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Datasheet for the decision of 14 May 2024

Case Number: T 2086/21 - 3.3.02

Application Number: 13800681.2

Publication Number: 2858985

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

Opponents:
Sagittarius Intellectual Property LLP
Generics (U.K.) Limited
Luigi, Rumi

Relevant legal provisions:
EPC Art. 56
RPBA 2020 Art. 13(2)

Keyword:
Inventive step

Decisions cited:
G 0002/21, T 1329/04, T 0777/08, T 1914/12, T 1317/13, T 0325/16, T 0041/17, T 1065/18

Catchword:
Inventive step of crystalline form: unexpected beneficial combination of properties - yes (points 3.5.5 and 3.6 of the reasons)

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Case Number: T 2086/21 - 3.3.02

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

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 27 September 2021 rejecting the opposition filed against European patent No. 2858985 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 appeals of opponents I and II (hereinafter appellants I and II) lie from the decision of the opposition division to reject the oppositions against European patent EP 2 858 985.

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

D1 : WO 2007/126765 A2
D2 : WO 2008/119015 A2
D3 : Experimental report: "Preparation of A52 according to para [0065] and [0066] of WO 2007/126765"
D4 : ICH Guidelines 2003 Q1 A(R2), "Stability Testing of new Drug Substances and Products"
D6 : S Byrn *et al.*, Pharm. Res. 1995, 12(7), 945-954
D8 : Chapter 8 "Preformulation" from "Pharmaceutics: The Science of Drug Design", 2002
D9 : Amorphous apalutamide stability study
D10: Clegg *et al.*, Cancer Research, 72(6), 2012, 1494-1503
D18: European Pharmacopoeia 5.0, 5.11. "Characters section in monographs"
D19: "Experimental Information" - Dynamic Moisture Sorption experiment
D27: Chapter 9 of "Drug Stability - Principles and Practices", 3rd Edition Edited by JT Carstensen and CT Rhodes (2000)
D28: Additional stability test results
D33: Decision T 41/17

III. According to the contested decision, *inter alia* the ground for opposition under Article 100(a) EPC in

combination with Article 56 EPC did not prejudice the maintenance of the patent as granted.

IV. 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) EPC did not prejudice maintenance of the patent as granted.

V. Oral proceedings by videoconference took place as scheduled on 14 May 2024 in the presence of both appellants and the patent proprietors (hereinafter respondents).

VI. Requests relevant to the present decision

Appellants I and II requested that the decision under appeal be set aside, and that the patent be revoked in its entirety.

The respondents requested dismissal of the appeal and maintenance of the patent as granted.

Opponent 3, party as of right to the present proceedings, neither filed any submissions nor submitted any requests in appeal proceedings.

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

VIII. 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 crystalline Form B of 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide that 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 of claim 1 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 polymorphic Form B of apalutamide as defined in claim 1.

1.3 Appellant II 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. The basis provided by the respondents for claim 1 was claim 15 of the application as filed. However, according to appellant II, the latter claim was directed to crystalline Form B characterised as having one of the properties (a) to (i) or combinations thereof (item (j) in claim 15 as filed). In claim 1 of the main request however, properties (d), (e), (f) and (i) stipulated in claim 15 of the application as filed had been deleted, with properties (a), (b), (c), (g) and (h) remaining.

1.4 According to appellant II, claim 1 of the main request thus resulted from a selection of certain properties from the listed properties in claim 15 of the application as filed. Such a limitation was only allowable if it did not result in the singling out of a particular combination of specific features, but maintained the remaining subject-matter as a generic group which differed from the original group only by its smaller size. Since claim 1 defined a single physical form, the claimed subject-matter was not a generic group, and hence the limitation constituted

added subject-matter. Additionally, there was no basis in the application as filed for the term "at least one" applied to the list of properties in claim 1.

1.5 The board disagrees. As argued by the respondents, claim 15 of the application as filed provides a number of different ways to characterise the same crystalline form of apalutamide denominated "Form B" – these ways are all part of the same embodiment, because they all characterise what is disclosed as Form B by different properties. 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.

1.6 Additionally, the appellant's objection that there is no basis for the expression "at least one of" in claim 1 of the main request is not convincing. 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.

1.7 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 Appellant II submitted that if claim 1 of the main request were interpreted in such a way as to encompass polymorphic forms other than Form B, a lack sufficiency of disclosure would arise.

2.2 As stated by the respondents, this objection constitutes an allegation of lack of clarity based on the fact that claim 1 provides multiple ways of defining the same physical form. However clarity is not a ground for opposition and therefore is irrelevant in relation to the claims as granted. The appellant's objection nevertheless fails, because each of the properties in claim 1 appear to be characteristic of Form B and appellant II did not provide evidence that any of these characteristics was shared by a different polymorphic form of apalutamide.

2.3 Furthermore, as stated by the respondents, the patent provides clear instructions on how to prepare and characterise Form B (paragraph [0152] and examples 3 to 9). No evidence has been provided that a crystalline form exists that both falls within the scope of claim 1 and cannot be prepared using common general knowledge in combination with the teaching of the patent.

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

3. Inventive step - Article 100(a) and 56 EPC

3.1 As set out above, claim 1 of the main request relates to crystalline Form B of apalutamide.

Both appellants and the respondents agreed that D1 represented the closest prior art, while appellant II also submitted that claim 1 lacked inventive step over D2 as closest prior art.

3.2 Distinguishing features

3.2.1 D1 discloses the preparation of apalutamide as compound A52 on page 28 (scheme at the top of the page). The physical form of the apalutamide product prepared is not provided (page 28, lines 10-12).

3.2.2 In experimental report D3, appellant I reworked the preparation of apalutamide according to D1 and obtained a solid which when analysed by XRPD was revealed as amorphous. Since this conclusion was not disputed by the respondents, it is accepted in the following that apalutamide prepared according to D1 is amorphous.

3.2.3 Patent document D2 discloses the preparation of apalutamide and its recrystallisation from DCM/EtOH (paragraph [0091]). There is no information in D2 nor has any evidence been provided by any of the parties as to the specific form of the crystalline material prepared according to D2.

3.2.4 Claim 1 of the main request is therefore distinguished from both D1 and D2 in that a specific crystalline form of apalutamide denoted Form B is provided, while D1

discloses the amorphous form and D2 discloses an undefined crystalline form.

3.3 Technical effects and objective technical problem

3.3.1 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.

3.3.2 Hygroscopicity

3.3.3 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 D1 and the other forms disclosed in the patent.

3.3.4 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])).

3.3.5 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).

3.3.6 Appellant I argued that the evidence in D19 was insufficient to demonstrate the alleged effect as the hygroscopicity demonstrated for Form B and the amorphous form was essentially the same.

3.3.7 The board disagrees. As noted by the respondents, the y-axis in figure 2 for Form B runs from -0.5 to 0.5, which is three times smaller than the -1.5 to 1.5 y-axis for the amorphous form in figure 3. Hence, the water absorption displayed in figure 3 is comparatively much stronger than a simple visual comparison of figures 2 and 3 would appear to suggest. Hence, Form B is less hygroscopic than the amorphous form. As stated by the respondents, D19 demonstrates that Form B is negligibly hygroscopic in absolute terms, having a water uptake (increase in mass) of less than 0.2%. This is supported by D18, an excerpt from the European pharmacopoeia cited by the respondents in this context, in which "slightly hygroscopic" is defined as displaying an increase in mass of less than 2% and more than 0.2%. A water uptake of less than 0.2% as observed for Form B thus implies negligible hygroscopicity.

3.3.8 Appellant I also argued that even if a difference in hygroscopicity of Form B and the amorphous form in D19 could be discerned, it was insignificant and not of any practical significance.

3.3.9 The board disagrees. As stated by the respondents, the effect of negligible hygroscopicity is of direct practical relevance to the reproducibility and

processability of Form B, since being negligibly hygroscopic removes any concerns relating to the uptake of water during processing, and as a result of the absence of water, the amount of active compound present in a given sample of Form B.

3.3.10 Appellant I also argued that there was no evidence that Form B had lower hygroscopicity than the other forms of apalutamide disclosed in the patent, in particular in its example 7. Specifically, example 7 indicated that Form A had a water content of 2.5% (w/w) (patent, paragraph [0234]), while D19 indicated a total water uptake of 1.8% by weight (figure 1) for Form A. The value reported in D19 for Form A was therefore 0.7% less than that in example 7 of the patent. This had a consequence for the water contents reported in example 7 of the patent for forms C, D and J. More specifically, the example reports for these forms a water content of 0.4, 0.3 and 0.3% respectively (patent, paragraphs [0235], [0236] and [0237]). Therefore, had forms C, D and J been tested according to the method of D19 rather than that of example 7, the application of the same difference in values obtained between D19 and example 7 for Form A would yield a water content of below 0.2% for Forms C, D and J. Hence, Forms C, D and J disclosed in the patent were at least equal to Form B in terms of hygroscopicity.

3.3.11 The board disagrees. As argued by the respondents, the extrapolation made by the appellant is not a reasonable one. Firstly, the methods of example 7 and D19 are completely different and hence not comparable. Example 7 is a determination of water content by the Karl Fischer method. D19 on the other hand concerns dynamic moisture sorption experiments in which adsorption/ desorption isotherms were measured at increasing

relative humidity. Therefore, the alleged difference of 0.7% between Form A in example 7 and Form A in D19 arises from the different parameters measured, and hence cannot be extrapolated to any other values in a scientifically credible manner.

3.3.12 On the contrary, as argued by the respondent, in relation to hygroscopicity, example 7 of the patent indicates that Forms C, D and J are "slightly hygroscopic" according to the definition provided in D18, addressed above, in contrast to Form B, which was demonstrated as negligibly hygroscopic. Since as set out above D19 also demonstrates that Form A is more hygroscopic than Form B, in the absence of any evidence to the contrary, it can be accepted that Form B is less hygroscopic than the other forms disclosed in the patent.

3.3.13 In a similar argument, appellant II submitted that on the basis of example 7 of the patent, the low water content for Forms C, D and J could indicate a better hygroscopicity compared to Form B.

3.3.14 The board disagrees. As stated above, improved hygroscopicity, and indeed negligible hygroscopicity in absolute terms was demonstrated for Form B. In the absence of evidence to the contrary, the allegation that one of the forms subjected to Karl Fischer analysis in example 7 of the patent is equally non-hygroscopic amounts to an unsubstantiated allegation. Hence, this argument fails.

3.3.15 Appellant II argued that no improvement in hygroscopicity was demonstrated in relation to other polymorphic forms, in particular the undefined form of D2.

3.3.16 The board disagrees. As argued by the respondents, the disclosure of D2 in relation to the crystalline form obtained 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. The burden of proof in demonstrating a equally low hygroscopicity for other crystalline forms or the undefined form of D2 therefore lies with the appellants.

3.3.17 In a further argument, appellant I, referring to T 1329/04, submitted that even if D19 demonstrated an improvement in hygroscopicity, it was post-published, and therefore should not be taken into account on the basis that the effect was not made plausible by the contents of the application as filed.

3.3.18 The board disagrees. As follows from G 2/21 (point 2 of the order), published subsequent to the filing of the appellant's grounds of appeal, 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 [00236]) 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 appellants neither in writing nor during oral proceedings before the board. Hence insofar

as G 2/21 is concerned, the effect of improved hygroscopicity can be relied upon for inventive step.

3.3.19 Consequently, an improvement (i.e. reduction) in hygroscopicity relative to the amorphous form of D1 and the undefined form disclosed in D2 can be relied on in defining the objective technical problem.

3.4 High thermodynamic stability

3.4.1 According to the patent, Form B has an onset temperature of 194°C as established by DSC (figure 11 and paragraph [0207] of the patent). Furthermore, according to paragraph [0221] of the patent, no difference in the XRPD patterns for Form B was observed after storage at 25 °C and 92% RH for 12 days, indicating 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] of the patent) Hence, Form B is thermodynamically stable.

3.4.2 In view of the fact that the appellants' 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 the thermodynamically most stable crystalline form of apalutamide, with the exception of the specific argument addressed below, the appellants accept that Form B is thermodynamically stable.

3.4.3 Appellant II nevertheless also argued that Form J (patent, figure 18) was just as stable as Form B, and hence Form B had no unique or unexpected properties. Furthermore, no comparison with D1 had been provided, and no improvement had been demonstrated over the undefined crystalline form disclosed in D2.

3.4.4 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.

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

3.5 High polymorphic stability

3.5.1 As stated by the respondents 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. Polymorphic interconversion is undesirable when seeking to provide a safe and reliable form of a drug, since different polymorphs often exhibit significantly different properties.

3.5.2 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 appellant II 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.

3.5.3 Appellant I 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.

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

3.5.5 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 D1 and D2.

3.5.6 In this regard, during oral proceedings, appellant II argued that Form B had no unique beneficial combination of properties since other forms of apalutamide had similar properties. To illustrate its argument, the appellant referred to the data in the patent relating to Form H and noted that this form *inter alia* had a

similar thermodynamic stability and similar polymorphic stability to Form B. Hygroscopicity had been assessed for Forms A and B only.

3.5.7 The respondents requested not to admit the new allegation that, in terms of properties, Form H of apalutamide was similar to Form B.

3.5.8 Appellant II conceded that the comparison of Form H with Form B had not been submitted in appeal proceedings prior to the oral proceedings before the board. It however submitted that it did not represent a new fact, but a mere illustration of an argument, the argument being that the alleged combination of effects was not linked to a technical teaching.

3.5.9 The board disagrees. According to T 1914/12 (reasons 7.1.4), a "fact" is to be understood as a piece of (allegedly) factual information or a circumstance on which a party based its case, whereas an "argument" is a contention that is based on one or more such facts and that supports the ground it is invoking. In the present case, the data in the patent relating to Form H is such a fact, and not an argument in itself. The argument relates to the comparison of Form H with Form B. Therefore, the invocation of the data in the patent concerning Form H represents an amendment to the appellant's case in accordance with Article 13(2) RPBA, which stipulates that such an amendment shall, in principle, not be taken into account unless there are exceptional circumstances, which have been justified with cogent reasons by the party concerned.

3.5.10 Since no exceptional circumstances were identified by the appellant, the board decided not to admit this allegation into the appeal proceedings.

3.5.11 On the basis of the foregoing, the objective technical problem underlying claim 1 starting from either of D1 or D2 is essentially that proposed by the respondents, namely the provision of a form of apalutamide with a beneficial combination of properties, namely improved hygroscopicity, high thermodynamic stability and high polymorphic stability.

3.6 Obviousness

3.6.1 The appellants' arguments on obviousness were not specifically directed to the obviousness of the solution to the objective technical problem as formulated above, namely the provision of a form of apalutamide with a beneficial combination of properties.

3.6.2 Appellant I submitted that in view of the fact that apalutamide was the subject of an Investigational New Drug (IND) filing before the filing date of the patent as evidenced by D10, 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, D4, D6, D8 and D27, 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 Form B in an obvious manner.

3.6.3 D4 is the EMA 2003 version of the "ICH Guidance on Stability testing on ... drug substances and products",

and teaches in relation to the information to be submitted in registration applications for new drug products, that stability and sensitivity to moisture should be investigated (D4, sections 1.2, 2.1.1 and 2.2.7). Review article D6 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). Appellant I argued that 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 this routine analysis. Book excerpt D8 teaches routine polymorph screening and the determination of the most stable form, in particular if polymorphism occurs. The desire that drug substances should be non-hygroscopic is also expressed (D8, page 126, right column, first full paragraph; page 132, "Hygroscopicity", last two sentences). Finally, book excerpt D27 teaches that IND applications require stability testing and information on hygroscopicity (pages 238-239, section 1; page 251, "Hygroscopicity").

3.6.4 Appellant I also referred to stability reports D9 and D28, submitted to demonstrate that by application of routine stability testing taught by the common general knowledge D4, amorphous apalutamide converted to Form B under routine conditions. Hence, the skilled person would have obtained Form B by carrying out routine tests, and thereby would have arrived at the subject-matter of claim 1 in an obvious manner.

3.6.5 The board disagrees. The appellants' 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*.

3.6.6 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 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.

3.6.7 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.

3.6.8 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 made above.

3.6.9 Appellant I's reliance on its stability testing in D9 and D28 does not alter this conclusion. According to the appellant, these tests demonstrate that under stability testing, amorphous apalutamide converted to Form B. However, although the skilled person could have performed this stability test before the filing date of the patent, there would have been no reason to do so in the expectation of solving the technical problem set out above, i.e. of producing a form of apalutamide with the aforementioned beneficial combination of properties.

3.6.10 In a further argument, both appellants 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 the thermodynamically most stable form was obtained, any further advantageous properties would be no more than bonus effects. Appellants I and II referred in this regard to decisions T 1065/18 and T 1317/13 respectively to support their case.

3.6.11 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.

3.6.12 Furthermore, neither of decisions T 1065/18 and T 1317/13 support the appellants' positions.

3.6.13 In T 1065/18 the board decided that the skilled person aiming at higher solubility would have performed a DSC analysis on the crystalline Form A of febuxostat disclosed in the prior art, and thereby would have arrived at the claimed form I. The fact that form I *retained* the non-hygroscopicity of form A was considered merely as a bonus effect that the skilled person would inevitably achieve, because they were primarily looking for a crystalline form of febuxostat

with higher solubility. As stated by the respondents, this situation is different from the present case in which no specific crystalline forms are known from the prior art, and in which a property, namely hygroscopicity, is improved compared to the prior art, rather than being merely retained. Hence, the conclusion in T 1065/18 is not relevant to the present case.

3.6.14 In T 1317/13, as argued by the respondents, 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.

3.6.15 Both appellants 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 the thermodynamically most stable form. The appellants argued on this basis that the same applied in the present case, and the skilled person would inevitably arrive at the claimed subject-matter.

3.6.16 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 solution 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 the thermodynamically most stable form was an obvious solution to that specific problem.

3.6.17 In the present case in contrast, 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 the thermodynamically most stable form of apalutamide. Hence the conclusions in T 41/17 do not support the appellants' case.

3.6.18 Finally, appellant I submitted that the skilled person starting from the amorphous apalutamide of D1 would have been in a "try and see" situation. Specifically, the skilled person would have carried out a routine polymorphic screening as addressed above and thereby would have arrived at Form B as claimed. Citing from the Case Law of the Boards of Appeal (section 1.D.7.2 of the most recent 10th edition), it argued that when neither the implementation nor the testing of an

approach suggested by the prior art involved any particular difficulties, the consideration that the skilled person would have adopted a "try and see" attitude was a reason for denying inventive step. This situation applied in the present case.

3.6.19 The board disagrees for the reasons provided by the respondents. Specifically, the "try and see" case law cited by the appellant concerns the situation in which the prior art suggested that a clear way forward would solve the technical problem at hand, i.e. an "approach suggested by the prior art" as mentioned in the text of the case law cited by the appellant above. Hence, the try and see situation is entirely predicated on the existence of a pointer to the solution in the prior art. In the present case, as established above, there is no pointer in the prior art that leads the skilled person confronted with the above-defined objective technical problem to the solution provided by claim 1. Hence, the "try and see" case law is not relevant in the present situation.

3.7 In view of the foregoing, the subject-matter of claim 1 of the main request involves an inventive step starting from each of D1 and D2. The same applies by extension to claims 2-6 dependent on claim 1, pharmaceutical composition claims 7-12 comprising Form B and corresponding medical use claims 13-15.

3.8 Consequently, the appellants' appeals are to be dismissed.

Order

For these reasons it is decided that:

The appeals are dismissed.

The Registrar: The Chairman:

K. Boelicke M. O. Müller

Decision electronically authenticated