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Datasheet for the decision of 19 November 2024

Case Number: T 1418/22 - 3.3.02

Application Number: 16735945.4

Publication Number: 3317281

IPC: C07D487/04, A61K31/4985, A61P35/00

Language of the proceedings: EN

Title of invention:
SOLID FORMS AND FORMULATIONS OF (S)-4-(8-AMINO-3-(1-(BUT-2-YNOYL)PYRROLIDIN-2-YL)IMIDAZO[1,5-A]PYRAZIN-1-YL)-N-(PYRIDIN-2-YL)BENZAMIDE

Patent Proprietor:
Acerta Pharma B.V.

Opponent:
Kraus & Lederer PartGmbB

Headword:
ACERTA PHARMA / ACALABRUTINIB POLYMORPHIC FORM

Relevant legal provisions:
EPC Art. 56
RPBA 2020 Art. 12(4), 12(6)

Keyword:
Inventive step - (yes)
Late-filed evidence - admitted (no)

Decisions cited:
T 0777/08, T 1684/16, T 0041/17

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

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Case Number: T 1418/22 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 19 November 2024

Appellant: (Opponent)	Lederer & Keller Patentanwälte Partnerschaft mbB Unsöldstr. 2 80539 München (DE)
Representative:	Kraus & Lederer PartGmbB Thomas-Wimmer-Ring 15 80539 München (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:	**Decision of the Opposition Division of the European Patent Office posted on 1 April 2022 rejecting the opposition filed against European patent No. 3317281 pursuant to Article 101(2) EPC**

Composition of the Board:

Chairman	M. O. Müller
Members:	M. Maremonti
	M. Blasi

Summary of Facts and Submissions

I. The appeal by the opponent (appellant) lies from the decision of the opposition division to reject the opposition against European patent No. 3 317 281 (the patent).

II. Claim 1 as granted reads as follows:

"*1. A composition comprising crystalline (S)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-alpyrazin-1-yl)-N-(pyridin-2-yl)benzamide free base wherein the crystalline (S)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-alpyrazin-1-yl)-N-(pyridin-2-yl)benzamide free base is* ***characterized by*** *a transmission X-ray powder diffraction pattern comprising peaks at 6.4, 8.6, 10.5, 11.6, and 15.7* °2θ ± 0.2 °2θ, *wherein the X-ray powder diffraction pattern was acquired using Cu-$K_{\alpha 1}$ radiation source.*"

As done by the parties in their submissions, the board in the following refers to the crystalline form of (S)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-alpyrazin-1-yl)-N-(pyridin-2-yl)benzamide free base defined in claim 1 as granted as form I of compound (1).

III. The opposition was based on the ground of lack of inventive step under Article 100(a) EPC in combination with Article 56 EPC. Reference was made, *inter alia*, to the following documents:

D3: WO 2013/010868 A1

D6: Byrn *et al.*, "*Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations*", Pharmaceutical Research 12(7), 1995, 945-54

D7: Guillory, J.K., Polymorphism in Pharmaceutical Solids, H. G. Brittain (ed.), Marcel Dekker, lnc, 1999, Chapter 5, "*Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids*", 183-226

D9: Chen, D., "*Hygroscopicity of Pharmaceutical Crystals*", Dissertation submitted to the Faculty of Graduate School of the University of Minnesota, January 2009, Chapters 1 and 2, 1-103

IV. The opposition division came to, *inter alia*, the following conclusion.

- The subject-matter of the claims as granted involved an inventive step in view of D3 taken as the closest prior art.

V. In its appeal submissions, the appellant contested the opposition division's reasoning and argued that the subject-matter of claim 1 as granted did not involve an inventive step. The appellant corroborated its arguments by filing the following new item of evidence (labelled D14 by the appellant, new numeration introduced by the board):

A14: Experimental report by Prof. Kirschning dated 27 July 2022

VI. The patent proprietor (respondent) rebutted the arguments of the appellant maintaining that the ground for opposition under Article 100(a) in combination with Article 56 EPC did not prejudice the maintenance of the patent as granted. In response to the filing of A14, the respondent filed the following new items of evidence (labelled D15 and D16 by the respondent, new numeration introduced by the board):

A15: D.K. Bucar *et al.*, "*Disappearing Polymorphs Revisited*", Angew. Chem. Int. Ed. 54, 2015, 6972-93

A16: C. Holder and R.E. Schaak, "*Tutorial on Powder X-ray Diffraction for Characterizing Nanoscale Materials*", ACS Nano 13, 2019, 7359-65

VII. Each party made a further written submission on the substance of the case.

VIII. The parties were summoned to oral proceedings as per their requests. In preparation for the oral proceedings, the board issued a communication under Article 15(1) RPBA. In that communication, the board expressed, *inter alia*, the preliminary opinion that A14 should not be admitted into the proceedings and that the subject-matter of the claims as granted involved an inventive step in view of D3 taken as the closest prior art.

IX. Oral proceedings before the board were held by videoconference on 19 November 2024 in the presence of both parties.

X. Final requests relevant to the decision

The appellant requested that the appealed decision be set aside and that the patent be revoked in its entirety. It further requested that A14 be admitted.

The respondent requested that the appeal be dismissed and that the patent be maintained as granted. The respondent further requested that A14 not be admitted or, alternatively, i.e. should A14 be admitted, that A15 and A16 also be admitted.

XI. As regards the parties' submissions that are relevant to the decision, reference is made to them in the reasons for the decision below.

Reasons for the Decision

Documents A14 to A16 - admittance into the proceedings under Article 12(4) and (6) RPBA

1. Document A14

1.1 Experimental report A14 was filed by the appellant with the statement of grounds of appeal. The respondent requested that A14 not be admitted.

1.2 Since A14 was filed only on appeal, its submission represents an amendment of the appellant's case within the meaning of Article 12(4) RPBA. Any such amendment may only be admitted at the board's discretion, exercised, *inter alia*, in view of the complexity of the amendment and procedural economy. Moreover, under Article 12(6) RPBA, the board shall not admit, *inter alia*, items of evidence that should have been submitted before the opposition division.

1.3 The appellant submitted that as early as in the notice of opposition, it had been put forward that the claimed crystalline form I of compound (1) would have been obtained by the skilled person when carrying out a routine screening for polymorphs of compound (1). A14 had then been filed in direct response to the statement made by the opposition division that "*even if the skilled person would try crystallisation solvents mentioned in the prior art, such as for example the solvents recited in D7, he wouldn't arrive to the presently claimed crystalline form*". This statement had been made by the opposition division in the appealed decision for the first time (see point 11.7.5 on page 9 of the decision under appeal). Indeed, in the preliminary opinion issued on 16 September 2021 in preparation for the oral proceedings, the opposition

division in point 10.7.5 had stated that the skilled person *could* have performed a routine crystallisation procedure but *would* not have arrived at form I of compound (1). Therefore, the above-mentioned statement in the appealed decision constituted a change of mind by the opposition division in that even the *could* step had been denied. This change of position by the opposition division had triggered the experiments reported in A14 and its filing on appeal. A14 demonstrated that if the skilled person had tried standard crystallisation solvents as disclosed e.g. in D7, they would necessarily have arrived at form I of compound (1) as defined in granted claim 1. A14 also showed that no other solid form was crystallised.

Therefore, A14 constituted a legitimate reaction to the above statement made by the opposition division for the first time in the appealed decision. As such, A14 was not late filed. Moreover, A14 was *prima facie* highly relevant for inventive step. Hence, A14 should be admitted.

1.4 However, as observed by the respondent, the patent reports in table 1 (pages 20 to 25) the attempts to crystallise form I of compound (1) as defined in granted claim 1. In 75 experiments with different single solvents and solvent mixtures, form I of compound (1) was obtained only in four cases (see samples 23, 24, 39 and 58). On this basis, the patent states in paragraph [0121] that "*[f]orm I is difficult to crystallize but may be prepared from a very limited set of solvents, in particular certain mixtures with n-heptane (e.g., with acetone)*".

1.4.1 The board acknowledges that in the notice of opposition (points 4.4.2.3 to 4.4.2.5 on pages 13 and 14), the appellant had challenged this conclusion of the patent by arguing that by screening a variety of standard

solvents as disclosed e.g. in table 1 on page 189 of D7, and mixtures of these, the skilled person would have automatically arrived at form I of compound (1). However, this argument was not corroborated by any experimental data. A14 contains such data, but it was only filed with the statement of grounds of appeal, whereas it should have been filed with the notice of opposition to support the above argument.

1.4.2 Moreover, as brought forward by the respondent, in its preliminary opinion (see point 10.7 on page 7), the opposition division provisionally agreed with the above-mentioned conclusion of the patent by stating that crystalline form I of compound (1) could be prepared only in a particular solvent system and that the results in tables 1 and 2 of the patent indicated the difficulty of preparing any crystalline form of compound (1), let alone form I. At least in response to the opposition division's preliminary opinion, A14 should have been filed to contest the above conclusion. However, the appellant decided not to do so and instead to wait for the statement of grounds of appeal.

1.4.3 The board fails to see any change in the opposition division's position between its preliminary opinion and the statement in point 11.7.5 of the appealed decision referred to by the appellant. In fact, contrary to the appellant's view, in the appealed decision, the opposition division did not deny that the skilled person could have routinely screened for polymorphs. On the contrary, in points 11.7.4 and 11.7.5 of the appealed decision, the opposition division even stated that the skilled person *would* have routinely screened for polymorphic forms of compound (1) and *would* have tried crystallisation solvents mentioned in the prior art. Nevertheless, the opposition division maintained the preliminary opinion expressed in point 10.7.5 by

stating in point 11.7.5 of the appealed decision that no pointer was present in the prior art that would have let the skilled person reasonably expect that these solvents would have led to a crystalline form of compound (1), let alone to claimed form I.

1.4.4 For these reasons, the filing of A14 only on appeal was not justified by the statement made by the opposition division in the appealed decision and invoked by the appellant since in this statement the opposition division merely reiterated its previous provisional position based on the results of the patent.

1.4.5 Furthermore, the filing of A14 raises complex issues. In fact, admitting A14 would require, for example, considering whether a characterisation by X-ray powder diffraction of the starting sample used in A14 unambiguously allows concluding that the starting material was in amorphous state and that no crystalline material was present. This was contested by the respondent. It would also require assessing whether the crystallisation procedure followed in A14 was such to unambiguously exclude the presence of unintentional seeding. The discussion and consideration of these complex issues would have been detrimental to procedural economy and contrary to the primary object of the appeal proceedings to review the appealed decision in a judicial manner (Article 12(2) RPBA).

1.5 For these reasons, the board decided not to admit A14 into the proceedings, pursuant to Article 12(4) and (6) RPBA.

2. Documents A15 and A16

The respondent requested that A15 and A16 be admitted only if A14 was admitted. In view of the above-

mentioned decision of the board not to admit A14, there was no need to consider the admittance of A15 and A16.

Main request - the patent as granted - claim 1 - ground for opposition under Article 100(a) EPC - inventive step under Article 56 EPC

3. Closest prior art

3.1 In accordance with the appealed decision (points 11.4 and 11.5 on pages 5 and 6), both parties indicated the compound of example 6 of document D3 to represent the closest prior art for the assessment of inventive step.

3.2 Document D3 (page 1, lines 6 to 9) concerns 6-5 membered fused pyridine ring compounds to be especially used in pharmaceutical compositions for the treatment of Bruton's tyrosine kinase (BTK) mediated disorders. This aim is shared with the patent (see paragraphs [0002] to [0004]). Example 6 of D3 (pages 35 to 37) discloses a process for preparing compound (1) referred to in claim 1 as granted. This compound is stated in D3 (table 1, page 94) to be a BTK inhibitor.

4. Distinguishing features

It is common ground that compound (1) as prepared in example 6 of D3 is in amorphous form (see also example 5 of the patent, reproducing example 6 of D3). Therefore, the feature distinguishing the subject-matter of claim 1 as granted from example 6 of D3 is that compound (1) is in the crystalline form I.

5. Objective technical problem

5.1 In its written submissions, the appellant contested the formulation of the technical problem by the opposition division (appealed decision, point 11.7.1 on page 8). While it was agreed that the crystalline form was more stable than the amorphous form, the appellant contested

that form I as defined in granted claim 1 would be non-hygroscopic as stated by the opposition division. Paragraph [0135] of the patent disclosed a weight gain of 0.17% between 0% relative humidity (RH) and 80% RH. This meant that form I was not *non-hygroscopic* but only *less* hygroscopic than the amorphous form. Therefore, the appellant submitted in writing that the objective technical problem should be formulated as the provision of a polymorphic form of compound (1) which is thermodynamically stable and less hygroscopic than the amorphous form.

5.2 However, as argued by the respondent, paragraph [0135] of the patent reports the results of a gravimetric vapour sorption study. Form I shows a total weight gain between 0% RH and 80% RH of 0.17%. This indicates that form I is non-hygroscopic according to the European Pharmacopoeia classification. In contrast, paragraph [0177] of the patent reports the vapour sorption results obtained with the amorphous form of compound (1). The results indicate a total weight gain between 0% RH and 80% RH of 6% for the amorphous form, which is thus classified as hygroscopic according to the European Pharmacopoeia classification. Therefore, the claimed form I does not merely achieve a somewhat reduced hygroscopicity but is instead non-hygroscopic.

5.3 The board thus considers that the objective technical problem should at least be seen as the provision of a more stable and non-hygroscopic form of compound (1). In fact, at the oral proceedings, both parties agreed on this formulation of the objective technical problem.

6. Obviousness of the claimed solution

6.1 As a solution to the above-mentioned objective technical problem, claim 1 as granted proposes form I of compound (1).

6.2 The appellant referred to document D9 and argued that it belonged to common general knowledge that crystalline forms took up less water and were more stable than amorphous forms. Moreover, in accordance with the teaching of D6, when starting from the amorphous form of compound (1) known from example 6 of D3, the skilled person would have routinely screened for polymorphs. D6 disclosed in figure 1 a decision tree as a tool for determining polymorphs. According to the first step, a crystallisation from different solvents and mixtures of solvents should be tried. Standard solvents were shown in table 1 on page 189 of D7, which on the same page disclosed cooling crystallisation as a standard technique. By using this teaching, the skilled person would inevitably have arrived at form I of compound (1) when carrying out a routine screening. This was confirmed by the patent itself, indicating in table 1 on pages 20 to 25 that in 40 out of 75 crystallisation attempts, cooling crystallisation had indeed been used. The sole crystalline form obtained was form I (see samples 23, 24 and 39). At the oral proceedings, the appellant put forward that 40 combinations of solvents did not represent an excessive number, especially in view of the fact that these crystallisation experiments were routinely performed in parallel in an automated way. Thus, there was nothing in the patent indicating a procedure going beyond a routine screening for polymorphs.

The fact that heptane was used as a solvent in the patent instead of hexane, mentioned as standard in D7, did not alter the screening routine of the skilled person since heptane was also commonly used and similar to hexane in terms of polarity. Also, the fact that the solvents used in the patent to crystallise form I were different from those mentioned in D7 did not mean that

form I could not be obtained by using standard solvents. Thus, the skilled person would have had a reasonable expectation of finding the most thermodynamically stable and non-hygroscopic crystalline form of compound (1). When following this routine practice, the skilled person would thus have automatically found the claimed form I of compound (1). Therefore, the subject-matter of claim 1 as granted was obvious starting from example 6 of D3, taking into consideration the common general knowledge of the skilled person as reflected by D6 and D7. Document A14 confirmed that, apart from methanol leading again to the amorphous form, recrystallisation of the amorphous form of compound (1) from acetone, ethanol, n-propanol and iso-propanol directly led to the formation of crystalline form I of compound (1) as the sole crystalline form. Hence, A14 demonstrated that form I was obtained by using a small collection of standard solvents and routine crystallisation techniques. Since form I of compound (1) would have been obtained with a routine procedure, no pointer to additional properties was needed. The non-hygroscopicity of form I would have been identified by the skilled person once form I had been obtained by routine screening. The appellant referred to decisions T 41/17 and T 777/08. A stable polymorph resulting from routine screening did not confer inventive step.

6.3 These arguments are not convincing.

6.3.1 As stated above, A14 was not admitted into the proceedings. Therefore, this document, and any submissions based on it, had to remain unconsidered when deciding on inventive step.

6.3.2 Document D6, which can be accepted to reflect the common general knowledge in the field of pharmaceutical solids, discloses (page 945, left-hand column) that in

drug development, appropriate analytical procedures should be used to detect, *inter alia*, polymorphic forms of the drug substance of interest. According to D6 (page 946, right-hand column and figure 1), the first step in the polymorphs decision tree is to crystallise the substance from a number of different solvents to attempt to determine whether polymorphs of the substance of interest exist. A recrystallisation from solvents like water, methanol, ethanol, propanol, isopropanol, acetone, acetonitrile, ethyl acetate, hexane and mixtures of these if appropriate is suggested in D6 (*loc. cit.*). Analogous disclosure is found in document D7 (pages 188 to 190), as brought forward by the appellant.

6.3.3 The board therefore acknowledges that on the basis of common general knowledge, it can be accepted that the skilled person would have known it to be advisable to screen for polymorphs early on in the drug development process and would have been familiar with routine methods for screening for polymorphs by crystallisation from a range of different solvents under different conditions. However, the mere fact that the skilled person is taught in the prior art to investigate polymorphs to isolate the crystalline form having the most desirable properties is in itself not necessarily sufficient to consider a specific polymorphic form having a certain desired property obvious (T 1684/16, point 4.3.4 of the reasons).

6.3.4 Moreover, as pointed out by the respondent, example 1 of the patent (page 19) shows the crystallisation procedure used to achieve form I of compound (1). Among a high number of single solvents and solvent combinations used (75 in total, see table 1 on pages 20 to 25), only four mixtures of solvents (samples 23, 24, 39 and 58) led to form I. In the other cases, when

solids were obtained, these represented the amorphous form or, in two instances (samples 53 and 69), a different polymorphic form of compound (1) named form II. Anti-solvent experiments did not lead to form I of compound (1) either (see paragraph [0122] and table 2 on page 26). Contrary to the appellant's view, the board thus agrees with the respondent that these results convincingly demonstrate the technical difficulty of crystallising form I of compound (1). There is no indication in the prior art that would have prompted the skilled person to use exactly the solvent mixtures which are reported in table 1 of the patent to lead to form I of compound (1). Also, the appellant's argument that for the skilled person heptane as used in the patent would have been an obvious equivalent to hexane disclosed in D7 was not corroborated by any evidence and therefore amounts to mere speculation.

6.3.5 Additionally, while it can be accepted that it would have been expected by the skilled person that crystalline forms are more stable than amorphous forms, the results of the patent (see summary provided by the respondent on page 13 of the reply to the statement of grounds of appeal) show that two further polymorphic forms (form II and form III) of compound (1) were found to be more hygroscopic than form I. No indication is present in the prior art cited by the appellant that would have prompted the skilled person to expect to find polymorphic forms with no-hygroscopicity according to the European Pharmacopoeia classification.

6.3.6 For these reasons, when considering the technical difficulty of obtaining form I of compound (1) and its unexpected non-hygroscopicity, the skilled person would not have had a reasonable expectation of arriving at form I of compound (1).

6.3.7 The case law cited by the appellant cannot support its case either.

In decision T 777/08 (point 5 of the reasons), like in the current case, the closest prior art was the amorphous form of the claimed compound. The objective technical problem was the provision of the compound "*in a form having improved filterability and drying characteristics*". The entrusted board concluded that on the basis of common general knowledge, the skilled person would have expected crystalline forms of the claimed compound to have improved filterability and drying characteristics. Therefore, in contrast to the case at hand, the skilled person would have expected the property alleged for the claimed compound. Also in contrast to the case at hand, no technical difficulties for crystallising the claimed polymorphic form had been identified. Lastly, as set out above, form I has a lower hygroscopicity than forms II and III. Thus, in contrast to the condition referred to under point 5.2 of the reasons of decision T 777/08 for denying inventive step, form I, in terms of its hygroscopicity, is not an arbitrary selection of a specific polymorph from a group of equally suitable candidates.

In decision T 41/17 (points 1.1 to 1.3 of the reasons), the closest prior art was an unspecified solid form of the claimed compound. The objective technical problem was the provision of a stable crystalline form of the claimed compound "*suitable for the preparation of a pharmaceutical tablet*". The entrusted board concluded that the claimed polymorphic form was obvious in view of the cited prior art since the skilled person would have performed a polymorph screening and identified the claimed polymorphic form as the most thermodynamically stable form. Being the most stable form, the skilled person would have expected it not to convert to other

forms under mechanical stress, thus making it suitable to solve the posed technical problem. Therefore, in contrast to the case at hand, not only was the property alleged for the claimed compound expected but also no technical difficulties for crystallising the claimed polymorphic form had been identified.

6.4 For these reasons, the board concluded that the subject-matter of claim 1 as granted involves an inventive step within the meaning of Article 56 EPC. Hence, the ground for opposition under Articles 100(a) and 56 EPC invoked by the appellant does not prejudice maintenance of the patent as granted.

7. The appellant had challenged the validity of the priorities claimed for the patent.

However, since no intermediate documents had been referred to by the parties, the question of the validity of the claimed priorities was irrelevant to these proceedings, and no decision had to be taken on this issue.

Conclusion

8. The appeal against the opposition division's decision rejecting the opposition is not allowable, implying that the patent is maintained as granted.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

U. Bultmann M. O. Müller

Decision electronically authenticated