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Datasheet for the decision of 9 July 2025

Case Number: T 0722/24 - 3.3.07

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Language of the proceedings: EN

Title of invention:
FORMULATIONS OF ENZALUTAMIDE

Patent Proprietor:
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Headword:
Enzalutamide/MEDIVATION

Relevant legal provisions:
EPC Art. 76(1), 123(2), 83, 87(1), 56, 115
RPBA 2020 Art. 12(2), 12(4), 12(6), 13(2)

Keyword:
Late-filed evidence - admittance
Observations by third parties - admittance (no)
Amendments - allowable (yes)
Sufficiency of disclosure - (yes)
Priority - basis in priority document (yes)
Inventive step - (yes)

Decisions cited:
G 0002/21, T 1439/09, T 2255/15, T 2070/19

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Beschwerdekammern

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Case Number: T 0722/24 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 9 July 2025

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Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 8 May 2024 concerning maintenance of the European Patent No. 3725778 in amended form.**

Composition of the Board:

Chairman	A. Usuelli
Members:	M. Steendijk
	S. Ruhwinkel

Summary of Facts and Submissions

I. European patent 3 725 778 ("the patent") was granted with twenty claims. It derived from a divisional application of the earlier European Patent Application No. 13766437.1, originally published as PCT application WO 2014/043208 A1.

II. Eleven oppositions were filed against the grant of the patent on the grounds that its subject-matter lacked an inventive step, that the claimed invention was not sufficiently disclosed and that the patent comprised subject-matter extending beyond the content of the parent and the subsequent divisional application as originally filed.

Opponents 1–6, 9, and 11 lodged appeals against the interlocutory decision of the Opposition Division, which found that the patent, as amended in accordance with the patent proprietor’s main request filed on 12 December 2022, met the requirements of the EPC.

Claim 1 of the main request corresponded to claim 1 as granted, defining:

"A solid pharmaceutical composition comprising a solid dispersion containing amorphous enzalutamide and a concentration-enhancing polymer, wherein the polymer is hydroxypropyl methylcellulose acetate succinate."

Claim 2 additionally defined that the amount of the polymer is 3 to 5 parts by weight per 1 part by weight of the enzalutamide.

Claim 3 further defined the amount of the polymer as 5 parts by weight per 1 part by weight of the enzalutamide.

Claim 4 defined the composition of claim 1 to be in unit dosage form, containing 40 to 160 mg of enzalutamide per unit.

Claim 5 defined that at least 80% of the total enzalutamide present in the composition of claim 1 is in amorphous form.

Claim 7 defined the composition of claim 1 as a tablet.

Claim 8 defined the composition of claim 1 for use in the treatment of a hyperproliferative disorder which is prostate cancer.

Claim 9 defined the composition of claim 8 further, specifying that the prostate cancer is selected from hormone-refractory and hormone-sensitive prostate cancer.

The opposition division cited *inter alia* the following documents:

D1: US 2007/004753 A1
D3: Prescribing information for XTANDI capsules, 08/2012
D4: Molecular Pharmaceutics, 2008, 5(6):1003-1019
D6: Pharmaceutical Research, 2009, 26(6):1419-1431
D7: US 2002/0009494 A1
D10: AAPS PharmSciTech, 2008, 9(3):991-997
D17: Drug Development and Industrial Pharmacy, 2017, 43(11):1743-1758

D18: United States Environmental Protection Agency, "The Presidential Green Chemistry Challenge Awards Program: Summary of 2010 Award Entries and Recipients", June 2010, pages 1-52
D19: Drug Development & Delivery, Issue: July/August 2012, pages 1-9
D22: Drug Development and Industrial Pharmacy, 2004, 30(1):9-17
D23: Journal of Drug Targeting, 2010, 18(10):704-731
D25: Pharmaceutical Research, 2009, 26(12):2599-2606
D35: ClinicalTrials.gov Identifier NCT01911741, 30 July 2013
D36: The AAPS Journal, 2012, 14(4):703-713
D38: International Journal of Pharmaceutics, 2011, 419:12-19
D48: US FDA Multi-Discipline Review(s) for Xtandi Tablets, signed 4 August 2020
D49: Summary of Studies
D50: US FDA Product Quality Review(s) for Xtandi Tablets, signed 14 July 2020
D51: Expert Opin. Drug Deliv., 2011, 8(10):1361-1378
D52: The AAPS Journal, 2012, 14(3):380-388
D53: Drug Discovery Today: Technologies, 2012, 9(2):e79-e85
D54: Journal of Pharmacy and Pharmacology, 2009, 61: 1571-1586
D55: Molecular Pharmaceutics, 2010, 7(4):1328-1337
D56: Drug Delivery (2020), 27(1):110-127
D61a: Expert opinion from Prof. Dr. Thomas Rades of 17 November 2023
D61c: International Journal of Pharmaceutics, 2023, 631, 122564:1-8
D65: FASTtrack - Pharmaceutics: Drug Delivery and Targeting, Second Edition (2012); Yvonne Perrie and Thomas Rades, Chapter: Immediate-Release Drug Delivery

Systems I: Increasing the solubility and dissolution rate of drugs; pages 35-50
D68: Amorphous Solid Dispersions; Chapter 9: Design and Development of HPMCAS-Based Spray-Dried Dispersions, 2014, Vodak and Morgen, pages 303-322
D69: Journal of Controlled Release, 2018, 292:172-182
D70: Expert Declaration Prof. Wagner of 5 February 2024
D72: Formulating Poorly Water Soluble Drugs, 2012, Williams III et al., pages v-xii and 27-131
D74: Drug Development and Industrial Pharmacy, 2013, 39(2):402–412
D77: Drug Development and Industrial Pharmacy, 2012, 38(2):180-189
D78: Declaration Prof. Wagner of 4 April 2024
D79: European Journal of Pharmaceuticals and Biopharmaceutics, 2014, 87:264 – 270

The opposition division arrived at the following conclusions:

(a) The main request did not comprise subject-matter extending beyond the content of the parent or the subsequent divisional application as originally filed. The parent and divisional application as filed disclosed a pharmaceutical composition comprising a solid dispersion containing amorphous enzalutamide and a polymer which is hydroxypropyl methylcellulose acetate succinate (HPMC-AS) in claims/clauses 83, 84 and 86. The skilled person recognized from claims/clauses 7, 14 and 15 and paragraph [68] that HPMC-AS represented a concentration-enhancing polymer as defined in claim 1 of the main request. The skilled person furthermore recognized from paragraphs [03] and [150]-[151] of the parent application that the

disclosed pharmaceutical compositions were in particular solid compositions.

The further features of dependent claims 2, 3, 5, and 7 were also directly and unambiguously derivable from the original disclosure.

(b) The opponents had not demonstrated that the claimed invention was insufficiently disclosed in the patent.

(c) The priority of 11 September 2012 was validly claimed for the subject-matter of the main request.

(d) Document D3 represented the closest prior art. This document referred to enzalutamide as practically insoluble in water and described the commercial product XTANDI as a liquid-filled soft gelatin capsule containing 40 mg of enzalutamide as a solution in caprylocaproyl polyoxylglycerides (Labrasol). Document D1 represented less pertinent prior art, because it lacked a disclosure of an individualized and specific pharmaceutical composition for the sparingly soluble enzalutamide.

The subject-matter of claim 1 of the main request differed from the XTANDI product of document D3 in that the enzalutamide was provided in a solid dispersion containing amorphous enzalutamide and HPMC-AS as a concentration enhancing polymer.

The patent demonstrated with the results from human *in vivo* tests reported in Example 15 that the claimed composition provided for comparable bioavailability in terms of area under the curve (AUC) values with respect to the liquid-filled soft

gelatin capsule of the prior art. The objective technical problem was therefore defined as the provision of a further pharmaceutical composition comprising enzalutamide in amorphous form which gives rise to comparable bioavailability or which has similar AUC values found in human *in vivo* tests compared with the approved XTANDI capsule formulation.

In view of the unpredictability of the performance of solid drug dispersions of poorly soluble drugs, as indicated by for instance documents D36 and D51-D54, the skilled person would not have provided the claimed subject-matter with any reasonable expectation of success as solution to the identified objective technical problem. The subject-matter of the main request therefore involved an inventive step.

III. The following additional documents were filed by the parties to the appeal proceedings:

A80: EMA Guideline on the Investigation of Bioequivalence 20 January 2010
A81: "Bioequivalence of Pilot Tablet Formulations of Ritonavir (RVT) to the Marketed Soft gel Capsule (SGC) at a Dose of 100 mg", 14th Conference on Retroviruses and Opportunistic Infections, Los Angeles, Feb 25-27 2007
by O2 with the statement of grounds of appeal

A82: (labelled as "D80"): Mutschler, Arzneimittelwirkungen, Wissenschaftliche Verlagsgesellschaft mbH
Stuttgart, 2008, pp. 5-9
by O9 with the statement of grounds of appeal

A83: Judgement of district court of the Hague "C/ 09/654337 /HAZA 23-858"
A83a: English translation of document A83
by the patent proprietor with the reply to the appeals

A84: Systematic Reviews (2019), 8:112 ("Medication adherence influencing factors - an (updated) overview of systematic reviews")
by O1 with the letter of 28 April 2025.

In addition, anonymous third party observations under Article 115 EPC were filed on 1 May 2025, 6 May 2025 (at 12:47 and at 14:09), and 30 June 2025. The following document was filed with the observations of 1 May 2025:

A85: "Public Assessment Report, Scientific discussion, Enzalutamide PharOS 40 mg and 80 mg film-coated tablets (enzalutamide)", College ter Beoordeling van Geneesmiddelen (28 August 2024).

IV. With the reply to the appeal, the patent proprietor maintained the main request as filed before the opposition division on 12 December 2022.

V. In its communication pursuant to Article 15(1) RPBA of 6 March 2025, the Board expressed the preliminary opinion that the main request on which the decision under appeal was based met the requirements of the EPC.

VI. O6 referred in their letter of 26 May 2025 to the observations submitted by a third party stating that the arguments and evidence presented therein are made part of their pleadings, because these observations support and confirm their earlier arguments.

VII. Oral proceedings were held on 8 and 9 July 2025.

VIII. The arguments of the opponents relevant to the present decision are summarised as follows:

(a) Admittance of evidence and third party observations

The post-published documents D48-D50 were cited by the patent proprietor in support of the alleged technical effect of comparable bioavailability to XTANDI capsules. These documents should not be admitted, because this effect could not be derived as encompassed by the technical teaching and embodied by the same originally disclosed invention.

Document A80 was evidence of the common general knowledge concerning the relevance of the C_{max} and t_{max} for the determination of bioequivalence. It was cited in response to findings in the decision under appeal regarding the selection of the closest prior art and the skilled person's motivation to develop an alternative composition with the same safety and efficacy as XTANDI capsules.

Document A81 supported the argument that, contrary to the finding in the decision under appeal, it was known that the formulation in a solid dispersion improves the bioavailability of poorly soluble compounds such as ritonavir and that bioequivalence and a smaller tablet size with respect to ritonavir soft gel capsules had been achieved by the formulation of ritonavir in a solid dispersion.

Document A82 supported the argument that, contrary to the finding in the decision under appeal, the skilled person would have considered the physico-chemical properties of an active pharmaceutical ingredient such as enzalutamide in the development of a dosage form comprising such ingredient.

Document A84 represented evidence of common general knowledge that the impact on patient adherence due to the number of tablets to be taken in oral anti-cancer treatment has not been proven.

Document A85 demonstrated that the use of HPMC-AS as a concentration enhancing polymer does not result in an advantage concerning the bioavailability compared to a methacrylic acid-ethyl acrylate (1:1) copolymer.

The third party observations supported and confirmed the arguments as presented by O6 during the appeal proceedings.

(b) Amendments - Articles 76(1) and 123(2) EPC

Claim 83 as originally filed defined any pharmaceutical composition comprising a solid dispersion containing enzalutamide and a polymer, not specifically a solid pharmaceutical composition. The original disclosure distinguished in paragraph [03] between solid formulations comprising amorphous enzalutamide and pharmaceutical compositions comprising such formulations. The application as originally filed described various examples of liquid pharmaceutical compositions, such as creams and suspensions, as well as various particular types of solid

pharmaceutical compositions, but not the solid pharmaceutical compositions as a general category as defined in claim 1 of the main request. Claim 1 of the main request therefore involved an impermissible intermediate generalisation.

The application as originally filed disclosed in claim 84 a pharmaceutical composition wherein enzalutamide was "an amorphous state" and thereby required in line with the original description a majority of the enzalutamide to be in an amorphous state. Original claim 84 did therefore not provide an adequate basis for claim 1 of the main request which defined that the composition comprising a solid dispersion merely contains amorphous enzalutamide.

Claim 1 of the main request furthermore involved multiple selections with respect to the original disclosure, including the choice of the class of ionizable cellulosic polymers for the concentration enhancing polymer and within that class the selection of HPMC-AS as the specific polymer in the solid dispersion. Whilst claim 86 as originally filed defined HPMC-AS as the polymer of the composition of claim 83, this claim 86 did not refer back to claim 84.

Claims 2-3 involved the additional selection of the amount of enzalutamide relative to the polymer. This selection could not be based on claims 89-91 of the original disclosure, which only referred to independent claim 83.

Claim 4 involved the additional selection of the absolute amount of enzalutamide in a unit dosage form.

The definition in claim 5 of at least 80% of the enzalutamide in the composition being present in an amorphous form did not find a basis in the application as originally filed.

Claim 7 involved the additional selection of the form of a tablet.

Claims 8-9 could not be based on the definition of the hyperproliferative disorders to be treated in original claims 62-64, because these claims did not refer to a solid pharmaceutical composition comprising a solid dispersion with HPMC-AS.

(c) Priority

The passage in the priority document which corresponded to paragraph [03] of the application as originally filed merely referred to solid formulations of enzalutamide. Unlike the application as originally filed, the priority document did not mention solid formulations comprising amorphous enzalutamide and pharmaceutical compositions comprising a solid dispersion containing enzalutamide and a polymer in this passage. The solid pharmaceutical compositions of claim 1 of the main request did therefore not enjoy the claimed priority.

(d) Sufficiency - Article 83 EPC

The patent did not credibly disclose the suitability of enzalutamide in the treatment of "androgenic hormone-independent prostate cancer" as opposed to "androgenic hormone-dependent prostate cancer", which are both covered by claims 8 and 9 of the main request.

Enzalutamide was known to block the androgen receptor and could therefore inhibit androgen-dependent growth signals in prostate cancer caused by androgenic hormones. However, the patent did not provide any evidence that compositions comprising enzalutamide as defined in claim 1 of the main request could be plausibly used for treatment of androgenic hormone-independent prostate cancer that may be caused by alternative growth signals.

(e) Inventive step - Article 56 EPC

- The claimed subject-matter lacked an inventive step starting from document D35, which described a study to evaluate the bioavailability of enzalutamide formulated as a solid spray-dried tablet compared to oral liquid-filled capsules.

- The subject-matter of claim 1 of the main request also lacked an inventive step starting from document D3, which described capsules comprising a liquid solution of dissolved enzalutamide in a solvent mixture (XTANDI capsules) instead of a solid pharmaceutical composition comprising a solid dispersion containing amorphous enzalutamide and HPMC-AS as a concentration enhancing polymer.

Any advantage in terms of convenience of administration or patient adherence with respect to the XTANDI capsules of document D3 would depend on the size and dosage of the composition and could therefore not be attributed to the distinguishing features of the claimed subject-matter.

The effect of a comparable bioavailability in humans with respect to the XTANDI capsules of document D3 could also not be taken into account in the formulation of the objective technical problem. The teaching of the patent was not limited to treatment of human patients. Moreover, the patent reported in Example 15 results of a study demonstrating that a tablet comprising a solid dispersion of enzalutamide was actually not bioequivalent to the XTANDI capsules in view of the reported C_{Max} and t_{max} values. The effect of merely a comparable AUC was furthermore not defined in the patent and lacked technical significance. In view of the considerations in G 2/21, the patent proprietors could therefore also not rely on the post-published documents D48-D50 as proof of such effect. The effect of a comparable bioavailability with respect to the XTANDI capsules of document D3 was in any case not credibly achieved over the whole scope of the claims. The results of example 15 in the patent only concerned one particular tablet formulation and only its administration in human patients. However, as demonstrated by the results reported in tables 4.2, 9.2, 11.2, 12.1, 13.1 and 19 of the patent, the results in the post-published documents D48 and D49 as well as the results in the post-published document D69 the AUC critically depended on features of the composition and the solid dispersion that are not defined in

claim 1 of the main request, in particular the enzalutamide to HPMC-AS weight ratio, the presence of crystalline enzalutamide, the preparation of the solid dispersion by hot melt extrusion and the resulting variation in particle sizes, the type of HPMC-AS as well as the presence of other excipients. The description of the patent furthermore explicitly stated that substantially homogeneous dispersions generally have improved bioavailability relative to non-homogeneous dispersions. The opponents could not be required to provide additional evidence based on experiments in human subjects, in particular in view of the teaching in the patent itself that results from *in vitro* experiments and animal studies were predictive for effects in human subjects.

The patent did not demonstrate any effect concerning the stability in comparison to the XTANDI capsules of document D3. Moreover, the experimental results reported in example 6 of the patent actually indicated that no particular stability had been achieved, at least not over the whole scope of the claims. The description of the patent further explicitly stated that substantially homogeneous dispersions are generally more physically stable relative to non-homogeneous dispersions and that a glass transition temperature of the composition above the storage temperature was required for stability.

The objective technical problem therefore merely concerned the provision of a suitable further solid formulation of enzalutamide without any additional qualification.

Even if the objective technical problem was further qualified in terms of convenience, comparable bioavailability and stability, the claimed subject-matter would still represent an obvious solution to the skilled person.

As illustrated by document D6, the skilled person who started from the XTANDI capsules of document D3 was evidently motivated to seek a solid oral dosage form for enzalutamide which avoids the practical constraints of liquid filed capsules.

As evidenced by documents D4 and D6, D7 and D10, D18, D19, D22, D23, D25, D36 and D38 as well as the post-published documents D17 and D68, the skilled person was familiar with the approach of formulating a sparingly soluble active pharmaceutical ingredient (API) in the form of an amorphous solid dispersion to enhance its bioavailability. It was also well known that the use of HPMC-AS as polymer in such amorphous solid dispersions allows for the broad application of this approach by providing superior solubilisation, precipitation inhibition and stability of the solid state with respect to other polymers. In view of the prior art it was therefore obvious for the skilled person to try this approach for enzalutamide using HPMC-AS as concentrating polymer. In particular the explanations in documents D4 and D6 provided the skilled person with a reasonable expectation of success.

The known successful formulation of lopinavir and ritonavir as a solid dispersion following their initial marketing as liquid-filled soft gelatin capsules confirmed the skilled person's reasonable

expectation that enzalutamide could also be successfully formulated as a solid dispersion.

The skilled person's expectation from the prior art with regard to the successful formulation of enzalutamide in a solid dispersion with HPMC-AS would not be affected by any general statement in documents D36 or D51-D54 questioning the predictability of the performance of compositions comprising an amorphous solid dispersion of poorly soluble APIs in general. Document D36 actually indicated HPMC-AS as highly effective in such compositions and documents D51-D54 did not mention HPMC-AS.

- The subject-matter of claim 1 of the main request furthermore lacked an inventive step starting from document D1. This document disclosed enzalutamide as an example of a compound with utility in the treatment of prostate cancer which may be administered orally, for instance in the form of a tablet or capsule. Document D1 therefore represented a suitable alternative starting point in the prior art. The differentiating features of the claimed subject-matter involved the formulation of enzalutamide in amorphous form in a solid dispersion with HPMC-AS as a concentration enhancing polymer. No particular effects had been shown to result from these differences. XTANDI capsules were not part of the teaching of document D1 and the skilled person had no need to consider such capsules starting from document D1. A comparison to the bioavailability of dissolved enzalutamide in XTANDI capsules could therefore not demonstrate any effect related to the differentiating features with respect to

document D1. The objective technical problem starting from document D1 could therefore only concern the provision of an oral formulation which is stable and bioavailable. The provision of enzalutamide in the form of an amorphous solid dispersion as defined in claim 1 of the main request was obvious to the skilled person as a solution to this problem, because it was well known to formulate a poorly soluble active pharmaceutical ingredient (API) in the form of an amorphous solid dispersion to enhance its bioavailability and because documents D4 and D6 already described HPMC-AS as a particularly suitable concentration enhancing polymer. Any achievement of comparable bioavailability of the enzalutamide compared to a liquid-filled capsule would at best represent a mere bonus effect.

IX. The arguments of the patent proprietors relevant to the present decision are summarized as follows:

(a) Admittance of evidence and third party observations

Documents D61a, D65, D68, D69, D70, D77, D78, and D79 added nothing to the initially filed documents. These subsequently filed documents should thus not have been admitted by the opposition division for lacking *prima facie* relevance. The late filing of documents D61a and D69 was also objectionable, because these documents could have been filed earlier during the opposition proceedings.

Document D61c represented a justified response to the filing of document D61a. This document should have been admitted by the opposition division and was in any case relevant to the appeal proceedings.

Documents A80-A82 did not address the issues which had led to the decision under appeal and should therefore not be admitted into the appeal proceedings.

Documents A83/A83a concerned the judgement of the District Court of The Hague upholding the main request in the Netherlands issued on 22 January 2025. This judgement was evidently of interest and should therefore be admitted.

The late filing of documents A84 and A85 was not justified by any exceptional circumstances.

The anonymous third party observations were inadmissible, in line with the considerations in T 1439/09 as well as in T 2255/15. These third party observations were not rendered admissible by the general reference by O6 to these submissions.

(b) Amendments - Articles 76(1) and 123(2) EPC

The application as originally filed defined in claim 83 "a pharmaceutical composition comprising a solid dispersion containing enzalutamide and a polymer", wherein according to dependent claim 84 "enzalutamide is an amorphous state" and wherein according to dependent claim 86 "the polymer is hydroxypropyl methylcellulose acetate succinate" (HPMC-AS). The application as originally filed explicitly referred to solid formulations of enzalutamide and described specific dosage forms as examples of solid pharmaceutical compositions. The original disclosure thereby provided an adequate

basis for the definition of a solid pharmaceutical composition in claim 1 of the main request.

The definition in original claim 84 concerning enzalutamide in an amorphous state did not require that the majority of the enzalutamide was in an amorphous state. The original disclosure merely indicated that in some embodiments at least a major portion of the enzalutamide in the composition is amorphous.

The additional features of the dependent claims had been highlighted in the application as originally filed and thus found an adequate basis in the original disclosure.

(c) Priority

In line with the application as originally filed, the priority document explicitly referred to the disclosure as relating to solid formulations of enzalutamide and described specific dosage forms as examples of solid pharmaceutical compositions.

The solid pharmaceutical compositions of claim 1 of the main request therefore enjoyed the claimed priority.

(d) Sufficiency - Article 83 EPC

According to document D3, enzalutamide was authorized for use in the treatment of patients with castration-resistant prostate cancer, which is explained to be prostate cancer that is resistant to medical or surgical treatments that lower testosterone. The skilled person would therefore

have no reason to doubt the suitability of the defined composition for the treatment of prostate cancer according to claims 8 and 9 of the main request, including the treatment of androgenic hormone-independent prostate cancer.

(e) Inventive step - Article 56 EPC

- Document D35 could not represent a starting point in the assessment of inventive step, because this document did not form part of the prior art.

- The distinguishing features of the claimed subject-matter with respect to the marketed XTANDI capsules comprising dissolved enzalutamide described in document D3 concerned the formulation of a solid dispersion comprising enzalutamide in amorphous form with HPMC-AS instead of an encapsulated solution of enzalutamide.

  The distinguishing features provided the technical effects of improved convenience of administration, comparable bioavailability in humans relative to the XTANDI capsules and excellent physical stability.

  Due to the limited solubility of enzalutamide in Labrasol the XTANDI capsules of the prior art required the inconvenient administration of 4 large 40 mg capsules to achieve the recommended dose of 160 mg, whereas example 15 of the patent demonstrated in a like-for-like comparison that the distinguishing features allow the administration of the 160 mg dose of enzalutamide with conveniently fewer and/or smaller dosage forms.

The original disclosure referred in paragraph [05] to the advantage of a suitable alternative to the liquid-filled XTANDI capsules and indicated in paragraph [226] the equivalent bioavailability in terms of the AUC achieved in humans with a tablet containing a spray-dried solid dispersion of enzalutamide in HPMC-AS as compared to liquid-filled capsules. The effect of comparable bioavailability in humans relative to XTANDI capsules was thus encompassed by the technical teaching and embodied by the same invention. Bioequivalence in a strict sense, including the aspects of an equivalent C_{max} and T_{max}, was not required for the effect of comparable bioavailability in terms of the AUC to be technically meaningful.

The data reported in example 15 of the patent and the post-published documents D48-D50 demonstrated in a like-for-like comparison that the solid dispersion defined in claim 1 of the main request indeed provided the effect of comparable bioavailability in humans. Whilst it would always be possible to use an invention in such a way that its effects are not optimally achieved, neither the results in the patent nor the results reported in documents D48, D49 and D69 as relied on by the opponents provided evidence of solid dispersions as defined in claim 1 that failed to achieve this effect.

The patent also demonstrated excellent physical stability for the claimed composition in examples 5, 6, 26 and 28. This stability of the claimed composition was further confirmed in document D49. The effect of the defined solid dispersion with

regard to stability was not challenged by the reference to fusion of particles under extreme conditions in three of four samples reported in example 6 of the patent. The excellent stability of the claimed compositions represented an important property of the claimed composition, which was *per se* relevant for the formulation of the objective technical problem, irrespective of the absence of a comparison with the XTANDI capsules of the prior art.

The objective technical problem should therefore be formulated as the provision of a formulation of enzalutamide for delivering comparable oral bioavailability to XTANDI capsules in humans with excellent physical stability which allows for improved convenience of administration.

As evidenced by documents D36, D51, D52, D53, D54, D56 and D72, it was common knowledge that the development of suitable formulations of poorly soluble APIs remained in general difficult and was driven by trial and error of many potential approaches. The formulation of APIs in an amorphous form such as in solid dispersions was especially challenging, because the stability of the amorphous form in such formulations could not be predictably preserved by the selection of carriers. Enzalutamide was a particularly challenging agent due to its strong tendency to crystallize. Whilst documents D23 and D36 referred to HPMC-AS as an advantageous excipient, these documents still underlined the persisting difficulty of providing suitable amorphous solid dispersions for poorly soluble APIs. Documents D55 and D74 confirmed that the suitability of HPMC-AS depends unpredictably on

the API to be formulated. The skilled person would be aware of this unpredictability when considering reports of the successful formulation of agents such as lopinavir and ritonavir in the form of solid dispersions and the discussions in documents D4, D6, D18 and D19 regarding the advantageous properties of HPMC-AS for the formulation of APIs in solid dispersions. The prior art did therefore not provide the skilled person with a reasonable expectation regarding the provision of enzalutamide in the form of a solid dispersion with HPMC-AS as a solution to the formulated qualified objective technical problem with respect to the XTANDI capsules of the prior art.

Without any motivation based on a reasonable expectation of success to solve the objective technical problem, the skilled would not arrive at the claimed composition as a matter of obviousness.

- In view of the known oral compositions of enzalutamide in the form of the XTANDI capsules, document D1 did not realistically represent the closest prior art, because it only described enzalutamide amongst other examples of agents with utility in treatment of hormone refractory prostate cancer without disclosing any specific pharmaceutical composition comprising enzalutamide. Starting from document D1, the skilled person would in any case appreciate that the achievement of a comparable bioavailability in terms of AUC with respect to dissolved enzalutamide in a soft capsule and the excellent stability represented relevant effects from the claimed invention. These effects were therefore also to be taken into account in the formulation of the objective technical problem

starting from document D1. The subject-matter of claim 1 was therefore not obvious for the same reasons as when starting from the XTANDI capsules.

X. The appellants-opponents requested insofar as relevant to the decision that the decision under appeal be set aside and that the patent be revoked in its entirety.

Appellant-opponent O2 requested that documents D48-D50 not be considered in the appeal proceedings.

XI. The respondents-patent proprietors requested insofar as relevant to the decision that the appeals be dismissed.

The patent proprietors also requested that

- documents D61a, D65, D68, D69, D70, D77, D78 and D79, which were admitted by the opposition division, documents A80-A82, document A84 filed on 28 April 2025 by appellant-opponent O1 , as well as the anonymous third party observations and document A85 cited therein not be admitted in the appeal proceedings, and

- document D61c and document A83/A83a be admitted into the appeal proceedings.

XII. The opponents O7, O8 and O10, who are parties as of right under Article 107, second sentence, EPC, did not file any substantive observations or requests during the appeal proceedings.

Reasons for the Decision

1. Admittance of evidence and third party observations

1.1 Documents D48-D50, D61a, D65, D68, D69, D70, D77-D79

The opposition division found documents D48-D50, D61a, D65, D68, D69, D70 and D77-D79 to be *prima facie* relevant and therefore admitted these documents into the proceedings. The circumstance that not each of these documents is cited or may be considered essential in the final reasons on substantive issues in the decision does not imply that these documents lacked *prima facie* relevance. In line with the established jurisprudence (see Case Law of the Boards of Appeal of the European Patent Office, 10th edition, 2022, V.A.3.4.4), the Board does not recognize a basis for overruling this finding in the appeal proceedings. Documents D48-D50, D61a, D65, D68, D69, D70, D77-D79 have therefore been considered to be part of the appeal proceedings under Article 12(1)(a) and (2) RPBA.

1.2 Document D61c

The opposition division did not admit the post-published document D61c, because it was filed at a late stage in the proceedings and lacked *prima facie* relevance.

The Board deems this to be free of errors in the use of discretion and does not see any circumstances of the appeal case that justify the admission either. The Board has therefore not admitted document D61c into the appeal proceedings under Article 12(6), first sentence, RPBA.

1.3 Documents A80-A82

Document A80 merely confirms that the concept of bioequivalence in a strict sense as applied by regulatory agencies such as EMA is determined on the basis of the AUC, C_{max} and t_{max} (see A80, page 4/27, section 1.1, and page 10/27, section 4.1.5). The filing of document A80 does thereby not address the relevant issue leading to the relevant finding in the decision under appeal that the recognition of a technical contribution over the prior art in terms of "comparable bioavailability" is not affected by the strict regulatory standards for formal "bioequivalence".

Document A81 was filed to support the argument that it was known that the formulation in a solid dispersion improves the bioavailability of poorly soluble compounds such as ritonavir. Furthermore, it would demonstrate that the formulation of ritonavir in a solid dispersion can achieve bioequivalence and a smaller tablet size compared to ritonavir soft gel capsules can be achieve. However, the filing of document A81 does thereby not address the relevant consideration in the decision under appeal that, as indicated by for instance document D36, the actual performance of solid drug dispersions of poorly soluble drugs remained unpredictable.

Document A82 was filed to support the argument that the skilled person would have considered the physico-chemical properties of an active pharmaceutical ingredient such as enzalutamide in the development of a dosage form comprising such ingredient. The filing of document A82 does thereby not address the relevant consideration in the decision under appeal, that in

view of the many available formulation options the physico-chemical characterization of enzalutamide would anyway not lead the skilled person to the claimed solution of the identified objective technical problem.

The Board has therefore not admitted documents A80-A82 into the appeal proceedings under Article 12(4) RPBA.

1.4 Document A83/A83a

The Board observes that the instances of the EPO may generally take notice of decisions from other jurisdictions, either *ex officio* or following the submission by a party. This applies in particular to document A83/A83a, which concerns a court decision from a contracting state on the validity of the same European patent in view of the same prior art as that under consideration in the present appeal proceedings. However, due to the nature of legal proceedings the facts and outcome of a decision from another jurisdiction cannot to be regarded as evidence on which a pending case is to be decided.

1.5 Documents A84 and A85

Document A84 was filed by appellant-opponent O1 after the Board had issued its communication pursuant Article 15(1) RPBA as evidence of the common general knowledge that the impact of the number of tablets taken in oral anti-cancer treatment on the patient adherence has not been proven.

Document A85 was filed after the Board had issued its communication pursuant Article 15(1) RPBA as part of a third party observation as evidence that no advantage in bioavailability results from the use of HPMC-AS over

methacrylic acid-ethyl acrylate copolymer (1:1) polymer.

In its communication pursuant Article 15(1) RPBA (see section 7.2.3a), the Board indicated that a pharmaceutical composition based on a solid dispersion as defined in claim 1 of the main request is evidently free from the practical constraints of soft gel compositions such as the XTANDI capsules and that the improved convenience associated with the claimed subject-matter relied on by the patent proprietors with reference to the potential for improved treatment adherence was to be considered in this context.

In its communication pursuant Article 15(1) RPBA (see section 7.2.2d), the Board further observed that the patent proprietors did not rely on the effect of improved bioavailability profiles from HPMC-AS compared to other polymers in formulating the objective technical problem, but rather to demonstrate that the selection of HPMC-AS was not an arbitrary choice.

The filing of documents A84 and A85 therefore cannot be considered as a response to any new issue raised by the Board in its communication. Moreover, no further exceptional circumstances justifying the admittance of documents A84 and A85 have been presented.

The Board has therefore not admitted documents A84 and A85 into the appeal proceedings under Article 13(2) RPBA.

1.6 Third party observations

The anonymous third party observations of 1 May 2025, 6 May 2025 and 30 June 2025 and the reference in the

letter of 26 May 2025 by appellant-opponent O6 to the submitted third party observations were filed after the Board had issued its communication pursuant Article 15(1) RPBA.

In line with the established jurisprudence the restrictive criteria for the admittance of late filed submissions by parties during appeal proceedings also apply to third party observations under Article 115 EPC (see Case Law of the Boards of Appeal of the European Patent office, *supra*, III.N.4.4.1; see also decision T 2255/15, reasons point 1.5).

Neither the third party observations themselves nor the letter of 26 May 2025 by appellant-opponent O6 referring to the submitted third party observations indicate any exceptional circumstances justifying the admittance of these third party observations.

The Board has therefore not admitted these third party observations into the appeal proceedings under Article 13(2) RPBA.

Main request

2. Amendments - Articles 76(1) and 123(2) EPC

2.1 It was common ground that the technical content of the divisional application as originally filed from which the patent derives corresponds to the content of the earlier application as published in WO 2014/043208 A1.

The Board therefore refers to this content as published in WO 2014/043208 A1 for the assessment of the requirement that amendments must not result in subject-matter extending beyond the content of the original

application as set out in Articles 76(1) and 123(2) EPC.

2.2 Claim 1

2.2.1 Claim 83 of the original application defines:

"A pharmaceutical composition comprising a solid dispersion containing enzalutamide and a polymer."

Dependent claim 84 as originally filed defines the composition according to claim 83, "wherein enzalutamide is an amorphous state".

Dependent claim 86 as originally filed defines via dependent claim 85 the composition according to claim 83, "wherein the polymer is hydroxypropyl methylcellulose acetate succinate" (HPMC-AS).

Claim 1 of the main request defines a solid pharmaceutical composition comprising a solid dispersion containing amorphous enzalutamide and a concentration-enhancing polymer, wherein the polymer is hydroxypropyl methylcellulose acetate succinate [underlining by the Board].

2.2.2 The original disclosure explains in paragraphs [130]:

"The pharmaceutical compositions comprising the solid dispersion, can be formulated into various dosage forms, including tablets, powders, fine granules, granules, dry syrups, capsules and the like as well as the solid dispersion itself. In some embodiments, the solid pharmaceutical composition is in tablet form"

and in paragraph [151]:

"For example, the solid pharmaceutical composition in the form of powders, fine granules, granules or dry syrups can be produced by a process including the steps of (1) mixing the solid dispersion with one additive or two or more additives using blender, and (2) granulating the resulting mixture by dry granulation using dry granulator" [underlining by the Board].

The skilled person understands from these explanations that the mentioned specific solid forms, including tablets, are presented as examples, and that solid pharmaceutical compositions are disclosed in the application as originally filed as a general category for the described pharmaceutical compositions. This general category is directly applicable to the composition defined in original claim 83 and its dependent claims. The corresponding definition of the pharmaceutical composition as solid in claim 1 of the main request does therefore not give rise to any impermissible intermediate generalisation.

2.2.3 The application as originally filed explicitly describes in paragraph [30] in the first place that in some embodiments the intended compositions comprise solid amorphous dispersions of enzalutamide and a concentration enhancing polymer, and subsequently that in some embodiments at least a major portion of the enzalutamide in the composition is amorphous. The skilled person would therefore understand that the feature "wherein enzalutamide is an amorphous state" in original claim 84 means that the solid dispersion contains amorphous enzalutamide as defined in claim 1 of the main request.

2.2.4 The application as originally filed expresses in dependent claim 86 a preference for compositions of claim 83 comprising HPMC-AS, which undisputedly represents an originally disclosed concentration enhancing polymer. The skilled person understands that this preference also applies to the embodiment of claim 84 relating to a composition of claim 83 comprising a solid dispersion containing amorphous enzalutamide. The definition of the solid pharmaceutical composition comprising a solid dispersion containing amorphous enzalutamide and a concentration enhancing polymer which is HPMC-AS in claim 1 of the main request does therefore not result from a combination of multiple selections that could not be directly and unambiguously derived from the original disclosure.

2.2.5 Accordingly, claim 1 of the main request does not comprise subject-matter extending beyond the content of the application as originally filed.

2.3 Dependent claims

In the communication pursuant Article 15(1) RPBA, the Board expressed the preliminary opinion that the additional features defined in the dependent claims of the main request did not result in subject-matter extending beyond the original disclosure:

- claims 89 and 91 and paragraph [89] of the original disclosure already highlighted the defined relative amounts of enzalutamide and the polymer in a composition as defined in claim 83, which provided an adequate basis for the additional features as defined in claims 2-3

paragraph [26] of the original disclosure already highlighted the defined amounts of enzalutamide, which provided an adequate basis for the additional feature as defined in claim 4

- paragraph [21] and claims 6 and 13 of the original disclosure already highlighted that in the context of the original disclosure the amorphous enzalutamide may make up at least about 80% of the enzalutamide of the compositions, which provided an adequate basis for the additional feature as defined in claim 5

- paragraph [130] of the original disclosure already highlighted the dosage form of a tablet, which provided an adequate basis for the additional feature as defined in claim 7

- paragraph [164] of the original disclosure already highlighted the defined treatment of prostate cancer, which provided an adequate basis for the additional features as defined in claims 8-9.

No substantive arguments were submitted by the opponents in response to the Board's preliminary opinion regarding the basis for additional features as defined in the dependent claims.

The Board has therefore confirmed the opinion expressed in the communication pursuant to Article 15(1) RPBA.

2.4 Accordingly, the Board concludes that the main request complies with Articles 76(1) and 123(2) EPC.

3. Priority - Article 87(1) EPC

Claims 83-86 of the priority document are identical to claims 83-86 of the application as originally filed. Moreover, the priority document explicitly refers in paragraphs [126] and [147] to solid pharmaceutical compositions comprising the solid dispersions in the same terms as paragraphs [130] and [151] of the application as originally filed as cited in section 2.2.2 above and includes in paragraph [26] the same technical information as contained in paragraph [30] of the application as originally filed.

The Board therefore considers that the priority document discloses in accordance with Article 87(1) EPC the same invention as claim 1 of the main request for essentially the same reasons as outlined in section 2.2 above in relation to the compliance with Articles 76(1) and 123(2) EPC.

These reasons are not affected by the circumstance that the passage in paragraph [02] of the priority document differs from the corresponding paragraph [03] of the application as originally filed in that it does not refer to pharmaceutical compositions comprising a solid dispersion containing enzalutamide and a polymer.

The Board therefore concludes that the subject-matter of the main request enjoys the claimed priority of 11 September 2012.

4. Sufficiency - Article 83 EPC

The patent reports that enzalutamide has been used as an agent for treating castration resistant prostate cancer (see the patent paragraph [0003], compare the

original disclosure, paragraph [05]). Document D3 demonstrates that enzalutamide was indeed authorized for use in the treatment of patients with castration-resistant prostate cancer, which is explained as prostate cancer that is resistant to medical or surgical treatments that lower testosterone (see D3, page 14, under "What is XTANDI?"). Moreover, as pointed out in the decision under appeal (see page 23), document D1 indicates enzalutamide to be useful for the treatment of hormone refractory prostate cancer (see D1, paragraph [0001]).

The Board does therefore not recognize why the skilled person would doubt the suitability of the defined composition for the treatment of prostate cancer according to claims 8 and 9 of the main request, including its suitability in the treatment of "androgenic hormone-independent prostate cancer".

The Board thus agrees with the finding in the decision under appeal that the main request complies with Article 83 EPC.

5. Inventive step - Article 56

5.1 Starting point in the prior art.

5.1.1 The patent addresses in the section "BACKGROUND" (see paragraph [0003]) the issue that enzalutamide is provided commercially in the form of a liquid-filled soft capsule comprising 40 mg enzalutamide requiring the daily administration of 4 capsules to achieve the daily dosage of 160 mg. The patent observes in this context that, among other things, a suitable single tablet of reasonable size comprising the prescribed amount of enzalutamide and having suitable and

advantageous solubility and/or dissolution stability and absorption would be advantageous as a suitable alternative to soft capsules. The patent presents in the introduction of the section "DETAILED DESCRIPTION" (see paragraphs [0009] and [0012]) a solid dispersion having the properties of improved solubility and absorption of enzalutamide as well as a pharmaceutical composition with dissolution stability containing such a solid dispersion, which provides the opportunity to dose the entire daily therapeutic dose in a single dosage unit. The patent further describes in the experimental section (see paragraphs [0225]-[0231], Example 15) a human pharmacokinetics study comparing the bioavailability of enzalutamide from a tablet containing 160 mg enzalutamide in the form of a spray-dried dispersion with HPMC-AS with the bioavailability from four liquid-filled soft gelatine capsules containing 40 mg enzalutamide dissolved in Labrasol, which evidently correspond to the XTANDI capsules mentioned in paragraph [0003] of the patent. The application as originally filed presents the same technical content in paragraphs [05], [16], [19], [221]-[226].

In this context claim 1 of the main request defines a solid pharmaceutical composition comprising a solid dispersion containing amorphous enzalutamide and the concentration-enhancing polymer HPMC-AS.

5.1.2 The opponents relied on documents D1, D3 and D35 as suitable starting points in the prior art.

The board notes that the problem-solution approach implies that if an inventive step is convincingly denied in view of a realistic starting point in the prior art, an argument that the claimed subject-matter

nevertheless involves an inventive step in view of a supposedly closer prior art is generally unconvincing, since in such a case the supposedly closest prior art appears to be less promising. However, if an inventive step can be acknowledged starting from a particular prior art that is convincingly identified as the most promising starting point and therefore indeed constitutes the closest prior art, the attempt to deny an inventive step starting from a less promising starting point must fail (see Case Law of the Boards of Appeal of the European Patent Office, supra, I.D.3.1 to I.D.3.4; see also T 2070/19, reasons 3.1.1).

The concept of the closest prior art in the problem solution approach not only obviates the need to address repetitive lines of argument, it also allows for the due appreciation of specific effects in relation to the prior art that may be associated with the distinguishing features (compare Case Law of the Boards of Appeal of the European Patent Office, supra, I.D. 3.5.5).

Certainly, there may be situations in which it is not possible to determine whether a particular document is closer to the subject-matter of the invention than any other documents, thereby making it impossible to identify the "closest prior art". Only in such cases, it is necessary to assess inventive step starting from any suitable prior art document before concluding that the claimed subject-matter is inventive.

5.1.3 As explained in section 3 above, the main request enjoys the claimed priority of 11 September 2012. It was not in dispute that document D35 was published after the claimed priority date. Document D35 is therefore not part of the prior art and therefore

cannot serve as a starting point for the assessment of inventive step.

5.1.4 Document D1 describes a generic formula for diarylhydantoin compounds with utility in the treatment of a hyperproliferative disorder, in particular hormone refractory prostate cancer, wherein the compound may be administered orally, for instance in the form of a capsule, tablet or pill (see D1, paragraphs [0001] and [0011] and claims 1, 21, 23, 28 and 31-35). Document D1 describes enzalutamide as one example among other examples of such diarylhydantoin compounds (see D1, paragraph [0302] example 56-1 (RD162'), claims 15-19 and claim 36) without disclosure of a specific pharmaceutical composition comprising enzalutamide.

Document D3 represents the prescribing information for XTANDI capsules. The document describes enzalutamide as a crystalline non-hygroscopic solid which is practically insoluble in water and presents XTANDI capsules as liquid-filled soft gelatin capsules for oral administration comprising 40 mg of enzalutamide as a solution in caprylocaproyl polyoxylglycerides (see D3, pages 6-7, section 11). The document indicates the use in the treatment of patients with metastatic castration-resistant prostate cancer at a recommended dose of 160 mg (four capsules) administered orally once daily (D3, see page 1, sections 1-2). The document further instructs the storage of XTANDI capsules dry in a tightly closed container at a temperature of 20-25°C (see D3, page 15, under "How should I store XTANDI").

5.1.5 The Board agrees with the finding in the decision under appeal (see section 16.2) that the skilled person would not start from document D1 to develop a solid pharmaceutical composition for enzalutamide while

ignoring the approved and marketed XTANDI capsules as described in document D3. Document D1 lacks a disclosure of an individualized and specific pharmaceutical composition of enzalutamide and only suggests in a generic manner a range of possible formulations. From an objective point of view, document D1 is therefore further removed from the claimed composition than document D3, which does describe XTANDI capsules as a specific pharmaceutical composition comprising enzalutamide.

5.2 Objective technical problem

5.2.1 The difference between the pharmaceutical composition defined in claim 1 of the main request and the closest prior art represented by the XTANDI capsules described in document D3 was not in dispute and concerns the formulation of enzalutamide in a solid dispersion comprising enzalutamide in amorphous form with HPMC-AS instead of in an encapsulated solvent mixture.

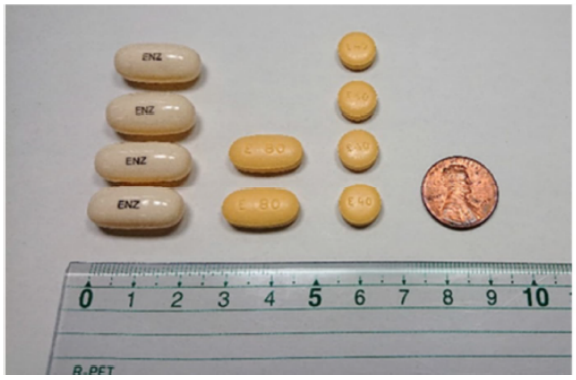
5.2.2 The effect of convenience with respect to liquid-filled capsules

Claim 1 of the main request does not define the overall concentration of enzalutamide in the pharmaceutical composition nor the concentration of enzalutamide in the solid dispersion. The claim therefore does not define any feature determining the size in relation to the amount of enzalutamide in the dosage form in which the defined pharmaceutical composition is to be administered. This is actually illustrated by the different sizes of the tablets of examples 16-23 presented in Table 16 of the patent represented below:

Table 16

component	Example 16	Example 17	Example 18	Example 21	Example 22	Example 23
enzalutamide	80.0	80.0	80.0	160	80.0	80.0
hydroxypropyl methylcellulose acetate succinate	240.0	240.0	160.0	106.7	400.0	80.0
hypromellose	-	-	-	-	-	160.0
calcium hydrogen phosphate hydrate	160.6	160.6	240.6	-	54.0	256.0
colloidal silicon dioxide	-	-	-	2.5	-	-
light anhydrous silicic acid	-	-	-	-	-	16.0
microcrystalline cellulose	-	-	-	94.8	-	-
lactose monohydrate	-	-	-	94.7	-	-
crospovidone	-	-	-	-	-	40.0
croscarmellose sodium	54.0	54.0	54.0	40.0	60.0	160.0
magnesium stearate	5.4	5.4	5.4	1.30	6.0	8.0
filmcoating agent	-	16.2	-	17.5	18.0	24.0
total (mg)	540.0	556.2	540.0	517.5	618.0	824.0
tablet size	14.8mm×7.8mm			Round, approx. 10.5mm	14.8mm ×7.8mm	18.3mm ×7.8mm

However, it is immediately evident to the skilled person that a pharmaceutical composition based on a solid dispersion as defined in claim 1 of the main request is freed from the practical constraints of the liquid-filled XTANDI capsules of the prior art, in which the solubility of enzalutamide in the solvent determines the size and required number of the dosage forms to be administered. Notably, one XTANDI capsule only contains 40 mg of enzalutamide and is almost 1 g in weight and 2 cm in length (see the patent proprietors' reply to the appeals, page 49).



The Board therefore considers that the difference involving the formulation of amorphous enzalutamide in a solid dispersion with HPMC-AS is associated with the absence of the practical constraints of the XTANDI capsules, which allows for the choice of a dosage form with a size in relation to its dose based on convenience, precisely as demonstrated in Table 16 of the patent.

5.2.3 The effect of comparable bioavailability in humans with respect to liquid-filled capsules

(a) Significance of the effect

As outlined in Section 5.1.1 above, the patent and the application as originally filed disclose a pharmaceutical composition comprising a solid dispersion of enzalutamide. This formulation is presented as a suitable and advantageous alternative to the liquid-filled XTANDI soft gelatin capsules. In this context, the patent and the application as originally filed describe a human pharmacokinetics study comparing the bioavailability of enzalutamide, including the AUC, between a tablet containing a spray-dried solid dispersion of enzalutamide in HPMC-AS and XTANDI capsules containing an equal amount of enzalutamide.

Based on the direct reference to an advantageous alternative to the XTANDI capsules and the explicit mention of the bioavailability in humans in terms of area under the curve (AUC) in comparison to the XTANDI capsules, the skilled person would unmistakably derive the effect of achieving of a comparable bioavailability in terms of AUC in humans with respect to the XTANDI capsules of document D3 as encompassed by the technical

teaching and embodied by the same invention as originally disclosed. In line with the considerations in G 2/21, the patent proprietors may therefore in support of this effect also rely on post-published evidence such as documents D48-D50.

The skilled person would appreciate that a comparable bioavailability in terms of AUC in humans is achieved if the bioavailability from the same dose of the compared compositions is in the same order of magnitude to allow for the expectation of approximately similar pharmacological effects in a clinical setting. The effect of a comparable bioavailability in terms of AUC does therefore not require a specific quantitative definition nor the associated effects in terms of C_{max} / t_{max}, such as in formal criteria for determining bioequivalence as applied by regulatory authorities, for it to represent a technically meaningful effect. Notably, the post-published document D48 explains with reference to the long half-life of enzalutamide that the lower single dose C_{max} for a tablet comprising a solid dispersion as compared to the XTANDI capsules is in any way unlikely to impact clinical outcomes.

The significance of the effect of a comparable bioavailability in humans for the formulation of the objective technical problem is not affected by the opponents' argument that the teaching of the patent is not limited to treatment of human patients.

(b) Assessment of the evidence

The patent presents the results of the mentioned human pharmacokinetics study of Example 15 in Table 15.1, reproduced below.

Table 15.1. Analysis of Formulation Bioequivalence: Geometric Mean (CV%) Plasma Enzalutamide Pharmacokinetic Parameter Values by Treatment and Food Condition

A. Comparison of Tablet and Capsule Formulations under Fasted Conditions					
Pharmacokinetic Parameters (Units)[a]	**Tablet Formulation, Fasted Conditions (Test)**	**Liquid-Filled Soft Gelatin Capsule Formulation, Fasted Conditions (Reference)**	**Ratio[b] (%)**	**90% Confidence Interval (%)**	
				Lower	**Upper**
n	28	29	--	--	--
AUC_{Day1-7} (μg•h/mL)	177 (24)	185 (25)	95	92	97
AUC_{0-t} (μg•h/mL)	255 (29)	269 (30)	95	92	97
AUC_{0-inf} (μg•h/mL)	263 (28)	278 (29)	94	92	97
C_{max} (μg/mL)	2.98 (24)	5.16(20)	57	54	62
t_{max}[c] (h)	4.00 (2.00 - 6.00)	1.00 (0.75 - 3.00)	--	--	--
$t_{1/2}$ (days)	3.45 (36)	3.67 (32)	--	--	--
B. Comparison of Tablet and Capsule Formulations under Fed Conditions					
Pharmacokinetic Parameters (units)	**Tablet Formulation, Fed Conditions (Test)**	**Liquid- Filled Soft Gelatin Capsule Formulation, Fed Conditions (Reference**	**Ratio[d] (%)**	**90% Confidence Interval (%)**	
				Lower	**Upper**
n	15	15	--	--	--
AUC_{Day1-7} (μg•h/mL)	191 (20)	187 (19)	102	91	114
C_{max} (μg/mL)	2.96 (25)	3.86 (35)	77	65	91
t_{max}[c] (h)	1.00 (4.00 - 24.00)	2.00 (0.50 - 6.00)	--	--	--

n = total number of subjects contributing to the summary statistics for PK parameters
[a] Area under the plasma concentration-time profile from time zero to Day 7 (AUC_{Day1-7}), AUC from time zero to the last measurable concentration (AUC_{0-t}), AUC from time zero to infinity (AUC_{0-inf}), maximum plasma concentration (C_{max}), and time to maximum plasma concentration (t_{max}).
[b] Ratio of least squares means (Test/Reference) based on crossover-treatment bioequivalence statistical tests.
[c] Median (range).
[d] Ratio of least squares means (Test/Reference) based on parallel-treatment bioequivalence statistical tests.

It was common ground that according to the FDA criteria, compared values of pharmacokinetic parameters are equivalent if the 90%-confidence interval for the ratio of these values falls within the range of 80%-125%. As explicitly concluded in paragraph [0231] of the patent, the results in Table 15.1 demonstrate that the administration of the tablet containing 160 mg enzalutamide in the form of a spray-dried dispersion in a concentration of 60% in HPMC-AS (type M) (see paragraph [0225]) achieves a bioavailability in terms of AUC in humans (healthy male subjects) which is equivalent and thus clearly comparable to that following the administration of the same dose of enzalutamide in the form of 4 soft gelatin capsules

comprising each 40 mg enzalutamide dissolved in Labrasol, which are representative for the XTANDI capsules described in document D3.

The post-published document D49 (see pages 1-8) summarizes the results of 5 further clinical studies mentioned in document D48 (see Table 2 on page 25, Table 4, page 28 and Table 5 on page 29) and document D50 (see Table 2, page 25 of the PDF). Study 1 involves, like Example 15 and Example 21 in Table 16 of the patent, a tablet containing 160 mg enzalutamide in a spray-dried dispersion at a concentration of 60% in HPMC ("tablet A" in Study 1 of D49), which is administered daily to cancer patients for 57 days. Study 2 involves tablets containing 80 mg enzalutamide in a spray-dried dispersion in a 1:5 ratio (17%) in HPMC ("tablet C" in Study 2 of D49) with the same composition as the tablet of Example 22 in Table 16 of the patent, which are administered to healthy males in a single dose of 160 mg enzalutamide. Study 3 also involves tablets containing 80 mg enzalutamide in a spray-dried dispersion in a 1:5 ratio (17%) in HPMC ("tablet E" and "tablet F") administered to healthy males in a single dose of 160 mg enzalutamide. Studies 4 and 5 involve again a tablet of 80 mg enzalutamide in a spray-dried dispersion (17%) in HPMC as a 160 mg single dose or in a simulated daily administration over 56 days. The results of each of the studies 1 and 3-5 reported in document D49 indicate that the tested tablets comprising the spray-dried solid dispersions of enzalutamide achieve an equivalent and thus clearly comparable AUC compared to the liquid-filled XTANDI capsules (ratio with 90%-confidence interval within the range of 80%-125%).

Whilst the results for tablet C, which includes other excipients than those used for the tablet of Example 15 of the patent, marginally exceeded with a reported 90% confidence interval of 96.44%-125.73% for the ratio of the AUC with the XTANDI capsules the mentioned statistical standard for equivalence applied by the FDA, tablet C still demonstrated a comparable bioavailability in terms of AUC as compared to the XTANDI capsules, because the reported ratio of circa 110% may well be considered to allow for the expectation of approximately similar pharmacological effects in a clinical setting.

The opponents' argument that the reported results for tablet C demonstrate that the effect of comparable bioavailability is not achieved depending on the choice of excipients is therefore not convincing.

Example 27 of the patent describes experiments in dogs in which the tablets of examples 16, 18, 21, 22 and 23 presented in the above-mentioned Table 16 containing enzalutamide in concentrations of 25%, 33%, 60%, 17% and 50% respectively, were used. The results reported in Table 19 as represented below only confirm that the use of a solid dispersion allows for achieving a comparable bioavailability in terms of AUC over a wide range of concentrations of enzalutamide in the HPMC-AS.

Table 19

	Dog PK results	
	% Cmax	% AUC
Example 16	102	99
Example 18	92	84
Example 21	72	70
Example 22	102	104
Example 23	112	110
Soft Capsule	100	100

The reported bioavailability of 70% in dogs for the tablet of Example 21 in dogs is still within the same order of magnitude as the other results. Contrary to the opponents' arguments, this somewhat lower value does therefore not disqualify this tablet as failing to achieve comparable bioavailability in terms of AUC. Notably, the content of the tablet of example 21 corresponds to that of the tablet of Example 15 of the patent and "tablet A" of document D49 which, as discussed above, were shown to provide equivalent bioavailability in terms of AUC to the XTANDI capsules in humans.

The same consideration applies with regard to results reproduced and highlighted below in Tables 12.1 and 13.1 from the experiments in rats of Examples 12 and 13 of the patent, wherein the bioavailability of orally administered suspensions of solid dispersions of enzalutamide in HPMC-AS at concentrations of 25% and 60% prepared by spray drying or hot melt extrusion was compared with that of enzalutamide in the form of a solution.

Table 12.1. Mean pharmacokinetic parameters (± standard deviation) in rats for enzalutamide formulations. Crystalline drug, amorphous drug, and SDDs were dosed in suspension in a 0.5% methylcellulose vehicle. Control 1, Control 2, and spray-dried amorphous drug are reference formulations.

enzalutamide Formulation	C_{max} (µg/ml)	T_{max} (hr)	AUC $_{0-72}$ (µg•hr/ml)
Crystalline drug (Control 1)	3.53±0.66	6.05±0.92	72.7±18.4
Solution in Labrasol (4.23 mg/ml) (Control 2)	10.1±1.38	5.86±0.99	201±42.9
Spray-dried amorphous drug	7.14±0.97	2.55±0.57	121±16.4
25%A:HPMCAS-M	10.8±1.63	2.96±0.65	171±40.2
60%A:HPMCAS-M	10.3±1.66	3.30±0.77	196±39.6

Table 13.1. Mean AUC $_{0-inf}$ and % Bioavailability in rats for enzalutamide formulations. Crystalline drug, amorphous drug, and HME dispersion formulations were dosed in suspension in a 0.5% methylcellulose vehicle. For intravenous dosing, enzalutamide was dissolved in 50% polyethyleneglycol-400/20% ethanol (200 proof)/30% sterile water for injection (USP), and was dosed via tail vein. Only the dispersion with HPMCAS is according to the claimed invention.

enzalutamide Formulation	Mean AUC $_{0-inf}$ (µg•hr/ml)	Bioavailability (%)*
Intravenous (IV)	231	-
Crystalline drug (Control 1)	62.6	27.1
Solution in Labrasol (4.23 mg/ml) (Control 2)	225	97.4
Spray-dried amorphous drug	132	57.1

enzalutamide Formulation	Mean AUC $_{0-inf}$ (µg•hr/ml)	Bioavailability (%)*
25%A:PVP-VA64 HME dispersion	167	72.3
60%A: PVP-VA64 HME dispersion	142	61.5
25%A:HPMCAS HME dispersion	187	81.0
* Bioavailability = Mean AUC $_{0-inf}$/IV Mean AUC $_{0-inf}$. For example, 62.6/231 = 27.1 %		

The post-published document D69 also presents a bioavailability study in rats involving a comparison of suspensions of solid dispersions of amorphous enzalutamide in HPMC-AS at different concentrations with a suspension of crystalline enzalutamide. The solid dispersion with 10% enzalutamide in HPMC-AS failed to show the enhanced bioavailability with respect to crystalline enzalutamide that was observed for the solid dispersion with 50% enzalutamide (see D69, page 178, Figure 7). The observed differences between the *in vivo* performance of the solid dispersions in HPMC-AS with 10% and 50% enzalutamide in rats were consistent with their *in vitro* dissolution profiles (see D69, page 176, Figure 3; see also page 178, right column). However, document D69 attributes the poor performance of the 10% dispersion to the rapid

matrix crystallization of enzalutamide therein upon contact with water (see D69, page 181, left column). Whilst the solid dispersions in document D69 were found to contain amorphous enzalutamide immediately following their production (see D69, page 176, right column), it is therefore not evident that following the preparation of the liquid suspension with the 10% enzalutamide dispersion to be administered to the rats in HPMC-AS, the enzalutamide was therein still present in amorphous form as required according to claim 1 of the main request. The Board further observes that the review article in document D53 calls upon caution in the interpretation of preclinical data in view of the differences in morphology of the mammalian GI tract among species (see D53, page e83). The above discussed difference in performance of the tablet of Example 21 of the patent in dogs and humans illustrates the relevance of this warning. Notably, the results reported in document D49 indicate consistently high bioavailability in humans for tablets prepared with solid dispersions of amorphous enzalutamide in HPMC-AS at enzalutamide concentrations ranging from 17%-60%. The Board therefore considers that, contrary to the opponents' arguments, the results reported in document D69 do not demonstrate that a solid dispersion containing amorphous enzalutamide in HPMC-AS at a concentration of 10% in a solid pharmaceutical composition does not allow for achieving a comparable bioavailability to that of the XTANDI capsules.

The opponents' arguments that the effect of comparable bioavailability is not achieved depending on the enzalutamide to HPMC-AS weight ratio thus remained unsubstantiated and are therefore not considered convincing.

The results from *in vitro* dissolution experiments in Example 4 of the patent, reported in Table 4.2 represented below, demonstrate for exemplified solid dispersions of enzalutamide with a range of different concentrations and different grades of HPMC-AS bioavailability in terms of AUC_{90} which is greatly enhanced in comparison to crystalline enzalutamide and which tends towards the value of the AUC_{90} of enzalutamide dissolved in Labrasol.

Table 4.2. Microcentrifuge dissolution data (C_{max} and AUC_{90}) for enzalutamide spray-dried dispersions (SDDs), amorphous enzalutamide, and controls. Control 1, Control 2, formulations D2, D10, and BREC-0035-09B(V) are reference formulations.

Sample Tested (Dispersion #)	C_{max}, 90[a] (μg/mL)	AUC_{90}[b] (min*μg/mL)
25%A HPMCAS-M SDD (D4)	160	13,600
40%A HPMCAS-M SDD (D5)	120	9,200
60%A HPMCAS-M SDD (D6)	110	8,500
80%A HPMCAS-M SDD (D7)	130	11,200
25%A HPMCAS-H SDD (D8)	110	9,800
40%A HPMCAS-H SDD (D9)	110	9,700
25%A PVP VA64 SDD (D2)	110	9,700
40%A PVP VA64 SDD (D10)	110	9,800
Amorphous (spray-dried) enzalutamide BREC-0035-09B(V)	120	9,500
Crystalline enzalutamide (Control 1)	7	500
4.23 mgA/mL enzalutamide in Labrasol (Control 2)	180	15,200

[a] $C_{max, 90\ min}$ = maximum drug concentration through 90 minutes.
[b] $AUC_{90\ min}$ = area under the curve at 90 minutes.

The results from *in vitro* dissolution experiments in Example 9 of the patent reported in the below represented Table 9.2 only confirm this performance for a further exemplified solid dispersion of enzalutamide in HPMC-AS with respect to crystalline enzalutamide.

Table 9.2. C_{max} and AUC_{90} values for various enzalutamide SDDs and crystalline enzalutamide (microcentrifuge dissolution test).

Sample (Dispersion #)	C_{max}, 90 min[a] (μg/mL)	AUC_{90} min[b] (min*μg/mL)
60%A HPMCAS-M SDD (D12)	110	8,800
60%A HPMC E3 Prem SDD (D14)	110	9,500
60%A HPMCP-55 SDD (D15)	110	7,400
60%A Eudragit-L100 SDD (D16)	90	6,100
Crystalline enzalutamide (Control 1)	10	740

[a] $C_{max,\ 90\ min}$ = maximum drug concentration through 90 minutes.
[b] $AUC_{90\ min}$ = area under the curve at 90 minutes.

The in vitro dissolution experiments in Example 11 of the patent, presented in Tables 11.1 and 11.2 below, further support the enhanced bioavailability in terms of AUC_{90} provided by solid dispersions of enzalutamide in HPMC-AS, whether formulated as spray-dried dispersions (SDD) containing fully amorphous enzalutamide or as hot-melt extruded (HME) dispersions comprising partially crystalline enzalutamide.

Table 11.1. Extrusion temperature, and extrudate properties after milling with mortar and pestle. Formulations D19-D23 are reference formulations.

Formulation (Dispersion #)	Control Temp.[a] (°C)	Crystallinity by PXRD & Differential Scanning Calorimetry	T_g (°C)
25%A:PVP-VA64 (D19)	150	Amorphous	104
25%A:PVP-VA64 (D20)	195	Amorphous	104
40%A:PVP-VA64 (D21)	195	Amorphous	103
60%A:PVP-VA64 (D22)	170	Crystalline	103
60%A:PVP-VA64 (D23)	190	Amorphous	99
25%A:HPMCAS-M (D24)	170	Partially Crystalline*	93
25%A:HPMCAS-M (D25)	190	Partially Crystalline	95
25%A:HPMCAS-M (D26)	195	Partially Crystalline	95
40%A:HPMCAS-M (D28)	195	Partially Crystalline	90

(continued)

Formulation (Dispersion #)	Control Temp.[a] (°C)	Crystallinity by PXRD & Differential Scanning Calorimetry	T_g (°C)
40%A:HPMCAS-M (hot plate) b (D29)	220	Amorphous	88
60%A:HPMCAS-M (D30)	170	Crystalline	--
* Partially Crystalline means that while a Tg was observed, a crystalline drug melt peak was also observed. The PXRD showed evidence that some crystals were present. Controls were not performed to identify the amount of drug that was amorphous or crystalline.			
a: This is the control temperature for the terminal extruder barrels and the die. The actual product temperature is higher in the extruder due to additional frictional heat. It is difficult to measure the actual product temperature but was done using a temperature probe during the preparation of Dispersion D26. In that case, the extruder control temperature was 195°C and the product temperature was measured at approximately 215°C. b: This sample was prepared on a hot plate at a temperature higher than was possible using the MP&R extruder.			

Table 11.2. Microcentrifuge dissolution test results for enzalutamide dispersions prepared by hot melt extrusion. Samples D2, D10, D20, and D21 are reference samples. The total amount of sample dosed was 200 mcg per ml of dissolution medium. The dissolution medium was Model Fasted Duodenal Solution (MFDS) (0.5 wt% NaTC/POPC in PBS, pH 6.5, 290 mOsm). Results for SDDs of similar composition are presented for comparison.

Sample (Dispersion #)	C_{max90}[a] (μg/mL)	AUC_{90}[b] (min* μg/mL)
25%A HPMCAS-M SDD (D11)	130	11,000
25%A HPMCAS-M HME dispersion (150 to 355 μm) (D26)	110	6,000
25%A HPMCAS-M HME dispersion (50 to 150 μm) (D26)	140	10,700
25%A HPMCAS-M HME dispersion (<50 μm) (D26)	140	11,600
40%A HPMCAS-MG SDD (D31)	110	9,100
40%A HPMCAS-MG HME dispersion (150 to 355 μm) (D28)	40	2,300
40%A HPMCAS-MG HME dispersion (50 to 150 μm) (D28)	80	6,200
40%A HPMCAS-MG HME dispersion (< 50 μm) (D28)	110	8,800
25%A PVP VA SDD (D2)	130	9,700

(continued)

Sample (Dispersion #)	C_{max90}[a] (μg/mL)	AUC_{90}[b] (min* μg/mL)
25%A PVP VA HME dispersion (150 to 355 μm) (D20)	90	6,400
25%A PVP VA HME dispersion (50 to 150 μm) (D20)	110	7,900
25%A PVP VA HME dispersion (< 50 μm) (D20)	130	9,000
40%A PVP VA SDD (D10)	110	7,500
40%A PVP VA HME dispersion (150 to 355 μm)	60	4,700
(D21)		
40%A PVP VA HME dispersion (50 to 150 μm) (D21)	100	8,200
40%A PVP VA HME dispersion (< 50 μm) (D21)	130	8,500
[a] C_{max90} = maximum drug concentration through 90 minutes [b] AUC_{90} = area under the time/concentration curve at 90 minutes		

Whilst the results indicate some variation in the AUC_{90} values ranging from 11600 for "25%A HPMCAS-M HME dispersion (<50 μm) (D26)" to the above highlighted 2300 for "40%A HPMCAS-MG HME dispersion (150 to 355 μm) (D28)", this value of 2300 still represents a greatly enhanced bioavailability in terms of AUC_{90} in comparison to the values for crystalline enzalutamide reported in Tables 4.2 and 9.2. The reported lower AUC_{90} for solid dispersions prepared by HME with larger particle sizes may be explained by an expected longer dissolution time of the larger particles in these dispersions and the limited time span of 90 minutes of the *in vitro* AUC_{90} assay, which does not reflect the transit time in the human intestine (see the patent, paragraph [0034]). Notably, the review article in document D53 points out that the correlation between in vitro dissolution data and in vivo absorption is not straightforward (see D53, page e83). Contrary to the opponents' arguments, the lower *in vitro* AUC_{90} values reported in Table 11.2 do therefore not disqualify these dispersions as unsuitable for achieving a

comparable bioavailability in terms of AUC in humans compared to XTANDI capsules.

The opponents' arguments, that the effect of a comparable bioavailability is not achieved depending on the type of HPMC-AS, the presence of crystalline enzalutamide in the dispersion, the preparation of the solid dispersion by hot melt extrusion or differences in particle sizes, thus also remained unsubstantiated and are therefore not considered persuasive.

The description of the patent (see paragraphs [0028]and [0069]-[0072]) further states that in general substantially homogeneous dispersions have improved bioavailability relative to non-homogeneous dispersions and that it is therefore highly preferred for the dispersions to be as homogeneous as possible. However, in view of the above discussed actual evidence concerning the bioavailability from a variety of exemplified solid dispersions comprising amorphous enzalutamide in HPMC-AS as the concentration enhancing polymer, this statement as to the effect of the homogeneity of the dispersion in general does not support the opponents' contention that the solid dispersion of enzalutamide in HPMC-AS as specifically defined in claim 1 of the main request does not allow the achievement of the effect of comparable bioavailability to XTANDI capsules depending on its level of homogeneity.

(c) The Board's conclusion regarding the effect

In view of the above discussed significance and evidence, the Board concludes that the difference involving the formulation of amorphous enzalutamide in a solid dispersion with HPMC-AS is associated with the

effect of a sufficiently enhanced bioavailability of the enzalutamide relative to crystalline enzalutamide to allow for the provision of dosage forms with a comparable AUC with respect to the XTANDI capsules of the prior art.

In this context, the Board acknowledges that it may not be feasible for opponents to perform experiments in human subjects for the purpose of demonstrating that a dispersion covered by the definition of claim 1 of the main request would not allow for the mentioned comparable AUC in humans. In line with the reference in the patent to an enhanced drug concentration *in vitro* dissolution tests as a good indicator of *in vivo* bioavailability (see the patent, paragraph [0029], see also Examples 4, 9 and 11) and the teaching in the patent that the relative bioavailability of enzalutamide in the dispersions can be tested *in vivo* in animals and humans (see the patent, paragraph [0037], see also Examples 12, 13 and 27), the Board does not exclude that *in vitro* dissolution tests or animal experiments may be used for such a purpose instead. However, the Board considers for the reasons as set out above that the opponents have failed to demonstrate with the results from *in vitro* dissolution tests and animal experiments that any solid dispersions within the definition of the claim would not allow for achieving a comparable AUC in humans.

5.2.4 The effect of outstanding stability

The patent explains in Example 5 (see paragraphs [0179] and [0181]) that in order to assure that a dispersion maintains its amorphous character, it is desirable to choose a dispersion composition with Glass Transition Temperature (T_g) above the temperature at which the

product may be stored. The below reproduced Table 5.1 of Example 5 of the patent presents the values of the T_g at a relative humidity (RH) of 5% and 75% of spray-dried dispersions of enzalutamide in HPMC-AS at concentrations ranging from 25%-80%.

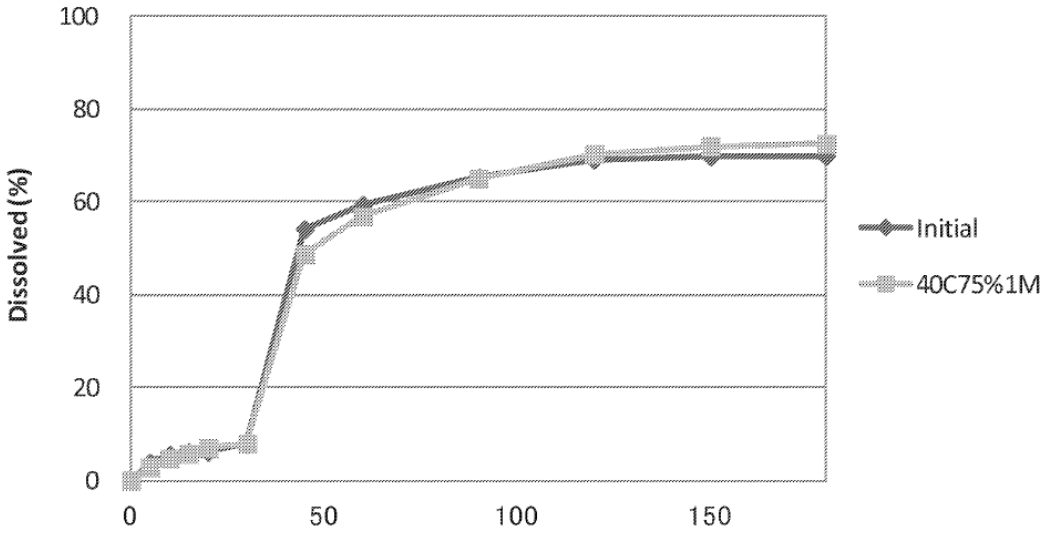
Table 5.1. T_g as a Function of Relative Humidity (RH) for enzalutamide SDDs

SDD Formulation (Dispersion #)	T_g (°C)	
	<5% RH	75% RH
Amorphous (spray-dried) MDV-3100	88.5	64.0
80%A HPMCAS-M (D7)	90.4	59.3
60%A HPMCAS-M (D6)	87.1	52.0
25%A HPMCAS-M (D4)	93.1	50.7
40%A HPMCAS-M (D5)	91.3	51.9
25%A HPMCAS-H (D8)	94.0	51.2
40%A HPMCAS-H (D9)	91.1	51.2
40%A PVP VA64 (D10)	103.3	34.9
25%A PVP VA64 (D2)	105.5	30.8

The results demonstrate that the dispersions of enzalutamide in HPMC-AS exhibit even at 75% RH a T_g above 50°C, which is far above normal storage conditions. The results thus indicate for dispersions of enzalutamide in HPMC-AS an outstanding stability of the amorphous form of the contained enzalutamide even under conditions of high humidity.

Example 6 of the patent confirms this high stability of the amorphous form in dispersions of enzalutamide in HPMC-AS under the harsh conditions of 50°C at 75% RH, although after one day under these harsh conditions some fusion of particles to form larger particles was observed in an 80% dispersion of enzalutamide in HPMC-AS, whereas no such fusion was observed with the 60% dispersion.

Example 26 of the patent describes a dissolution test for the tablet of Example 17 comprising a 25% dispersion of enzalutamide in HPMC-AS immediately after its preparation and after storage at 40°C and 75% RH for one month. The result in the below reproduced Figure 5 demonstrates that the dissolution profile was not affected following storage.



Example 28 of the patent further confirmed that the solid dispersions prepared in Examples 16, 18, 22 and 23 were amorphous and that after storage at 40°C and 75% RH for 1 month the tablet of Example 17 was also amorphous.

Document D49 reports results of additional stability studies which demonstrate that 80 mg and 40 mg tablets comprising a spray-dried dispersion of enzalutamide (17%) in HPMC-AS did not show any crystallization upon storage even under long-term (25°C/60% RH for 60 months), accelerated (25°C/60% RH for 60 months), high temperature (50°C/ambient humidity for 3 months) or high humidity (25°C/75% RH for 6 months) conditions. The results in document D49 thus further confirm the stability associated with the formulation of

enzalutamide in a solid dispersion as defined in claim 1 of the main request.

The opponents argued that no outstanding stability is generally associated with the defined dispersions in view of the reported fusion of particles for the 80% enzalutamide dispersion in HPMC-AS, which according to Example 6 is indicative of the need of controlled storage conditions. However, in spite of the harsh conditions (50°C/75% RH) applied in Example 6, the 80% enzalutamide dispersion in HPMC-AS still demonstrated remarkable stability of the amorphous form. The Board further considers that in view of these harsh conditions the observed particle fusion reported as indicative of the need of controlled storage conditions in Example 6 does not negate the still outstanding stability associated with the solid dispersion as defined in claim 1 demonstrated in Examples 5, 26 and 28 of the patent and Studies 6-7 of document D49. Notably, document D3 also instructs to store XTANDI capsules at the controlled storage conditions of a temperature between 20°C-25°C and dry in a tightly closed container (see D1, page 15).

The opponents also argued that the patent itself states that the physical stability of solid dispersions generally depends on the homogeneity of the dispersions (see the patent, paragraphs [0028] and [0069]) and that the T_g of the composition must be above the storage temperature to assure its stability (see the patent, paragraph [0181]). However, in view of the above discussed actual evidence concerning the stability of exemplified solid dispersions comprising amorphous enzalutamide in HPMC-AS as the concentration enhancing polymer, the mere statement as to the effect of the homogeneity of the dispersion in general in the patent

does not support the opponents' contention that the solid dispersion of enzalutamide in HPMC-AS as specifically defined in claim 1 of the main request does not provide outstanding stability depending on its level of homogeneity. The above discussed results of Example 5 in Table 5.1 of the patent furthermore indicate that the formulation of solid dispersions of enzalutamide in HPMC-AS indeed results in a T_g above normal storage conditions and thereby assures the stability of the amorphous form. The opponents' arguments relying on the statements concerning the homogeneity and the T_g of the composition in the patent are therefore not considered convincing.

The opponents further contended that, in the absence of a comparison to the XTANDI capsules as the starting point in the prior art, any stability demonstrated for the claimed pharmaceutical composition comprising the defined solid dispersion could not be taken into account in the formulation of the objective technical problem with respect to this starting point. However, the demonstrated outstanding stability associated with the dispersion comprising amorphous enzalutamide defined in claim 1 of the main request is evidently an important property of the claimed pharmaceutical composition, especially in view of the reference in the patent to the risk of crystallization of the amorphous enzalutamide (see the patent, paragraph [0181]). It would therefore not be justified to disregard this property in the formulation of the objective technical problem.

The Board therefore concludes that the difference involving the formulation of amorphous enzalutamide in a solid dispersion with HPMC-AS is also associated with the effect of outstanding stability and that this

effect is to be taken into account in the formulation of the objective technical problem.

5.2.5 Formulation of the objective technical problem

In view of the effects associated with the formulation of enzalutamide in a solid dispersion comprising enzalutamide in amorphous form with HPMC-AS instead of in a soft gel encapsulated solvent mixture discussed in sections 5.2.2, 5.2.3 and 5.2.4 above, the Board formulates the objective technical problem as the provision of a further pharmaceutical composition comprising enzalutamide which

- is freed from the practical constraints of the XTANDI capsules and thereby allows the choice of a dosage form with a convenient size in relation to its dose

- exhibits sufficient bioavailability of the enzalutamide to allow the formulation of dosage forms with a comparable AUC in humans with respect to the XTANDI capsules of the prior art

- exhibits outstanding physical stability.

The Board observes that it is in this case not required that each imaginable dosage form falling within the breadth of claim 1 of the main request has a convenient size in relation to its dose or provides comparable bioavailability to XTANDI capsules in terms of AUC. However, the opponents have not presented an actual example of a corresponding dosage form which does not achieve the mentioned comparable bioavailability at a convenient size. In any case, such dosage forms covered by claim 1 would still be liberated from the

constraints of the XTANDI capsules due to the presence of the defined solid dispersion in such dosage forms. Furthermore, in such dosage forms, the specified solid dispersion would continue to exert its positive effect on the bioavailability, potentially enabling the achievement of a comparable AUC, even if this comparable AUC is not ultimately realized due to additional implementation choices. The Board thus agrees with the corresponding considerations in the judgement of the District Court of The Hague in document A83/83a (see paragraphs 4.35 and 4.50).

5.3 Assessment of the solution

5.3.1 As is evident from document D6 (see page 1419, right column), the constraints of liquid-filled capsules would have been evident to the skilled person, who would therefore be motivated to seek alternative formulations to the XTANDI capsules to avoid these constraints.

In line with the established jurisprudence (see Case Law of the Boards of Appeal of the European Patent Office, supra, I.D.5, "Could-would approach" and I.D.7.1), any relevant motivation to try a particular measure to solve a particular technical problem generally requires a reasonable expectation that such a measure will solve that technical problem.

The reviews in documents D51 and D53 and the textbook excerpt of document D72 explain that the development of suitable formulations of poorly soluble active pharmaceutical ingredients (APIs) was driven by trial and error of a variety of potential approaches and that this development was complicated by the need for *in vivo* testing in a suitable animal model and ultimately

clinical testing in humans (see D51, Abstract; D53, page e83, right column; D72, Preface page vi, page 56 section 2.3 and pages 67-68, section 2.4.2). The Board therefore rejects the opponents' argument that the situation in the present case corresponds to an exceptional "try and see situation" (see Case Law of the Boards of Appeal of the European Patent Office, *supra*, I.D.7.2).

Following the identification of the objective technical problem in section 5.2.5 above, the assessment of inventive step of the claimed subject-matter therefore crucially depends on whether the skilled person had a reasonable expectation that in a solid pharmaceutical composition, the formulation of a solid dispersion containing amorphous enzalutamide and HPMC-AS allows the provision of a dosage form with a comparable bioavailability in humans with respect to the XTANDI capsules of the prior art, while maintaining outstanding physical stability.

5.3.2 The opponents argued that the skilled person derived from any of the documents D4, D6, D7, D10, D18, D19, D22, D23, D25, D36 and D38 as well as the post-published documents D17 and D68 a reasonable expectation of success with regard to the formulation of a solid dispersion containing amorphous enzalutamide and HPMC-AS.

Document D4 explicitly reports the broad applicability of HPMC-AS based spray-dried dispersions (SDD) and explains the relevance of the T_g/T_m ratio (glass transition temperature vs melting point) and the LogP value (lipophilicity) of the active pharmaceutical ingredient (API) in such dispersions (see D4, pages 1016-1019 under "In Vivo Performance"). This utility of

HPMC-AS is illustrated by the mapping in Figure 14 in document D4 (see D4, page 1018) of the concentrations of 139 APIs formulated as spray-dried solid dispersions (SDD) with HPMC-AS as a function of the T_g/T_m and LogP of the APIs. For enzalutamide, which has a T_g/T_m of 1.28 and a LogP value of 2.98, this mapping would suggests that it could be formulated in a spray-dried solid dispersion at a concentration of 35 to 50% (see D4, Figure 14, "Group 2").

Document D6 also identified HPMC-AS as a uniquely effective polymer for solubilizing a wide variety of low solubility drugs in the form of SDDs, which is demonstrated in document D6 with a variety of APIs, including compounds which have in comparison to enzalutamide a similar or higher T_m and LogP (see D6, page 1427, left column, under "Discussion"). Document D6 further highlights the relatively high and humidity independent T_g of HPMC-AS as favoring the stability of such SDDs (see D6, page 1430, right column).

Document D19 presents a review on spray-dried dispersion technology from the perspective of the company "Bend Research", which is identified as a "problem solving drug formulation development and manufacturing company (...) well known for its spray-dried dispersion technology" (see page 1, "Introduction"). The document reports the company's experience in the formulation of more than 500 low-solubility compounds according to which spray-drying amorphous dispersions is the most widely applicable approach in the formulation of poorly soluble compounds (see page 3, left column). The document states that the company found fewer than 10 compounds which could not be formulated as amorphous dispersion due to their

reactivity or very high melting point (see page 4). The document further recommends HPMC-AS as a concentration enhancing polymer for compounds with a tendency to crystallize in solution or the solid state, because it provides superior performance for more than half of the compounds the company has worked on (see page 6). The earlier published document D18 also refers to the HPMC-AS based technology applied by Bend Research. Document D18 states that over 400 candidate drug compounds have been successfully formulated as HPMC-AS SDDs, of which 28 have advanced to human clinical testing, including 1 in Phase 3 (see D18, pages 16-17).

The additionally cited documents D7, D10, D22, D23, D25, D36 and D38 essentially confirm the known advantageous properties of HPMC-AS in the preparation of SSDs of poorly soluble drugs as described in documents D4, D6, D18 and D19 (see D7, paragraph [0039]; D10, page 991, right column; D22, page 16, "Conclusion"; D23, page 718, left column; D25, Abstract; D36, page 4, right column and page 8, right column; D38, Abstract). The post-published textbook excerpt of document D68 refers to documents D4 and D6 (see D68, page 308) and concludes that HPMC-AS SDDs are a particularly effective platform for enhancing the oral bioavailability of poorly soluble drugs (see D68, page 321). The post-published review in document D17 on lipid-based drug delivery systems refers to the challenge of formulating poorly soluble drug molecules ("BCS Class 2", "DCS Class IIb") and merely mentions in this context the formulation of amorphous solid dispersions as an alternative approach (see D17, page 1, left column and page 10 under "Classification according to BCS and DCS").

5.3.3 In contrast, the review articles in documents D51, D52, D53 and D54 explain that although at the time of the priority date solid dispersion approaches had been extensively explored, the development of amorphous solid dispersions for the oral formulation of poorly soluble drugs which provide adequate bioavailability in combination with physical stability was difficult and based on trial and error (see D51, abstract; page 1362, "Article highlights"; page 1367, left column; page 1373 right column; see D52, page 387, left column; see D53, pages e83-e84, bridging sentence; see D54, page 1573, left column and page 1575, right column). This difficulty is confirmed by the review article in document D56 published well after the priority (see page 110, right column). Moreover, although the review documents D23 and D36 refer to HPMC-AS as an advantageous excipient, these documents still underline the persisting difficulty of providing suitable amorphous solid dispersions for poorly soluble APIs due to a lack of fundamental understanding (see D23, page 718, right column and page 728, left column; see D36, page 2, left column). Document D36 states in this context literally that the development of such formulations "still primarily relies on tedious trial-by-error approach and *in vivo* screening in animal models".

In this context, the Board further observes that, whilst document D4 mentions a high number of drugs formulated as SSDs with HPMC-AS that were tested in animal models and documents D18 and D19 refer to even higher numbers of successfully formulated agents as SSD with failures representing the exception, reports of such formulations in human clinical testing were more limited (see D18, page 17; see also D4, page 1016, right column) and products reaching the market remained

the exception (see for instance D51, page 1373, right column).

The Board further notes that none of documents D4, D6, D18 and D19 refer to the challenge of formulating an API in an amorphous solid dispersion which actually achieves in humans a comparable bioavailability to a capsule containing a solution of that API. Document D4 states that more than 100 different drugs have been formulated as SSDs and tested in various animal models and that the SSD absorption enhancement relative to crystalline drugs ranged from around 2-fold to near 40-fold (see D4, page 1016 under the heading "*In vivo* Performance"). However, this wide range for the enhancement in absorption from the SSDs relative to the crystalline drugs does not support any reasonable expectation that the formulation of a drug such as enzalutamide in an SSD with HPMC-AS allows for a comparable bioavailability relative to a liquid-filled capsule, especially since enzalutamide would be particularly challenging due to its strong tendency to crystallize (see post-published document D59, page 6).

Document D55 (see page 1334, left column and page 1335, Figure 6) and document D74 (see abstract and Tables 7-8) further confirm that the suitability of HPMC-AS as a concentration enhancing polymer depends unpredictably on the API to be formulated. The successful formulation of lopinavir and ritonavir as a solid dispersion following their initial marketing in the form of liquid-filled capsules referred to by the opponents does therefore also not support any reasonable expectation regarding the formulation of enzalutamide as a solid dispersion.

The skilled person would therefore not derive from the prior art any reasonable expectation of success that that in a solid pharmaceutical composition, the formulation of a solid dispersion containing amorphous enzalutamide and HPMC-AS allows the provision of a dosage form with a comparable bioavailability in humans with respect to the XTANDI capsules of the prior art, while maintaining outstanding physical stability.

Accordingly, the Board concludes that the claimed subject-matter is not obvious to the skilled person in view of document D3 as the closest prior art.

5.4 No different conclusion when starting from document D1

In view of the Board's finding under section 5.1.5,a comprehensive evaluation of inventive step starting from document D1 is considered unnecessary. Nevertheless, in view of the parties submissions on this matter during the oral proceedings, the Board presents the following assessment.

The distinguishing features of the subject-matter of claim 1 over the teaching of document D1 involve the formulation of the enzalutamide in a solid dispersion containing amorphous enzalutamide and HPMC-AS.

The experimental data presented in the patent, comparing the composition of claim 1 with the XTANDI capsules (see Table 15.1), represent evidence of the properties of the claimed composition characterized by these features. In view of the lack of disclosure of an individualized and specific pharmaceutical composition of enzalutamide in document D1, the encapsulated enzalutamide solution in a solvent mixture represents a meaningful external reference point to approximate the

bioavailability level of the claimed composition based on experimental data. Accordingly, the comparative experimental data cannot be neglected when formulating the objective technical problem on the basis of document D1 instead of the XTANDI capsules.

Having regard to the evidence discussed in section 5.2 above and for analogous reasons explained therein, the objective technical problem starting from document D1 may therefore realistically be formulated as the provision of a pharmaceutical composition comprising enzalutamide exhibiting outstanding stability and providing a bioavailability which allows the formulation of a dosage form with bioavailability comparable to a solution of enzalutamide in a solvent mixture.

Given the multiple strategies for formulating poorly soluble APIs and the related complexities (see section 5.3.1), achieving bioavailability comparable to enzalutamide solution capsules is not merely a bonus effect of an in any case obvious development (compare Case Law of the Boards of Appeal of the European Patent Office, *supra*, I.D.10.8).

For the same reasons as set out in section 5.3 above, the subject-matter of claim 1 would not be obvious to the skilled person as a solution to the identified problem.

5.5 Accordingly, the Board concludes that claim 1 of the main request also complies with the requirement of inventive step of Article 56 EPC.

Order

For these reasons it is decided that:

The appeals are dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated