judgment

DISTRICT COURT THE HAGUE

Civil law

Seat in The Hague

Case number: C/09/654337 /HAZA 23-858

Judgment dated 22 January 2025

in the case of

SYNTHON B.V.,
Nijmegen, ,
hereinafter referred to as: Synthon,
lawyer: mr. K.M.L. Bijvank,

versus

I. foreign-law company
ASTELLAS PHARMA, INC,
Tokyo, Japan,
2. foreign-law company
MEDIVATION PROSTATE THERAPEUTICS, LLC.,
Delaware (United States of America)),
defendants,
hereinafter together referred to as:
Astellas,
lawyer: mr. F.W.E. Eijsvogels.

The case was substantively handled for Synthon by Mr Bijvank aforementioned, M.G.R. van Gardingen, J. de Groot and B.B. van der Wansem, lawyers in Amsterdam. The substance of the case was handled for Astellas by the aforementioned Mr Eijsvogels, Mr T.M. Blomme, Mr N.C. Rodriguez Arigon and Mr I.M. ten Brink, lawyers in Amsterdam, and Dr J.H.J. den Hartog, patent attorney.

1. The procedure

1.1. The conduct of the proceedings is evidenced by:
- The order of the interim relief judge of this court dated 8 June 2023, allowing litigation under the accelerated regime in patent cases;
- the writ of summons dated 13 June 2023;
- the deed submitting exhibits, by Synthon dated 27 September 2023, with exhibits EP01 to EP51;
- Astellas' statement of defence dated 6 December 2023, with exhibits GP01 to GP22;
- deed submitting further exhibits by Synthon dated 10 April 2024, with exhibits EP52 to EP55;

- deed submitting further exhibits by Astellas dated 10 April 2024, with exhibits GP23 to GP26;
- the parties' e-mail messages of 12 and 15 April 2024 and the Court's decision thereon of 16 April 2024, to the effect that exhibit EP52 as submitted is rejected for exceeding the word limit of Article 6.2 VRO Regulation, that Synthon is given the opportunity to submit exhibit EP52 shortened to 3,000 words and that Synthon should withdraw exhibit EP55;
- Synthon's submission of revised version of exhibit EP52 and withdrawal of exhibit EP55;
- Synthon's deed submitting reactive exhibits dated 8 May 2024, with exhibits EP56 to EP59;
- Astellas' deed submitting reactive exhibits dated 8 May 2023, with exhibits GP27 and GP28;
- Astellas' deed submitting additional exhibits dated 10 May 2024, with exhibits GP29 and GP30;
- the parties' e mails of 15 and 16 May 2024 and this court's decision of 17 May 2024, allowing exhibits GP29 and GP30 and a larger word count in the written pleading notes in connection therewith, and in which the latter e-mail also invited the parties to comment on a possible stay of proceedings pending the decision of the Technical Board of Appeal of the EPO[1], assuming that the decision of the Opposition Division of the EPO (hereinafter; the OD) is appealed; provides a final decision on validity;
- the parties' e-mails of 21 and 22 May 2024 and the court's e-mail of 24 May 2024 deciding that, in view of the content of the parties' responses, the proceedings will continue;
- Synthon's pleading notes;
- Astellas' pleading notes;
- Astellas' response to Synthon's pleading notes.

l .2. On 7 June 2024, the oral proceedings took place in hybrid format, with some of those present in the courtroom and some participating via video link (MCU). Participating in the hearing were: the parties, their lawyers, the patent attorney, the expert on the side of Synthon Dr D. Miller and the experts on the side of Astellas Prof G. van den Mooter and Prof H.W. Frijlink. The court asked questions and the parties then replied and rejoined, Synthon on the basis of a reply submitted in writing.

1.3. Judgment is further set for today.

2. The facts

Parties

2. l. Synthon is a global Dutch company that develops and produces generic drugs.

[1] European Patent Office

2.2. Astellas Pharma Inc. is a global Japanese company engaged in drug research, development and marketing.

2.3. Medivation Prostate Therapeutics LLC is a US company dedicated to developing therapies to treat serious diseases for which there are limited treatments available. Medivation worked with Astellas to develop a drug to treat prostate and breast cancer (enzalutamide) and was acquired by Pfizer in 2016.

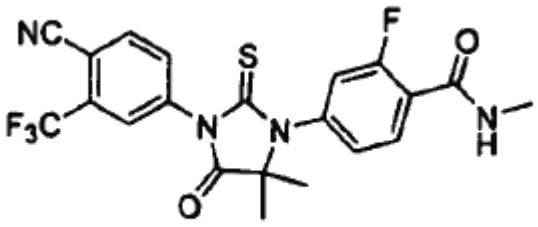
Enzalutamide

2.4. Enzalutamide is the active substance in the drug in Europe under the (brand) name Xtandi® by Astellas. Xtandi is indicated for the treatment of prostate cancer. Xtandi was initially available in the of capsules containing 40 mg enzalutamide. These capsules were relatively large (approximately 20 mm x 9 mm). The daily dosage was 160 mg. Later, the capsules were replaced by tablets containing 40 mg and 80 mg enzalutamide.

2.5. Enzalutamide is under protection in European Patent EP 1 893 196 B1 (hereinafter EP 196) for *"diarylhydantoin compound"*. EP 196 is held by The Regents of the University California. EP 196 was granted on 18 January 2012 on an international application dated 29 March 2006 published as a PCT application
WO 2006/124118. EP 196 is valid until 29 March 2026. OCNL granted a supplementary protection certificate number 300632 (hereinafter SPC 632) on the basis of EP 196 for "Enzalutamide, if desired in the form of a pharmaceutically acceptable salt thereof". SPC 632 has legal force from 29 March 2026 to 24 June 2028.
EP 196 was the subject of invalidity actions brought by several parties before this court[2] and in courts abroad, including the UK and Germany.

2.6. Claim l of EP 196 reads:

1. A compound having the formula



[RD162']

or a pharmaceutically acceptable salt thereof.

[2] Accord Healthcare Ltd and Accord Healthcare B.V. v. The Regents of the University of California and Astellas Pharma Inc (C/09/654970. 23/903); Sandoz AG v. The Regents of the University of California and Astellas Pharma Inc (C/09/654975, 23/904). Oral proceedings in both cases took place on 28June 2024.

The patent EP 778

2.7. Astellas holds European Patent EP 3 725 778 B1 (hereinafter EP 778 or the patent) for *"Formulations of Enzalutamide".* EP 778 was granted on 18 August 2021 on an application dated 11 September 2013, claiming priority from US 201261699351 dated 11 September 2012 (hereinafter priority date). EP 778 is effective in, among others, the Netherlands.

2.8. EP 778 is a derivative *(divisional)* of EP 2 895 463 Al (hereinafter EP 463), filed as PCT application WO 2014/043208 Al (hereinafter WO 208). EP 463 was withdrawn during the granting procedure at the EPO on 26 June 2020. Astellas filed several divisionals based on EP 463.

2.9. The granting of EP 778 was opposed by 11 parties, including Synthon. At the end of the oral hearing on 8 and 9 April 2024, the OD announced that EP 778 (in the form of a new main request, see 4.16 below) meets the requirements of the EPC[3]. This decision was put in writing on 8 May 2024. The decision was appealed - inter alia by Synthon -.

2.10. The claims of EP 778 in the original English language read as follows.

I. A solid pharmaceutical composition comprising a solid dispersion containing amorphous enzalutamide and a concentration-enhancing polymer, wherein the polymer is hydroxypropyl methylcellulose acetate succinate.
2. The solid pharmaceutical composition according to claim 1, wherein the amount of the polymer is 0.5 to 7 parts by weight, with respect to 1 part by weight of the enzalutamide.
3. The solid pharmaceutical composition according to claim 1, wherein the amount of the polymer is 0.5 to 3 parts by weight, with respect to 1 part by weight of the enzalutamide.
4. The solid pharmaceutical composition according to claim 1, wherein the amount of the polymer is 3 to 5 parts by weight, with respect to 1 part by weight of the enzalutamide.
5. The solid pharmaceutical composition according to claim 1, wherein the amount of the polymer is 3 parts by weight. with respect to 1 part by weight of the enzalutamide.
6. The solid pharmaceutical composition according to claim 1, wherein the amount of the polymer is 5 parts by weight. with respect to 1 part by weight of the enzalutamide.
7. The solid pharmaceutical composition according to claim 1, wherein the pharmaceutical composition is in unit dosage form, containing 40 to 160mg of the enzalutamide per unit dosage form.
8. The solid pharmaceutical composition according to claim 1, wherein the composition comprises more than one concentration-enhancing polymer.
9. The solid pharmaceutical composition according to claim 1, wherein at least 80% of the total amount of enzalutamide present is in an amorphous form.
10. The solid pharmaceutical composition according to claim 1, wherein the solid dispersion comprises between 50% and 70% of enzalutamide.
11. The solid pharmaceutical composition according to claim 1. wherein the solid dispersion is substantially homogenous such that the fraction of enzalutamide that is in relatively pure amorphous domains within the solid dispersion is less than 20% by weight of the total amount of enzalutamide.
12. The solid pharmaceutical composition according to claim 1, wherein the solid dispersion is prepared by spray drying.

[3] European Patent Convention

13. The solid pharmaceutical composition according to claim 1, wherein the solid dispersion is prepared by hot melt extrusion.
14. The solid pharmaceutical composition according to claim 1, further comprising a filler, a binder, a disintegrator, an acidulant. an effervescent agent, an artificial sweetener, a flavouring. a lubricant, a colouring agent, a stabilising agent. a buffer, an antioxidant. a glidant or mixture thereof.
15. A process of manufacturing a solid pharmaceutical composition according to claim 1, comprising:
(i) preparing the solid dispersion of amorphous enzalutamide and the polymer
(2) mixing and/ or granulating the solid dispersion, and
(3) tableting the solid dispersion.
16. The process of claim 15 wherein step 2) comprises mixing the solid dispersion with one additive or two or more additives and granulating the mixture, and further comprising a step oftableting granules of the mixture.
17. The solid pharmaceutical composition of claim 1, which is a tablet.
18. The solid pharmaceutical composition of claim 17, wherein the tablet comprises 45-70 wt% of the solid dispersion, the dispersion comprising 55-65 wt% of the enzalutamide and hydroxypropyl methylcellulose acetate succinate; preferably wherein the tablet comprises 45-55 wt% of the solid dispersion; or wherein the tablet comprises 55.3 wt% of the solid dispersion, the dispersion comprising 60 wt% of the enzalutamide and hydroxypropyl methylcellulose acetate succinate.
19. The solid pharmaceutical composition of claim 1 for use in the treatment of hyperproliferative disorder.
20. The solid pharmaceutical composition for use according to claim 19, wherein:
i) the hyperproliferative disorder is selected from the group consisting of benign prostatic hyperplasia, prostate cancer, breast cancer and ovarian cancer; or
ii) the hyperproliferative disorder is prostate cancer and the prostate cancer is selected from the group consisting of hormone-refractory prostate cancer and hormonesensitive prostate cancer.

2.11. The uncontested Dutch translation of the claims reads as follows.

1. Vaste farmaceutische samenstelling, omvattende een vaste dispersie die amorf enzalutamide en een concentratieverhogend polymeer bevat, waarbij het polymeer hydroxypropylmethylcelluloseacetaatsuccinaat is.
2. De vaste farmaceutische samenstelling volgens conclusie 1, waarbij de hoeveelheid van het polymeer 0,5 tot 7 gewichtsdelen is, ten opzichte van 1 gewichtsdeel van het enzalutamide.
3. De vaste farmaceutische samenstelling volgens conclusie 1, waarbij de hoeveelheid van het polymeer 0,5 tot 3 gewichtsdelen is, ten opzichte van 1 gewichtsdeel van het enzalutamide.
4. De vaste farmaceutische samenstelling volgens conclusie 1, waarbij de hoeveelheid van het polymeer 3 tot 5 gewichtsdelen is, ten opzichte van 1 gewichtsdeel van het enzalutamide.
5. De vaste farmaceutische samenstelling volgens conclusie 1, waarbij de hoeveelheid van het polymeer 3 gewichtsdelen is, ten opzichte van 1 gewichtsdeel van het enzalutamide.
6. De vaste farmaceutische samenstelling volgens conclusie 1, waarbij de hoeveelheid van het polymeer 5 gewichtsdelen is, ten opzichte van 1 gewichtsdeel van het enzalutamide.
7. De vaste farmaceutische samenstelling volgens conclusie 1, waarbij de farmaceutische samenstelling in de vorm van een eenheidsdosis is, bevattende 40 tot 160 mg van het enzalutamide per vorm van de eenheidsdosis.
8. De vaste farmaceutische samenstelling volgens conclusie 1, waarbij de samenstelling meer dan één concentratieverhogend polymeer omvat.
9. De vaste farmaceutische samenstelling volgens conclusie 1, waarbij ten minste 80% van de totale hoeveelheid enzalutamide die aanwezig is, in een amorfe vorm is.
10. De vaste farmaceutische samenstelling volgens conclusie 1, waarbij de vaste dispersie tussen 50% en 70% enzalutamide omvat.
11. De vaste farmaceutische samenstelling volgens conclusie 1, waarbij de vaste dispersie nagenoeg homogeen is, zodat de fractie van enzalutamide die in relatief zuivere amorfe domeinen binnen de vaste dispersie aanwezig is, minder is dan 20% op basis van gewicht van de totale hoeveelheid enzalutamide.

12. De vaste farmaceutische samenstelling volgens conclusie 1, waarbij de vaste dispersie wordt bereid door sproeidrogen.
13. De vaste farmaceutische samenstelling volgens conclusie 1, waarbij de vaste dispersie wordt bereid door hetesmeltextrusie.
14. De vaste farmaceutische samenstelling volgens conclusie 1, verder omvattende een vulmiddel, een bindmiddel, een desintegreermiddel, een aanzuurmiddel, een bruismiddel, een kunstmatig zoetmiddel, een smaakstof, een smeermiddel, een kleurmiddel, een stabilisatiemiddel, een buffer, een antioxidant, een glijmiddel of mengsel daarvan.
15. Werkwijze voor het vervaardigen van een vaste farmaceutische samenstelling volgens conclusie 1, omvattende:
(1) het bereiden van de vaste dispersie van amorf enzalutamide en het polymeer
(2) het mengen en/of granuleren van de vaste dispersie en
(3) het tabletteren van de vaste dispersie.
16. De werkwijze volgens conclusie 15, waarbij stap (2) het mengen van de vaste dispersie met één additief of twee of meer additieven en het granuleren van het mengsel omvat, en verder omvattende een stap van het tabletteren van granules van het mengsel.
17. De vaste farmaceutische samenstelling volgens conclusie 1, die een tablet is.
18. De vaste farmaceutische samenstelling volgens conclusie 17, waarbij de tablet 45-70 gew.-% van de vaste dispersie omvat, waarbij de dispersie 55-65 gew.-% van het enzalutamide en hydroxypropylmethylcelluloseacetaatsuccinaat omvat: bij voorkeur waarbij de tablet 45-55 gew.-% van de vaste dispersie omvat, of waarbij de tablet 55,3 gew.- % van de vaste dispersie omvat, waarbij de dispersie 60 gew.-% van het enzalutamide en hydroxypropylmethylcelluloseacetaatsuccinaat omvat.
19. De vaste farmaceutische samenstelling volgens conclusie 1 voor gebruik bij de behandeling van een hyperproliferatieve stoornis.
20. De vaste farmaceutische samenstelling voor gebruik volgens conclusie 19, waarbij:
i) de hyperproliferatieve stoornis is gekozen uit de groep die bestaat uit benigne prostaathyperplasie, prostaatkanker, borstkanker en eierstokkanker; of
ii) de hyperproliferatieve stoornis prostaatkanker is en de prostaatkanker is gekozen uit de groep die bestaat uit hormoonresistente prostaatkanker en hormoongevoelige prostaatkanker.

2.12. The description of EP 778 includes - as far as relevant here - the following.

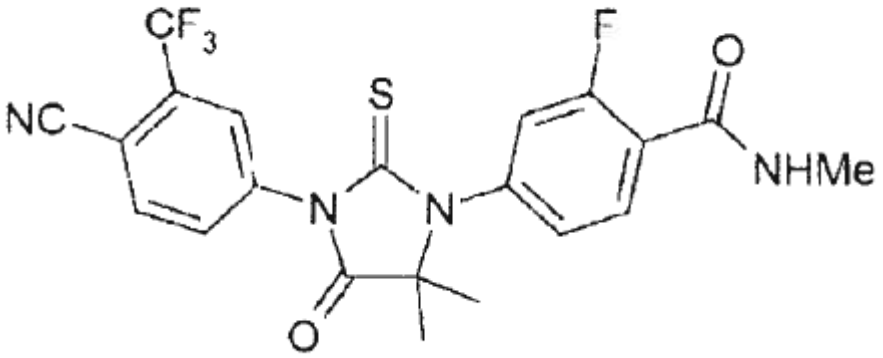
Description

TECHNICAL FIELD

[0001] This disclosure relates to solid formulations of enzalutamide. More particularly, this disclosure relates to pharmaceutical compositions comprising a solid dispersion containing enzalutamide and at least one polymer. Furthermore, this disclosure relates to methods for manufacturing such formulations and compositions, and to their use.

BACKGROUND

[0002] Enzalutamide is an androgen receptor signalling inhibitor. The chemical name is 4-{3-[4-cyano-3-(trifluoromethyl) phenyl]-5, 5-dimethy1-4-oxo-2-sulfanylideneimidazolid in-1-yl)-2-fluoro-N-methylbenzamide. The structural formula is:



[0003] Enzalutamide is used as an agent for treating castration-resistant prostate cancer. *See, e.g.* , US 7,709,517. Enzalutamide is provided commercially as a soft capsule (brand name "XTANDI® ") filled with a liquid comprising 40 mg of enzalutamide per one capsule and pharmaceutical excipients. The daily dosage is 160 mg. and a patient therefore needs to take four capsules daily. 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.

[0004] The patent literature reports a sparingly soluble compound held on a gel-forming water-soluble polymer such as hydroxypropyl methylcellulose or hydroxypropylcellulose, as a solid dispersion, wherein the composition contains a salt substance to improve a disintegration time and dissolution profile and the like. *See,* e.g. , US2002/003 I 547. Use of hydroxypropylmethylcellulose acetate succinate in a pharmaceutical composition comprising a sparingly soluble compound, prepared by a spray drying method, has also been reported to improve aqueous solubility and/or bioavailability. *See, e.g.* , US2002/0009494. Combining drugs with solubilising polymers does not always improve bioavailability for a low-solubility drug, however. Solubilization of a specific drug depends on its chemical structure and physical properties; therefore, whether any particular polymer will solubilize a specific drug is not necessarily predictable. It is often difficult and time-consuming to select polymers which achieve improved solubilization, because the drug-polymer interaction is poorly understood. For example, addition of polymers may actually speed dissolution of a drug, rather than provide enhanced concentration.

BRIEF DESCRIPTION OF THE DRAWINGS

[0005]

FIG. 1. PXRD Diffractograms of amorphous enzalutamide. three spray-dried dispersions of enzalutamide with concentration-enhancing polymers, and crystalline enzalutamide. See Example 3.

FIG. 2. Scanning Electron Micrograph (SEM) images of amorphous enzalutamide (100%A Spray-dried) and spray-dried dispersions (SDDs) comprising enzalutamide and HPMCAS or PVPVA. Before (Initial) and after 1 day exposure to a 50° C/75%RH environment. See Example 6.

FIG. 3 is a dissolution profile of the solid dispersions obtained by Example 17 (1:3). 18 (1:2), 19 (1: 1. 5). 20 (1:1), 21 (1:0.67) and 22 (1:5) in Example 25.

FIG. 4 is a dissolution profile of the tablets obtained by Example 16 (1:3). 18 (1:2). and 21 (1:0.67) in Example 25.

FIG. *5* is a dissolution profile of the initial tablet obtained by Example 17 and the tablet stored at 40° C and 75% relative humidity for 1 month in Example 26.

FIG. 6 is an X-ray diffraction spectrum of the solid dispersions prepared in Example 16 (1:3), 18 (1:2), 22 (1:5) and 23 (1:3) and crystalline drug substance obtained by measuring it immediately after its preparation.

FIG. 7 is an X-ray diffraction spectrum of the solid dispersion which was prepared in Example 17 and stored at 40° C and 75% relative humidity for 1 month in Example 29.

DETAILED DESCRIPTION

(...)

[0007] Enzalutamide is used as an agent for treating castration-resistant prostate cancer who have received docetaxel therapy; enzalutamide is also disclosed for treating breast cancer. prostate cancer, benign prostate hyperplasia and ovarian cancer: *See, e.g.,* U.S. Patent 7,709,517.

[0008] The present invention is defined by the scope of the claims. Consequently, the invention relates to solid pharmaceutical compositions comprising a solid dispersion containing amorphous enzalutamide and a concentration-enhancing polymer, wherein the polymer is hydroxypropyl methylcellulose acetate succinate. The invention also relates to a process of manufacturing of said pharmaceutical composition, comprising: (i) preparing the solid dispersion of amorphous enzalutamide and the polymer, (2) mixing and/ or granulating the solid dispersion, and (3) tableting the solid dispersion. The invention moreover relates to said compositions for use in the treatment of a hyperproliferative disorder. Other described disclosures or embodiments, which are not according to the claims, are for illustrative purposes only.

[0009] The present disclosure provides a solid dispersion having the properties such as improvement solubility and absorption of enzalutamide, and a pharmaceutical composition containing the solid dispersion which has dissolution stability.

[0010] Further, the present disclosure provides a method for making pharmaceutical composition which has dissolution stability of enzalutamide.

[0011] According to the present disclosure, (i) a pharmaceutical composition which improves solubility and absorption of enzalutamide, (2) a pharmaceutical composition which has rapid disintegrating property and dispersibility of enzalutamide when said pharmaceutical composition (tablet and the like) is used, and (3) a process of manufacturing the pharmaceutical composition which has said effect, can be provided.

[0012] These dosage forms provide unusually large enhancements in aqueous concentration in an environment of use. These compositions also provide the opportunity to dose the entire daily therapeutic dose of enzalutamide in a single dosage unit, by improving the oral bioavailability of the drug.

Amorphous enzalutamide

[0013] In the present invention, enzalutamide is amorphous *(i.e.,* in a non-crystalline state). Amorphous enzalutamide dissolves more quickly and to a greater extent than crystalline enzalutamide in an aqueous use environment, such as an aqueous dissolution medium of an *in vitro* dissolution test *(e.g.* , phosphate buffered saline or model fasted duodenal fluid or simulated gastric fluid) or the *in vivo* environment of the stomach or small intestine. This enhanced dissolution results in higher enzalutamide oral bioavailability. compared to crystalline drug. An example of a crystalline form of enzalutamide is Form A, characterised by the powder x-ray diffraction pattern designated 'Bulk Crystalline Drug' in FIG. 1.

[0014] In some embodiments, enzalutamide is greater than 80% amorphous *(i.e.* , containing less than 20% crystalline enzalutamide). In some embodiments, enzalutamide is greater than 90% amorphous *(i.e.* , containing less than 10% crystalline enzalutamide). In some embodiments. enzalutamide is greater than 95% amorphous *(i.e.* , containing less than 5% crystalline enzalutamide). In some embodiments. enzalutamide exhibits no crystalline character when measured by powder x-ray diffraction. by low angle x- ray scattering. by 13C-NMR. or by 19F-NMR.

[0015] Amorphous enzalutamide may be prepared by any known means. including spray-drying. hot melt extrusion, and precipitation from solution on addition of a non-solvent.

Pharmaceutical compositions

[0016] The exact amount (effective dose) of enzalutamide will vary from subject to subject. depending on, for example. the species. age, weight and general or clinical condition of the subject, the severity or mechanism of

any disorder being treated. the particular agent or vehicle used, the method and scheduling of administration, and the like.

[0017] The particular mode of administration and the dosage regimen will be selected by the attending clinician, taking into account the particulars of the case (e.g. the subject. the disease, the disease state involved, and whether the treatment is prophylactic). Treatment may involve daily or multi- daily doses of compound(s) over a period of a few days to months, or even years.

[0018] In general, however, a suitable dose will be in the range of from about 0.001 to about 100 mg/kg, e.g., from about 0.01 to about 100 mg/kg of body weight per day, such as above about 0.1 mg per kilogram, or in a range of from about 1 to about 10 mg per kilogram body weight of the recipient per day. For example. a suitable dose may be about 1 mg/kg. 10 mg/kg. or 50 mg/kg of body weight per day.

[0019] Enzalutamide conveniently administered in unit dosage form; for example, containing 0.05 to 10000 mg. 0.5 to 10000 mg. 5 to 1000 mg. 10 to 200 mg. or 40 to 160 mg of enzalutamide per unit dosage form. **[0020]** Enzalutamide may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example. as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator.

[0021] In the present invention, compositions comprise amorphous enzalutamide and a concentration-enhancing polymer, wherein the polymer is hydroxypropyl methylcellulose acetate succinate. In some embodiments, compositions comprise amorphous enzalutamide and more than one concentration-enhancing polymer.

[0022] Amorphous enzalutamide and a concentration-enhancing polymer may be physically mixed, that is the two materials, as separate powders, may be blended by methods known in the pharmaceutical arts, including dry blending. dry-granulation, and wet granulation.

[0023] In the present invention, compositions comprise solid amorphous dispersions of enzalutamide and a concentration-enhancing polymer, wherein the polymer is hydroxypropyl methylcellulose acetate succinate. In some embodiments, at least a major portion of the enzalutamide in the composition is amorphous. As used herein, the term "a major portion" of the enzalutamide means that at least 60% of the enzalutamide in the composition is in the amorphous form, rather than the crystalline form. In some embodiments. the enzalutamide in the dispersion is substantially amorphous. As used herein, "substantially amorphous" means that the amount of the enzalutamide in crystalline form does not exceed about 20%. In some embodiments, the enzalutamide in the dispersion is "almost completely amorphous, meaning that the amount of enzalutamide in the crystalline form does not exceed about 10%. Amounts of crystalline enzalutamide may be measured by powder X-ray diffraction, low angle x-ray scattering, differential scanning calorimetry (DSC), solid state l 9F-NMR, solid state 13C-NMR, or any other standard quantitative measurement.

[0024] Compositions may contain from about 1 to about 80 wt% enzalutamide, depending on the dose of the drug and the effectiveness of the concentration-enhancing polymer. Enhancement of aqueous enzalutamide concentrations and relative bioavailability are typically best at low enzalutamide levels in the dispersion. typically less than about 75 wt%. In some embodiments, dispersions comprise greater than 20wt% and less than 75wt% enzalutamide. In some embodiments. dispersions comprise greater than 25wt% and less than 75wt% enzalutamide. In some embodiments, dispersions comprise greater than 50wt% and less than 70wt% enzalutamide.

(...)

[0037] Relative bioavailability of enzalutamide in the dispersions can be tested *in vivo* in animals or humans using conventional methods for making such a determination. An *in vivo* test, such a crossover pharmacokinetic study, may be used to determine whether a composition of enzalutamide and concentration enhancing polymer (or a composition comprised of amorphous enzalutamide without a concentration-enhancing polymer) provides an enhanced relative bioavailability compared with a control composition comprised of crystalline enzalutamide but no polymer as described above. In an *in vivo* crossover study a "test composition" of enzalutamide and polymer is dosed to half a group of test subjects and. after an appropriate washout period (at least 42 days) the same subjects are dosed with a "control corn-position" that comprises an equivalent quantity of

crystalline enzalutamide with no concentration-enhancing polymer present. The other half of the group is dosed with the control composition first, followed by the test composition. The relative bioavailability is measured as the area under the plasma drug concentration versus time curve (AUC) determined for the test group divided by the plasma AUC provided by the control composition. In some embodiments. this test/control ratio is determined for each subject. and then the ratios are averaged over all subjects in the study. *In vivo* determinations of AUC can be made by plotting the plasma concentration of drug along the ordinate (y-axis) against time along the abscissa (x-axis). and using the trapezoidal rule method.

[0038] Thus, as noted above, one embodiment is one in which the relative bioavailability of the test composition is at least about 1.25 relative to a control composition comprised of crystalline enzalutamide but with no concentration-enhancing polymer as described above. (That is, the *in vivo* AUC provided by the test composition is at least about 1.25-fold the *in vivo* AUC provided by the control composition). In some embodiments. the relative bioavailability of the test composition is at least about 2, relative to a control composition composed of crystalline enzalutamide but with no concentration-enhancing polymer present, as described above. The determination of AUCs is a well-known procedure and is described, for example, in Welling. "Pharmacokinetics Processes and Mathematics," ACS Monograph 185 (1986).

[0039] To carry out the *in vivo* AUC measurements for enzalutamide, the enzalutamide test and control compositions should be dosed at a 160 mg dose to a cohort of at least 24 subjects in the fasted state. Blood samples should be collected at 0 time (pre-dose). and at post-dose times 15. 30, and 45 minutes; and at 1, 2, 3, 4, 6, 8, and 12 hours; and at 0 and 12 hours on day 2; and at 0 hours on days 3, 5, and 7 (where 0 hours on days 2. 3, 5, and 7 correspond to the time of day when dosing occurred on day 1).

[0040] Relative bioavailability is measured using AUC_{0-7}days. The absolute value of the AUC_{0-7}days is also used to determine if a dispersion formulation falls within compositions of this disclosure: *i.e.* pharmaceutical compositions comprising a solid amorphous dispersion of enzalutamide and a concentration-enhancing polymer, which when dosed to a cohort of 24 or more humans at a dose of 160 mg provides a mean area under the plasma enzalutamide concentration vs. time curve from the time of dosing to 7 days after dosing, AUC_{0-7}days, which is greater than 150 µg-hr/ml. This constraint applies to other doses as well, providing a plasma AUC_{0-7}days which is greater than (150 µg-hr/ml)/(160 mg) or more generally greater than 0.94-g-hr/ml-mg, where mg refers to the weight of the enzalutamide dose.

[0041] Inspection of the plasma enzalutamide concentration versus time curves for the dosed subjects will give the maximum enzalutamide concentration Cmax achieved during the post-dose period. A mean Cmax can be calculated for the cohort of subjects. This disclosure provides a pharmaceutical composition comprising a solid amorphous dispersion of enzalutamide and a concentration-enhancing polymer, said dispersion when dosed to a cohort of24 or more humans at a dose of 160 mg providing a mean maximum plasma enzalutamide concentration Cmax which is greater than 2 µg/ml, In some embodiments, greater than 2.5 µg/ml. This constraint applies to other doses as well. providing a Cmax, greater than (2 µg/ml)/(160 mg), where mg refers to the weight of the enzalutamide dose. In some embodiments, Cmax is greater than (2.5 µg/ml)/(160 mg); this constraint can be expressed as providing a Cmax greater than 12.5 ng/ml-mg. In some embodiments, Cmax is greater than 15.6 ng/ml-mg.

[0042] Concentration-enhancing polymers suitable for in the compositions are be inert. in the sense that they do not chemically react with enzalutamide. are pharmaceutically acceptable *(i.e.* are non-toxic), and have at least some solubility in aqueous solution at physiologically relevant pHs (e.g. 1-8). The concentration-enhancing polymer can be neutral or ionizable, and should have an aqueous-solubility of at least 0.1 mg/ml over at least a portion of the pH range of **1-8.**

[0043] A polymer is a "concentration-enhancing polymer" if it meets at least one, or, in some embodiments. both, of the following conditions. The first condition is that the concentration-enhancing polymer increases the *in vitro* MDC of enzalutamide in the environment of relative to a control composition consisting of an equivalent amount of crystalline enzalutamide but no polymer. That is. once the composition is introduced into an environment of use, the polymer increases the aqueous concentration of enzalutamide relative to the control composition. In some embodiments. the polymer increases the MDC of enzalutamide in aqueous solution by at

at least 2-fold relative to a control composition: in some embodiments. by at least 5-fold; in some embodiments, by at least 10-fold. The second condition is that the concentration-enhancing polymer increases the AUC90 of the enzalutamide in the *in vitro* environment of use relative to a control composition consisting of enzalutamide but no polymer as described above. That is, in the environment of use, the composition comprising the enzalutamide and the concentration-enhancing polymer provides an area under the concentration versus time curve (AUC90) for any period of 90 minutes between the time of introduction into the use environment and about 270 minutes following introduction into the use environment that is at least 2-fold that of a control composition comprising an equivalent quantity of enzalutamide but no polymer. In some embodiments, the AUC provided by the composition is at least 5-fold: in some embodiments. at least 10-fold that of the control composition.
(...)
[0061] While, as listed above, a wide range of polymers may be used to form dispersions of enzalutamide. the inventors have found that relatively hydrophobic polymers have shown the best performance as demonstrated by high MDC and AUC90 *in vitro* dissolution values. In particular, cellulosic polymers that are aqueous insoluble in their nonionised state but are aqueous soluble in their ionised state perform particularly well. A particular subclass of such polymers are the so-called "enteric" polymers which include, for example, hydroxypropylmethylcellulose acetate succinate (HPMCAS) and certain grades of hydroxypropyl methyl cellulose acetate phthalate (HPMCAP) and cellulose acetate trimellitate (CAT). Dispersions formed from such polymers generally show very large enhancements in the maximum drug concentration achieved in dissolution tests relative to that for a crystalline drug control.
[0062] In some embodiments, concentration-enhancing polymers for use in dispersions with enzalutamide are hydroxypropylmethylcellulose acetate succinate (HPMCAS), hydroxypropylmethylcellulose (HPMC), hydroxypropylmethylcellulosephthalate (HPMCP), polyvinylpyrrolidonevinylacetate (PVP-V A), copolymers of methacrylic acid and methyl-methacrylate (approximate 1:1 ratio) available as EU DRAG IT L-100®, and graft copolymers of polyethyleneglycol. polyvinylcaprolactam, and polyvinylacetate, one commercially available version of a graft copolymer is known as SOLU PLUS®. Only compositions, which contain hydroxypropyl methylcellulose acetate succinate as concentration-enhancing polymer, are according to the claimed invention.
(...)
[0065] To obtain the best performance, particularly upon storage for long times prior to use. it is preferred that the enzalutamide remain, to the extent possible, in the amorphous state. The inventors have found that this is best achieved when the glass-transition temperature, Tg, of the solid amorphous dispersion is substantially above the storage temperature of the composition. In particular, it is preferable that the Tg of the amorphous state of the dispersion be at least 40° C. In some embodiments, the Tg of the amorphous state of the dispersion is at least 60° C. To achieve a high Tg for an enzalutamide/polymer dispersion. it is desirable that the polymer have a high Tg.
[0066] Exemplary high Tg concentration-enhancing polymers are HPMCAS. HPMCP, CAP, CAT.
(...)
Preparation of compositions
(...)
[0083] The amount of concentration-enhancing polymer relative to the amount of enzalutamide present in the dispersions may Val)' widely. The composition of enzalutamide/polymer dispersions is expressed, for example. as 25%A:HPMCAS-M. where 25%A means "25% active" and the dispersion contains 25% (by weight) enzalutamide and 75% (by weight) hydroxypropylmethlycellulose acetate succinate M-grade. In enzalutamide dispersions described herein. the enzalutamide content is generally greater than 20%A; in some embodiments, from 25%A to 75%A; in some embodiments, from 50%A to 70%A. For a specific concentration-enhancing polymer, the enzalutamide/polymer ratio that yields optimum results is best determined in *in vitro* dissolution tests and/or *in vivo* bioavailability tests.
[0084) The ratio of the polymer to enzalutamide is not particularly limited, so long as enzalutamide can be formed the solid dispersion. In some embodiments, the ratio of the polymer to enzalutamide is not particularly limited. so long as enzalutamide can be an amorphous state. The ratio of the polymer is specifically 0.5 to 7 parts

by weight in some embodiments. 0.5 to 3 parts by weight in some embodiments, 1 to 3 parts by weight in some embodiments. 2 to 3 parts *./5* by weight in some embodiments. 3 to 5 parts by weight in some , and 5 parts by weight in some embodiments, with respect to 1 part by weight of enzalutamide.

[0085) In addition, the amount of concentration-enhancing polymer that can be used in a dosage form is often limited by the total mass requirements of the dosage form. For example, when oral dosing to a human is desired, at low enzalutamide-to-polymer ratios the total mass of drug and polymer may be unacceptably large for delivery of the desired dose in a single tablet or capsule. Thus, it is often necessary to use enzalutamide-to polymer ratios that are less than optimum in specific dosage forms to provide a sufficient enzalutamide dose in a dosage form that is small enough to be easily swallowed by a human.

(...)

Excipients and Dosage Forms

(**...**)

Tablet Formulations

(...)

[0165] In the examples below, "Control 1" is crystalline enzalutamide, obtained as described in US7,709,517B2, in which this compound is called RDl62'; and "Control 2" is a 4.23 mg/ml solution of enzalutamide in LABRASOL® (Capry-locaproyl polyoxylglycerides).

(...)

EXAMPLES

[0178] Glass Transition Temperatures (Tgs) as a function of relative humidity.

[0179] Below Tg, an amorphous material is said to be in a "glassy" state in which molecular mobility is severely restricted. Above Tg, an amorphous material is in a state in which molecular mobility is increased significantly relative to the "glassy" state. Glass transition temperatures Tg were determined for amorphous enzalutamide, and for spray-dried dispersions (SDDs) of enzalutamide with HPMCAS-M or PVP-VA64. at< 5% and 75% relative humidity (RH). Tgs were determined by modulated differential scanning calorimetry (mDSC), utilising the following protocol. Samples (about 5 mg) were equilibrated at the desired RH overnight in an environmental chamber at ambient temperature. The samples were then loaded into pans and sealed inside the environmental chamber. The samples were analysed on a Q1000 mDSC (TA Instruments. New Castle, Delaware). Samples were typically scanned over the temperature range of -40° C to 180° C, at a scan rate of 2.5° C/min, and a modulation rate of± l.5° C/min. The data sampling interval was 0.20 sec/point. The Tg was calculated based on half height.

[0180] Tg data are presented in Table 5.1. As is generally observed, Tg decreases with increasing RH because the amorphous material is plasticised by incorporated water vapour as the %RH increases. Generally, Tg decreases approximately linearly as %RH increases. Formulations MDV-3100. D2, and D10 are reference formulations.

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

[0181] In order to assure that a dispersion will maintain its amorphous character (and thus its capacity to supersaturate a solution), it is desirable to choose a dispersion composition whose Tg is above the temperatures at which the product may be stored. If the product is stored at a temperature above its Tg, the amorphous drug within the dispersion will be relatively mobile and can diffuse into drug-rich patches and can crystallize. This is undesirable. Typical storage challenge conditions dictated by the US Food and Drug Administration are 40° C/25%RH, 50° C/20%RH, 30°C/60%RH, and 40°C/75%RH. At 75% RH, 100%A spray-dried enzalutamide (pure amorphous enzalutamide) and the enzalutamide/HPMCAS SDDs exhibit Tgs which are above each of the FDA challenge conditions (30°C, 40°C, 50°C). This is highly desirable, and these materials will not need protective packaging to protect them in high humidity environments.

[0182] The 25%A and 40%A enzalutamide dispersions with the concentration-enhancing polymer PVP-VA64 exhibit Tgs at 30.8°C and 34.9°C, respectively. If enzalutamide/PVP-VA dispersions encounter storage conditions above their Tgs (such as 40°C), they can possibly undergo undesirable change. Thus enzalutamide/PVP-VA dispersions should be stored in protective packaging (such as foil-foil blisters) which prevents ingress of water vapour into the dispersion.

[0183] Amorphous enzalutamide and MCV3 100/HPMCAS dispersions have high Tgs.

EXAMPLE 6

[0184] Particle morphology of amorphous enzalutamide, and SDDs of enzalutamide with HPMCAS and PVP VA. The formulations with PVP-VA are reference formulations.

[0185] Scanning electron micrographs (SEMs) were obtained for samples before and after 1 day exposure to a 50° C/75%RH environment. These SEMs are presented in Figure 2. After exposure of these samples to this challenging storage environment, no crystals were seen, indicative of the ability of these samples to maintain the amorphous character of enzalutamide. For three of the four samples, the 1 day storage challenge resulted in fusion of particles to form larger particles (100%A Spray-dried, 80%A:HPMCAS-MG, 40%A:PVPV A). with this effect being extreme for 40%A:PVPVA. Thus these three embodiments would require controlled storage conditions to maintain their efficacy. The 60%A:HPM-CAS-MG SDD did not undergo fusion to larger particles over the 1 day storage challenge, and would not require controlled
storage conditions to maintain efficacy.

[0186] In some embodiments, enzalutamide/HPMCAS SDDs have a drug content less than 80%.

(…)

EXAMPLE9

[0193] With the exception of the HPMCAS-containing dispersion D12, all dispersions in this example are reference examples.

[0194] Enzalutamide SDDs with the polymers HPMC, HPMCP, and EUDRAGIT-L 100.

[0195) A 60%A enzalutamide SDD was prepared with each of three polymers:

hydroxypropylmethylcellulose (E3 Prem grade) (HPMC E3 Prem); hydroxymethylcellulose phthalate(gradewith nominal phthalate contentof31 %) (HPMCP-55); anionic 1:1 copolymer of methacrylic acid and methylmethacrylate (EUDRAGIT L100®). 60%A SDDs were prepared with these three polymers, using the mini spray drier, and the conditions shown in Table 2. Each of the three 60%A SDDs exhibited no sharp features in their PXRD diffactograms, and were thus amorphous.

[0196] The three 60% SDDs were tested in the *in vitro* microcentrifuge dissolution test, in addition to a 60%A HPMCAS-M dispersion and Control 1 (crystalline enzalutamide). Table 9.1 presents the dissolution data, and Table 9.2 presents Cmax and AUC, values derived from these dissolution data. All four SDDs exhibited enzalutamide supersaturation (Cmax) and sustained supersaturation ($AUC_{..}$), relative to crystalline drug (Tables 9.1 and 9.2).

[0197] Table 9.1 shows that the enzalutamide SDDs with HPMCP-55 and with EUDRAGIT L 100® exhibit decreased enzalutamide concentration in solution after the 40 minute time point. while SDDs with HPMCAS and HPMC E3 Prem do not. This is reflected in the *in vitro* AUC data shown in Table 9.2.

Table 9.1 . *In vitro* dissolution (microcentrifuge dissolution test) of various enzalutamide SDDs and crystalline enzalutamide

Time (min)	Average µg/mL				
	60%A:HPMCAS-M (Disp D12)	60%A:HP MC (Disp D14)	60%A:HPMCP (Disp D15)	60%A:Eudragit (Disp D16)	Crystalline enzalutamide
0	0.00	0.00	0.00	0.00	0.32
4	77.69	108.33	90.21	57.80	5.23
10	84.96	108.65	88.19	68.93	8.04
20	93.53	109.16	100.48	81.42	7.69
40	102.73	109.70	109.37	91.94	8.65
90	108.32	104.10	36.07	34.19	9.14
1200	58.82	36.29	21.75	23.66	12.12

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.

Table 9.3. Membrane-Permeation Test Results for SDDs and Crystalline enzalutamide

Formulation (Dispersion #)	Maximum Flux (μg/cm^2-min)	Total Drug Recovery (%)
60%A:HPMCAS-MG SDD (D12)	3.7	81
60%A:HPMC E3 Prem SDD (D14)	2.1	75
60%A:HPMCP HP55 SDD (D15)	1.6	62
60%A:Eudragit L100 SDD (D16)	1.7	55
Crystalline enzalutamide (Control 1)	0.4	35

[0198] The membrane permeation test was carried out for 60%A enzalutamide SDDs with HPMCAS-M, HPMC E3 Prem, HPMCP-55, and Eudragit-L 100, as described in Example 8. Only sample D12 is according to the claimed invention.
The data in Table 9.3 demonstrate that each of the four SDDs exhibit higher transmembrane flux than crystalline enzalutamide, and have the capacity to replace absorbed free drug. The data in Table 9.3 also demonstrate that the SDDs with HPMCAS-M and HPMC E3 Prem have greater transmembrane flux and thus greater capacity to replace absorbed free drug than do SDDs with HPMCP-55 and Eudragit-L 100.

(...)

EXAMPLE 15

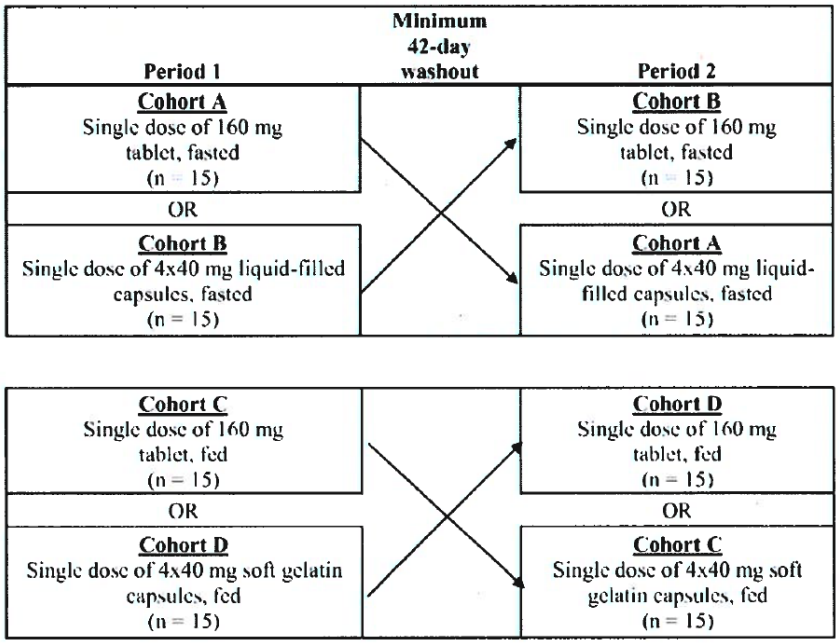
Human pharmacokinetics study

[0225] A randomised, two-period crossover pilot bioequivalence and food effect study was carried out in humans. This study compared two formulations. The reference formulation was a liquid-filled, soft gelatin capsule containing 40 mg enzalutamide dissolved in Labrasol; four such capsules are required to deliver a 160 mg dose. The test formulation was a tablet containing 160 mg enzalutamide in the form of a 60%A:HPMCAS-M spray-dried dispersion. The liquid-filled capsule formulation had previously been used in clinical studies in castration-resistant prostate cancer. The four-capsule regimen is inconvenient because of the number of capsules that must be taken, particularly in the light of fact that cancer patients have to take multiple drugs. The objectives of the human pharmacokinetics study were as follows:
1. To evaluate the bioequivalence of two oral formulations of enzalutamide following a single 160 mg dose in healthy male subjects under fasted conditions;
2. To evaluate the bioequivalence of two oral formulations of enzalutamide following a single 160 mg dose in healthy male subjects under fed conditions;

3. To assess the effects of food on the rate and extent of absorption of two oral formulations following a single 160 mg dose in healthy male subjects:

4. To evaluate the safety and tolerability of two oral formulations of enzalutamide following a single 160 mg dose in healthy male subjects under fasted or fed conditions.

[0226] Sixty healthy adult male subjects were divided into four cohorts as follows.



[0227] The fasted conditions involved an overnight fast from food (minimum 10 hours) prior to dosing. and the fed conditions involved a standard high-fat, high-calorie meal that was ingested within 30 minutes prior to dosing. The high-fat, high-calorie meal was described in "US FDA Guidance for Industry: Food Effect Bioavailability and Fed Bioequivalence Studies (December 2002)." In both the fasted and fed conditions. the clinical research personnel administered the study medication at approximately 0800 hours with ambient temperature water to a total volume of about 240 ml. Subjects were required to swallow the study medication whole and not chew the medication prior to swallowing. The subjects were required to refrain from drinking beverages other than water during the first4 hours after dosing. Water was allowed except 1 hour pre and post dose. Lunch was served- 4 hours post dose, and dinner was served~ 9 to 10 hours post dose.

[0228] Blood samples for pharmacokinetics determinations were collected in each period as follows:

Day 1: pre-dose (0 hr) and post-dose 15, 30, and 45 minutes: and at 1, 2. 3. 4. 6. 8. and 12 hours;

Day 2: 0 and 12 hours;

Days 3, 5. 7. 14. 21. 28. 35, and 42: 0 hours.

(…)

[0230] A summary of pharmacokinetic parameters is presented in Table 15.1.

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 tc 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.

[0231] The analysis showed the extent of oral bioavailability for the Test and Reference formulations to be equivalent, the AUCs for the two formulations being essentially the same regardless of food conditions (fasted or fed).

EXAMPLE 16

[0232] After 1 part by weight of enzalutamide (MDV) 100) and 3 parts by weight of hydroxypropylmethylcellulose acetate succinate (HPMCAS-MG, Shin-Etsu Chemical Co., Ltd.: the same was used hereafter) were dissolved in acetone, a spray dryer (QSD-0.8-CC, GEA) was used to obtain a solid dispersion (amorphous enzalutamide).
[0233] After the solid dispersion was mixed with calcium hydrogen phosphate hydrate, croscarmellose sodium and magnesium stearate by mortar and pestle, the mixture was formed into tablets by using an oil press tableting machine to obtain a tablet containing the solid dispersion at 12kN of tableting pressure. The formulation is shown in Table 16.

EXAMPLE 17

[0234] After 1 part by weight of enzalutamide and 3 parts by weight of hydroxypropylmethylcellulose acetate succinate were dissolved in acetone, a spray dryer (QSD-0.8-CC, GEA) was used to obtain a solid dispersion.
[**0235]** After the solid dispersion was mixed with calcium hydrogen phosphate hydrate. croscarmellose sodium and magnesium stearate. the mixture was formed into granules using dry granulation machine (roller compactor. TF-MINI, FREUND). After the resulting granules were mixed with croscarmellose sodium and magnesium

stearate. the mixture was formed into tablets using a rotary tableting machine to obtain a tablet containing the solid dispersion. After tableting. the tablet was filmcoated by using filmcoating machine (HCT-30 Hi coater 30. FREUND). The formulation is shown in Table 16.

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	3.0
filmcoating agent	-	16.2	-	17.5	18.0	24.0
total (mg)	540.0	556.2	540.0	517.5	618.0	324.0
tablet size	14.8mm×7.8mm			Round. approx. 10.5mm	14.8mm ×7.8mm	18.3mm ×7.8mm

EXAMPLE 18

[0236] After 1 part by weight of enzalutamide and 2 parts by weight of hydroxypropyl methylcellulose acetate succinate were dissolved in acetone. a spray dryer (QSD-0.8-CC, GEA) was used to obtain a solid dispersion. Further. a tablet was prepared as the same method as Example 16. The formulation is in Table 16.
(…)

EXAMPLE 21

[0239] A solid dispersion, which comprises 1 part by weight of enzalutamide and 0.67 part by weight of hydroxypropyl methylcellulose acetate succinate. was prepared as the same method as Example 18.

[0240] The solid dispersion was mixed with colloidal silicon dioxide. Microcrystalline cellulose, lactose monohydrate, and croscarmellose sodium are added to the mixture and blending is continued. The mixture is then milled. After magnesium stearate is mixed with the milled mixture, core tablets are compressed on a tablet press. The tablet was filmcoated by using filmcoating machine.

EXAMPLE22

[0241] After 1 part by weight of enzalutamide and 5 parts by weight of hydroxypropyl methylcellulose acetate succinate (HPMCAS-MG. Shin-Etsu Chemical Co., Ltd) were dissolved in acetone, a spray dryer (QSD-0.8-CC. GEA) was used to obtain a solid dispersion.

[0242] After the solid dispersion was mixed with calcium hydrogen phosphate hydrate and croscarmellose sodium. the mixture was formed into granules using dry granulation machine (roller compactor, TF-MINI. FREUND). After the resulting granules were mixed with croscarmellose sodium and magnesium stearate. the mixture was formed into tablets using a rotary tableting machine to obtain a tablet containing the solid dispersion. After tableting. the was film-coated by using film-coating machine (HCT-30 Hi coater 30, FREUND). The formulation is shown in Table 16.

EXAMPLE23

[0243] After 1 part by weight of enzalutamide, 2 parts by weight of Hypromellose. and 1 parts by weight of hydroxypropylmethylcellulose acetate succinate (HPMCAS-MG, Shin-Etsu Chemical Co. Ltd) were dissolved in a mixture of water and acetone, a spray dryer (QSD-0.8-CC. GEA) was used to obtain a solid dispersion. **[0244]** After the solid dispersion was mixed with light anhydrous silicic acid. calcium hydrogen phosphate hydrate and croscarmellose sodium. the mixture was formed into granules using a dry granulation machine (roller compactor. TFMINI, FREUND). After the resulting granules were mixed with croscarmellose sodium, crospovidone and magnesium stearate, the mixture was formed into tablets using a rotary tableting machine to obtain a tablet containing the solid dispersion. After tableting. the tablet was film-coated by using film-coating machine (HCT-30 Hi coater 30, FREUND). The formulation is shown in Table 16.

(**…**)

EXAMPLE25: Dissolution test

[0249] A drug release property from each of the solid dispersion prepared in Examples 17 to 22 or each of the tablet prepared in Examples 16, 18 and 21 was evaluated by a liquid replacement dissolution test. in which a paddle method (50rpm) was started using 300ml of 0.03N hydrochloric acid (pH 1.2), and the liquid conditions for the dissolution were changed to pH6.8 and 900ml 30 minutes after the beginning of the USP 34-NF 29. The drug release property was evaluated. The dissolution profiles of the enzalutamide from the solid dispersion and the tablet are shown in Figure 3, Figure 4, respectively.

(...)

EXAMPLE26: Evaluation of dissolution stability

[0249] The tablet obtained in Example 17 was subjected to a dissolution test to study their dissolution immediately after formulation (at the start of storage) and after storage at 40° C and 75% relative humidity for 1 month. The dissolution test was accomplished by the paddle method described the United States Pharmacopoeia. A liquid replacement dissolution test, in which a paddle method (50rpm) was started using 300ml of 0.03N hydrochloric acid (pH 1.2). and the liquid conditions for the dissolution test were changed to pH6.8 and 900ml 30 minutes after the beginning of the USP 34-NF 29. The drug release property was evaluated. The dissolution profile is shown in Figure 5.

EXAMPLE27: Dog absorption test

[0250] The tablets prepared in Examples 16, 18, 21, 22 and 23 and a soft capsule for control were administered orally to dogs. The formulation of the soft capsule is in Table 18. Percentage of blood exposure of enzalutamide compared to the soft capsule. %AUC and %Cmax, were evaluated.

(0251] The test formulations were administered with 50 ml of water to dogs had been fasted over night. The test formulations were used one tablet in case of the tablet comprised 160mg enzalutamide (Example 21). two tablets in case of the tablet comprised 80mg enzalutamide (Example 16. 18, 22 and 23), or four capsules comprised 40mg enzalutamide for control.

[0252] After orally administered the test formulations, blood samples were collected with time. A drug concentration in the plasma (ng/ml) was measured and calculated maximum drug concentration (Cmax) and AUC for 168 hr (AUC 0-168h:ng*h/ml). The dogs adjusted acid condition in the stomach were used in this test on the assumption of healthy individuals.

[0253] %AUC and %Cmax of each formulation are shown in Table 19.

Table 18

	soft capsule
enzalutamide	40.000
caprylocaproyl polyoxylglycerides	904.96
BHA	0.946
BHT	0.095
total (mg)	946.0

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

EXAMPLE28: X-ray analysis

[0254] The solid dispersions prepared in Examples 16, 18. 22 and 23 and crystalline enzalutamide were evaluated for crystallinity using X rays. In addition, the initial tablet prepared in Example 17 and the tablet after stored at 40° C and 75% relative humidity for 1 month in Example 17

[0255] As shown in Figure 6. the solid dispersions prepared in Examples 16, 18. 22 and 23 were amorphous. As shown in Figure 7, the tablet obtained by storing the solid dispersion prepared in Example 17 at 40° C and 75% relative humidity for 1 month in Example 17 was also amorphous.

2.13. EP 778 includes the following figures.

FIG. 3

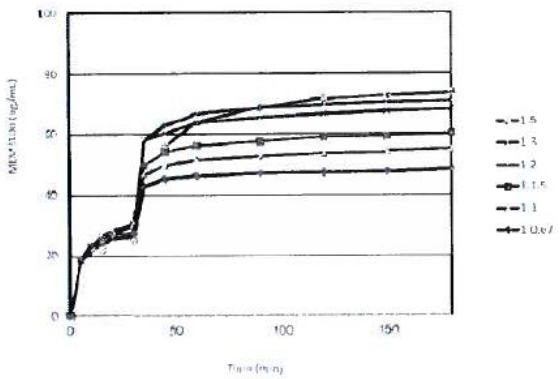


FIG. 4

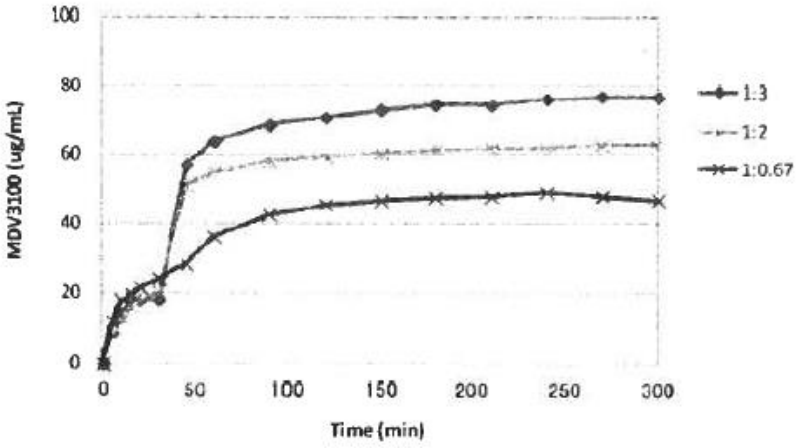


FIG. 5

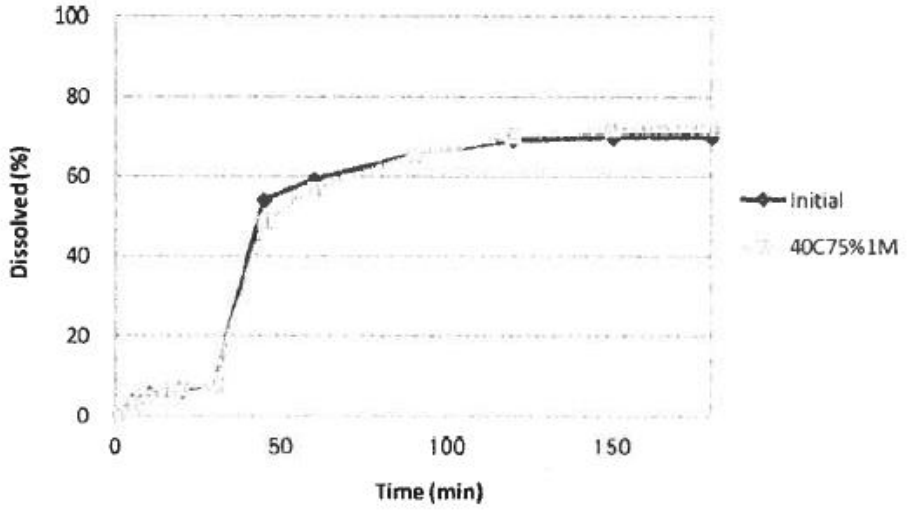
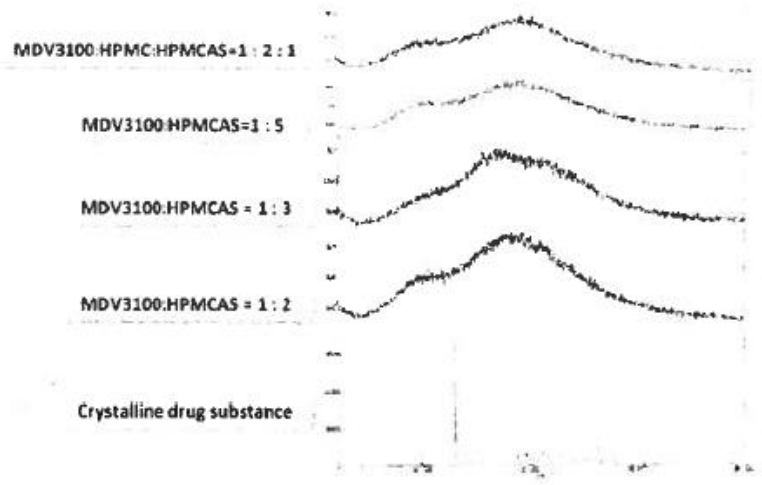


FIG. 6



WO 208

2.14. Claims 83 to 86 of the original application for EP 778, WO 208, read:

83. A pharmaceutical composition comprising a solid dispersion containing enzalutamide and a polymer.
84. The pharmaceutical composition according to claim 83, wherein enzalutamide is an amorphous state.
85. The pharmaceutical composition according to claim 83, wherein the polymer is a polymer or two or more polymers selected from the group consisting of polyvinyl pyrrolidone. polyethyleneoxide, poly(vinyl pyrrolidone-co-vinyl acetate), polymethacrylates, polyoxyethylene alkyl ethers, polyoxyethylene castor oils, polycaprolactam. polylactic acid. polyglycolic acid, poly(lactic-glycolic)acid, lipids. cellulose, pullulan, dextran, maltodextrin, hyaluronic acid, polysialic acid, chondroitin sulphate, heparin, fucoidan. pentosan polysulphate. spirulan, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, carboxymethyl ethylcellulose. hydroxypropyl methylcellulose acetate succinate, cellulose acetate phthalate, cellulose acetate trimellitate, ethyl cellulose, cellulose acetate, cellulose butyrate, cellulose acetate butyrate, and dextran polymer derivative.
86. The pharmaceutical composition according to claim 85, wherein the polymer is hydroxypropyl methylcellulose acetate succinate.

2.15. The description of WO208 reads as follows:

[03] This disclosure relates to solid formulations of enzalutamide. More particularly, this disclosure relates to solid formulations comprising amorphous enzalutamide. and to pharmaceutical compositions comprising a solid dispersion containing enzalutamide and at least one polymer. Furthermore, this disclosure relates to methods for manufacturing such formulations and compositions. and to their use.
(...)
[05] Enzalutamide is used as an agent for treating castration-resistant prostate cancer. *See, e.g.,* US 7,709,517. Enzalutamide is provided commercially as a soft capsule (brand name --XTANDI ') filled with a liquid comprising 40 mg of enzalutamide per one capsule and pharmaceutical excipients. The daily dosage is 160 mg, and a patient therefore needs to take four capsules daily. 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 advantageous as a suitable alternative to soft capsules.
(...)
[31] Compositions may contain from about 1 to about 80 wt% enzalutamide. depending on the dose of the drug and the effectiveness of the concentration-enhancing polymer. Enhancement of aqueous enzalutamide concentrations and relative bioavailability are typically best at low enzalutamide levels in the dispersion, typically less than about 75 wt%. In some embodiments, dispersions comprise greater than 20wt% and less than 75wt% enzalutamide. In some embodiments. dispersions comprise greater than 25wt% and less than 75wt% enzalutamide. In some embodiments, dispersions comprise greater than 50wt% and less than 70wt% enzalutamide.
(...)
[36] Compositions comprising the enzalutamide and a concentration-enhancing polymer provide enhanced concentration of the dissolved enzalutamide in *in vitro* dissolution tests. It has been determined that enhanced drug concentration in *in vitro* dissolution tests in Model Fasted Duodenal (MFD) solution (MFDS) or Phosphate Buffered Saline (PBS) is a good indicator of *in vivo* performance and bioavailability. An appropriate PBS solution is an aqueous solution comprising 20 mM sodium phosphate (Na2HPO4). 47 mM potassium phosphate (KH2PO4). 87 mM NaCl. and 0.2 mM KCI, adjusted to pH 6.5 with NaOH. An appropriate MFD solution is the same PBS solution wherein additionally is present 7.3 mM sodium taurocholic acid and 1.4 mM l-palmitoyl-2-oleyl-sn-glycero-3-phosphocholine. A composition can be dissolution tested by adding it to MFD or PBS solution

and agitating to promote dissolution. Generally, the amount of composition added to the in such a test is an amount that. if all the drug in the composition dissolved, would produce an enzalutamide concentration that is at least about 2-fold and, in some embodiments. at least 5-fold the equilibrium solubility of the crystalline enzalutamide alone in the test solution.

(...)

[43) Relative bioavailability of enzalutamide in the dispersions can be tested *in vivo* in animals or humans using conventional methods for making such a determination. An *in vivo* test. such as a crossover pharmacokinetic study. may be used to determine whether a composition of enzalutamide and concentration-enhancing polymer (or a composition comprised of amorphous enzalutamide without a concentration enhancing polymer) provides an enhanced relative bioavailability compared with a control composition comprised of crystalline enzalutamide but no polymer as described above. In an *in vivo* crossover study a "test composition" of enzalutamide and polymer is dosed to half a group of test subjects and, after an appropriate washout period (at least 42 days) the same subjects are dosed with a "control composition" that comprises an equivalent quantity of crystalline enzalutamide with no concentration-enhancing polymer present. The other half of the group is dosed with the control composition first. followed by the test composition. The relative bioavailability is measured as the area under the plasma drug concentration versus time curve (AUC) determined for the test group divided by the plasma AUC provided by the control composition. In some embodiments, this test/control ratio is determined for each subject, and then the ratios are averaged over all subjects in the study. *In vivo* determinations of AUC can be made by plotting the plasma concentration of drug along the ordinate (y-axis) against time along the abscissa (x-axis), and using the trapezoidal rule method.

[44] Thus, as noted above, one embodiment is one in which the relative bioavailability of the test composition is at least about 1.25 relative to a control composition comprised of crystalline enzalutamide but with no concentration-enhancing polymer as described above. (That is, the *in vivo* AUC provided by the test composition is at least about 1.25-fold the *in vivo* AUC provided by the control composition.) In some embodiments, the relative bioavailability of the test composition is at least about 2, relative to a control composition composed of crystalline enzalutamide but with no concentration-enhancing polymer present, as described above. The determination of AUCs is a well-known procedure and is described, for example, in Welling, "Pharmacokinetics Processes and Mathematics," ACS Monograph 185 (1986).

[45] To carry out the *in vivo* AUC measurements for enzalutamide, the enzalutamide test and control compositions should be dosed at a 160 mg dose to a cohort of at least 24 subjects in the fasted state. Blood samples should be collected at O time (pre-dose), and at post-dose times 15, 30, and 45 minutes; and at 1, 2. 3, 4, 6, 8, and 12 hours; and at 0 and 12 hours on day 2; and at 0 hours on days 3, 5, and 7 (where 0 hours on days 2, 3, 5, and 7 correspond to the time of day when dosing occurred on day 1).

[46) Relative bioavailability is measured using AUCn.1c1a),- The absolute value of the AUC11.,c1a,, is also used to determine if a dispersion formulation falls within compositions of this disclosure; *i.e*, pharmaceutical compositions comprising a solid amorphous dispersion of enzalutamide and a concentration-enhancing polymer, which when dosed to a cohort of 24 or more humans at a dose of 160 mg provides a mean area under the plasma enzalutamide concentration vs. time curve from the time of dosing to 7 days after dosing, AUC11-,d.l)-- which is greater than 150 µg-hr/ml. This constraint applies to other doses as well. providing a plasma AUCn.1dm which is greater than (150 µg-hr/ml)/(160 mg) or more generally greater than 0.94 µg-hr/ml -mg, where mg refers to the weight of the enzalutamide dose.

[68) In some embodiments, concentration-enhancing polymers for use in dispersions with enzalutamide are hydroxypropylmethylcellulose acetate succinate (HPMCAS), hydroxypropylmethylcellulose (HPMC), hydroxypropylmethylcellulosephthalate (HPMCP), polyvinylpyrrolidonevinylacetate (PVP-V A), copolymers of methacrylic acid and methylmethacrylate (approximate 1:1 ratio) available as EUDRAGIT L100, and graft copolymers of polyethylene glycol, polyvinylcaprolactam, and polyvinylacetate. one commercially available version of a graft copolymer is known as SOLUPLUS®.

(...)

[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.

(...)

[150] The pharmaceutical composition can be produced. for example. by any known process including the steps of blending. granulation, specific size controlling. tableting. film coating and the like.

[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 (i) 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. In a case where the above various pharmaceutical additives are used as needed, these pharmaceutical additives may be added at any stage, e.g., during step (i), between steps (i) and (2), or during step (2).

(…)

[22 I] A randomised, two-period crossover pilot bioequivalence and food effect study was carried out in humans. This study compared two formulations. The reference formulation was a liquid-filled, soft gelatin capsule containing 40 mg enzalutamide dissolved in Labrasol; four such capsules are required to deliver a 160 mg dose. The test formulation was a tablet containing 160 mg enzalutamide in the form of a 60%A:HPMCAS-M spray-dried dispersion. The liquid-filled capsule formulation had previously been used in clinical studies in castration-resistant prostate cancer. The four-capsule regimen is inconvenient because of the number of capsules that must be taken. particularly in the light of the fact that cancer patients have to take multiple drugs. (...)

State of the art

2.16. Xtandi has been marketed in the US as a product containing 40 mg enzalutamide in capsule form since 31 August 2012. The available prior art for EP 778 includes the *Prescribing Information* document for these Xtandi capsules as published by the US *Food and Drug Administration (FDA)* (hereinafter: the PI Xtandi capsules). This document - as far as relevant here – (inter alia) entails:

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use XTANDI® safely and effectively. See full prescribing information for XTANDI.

XTANDI® (enzalutamide) capsules for oral use
Initial U.S. Approval: 2012

----------INDICATIONS AND USAGE----------
XTANDI is an androgen receptor inhibitor indicated for the treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxel. (1)

----------DOSAGE AND ADMINISTRATION----------
XTANDI 160 mg (four 40 mg capsules) administered orally once daily. Swallow capsules whole. XTANDI can be taken with or without food. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
Capsule 40 mg (3)

----------CONTRAINDICATIONS----------
Pregnancy (4, 8.1)

----------WARNINGS AND PRECAUTIONS----------
Seizure occurred in 0.9% of patients receiving XTANDI. There is no clinical trial experience with XTANDI in patients who have had a seizure, in patients with predisposing factors for seizure, or in patients using concomitant medications that may lower the seizure threshold. (5.1)

----------ADVERSE REACTIONS----------
The most common adverse reactions (≥ 5%) are asthenia/fatigue, back pain, diarrhea, arthralgia, hot flush, peripheral edema, musculoskeletal pain, headache, upper respiratory infection, muscular weakness, dizziness, insomnia, lower respiratory infection, spinal cord compression and cauda equina syndrome, hematuria, paresthesia, anxiety, and hypertension. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Astellas Pharma US, Inc. at 1-800-727-7003 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- **Avoid strong CYP2C8 inhibitors, as they can increase the plasma exposure to XTANDI. If co-administration is necessary, reduce the dose of XTANDI. (2.2, 7.1)**
- **Avoid strong or moderate CYP3A4 or CYP2C8 inducers as they can alter the plasma exposure to XTANDI. (7.1, 7.2)**
- **Avoid CYP3A4, CYP2C9 and CYP2C19 substrates with a narrow therapeutic index, as XTANDI may decrease the plasma exposures of these drugs. If XTANDI is co-administered with warfarin (CYP2C9 substrate), conduct additional INR monitoring. (7.3)**

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 08/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

XTANDI is indicated for the treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxel.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended dose of XTANDI is 160 mg (four 40 mg capsules) administered orally once daily. XTANDI can be taken with or without food *[see Clinical Pharmacology (12.3)]*. Swallow capsules whole. Do not chew, dissolve, or open the capsules.

2.2 Dose Modifications

If a patient experiences a ≥ Grade 3 toxicity or an intolerable side effect, withhold dosing for one week or until symptoms improve to ≤ Grade 2, then resume at the same or a reduced dose (120 mg or 80 mg), if warranted.

Concomitant Strong CYP2C8 Inhibitors
The concomitant use of strong CYP2C8 inhibitors should be avoided if possible. If patients must be co-administered a strong CYP2C8 inhibitor, reduce the XTANDI dose to 80 mg once daily. If co-administration of the strong inhibitor is discontinued, the XTANDI dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

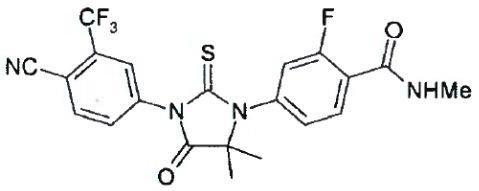
XTANDI 40 mg capsules are white to off-white oblong soft gelatin capsules imprinted in black ink with MDV.

(…)

11 DESCRIPTION

Enzalutamide is an androgen receptor inhibitor. The chemical name is 4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluoro-*N*-methylbenzamide.

The molecular weight is 464.44 and molecular formula is $C_{21}H_{16}F_4N_4O_2S$. The structural formula is:



Enzalutamide is a white crystalline non-hygroscopic solid. It is practically insoluble in water.

XTANDI is provided as liquid-filled soft gelatin capsules for oral administration. Each capsule contains 40 mg of enzalutamide as a solution in caprylocaproyl polyoxylglycerides. The inactive ingredients are caprylocaproyl polyoxylglycerides, butylated hydroxyanisole, butylated hydroxytoluene, gelatin, sorbitol sorbitan solution, glycerin, purified water, titanium dioxide, and black iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Enzalutamide is an androgen receptor inhibitor that acts on different steps in the androgen receptor signaling pathway. Enzalutamide has been shown to competitively inhibit androgen binding to androgen receptors and inhibit androgen receptor nuclear translocation and interaction with DNA. A major metabolite, N-desmethyl enzalutamide, exhibited similar *in vitro* activity to enzalutamide. Enzalutamide decreased proliferation and induced cell death of prostate cancer cells *in vitro*, and decreased tumor volume in a mouse prostate cancer xenograft model.

12.3 Pharmacokinetics

The pharmacokinetics of enzalutamide and its major active metabolite (N-desmethyl enzalutamide) were evaluated in patients with metastatic castration-resistant prostate cancer and healthy male volunteers. The plasma enzalutamide pharmacokinetics are adequately described by a linear two-compartment model with first-order absorption.

Absorption

Following oral administration (XTANDI 160 mg daily) in patients with metastatic castration-resistant prostate cancer, the median time to reach maximum plasma enzalutamide concentrations (C_{max}) is 1 hour (range 0.5 to 3 hours). At steady state, the plasma mean C_{max} values for enzalutamide and N-desmethyl enzalutamide are 16.6 µg/mL (23% CV) and 12.7 µg/mL (30% CV), respectively, and the plasma mean predose trough values are 11.4 µg/mL (26% CV) and 13.0 µg/mL (30% CV), respectively.

With the daily dosing regimen, enzalutamide steady state is achieved by Day 28, and enzalutamide accumulates approximately 8.3-fold relative to a single dose. Daily fluctuations in enzalutamide plasma concentrations are low (mean peak-to-trough ratio of 1.25). At steady state, enzalutamide showed approximately dose proportional pharmacokinetics over the daily dose range of 30 to 360 mg.

A single 160 mg oral dose of XTANDI was administered to healthy volunteers with a high-fat meal or in the fasted condition. A high-fat meal did not alter the AUC to enzalutamide or N-desmethyl enzalutamide. The results are summarized in Figure 1.

Distribution and Protein Binding

The mean apparent volume of distribution (V/F) of enzalutamide in patients after a single oral dose is 110 L (29% CV).

Enzalutamide is 97% to 98% bound to plasma proteins, primarily albumin. N-desmethyl enzalutamide is 95% bound to plasma proteins.

Metabolism

Following single oral administration of ^{14}C-enzalutamide 160 mg, plasma samples were analyzed for enzalutamide and its metabolites up to 77 days post dose. Enzalutamide, N-desmethyl enzalutamide, and a major inactive carboxylic acid metabolite accounted for 88% of the ^{14}C-radioactivity in plasma, representing 30%, 49%, and 10%, respectively, of the total ^{14}C-$AUC_{0\text{-}inf}$.

In vitro, human CYP2C8 and CYP3A4 are responsible for the metabolism of enzalutamide. Based on *in vivo* and *in vitro* data, CYP2C8 is primarily responsible for the formation of the active metabolite (N-desmethyl enzalutamide).

Elimination

Enzalutamide is primarily eliminated by hepatic metabolism. Following single oral administration of ^{14}C-enzalutamide 160 mg, 85% of the radioactivity is recovered by 77 days post dose: 71% is recovered in urine (including only trace amounts of enzalutamide and N-desmethyl enzalutamide), and 14% is recovered in feces (0.4% of dose as unchanged enzalutamide and 1% as N-desmethyl enzalutamide).

The mean apparent clearance (CL/F) of enzalutamide in patients after a single oral dose is 0.56 L/h (range 0.33 to 1.02 L/h).

The mean terminal half-life ($t_{1/2}$) for enzalutamide in patients after a single oral dose is 5.8 days (range 2.8 to 10.2 days). Following a single 160 mg oral dose of enzalutamide in healthy volunteers, the mean terminal $t_{1/2}$ for N-desmethyl enzalutamide is approximately 7.8 to 8.6 days.

(...)

16 HOW SUPPLIED/STORAGE AND HANDLING

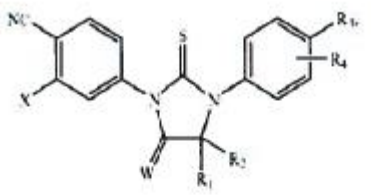
- XTANDI (enzalutamide) 40 mg capsules are supplied as white to off-white oblong soft gelatin capsules imprinted in black ink with MDV. XTANDI capsules are available in the following package sizes:
  - Bottles of 120 capsules (NDC 0469-0125-99)

Recommended storage: Store XTANDI capsules at 20°C to 25°C (68°F to 77°F) in a dry place and keep the container tightly closed. Excursions permitted from 15°C to 30°C (59°F to 86°F).

2.17. The prior art for EP 778 also includes the US patent application US 2007/00004753 (hereinafter US 753) for *"diarylhydantoin compounds"* by The Regents of the University of California, with publication date 4 January 2007. This application is related to three US patent applications of which the substance patent for enzalutamide, EP 196, claims priority.

2.18. Claims 1 and 16 of US 753 read:

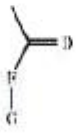
1. A compound having the formula



wherein X is selected from the group consisting of trifluoromethyl and iodo.

wherein W is selected from the group consisting of O and NR5,

wherein R5 is selected from the group consisting of H, methyl, and



wherein D is S or O and E is N or O and G is alkyl, aryl, substituted alkyl or substituted aryl; or

D is S or O and E-G together are C1-C4 lower alkyl,

wherein R1 and R2 together comprise eight or fewer carbon atoms and are selected from the group consisting of alkyl, substituted alkyl including haloalkyl, and, together with the carbon to which they are linked, a cycloalkyl or substituted cycloalkyl group,

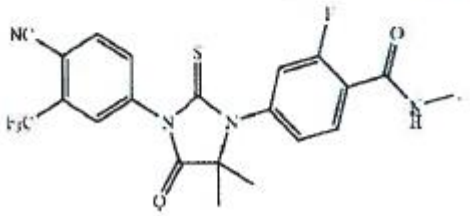
wherein R3 is selected from the group consisting of hydrogen, halogen, methyl, C1-C4 alkoxy, formyl, haloacetoxy, trifluoromethyl, cyano, nitro, hydroxyl, phenyl, amino, methylcarbamoyl, methoxycarbonyl, acetamido, methanesulfonamino, methanesulfonyl, 4-methanesulfonyl-1-piperazinyl, piperazinyl, and C1-C6 alkyl or alkenyl optionally substituted with hydroxyl, methoxycarbonyl, cyano, amino, amido, nitro, carbamoyl, or substituted carbamoyl including methylcarbamoyl, dimethylcarbamoyl, and hydroxyethylcarbamoyl,

wherein R4 is selected from the group consisting of hydrogen, halogen, alkyl, and haloalkyl,

wherein R3 is not methylaminomethyl or dimethylaminomethyl.

16. The compound of claim 1, having the formula

[RD16]



2.19. Paragraphs [0027] and [0390] of US 753 read:

[0027] The compound may be administered by intravenous injection, by injection into tissue, intraperitoneally, orally, or nasally. The composition may have a form selected from the group consisting of a solution, dispersion, suspension, powder, capsule, tablet, pill, time release capsule, time release tablet, and time release pill.

(...)

[0390] Thus, diarylhydantoin compounds of the invention may be systemically administered, e.g., orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier; or by inhalation or insufflation. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the diarylhydantoin compounds may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. The diarylhydantoin compounds may be combined with a fine inert powdered carrier and inhaled by the subject or insufflated. Such compositions and preparations should contain at least 0.1% diarylhydantoin compounds. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2% to about 60% of the weight of a given unit dosage form. The amount of diarylhydantoin compounds in such therapeutically useful compositions is such that an effective dosage level will be obtained.

Correspondence between parties on EP 778

2.20. By letter dated 18 April 2023, Synthon's lawyer informed Astellas' lawyer that Synthon believes that the Dutch part EP 778 is invalid and requested confirmation that Astellas will not invoke or enforce that patent, by which failure to provide this Synthon would initiate proceedings. By e-mail message dated 10 May 2023, Astellas' lawyer informed that Astellas does not agree with Synthon's position and that the requested confirmation will not be given.

Proceedings abroad

2.21. Synthon also initiated invalidity actions against EP 778 in Italy and Spain.

3. The dispute

3.1. Synthon requests - in summary - by means of a judgment, in as far as possible provisionally enforceable, the invalidation of the Dutch part of EP 778, to rule that on the priority date it was obvious for the average skilled person to formulate enzalutamide in amorphous form with the polymer hydroxypropylmethylcellulose acetate succinate (hereinafter: HPMCAS) to be formulated in the form of a solid dispersion and to order Astellas to pay the costs of the proceedings section 1019h DCCP[4], increased with the statutory interest.

3.2. In support of its claims, Synthon argues that EP 778 is not inventive because it is obvious in view of the PI Xtandi capsules and US 753 in combination with common general knowledge and (other) prior art. Therefore, even a future (divisional) patent covering the formulation under protection in EP 778 cannot be valid, Synthon has argued. Synthon further argues that EP 778 contains added matter.

3.3. Astellas put forward a defence seeking a dismissal of the claims, to order by means of a judgment that Synthon pay the costs of the proceedings pursuant to Article 1019h of the Dutch Code of Civil Procedure.

3.4. To this end, Astellas argues that EP 778 is inventive because at the priority date, it was not obvious to the skilled person to choose the claimed formulation because developing a new formulation for enzalutamide required a lengthy *trial-and-error process* and the skilled person would not expect a new formulation to have bioavailability comparable to the Xtandi capsules and to be physically stable. Astellas further argues that the matter claimed in EP 778 is directly and unambiguously derivable from WO 208 so there is no added matter.

3.5. The parties' contentions are discussed in more detail below, to the extent necessary.

4. The assessment

Jurisdiction

4.1. The court has international jurisdiction to hear the claims pursuant to Article 24 preamble and based on art. 4 Brussels I bis-Vo[5]. Relative jurisdiction is based on Article 80(1)(a) DPA[6]. The international and relative jurisdiction of this court have not been contested.

[4] Code of Civil Procedure
[5] Regulation (EU) 1215/2012 of the European Parliament and of the Council of 12 December 2012 on jurisdiction and the recognition and enforcement of judgments in civil and commercial matters
[6] National Patent Act 1995

Technical background

4.2. The following introduction to the technique of the patent is drawn from undisputed parts of the submissions, the exhibits submitted by the parties and what was discussed at the hearing.

4.3. The patent covers a solid pharmaceutical composition in the form of a solid dispersion (see 4.14 below) containing amorphous enzalutamide and the concentration-enhancing polymer HPMCAS.

4.4. Enzalutamide is a drug indicated for the treatment of castration-resistant prostate cancer. Prostate cancer is one of the most common cancers in men. Castration-resistant prostate cancer is an incurable form that develops mainly while treating metastases. Enzalutamide is an anti-androgen. Androgens, such as testosterone, are hormones responsible for the development and maintenance of secondary male sexual characteristics. Androgens bind to androgen receptors, allowing them to have their effects. Androgen receptors are located in various places in the body, including on cells of the prostate. By binding to androgen receptors, enzalutamide - which takes the place of testosterone - counteracts the stimulatory effect of testosterone on the growth of cancer cells. Treatment with enzalutamide can prolong the life of patients with castration-resistant prostate cancer and improve quality of life.

4.5. Enzalutamide is a poorly water-soluble substance.

4.6. Drugs need to be formulated in a particular form of administration (also called a dosage form) to be administered to patients. There are different routes of drug administration, such as oral (by mouth) or intravenous (into a vein). Oral administration is often preferred. Examples of oral dosage forms include solid dosage forms such as tablets, capsules and powders, and liquid dosage forms such as syrups.

4.7. Tablets are the most commonly used solid oral form of administration and are manufactured by compressing powder consisting of the active substance and various additives (called excipients). After tablets, capsules are the most commonly used. Capsules are (mostly) classified as a solid form of administration. Capsules are usually made of hard or soft gelatine. The active substance may be present in the capsule in solid form (powder), as a paste or as a liquid (usually a solution).

4.8. Biological availability (bioavailability) refers to the extent to which a substance or drug has reached the bloodstream and therefore becomes available at its biological destination site(s). Bioavailability can be measured by determining the concentration of the drug in the blood. During absorption (uptake), the concentration will first increase and reach a maximum (C_{max}) and then gradually decrease through excretion. When the measured concentration is plotted against time in a graph, a curve is obtained where the area under the curve *(AUC)* is a measure of bioavailability.

4.9. A drug is absorbed by the body via the oral route when the active substance dissolves in the fluids in the gastrointestinal system, then penetrates the intestinal wall, passes the liver without being inactivated and finally enters the bloodstream. Some factors that have a negative impact on bioavailability are poor solubility and low dissolution rate of the active substance, low permeability (the degree and rate at which the active substance passes the intestinal wall), instability in the gastrointestinal environment and *high first pass metabolism/effect* (degradation on first passage of the liver, among others).

4.10. Active substances that have low water solubility are more difficult to formulate into an oral form that gives sufficient bioavailability. For this, it is often necessary to use a formulation that increases bioavailability, for example by using techniques that allow the active substance to dissolve completely and remain dissolved until it reaches the bloodstream.

4.11. When a substance has a crystalline structure, the molecules are arranged at long distance from each other in an ordered manner. Amorphous means that the molecules are arranged at a very short distance from each other and in a random manner. The amorphous form of a drug has a higher free energy than the crystalline form and can therefore provide better solubility and dissolution rate. However, amorphous forms are thermodynamically unstable and have the risk of crystallisation. This negatively affects the dissolution behaviour.

4.12. An active substance can be dissolved above its saturation concentration (supersaturation), meaning that a solution contains more of an active substance than normal saturation of that compound. In an (amorphous) solid dispersion, supersaturation of an active substance can be achieved.

4.13. When the dissolved amount of an active substance has reached the saturation concentration, the risk of precipitation (precipitation) arises. Precipitation is the process by which a dissolved substance transforms to an undissolved solid. If an active substance precipitates before it reached the intestinal wall, this negatively affects absorption and bioavailability.

4.14. A dispersion is a mixture in which the particles of an active substance are distributed in another substance (carrier). In a solid dispersion, the active substance is distributed in a solid carrier. If the carrier dissolves well, the active substance is very finely distributed and thus dissolves better and faster. Techniques to manufacture a solid dispersion include *spray drying*, *solvent evaporation* and *hot melt extrusion.*

4.15. A polymer can be added as a carrier in a dispersion to prevent crystallisation and/or precipitation and thus ensure that the active substance remains amorphous and above saturation concentration for longer. A polymer can also increase the dissolution rate.

The main request

4.16. Astellas relies on a new main request in these proceedings (as in the opposition proceedings at the EPO). In the main request – in short - original claim 1 has remained the same, original claims 2, 3, 5, 8, 10 to 14, 16 and 18 have lapsed, original claims 4, 5, 6, 7 (slightly amended), 9, 15 and 17 were retained and renumbered as claims 2 to 7, and original claims 19 and 20 were merged and reformulated into new claims 8 and 9. The nine claims of the main request read in the original English language as follows.

1. A solid pharmaceutical composition comprising a solid dispersion containing amorphous enzalutamide and a concentration-enhancing polymer, wherein the polymer is hydroxypropyl methylcellulose acetate succinate.
2. The solid pharmaceutical composition according to claim 1, wherein the amount of the polymer is 3 to 5 parts by weight, with respect to 1 part by weight of the enzalutamide.
3. The solid pharmaceutical composition according to claim 1, wherein the amount of the polymer is 5 parts by weight, with respect to 1 part by weight of the enzalutamide.
4. The solid pharmaceutical composition according to claim 1. wherein the pharmaceutical composition is in unit dosage form, containing 40 to 160mg of enzalutamide per unit dosage form.
5. The solid pharmaceutical composition according to claim 1, wherein at least 80% of the total amount of enzalutamide present is in an amorphous form.
6. A process of manufacturing a solid pharmaceutical composition according to claim 1, comprising:
(1) preparing the solid dispersion of amorphous enzalutamide and the polymer
(2) mixing and/ or granulating the solid dispersion, and
(3) tableting the solid dispersion.
7. The solid pharmaceutical composition of claim 1. which is a tablet.
8. The solid pharmaceutical composition of claim 1 for in the treatment of hyperproliferative disorder. wherein the hyperproliferative disorder is prostate cancer.
9. The solid pharmaceutical composition for use according to claim 8, wherein the prostate cancer is selected from the group consisting of hormone-refractory prostate cancer and hormone-sensitive prostate cancer.

Inventive step

4.17. Synthon argues that EP 778 is not inventive in the sense that it was obvious to the skilled person on the priority date from the state of the art (the PI Xtandi capsules or US 753) to formulate enzalutamide as an amorphous solid dispersion with the concentration-enhancing polymer HPMCAS as a carrier.

4.18. An invention is considered to be the result of an inventive step if it does not follow from the prior in an obvious way for the skilled person (Article 56 EPC). In the assessment of inventive step, the parties have applied the *problem-solution-approach* (PSA) and the district court will follow this approach.

The skilled person

4.19. In accordance with the parties' submissions, the court in this case will identify a formulation expert as a relevant skilled person.

The closest prior art

4.20. The parties both regard the PI Xtandi capsules as the closest prior art for EP 778. The court will follow this assumption.

4.21. The PI Xtandi capsules disclose liquid-filled soft gelatine capsules for oral administration. Each capsule contains 40 mg enzalutamide as a solution in caprylocaproyl polyoxylglycerides (Labrasol). The indication is the treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxel. The recommended dose is 160 mg (four 40 mg capsules) administered orally once daily.

Distinguishing features

4.22. Claim 1 of the main request will be divided into the following sub-features, in accordance with the parties' submissions:

> 1a. a solid pharmaceutical composition comprising a solid dispersion containing
> 1b. amorphous enzalutamide
> 1c. and a concentration-enhancing polymer, wherein the polymer is hydroxypropyl methylcellulose acetate succinate.

4.23. The parties (in essence) agree that the distinguishing features to the PI Xtandi capsules can be identified as the pharmaceutical composition being a (1) solid dispersion that contains (2) amorphous enzalutamide and (3) HPMCAS.

Technical effects and objective problem formulation

4.24. The parties do not agree on the technical effects of the distinguishing features. Astellas maintains that those effects concern (1) improved treatment adherence through fewer and/or smaller dosage forms, (2) comparable bioavailability to the Xtandi capsules and (3) very good physical stability. According to Astellas, the objective technical problem should be formulated as providing a formulation of enzalutamide that achieves comparable bioavailable in humans to the Xtandi capsules, that ensures improved treatment adherence and that is physically very stable.

4.25. Synthon disputes that the technical effects claimed by Astellas are realised (over the whole scope of) Claim 1. It argues that the objective technical problem should be formulated as (only) the provision of an alternative oral solid pharmaceutical composition that contains enzalutamide.

4.26. The court decides as follows. The patent describes in paragraph [0003] the commercially available Xtandi capsules containing 40 mg enzalutamide and the daily

dose thereof of 160 mg, requiring the patient to take four capsules per day. It is described that (among other things) a suitable single tablet of a reasonable size containing 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. In paragraph [0009], it was mentioned, inter alia, that the invention provides a solid dispersion having properties such as improved solubility and absorption of enzalutamide, and a pharmaceutical composition containing a solid dispersion with dissolution stability. Paragraph [0012] states that the dosage forms according to the invention provide for unusually high improvements in concentration and also provide the possibility of dosing the entire daily therapeutic dose of enzalutamide in a single dosage unit, by improving the oral bioavailability of the drug.

Comparable bioavailability

4.27. As the patent provides for an alternative formulation for enzalutamide with respect to the PI Xtandi capsules, achieving comparable bioavailability to that of the Xtandi capsules can be taken into account as a technical effect. Indeed, the skilled person seeking an alternative formulation to an existing and approved formulation of the same active substance for the same indication will value that comparable bioavailability. Unlike Synthon has argued, the skilled person will also realistically base its research on the same (total) dosage as the existing product, partly because (clinical) efficacy and safety studies have been conducted and licences have been granted for that particular dosage.

4.28. The application (WO 208) also describes in several paragraphs a comparison of bioavailability of formulations according to the invention with other formulations. For example, paragraphs [42) - [43][7] relate to a comparison of the (in vivo) bioavailability of enzalutamide in pharmaceutical compositions according to the invention with a *"control composition"* containing an equivalent amount of crystalline enzalutamide. Furthermore, in Example l5[8], in a pharmacokinetic study in humans a pharmaceutical composition according to the invention is compared to a reference formulation, namely a liquid-filled, soft gelatine capsule containing 40 mg enzalutamide dissolved in Labrasol. The skilled person will recognise this formulation as the Xtandi capsule (see also paragraph [170] of WO 208[9]), not only because of its composition, but also because it has been mentioned that this formulation has previously been used in clinical studies in castration-resistant prostate cancer. Paragraph [226][10] of WO 208 includes the following about this comparison:

The analysis showed the extent of oral bioavailability for the Test and Reference formulations to be equivalent. the AUCs for the two formulations being essentially the same regardless of food conditions (fasted or fed).

4.29. On the basis of the application considered as a whole and in particular the information referred to above, the test set out in G2/21[11] that the

[7] These paragraphs are similar to paragraphs [0036]-[0037] of EP 778.
[8] The numbering of the examples and figures in WO 208 is the same as in EP 778.
[9] This paragraph is similar to paragraph [0165] of EP 778.
[10] See paragraph [0231] of EP 778.
[11] Enlarged Board of Appeal of the European Patent Office 23 March 2023, ECLI:EP:BA:2023:G00022 I .20230323

skilled person, using his/her common general knowledge and based on the application as originally filed, would derive the technical effect of comparable bioavailability as encompassed by the technical teaching and embodied by the same originally disclosed invention. Astellas may therefore rely on this technical effect for inventive step.

4.30. Examples 15 (the aforementioned pharmacokinetic study) and 27 (an absorption test in dogs) also show results from which it follows that pharmaceutical compositions according to the invention have comparable bioavailability to the Xtandi capsules. Table 15.1 shows the results of a study in humans with a test formulation being a tablet containing 160 mg enzalutamide (in the form of a 60%A:HPMCAS-M spray-dried dispersion) and, as a reference formulation, four 40-mg Xtandi capsules.

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

4.31. In its analysis of the results, Astellas relies on the AUC values. The Court rejects Synthon's defence that the C_{max} values should also be considered and that these were not sufficient. It is not in dispute between the parties that AUC values are a measure to express bioavailability. The fact that C_{max} values are also used in bioequivalence studies does not mean that bioavailability, and comparability of bioavailability, cannot be expressed in (exclusively) AUC values. Bioequivalence (in the context of

authorisation) is subject to established requirements, as laid down for example in the *Guideline on the Investigation of Bioequivalence* by the *European Medicines Agency* (EMA). However, bioequivalence is not the technical effect relied on by Astellas.

4.32. Table 15.1 shows the ratio of (among other things) the AUC of the test formulation to the reference formulation. This is between 94 and 102, with 90% confidence intervals between 91 and 114. That these values can be considered comparable is confirmed by the range for AUC values for bioequivalence in the aforementioned EMA guideline. Therein, percentages for the 90% confidence interval may range from 80 to 125.

4.33. Table 19 at example 27 shows results of an absorption test in dogs of tablets according to examples 16, 18, 21, 22 and 23 and a soft capsule as a control formulation. Administered were 1 tablet containing 160 mg enzalutamide (example 21) or two tablets of 80 mg (examples 16, 18 and 22) or four capsules containing 40 mg enzalutamide. The percentage of exposure in the blood of enzalutamide for the tablets compared with the capsule is shown.

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

4.34. These AUC values also show comparable bioavailability to the capsules. To the extent that the AUC value for Example 21 (70) should be considered not comparable, a tablet with a corresponding composition (60% enzalutamide) does show comparable bioavailability in the study in humans (Table 15.1 of Example 15), which test the average skilled person would consider more relevant.

4.35. Synthon's contention that the technical effect of comparable bioavailability should not be taken into account because this effect does not occur across the entire breadth of claim 1 is rejected. The results of the tests in Examples 15 and 27 cover a range of ratios of enzalutamide and HPMCAS of 1:0.67 - 1:5[12], which can be regarded as a sufficient range. That comparable bioavailability is for every possible compound within the scope of claim 1 is not necessary for this case.

[12] See examples 15, 16, 18, 21 and 22 and table 16.
Example 15: 1:0.67
Example 16: 1:3
Example 17: 1:3
Example 21: 1:0.67
Example 22: 1:5

4.36. In view of the above, comparable bioavailability can already be taken into account as a technical effect of the distinguishing features on the basis the content of the application when assessing the inventive step of claim 1. Documents published after the application can therefore be disregarded.

Physical stability

4.37. Physical stability is also a technical effect that can be taken into account when formulating the objective technical problem in the context of the inventive step assessment. Contrary to Synthon's submission[13], the court does not consider it necessary for this purpose that the stability of the Xtandi capsules was a problem and/or that the claimed formulation has better stability compared to those capsules. After all, the skilled person knows that when changing the formulation of a poorly water-soluble substance, stability is not a given and may be reduced[14], while sufficient stability is a prerequisite for a pharmaceutical composition to be administered to patients.

4.38. Among others, paragraphs [05] and [16][15] of application WO 208 describe the stability of pharmaceutical compositions according to the invention. Examples 26 and 28, Figures 5 and 6 and Examples 5 and 6 of WO 208 also relate to stability.

4.39. Example 26 concerns an evaluation of dissolution stability and describes the dissolution profile of the tablet of Example 17 (ratio enzalutamide - HPMCAS l :3) immediately after manufacture and after storage at 40° C and 75% relative humidity for l month. Figure 5 shows that for the initial tablet and the stored tablet, the dissolved percentage matches.

4.40. Example 28 involves an *x-ray* analysis of the solid dispersions of examples 16, 18, 22 and 23, which Figure 6 shows were amorphous. The initial tablet according to Example 17 and the tablet according to Example 17 after storage at 40°C and 75% relative humidity for l month were also amorphous (see Figure 7).

4.41. It follows from Example 5 and Table 5.1 that solid dispersions of 25%-80% enzalutamide with HPMCAS have a glass transition temperature between 87.1 and 94.0°C at 5% relative humidity (RH) and between 5 l .2°C and 59.3°C at 75% RH. At higher RH, the glass transition temperature is lower. It has been mentioned that at temperatures above the glass transition temperature, a dispersion loses its amorphous character and hence its ability to supersaturate. It is therefore desirable for a dispersion to have a glass transition temperature above the temperature at which it can be stored. Typical storage conditions prescribed by the *US Food and Drug Administration* (FDA) are 40°C/25%RH, 50°C/20%RH, 30°C/60%RH and 40° C/75%RH (see paragraph [181]). Solid dispersions of 25%-80% enzalutamide with HPMCAS have a glass transition temperature above these conditions.

4.42. It follows from Example 6 that *samples* of solid dispersions of 60% and 80% enzalutamide and HPMCAS after 1 day of exposure to 50°C/75%RH did not show crystals.

[13] And the OD has adopted
[14] See EP 10. Willliams, Watts, Miller, Formulating Poorly Water Soluble Drugs. 2012. p. 56. Par. 2.3
[15] These paragraphs are similar to paragraphs [0003] and [0009] of EP 778.

The solid dispersion of 80% enzalutamide and HPMCAS did show fusion of particles, which, according to the example, means that storage under controlled conditions would be necessary. This did not apply to the solid dispersion of 60% enzalutamide and HPMCAS. Here, however, these conditions *(challenging conditions* according to the patent) are more challenging than the aforementioned conditions applied by the FDA. This also follows, for example, from the PI Xtandi capsules, where storage below 20°C to 25°C is recommended.

4.43. It follows from the above, on the one hand, that the skilled person would infer from the application as originally filed the technical effect of at least a sufficient stability as encompassed by the technical doctrine and embodied by the same originally disclosed invention[16] and, on the other hand, that this technical effect in fact occurs. This technical effect may therefore be taken into account in the assessment of the inventive step.

Improved treatment adherence through fewer and/or smaller dosage forms

4.44. The form of administration can also be regarded as a technical effect. Paragraph (05)[17] of application WO 208 includes, amongst others, that the Xtandi capsules contain 40 mg enzalutamide and that the daily dosage is 160 mg, the patient should take four soft capsules per day. It is then stated, inter alia, that a suitable single tablet of a reasonable size containing the prescribed amount of enzalutamide would be advantageous as a suitable alternative to soft capsules.

4.45. Paragraph [221][18] describes, amongst others, that two formulations are compared in Example 15. The first is a reference formulation, namely a liquid-filled, soft gelatine capsule containing 40 mg enzalutamide dissolved in Labrasol. The skilled person will recognise this formulation as the Xtandi capsule (see above under 4.28). The second is a test formulation, namely a tablet containing 160 mg enzalutamide (in the form of a 60%A:HPMCAS-M *spray-dried* dispersion). It is also stated that the four-capsule regimen is uncomfortable *(inconvenient)* because of the number of capsules to be taken, especially in light of the fact that cancer patients need to take multiple drugs.

4.46. Tablet 16[19] of the application provides the formulation of examples 16, 17, 18, 21, 22 and 23. For examples 16, 17, 18 and 22, an amount of enzalutamide of 80 (mg) is shown and the tablet size is 14.8 mm x 7.8 mm. For example 21, it concerns 160 (mg) enzalutamide in a round tablet (with a diameter) of about 10.5 mm.

4.47. The PI Xtandi capsules does not mention the format of the capsules. However, the skilled person would know or be able to easily find out this size of the Xtandi capsules available on the market. This size is approximately 20 mm x 9 mm[20].

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[16] See G2/2J (footnote 11)
[17] This paragraph is identical to paragraph [0003] of the patent.
[18] This paragraph is identical to paragraph [0225] of the patent.
[19] See Table 16 of the patent.
[20] See EP46: summary product characteristics, p. 2

4.48. It is not in dispute between the parties that a tablet is easier to administer than a (soft) capsule. In addition, it follows from the above that, based on the daily dosage of 160 mg included in the PI Xtandi capsules (four 40 mg capsules once a day), the formulation according to claim 1 allows for fewer and/or smaller dosage forms. Fewer or smaller tablets are easier to be administered. That this also leads to improved treatment adherence, as argued by Astellas, is not sufficiently substantiated, according to the District Court. The reference by Astellas to a publication about a study from which the preference for a tablet over a capsule follows[21], is in this case not sufficient to be able to draw conclusions about an actual improved treatment adherence. After all, a preference does not always lead to improved treatment adherence.

4.49. The technical effect comprising easier intake will be inferred by the skilled person in view of the above passages from the application as originally filed, as encompassed by the technical teaching and embodied by the same originally disclosed invention[22]. Indeed, it is discussed that the patient should swallow four soft capsules and that a single tablet would be advantageous as an alternative to it. The four-capsule regime is also described as uncomfortable. The skilled person would infer that an objective of the invention is to provide an easier-to-administer alternative to the four Xtandi capsules.

4.50. Moreover, it follows from the application that this technical effect in fact occurs. Again, examples 16, 17, 18 and 22 represent four dosages and formats of tablets according to claim 1 that cover a sufficient range. Proving the effect for each possible form of administration falling within the breadth of claim 1 is not necessary in this (see also above under 4.35), especially as the skilled person will in principle strive for the most optimal form of administration.

4.51. In view of the above, the objective technical problem can be formulated as providing an alternative oral solid pharmaceutical formulation containing enzalutamide, with bioavailability comparable to the Xtandi capsules and sufficient stability, which can be more easily administered. The court hereby assumes that, starting from an existing solid oral formulation with adequate bioavailability, the skilled person will not consider forms of administration other than oral solid forms, which are generally preferred.

Is the solution inventive?

4.52. The next question that must be answered is whether the invention was obvious to the average skilled person on the priority date, based on this problem formulation.

4.53. The following is the starting point in the assessment. A patent lacks inventive step if the average skilled person, starting from the relevant prior art, would - and not merely could - have solved the problem in the manner claimed in the patent. Because the invention is the result of further research, the invention is not

[21] GP09, Ninomiya et al, Preference for enzalutamide capsules versus tablet pills in patients with prostate cancer. International Journal of Urology (2019). The study on adherence referred to in this article has not been submitted by Astellas.
[22] See G2/21 (footnote 11).

obvious only if the average skilled person would have conducted that research and the results are clearly predictable, but also if there is a reasonable expectation of success due to an inducement in the prior art. That is, the skilled person is able to reasonably predict a successful end to a research project within acceptable time. It may be of importance whether the studies to be conducted are time-consuming and/or complex and whether only routine experiments are needed. It is not necessary that success could be predicted with certainty, but insufficient is the mere *"hope to succeed"*.[23]

4.54. The court first states that it follows from the documents submitted by the parties in these proceedings that the skilled person had no information about the compound enzalutamide on the priority date other than that contained in the PI Xtandi capsules and US 753. US 753 only discloses the structural formula of enzalutamide and information on the therapeutic action and application of the group of disclosed compounds. Furthermore, it contains only general options for possible dosage forms for that group of compounds. About the physical and chemical properties of the substance enzalutamide, US 753 contains no information. The PI Xtandi capsules include that enzalutamide is practically insoluble in water. Furthermore, information on the pharmacokinetic properties of the Xtandi capsules, such as absorption, distribution, metabolism and elimination, is included. Other information on the physical and chemical properties of enzalutamide is lacking. This means it must be assumed that the skilled person had to conduct his own research on those properties. See, for example, Williams' handbook:

In order to optimise the formulation of a poorly water-soluble drug it is imperative to gain an understanding of the physical and chemical nature of the compound. This can be accomplished through prefomulation studies, including solubility screenings, solid-state characterisation. dissolution testing. and in vivo studies[24].

4.55. Based on the poor water solubility of enzalutamide, the skilled person would look for formulation strategies for such substances. It follows from the common general knowledge presented that several options were available for this purpose. This follows, for instance, from the textbooks by Swarbrick[25] and Williams[26], the review article by Warren[27] and the review article by Singh[28]. The latter mentions, for example, *solid dispersions*, *soluble cylodextrin complexes, self-emulsifying drug delivery systems, nanocrystals* and *ordered mesoporous silica*[29]

4.56. Sython's expert Prof Wagner[30] also discloses several options generally available to the skilled person[31]. This also applies to the

[23] See, inter alia, Court of Appeal of The Hague 10 June 2014, ECLI:NL:GHDHA:2014:2500, paragraphs 14 et seq. and Case Law Boards of Appeal EPA 2022, 7.1
[24] Williams 2012. p. 74. para. 2.5. p. 123. para. 3.5
[25] EP08, Swarbrick. Enclyclopedia of Pharmaceutical technology. Third Edition, volume I, 2007. p. 1245, left column halfway down and right column at top.
[26] Williams 2012. p. 27, para. 2.1
[27] EP36, Warren et al, Using polymeric precipitation inhibitors to improve the absorption of poorly water-soluble drugs: A mechanistic basis for utility. Journal of Drug Targeting, 20 10, p. 704. Introduction. left column
[28] GP02. Singh et al. Oral formulation strategies to improve solubility of poorly water-soluble drugs, Expert Opin. Drug Deliv. 2011
[29] Singh 2011, paras 2.1 to 2.5. table 1, 2 and 4
[30] EP53, para. 8
[31] Before arguing that he would try an amorphous solid dispersion first.

article by Friesen[32] submitted by Synthon (which does not form part of the common general knowledge), which speaks of a variety of techniques, including: *(a) formation of salts for ioniable compounds: (b) solutions in solvents, cosolvents, and lipids; (c) micelle systems, including self emulsifying drug-delivery systems (SEDDS): (d) particle size reduction, including the use of attrition-milled nanocrystalline forms: (e) complexation: (j) prodrugs; and (g) amorphous solids and solid dispersions*[33] [34]. Astellas' expert Prof Dr Van den Mooter also mentions the technique of *co-crystals,* which is also discussed in Williams' textbook[35].

4.57. Even if it should be assumed that the skilled person would rely on techniques that provide supersaturation, several options exist, as follows, for example, from the review article by Brouwers[36].

4.58. It cannot be deduced from the (common general knowledge) literature submitted by the parties that, of the available formulation strategies for poorly water-soluble substances, the skilled person would only consider (amorphous) solid dispersion, as Synthon is trying to argue. In the publications mentioned, advantages and disadvantages of the various techniques are discussed, but no unambiguous preference is expressed for one technique. Also, the articles that specifically discuss (amorphous) solid dispersions and report positive results thereof, are more in the nature of elaborating on a particular technique than teaching the skilled person a general preference for that specific technique. Thereby, the (common general knowledge) literature clearly shows that the choice of technique strongly depends on the properties of a specific active substance[37], so that the skilled person would not exclude certain techniques in advance for that reason too. This also applies to the technique as applied to the Xtandi capsules, which contain enzalutamide dissolved in an oil[38]. Several options exist for this technique for poorly water-soluble substances[39] and the average skilled person will also consider optimising this technique[40]. In any case, he will not disregard this technique just because it has already been applied in some form in the Xtandi capsules. On the contrary, mindful of the desire to achieve bioavailability comparable to those capsules, he will also consider this technique.

4.59. That the skilled person would in no case consider a crystalline form of the active substance, so that techniques - such as some mentioned by Astellas - that apply a crystalline form would be excluded in advance, as Synthon has argued, also does not follow as a rule from the submitted literature. The crystalline form

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[32] EP22, Friesen et al, Hydroxypropyl Methylcellulose Acetate Succinate-Based Spray-Dried Dispersions: An overview, Molecular Pharmaceutics. 2008, p. 1003-1019

[33] Friesen 2008. p. 1004, left and right columns

[34] The parties agree that in the circumstances of this case, salts and prodrugs would not be considered a possibility by the average skilled person.

[35] Williams 2012. p. 116, para. 3.4

[36] EP 52.5. Brouwers et al, Supersaturating Drug Delivery Systems: The Answer to Solubility-Limited Oral Bioavailability? Journal of Pharmaceutical Sciences. 2008, pp. 2549-2572 and table I

[37] See, for example, Singh 2011, p. 1362, article highlights, *"It remains difficult, if possible at all. to predict which strategy will be the best for a given poorly water-soluble drug based on its physicochemical profile....*

[38] This technique falls into the categories described as *"solubilised formulations of enzalutamide in non-aqeuous vehicles"* (Synthon's expert Dr Miller) "*lipid-based formulations"* (Swarbrick 2007), *"self-emulsifying drug delivery systems"* (Singh 2011)

[39] Swarbrick, p. 1258. Warren 2010. p. 706, left column

[40] See also Opposition Division decision of 8 May 2024. no. 19.1

is certainly described as the form with the most advantages in terms of solubility, but it also has disadvantages (particularly in terms of stability) and techniques using the crystalline form of the active substance are also discussed as a possibility for formulating a poorly water-soluble substance. That even for solid dispersions there was interest in crystalline forms is because of their better stability, which follows from a review article on solid dispersions by Srinarong[41] submitted by Synthon itself.

4.60. Several options also existed for adding a polymer as a carrier. In the handbook by Williams[(42),] many *"commonly used"* polymers are described. Warren and Singh's (review) articles also mention several examples of (commonly used) polymers[43]. The fact that some publications mention positive results of HPMCAS does not mean that this polymer would be the *only* polymer the skilled person would consider (see also below under 4.69 and onwards). After all, common general knowledge indicates that the interaction between a polymer and the specific active substance is important, and positive publications about HPMCAS are offset by publications in which this polymer performs less well than other polymers with certain active substances.

4.61. The conclusion from the above is that the skilled person *would* not initially choose an amorphous solid dispersion of enzalutamide with HPMCAS. However, the invention may not be inventive if the skilled person would conduct research with a reasonable expectation of success and thereby arrive at the invention.

4.62. In the search for a solution to the problem of finding an alternative formulation for enzalutamide with bioavailability comparable to the Xtandi capsules and sufficient stability, which is easier to be administered, the skilled person would realise that the Xtandi capsules contain fully dissolved enzalutamide. Labrasol is furthermore an excipient that – in short - enhances the solubility, permeability and absorption of a substance. These factors have a positive impact on bioavailability. This knowledge affects the skilled person's expectation of success in obtaining comparable bioavailability by alternative means.

4.63. As mentioned, the skilled person had little information on enzalutamide at the priority date. Information on dissolution behaviour, permeability and stability and on possible suitable formulation strategies was lacking. Hence, the skilled person first had to carry out preformulation studies (see above under 4.54). Such studies are described in Williams' handbook[44]. On the basis of these results, the skilled person would further determine, elaborate and investigate the appropriate different formulation strategies.

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[41] Srinarong et al, Improved dissolution behaviour of lipophilic drugs by solid dispersions: the production process as starting point for formulation considerations, Expert Opinion Drug Delivery, 2011, p. 1121: *"Furthermore, application of crystalline solid dispersions is gaining increasing interest because they are thermodynamically more stable than amorphous solid dispersions.* "

[42] EP 52.3, Willliams, Watts, Miller. Formulating Poorly Water Soluble Drugs, 2012, chapter 8 p. 278-279 table 8.3. chapter 9, table 9.2 and chapter 10, label 10.10

[43] Warren 2010, pp. 714-717, tables 1 and 2, Singh 2011. p. 1367, left column

[44] EP10. Williams 2012. chapter 2, pp. 27-93

4.64. Assuming that the skilled person would also consider an amorphous solid dispersion (ASD) as a solution to the formulated objective technical problem, he would then research that as well. In Williams' handbook[45] published shortly before the priority date, for formulating an ASD for a poorly water-soluble substance, the challenges and various steps are described. The introduction mentioned that ASDs can be a useful approach for improving the bioavailability of poorly water-soluble substances, but that amorphous substances are unstable and can crystallise. Stabilisation by combination with a polymer is possible, with the properties of the ASD influenced by the properties of both the active substance and the polymer. Williams describes that despite increased theoretical and practical knowledge and modern techniques, very few ASDs have been introduced to the market. The possible reasons given for this are:

- Insufficient knowledge of the physicochemical properties of drugs and stabilisers (polymers) and their interactions
- Limitation of API availability during the early stages of development
- Lack of available techniques for prediction of amorphous formulation stability
- Availability of representative processing techniques during early-stage development, especially on small scales (or miniaturised) for formulation screening
- Insufficient time available for structured development

It is concluded as follows:

Thus. the formulation scientist uses an empirical approach to develop early formulations using some known polymers at some arbitrary drug loading by solvent evaporation methods.

4.65. By the priority date, about 30 drugs dissolved in soft gelatine capsules were available.[46] About 11 ASDs were on the market at the same time. Only two of these[47] involved an active substance previously formulated as soft gel capsules (see 4.71). This was even though the technique of ASD had been known since the 1960s and many of the newly developed drugs were poorly water-soluble substances[48], so techniques to formulate them were in high demand. There were therefore few successful examples from which the skilled person could derive expectations.

4.66. That the formulation of a poorly water-soluble substance in general and the development of an ASD in particular was an empirical and unpredictable process, involving lack of knowledge, understanding and predictability, and the absence of models, especially regarding bioavailability and stability, also follows from other literature prior to the priority date, including (in order of year):

Warren 2010

The development of effective formulation approaches to facilitate oral absorption of poorly water-soluble drugs is a considerable challenge. Whilst advances have been made in the design of delivery technologies such as solid dispersions, lipid-based formulations. and micro- and nanosuspensions. in many cases formulation development

[45] EP 52.3. Williams 2012, para 8.1, p. 268
[46] Astellas' pleading notes, paragraph 88
[47] Norvir and Kaletra, both containing the active substance ritonavir, Kaletra also contains lopinavir.
[48] Percentages in the submitted literature vary. Williams 2012 cites 60%. p. 27-28.

remains empirical and uncertain.[49]

Singh 2011

There exist a wide variety of possible formulation strategies, each with their specific advantages and disadvantages. A SWOT (Strength. Weakness, Opportunity, Treath) analysis of the different strategies is presented in **Table 4.** Their aim is to improve bioavailability and stability, but the formulation process of poorly soluble compound is still driven by trial and error. It remains difficult, if possible at all. to predict which strategy will be the best for a given PWSD based on its physicochemical profile. This makes formulation development a time-consuming process since all possible formulation strategies need to be explored. without guarantee for eventual success. This is a serious threat for the pharmaceutical industry and in turn the patient.
Despite their unfavourable physical stability profile. solid dispersions have been widely investigated as a formulation strategy mainly because of their significant solubility/dissolution rate enhancement compared with crystalline forms. The first scientific report on the use of solid dispersions as a tool to improve the solubility and dissolution rate of poorly soluble drugs was already published in 1961 by Sekiguchi and Obi. In spite of the extensive research and the number of scientific papers and patents that were published during the past 50 years, few products relying on solid dispersion technology have reached the market. A whole array of excipients (carriers) can be used to stabilise the amorphous form. but it is not completely clear why a certain carrier is suitable where another one fails or why some polymeric carriers maintain the supersaturated state of the API after dissolution, while others do not. Although some general rules can be used such as selection of carriers with high *Tg,* it illustrates the necessity to improve our knowledge about the physics of amorphous materials. While high- and semi-throughput systems enable to empirically select carriers based on their solid dispersion potential (kinetic solubility or miscibility) and dissolution improvement, physical models to predict solid state solubility/miscibility and stability are still lacking and limit a complete breakthrough of solid dispersion technology.[50]

Van den Mooter 2012

The number of scientific papers published in the past 50 years proves that solid dispersions and more specifically amorphous solid dispersions are certainly a valuable formulation strategy to enhance the solubility and dissolution rate of a poorly soluble APL One striking observation is that in spite of enormous research efforts both in academia and pharmaceutical industry very few products relying on solid dispersion technology reached the market. Problems of physical stability (amorphous-amorphous phase separation, nucleation and crystallization of the API) during shelf life are recognised as the primary reason for this discrepancy. However, the deeper reason is the lack of understanding of the physical chemistry of amorphous materials. More in particular the understanding of thermodynamics of solid state APl-polymer miscibility, kinetics of solid state phase separation, nucleation and crystallization, or stability of the dissolved state of the AP10nce it has been released from the polymer matrix in the GI tract (maintenance of supersaturated state). Moreover, the link between manufacturing process parameters and formulation parameters with the obtained physical structure and pharmaceutical performance of the solid dispersion is still not completely understood. A whole array of excipients (carriers) can be used to stabilise the amorphous form. but it is not completely why a certain carrier is suitable where another fails or why some polymeric carriers maintain the supersaturated state of the API after dissolution, while others do not.[51]

Gao 2012

While supersaturatable formulation approaches including solid dispersions are being widely explored in pharmaceutical industry and have been demonstrated to improve oral absorption of poorly soluble drugs. there is

[49] Warren 2010, p. 704
[50] Singh 2011, p. 1373, left and right columns
[51] GP4, Van Mooter, The use of amorphous solid dispersions: A formulation strategy to overcome poor solubility and dissolution rate. Drug Discovery Today: Technologies, 2012, pp. 83-84

still lack of fundamental understanding of such formulations regarding to how to achieve and sustain a supersaturated state in the light of drug-polymer interaction. Application of precipitation inhibition involving selection of a polymeric precipitation inhibitor (PPI) is still based on empirical approaches, and structure-activity relationships have not been established. It is understood that the kinetic solubility, the degree of supersaturation, and the rate at which supersaturation is generated affect the rate and mechanisms by which precipitation occurs. Development of supersaturatable formulations still primarily relies on tedious trial-by-error approach and *in vivo* screening in animal models. Rational design of supersaturatable formulations is of great interests and presents a challenge to pharmaceutical scientists.[52]

Sun 2012

Important questions remain concerning the stability of amorphous drugs against crystallisation. The mechanistic details are still lacking for fast crystal growth in the bulk and at the surface of organic glasses, and for the emergence of fast modes of crystal growth as organic liquids are cooled to become glasses. It is unclear what factors define the degree to which crystal growth rate is enhanced on going from the interior to the surface of an organic glass, and why fast surface crystal growth seems more prevalent for organic glasses. The molecular motions responsible for crystallization in glasses remain to be better understood. It is unknown how different factors combine to define effective crystallization inhibitors for amorphous drugs: strength of "direct" intermolecular interactions, molecular weight, miscibility, and perhaps others. We still do not know whether the mechanism of crystal growth changes with increasing concentrations of polymer additives. With better understanding of crystallization in organic glasses. more accurate models may be formulated and more informative experiments be conducted to design amorphous pharmaceutical formulations with good physicochemical stability.[53]

4.67. These were actual problems shortly before the priority date. The Williams 2012 handbook described the various methods for the many different stages in the formulation process of an ASD, in the hope of improving it.[54]

4.68. That the aforementioned problems of lack of knowledge and predictability, however, were still present even at and after the priority date follows from Schnitty's review article from 2020, published well after that date. That article states that only 24 ASDs were still on the market at that time, about 0.6% of all drugs on the market. The reasons for this were described:

Reasons for this could be that ASDs are more complex systems (Park, 2015) compared to standard drug formulations: At first, the ability of an AP1 to form an ASD with a specific polymer is not guaranteed, as the process of mixing or dissolution, e.g. in a molten state. of an API in a polymer might not be favourable from a thermodynamic point of view; therefore, ASDs. if formed under such , are either unstable or cannot be manufactured. Second. the production involves complex processes such as hot-melt extrusion. Once produced, stability for suitable shelf life is still a vital , as crystallization can occur post-production. These hurdles result in high development costs without a guarantee of an increased bioavailability. To enhance the mechanistic understanding of increased bioavailability through ASDs. research activities are ongoing. However, this process is far from being entirely understood (Tho et al. 2010: Park. 2015: Fong et al. 2017).[55]

[52] GP05, Gao and Shi. Characterisation of Supersaturatable Formulations for Improved Absorption of Poorly Soluble Drugs, The AAPS Journal, 2012. p. 2, left column
[53] GP03, Sun et al. Stability of Amorphous Pharmaceutical Solids: Crystal Growth Mechanisms and Effect of Polymer Additives. The AAPS Journal. 2012. p. 387, left column
[54] Williams 2012. chapter 8, p. 267-3 IO
[55] GP I 6, Schnitty et al. Mechanisms of increased bioavailability through amorphous solid dispersions: a review. Drug Delivery. 2020. p. 110-111

4.69. Furthermore, when the skilled person would investigate an ASD, he had to choose a polymer. In doing so, he also could not predict whether and, if so, which polymer would give the desired solubility, bioavailability and stability to an ASD containing enzalutamide. Synthon submitted publications describing positive results of HPMCAS for a number of active substances and identifying HPMCAS as promising and applicable for several substances.[56] Against those publications, however, there are also articles (also of later date) concerning research with active substances where HPMCAS was the less or least performing polymer[57]. It follows, as also described in the literature, that the performance of the polymer depends on its interaction with the active substance. In a 2010 article by Van Eerdenbrugh & Taylor on stability of ASDs, the question whether there is a polymer that is universally superior is clearly answered in the negative, as the action depends strongly on the specific active compound:

A question of interest to address is as follows: do higher average values indicate superior performance of the polymer, irrespective of the drug? In other words, do these results suggest that a particular polymer is universally superior to others in terms of its ability to inhibit crystallization during rapid solvent evaporation? The answer is clearly no, as can be seen upon closer evaluation of the data (Table 1). Here it is readily apparent that the ability of a given polymer to inhibit crystallization is highly dependent on the specific compound studied.[58]

4.70. Also, Warren's 2010 review article submitted by Synthon, which discusses some of the articles relied on by Synthon (including Friesen et al. and Curatolo et al.), that scarcity of data and the complexity of the gastrointestinal environment preclude definition of favourable properties of polymers beyond a limited number of specific examples, and argues that more research is needed to define drug-polymer relationships:

[56] EP36, Warren et al. Using polymeric precipitation inhibitors to improve the absorption of poorly water-soluble drugs: A mechanistic basis for utility. Journal of Drug Targeting.2010, p. 704-731,
EP33, Tanno et al, Evaluation of Hypromellose Acetate Succinate (HPMCAS) as a Carrier in Solid Dispersions. Drug Development and Industrial Pharmacy. 2004, p. 9-17 ,
EP22, Friesen et al, Hydroxypropyl Methylcellulose Acetate Succinate-Based Spray-Dried Dispersions: An Overview, Molecular Pharmaceutics, 2008, pp. 1003-1019 ,
EP34, Konno and Taylor, Ability of Different Polymers to Inhibit the Crystallization of Amorphous Felodipine in the Presence of Moisture, Pharmaceutical Research. 2008, p. 969-978,
EP37, Curatolo et al. Utility of Hydroxypropylmethylcellulose Acetate Succinate (HPMCAS) for Initiation and Maintenance of Drug Supersaturation in the GI Environment. Pharmaceutical Research, 2008, pp. 1419-1431.
EP35, EP I 741 424.
The court here leaves aside the debate between the parties as to whether or not the good efficacy of HPMCAS in the studies in question was due to the addition of soapy substances.
[57] GP24.4. Van Eerdenbrugh and Taylor, Small Scale Screening To Determine the Ability of Different Polymers To Inhibit Drug Crystallisation upon Rapid Solvent Evaporation, Molecular Pharmaceutics, 2010, pp. 1328-1337
GPI 9 Zhao et al, Development of fully amorphous dispersions of a low Tg drug via co-spray drying with hydrophilic polymers, European Journal of Pharmaceutics and Biopharmaceutics, 2012, pp. 572-579
GP20, Kestur and Taylor. Role of polymer chemistry in influencing crystal growth rates from amorphous Felodipine. CrystEngComm. 2010, pp. 2390-2397
GP22. Kennedy et al, Enhanced Bioavailability of a Poorly Soluble YR I Antagonist Using an Amorphous Solid Dispersion Approach: A Case Study, Molecular Pharmaceutics, 2008. p. 981-993
[58] Van Eerdenbrugh and Taylor 2010. p. 1334

Collectively, these data and the data from the literature suggest that there are likely to be common functional attributes of "good" PPIs [polymeric precipitation inhibitors. court]: however to this point. the scarcity of data and the complexity of the GI environment have precluded definition of these attributes beyond a limited number of specific examples. More detailed studies are therefore required to elucidate these mechanisms in detail. in an effort to define the relationships between drugs and polymers that control stabilisation.[59]

4.71. In view of the above, the circumstance that the last three ASDs with other active substances that had entered the market before the priority date also contained HPMCAS, as Synthon has argued, would not have put the skilled person on track to try HPMCAS alone, either. The two ASDs on the market for a substance for which a soft gelatine capsule was already on the market (Kaletra and Norvir) (previously) and to which the skilled person would have paid attention for that reason, were manufactured with a different polymer (PVPVA) because research into a suitable polymer for an amorphous dispersion with ritonavir showed that HPMCAS was unable to stabilise the supersaturation of that substance.

4.72. Although it can be assumed that the skilled person would consider and include HPMCAS in his study, he would not assume in advance that HPMCAS would be the best polymer for all active substances and would therefore also give good results with enzalutamide. He would therefore have to investigate multiple polymers, with limited predictability of results.

4.73. Furthermore, where in the gastrointestinal system the administration form breaks down is important in the complex process of dissolution behaviour, absorption and eventual bioavailability. Xtandi capsules dissolve directly in the (acidic) gastric environment. Where an ASD tablet dissolves depends on the polymer used. An ASD containing HPMCAS (an enteric polymer) only dissolves after passing the stomach, in the (small) intestines, in a less acidic environment. This may affect bioavailability. That on the priority date it was easy for the skilled person to predict what effect this difference would have on bioavailability has been argued by (the expert of) Synthon, but, in view of Astellas' reasoned defence, has not been sufficiently substantiated, so that this assertion cannot be assumed.

4.74. Finally, it is clear from the submitted literature that for a formulation of poorly water-soluble active substances, *in vitro* results have limited predictive value for effects *in vivo*. This was the case (shortly) before the priority date, as shown, for example, by Williams 2012[60] and Van den Mooter 2012[61], but also afterwards, as follows from Schnitty 2020[62]. This means, on the one hand, that in vitro results from previous studies had limited predictive value and, on the other hand, that in the search for an alternative formulation for enzalutamide, in vivo testing was (also) required, with limited predictability of outcome beforehand.

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[59] Warren et al, Using polymeric precipitation inhibitors to improve the absorption of poorly water-soluble drugs: A mechanistic basis for utility, Journal of Drug Targeting. 20 10, p. 727, left and right columns

[60] EP10, Williams 2012, para2.4.2, p. 67, *"However, these studies are only indicative of performance. not absolute, as the physiological environment is far more complex than the conditions used in the laboratory.(...), in order to truly understand the ability of a formulation to provide enhanced bioavailability of a poorly water soluble compound animal models must be employed.* "

[61] Van den Mooter 2012, p. 83, left and right column: *"The correlation between in vitro dissolution data and in vivo absorption is not straightforward.* "

[62] Schnitty 2020. p. 123, right column *"Translation from in vitro to in vivo remains a challenge."*

4.75. At the priority date, the skilled person therefore did not have a sufficient scientific basis to predict whether a (suitable) alternative formulation for enzalutamide was possible, whether the formulation of a (suitable) ASD with enzalutamide was possible and certainly not whether it could achieve a bioavailability comparable to the Xtandi capsules and would be sufficiently stable. This was all the more true because no (research) data were yet known about enzalutamide and results for other active substances could not be extrapolated to enzalutamide. The research that the skilled person needed to conduct to find an alternative formulation for enzalutamide with comparable bioavailability to the Xtandi capsules and sufficient stability, which can be more easily administered, required a considerable amount of choices and research and should be classified as an empirical process, requiring both in vitro and in vivo studies and involving considerable time and costs. At best, the skilled person would start this research in the hope of succeeding *(hope to succeed),* but in the absence of sufficient substantiation with technical facts to do so, would have no reasonable expectation of success. A situation in which the skilled person would adopt a neutral *try-and-see* attitude is also out of the question because of the complexity and unpredictability of the research to be carried out.

4.76. That achieving the technical effect of the distinguishing features would only be a surprise or bonus effect, as Synthon argues, is not at issue in this case. This requires that this effect be achieved by following non-inventive, clear sequential steps *(one-way-street).* This is not the case given the skilled person's research process described above.

4.77. Nor does the so-called *several steps* approach apply in this case. Under this approach, there can be no question of inventive step if several successive steps are required to solve the objective technical problem, if and to the extent that taking each step in itself was obvious to the average skilled person, given what he had achieved in the previous step and what else he has to do to finally arrive at the solution. This requires that the first step to be taken is obvious in view of the state of the art on the priority date to the average skilled person and he had to have a reasonable expectation of success that it would (eventually) lead him to the solution of his problem[63]. In view of the above, this is not the case in this event.

4.78. In conclusion, starting from the PI Xtandi capsules, claim 1 of EP 778 is inventive.

US753

4.79. US 753 is a US patent application for the class of compounds to which enzalutamide belongs. Enzalutamide is disclosed in claim 16 of the application as RD 162'. Paragraph [0390] of US 753 describes that the compounds can be administered, for example, orally, in combination with a pharmaceutically acceptable carrier. Possible forms of administration include the mentioned

[63] See, for example, Court of Appeal The Hague, 27 August 2019.ECLI:NL:GHDHA:2019:3155 (Icos/Teva: tadalafil)

tablets and capsules. However, US 753 does not teach a concrete pharmaceutical composition containing enzalutamide, nor a recommended dosage.

4.80. Claim 1 of EP 778 contains the same distinguishing features compared to US 753 as compared to the PI Xtandi capsules.

4.81. In dispute between the parties is whether US 753 also qualifies as the closest prior art for EP 788. The starting point is that a patent must be inventive in relation to all relevant prior art. A disclosure qualifying as the closest prior art must relate to the same objective or have the same technical effect as the claimed invention and thus share the most relevant technical features. A further criterion is the comparability of the technical problem. If there are several potential starting points, it may be necessary to assess the inventive step on the basis of all these starting points. This does require that they are equivalent, realistic starting points. The objective when assessing inventive step is to start from a situation that is the closest possible to that of the inventor.[64]

4.82. Given the objective of the patent described above at 4.26, aimed at finding a suitable alternative formulation to the (Xtandi) soft gelatine capsules, US 753 does not constitute a realistic starting point for assessing the inventive step of the patent, at least not without the PI Xtandi capsules. After all, the skilled person would not disregard a product already approved and marketed for enzalutamide on the priority date when searching for a formulation for that substance. Therefore, US 753 is not detrimental to the inventive step of claim 1 of the main request.

Added matter

4.83. Finally, Synthon argued that claim 1 is invalid because it contains added matter compared to WO 208 (the parent application). First, it argues that there is no basis in WO 208. To this end, it argues that
(i) claim 83 of WO 208 did mention that the pharmaceutical composition is a solid dispersion, but that is not the same as a solid pharmaceutical composition,
(ii) that in paragraphs [130] and [151] of WO 208, the term solid pharmaceutical composition is only used in conjunction with specific administration forms, i.e. tablets [130], fine grains, granules or dry syrup [151], while these restrictions are absent from Claim 1 of EP 778, thus constituting an *'intermediate generalisation'* and
(iii) that although paragraph [03] of WO 208 mentions 'solid formulations of enzalutamide' and 'pharmaceutical compositions comprising a solid dispersion', they are mentioned separately and are parts of one phrase and should not be read together with the other.

4.84. Synthon further argues that there is no basis in WO 208 for the specific combination in claim 1 of amorphous enzalutamide with HPMCAS, as the use of HPMCAS is only mentioned in paragraph [0068], where HMPCAS is only

[6] See Case Law Boards of Appeal EPA, 2022, 3.1. see also Court of Appeal of The Hague 18 August 2020. ECLI:NL:GHDHA:2020:1621. para. 4.12 and Conclusion A-G Van Peursem 12 November 2021. ECLI:NL:PHR:2021:1058. paras. 3.11 and 3.12 (Shire-NPS/Accord: cinacalcet)

mentioned as an option from a list of polymers that can be used in dispersions with enzalutamide, while no reference is made to amorphous enzalutamide.

4.85. In its statement of defence, Astellas disputed Synthon's contentions with reasons. Synthon did not elaborate on this in its pleading notes. To the extent that it wished to maintain its position, it is considered as follows. The District Court first of all stated that amendments to a European patent application (of both description and claims) are only allowed within the limits of what the skilled person, with his or her expertise and objectively on the filing date, can directly and unambiguously, implicitly or explicitly, deduce from the original application (in this case: the parent application WO 208) (the so-called *'disclosure test'* or 'gold standard'). After said changes, in other words, the skilled person may not be confronted with new technical information. It is not required that the change is literally reflected in the application in the relevant amended form. What matters is whether the amended or added parts reflect the same technical information that the skilled person would have derived from the content of that application as a whole.[65]

4.86. The rationale of this validity objection is that, for reasons of legal certainty for third parties, the patentee may not improve his legal position by claiming protection for matter not disclosed in the original application. This follows from Article 75(1)(c) DPA, which provides that a patent shall be invalidated by the court to the extent that: "(...) c. the subject matter of the patent is not covered by the contents of the application filed or, if the patent was granted on a divisional or amended application (...), by the contents of the original application".

4.87. In the case law of the Boards of Appeal of the European Patent Office (EPO), criteria have been developed that are used for added matter examination in specific situations, such as additions to or omissions from originally filed claims, or the generalisation in a claim of a feature of a certain embodiment without generalising the other features thereof ('*intermediate generalisation').* Synthon invoked, inter alia, a judgment of the Court of Appeal of The Hague[66] on the rule developed in EPO case-law that an *'intermediate generalisation*' is only admissible if it is clear to the skilled person that there is no functional or structural link between the generalised feature and the other features of the embodiment from which the feature has been derived.
The court will also refer to this rule. In line with G2/10 and as also has been decided by the Court of Appeal, this rule is only an aid and ultimately the answer to the main question formulated earlier (the *'disclosure test'* or 'gold standard') is decisive.

Solid pharmaceutical composition

4.88. Regarding the "solid pharmaceutical composition" element in claim 1, the general paragraph [03] of WO 208 states as follows:

[65] G2/10 of August 2011, ECLl:EP:BA:2011:G000210.20110830 (https://www.epo.org/law-practice/case law-appeals/recent/g 10000zex I .html)
[66] The Hague Court of Appeal 16 March 20221, ECLI:NL:GHDHA:2021:2057 (Assia/KPN)

[03] This disclosure relates to solid formulations of enzalutamide. More particularly. this disclosure relates to solid formulations comprising amorphous enzalutamide. and to pharmaceutical compositions comprising a solid dispersion containing enzalutamide and at least one polymer. (...)

4.89. The skilled person reads here that the application covers solid formulations of enzalutamide in general and, within that category, in particular, solid formulations that contain amorphous enzalutamide and pharmaceutical compositions consisting of a solid dispersion containing enzalutamide and at least one polymer. The latter pharmaceutical compositions are therefore a specialisation of the general category of solid formulations. Therefore, it is clear to the skilled person that those pharmaceutical compositions are solid.

4.90. Paragraph [130] of WO 208 states as follows:

[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.

4.91. Here, the skilled person reads that the pharmaceutical compositions containing the solid dispersions may be formulated in different dosage forms, whereby some examples of solid dosage forms are provided. It is further stated that in some embodiments, the solid pharmaceutical composition is in tablet form. From this, the skilled person understands that the tablet form is an example of the general category of solid pharmaceutical compositions.

4.92. Paragraphs [150] and [151] of WO 208 read as follows:

[150] The pharmaceutical composition can be produced, for example, by any known process including the steps of blending. granulation, specific size controlling. tableting. film coating and the like.
[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 (i) mixing the solid dispersion(...)

4.93. Again, the dosage forms mentioned for the solid pharmaceutical composition are examples, whereby there is no functional or structural link. Therefore, the fact that Claim 1 of EP 778 generally refers to solid pharmaceutical compositions does not constitute an inadmissible generalisation ("*intermediate generalisation").*

4.94. It follows from the above that the skilled person could directly and unambiguously derive the element "solid pharmaceutical compositions" from WO 208, so that the patent does not contain unlawful added matter.

Amorphous enzalutamide with HPMCAS

4.95. Regarding the specific combination in claim 1 of amorphous enzalutamide with HPMCAS, the court considers as follows.

4.96. Claims 83 to 86 of WO 208 read:

83. A pharmaceutical composition comprising a solid dispersion containing enzalutamide and a polymer.
84. The pharmaceutical composition according to claim 83, wherein enzalutamide is an amorphous state.
85. The pharmaceutical composition according to claim 83. wherein the polymer is a polymer or two or more polymers selected from the group consisting of polyvinyl pyrrolidone, polyethyleneoxide. poly(vinyl pyrrolidone-co-vinyl acetate), polymethacrylates, polyoxyethylene alkyl ethers, polyoxyethylene castor oils. polycaprolactam. polylactic acid, polyglycolic acid, poly(lactic-glycolic)acid, lipids, cellulose, pullulan, dextran, maltodextrin. hyaluronic acid. polysialic acid, chondroitin sulphate. heparin. fucoidan. pentosan polysulphate, spirulan. hydroxypropyl methyl cellulose. hydroxypropyl cellulose, carboxymethyl ethyl cellulose, hydroxypropyl methylcellulose acetate succinate, cellulose acetate phthalate. cellulose acetate trimellitate. ethyl cellulose. cellulose acetate, cellulose butyrate. cellulose acetate butyrate, and dextran polymer derivative.
86. The pharmaceutical composition according to claim 85. wherein the polymer is hydroxypropyl methylcellulose acetate succinate.

4.97. The conjunction of these (independent and dependent) claims leads to a direct and unambiguous disclosure to the skilled person of a solid dispersion containing enzalutamide (claim 83) in amorphous form (claim 84) with a polymer (claim 85), the polymer being HPMCAS (claim 86). Therefore, there is no unlawful added matter by claiming a combination of amorphous enzalutamide with HPMCAS.

4.98. The conclusion from the foregoing is that claim 1 of the main request does not contain unlawful added matter.

Conclusion on the validity of claim 1 of the main request

4.99. It follows from the above that Synthon's validity objections to Claim 1 of the main request are unfounded and claim 1 is valid.

Validity of dependent claims of the main request

4.100. Because claims 2 to 9 of the main request depend on claim 1, these too are inventive. Synthon has not stated that these claims contain added matter (independently). Hence, the dependent claims of the main request are also valid.

Invalidation of the patent as granted

4.101. As Astellas is only relying on the main request in these proceedings and has not contested the invalidity of the claims of EP 778 in so far as they extend beyond this main request, the claims of EP 778 as granted will be set aside, except for the claims of the main request.

Declaratory judgment

4.102. Since it follows from what has been considered above that it was not obvious for the skilled person on the priority date to formulate enzalutamide in amorphous form with HPMCAS in the form of a solid dispersion, the declaratory judgment (the *Arrow declaration)* claimed by Synthon will be rejected.

Procedural costs

4.103. As the largely unsuccessful party, Synthon will be ordered to pay the costs of the proceedings. Astellas claimed payment of the procedural costs in accordance with Article 1019h DCCP, plus statutory interest. The parties have agreed that the total costs for this case, including disbursements, amount to € 150,000. This amount will be awarded.

5. The decision

The court

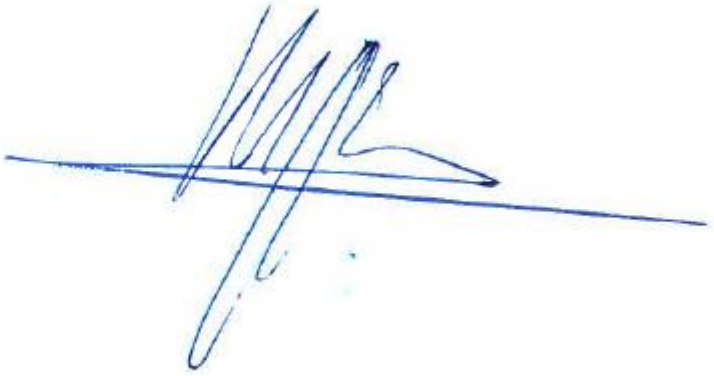
5.1. Invalidates the Dutch part of EP 3 725 778 B1 in so far as it goes beyond the claims of the main request referred to at 4.16,

5.2. orders Synthon to pay the costs of these proceedings, estimated to date at € 150,000 on the side of Astellas, plus statutory interest pursuant to Article 6:119[67] of the Dutch Code of Civil Procedure from the fifteenth day after service of this judgment until the day of payment in full,

5.3. declares the costs order provisionally enforceable,

5.4. the more or otherwise claimed is rejected.

This judgment has been rendered by M.J.J. Visser, J. Th. van Walderveen and Dr. Ir. C. Schüller and pronounced in public on 22 January .



[67] Dutch Civil Code