RPBA 2020.

3.4.8 Even if it were accepted that the issuance of G 2/21 represented an exceptional circumstance, it should be noted that this decision was published on 23 March 2023, i.e. roughly eight months before the oral proceedings. The respondent's new allegation of fact thus could have been made right after G 2/21 had been issued. The board does not see any reason, and none was provided by the respondent, why it waited until the oral proceedings to submit the new allegation of fact.

This is aggravated by the fact that the board informed the parties in its communication under Article 15(1) RPBA 2020 (point 16.5.2) that it would be discussed during the oral proceedings whether or not the effect relied upon by the respondent could be derived from the application as filed in the sense of G 2/21. Therefore, the new allegation of fact should have been submitted

in response to the board's communication under Article 15(1) RPBA 2020 at the latest; however, the respondent did not respond to the board's communication. Once again, the board sees no reason why it waited until the oral proceedings to submit the new allegation of fact.

The allegation should thus have been filed at an earlier stage in the appeal proceedings, and submitting it only during the oral proceedings is detrimental to procedural economy.

3.4.9 In view of the above, the board decided not to admit the new allegation of fact into the proceedings under Article 13 (1) and (2) RPBA 2020.

3.5 G 2/21 - taking into account the effect demonstrated in the post-published experimental data

3.5.1 According to G 2/21 (order no. 2), "*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*."

Considering order no. 2 of G 2/21, the question to be answered in the present case is thus whether the effect relied upon by the respondent and demonstrated in the post-published experimental data, namely the increased water solubility and bioavailability of Form 1 of vemurafenib over Form 2, can be derived by the skilled person, having the common general knowledge in mind and based on the application as filed, as being encompassed by the technical teaching and embodied by the same originally disclosed invention.

3.5.2 In the board's view, this question has to be answered in the negative.

3.5.3 The relevant passages in the application as filed are paragraphs [0040] to [0042], which read as follows:

"[0040] Compounds that have low solubility in water (for example, certain compounds in crystalline form), have a low dissolution rate and as a result can exhibit poor bioavailability. Poorly bioavailable compounds can present problems for therapeutic administration to a patient, often due to unpredictability in dose/therapy effects caused by erratic absorption of the compound by the patient. For example, the intake of food may affect the ability of the patient to absorb such poorly bioavailable compounds, thus potentially requiring dosing regimens to take into account the effect of food. In addition, when dosing, a large safety margin maybe required for the dose as a result of the unpredictable dose effects. Further, due to poor bioavailability, a large dose of the compound may be required to achieve a desired therapeutic effect, thus potentially resulting in undesired side effects.
[0041] Amorphous forms of Compound I [i.e. vemurafenib] have improved solubility in water as compared to the crystalline form, but is unstable as it has a tendency to crystallize. Thus it is desired to formulate Compound I so that it may stably exist primarily in amorphous form.
[0042] Thus, in some aspects and embodiments disclosed and described herein, techniques, methods and compositions for improving the solubility and/or bioavailability of Compound I are provided. In certain embodiments, provided are compositions and methods involving Compound I in a composition, form, or

formulation in which it has improved water solubility and/or bioavailability of [sic] as compared to Compound 1 in a crystalline form, or Compound I in a primarily crystalline form." (Addition in square brackets by the board.)

The purported technical effect of increased water solubility and bioavailability of Form 1 (a crystalline form) of vemurafenib in comparison with Form 2 (another crystalline form) is not disclosed in the above passages or taught anywhere else in the application as filed. Indeed, paragraph [0040] of the application as filed refers to certain compounds in crystalline form not having an increased dissolution rate, but a low dissolution rate, and as a result having poor bioavailability. Paragraph [0041] of the application as filed teaches that it is desired to formulate vemurafenib so that it may stably exist primarily in **amorphous** form. Lastly, paragraph [0042] of the application as filed teaches how to provide vemurafenib in a composition, form, or formulation in which it has improved water solubility and/or bioavailability as compared with vemurafenib in a crystalline form or in a primarily crystalline form. In the light of the preceding two paragraphs, the vemurafenib mentioned in paragraph [0042] as having improved water solubility and/or bioavailability as compared with vemurafenib in a crystalline form can only be amorphous vemurafenib. These passages of the application as filed thus teach the purported technical effect for amorphous vemurafenib in comparison with crystalline forms. Therefore, if anything, the skilled person would derive from the application as filed that amorphous forms are more soluble and bioavailable than crystalline forms. By no means could the skilled person derive from the application as filed that one particular crystalline

form, namely the claimed Form 1, has good solubility and bioavailability, let alone solubility and bioavailability that is better than that of another crystalline form (Form 2). It follows that, based on the application as filed, and having the common general knowledge in mind, the skilled person would not have derived the purported technical effect, i.e. the increased water solubility and bioavailability of Form 1 of vemurafenib over Form 2, as being encompassed by the technical teaching of the application as filed, let alone that the skilled person would have derived it as being embodied by the same originally disclosed invention. Therefore, it cannot be taken into account for formulating the objective technical problem, in accordance with G 2/21.

4. Inventive step - claim 1

4.1 Form 1 of vemurafenib according to claim 1 of the main request has suitable properties for use as a b-Raf kinase inhibitor (see paragraph [0033] of the patent). b-Raf kinase is an enzyme that helps to control cell growth and signalling. It may be found in a mutated form in some types of cancer, including melanoma and colorectal cancer. Blocking mutated b-Raf kinase proteins may help to keep cancer cells from growing.

4.2 The appellant objected to the inventive step of the subject-matter in view of D1 as the closest prior art in combination with the common general knowledge represented by D4.

4.3 D1 as the closest prior art

D1 (title) is concerned with providing pyrrolo-pyridine derivatives as protein kinase inhibitors, such as

vemurafenib. Vemurafenib is isolated in example 44 of D1 as a white solid (top of page 211).

It was common ground between the parties that D1 represented the closest prior art. The board sees no reason to deviate from the selection of D1 as the closest prior art.

4.4 Distinguishing feature

The distinguishing feature of the subject-matter of claim 1 of the main request over the disclosure of D1 is the specific crystalline form of vemurafenib. D1 discloses a white solid of vemurafenib. Claim 1 of the main request requires Form 1 of vemurafenib. The respondent submitted that the white solid isolated in example 44 of D1 was Form 2 of vemurafenib.

This was contested; however, for the sake of discussion, this is accepted. The difference is thus that claim 1 refers to Form 1 of vemurafenib while example 44 of D1 discloses, as assumed in the respondent's favour, Form 2.

4.5 Objective technical problem

4.5.1 Admittance of the respondent's new submission

The respondent argued that it could be derived from the DSC data contained in the patent that Form 1 of vemurafenib was thermodynamically less stable and hence had improved solubility in water and improved bioavailability compared with Form 2 at physiological temperature. The objective technical problem was thus to provide a form of vemurafenib having improved properties in which the improvement was the solubility and bioavailability at ambient/physiological temperatures.

However, as submitted by the appellant, this represented the same allegation of fact made in the context of the discussion of whether the technical effect relied upon by the respondent could be taken into account for the assessment of inventive step in accordance with G 2/21. The only difference is that now this allegation is based on the DSC data in the patent, while the previous allegation had been based on the same data in the application as filed. As also set out by the appellant, it does not matter and makes no difference whether the assessment is based on the application as filed or on the patent. Hence, for the reasons given above in section 3.4, the allegation now made on the basis of the patent cannot be admitted in view of Article 13(1) and (2) RPBA 2020.

The board therefore decided not to admit this allegation of fact.

4.5.2 The respondent did not rely on any other technical effect. In the absence of a technical affect achieved by the distinguishing feature of claim 1 of the main request, the objective technical problem is to provide an alternative crystalline form of vemurafenib, as formulated by the appellant.

4.6 Obviousness

As submitted by the appellant, Form 1 of vemurafenib as claimed is obtained according to example 19 of the patent by crystallising vemurafenib in a mixture of acetone and ethanol. Both acetone and ethanol are mentioned in the common general knowledge represented by D4 as candidate solvents for screening polymorphs (page 946, right column, last paragraph). Moreover, D4

(same passage) teaches that mixtures of solvents, if appropriate, may be used. Therefore, the selection of the solvent mixture as disclosed in example 19 of the patent for obtaining Form 1 is an arbitrary selection from the solvents disclosed in D4. Such an arbitrary selection is part of the routine abilities of the skilled person. By applying these routine abilities, the skilled person would thus have obtained Form 1 of vemurafenib as defined in claim 1.

The subject-matter of claim 1 of the main request thus lacks an inventive step in view of D1 in combination with the common general knowledge represented by D4.

5. The sole main request is not allowable.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

M. Schalow M. O. Müller

Decision electronically authenticated