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Datasheet for the decision of 14 May 2024

Case Number: T 1354/23 - 3.3.02

Application Number: 19169275.5

Publication Number: 3533792

IPC: C07D401/04, A61K31/4439, A61K31/4184, A61P35/00

Language of the proceedings: EN

Title of invention:
CRYSTALLINE FORMS OF AN ANDROGEN RECEPTOR MODULATOR

Patent Proprietor:
Aragon Pharmaceuticals, Inc.
Sloan Kettering Institute For Cancer Research

Opponent:
Generics [UK] Limited

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step

Decisions cited:
G 0002/21, T 0777/08, T 1317/13, T 0325/16, T 0041/17

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Case Number: T 1354/23 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 14 May 2024

Appellant: (Opponent)	Generics [UK] Limited Building 4, Trident Place Mosquito Way Hatfield Hertfordshire AL10 9UL (GB)
Representative:	Ter Meer Steinmeister & Partner Patentanwälte mbB Nymphenburger Straße 4 80335 München (DE)
Respondent: (Patent Proprietor 1)	Aragon Pharmaceuticals, Inc. 10990 Wilshire Blvd. Suite 300 Los Angeles, CA 90024 (US)
Respondent: (Patent Proprietor 2)	Sloan Kettering Institute For Cancer Research 1275 York Avenue New York, NY 10065 (US)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 9 May 2023 rejecting the opposition filed against European patent No. 3533792 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	M. O. Müller
Members:	P. O'Sullivan
	L. Bühler

Summary of Facts and Submissions

I. The appeal of the opponent (hereinafter appellant) lies from the decision of the opposition division to reject the opposition against European patent EP 3 533 792.

II. The following documents *inter alia* were submitted during the course of opposition proceedings:

D5 : WO 2007/126765 A2
D6 : WO 2008/119015 A2
D7 : S Byrn *et al.*, Pharm. Res. 1995, 12(7), 945-954
D8 : Polymorphism in pharmaceutical solids, 1999, page 193
D11: Opposition decision concerning EP 1557421
D12: Decision of the German federal court of justice X ZR 110/16
D19: "Experimental Information" - Dynamic Moisture Sorption experiment

III. In a communication pursuant to Article 15(1) RPBA sent in preparation for oral proceedings, the board *inter alia* expressed the preliminary view that the ground for opposition under Article 100 (b) and (c) did not prejudice maintenance of the patent as granted.

IV. Oral proceedings by videoconference originally scheduled for 15 May 2024 was rescheduled to 14 May 2024 in the presence of both parties, both of whom agreed to the rescheduled date.

V. Requests relevant to the present decision

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

The proprietors (hereinafter respondents) requested dismissal of the appeal and maintenance of the patent as granted.

VI. For the text of claim 1 of the main request, reference is made to the reasons for the decision set out below.

VII. For the relevant party submissions, reference is made to the reasons for the decision set out below.

Reasons for the Decision

Main request (patent as granted)

1. Amendments - Articles 100(c) and 123(2) EPC

1.1 Claim 1 of the main request reads as follows:

"*A pharmaceutical composition comprising 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide; wherein the 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is [sic] crystalline Form B; and wherein crystalline Form B is characterized as having at least one of:*

(a) an X-Ray powder diffraction (XRPD) pattern the same as shown in Figure 2;
(b) an X-ray powder diffraction (XRPD) pattern with characteristic peaks at 12.1±0.1° 2-Theta, 16.0±0.1° 2-Theta, 16.7±0.1° 2-Theta, 20.1±0.1° 2-Theta, 20.3±0.1° 2-Theta;
(c) unit cell parameters equal to the following at -173°C:

Crystal system	Monoclinic				
Space group	$P2_1/c$	*a*	17.7796(4)Å	α	90°
		b	12.9832(3)Å	β	100.897(2)°
		c	18.4740(4)Å	γ	90°
V	4187.57(16)Å^3				
Z	8				
Dc	1.515g.cm^{-1}				

(d) the same X-ray powder diffraction (XRPD) pattern as (a) or (b) post storage at 40°C and 75% RH for at least a week; or
(e) the same X-ray powder diffraction (XRPD) pattern as (a) or (b) post storage at 25°C and 92% RH for 12 days".

1.2 The compound 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is referred to in the following as "apalutamide", the API name employed by the parties in appeal proceedings. "Form B" in the following refers to the crystalline polymorphic Form B of apalutamide as defined in claim 1.

1.3 The appellant argued that claim 1 comprised added subject-matter. Form B was defined as having at least one of the properties (a) to (e) listed in claim 1. Claim 1 was based on claim 15 of the application as

filed. The latter claim was directed to crystalline Form B characterized as having one of the properties (a) to (i) or combinations thereof, (j). However, according to the appellant, "at least one" in claim 1 of the main request was not derivable from claim 15 of the application as filed. Specifically, option (j) in claim 15 of the application as filed encompassed all 512 possible combinations for each of the nine items listed as (a) to (i). Selecting the specific combination of claim 1 of the main request therefore added subject-matter over the application as filed.

1.4 The board disagrees. As set out by the respondents, claim 15 of the application as filed provides a number of different ways to characterise the same thing, namely Form B – these ways are all part of the same embodiment, namely they all characterise Form B. Hence, subject-matter was not added to claim 1 as granted, because identically to claim 15 of the application as filed, it characterises Form B. Furthermore, the properties listed in claim 1 can be derived by simple deletion from the single list of options provided in claim 15 of the application as filed.

1.5 Furthermore, the objection that there is no basis for the term "at least one of" in claim 1 of the main request is not convincing, since in terms of meaning, this expression is identical to the expression "combinations thereof" in option (h) of claim 15 of the application as filed: both expressions allow any one of the listed options alone, or several or all of the options together.

1.6 Consequently, the ground for opposition under Article 100(c) EPC does not prejudice the maintenance of the patent as granted.

2. Sufficiency of disclosure - Articles 100(b) EPC

2.1 The appellant argued that the conditions under which conversion of some forms into Form B occurred were not sufficiently taught in the patent (e.g. Form A converts to Form B according to paragraph [0206] of the patent). Therefore, a research program was required to prepare Form B. Additionally, the appellant argued that the breadth of claim 1 would lead to lack of sufficient disclosure, because Form B was characterised by all the properties listed in claim 1, whereas claim 1 only required "at least one" of them.

2.2 The board disagrees. As set out by the respondents, paragraph [0152] of the patent discloses the preparation of Form B, thus providing clear instructions to the skilled person on how to prepare it, as well as how to characterise it (examples 3 to 9). The appellant has not raised any serious doubts or verifiable facts casting doubt on this information, and hence the preparation of Form B, i.e. the claimed subject-matter, can be carried out by the person skilled in the art.

2.3 As regards the breadth of claim 1, the board notes that claim 1 merely provides different ways of characterising Form B. Claim 1 is specifically and explicitly directed to Form B - no other forms are mentioned. As stated by the respondent, when read with a mind willing to understand, claim 1 relates to a pharmaceutical composition comprising Form B, and no other unmentioned polymorphic forms are covered.

Consequently, the ground for opposition under Article 100(b) EPC does not prejudices maintenance of the patent as granted.

3. Article 100(a) and 56 EPC

3.1 Claim 1 is directed to a pharmaceutical composition comprising crystalline Form B.

3.2 Closest prior art

The appellant submitted that either of documents D5 or D6 represented suitable closest prior art disclosures. This was not disputed by the respondents.

3.3 Distinguishing features

3.3.1 Patent document D5 discloses the preparation of apalutamide, "A52" (page 19, paragraph [0055]). The reaction mixture comprising the product was extracted with ethyl acetate, dried and concentrated to provide the product "as a white powder". As stated in the board's communication pursuant to Article 15(1) RPBA for the present case, in related case T 2086/21 in which claim 1 of the main request is directed to Form B *per se*, D5 ("D1" in the related case) was reworked according to -in that case - D3, and an amorphous solid was obtained. Hence, it can be assumed that the product disclosed in D5 is an amorphous solid. This was not contested by the respondent in that case, nor in the present case.

3.3.2 Patent document D6 discloses the preparation of apalutamide and its recrystallisation from DCM/EtOH (paragraph [0091]). There is no information in D6 nor has any evidence been provided by any of the parties as

to the specific form of the crystalline material prepared according to D6.

3.3.3 Claim 1 of the main request is therefore distinguished from both D5 and D6 in that a pharmaceutical composition comprising a specific crystalline form of apalutamide denoted Form B is provided, while D5 discloses the amorphous form and D6 discloses an undefined form.

3.4 Technical effects and objective technical problem

3.4.1 The respondents argued that the advantageous effects of Form B included that it was:

- less hygroscopic,
- highly thermodynamically stable and
- highly polymorphically stable.

Each effect is addressed briefly in the following.

3.5 Hygroscopicity

3.5.1 The respondents, relying on evidence in the patent as well as D19, argued that a technical effect of Form B was that it was less hygroscopic than the amorphous form of D5 and the other forms disclosed in the patent.

3.5.2 The board agrees. As submitted by the respondents, paragraph [0220] of the patent indicates that Form B is not hygroscopic, having an uptake of water at a 90% RH of less than 0.2%, measured using Gravimetric Vapour Sorption (GVS (paragraph [0216])).

3.5.3 D19 is a post-published dynamic moisture sorption experiment conducted by the respondents. Figure 2 of

D19 shows that Form B absorbed essentially no water at RH levels up to 90%, as evidenced by the essentially flat line indicating no weight change in the sample at various RH levels. Hence D19 demonstrates that Form B is negligibly hygroscopic. On the other hand, the amorphous form (D19, figure 3) shows a water uptake of about 0.25% on the first adsorption run, and about 0.80% on the second adsorption run. D19 also indicates that another crystalline form, namely Form A is significantly more hygroscopic, demonstrating a weight change of about 1.8% (D19, figure 1).

3.5.4 The appellant questioned whether any other form disclosed in the patent was in fact hygroscopic, and whether negligible hygroscopicity was an advantage rather than a mere discovery, pointing to rifaximin as an example of a marketed hygroscopic drug. However, as stated by the respondent, physical forms with low hygroscopicity are advantageous because they do not lose or gain water from the atmosphere, meaning that their weight is less variable, and the moisture content of the resulting drug is stable.

3.5.5 The appellant also submitted that no improvement in hygroscopicity was demonstrated in relation to other polymorphic forms, in particular the undefined form of D6.

3.5.6 The board disagrees. As argued by the respondents, the disclosure of D6 in relation to the crystalline form is vague: the only information provided in paragraph [0091] thereof is that the obtained solid was recrystallised from DCM/EtOH. However, insufficient information is provided to reproduce the recrystallised product, such as relative amounts of the solvents mentioned, order of addition, addition rate, etc. As

stated by the respondents, the information in the patent in combination with D19 is sufficient to render credible the effect that Form B is negligibly hygroscopic.

3.5.7 Finally, the appellant argued that even if the effect of improved hygroscopicity were demonstrated in D19, it could not be relied upon for inventive step. Specifically, the appellant referred to Enlarged Board of Appeal decision G 2/21 and in particular to reasons, points 23 and 93, to argue that while the technical effect of negligible hygroscopicity may be "encompassed" by the teaching of the application as filed, it was not "embodied" by said teaching (see also G 2/21, headnote, II).

3.5.8 This argument is not convincing. As follows from G 2/21 (point 2 of the order), for a purported effect to be taken into account for inventive step, the effect must be encompassed by the teaching of the application as filed and embodied by the same originally disclosed invention. The fact that the application as filed (paragraph [0236]) states that Form B is not hygroscopic implies that the criteria of order number 2 of G 2/21 are met. No arguments to the contrary were advanced by the appellant. Hence insofar as G 2/21 is concerned, the effect of improved hygroscopicity can be taken into account for inventive step.

3.6 In view of the above, an improvement in hygroscopicity relative to the amorphous form of D5 and the undefined form of D6 can be taken into account when defining the objective technical problem.

3.7 High thermodynamic stability

3.7.1 According to the patent, Form B has an onset temperature of 194°C as established by DSC (paragraph [0207] and figure 11 of the patent). Furthermore, according to paragraph [0221], no differences in the XRPD patterns for Form B were observed after storage at 25 °C and 92% RH for 12 days, suggesting that form B was stable under said conditions. Form B was also stable at 40 °C and 75% RH for at least a week (paragraph [0222]) Hence, Form B is highly thermodynamically stable.

3.7.2 As stated by the respondents, the technical effect relied upon in relation to Form B is high thermodynamic stability, not improved thermodynamic stability. This effect is demonstrated in the patent as set out above, and there is no need for evidence that Form B represents an improvement over other forms.

3.7.3 In view of the fact that the appellant's submissions under obviousness rely to a significant extent on the argument that it would have been obvious to the skilled person to seek to prepare thermodynamically most stable crystalline form of apalutamide (e.g. with reference to decision T 41/17, see below), with the exception of the specific argument addressed below, the appellant accepts that Form B is thermodynamically stable.

3.7.4 The appellant nevertheless argued that many of the crystalline forms disclosed in the contested patent were stable. Hence, there was no general teaching concerning stability in the application as filed, such that the originally disclosed teaching was not based on an advantage achieved by stability. Hence, this effect did not embody the originally disclosed teaching in the

context of G 2/21 (headnote II), and hence could not be relied upon in support of inventive step.

3.7.5 The board disagrees. As set out above, the application as filed provides DSC data and storage stability data which explicitly indicates that this effect is a characteristic of crystalline Form B. Hence, there can be no doubt that this effect is encompassed and embodied by the application as filed such that it can be relied upon by the respondent for supporting inventive step in the light of G 2/21.

3.7.6 The effect of high thermodynamic stability can therefore be relied on in defining the objective technical problem.

3.8 High polymorphic stability

3.8.1 As stated by the respondent and demonstrated in the patent by the disclosure of 10 different polymorphic forms (see e.g. paragraph [0017]), apalutamide exhibits wide-ranging polymorphism. This in itself can be problematic, because interconversion between polymorphic forms can occur. This is undesirable when seeking to provide a safe and reliable form of a drug, since different polymorphs often exhibit significantly different properties.

3.8.2 Compared to other crystalline polymorphic forms of apalutamide (see paragraphs [0225] to [0232]), Form B was found to be polymorphically stable (paragraph [0220]). While it is true as stated by the appellant that other forms of apalutamide such as forms A, C, D, G and H (patent, paragraphs [0219], [0223], [0224], [0229] and [0230]) also exhibit polymorphic stability, as concluded above in relation to thermodynamic

stability, an improvement in relation to other forms is not required to accept that Form B displays high polymorphic stability.

3.8.3 The appellant also argued that polymorphic stability and thermodynamic stability were one and the same advantage, and hence both represented the same effect. However, as explained by the respondents, high polymorphic stability does not necessarily imply high thermodynamic stability because kinetic factors also play a role. The respondents in this regard provided a practical example from the patent: Form E disclosed in the patent has a main endotherm at about 116°C but converts to Form A under humid conditions (patent, paragraphs [0211], [0225]), while Form G had a main endotherm at the lower temperature of about 101 °C, suggesting lower thermodynamic stability, yet no reported polymorphic instability, i.e. conversion. Hence, it can be accepted that polymorphic stability and thermodynamic stability are not one and the same effect.

3.8.4 The effect of high polymorphic stability can therefore be relied upon in defining the objective technical problem.

3.9 As stated by the respondents, the effects of improved hygroscopicity, high thermodynamic stability and high polymorphic stability represent a beneficial combination of properties possessed by Form B of apalutamide compared to the physical forms disclosed in D5 and D6.

3.10 Objective technical problem

On the basis of the foregoing, the objective technical problem underlying claim 1 starting from either of D5 or D6 is essentially that proposed by the respondents, namely the provision of a pharmaceutical composition comprising a form of apalutamide with a beneficial combination of properties, namely improved hygroscopicity, high thermodynamic stability and high polymorphic stability.

3.11 Obviousness

The appellant's arguments on obviousness were not specifically directed to the obviousness of the solution to the objective technical problem as formulated above.

3.11.1 The appellant submitted that the skilled person would have been motivated to perform routine polymorphic analyses or screening. In particular, the skilled person would commence such analyses in the knowledge that apalutamide was at a development stage suitable for stage 2 clinical trials. Such analyses were known to the skilled person from common general knowledge represented by, for example, D7, and hence would have been carried out by the skilled person on apalutamide. Following such routine guidance, the skilled person would have arrived at the claimed pharmaceutical composition comprising Form B in an obvious manner.

3.11.2 Review article D7 teaches *inter alia* that a polymorph screening should be performed as part of an IND process and that the most physically stable crystalline form was usually the way to avoid interconversion of different forms (D6, page 945, left column, second

paragraph; page 946, right column, "formation of polymorphs"; page 947, right column, first paragraph; page 948, paragraph bridging the columns). In view of these teachings, the skilled person knew that polymorphic screening was an integral part of early preformulation studies, and in particular, knew to investigate for properties such as stability and hygroscopicity as part of a routine analysis.

3.11.3 The board disagrees with the appellant's arguments. The appellant's submissions fail to take into account the formulation of the objective technical problem set out above in accordance with the problem-solution approach. Specifically, as stated by the respondents, Form B displays a beneficial combination of properties as set out above which cannot have been expected by the mere provision of a crystalline form *per se*.

3.11.4 This corresponds to the principle set down in landmark decision T 777/08. According to that decision, the technical effects or properties of the claimed polymorph (improved filterability and drying characteristics) were effects which were expected merely by virtue of being crystalline. Hence, since it belonged to the routine tasks of the skilled person involved in the field of drug development to screen for solid-state forms of a drug substance, there was an incentive for the skilled person to arrive at the claimed form solution in the expectation of achieving these improved characteristics. The board stated (see headnote 2) that "*the arbitrary selection of a specific polymorph from a group of equally suitable candidates cannot be viewed as involving an inventive step*." The implication from T 777/08 is therefore that when the advantages or effects of the claimed crystalline form are unexpected, i.e. they are not arbitrary and do not

follow merely by virtue of being crystalline, then an inventive step is present.

3.11.5 In the present case, there is no absence of unexpected properties, and the selection of Form B is not arbitrary, since Form B possesses a beneficial combination of properties as set out above. As argued by the respondents, although the skilled person *could* have carried out a polymorphic screening, there is nothing in the prior art motivating the skilled person to have taken a particular path in the expectation of solving the aforementioned objective technical problem.

3.11.6 In T 325/16, cited by the respondents in this context, it was also alleged that the skilled person would have screened for polymorphic forms as a matter of routine. The board in that case stated (reasons, 16.5.2):

"*It is true that it is in the common general knowledge of the skilled person to screen for polymorphs having improved properties... this alone is not sufficient to deny inventive step to a solution by which this improvement is achieved. Only if the prior art either contains a clear pointer ...or at least creates a reasonable expectation that a suggested investigation would be successful, can an inventive step be denied*".

Hence, this decision supports the board's conclusion.

3.11.7 In a further argument, the appellant submitted that any unexpected effects associated with Form B, such as improved hygroscopicity, amounted to mere bonus effects on which acknowledgement of inventive step could not be based. Specifically, it was argued that it would have been a clear objective for the skilled person to identify the thermodynamically most stable form, as

other forms tend to convert to the most stable form. Once thermodynamically most stable form is obtained, any further advantageous properties would be no more than bonus effects. The appellant referred in this regard to decision T 1317/13 to support its case.

3.11.8 The board disagrees. As argued by the respondents, the objective technical problem solved by the claimed subject-matter is the provision of a beneficial combination of properties, i.e. the sum of the properties demonstrated for Form B, and not just a single property. Based on the cited prior art, there is no reason for the skilled person to assume that the thermodynamically most stable form would at the same time be also polymorphically stable and in addition display improved hygroscopicity, and no such reason was provided by the appellants.

3.11.9 Furthermore, decision T 1317/13 also does not support the appellant's position. As argued by the respondents, in that case, the content of the relevant prior art document D1 was largely identical to that of the application as filed, such that the complete experimental disclosure of the latter was already known to the skilled person (reasons, 14). The board decided that the prior art document provided clear pointers to two of three technical effects relied upon (longer duration of activity and the absence of toxic side-effects) by administering the claimed compound (reasons, 17), and the final effect (pain relief) was considered a bonus effect. This is different to the present case in which there is no pointer in the prior art to the beneficial combination of properties displayed by Form B, nor is there any prior art document disclosing any of the examples of the patent in relation to the formation of Form B.

3.11.10 In the same context the appellant referred to D11, a decision of an opposition division in relation to European patent EP1557421, and D12, a decision of the German federal court of justice.

3.11.11 D11 is however irrelevant to the present proceedings. While the boards are obliged pursuant to Article 20(1) RPBA to provide the grounds for deviation from a earlier decision of any board, the same does not apply to decisions of the opposition division.

3.11.12 A similar situation applies in relation to D12. Moreover, as argued by the respondent, the situation in D12 was different to that underlying the present case. In that case, inventive step was denied because it was demonstrated that the claimed polymorph could be isolated by reproducing the examples of the prior art disclosure. This is different from the present case in which none of the prior art discloses a method by which Form B may be obtained.

3.11.13 The appellant also relied on decision T 41/17 to support the argument that Form B was obvious. Specifically, in T 41/17 the board stated that the skilled person looking for a stable crystalline form of sorafenib tosylate would have screened for thermodynamically most stable form. The appellant argued on this basis that the same applied in the present case, and the skilled person would inevitably arrive at the claimed subject-matter.

3.11.14 The board disagrees. As stated by the respondents, in T 41/17, the claimed crystalline form was alleged to have the advantage that it did not convert to other forms during mechanical stress. The technical problem

was defined as the provision of a stable form suitable for the preparation of a pharmaceutical tablet, and the solutions was considered obvious because the skilled person would have performed a screening to identify the most thermodynamically stable form, which was also expected not to convert to other forms under mechanical stress (reasons, 1.3). Hence, the provision of thermodynamically most stable form was an obvious solution to that specific problem. In the present case, thermodynamic stability is only one property from the aforementioned beneficial combination of properties displayed by the claimed Form B of apalutamide. Therefore, even if the effect of thermodynamic stability were to have been considered obvious, the same does not apply to the beneficial combination, since, for example, there is no teaching in the prior art that the effect of lower hygroscopicity could be obtained with thermodynamically most stable form. Hence the conclusions in T 41/17 do not support the appellant's case.

3.12 In view of the foregoing, the subject-matter of claim 1 of the main request involves an inventive step starting from each of D5 and D6. The same applies by extension to claims 2-7 dependent on claim 1, claims 7 and 8 directed to a process comprising preparing Form B, medical use claims 10 and 11, process claims 12 and 13 and product claim 14.

3.13 Consequently, the appellant's appeal is to be dismissed.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

K. Boelicke M. O. Müller

Decision electronically authenticated