

GNRH ANTAGONIST FORMULATION

Description

5 FIELD OF THE INVENTION

The present invention generally relates to the field of GnRH antagonist formulations. More particularly, the invention relates to pharmaceutical compositions made of microparticles for the slow release of a GnRH antagonist, such as degarelix, medical
10 uses of such pharmaceutical compositions, a kit including such pharmaceutical compositions and methods for the preparation of such pharmaceutical compositions.

BACKGROUND

15 Gonadotropin-releasing hormone (GnRH) is a peptide hormone consisting of 10 amino acids, i.e. a decapeptide, important in human reproduction. It is produced in the neurons of the hypothalamus and induces the downstream production of sex hormones by the gonads. GnRH ultimately regulates puberty onset and sexual development, as well as ovulatory cycles in females.

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Prostate cancer is a severe cause of mortality among men. Many prostate carcinomas require testosterone, an androgen, to develop. Treatments that reduce androgen production by the testicles are currently the most commonly used hormone therapies for prostate cancer. GnRH antagonists are one group of compounds that are used in
25 the treatment of prostate cancer. In comparison to GnRH agonists, GnRH antagonists do not show a so-called testosterone flare, i.e. a temporary increase in testosterone levels in the body during the first weeks of treatment. GnRH antagonists act by competitively occupying the GnRH-receptor. Thereby, the release of two further gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from
30 the anterior pituitary gland is blocked.

Degarelix (IUPAC name: N-acetyl-3-(2-naphthyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridyl)-D-alanyl-L-seryl-4-((S)-dihydroorotamido)-L-phenylalanyl-4-ureido-D-phenylalanyl-L-leucyl-N6-isopropyl-L-lysyl-L-prolyl-D-alaninamide) is a synthetic
35 decapeptide which acts as a GnRH antagonist. It contains seven non-naturally

occurring amino acids: D-2-naphthylalanine, D-4-chlorophenylalanine, D-3-pyridylalanine, 4-aminophenylalanine(L-hydroorotyl), 4-aminophenylalanine(carbamoyl), N(epsilon)-isopropyllysine and D-alanine.

- 5 The peptide sequence of degarelix may be described as follows (SEQ ID NO.:1):

Ac-D-2Nal-D-4Cpa-D-3Pal-Ser-4Aph(I-Hor)-D-4Aph(Cbm)-Leu-ILys-Pro-D-Ala-NH₂.

- 10 The abbreviations mean: Ac, acetyl; 2Nal, 2-naphthylalanine; 4Cpa, 4-chlorophenylalanine; 3Pal, 3-pyridylalanine; Ser, serine; 4Aph, 4-aminophenylalanine; Hor, hydroorotyl; Cbm, carbamoyl; Leu, leucine; ILys, N(epsilon)-isopropyllysine; Pro, proline; Ala, alanine.

- 15 A formulation marketed under the trade name Firmagon® comprising degarelix as active pharmaceutical ingredient, in the form of degarelix acetate, is available in two packaging configurations, to deliver a starting dose of 240 mg in 2 injections for the first administration at 40 mg/ml (two-vial carton with each vial delivering 120 mg of degarelix (equivalent to the median value of 126 mg degarelix acetate)), and a maintenance dose of 80 mg at 20 mg/ml in 1 injection for the following administrations
20 (one-vial carton delivering 80 mg of degarelix (equivalent to the median value of 84 mg degarelix acetate)). Firmagon® is formulated for subcutaneous injection in 1-month intervals.

- 25 A further formulation marketed in Japan under the trade name Gonax® comprising degarelix as active pharmaceutical ingredient, in the form of degarelix acetate, is administered in a starting dose of 240 mg given as two subcutaneous injections of 120mg at 40 mg/ml. After 4 weeks from the initial dose, the maintenance dose of degarelix is 80 mg at 20 mg/ml given as one subcutaneous injection, every 4 weeks. Gonax is also available at a maintenance dose of 480 mg given as two subcutaneous
30 injections of 240 mg at 60 mg/ml at 12 weeks intervals.

Generally, sustained release compositions can serve to reduce the number of administrations needed over a prolonged treatment period. However, formulating

sustained release pharmaceutical compositions to have an acceptable release profile of degarelix for the specific therapeutic application is challenging.

Accordingly, there is a need for new pharmaceutical compositions that can provide a sustained release of degarelix, for example over at least a 3-month (12 weeks) interval after a single administration. In particular, there is a need for degarelix sustained release compositions that have acceptable release profiles. Further, there is a need for pharmaceutical compositions that are convenient and easy to use, that have an acceptable shelf life, that are safe and well tolerated by patients, and that minimize patient discomfort, e.g. caused by repeated administrations associated with long term treatment, and/or syringeability and injectability issues.

BRIEF SUMMARY OF THE INVENTION

Against this background, it is an object of the present invention to provide an improved degarelix formulation, i.e. a pharmaceutical composition comprising degarelix. It is a further object of the invention to provide the improved formulation for medical use in the treatment of prostate cancer. It is still a further aspect of the present invention to provide a method of preparation of the improved degarelix formulation, and to provide related kits and devices.

Accordingly, in a first aspect, the present invention relates to a pharmaceutical composition comprising degarelix in the form of a pamoate salt, wherein the degarelix pamoate salt is contained in microparticles of a biodegradable copolymer of lactide units and glycolide units (PLGA) and wherein the microparticles contain at least 50 wt% PLGA and from about 20 wt% to about 34 wt% degarelix free base equivalents.

In another aspect, the present invention relates to medical uses of the pharmaceutical composition according to the invention. Accordingly, the invention relates to a pharmaceutical composition as defined herein for use in the treatment of prostate cancer, and to a method for treating prostate cancer, comprising administering an effective amount of the pharmaceutical composition as defined herein to a subject in need thereof.

The inventors have surprisingly found that a peptide formulation comprising degarelix as a pamoate salt, which is substantially insoluble in water at room temperature, in combination with PLGA, can increase the relative bioavailability of degarelix at the same dosage level as prior degarelix formulations. It has further been surprisingly
5 found that by using, *inter alia*, degarelix pamoate salt with PLGA, it was possible to avoid high initial burst release in the days immediately following administration of the pharmaceutical composition.

In another aspect, the present invention relates to a method for the preparation of a
10 pharmaceutical composition as defined herein, comprising:

- (a) mixing degarelix, particularly in powder form, in the form of a pharmaceutically acceptable pamoate salt, with a biodegradable copolymer of lactide units and glycolide units (PLGA), particularly in powder form;
- (b) subjecting the mixture to progressive heating and extrusion;
- 15 (c) pelletizing the obtained extrudate;
- (d) grinding the obtained pellets at low temperature.

In yet another aspect, the invention relates to a pharmaceutical composition as defined herein, which is obtainable by the preparation method as defined herein.

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In yet another aspect, the invention relates to a kit comprising a device, such as a prefilled syringe or vial, containing a pharmaceutical composition as defined herein, and instructions for use.

25 In yet another aspect, the invention relates to a dual chamber device comprising either the pharmaceutical composition as defined herein in powder form in one chamber, and an aqueous vehicle in the other chamber, or the pharmaceutical composition as defined herein in powder form in one chamber, and an oily vehicle in the other chamber.

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In yet another aspect, the invention relates to a single chamber device comprising the pharmaceutical composition as defined herein in the form of a suspension in an oily vehicle. This may also be referred to as a ready-to-use device, where no reconstitution step is required before administration to the patient.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

So that the present disclosure can be more readily understood, certain terms are first
5 defined. As used in this application, except as otherwise expressly provided herein,
each of the following terms shall have the meaning set forth below. Additional
definitions are set forth throughout the application.

Unless defined otherwise, all technical and scientific terms used herein have the same
10 meaning as commonly understood by those skilled in the art.

The singular forms "a," "an," and "the" include plural referents unless the context
clearly dictates otherwise. The terms "a" (or "an"), as well as the terms "one or more,"
and "at least one" can be used interchangeably herein. In certain aspects, the term "a"
15 or "an" means "single." In other aspects, the term "a" or "an" includes "two or more" or
"multiple".

Furthermore, "and/or" where used herein is to be taken as specific disclosure of each
of the two specified features or components with or without the other. Thus, the term
20 "and/or" as used in a phrase such as "A and/or B" herein is intended to include "A and
B," "A or B," "A" (alone), and "B" (alone). Likewise, the term "and/or" as used in a
phrase such as "A, B, and/or C" is intended to encompass each of the following
aspects: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A
(alone); B (alone); and C (alone).

25 The term "about" is used herein to mean approximately, roughly, around, or in the
regions of. When the term "about" is used in conjunction with a numerical range, it
modifies that range by extending the boundaries above and below the numerical
values set forth. In general, the term "about" can modify a numerical value above and
30 below the stated value by a variance of, e.g., 10 percent, up or down (higher or lower).
In some aspects of the disclosure, the term "about" encompasses a deviation from the
recited value of between 0.001% and 10%, inclusive of the endpoints. In some aspects,
the term "about" encompasses an increase from the recited value of between 0.001%
and 10%, inclusive of the endpoints. In some aspects, the term "about" encompasses

a decrease from the recited value of between 0.001% and 10%, inclusive of the endpoints.

Units, prefixes, and symbols are denoted in their *Système International de Unites* (SI)
5 accepted form.

Numeric ranges are inclusive of the numbers defining the range. Where a range of values is recited, it is to be understood that each intervening integer value, and each fraction thereof, between the recited upper and lower limits of that range is also
10 specifically disclosed, along with each subrange between such values.

The upper and lower limits of any range can independently be included in or excluded from the range, and each range where either, neither or both limits are included is also encompassed within the disclosure. Thus, ranges recited herein are understood to be
15 shorthand for all of the values within the range, inclusive of the recited endpoints. For example, a range of 1 to 10 is understood to include any number, combination of numbers, or sub-range from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10.

Any numerical value inherently contains certain errors necessarily resulting from the
20 standard deviation found in their respective measurements. Additionally, all ranges disclosed herein are to be understood to encompass any and all subranges subsumed therein. For example, a stated range "1 to 10" should be considered to include any and all subranges between (and inclusive of) the minimum value of 1 and the maximum value of 10; that is, all subranges beginning with a minimum value of 1 or more, such
25 as 1 to 6.1, and ending with a maximum value of 10 or less, such as 5.5 to 10.

Where a value is explicitly recited, it is to be understood that values, which are about the same quantity or amount as the recited value are also within the scope of the disclosure. Where a combination is disclosed, each sub-combination of the elements
30 of that combination is also specifically disclosed and is within the scope of the disclosure. Conversely, where different elements or groups of elements are individually disclosed, combinations thereof are also disclosed. Where any element of a disclosure is disclosed as having a plurality of alternatives, examples of that disclosure in which each alternative is excluded singly or in any combination with the

other alternatives are also hereby disclosed; more than one element of a disclosure can have such exclusions, and all combinations of elements having such exclusions are hereby disclosed.

- 5 As mentioned above, the present invention relates to a pharmaceutical composition comprising degarelix in the form of a pamoate salt, wherein the degarelix pamoate salt is contained in microparticles of a biodegradable copolymer of lactide units and glycolide units (PLGA) and wherein the microparticles contain at least 50 wt% PLGA and from about 20 wt% to about 34 wt% degarelix free base equivalents.

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- According to the present invention, the active pharmaceutical ingredient (API) of the pharmaceutical composition is degarelix, present as degarelix pamoate. Pamoates or embonates are the salts of pamoic or embonic acid (IUPAC: 4,4'-Methylenebis(3-hydroxynaphthalene-2-carboxylic acid), a dicarboxylic acid which is practically
15 insoluble in water. By salt formation of degarelix with pamoic acid, its solubility in water and aqueous media is drastically reduced. Degarelix pamoate has a solubility in water at ambient temperature of only 0.004 mg/mL. In certain embodiments, degarelix, in the form of a pamoate salt thereof, may be the only API in the pharmaceutical composition according to the invention.

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- According to the commercial formulations in the prior art (e.g. Firmagon[®], Gonax[®]), degarelix is administered in the form of its highly water-soluble acetate salt (100 mg/mL). When administered by subcutaneous injection, the peptide forms a gel depot at the site of injection by fibrillation of the peptide, from where degarelix is slowly
25 released into the blood stream. It has been described that the sustained release of degarelix in such commercial formulations mainly depends on the degarelix acetate concentration of the initial formulation. The underlying mechanism is a gel desegregation or defibrillation.

- 30 By contrast, the pharmaceutical composition of the present invention is based on a practically water-insoluble compound, degarelix pamoate, embedded within PLGA microparticles. Due to its insolubility in water, degarelix pamoate does not form a gel depot like the water-soluble acetate.

PLGA microparticles have been previously described for generating sustained release formulations. Surprisingly, however, it has now been found that contrary to expectations, the combination of a water-insoluble salt of API, i.e. degarelix pamoate, and PLGA polymer, as specified herein, does not lead to a formulation with extremely slow and thus undesirable release characteristics. Rather, the inventors have found that when formulated according to the present invention, degarelix shows a favorable dissolution kinetic and an improved relative bioavailability. It seems that the water insoluble degarelix pamoate in the microparticles according to the present invention may allow reducing hydrolysis and other undesired degradation pathways of the peptide associated with the presence of water. Moreover, initial burst release could be substantially reduced (see below). Still further, it was surprisingly found that the use of PLGA in combination with degarelix pamoate does not decrease, but enhances release of degarelix into the bloodstream. The continuous release can be upheld for at least 12 weeks following administration. Thus, despite using the same dose level of API as commercial degarelix acetate formulations, with the pharmaceutical composition according to the invention, an increase in relative bioavailability of degarelix could be achieved.

Accordingly, the present invention provides a clearly advantageous pharmaceutical composition. Possible embodiments and additional advantages will now be described in more detail.

As used herein, the term "microparticles" generally refers to monolithic particles with a size of from about 1 μm to about 1 mm. In some embodiments, microparticles may have a size of from about 1 μm to about 200 μm . The microparticles may have an internal continuous biodegradable polymer matrix. The microparticles may be of any shape, including a spherical shape or irregular shape. The term encompasses microspheres and microgranules.

As used herein, "microgranules" are a subgroup of microparticles and are characterized as being non-spherical irregularly shaped monolithic microparticles formed from one or more biodegradable polymers or copolymers. Microgranules herein described generally have a size of less than 110 μm in diameter. They may particularly be obtained by a dry process, e.g. by extrusion and grinding.

As used herein, the term “microspheres” are a subgroup of microparticles and are characterized as being spherical or substantially spherical regularly shaped monolithic microparticles formed from one or more biodegradable polymers or copolymers. They may particularly be obtained by a wet process e.g., emulsion and precipitation.

The microparticles according to the invention comprise a biodegradable copolymer of lactide units and glycolide units (PLGA, also referred to as poly(lactic-co-glycolic acid)). In certain embodiments, PLGA may be poly D, L-lactide-co-glycolide copolymer.

The term “biodegradable copolymer” as used herein, means a copolymer or a mixture of copolymers that are degraded *in vivo* enzymatically and/or non-enzymatically to produce biocompatible degradation products that can be further metabolized by humans and animals. Biodegradation may be triggered in response to contact with bodily fluid e.g., after injection into a patient. In some aspects, the PLGA copolymer may be degraded via hydrolysis in response to contact with bodily fluid after administration, e.g. injection, into a patient.

According to the invention, the microparticles contain at least 50 wt% PLGA. In some embodiments, the microparticles may contain from about 55 to about 75 wt% PLGA, from about 60 to about 70 wt% PLGA, or from about 60 to about 65 wt% PLGA. In certain preferred embodiments, the microparticles may contain from about 60 to about 65 wt% PLGA.

PLGA can generally be prepared at different ratios between its constituent monomers lactic acid and glycolic acid. Within the copolymer, reference is made to lactide units and glycolide units. PLGA according to the invention may be linear or branched, hyperbranched, comb-like branched, dendrimer-like branched, T-shaped, star-shaped, or any mixture thereof. In particular, PLGA may be linear PLGA. In certain embodiments, the PLGA may be a linear polyester with random order of lactide units and glycolide units. The molar ratio of lactide units to glycolide units can generally be in a range of about 70:30 to about 90:10, particularly from about 75:25 to about 85:15.

In certain embodiments, the molar ratio of lactide units to glycolide units may be about 75:25, about 80:20, or about 85:15.

5 In some embodiments, the PLGA comprises less than about 5% of residual lactide and/or glycolide monomer. In some embodiments, the initial residual monomer content is from 0% to about 5%, or from 0% to about 3%. In particular, the PLGA may be free from residual lactide and/or glycolide monomer, i.e., have 0% initial residual lactide and/or glycolide monomer content. In exemplary embodiments, the PLGA has 0% initial residual lactide and glycolide monomer content.

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The end groups of PLGA used according to the invention are not limited. Examples of possible end groups include hydroxy, ester (e.g., stearyl), acidic (e.g., carboxy), or the like.

15 In certain embodiments of the invention the end groups of PLGA may be acidic and preferably may be carboxy groups, i.e. the PLGA is "acid-terminated".

20 In some embodiments, the biodegradable polymer microgranules of the pharmaceutical compositions described herein comprise a PLGA having a molecular weight (M_n) of about 20,000 g/mol to about 50,000 g/mol and/or (M_w) of about 30,000 g/mol to about 80,000 g/mol.

The molar ratio of lactide units to glycolide units of PLGA can be measured by using conventional methods, for example Nuclear Magnetic Resonance (^1H NMR).

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Nonlimiting examples of commercially available PLGA sources include RESOMER[®] by Evonik, LACTEL[®] (by Evonik), MEDISORB[®] by Evonik, PURASORB[®] by Corbion, and Expansorb[®] by Seqens.

30 According to the invention, the pharmaceutical composition contains the API degarelix in the form of a pharmaceutically acceptable salt thereof, i.e. in the form of the pamoate salt. To facilitate calculations, the amounts herein are expressed in "free base equivalents" or correspond to the amount of degarelix free base. It is to be

understood that the actual amount of the degarelix in pamoate form is higher than the amount of degarelix in free base form, due to the weight of the pamoate salt.

5 The term “drug loading” as used herein, which is sometimes used interchangeably with the term “core loading”, refers to the weight ratio (presented as a percentage) of the degarelix free base to the total mass of the biodegradable polymer microparticles (BPM) i.e., as expressed by the following equation:

$$\text{Drug loading (DL\%)} = m(\text{degarelix}) / m(\text{BPM}) \times 100$$

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with m(degarelix) representing the mass of the degarelix and m(BPM) representing the mass of biodegradable polymer microparticles.

15 The pharmaceutical composition described herein generally has a drug loading, based upon degarelix free base, of about 20 wt% to about 34 wt%, i.e. the PLGA microparticles contain about 20 wt% to about 34 wt% degarelix free base equivalents. In some embodiments, the drug loading of degarelix pamoate, based on degarelix free base, may be about 20 wt%, about 21 wt%, about 22 wt%, about 23 wt%, about 24 wt%, about 25 wt%, about 26 wt%, about 27 wt%, about 28 wt%, about 29 wt%, about 20 wt%, about 31 wt%, about 32 wt%, about 33 wt%, or about 34 wt%. In certain 20 embodiments, the PLGA microparticles may contain from about 28 wt% to about 33 wt% degarelix free base equivalents. In exemplary embodiments, the PLGA microparticles contain about 28 wt%, about 30 wt%, or about 33 wt% degarelix free base equivalents. According to a non-limiting example, PLGA microparticles according 25 to the invention contain about 30 wt% degarelix free base equivalents.

In the case of using degarelix pamoate, i.e. a pharmaceutically acceptable salt of GnRH antagonist, the weight ratio may be calculated on the basis of the weight of a molar amount of degarelix free base, which is the same molar amount as degarelix 30 pamoate comprised in the biodegradable polymer microparticles.

Drug loading can be measured using conventional methods, for example using high performance liquid chromatography (HPLC). For instance, an appropriate weight, e.g.

20 mg, of the biodegradable polymer microparticles can be weighed, dissolved in dimethyl sulfoxide (DMSO), and the sample can be analysed by HPLC assay.

The present invention further relates to a pharmaceutical composition comprising
5 degarelix in the form of a pharmaceutically acceptable pamoate salt as an active
pharmaceutical ingredient, wherein the degarelix pamoate salt is contained in
microparticles of a biodegradable copolymer of lactide units and glycolide units
(PLGA), wherein the microparticles contain at least 50 wt% PLGA and from about 20
wt% to about 34 wt% degarelix free base equivalents, and wherein the composition
10 releases degarelix continuously and significantly, with a limited burst, to achieve a
therapeutic effect within 14 days of administration, and maintain such effect for a
period of at least 12 weeks after administration.

As used herein, the term "therapeutic effect" means that a chemical castration of the
15 patient is achieved. Upon therapy with GnRH agonists or antagonists, serum
testosterone levels of equal to or less than 50 ng/dL, i.e. ≤ 0.5 ng/mL (1.735 nmol/L)
are considered chemical castration. These levels should be achieved within 14 days
of administration of the API and maintained until administration of the next API dose.
According to the invention, serum testosterone levels ≤ 0.5 ng/mL are achieved within
20 14 days of administration and maintained for a period of at least 12 weeks after
administration.

In some embodiments, serum testosterone levels ≤ 0.5 ng/mL may be achieved within
7 days of administration and maintained for a period of at least 12 weeks after
25 administration. In some embodiments, serum testosterone levels ≤ 0.5 ng/mL may be
achieved within 3 days of administration and maintained for a period of at least 12
weeks after administration.

In some embodiments, serum testosterone levels < 0.5 ng/mL may be achieved within
30 14 days of administration and maintained for a period of at least 12 weeks after
administration. In some embodiments, serum testosterone levels < 0.5 ng/mL may be
achieved within 7 days of administration and maintained for a period of at least 12
weeks after administration. In some embodiments, serum testosterone levels < 0.5

ng/mL may be achieved within 3 days of administration and maintained for a period of at least 12 weeks after administration.

In some embodiments, even serum testosterone levels of equal to or less than 20 ng/dL, i.e. ≤ 0.2 ng/mL (0.69 nmol/L) may be achieved within 14 days of administration and maintained for a period of at least 12 weeks after administration. In some embodiments, serum testosterone levels of equal to or less than 20 ng/dL, i.e. ≤ 0.2 ng/mL (0.69 nmol/L) may be achieved within 7 days of administration and maintained for a period of at least 12 weeks after administration. In some embodiments, serum testosterone levels of equal to or less than 20 ng/dL, i.e. ≤ 0.2 ng/mL (0.69 nmol/L) may be achieved within 3 days of administration and maintained for a period of at least 12 weeks after administration.

As used herein, the term "releases continuously" means that at any time during at least 12 weeks after administration, there is a significant release of degarelix from the composition; there is no interruption in release (i.e. no time interval(s) where release from the composition is zero), which would be defined as "releases intermittently".

As used herein, the term "releases significantly" means that a degarelix threshold level of > 3.0 ng/mL in plasma is maintained over at least 12 weeks.

In some embodiments, the pharmaceutical composition according to the present invention may release degarelix above a threshold level of 8.0 ng/mL (i.e., > 8.0 ng/mL), or above a threshold level of 9.0 ng/mL (> 9.0 ng/mL) in plasma, and this threshold level is maintained over at least 12 weeks.

"Dose normalization" is a common calculation performed with pharmacokinetic parameters. The general process is to divide the PK parameters by the administered dose. This may be done for each individual or treatment group in a study, and then comparisons of dose-normalized parameters can be performed.

"Burst" or "initial burst" is a phenomenon in release kinetics known for most PLGA microparticle formulations. It refers to a strong initial release of the API which may consume up to, e.g., 50% of the total API administered in the first few days after

administration, such as from day 1 to day 7 post administration, or from day 1 to day 3 post administration. This poses, *inter alia*, a serious toxicity threat for treated subjects and leads to low remaining drug loading for the rest of the treatment time. The present inventors surprisingly have found that the pharmaceutical composition according to the invention shows, upon administration, a substantially lower dose normalized burst than that observed for a marketed 12-week degarelix acetate formulation (Gonax®), and for a marketed 1-month degarelix acetate formulation (Firmagon®). As used herein, the term “substantially lower” means at least about 25% lower. The burst can for example be determined by measuring the *in vivo* API (drug) concentration in plasma. According to the invention, the average degarelix plasma concentration from day 1 to day 7 post administration may be less than 100 ng/mL, corresponding to a “limited burst” (also referred to as “low burst”) herein. In particular embodiments, the average degarelix plasma concentration from day 1 to day 7 post administration may be less than 80 ng/mL, less than 60 ng/mL, less than 50 ng/mL, less than 40 ng/mL, or less than 30 ng/mL. In other embodiments, the average degarelix plasma concentration from day 1 to day 3 post administration may be less than 100 ng/mL, less than 80 ng/mL, less than 60 ng/mL, less than 50 ng/mL, less than 40 ng/mL, or less than 30 ng/mL.

In some embodiments according to the invention the mean degarelix maximum concentration (C_{max}) in plasma after administration may be less than 120 ng/mL, less than 100 ng/mL, less than 80 ng/mL, less than 60 ng/mL, less than 50 ng/mL, less than 40 ng/mL or less than 30 ng/mL. In exemplary embodiments, it may be possible to have a mean C_{max} of degarelix in plasma of less than 40 ng/mL.

In some embodiments, the PLGA microparticles of the pharmaceutical composition according to the invention may have a particle size distribution defined as

- D (v,0.1) of from about 5 to about 22 µm
- D (v,0.5) of from about 25 to about 45 µm
- D (v,0.9) of from about 55 to about 90 µm.

In this context, “D (v,X)” means that X·100% of the volume of a biodegradable polymer microparticle sample is below the indicated diameter value. For instance, a D (v,0.5)

of 40 μm means that 50% of the volume of the biodegradable polymer microparticle sample is below 40 μm in diameter e.g. 10 μm , 20 μm , 30 μm , in diameter. The $D(v,X)$, e.g. $D(v,0.5)$, may be determined by wet laser diffraction e.g., as described in the European pharmacopoeia V11.3 chapter 2.9.31. The particle size measurement
5 may be conducted by wet laser diffraction, e.g., using a Malvern Mastersizer 3000 equipped with a Hydro Medium Volume (MV) dispersion unit. For example, the biodegradable polymer microparticles may be suspended (at room temperature, i.e. 20-25°C) in an aqueous based medium comprising a surfactant e.g., polysorbate 80 (0.1%), the sample may then be dispersed in purified water in a hydro MV dispersion
10 unit (Stirring speed 2000 rpm) until reaching an obscuration between 10% and 20%. Following this, the sample undergoes ultra-sonification for 2 min (hydro MV dispersion unit setting medium (50%)), the sample is then analyzed using a Malvern Mastersizer 3000. Results are calculated based on the Mie theory (real particle refractive index of 1.52 and imaginary particle refractive index of 0.001). The “analysis model general
15 purpose” may be used. $D(v,0.5)$ is also sometimes noted $Dv50$, $D(v,0.1)$ is also sometimes noted $Dv10$, $D(v,0.9)$ is also sometimes noted $Dv90$.

The biodegradable polymer microparticles, e.g., biodegradable polymer microgranules, comprised in the pharmaceutical composition of the invention may
20 have a median particle size, i.e. a $D(v,0.50)$, of from about 25 to about 45 μm , e.g., 25 μm to 45 μm or about 25 μm to about 40 μm .

Said biodegradable polymer microparticles may also additionally have one or more of the following particle size values:

- 25
- a $D(v,0.9)$ of from about 55 to about 90 μm , such as 55 μm to 90 μm , or about 60 μm to about 90 μm ;
 - a $D(v,0.1)$ of from about 5 to about 22 μm , such as 5 μm to 22 μm , or about 5 μm to about 15 μm .

30 In some embodiments, the pharmaceutical composition may consist of a single group of biodegradable microparticles as defined herein. A “single group” in this context means that all microparticles have essentially the same characteristics, for instance with regard to particle size distribution, PLGA polymer properties, etc.

As used herein, the “inherent viscosity” of a biodegradable polymer (e.g., PLGA) is based on the flow time of the biodegradable polymer in solution (polymer solubilized in a given solvent) through a narrow capillary relative to the flow time of the pure solvent through the same capillary. According to IUPAC, the inherent viscosity is defined as the ratio of the natural logarithm of the relative viscosity to the mass concentration of the polymer. The inherent viscosity of a biodegradable polymer (e.g., PLGA) may be measured using conventional methods e.g., The Capillary Viscometer Method as described in “European Pharmacopoeia”, V11.3, chapter 2.2.9. For example, the inherent viscosity of a polymer can be measured at a concentration of 0.5g/dL in chloroform at 30°C, e.g. using a Cannon-Fenske Routine size25 viscometer.

As used herein, the “initial inherent viscosity” (i.v.) of a biodegradable polymer (e.g., PLGA) refers to the inherent viscosity of the biodegradable polymer as a starting material, i.e. before it enters into a process of preparation of microparticles. According to some embodiments of the invention, the initial inherent viscosity (i.v.) of the PLGA may be from about 0.3 dL/g to about 0.5 dL/g. In particular embodiments, the initial i.v. of the PLGA may be from about 0.35 dL/g to about 0.45 dL/g. In particular embodiments, the initial i.v. of the PLGA may be from about 0.39 dL/g to about 0.45 dL/g, e.g. with the objective to get a resulting average i.v. of 0.42 dL/g. According to exemplary embodiments, the initial i.v. of the PLGA is about 0.30 dL/g, or about 0.40 dL/g, or about 0.42 dL/g, or about 0.50 dL/g. Sometimes, reference herein is made to “short” PLGA. A short PLGA corresponds to a PLGA with a low initial i.v., such as 0.4 dL/g.

The inventors have surprisingly found that use of short PLGA (e.g. initial inherent viscosity about 0.4 dL/g) in the pharmaceutical composition according to the invention can enhance the peptide release over time.

As understood by the skilled person, the inherent viscosity and molar ratio of lactide to glycolide of PLGA are an average over a certain range, e.g., indicated in the specifications of the manufacturers of PLGA.

Any PLGA having the required attributes, e.g., molar ratio of lactide to glycolide and inherent viscosity, as set out herein, may be comprised in the biodegradable polymer defined herein, i.e. the biodegradable polymer used to form the biodegradable polymer microparticles defined herein and comprised in the pharmaceutical composition of the invention.

The pharmaceutical composition described herein may be a composition of dried biodegradable PLGA microparticles as described herein, e.g. PLGA microgranules, ready for suspension in a liquid vehicle prior to administration, or the pharmaceutical composition described herein may already further comprise a liquid vehicle. In some embodiments, the pharmaceutical compositions described herein can be in the form of a suspension, such as a ready to use suspension comprising a liquid vehicle and the PLGA microparticles described herein. The liquid vehicle in the pharmaceutical compositions described herein can be an aqueous (water-based) or an oily vehicle.

In some embodiments, water is the main ($\geq 50\%$ (w/v)) component of the aqueous vehicle. In some embodiments, the aqueous vehicle comprises more than 50%, more than 55%, more than 60%, more than 65%, more than 70%, more than 75%, more than 80%, more than 85%, more than 90%, more than 91%, more than 92%, more than 93%, more than 94%, more than 95%, more than 96%, more than 97%, more than 98%, more than 99%, or 100% water. These percentage indications are (w/v) percentages.

In some embodiments, the aqueous vehicle may contain additional pharmaceutical excipients. The additional excipients can be used to ensure isotonicity and to improve the wettability and non-sedimentation properties of the microspheres. Examples of pharmaceutical excipients include, but are not limited to, mannitol, sodium chloride, glucose, dextrose, sucrose, or glycerines, non-ionic surfactants e.g., poloxamers, poly(oxyethylene)-sorbitan-fatty acid esters, carboxymethyl cellulose sodium (CMC-Na), sorbitol, poly(vinylpyrrolidone), or aluminium monostearate, polyethylene glycol (PEG) e.g., PEG 4000.

Where the vehicle is a non-aqueous vehicle, particularly an oily or lipidic vehicle, it is substantially free from water or (completely) free from water. "Oily vehicle" and "lipidic

vehicle” are used interchangeably herein. Accordingly, the oily vehicle may, e.g., comprise 0.25% (w/v) water or less, 0.1% water or less, or 0.05% (w/v) water or less.

5 The water content of the non-aqueous vehicle can be measured using conventional methods e.g., the method “Water: Micro Determination” as described in “European Pharmacopoeia”, V11.3, chapter 2.5.32.

10 The oily vehicle can be a pharmaceutically acceptable oil or any mixture thereof. In preferred embodiments, the oil may be in a viscous liquid state at ambient temperature (20°C-25°C), or slightly warmer (up to 30°C or up to standard mammalian body temperature, i.e. 37°C), and is both hydrophobic (immiscible with water) and lipophilic (miscible with other oils). Nonlimiting examples of suitable oils include vegetable oils e.g., coconut oil, palm oil, palm kernel oil, sesame oil, soybean oil, almond oil, rapeseed oil, corn oil, sunflower oil, peanut oil, olive oil, castor oil, soybean oil, 15 safflower oil, cottonseed oil, ethyl oleate, and any combinations thereof.

In some embodiments, the oily vehicle may comprise or consist of medium-chain triglycerides (MCTs). In certain embodiments, the oily vehicle is a mixture of medium-chain triglycerides. As used herein, “MCTs” are glyceride esters formed from glycerol 20 and three medium chain fatty acids; each of the three medium chain fatty acids being a C6 to C12 fatty acid, i.e. a carboxylic acid with an aliphatic chain of 6 to 12 carbon atoms e.g., C6 (for example hexanoic acid), C8 (for example octanoic acid), C10 (for example decanoic acid), C12 (for example dodecanoic acid). The three medium chain fatty acids from which the triglyceride is formed can all be the same, e.g., all three may 25 be medium chain fatty acids with aliphatic chains of, for example, 8 or 10 carbon atoms, or one or all of the medium chain fatty acids can be different from the others. The aliphatic chains of the MCTs can be saturated or unsaturated.

30 In some embodiments, the oily vehicle may essentially consist of C8 and/or C10 medium chain triglycerides. In certain embodiments, the oily vehicle may be a mixture of C8/C10 triglycerides, a mixture of C8 triglycerides, or a mixture of C10 triglycerides. In some embodiments, the pharmaceutical composition comprises MCT that are at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% saturated.

In certain embodiments, the oily vehicle may be a mixture of C8/C10 triglycerides, a mixture of C8 triglycerides, or a mixture of C10 triglycerides, wherein all the C8 fatty acids and C10 fatty acids present are saturated fatty acids. Exemplary saturated fatty acids for use according to the invention are caprylic acid ($\text{H}_3\text{C}-(\text{CH}_2)_6-\text{COOH}$) and capric acid ($\text{H}_3\text{C}-(\text{CH}_2)_8-\text{COOH}$). In exemplary embodiments, the oily vehicle is a mixture substantially (e.g. $\geq 90\%$, $\geq 95\%$, $\geq 96\%$, $\geq 97\%$, $\geq 98\%$, or $\geq 99\%$) consisting of triglycerides of caprylic acid and capric acid. In some embodiments, the oily vehicle is a mixture consisting of triglycerides of caprylic acid and capric acid.

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In some embodiments, the oily vehicle may consist of 50% to 80% of C8 MCTs, and 20% to 50% C10 MCTs, such as 58% C8 MCTs and 41% C10 MCTs as it is present in MIGLYOL® 812 mentioned below. The MCT content of the oil is measured by GC in accordance with the method set out in "European Pharmacopoeia", V11.3, chapter 2.4.22, without further conversion.

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Non-limiting examples of MCTs that may be used as an oily vehicle in the pharmaceutical compositions according to the invention include MIGLYOL® 810, 812, 818 (Sasol Germany GmbH, Witten, Germany). In exemplary embodiments, the oily vehicle is MIGLYOL® 812, for example MIGLYOL® 812 N.

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The inventors have found that use of an oily vehicle with the pharmaceutical composition according to the invention can significantly increase the peptide release over time as compared to other vehicles.

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In some embodiments, the pharmaceutical composition as described herein may be a suspension in an oily vehicle. In some embodiments, the pharmaceutical composition as described herein may be a suspension in a mixture of MCTs as defined above. In some embodiments, the pharmaceutical composition as described herein may be a suspension in a mixture of C8 and/or C10 triglycerides (C8/C10 triglycerides) as defined above. In some embodiments, the pharmaceutical composition as described herein may be a suspension in a mixture of triglycerides of saturated C8 and/or C10 fatty acids as defined above. In some embodiments, the pharmaceutical composition as described herein may be a suspension in a mixture substantially consisting of or

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consisting of caprylic acid and capric acid. In exemplary embodiments, the pharmaceutical composition as described herein may be a suspension in an oily vehicle, wherein the oily vehicle is MIGLYOL® 812, such as MIGLYOL® 812 N.

- 5 The concentration of the microparticles within the suspension can vary to a certain extent according to the invention. In some embodiments, the concentration of microparticles as defined herein, such as microgranules as defined herein, within the suspension may be from about 150 mg/mL to about 350 mg/mL. In certain preferred
- 10 about 180 mg/mL to about 300 mg/mL. Accordingly, in some embodiments, the pharmaceutical composition may be a suspension comprising the biodegradable PLGA microparticles as defined herein in a concentration of about 150 mg/mL to about 350 mg/mL, about 180 mg/mL to about 300 mg/mL, such as about 180 mg/mL, about 200 mg/mL, about 250 mg/mL, or about 300 mg/mL.

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It is further encompassed by the invention that the molar ratio of degarelix base to pamoate can have some variation. Accordingly, in some embodiments, the molar ratio of degarelix base to pamoate may be from about 1:1 to about 2:1.

- 20 The pharmaceutical composition described herein may additionally comprise one or more other pharmaceutical excipients e.g., pharmaceutical excipients ordinarily comprised in the type of formulation described herein. Such pharmaceutical excipients include, but are not limited to diluents, surfactants, stabilizers, release modifiers, preservatives, antioxidants, buffers, anti-agglomerating agents and the like.

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- Non-limiting examples of other pharmaceutical excipients that can be included in the pharmaceutical composition described herein include polyvinylalcohol, polyvinyl pyrrolidone, carboxymethyl cellulose sodium (CMC-Na), dextrin, polyethylene glycol, suitable surfactants such as poloxamers, also known as poly(oxyethylene-block-
- 30 oxypropylene), Poly(oxyethylene)-sorbitan-fatty acid esters known and commercially available under the trade name TWEEN® (e.g., Tween 20, Tween 40, Tween 60, Tween 80, Tween 65 Tween 85, Tween 21, Tween 61, Tween 81), Sorbitan fatty acid esters, e.g. of the type known and commercially available under the trade name SPAN®, Lecithins, inorganic salts such as zinc carbonate, magnesium hydroxide,

magnesium carbonate, or protamine, e.g., human protamine or salmon protamine, or natural or synthetic polymers bearing amine-residues such as polylysine, hydroxyethyl cellulose (HEC) and/or hydroxypropyl cellulose (HPC), Polyvinyl pyrrolidone), and gelatine, e.g. porcine or fish gelatine. Suitable anti-agglomerating agents include, for example, mannitol, glucose, dextrose, sucrose, sodium chloride, or water-soluble polymers such as polyvinyl alcohol, polyvinyl pyrrolidone or polyethylene glycol.

According to the invention, it is preferred that the pharmaceutical composition does not contain trehalose as an excipient, i.e. it is free from trehalose.

The term "administering", as used herein, refers to any mode of transferring, delivering, introducing, or transporting a therapeutic agent to a subject in need of treatment with such an agent. Such modes of administration include, but are not limited to, parenteral administration.

In some aspects, the pharmaceutical composition described herein can be administered to a subject (e.g., a human) parenterally. As used herein, the term "subject" refers to an animal, including, but not limited to, a primate (e.g., human), cow, sheep, goat, horse, dog, cat, rabbit, rat, or mouse. The terms "subject" and "patient" are used interchangeably herein in reference, for example, to a mammalian subject, such as a human subject.

Parenteral administration in the context of the invention may be subcutaneous (abbreviated s.c. or SC herein) administration or intramuscular (abbreviated i.m. or IM herein) administration. In some embodiments, parenteral administration may be via injection, in particular subcutaneous injection or intramuscular injection. In exemplary embodiments, a pharmaceutical composition according to the invention is administered via intramuscular injection.

The inventors have found that with an i.m. administration of the pharmaceutical composition according to the invention, a better exposure to the API can be achieved.

The pharmaceutical composition described herein comprises degarelix pamoate, i.e. a pamoate salt of the API. It is preferred according to the invention that the

pharmaceutical composition does not comprise metal salts of pamoate, such as alkali and earth alkali pamoate salts. Accordingly, it is preferred that the pharmaceutical composition according to the invention is free from alkali and earth alkali pamoate salts, i.e. it contains 0.01 wt% or less, 0.001 wt% or less, or 0.0001 wt% or less of any such salt.

As described, the pharmaceutical composition according to the invention is formulated such that degarelix is continuously and significantly released from the microparticles for a period of at least 12 weeks. In some embodiments, degarelix may be continuously and significantly released from the microparticles for even longer periods of time, for example for a period of at least 16 weeks, a period of at least 20 weeks, or a period of at least 24 weeks.

In specific exemplary embodiments, the pharmaceutical composition according to the invention comprises degarelix in the form of a pamoate salt, wherein degarelix pamoate is contained in PLGA microparticles, wherein the microparticles contain from about 60 to about 65 wt% PLGA and from about 28 to about 33 wt% degarelix base equivalents, wherein the PLGA has a molar ratio of lactide to glycolide units of about 75:25 and an initial inherent viscosity of from about 0.35 to 0.45 dL/g, such as about 0.42 dL/g, wherein the microparticles are microgranules having a particle size distribution defined as:

- D (v,0.1) of from about 5 to about 15 μm
- D (v,0.5) of from about 25 to about 40 μm
- D (v,0.9) of from about 60 to about 90 μm .

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A further advantage of the sustained release pharmaceutical composition of the invention is that only biodegradable PLGA microparticles as defined herein are needed in the pharmaceutical composition to achieve one or more of:

- a sustained release over 12 weeks or more, or even 16 weeks or more,
- a low initial release (burst), and
- a surprisingly high bioavailability of the degarelix pamoate for a sustained release formulation,

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following administration to a subject.

The present invention also relates to medical uses of a pharmaceutical composition comprising degarelix in the form of a pamoate salt, wherein the degarelix pamoate salt is contained in microparticles of a biodegradable copolymer of lactide units and glycolide units (PLGA) and wherein the microparticles contain at least 50 wt% PLGA and from about 20 wt% to about 34 wt% degarelix free base equivalents. Specific
5 embodiments of the pharmaceutical composition according to the invention are described hereinabove.

As used herein, the terms "treat," "treated," and "treating" mean both therapeutic
10 treatment and prophylactic or preventative measures wherein the object is to prevent or slow down (lessen) an undesired physiological condition, disorder, or disease, or obtain beneficial or desired clinical results. Thus, those in need of treatment include those already diagnosed with or suspected of having the disorder. Beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of
15 the extent of a condition, disorder, or disease; stabilized (i.e., not worsening) state of condition, disorder, or disease; delay in onset or slowing of condition, disorder, or disease progression; amelioration of the condition, disorder, or disease state or remission (whether partial or total), whether detectable or undetectable; an amelioration of at least one measurable physical parameter, not necessarily
20 discernible by the patient; or enhancement or improvement of condition, disorder, or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment.

Accordingly, the invention relates to a pharmaceutical composition as described
25 herein for use in the treatment of prostate cancer.

The pharmaceutical composition according to the invention is particularly suitable for treating prostate cancer. "Prostate cancer" is particularly understood to mean an adenocarcinoma of the prostate gland. Treatment may be at all stages of prostate
30 cancer upon confirmed diagnosis. In some embodiments, treatment may relate to treatment of advanced prostate cancer, with the aim of delaying or stopping cancer growth. In some embodiments, treatment may relate to treatment of locally advanced/metastatic prostate cancer.

The present invention further relates to a pharmaceutical composition comprising degarelix pamoate in PLGA microparticles as defined herein for use in extending the duration of exposure to degarelix in the treatment of prostate cancer in a patient.

5 "Extending the duration of exposure" in this context means that the therapeutic effect of a single administration of a pharmaceutical composition of degarelix according to the present invention may be longer than when using other degarelix formulations, e.g. commercially available 1- and/or 3-months formulations.

10 The invention also relates to a method for treating prostate cancer, comprising administering an effective amount of the pharmaceutical composition as described herein to a subject in need thereof.

In the context of medical uses of the pharmaceutical composition according to the invention, i.e. a pharmaceutical composition for use in the treatment of prostate cancer
15 or a method for treating prostate cancer, the composition may be prepared in a way that it can be administered parenterally. As already mentioned, parenteral administration may be subcutaneous (s.c.) administration or intramuscular (i.m.) administration. In some embodiments parenteral administration may be via injection,
20 in particular subcutaneous injection or intramuscular injection. In exemplary embodiments, a pharmaceutical composition according to the invention for use in the treatment of prostate cancer or for use in extending the duration of exposure to degarelix in the treatment of prostate cancer is administered via intramuscular injection. In some embodiments i.m. injection is selected as administration route and
25 combined with a pharmaceutical composition according to the invention suspended in an oily vehicle. This combination has surprisingly been found to provide additional advantages regarding pharmacokinetic performance (as compared to other administration routes and/or other vehicles).

30 The pharmaceutical composition for the medical uses as described herein can be provided in an injection device, e.g. a syringe e.g., ready for injection, e.g. intramuscular injection. For subcutaneous or intramuscular administration, e.g. injection, of PLGA microparticles relatively large needle diameters, due to broad particle-size distributions have been traditionally used. In embodiments of the

invention, the pharmaceutical composition for the medical use as described herein may be for i.m. injection via a needle of size G18 to G21. Needle size is also referred to as "needle gauge". In certain preferred embodiments, the needle size for medical uses of the pharmaceutical composition as described herein may be G18 to G20,
5 corresponding to a nominal inner diameter of about 0.8 mm (G18) to about 0.6 mm (G20).

The amount of API for administration per dose may also vary within certain limits according to the invention. According to some embodiments, degarelix may be for
10 administration in an amount of from about 200 mg to about 360 mg free base equivalents per dose. In certain embodiments, degarelix may be for administration in an amount of from about 200 mg to about 300 mg free base equivalents per dose. For example, the amount of degarelix free base equivalents per dose may be about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about
15 260 mg, about 270 mg, about 280 mg, about 290 mg, or about 300 mg.

According to some embodiments, the target amount of degarelix free base equivalents to be administered may exceed the available maximum amount of free base equivalents per dose. Accordingly, in some embodiments, degarelix may be for
20 administration in two administration steps, e.g. two injections, such as two i.m. injections. In an exemplary embodiment, degarelix may be for administration in a maximum total amount of 600 mg free base equivalents in two injections. In another exemplary embodiment, degarelix may be for administration in a maximum total amount of 400 mg free base equivalents in two injections.

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The API-containing microparticles (degarelix pamoate) may, for administration, be suspended in a liquid vehicle, e.g. an oily vehicle, as described above. For reasons of patient compliance, a small administration (e.g., injection) volume is desirable. Accordingly, it is encompassed by the invention that in some embodiments the
30 administration volume may be less than or equal to about 6 mL, in particular less than about 4 mL, such as less than about 4.0 mL. In certain embodiments, the administration volume of the pharmaceutical composition as described herein may be from about 2.0 mL to about 3.5 mL. In exemplary embodiments, the administration

volume of the pharmaceutical composition as described herein is about 2.2 ml, or about 3.0 ml, or about 3.3 ml.

For example, according to some embodiments, a pharmaceutical composition for a
5 medical use as described herein may comprise about 200 mg or 300 mg degarelix
free base equivalents per milliliter of suspension.

The pharmaceutical composition described herein may be administered to a subject
(e.g., a human) in need thereof that has not been previously treated for the disease or
10 disorder for which the pharmaceutical composition is administered (e.g., prostate
cancer), i.e. the patient is a treatment-naïve patient.

Alternatively, the pharmaceutical composition described herein may be administered
to a subject (e.g., a human) in need thereof that has been previously treated for the
15 disease or disorder (e.g., prostate cancer).

In some aspects, the subject (e.g., a human) in need thereof that has been previously
treated for the disease or disorder for which the pharmaceutical composition is
administered (e.g., prostate cancer), has been treated with a pre-loading dose. In
20 some aspects, the subject (e.g., a human) in need thereof that has been previously
treated for the disease or disorder for which the pharmaceutical compositions are
administered (e.g., prostate cancer), has been treated for at least one month, at least
two months, at least three months, at least four months, at least six months, at least
one year for example. The subject may have been previously treated for example with
25 a GnRH agonist, GnRH antagonist or GnRH analog.

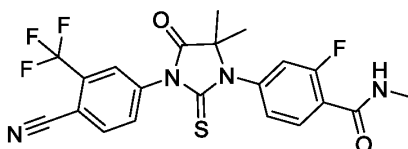
In some aspects, the subject (e.g., a human) in need thereof that has been previously
treated for the disease or disorder for which the pharmaceutical composition is
administered (e.g., prostate cancer), may previously have undergone androgen
30 deprivation therapy (ADT). ADT is understood to block the production of testosterone.
Exemplary active pharmaceutical ingredients that may be used in ADT are LHRH
agonists and antagonists, including leuporelin (leuprolide), goserelin, triptorelin,
histrelin, buserelin, and degarelix. Accordingly, the subject (e.g., a human) in need
thereof that has been previously treated for the disease or disorder for which the

pharmaceutical composition is administered (e.g., prostate cancer), may previously have been treated with leuporelin (leuprolide), goserelin, triptorelin, histrelin, buserelin or degarelix. ADT may have been performed according to established administration protocols in accordance with the terms of market authorization.

5

In some aspects, the subject (e.g., a human) in need thereof that has been previously treated for the disease or disorder for which the pharmaceutical composition is administered (e.g., prostate cancer), may previously have been treated with an androgen receptor inhibitor (ARI). ARIs disturb the interaction of testosterone and cancer cells. Exemplary ARIs are enzalutamide, abiraterone, apalutamide, darolutamide, bicalutamide, clascoterone, flutamide and nilutamide. Accordingly, the subject (e.g., a human) in need thereof that has been previously treated for the disease or disorder for which the pharmaceutical composition is administered (e.g., prostate cancer), may previously have been treated with enzalutamide, abiraterone, apalutamide, darolutamide, bicalutamide, clascoterone, flutamide or nilutamide. Treatment with ARIs may have been performed according to established administration protocols in accordance with the terms of market authorization.

In exemplary embodiments, the subject is a human subject having prostate cancer and has been previously treated with enzalutamide. Enzalutamide is a nonsteroidal antiandrogen medication which is used in the treatment of prostate cancer. The chemical structure of enzalutamide is shown below:



In some aspects, ARIs may also be used in combination with the pharmaceutical composition of the present invention. According to certain embodiments, the pharmaceutical composition described herein is for use in a combination therapy with an ARI, particularly an ARI selected from the groups consisting of enzalutamide, abiraterone, apalutamide, darolutamide, bicalutamide, clascoterone, flutamide and nilutamide. In exemplary embodiments, the pharmaceutical composition described herein is for use in a combination therapy with enzalutamide, wherein enzalutamide

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particularly is for administration according to established administration protocols in accordance with the terms of market authorization.

5 The pharmaceutical composition described herein can be administered as often as necessary, for example depending on the sustained release period of the composition. Due to its advantageous release properties, the pharmaceutical composition may be for administration once every 12 weeks (three months).

10 In exemplary embodiments, the pharmaceutical composition described herein is for administration in a total amount of about 200 mg degarelix free base equivalents, particularly 200 mg degarelix free base equivalents, every 12 weeks (3 months) in a single dose via i.m. administration, particularly i.m. injection. In further exemplary embodiments, the pharmaceutical composition described herein is for administration in a total amount of about 300 mg degarelix free base equivalents, particularly 300 mg
15 degarelix free base equivalents, every 12 weeks (3 months) in a single dose via i.m. administration, particularly i.m. injection.

In still further exemplary embodiments, the pharmaceutical composition described herein is for administration in a total amount of about 400 mg (particularly two doses
20 of 200 mg each) degarelix free base equivalents via i.m. administration, particularly i.m. injection as a loading dose. It is understood that the loading dose is for one-time administration at the start of the treatment. Subsequently, i.e. following administration of the loading dose, the pharmaceutical composition described herein is for administration as a maintenance dose in a total amount of about 200 mg degarelix
25 free base equivalents, particularly 200 mg degarelix free base equivalents, once every 12 weeks (3 months) in a single dose via i.m. administration, particularly i.m. injection, according to these exemplary embodiments.

It is also encompassed that the pharmaceutical composition described herein may be
30 for administration as a maintenance dose subsequent to a loading dose administration of another formulation comprising degarelix as active pharmaceutical ingredient in the form of degarelix acetate. For example, the pharmaceutical composition described herein may be for administration subsequent to a loading dose administration of a formulation of degarelix acetate marketed under the trade name Firmagon® or

Gonax®. Accordingly, in exemplary embodiments, degarelix acetate is for administration in a total amount of 240 mg (particularly two doses of 120 mg each) degarelix free base equivalents via s.c. administration, particularly s.c. injection, as a loading dose, followed by the pharmaceutical composition described herein, which is
5 for administration in a total amount of about 200 mg degarelix free base equivalents, particularly 200 mg degarelix free base equivalents, every 12 weeks (3 months) in a single dose via i.m. administration, particularly i.m. injection as a maintenance dose.

The pharmaceutical composition described herein may be administered in a dosing
10 regimen to achieve a desired hormonal suppression as compared with a subject to which the pharmaceutical composition described herein has not been administered, or as compared with a subject prior to administration of the pharmaceutical composition. Hormonal suppression can be assessed in various ways. For example, it can be determined whether the threshold for chemical castration is met. For prostate
15 cancer patients, in some embodiments, hormonal suppression can be characterized by testosterone suppression to castration levels, defined as serum testosterone ≤ 0.5 ng/mL. In some embodiments, hormonal suppression can be characterized by testosterone suppression to ≤ 0.2 ng/mL in serum.

20 After administration, e.g. s.c. or i.m. administration, e.g. injection, the API degarelix may be continuously released from the microparticles, thereby achieving the desired therapeutic effect. In certain embodiments, degarelix may be continuously released from the microparticles, thereby reaching and maintaining a mean plasma concentration of degarelix above a threshold of 3.0 ng/mL for a period of at least 12
25 weeks, or, in some embodiments, above a threshold of 8.0 ng/mL or 9.0 ng/mL for a period of at least 12 weeks. It is understood that the higher mean plasma concentrations (C_{max}) may be predominantly observed in the days immediately following administration.

30 In certain embodiments, degarelix may be continuously released from the microparticles, thereby reducing and maintaining serum testosterone levels to castration levels for a period of at least 12 weeks. In certain embodiments, degarelix may be continuously released from the microparticles, thereby reducing serum testosterone levels to less than or equal to 0.5 ng/mL (≤ 0.5 ng/mL) within 14 days of

administration, and maintaining serum testosterone levels ≤ 0.5 ng/mL for a period of at least 12 weeks from administration. In certain embodiments, degarelix may be continuously released from the microparticles, thereby reducing serum testosterone levels to less than or equal to 0.5 ng/mL (≤ 0.5 ng/mL) within 7 days of administration, and maintaining serum testosterone levels ≤ 0.5 ng/mL for a period of at least 12 weeks from administration.

In further embodiments, degarelix may be continuously released from the microparticles, thereby reducing serum testosterone levels to less than 0.5 ng/mL (< 0.5 ng/mL) within 14 days of administration, and maintaining serum testosterone levels < 0.5 ng/mL for a period of at least 12 weeks from administration. In certain embodiments, degarelix may be continuously released from the microparticles, thereby reducing serum testosterone levels to less than 0.5 ng/mL (< 0.5 ng/mL) within 7 days of administration, and maintaining serum testosterone levels < 0.5 ng/mL for a period of at least 12 weeks from administration. In certain embodiments, degarelix may be continuously released from the microparticles, thereby reducing serum testosterone levels to less than 0.5 ng/mL (< 0.5 ng/mL) within 3 days of administration, and maintaining serum testosterone levels < 0.5 ng/mL for a period of at least 12 weeks from administration.

In further embodiments, degarelix may be continuously released from the microparticles, thereby reducing serum testosterone levels to less than or equal to 0.2 ng/mL (≤ 0.2 ng/mL) within 14 days of administration, and maintaining serum testosterone levels ≤ 0.2 ng/mL for a period of at least 12 weeks from administration. In certain embodiments, degarelix may be continuously released from the microparticles, thereby reducing serum testosterone levels to less than or equal to 0.2 ng/mL (≤ 0.2 ng/mL) within 7 days of administration, and maintaining serum testosterone levels ≤ 0.2 ng/mL for a period of at least 12 weeks from administration. In certain embodiments, degarelix may be continuously released from the

microparticles, thereby reducing serum testosterone levels to less than or equal to 0.2 ng/mL (≤ 0.2 ng/mL) within 3 days of administration, and maintaining serum testosterone levels ≤ 0.2 ng/mL for a period of at least 12 weeks from administration.

- 5 As already mentioned above, the present inventors have surprisingly found that the pharmaceutical composition as described herein shows, upon administration to a subject, a strong sustained release with a low burst. In particular, the dose normalized burst is substantially lower than observed for a marketed 3-month degarelix acetate formulation (Gonax[®]), and, for a marketed 1-month degarelix acetate formulation
10 (Firmagon[®]). Accordingly, a pharmaceutical composition as described herein for use in the treatment of prostate cancer or a method for treating prostate cancer comprising administering a pharmaceutical composition as described herein may lead to an average degarelix plasma concentration from day 1 to day 7 post administration of less than 100 ng/mL, less than 80 ng/mL, less than 60 ng/mL, less than 50 ng/mL,
15 less than 40 ng/mL, or less than 30 ng/mL.

The invention further relates to a method for the preparation of a pharmaceutical composition as described herein (also referred to as “the preparation method” herein). The preparation method comprises mixing degarelix in the form of a pharmaceutically
20 acceptable pamoate salt, with a biodegradable copolymer of lactide units and glycolide units (PLGA). The mixing is also referred to herein as (a). Both components are weighed before mixing. It may for example be ensured that the degarelix pamoate starting material is free from metal salts of pamoic acid. It is also encompassed to mill, crush and/or sieve the components to start the method with more homogeneous
25 particles. If sieved, the components may for example be sieved using a mesh of 180 μm . Both degarelix pamoate and PLGA polymer may be in powder form to facilitate mixing. Mixing is performed until a homogeneous mixture of the two components is obtained.

- 30 The resulting mixture is then subjected to progressive heating and extrusion. The heating and extrusion is also referred to herein as (b). An exemplary method to perform (b) is hot melt extrusion. A commercially available extruder may be used, for example comprising a single screw or a double screw. The screw rotation speed and the temperature conditions may be adjusted to obtain a processable extrudate. For

example, in the context of the present invention, the temperature may range from about 50°C to about 100°C, such as about 80°C to about 90°C, and/or the screw rotation speed may range from about 50 to about 500 rpm, such as about 100 rpm.

- 5 The extrudate obtained after (b) is subsequently pelletized into pellets. Pelletization is also referred to herein as (c). For pelletization, a commercially available pelletizer may be used. The pellet size can be adjusted during processing, e.g. to a size of from 0.5 to 10 mm.
- 10 The pellets obtained after (c) are ground at low temperature. Low temperature may in particular be a temperature of 0°C or lower, such as from 0°C to about -100°C, for example about -80°C or about -100°C. Low temperature grinding is also referred to herein as (d). If desired, the microparticles obtained after grinding may be dried before being processed further.
- 15 After grinding, the obtained microparticles may be sieved to obtain a size of less than or equal to about 150 µm. Sieving is also referred to herein as (e). It is understood that in the method of preparation according to the invention, (a) to (d) are mandatory, whereas (e) to (h) are each optional, but may be advantageous. Sieving can be done
- 20 using a sieve with a mesh size that yields the desired particle sizes. In some embodiments, the sieve is a 106 µm sieve, although smaller or larger opening sizes such as about 50 µm or about 150 µm or any other value in the range of about 75 µm to about 106 µm can be used.
- 25 In particular embodiments, the microparticles resulting from the preparation method may for example have a particle size $D(v, 0.5)$ of about 25 to about 45 µm, such as about 25 to 40 µm. In specific embodiments, the particle size distribution of the microparticles may be as follows:
- $D(v, 0.1)$ of from about 5 to about 22 µm
 - 30 - $D(v, 0.5)$ of from about 25 to about 45 µm
 - $D(v, 0.9)$ of from about 55 to about 90 µm.

In further specific embodiments, the particle size distribution of the microparticles may be as follows:

- D (v,0.1) of from about 5 to about 15 μm
- D (v,0.5) of from about 30 to about 40 μm
- D (v,0.9) of from about 60 to about 90 μm .

5 The encapsulation efficiency of degarelix pamoate in the microparticles prepared by the method described herein may, in some embodiments, be from about 80% to about 99%, about 80% to about 95%, about 80% to about 90%, about 85% to about 99%, about 85% and about 95%, or about 90% and about 99%. In some embodiments, the encapsulation efficiency of degarelix pamoate in the microparticles prepared by the method described herein is about 80%, about 85%, about 90%, about 91%, about 10 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99%.

In embodiments, the preparation method may further comprise drying the microparticles obtained, after (d) or after (e), and/or after (f). Drying may be carried 15 out at elevated temperatures and reduced pressure, and/or using convection. For example, drying may be carried out at temperatures from about 20 to about 50°C. Additionally, specific pressures can be applied, such as from below 1 mbar to 1000 mbar. In specific embodiments, alternative pressure can be used, such as 10 mbar for 55min / 1000 mbar for 5min, etc. over several hours, or 50 mbar for 3h / below 1 mbar 20 for 12.5h. Drying may include a primary and a secondary drying.

In embodiments, the preparation method may further comprise filling the optionally dried or partially (e.g. primary) dried, and/or optionally sieved, microparticles into vials, 25 e.g. glass vials, or syringes, e.g. glass or polymeric syringes. An exemplary vial size for use according to the invention is 6 ml. Filling the vials or syringes is also referred to as (f) herein.

In embodiments, the filled vials obtained after (f) may then be closed, for example by 30 crimping with a metal cap. In embodiments, the filled syringes obtained after (f) may then be closed, for example via a plunger/stopper, e.g. a rubber plunger. Closing the vials or syringes is also referred to as (g) herein.

In embodiments, the closed vials or syringes obtained after (g) may be sterilized. Sterilization is also referred to as (h) herein. Several known sterilization methods are available. In some embodiments, the filled and closed vials containing the microparticles according to the invention may be sterilized by irradiation, e.g. X-ray or
5 gamma irradiation, for example using a dose of from about 25 to about 40 kGy. In some embodiments, sterilization is carried out via X-ray irradiation, using a dose of from about 25 to about 40 kGy.

In certain embodiments, the preparation method does not comprise lyophilization of
10 any intermediate or end product. In certain embodiments, the preparation method does not comprise milling before extrusion (i.e. before (b)). In certain embodiments, the preparation method does not comprise supercritical fluid processing.

In certain preferred embodiments, the preparation method does not comprise any of
15 lyophilization and supercritical fluid processing.

The product obtained after sterilization may be used as a pharmaceutical composition as described herein, for example in the medical uses as described above. In some embodiments, the microparticles obtained may be suspended in an oily vehicle as
20 described herein above, such as a mixture of C8/C10 triglycerides, a mixture of C8 triglycerides, or a mixture of C10 triglycerides, for example MIGLYOL® 812. For instance, suspending the microparticles in the oily vehicle may be performed within the vial into which the microparticles have been filled.

25 The invention further relates to a pharmaceutical composition as described herein, which is obtainable by the preparation method described above. In particular, the invention relates to a pharmaceutical composition comprising degarelix in the form of a pamoate salt, wherein the degarelix pamoate salt is contained in microparticles of a biodegradable copolymer of lactide units and glycolide units (PLGA) and wherein the
30 microparticles contain at least 50 wt% PLGA and from about 20 wt% to about 34 wt% degarelix free base equivalents, which is obtainable by a method comprising:

(a) mixing degarelix, particularly in powder form, in the form of a pharmaceutically acceptable pamoate salt, with a biodegradable copolymer of lactide units and glycolide units (PLGA), particularly in powder form;

- (b) subjecting the mixture to progressive heating and extrusion;
- (c) pelletizing the obtained extrudate;
- (d) grinding the obtained pellets at low temperature.

- 5 Further, the invention relates to a kit comprising a device containing a pharmaceutical composition according to the invention, and instructions for use. In some embodiments, the device may a prefilled syringe or vial. The syringe may comprise a needle with a needle gauge of G18 to G21, particularly G18 to G20.
- 10 The invention further relates to a dual chamber device (DCD). DCDs may particularly be provided in a prefilled form. DCDs are combination products containing a pharmaceutical composition in dry (or dried) form and a diluent in two separate chambers of the device. They provide high stability and convenience to patients and medical staff, which can significantly improve product quality and patient compliance.
- 15 Administration via a dual-chamber device requires first a reconstitution stage, in which the pharmaceutical composition is brought into contact with the diluent (e.g. an aqueous or oily vehicle) such that it can be suspended. Subsequently, the reconstituted composition (e.g. suspension) is ready for administration. In some embodiments, the DCD according to the invention may comprise a pharmaceutical
- 20 composition as described herein in powder form in one chamber, and an aqueous vehicle in the other chamber. In other embodiments, the DCD according to the invention may comprise a pharmaceutical composition as described herein in powder form in one chamber, and an oily vehicle in the other chamber.
- 25 The invention further relates to a single chamber device comprising pharmaceutical composition as described herein in the form of a suspension in an oily vehicle. This may also be referred to as a ready-to-use device. Exemplary single chamber devices are prefilled syringes containing a suspension of degarelix pamoate salt contained in microparticles of PLGA as described herein. For example, the prefilled syringe may
- 30 comprise microparticles containing at least 50 wt% PLGA and from about 20 wt% to about 34 wt% degarelix free base equivalents suspended in an oily vehicle as described herein, e.g. MIGLYOL® 812. Such prefilled single chamber device provide easier handling, as no reconstitution is required before administration to the patient.

The kit, the dual-chamber device and/or the single chamber device described above may, in some embodiments, be adapted for storage at room temperature. "Storage" as used herein means particularly storage for at least 6 months, at least 12 months or at least 24 months after the manufacturing date without significant deterioration.

- 5 "Without significant deterioration" in this context is understood as a loss of less than 5%, less than 3%, less than 1%, or even less than 0.5% PLGA microparticles containing degarelix pamoate according to the invention due to degradation processes.

The invention is further illustrated by the following items.

Item 1. A pharmaceutical composition comprising degarelix in the form of a pamoate salt, wherein the degarelix pamoate salt is contained in microparticles of a biodegradable copolymer of lactide units and glycolide units (PLGA) and
5 wherein the microparticles contain at least 50 wt% PLGA and from about 20 wt% to about 34 wt% degarelix free base equivalents.

Item 2. A pharmaceutical composition comprising degarelix in the form of a pharmaceutically acceptable pamoate salt as an active pharmaceutical
10 ingredient, wherein the degarelix pamoate salt is contained in microparticles of a biodegradable copolymer of lactide units and glycolide units (PLGA), wherein the microparticles contain at least 50 wt% PLGA and from about 20 wt% to about 34 wt% degarelix free base equivalents, and wherein the composition releases degarelix continuously and significantly, with a limited burst, to
15 achieve a therapeutical effect within 14 days of administration, and maintain such effect for a period of at least 12 weeks after administration.

Item 3. The pharmaceutical composition of item 2, wherein the composition releases degarelix continuously and significantly, with a limited burst, to
20 achieve a therapeutical effect within 7 days of administration, or within 3 days of administration.

Item 4. The pharmaceutical composition of any one of the preceding items, wherein the PLGA has a molar ratio of lactide units to glycolide units of from
25 about 75:25 to about 85:15.

Item 5. The pharmaceutical composition of any one of the preceding items, wherein the PLGA has a molar ratio of lactide units to glycolide units of about 75:25, about 80:20, or about 85:15.
30

Item 6. The pharmaceutical composition of any one of the preceding items, wherein the microparticles have a particle size distribution defined as
- D (v,0.1) of from about 5 to about 22 μm
- D (v,0.5) of from about 25 to about 45 μm

- D (v,0.9) of from about 55 to about 90 μm .

Item 7. The pharmaceutical composition of any one of the preceding items, wherein the microparticles have a particle size distribution defined as

- 5
- D (v,0.1) of from about 5 to about 15 μm
 - D (v,0.5) of from about 25 to about 40 μm
 - D (v,0.9) of from about 60 to about 90 μm .

10

Item 8. The pharmaceutical composition of any one of the preceding items, wherein the PLGA is a linear polyester with random order of lactide and glycolide units.

Item 9. The pharmaceutical composition of any one of the preceding items, wherein the PLGA is acid-terminated.

15

Item 10. The pharmaceutical composition of any one of the preceding items, wherein the microparticles contain from about 55 to about 75 wt% PLGA, from about 60 to about 70 wt% PLGA, or from about 60 to about 65 wt% PLGA.

20

Item 11. The pharmaceutical composition of any one of the preceding items, wherein the microparticles contain from about 60 to about 65 wt% PLGA.

Item 12. The pharmaceutical composition of any one of the preceding items, wherein the initial inherent viscosity (i.v.) of the PLGA is from about 0.3 dL/g to about 0.5 dL/g, or from about 0.35 dL/g to about 0.45 dL/g.

25

Item 13. The pharmaceutical composition of item 12, wherein the initial i.v. of the PLGA is about 0.30 dL/g, or about 0.40 dL/g, or about 0.50 dL/g.

30

Item 14. The pharmaceutical composition of item 12, wherein the initial i.v. of the PLGA is about 0.42 dL/g.

Item 15. The pharmaceutical composition of any one of the preceding items, further comprising a vehicle, which is an aqueous vehicle or an oily vehicle.

35

Item 16. The pharmaceutical composition of item 15, wherein the vehicle is an oily vehicle, particularly a mixture of medium-chain triglycerides.

- Item 17. The pharmaceutical composition of item 16, wherein the oily vehicle is a mixture of C8/C10 triglycerides, particularly a mixture of triglycerides of saturated C8/C10 fatty acids.
- 5 Item 18. The pharmaceutical composition of item 16 or 17, wherein the oily vehicle is a mixture substantially consisting of triglycerides of caprylic acid and capric acid.
- 10 Item 19. The pharmaceutical composition of any one of the preceding items, wherein the pharmaceutical composition is in the form of a suspension.
- Item 20. The pharmaceutical composition of item 19, wherein the suspension is a suspension in an oily vehicle as defined in any one of items 16 to 18.
- 15 Item 21. The pharmaceutical composition of item 19 or 20, wherein the concentration of microparticles within the suspension is from about 150 mg/mL to about 350 mg/mL, or from about 180 mg/mL to about 300 mg/mL.
- 20 Item 22. The pharmaceutical composition of any one of the preceding items, wherein the molar ratio of degarelix base to pamoate is from about 1:1 to about 2:1.
- Item 23. The pharmaceutical composition of any one of the preceding items, wherein the microparticles contain from about 28 wt% to about 33 wt% degarelix free base equivalents.
- 25 Item 24. The pharmaceutical composition of any one of the preceding items, wherein the microparticles contain about 28 wt%, about 30 wt%, or about 33 wt% degarelix free base equivalents.
- 30 Item 25. The pharmaceutical composition of any one of the preceding items, wherein the microparticles are microgranules.
- 35 Item 26. The pharmaceutical composition of any one of the preceding items, which is adapted for parenteral administration.

- Item 27. The pharmaceutical composition of any one of the preceding items,
which is adapted for subcutaneous or intramuscular administration.
- Item 28. The pharmaceutical composition of any one of the preceding items,
5 which is adapted for intramuscular administration.
- Item 29. The pharmaceutical composition of any one of the preceding items,
which is a suspension of PLGA microparticles with a molar ratio of lactide
units to glycolide units of about 75:25 containing degarelix pamoate in a
10 mixture of triglycerides of saturated C8/C10 fatty acids.
- Item 30. The pharmaceutical composition of item 29, wherein the microparticles
contain from about 28 wt% to about 33 wt% degarelix free base equivalents.
- Item 31. The pharmaceutical composition of item 29 or 30, wherein the initial i.v.
15 of the PLGA is from about 0.35 dL/g to about 0.45 dL/g.
- Item 32. The pharmaceutical composition of any one of the preceding items,
wherein the composition is free from alkali and earth alkali pamoate salts.
20
- Item 33. The pharmaceutical composition of any one of the preceding items,
wherein degarelix is continuously and significantly released from the
microparticles for a period of at least about 16 weeks, at least about 20
weeks, or at least about 24 weeks.
25
- Item 34. A pharmaceutical composition of any one of items 1 to 33 for use in the
treatment of prostate cancer.
- Item 35. A pharmaceutical composition comprising degarelix pamoate in PLGA
30 microparticles for use in extending the duration of exposure to degarelix in the
treatment of prostate cancer in a patient.
- Item 36. The pharmaceutical composition for use according to item 34 or 35,
wherein the composition is for parenteral administration, particularly for
35 subcutaneous or intramuscular administration.

Item 37. The pharmaceutical composition for use according to any one of items 34 to 36, wherein the composition is for administration once every 12 weeks.

5 Item 38. The pharmaceutical composition for use according to any one of items 34 to 37, wherein the composition is for intramuscular administration.

Item 39. The pharmaceutical composition for use according to item 38, wherein the composition is for intramuscular injection via a needle of size G18 to G21, particularly G18 to G20.

10 Item 40. The pharmaceutical composition for use according to any one of items 34 to 39, wherein degarelix is for administration in an amount of from about 200 mg to about 360 mg free base equivalents per dose, particularly about 200 mg to about 300 mg free base equivalents per dose.

15 Item 41. The pharmaceutical composition for use according to any one of items 34 to 40, wherein degarelix is for administration in a maximum total amount of 600 mg free base equivalents in two injections, or in a maximum total amount of 400 mg free base equivalents in two injections.

20 Item 42. The pharmaceutical composition for use according to any one of items 34 to 41, wherein the administration volume is less than or equal to about 6 mL, particularly less than 4 mL, more particularly from about 2.0 mL to about 3.5 mL.

25 Item 43. The pharmaceutical composition for use according to any one of items 34 to 42, wherein degarelix is continuously released from the microparticles, thereby reducing and maintaining serum testosterone levels to castration levels for at least 12 weeks.

30 Item 44. The pharmaceutical composition for use according to any one of items 34 to 43, wherein degarelix is continuously released from the microparticles, thereby reducing serum testosterone levels within 14 days of administration to ≤ 0.5 ng/mL and maintaining such levels for at least 12 weeks from administration.

35

- Item 45. The pharmaceutical composition for use according to any one of items 34 to 44, wherein degarelix is continuously released from the microparticles, thereby reaching and maintaining a mean plasma concentration of degarelix above a threshold of 3.0 ng/mL for a period of at least 12 weeks.
- 5
- Item 46. The pharmaceutical composition for use according to any one of items 34 to 44, wherein degarelix is continuously released from the microparticles, thereby reaching and maintaining a mean plasma concentration of degarelix above a threshold of 8.0 ng/mL or above a threshold of 9.0 ng/mL for a period
- 10 of at least 12 weeks.
- Item 47. The pharmaceutical composition for use according to any one of items 34 to 46, wherein the average degarelix plasma concentration from day 1 to day 7 post administration is less than 100 ng/mL, less than 80 ng/mL, less than
- 15 60 ng/mL, less than 50 ng/mL, less than 40 ng/mL, or less than 30 ng/mL.
- Item 48. A method for treating prostate cancer, comprising administering an effective amount of the pharmaceutical composition of any one of items 1 to 33 to a subject in need thereof.
- 20
- Item 49. The method of item 48, wherein said pharmaceutical composition is administered once every 12 weeks.
- Item 50. The method of item 48 or 49, wherein said pharmaceutical composition
- 25 is administered by intramuscular injection, particularly with a single injection.
- Item 51. The method of item 50, wherein the intramuscular injection is performed with needle of size G18 to G21, particularly G18 to G20.
- 30
- Item 52. The method of any one of items 48 to 51, wherein degarelix is administered in an amount of from about 200 mg to about 360 mg free base equivalents per administration dose, or from about 200 mg to about 300 mg free base equivalents per administration dose.

- Item 53. The method of any one of items 48 to 52, wherein the administration volume is less than or equal to about 6 ml, particularly less than 4 ml, more particularly from about 2.0 to about 3.5 ml.
- 5 Item 54. The method of any one of items 48 to 53, wherein degarelix is continuously and significantly released from the microparticles, thereby reaching and maintaining a mean plasma concentration of degarelix above a threshold of 3.0 ng/mL for a period of at least 12 weeks.
- 10 Item 55. The method of any one of items 48 to 54, wherein the average degarelix plasma concentration from day 1 to day 7 post administration is less than 100 ng/mL, less than 80 ng/mL, less than 60 ng/mL, less than 50 ng/mL, less than 40 ng/mL, or less than 30 ng/mL.
- 15 Item 56. A method for the preparation of a pharmaceutical composition of any one of items 1 to 33, comprising:
- (a) mixing degarelix, particularly in powder form, in the form of a pharmaceutically acceptable pamoate salt, with a biodegradable copolymer of lactide units and glycolide units (PLGA), particularly in powder form;
 - 20 (b) subjecting the mixture to progressive heating and extrusion;
 - (c) pelletizing the obtained extrudate;
 - (d) grinding the obtained pellets at low temperature.
- Item 57. The method of item 56, further comprising:
- 25 (e) sieving the obtained microparticles to a size of less than or equal to about 150 μm .
- Item 58. The method of item 56 or 57, further comprising:
- (f) filling the microparticles into vials or syringes;
 - 30 (g) closing the vials or syringes.
- Item 59. The method of item 58, further comprising:
- (h) sterilizing the filled and closed vials or syringes by X-ray irradiation or gamma irradiation.

Item 60. The method of item 58, further comprising:
(h) sterilizing the filled and closed vials by X-ray irradiation.

5 Item 61. The method of any one of items 56 to 60, further comprising
drying the microparticles after (d) or after (e) and/or after (f).

Item 62. The method of any one of items 56 to 61, further comprising suspending
the microparticles in an oily vehicle.

10 Item 63. The method of any one of items 56 to 62, wherein the method does not
comprise lyophilization.

Item 64. The method of any one of items 56 to 63, wherein the method does not
15 comprise milling before extrusion.

Item 65. The method of any one of items 56 to 64, wherein the method does not
comprise supercritical fluid processing.

20 Item 66. A pharmaceutical composition according to any one of items 1 to 33
obtainable by the method of any one of items 56 to 65.

Item 67. A kit comprising a device, such as a prefilled syringe, containing a
pharmaceutical composition according to any one of items 1 to 33, and
25 instructions for use.

Item 68. A dual chamber device comprising
a. the pharmaceutical composition of any one of items 1 to 33 in powder
form in one chamber, and an aqueous vehicle in the other chamber, or
30 b. the pharmaceutical composition of any one of items 1 to 33 in powder
form in one chamber, and an oily vehicle in the other chamber.

Item 69. A single chamber device comprising the pharmaceutical composition of
any one of items 1 to 33 in the form of a suspension in an oily vehicle.

Item 70. The kit according to item 67, the device according to item 68 or the device according to item 69, which is adapted for storage at room temperature.

5 Item 71. The pharmaceutical composition for use according to any one of items 34 to 47, wherein degarelix is for administration in an amount of about 200 mg degarelix free base equivalents, particularly 200 mg degarelix free base equivalents, and wherein the pharmaceutical composition is for intramuscular administration once every 12 weeks in a single dose.

10 Item 72. The pharmaceutical composition for use according to any one of items 34 to 47, wherein degarelix is for administration in an amount of about 300 mg degarelix free base equivalents, particularly 300 mg degarelix free base equivalents, and wherein the pharmaceutical composition is for intramuscular administration once every 12 weeks in a single dose.

Item 73. The pharmaceutical composition for use according to any one of items 34 to 47, wherein degarelix is (i) for a first intramuscular administration in a total amount of about 400 mg degarelix free base equivalents, particularly 400 mg
20 degarelix free base equivalents, and (ii) for subsequent intramuscular administration in an amount of about 200 mg degarelix free base equivalents, particularly 200 mg degarelix free base equivalents once every 12 weeks in a single dose.

25 Item 74. The pharmaceutical composition for use according to item 73, wherein the total amount of 400 mg degarelix free base equivalents is for administration in two injections of 200 mg degarelix free base equivalents each.

Item 75. The pharmaceutical composition for use according to item 71, which is
30 for administration to a patient having previously received degarelix acetate in an amount of 240 mg degarelix free base equivalents via s.c. administration, particularly via s.c. injection, more particularly via two s.c. injections of 120 mg degarelix free base equivalents.

35 Item 76. The pharmaceutical composition for use according to any one of items 71 to 75, wherein intramuscular administration is intramuscular injection.

Item 77. The method of any one of items 48 to 55, wherein degarelix is administered in an amount of about 200 mg degarelix free base equivalents, particularly 200 mg degarelix free base equivalents, and wherein the pharmaceutical composition is administered by intramuscular administration once every 12 weeks in a single dose.

Item 78. The method of any one of items 48 to 55, wherein degarelix is administered in an amount of about 300 mg degarelix free base equivalents, particularly 300 mg degarelix free base equivalents, and wherein the pharmaceutical composition is administered by intramuscular administration once every 12 weeks in a single dose.

Item 79. The method of any one of items 48 to 55, comprising (i) a first intramuscular administration of the pharmaceutical composition of any one of items 1 to 33 in a total amount of about 400 mg degarelix free base equivalents, particularly 400 mg degarelix free base equivalents, and (ii) subsequent intramuscular administrations in an amount of about 200 mg degarelix free base equivalents, particularly 200 mg degarelix free base equivalents once every 12 weeks in a single dose.

Item 80. The method according to item 79, wherein the total amount of 400 mg degarelix free base equivalents is administered in two injections of 200 mg degarelix free base equivalents each.

Item 81. The method according to item 77, wherein the pharmaceutical composition according to any one of items 1 to 33 is administered to a patient having previously received degarelix acetate in an amount of 240 mg degarelix free base equivalents via s.c. administration, particularly via s.c. injection, more particularly via two s.c. injections of 120 mg degarelix free base equivalents.

Item 82. The method according to any one of items 77 to 81, wherein intramuscular administration is intramuscular injection.

LEGENDS TO THE FIGURES

Figure 1: Graph of the mean plasmatic concentration (ng/mL) of degarelix in rats after SC administration of Compositions A (TF8) and Y (TF4) suspended in an aqueous vehicle, and administration of Reference Product as described in Example 3 a) (PK3).

Figure 2: Graph showing the same data as Figure 1 with a focus on the first 10 days post administration.

Figure 3: Graph of the mean plasmatic concentration (ng/mL) of degarelix in rats after IM administration of Compositions B (TF6) and Z (TF9) suspended in an aqueous vehicle, and administration of Reference Product as described in Example 3 b) (PK4).

Figure 4: Graph showing the same data as Figure 3 with a focus on the first 7 days post administration.

Figure 5: Graph of the mean plasmatic concentration (ng/mL) of degarelix in rats after IM administration of Compositions B (TF6) and W (TF8) suspended in an aqueous vehicle, and administration of Reference Product as described in Example 3 b) (PK4).

Figure 6: Graph of the mean plasmatic concentration (ng/mL) of degarelix in rats after IM administration of Compositions X (PK3-TF5) suspended in an aqueous vehicle as described in Example 3 a) and A (PK4-TF5) suspended in an aqueous vehicle as described in Example 3 b).

Figure 7: Graph of the mean plasmatic concentration (ng/mL) of degarelix in rats after IM (TF2) or SC (TF3) administration of Composition C suspended in an oily vehicle, and administration of Reference Product as described in Example 3 c) (PK5).

Figure 8: Graph of the mean plasmatic concentration (ng/mL) of degarelix in rats after IM administration of Composition C suspended in either an oily vehicle (TF2) or an aqueous vehicle (TF4), and administration of Reference Product as described in Example 3 c) (PK5).

Figure 9: Graph of the mean plasmatic concentration (ng/mL) of degarelix in rats after IM administration of Compositions D (TF6) and E (TF7) suspended in an oily vehicle, and administration of Reference Product as described in Example 3 c) (PK5).

5 **Figure 10:** Graph of the mean plasmatic concentration (ng/mL) of degarelix in rats after IM administration of Compositions F (TF1), G (TF3) and H (TF4) suspended in an oily vehicle as described in Example 3 d) (PK8).

10 **Figure 11:** Graph of the mean plasmatic concentration (ng/mL) of degarelix in rats after IM administration of Compositions F (TF1) and I (TF6) suspended in an oily vehicle as described in Example 3 d) (PK8).

15 **Figure 12:** Graph of the mean plasmatic concentration (ng/mL) of degarelix in rats after administration of Compositions F (TF1) and J (TF7) suspended in an oily vehicle as described in Example 3 d) (PK8).

EXAMPLES

20 **Characterization methods used in the microgranule preparation examples**

Molecular weight determination

In the following examples, the molecular weight of the polymer starting materials were measured using gel permeation chromatography (GPC) as follows. The sample was dissolved in tetrahydrofuran (THF) and analysed in isocratic elution with THF at
25 1mL/min on Styragel® columns HR 5, HR 4, HR 3 and HR 2 connected in series, heated at 40°C, and a refractive index detector. The number average polymer molecular weight (Mn), the weight average molecular weight (Mw) and the polydispersity index ($I_p = M_w/M_n$) were determined based on a calibration curve using narrow molecular weight polystyrene as standards obtained from Sigma Aldrich as
30 shown in Table 1:

Table 1 :

Standard polystyrene	Molecular weight
Polymer 1	1820
Polymer 2	17600
Polymer 3	63600
Polymer 4	229000
Polymer 5	9600
Polymer 6	28000
Polymer 7	141000
Polymer 8	526000

Drug loading and purity determination

In the following examples, the drug loading and purity were measured using (ultra) high performance liquid chromatography ((U)HPLC) as follows: from 2 to 15 mg, of the biodegradable polymer microparticles were weighed, dissolved in dimethyl sulfoxide (DMSO) or Dimethylformamide (DMF), and the sample analyzed in gradient elution mode using a C18 column, a water-TFA/acetonitrile TFA mobile phase and an UV detection at 280nm. More specifically, drug loading and purity of the Compositions tested in PK3, PK4 and PK5 were measured using the above method with 2 to 4 mg sample in DMF; drug loading and purity of the Compositions tested in PK8 were measured using the above method with 15 mg sample in DMSO. Drug loading and purity of Composition K was also tested using the above method with 15 mg sample in DMSO.

Determination of particle size

PLGA microparticles after pellet grinding

In the following examples, the size of particles of PLGA following grinding was determined by wet laser diffraction using Malvern mastersizer 3000, as follows: 40 to 80 mg of sample were suspended in an aqueous solution of sodium carboxymethyl cellulose (1.5% w/w), mannitol (4.25 % w/w) and polysorbate 80 (0.1% w/w) and then introduced into a hydro MV dispersion unit containing purified water (stirring at 2000rpm) until reaching a stable laser obscuration of 5% to 20%. The sample was then subjected to 3 min of ultra-sonification (MV dispersion unit setting medium (50%)). The volume-weighted size distribution was calculated by means of the Mie theory using the following parameters: dispersant refractive index of 1.33; real particle refractive index of 1.52; Absorption index of 0.001.

Microgranules of degarelix salt in PLGA

In the following examples, the particle size distributions of the various Compositions prepared were determined by wet laser diffraction using Malvern mastersizer 3000, as follows: Ca. 50 mg of sample were suspended in an aqueous solution of sodium carboxymethyl cellulose (1.5% w/w), mannitol (4.25 % w/w) and polysorbate 80 (0.1% w/w) and then introduced into a hydro MV dispersion unit containing purified water (stirring at 2000rpm) until reaching a stable laser obscuration of 10% to 20%. The sample was then subjected to 3 min of ultra-sonification (MV dispersion unit setting medium (50%)). The volume-weighted size distribution was calculated by means of the Mie theory using the following parameters: dispersant refractive index of 1.33; real particle refractive index of 1.56; Absorption index of 0.015.

Microparticles of degarelix pamoate

The particle size distributions of degarelix pamoate after crushing and sieving was determined by wet laser diffraction using Malvern mastersizer 3000. Ca. 2 mg of sample were suspended in 2 mL of Dichloromethane (DCM). Ca. 0.5 mL of the suspension was then introduced into a hydro SV dispersion unit containing DCM (stirring at 1500 rpm) until reaching a stable laser obscuration of 3% to 15%. The volume-weighted size distribution was calculated by means of the Mie theory using the following parameters: dispersant refractive index of 1.42; real particle refractive index of 1.56; Absorption index 0.010.

Support tables for the microgranule preparation examples

The starting materials and process parameters used in the methods described further in Examples 1 and 2 are summarized in Table 2. The characterization of the Compositions prepared according to Examples 1 and 2 are summarized in Table 3.

Table 2: starting materials and process parameters for microparticle preparation

	PLGA starting material				Degarelix Salt, Ratio of degarelix base to salt	Extrusion parameters			Batch size	PLGA amount	Degarelix salt amount	Target Drug Loading
	PLGA	initial iv	Mw	Mn	-	Screw design geometries	Screw rpm	Hot Melt Extrusion temperature °C	(g)	(g)	(g)	(as degarelix free base)
Composition												
A	PLGA 75:25 acid end	0,65	71277	45211	pamoate 1,05:1	5mm twin screw – 0 shear Ballmill PM100 mix	50	80/90/90	6	3,6	2,4	30%
B	PLGA 75:25 acid end	0,42	41625	25088	pamoate 1,05:1	9mm twin screw – 0 shear	100	80/90/90	5	3,0	1,99	30%
C	PLGA 75:25 acid end	0,42	41304	26188	Pamoate 1,05:1	9mm twin screw – 2 shear	100	80/90/90	9,5	4,55	4,95	40%
D	PLGA 75:25 acid end	0,42	41304	26188	pamoate 1,05:1	9mm twin screw – 2 shear	100	80/90/90	6	2,9	3,1	40%
E	PLGA 75:25 acid end	0,42	41304	26188	pamoate 1,05:1	9mm twin screw – 2 shear	100	80/90/90	6	2,09	3,92	50%
F	PLGA 75:25 acid end	0,42	41304	26188	pamoate 1,15:1	9mm twin screw – 2 shear	100	80/90/90	104	63	41	33%
G	PLGA 75:25 acid end	0,33	34985	22498	pamoate 1,15:1	9mm twin screw – 2 shear	100	80/90/90	39	23,6	15,4	33%
H	PLGA 75:25 acid end	0,50	48068	30098	pamoate 1,15:1	9mm twin screw – 2 shear	100	80/90/90	39	23,6	15,4	33%
I	PLGA 75:25 acid end	0,42	41304	26188	pamoate 2,06:1	9mm twin screw – 2 shear	100	80/90/90	20	12	8	33%

	PLGA starting material				Degarelix Salt, Ratio of degarelix base to salt	Extrusion parameters			Batch size	PLGA amount	Degarelix salt amount	Target Drug Loading
Composition	PLGA	initial iv	Mw	Mn	-	Screw design geometries	Screw rpm	Hot Melt Extrusion temperature °C	(g)	(g)	(g)	(as degarelix free base)
J	PLGA 75:25 acid end	0,42	41304	26188	pamoate 1,15:1	9mm twin screw – 2 shear	100	80/90/90	9,4	5,3	4,1	36,3%
K	PLGA 75:25 acid end	0,42	42700	23591	pamoate 1,25:1	9mm twin screw – 2 shear	100	80/90/90	2177	1357,4	820,0	31%
W	No PLGA				pamoate 1,05:1	No extrusion						
X	PLGA 75:25 acid end	0,65	71277	45211	acetate 1:1	9mm twin screw – 0 shear	50	80/90/90	20	12,6	7,4	34,8
Y	PLGA 75:25 acid end	0,65	62168	42302	acetate 1:1	9mm twin screw – 2 shears	200	80/90/90	10	6,3	3,7	34,8%
Z	PLGA 75:25 acid end	0,42	41304	26188	HCl 1:1	9mm twin screw – 2 shear	100	80/90/90	5	3,4	1,6	33%

Table 3: characterization of microparticles

Composition	Measured drug loading (as degarelix free base)	Drug product purity %	Particle size distribution		
			D (v, 0.1)	D (v, 0.5)	D (v, 0.9)
A	28,5%	96,9	23,3	53,0	97,9
B	22	97,32	19,76	44,36	84,56
C	32,9	99,02	11,8	36,8	75,8
D	28	99,0	11,70	31,60	62,90
E	43,3	99,02	8,37	25,60	52,50
F	32,3	98,36	7,7	27,7	70,5
G	31,3	98,46	6,5	24,2	60,3
H	30,4	98,06	8,1	29,4	72,5
I	32,3	95,32	8,9	30,0	68,3
J	34,3	98,16	8,7	28,3	66,5
K	30,3	99,6	11,5	34,0	70,7
W	75,6	97,5	13,0	56,7	115,4
X	31,6	96,1	9,7	40,1	93,4
Y	28,33	93,7	13,6	53,9	109,5
Z	25,8	96,5	15,6	43,3	95,5

Example 1: Microgranules of degarelix pamoate preparation (Compositions A to K)

The following method was used to make the microgranules of degarelix pamoate (Compositions A to J):

- 5 1. Pellets of the appropriate PLGA (Table 2, columns "PLGA" and "initial iv") were milled using a cryo milling equipment (annular milling) with a hole parameter of 250 microns, at -80°C. The Dv50 (or D (v,0.5)) of resulting PLGA microparticles, measured by wet laser diffraction, were about 100 µm. Polymer weight was determined by GPC (see Mw and Mn values in Table 2).
- 10 2. The appropriate degarelix pamoate was crushed and sieved on a mesh of 180 microns. The Dv50 of the resulting particles, measured by wet laser diffraction, were about 50 µm.
- 15 3. An appropriate amount of degarelix pamoate (Table 2, column "degarelix salt amount") was mixed with an appropriate amount of PLGA polymer (Table 2, column "PLGA amount") using a three-dimensional shaker equipment for 1 minutes at 101.min-1 rpm to obtain a target drug loading (Table 2, column "target drug loading") of degarelix free base.
- 20 4. The resulting mix was then extruded with an automatic feeder using an extruder, a rotation speed and temperatures as specified in Table 2, columns "extrusion parameters".
5. The extrudate was cut into pellets of 0,5 mm or 2 mm using a Pelletizer.
6. The pellets were milled into microgranules using a cryo milling equipment (annular milling) at - 80°C.
- 25 7. The microgranules were sieved on a 106 µm mesh. The microparticle size distributions were measured by wet laser diffraction (see Table 3).
8. The microgranules were then primary dried 15,5h at 30°C, using alternative pressure as follows: 10 mbar for 55min / 1000 mbar for 5min, etc. The microgranules were subjected to drug loading determination (see Table 3) and filled into vials.
- 30 9. Secondary drying for 24h at 30°C was carried out, followed by nitrogen inertisation.
10. The microgranules were then sterilized by gamma or Xray irradiation with a dose of 25 to 40 kGy.

The following method was used to make the microgranules of degarelix pamoate of Composition K (clinical trial batch to be used in Example 4):

1. Pellets of the appropriate PLGA (Table 2, columns "PLGA" and "initial iv") were milled using a cryo milling equipment (annular milling) with a hole parameter of 250 microns, at -70°C. The Dv50 of resulting PLGA microparticles, measured by wet laser diffraction, was about 100 µm. Polymer weight was determined by GPC (see Mw and Mn values in Table 2).
2. The appropriate degarelix pamoate was crushed and sieved on a mesh of 180 microns. The Dv50 of the resulting particles, measured by wet laser diffraction, was 105,7 µm.
3. An appropriate amount of degarelix pamoate (Table 2, column "degarelix salt amount") was mixed with an appropriate amount of PLGA polymer (Table 2, column "PLGA amount") using a three-dimensional shaker equipment for 1 minutes at 20.min-1 rpm to obtain a target drug loading (Table 2, column "target drug loading") of degarelix free base.
4. The resulting mix was then extruded with an automatic feeder using an extruder, a rotation speed and temperatures as specified in Table 2, columns "extrusion parameters".
5. The extrudate was cut into pellets of 0,5 mm using a Pelletizer.
6. The pellets were milled into microgranules using a cryo milling equipment (annular milling) at - 100°C.
7. The microgranules were sieved on a mesh of 106 µm. The microparticle size distribution was measured by wet laser diffraction (see Table 3).
8. The microgranules were then primary dried 15,5h at room temperature (17 to 24°C), using alternative pressure as follows: 50 mbar for 3h / below 1 mbar for 12,5h. The microgranules were subjected to drug loading determination (see Table 3) and filled into vials.
9. Secondary drying for 15h at room temperature (17 to 24°C) was carried out, followed by nitrogen inertisation.
10. The microgranules were then sterilized by Xray irradiation with a dose of 31.6 to 32.2 kGy.

Example 2 (comparative): Microgranules of degarelix soluble salt (HCl and Acetate) preparation, microparticles of degarelix pamoate preparation

The following method was used to make the **degarelix acetate** microgranules (Compositions X and Y):

- 5 1. Pellets of the appropriate PLGA (Table 2, columns "PLGA" and "initial iv") were milled using a cryo milling equipment (annular milling) with a hole parameter of 250 microns, at -80°C. The Dv50 of resulting PLGA microparticles, measured by wet laser diffraction, were about 100 µm.
- 10 2. An appropriate amount of degarelix acetate (Table 2, column "degarelix salt amount") was mixed with an appropriate amount of PLGA polymer (Table 2, column "PLGA amount") using a planetary ball mill equipment for 3 min to obtain a target drug loading (Table 2, column "target drug loading") of degarelix free base.
- 15 3. The resulting mix was then extruded with an automatic feeder using an extruder, a rotation speed and temperatures as specified in Table 2, columns "extrusion parameters".
4. The extrudate was cut into pellets of 2 mm using a pelletizer.
5. The pellets were milled into microgranules using a cryo milling equipment (annular milling) at - 80°C.
- 20 6. The microgranules were sieved on a mesh of 106 µm. The microparticle sizes were measured by wet laser diffraction (see Table 3).
7. The microgranules were then primary dried for 15,5h at 30°C, using alternative pressure as follows: 10 mbar for 55min / 1000 mbar for 5min, etc. The microgranules were subjected to drug loading determination (see Table 3) and
- 25 filled into vials.
8. Secondary drying for 24h at 30°C was carried out, followed by nitrogen inertisation.
9. The microgranules were sterilized by gamma or Xray irradiation with a dose of 25 to 40kGy.

The following method was used to make the **degarelix hydrochloride** microgranules (Composition Z):

1. PLGA (PLGA 75/25 acid end group iv 4.2dL/g) pellets were milled using a cryo milling equipment (annular milling) with a hole parameter of 250 microns, at - 80°C. The Dv50 of resulting PLGA microparticles, measured by wet laser diffraction, were about 100 µm.
2. 1,6 g of degarelix hydrochloride was mixed with 3,4 g of PLGA using a three-dimensional shaker equipment with 10g of 5mm inox stell ball for 1 minutes at 101.min-1 rpm to obtain a target drug loading of 33 % as degarelix free base.
3. The resulting mix was then extruded after manual feeding using an extruder, a rotation speed and temperatures as specified in Table 2, columns "extrusion parameters".
4. The extrudate was cut into pellets of 2 mm using a pelletizer.
5. The pellets were milled into microgranules using a cryo milling equipment (annular milling) at - 80°C.
6. The microgranules were sieved on a mesh of 106 µm. The microparticle sizes were measured by wet laser diffraction (see Table 3).
7. The microgranules were then primary dried for 15,5h at 30°C, using alternative pressure as follows: 10 mbar for 55min / 1000 mbar for 5min, etc. The microgranules were subjected to a drug loading determination (See Table 3) and filled into vials.
8. Secondary drying 24h at 30°C was carried out, followed by nitrogen inertisation.
9. The microgranules were sterilized by Xray irradiation with a dose of 25k to 40 kGy.

The following method was used to prepare the **degarelix pamoate microparticles** of Composition W:

1. Degarelix pamoate was crushed and sieved on a mesh of 106 microns. The microparticle sizes were measured by wet laser diffraction (see Table 3).
2. The microgranules were sterilized by Xray irradiation with a dose of 25 to 40kGy.

Example 3: In vivo pharmacokinetic profile of Compositions A to J and W to Z in rats

In all the PK studies herein, the sample analyses for degarelix concentrations were done as follows: degarelix was extracted from rat plasma using solid phase-based extraction and degarelix concentrations were determined using liquid chromatography with tandem mass spectrometry (LC-MS/MS).

All Tables with PK results, either with individual concentrations or mean values, are presented herein in a conventional 3-significant digit format. “SD” means Standard Deviation (a statistic that measures the dispersion of a dataset relative to its mean) and “CV%” means coefficient of variation (ratio of the standard deviation to the mean), expressed in percentage. The CV shows the extent of variability in relation to the mean of the population.

It is to be understood that the release of degarelix over the first 84 days (12 weeks) after administration is of particular interest in the context of the present invention.

a) PK study 3 (PK3)

The microparticles of Compositions A, X and Y were suspended in a physiologically acceptable aqueous vehicle as specified in Table 4 below.

A generic of Gonax® 12 weeks was used as reference product in this study, prepared as follows: 120 mg lyophilizate of degarelix acetate and mannitol (in 1 vial of commercially available Firmagon starting dose) were reconstituted in water for injection to obtain a degarelix concentration of 60 mg/ml.

Table 4

Composition	PK group	Vehicle	Degarelix suspension concentration (mg/mL)	Concentration of microparticles in suspension (mg/mL)	Route of administration
	Reference Product	Water for injection	60	N/A	SC
Y	PK3-TF4	*CMC-Na 1,5%, Tw80 0,1%,	62	206 mg/mL	SC

		Mannitol 4,25%			
A	PK3-TF8	CMC-Na 1,5%, Tw80 0,1%, Mannitol 4,25%	62	242 mg/mL	SC
X	PK3-TF5	CMC-Na 1,5%, Tw80 0,1%, Mannitol 4,25%	62	195 mg/mL	IM

*CMC-Na: sodium carboxymethyl cellulose, Tw80: Tween80

The resulting suspensions (aqueous vehicle) were injected subcutaneously (SC) (TF4, TF8 and Reference Product) or intramuscularly (IM) (TF5), in an amount equating to a single dose of degarelix of 50 mg/kg, into male Sprague Dawley rats weighing 200-250g (5-6 weeks old) at the day of treatment. After defined time periods, plasma samples were taken and analyzed for the degarelix concentrations. Results are shown in Tables 8 and 9, and Figures 1, 2 and 6 herein.

Data show that both Test Formulations (TF) TF4 and TF8 had lower C_{max} values compared to reference product. See in particular Figure 2, which shows the same data as Figure 1 with a focus on the first 10 days post administration.

Higher plasma concentrations (after approximately Day 7) and a longer release were observed for TF8 (PLGA microgranules containing degarelix pamoate salt) compared to TF4 (PLGA microgranules containing degarelix acetate salt) and Reference Product.

b) PK study 4 (PK4)

Compositions A, B, W and Z were suspended in a physiologically acceptable aqueous vehicle as specified in Table 5 below.

Commercially available Gonax® 12 weeks was used as reference product in this study. The content of 1 vial, i.e. 240 mg lyophilizate of degarelix acetate and mannitol, was reconstituted and solubilized with water for injection to obtain a degarelix concentration of 60 mg/mL.

Table 5

Composition	PK group	Vehicle	Degarelix suspension concentration mg/mL	Concentration of microparticles in suspension (mg/mL)	Route of administration
	PK4-Reference Product	Water for injection	60	N/A	SC
A	PK4-TF5	CMC Na 1,5%, Tw80 0,1%, Mannitol 4,25%	31	120	IM
B	PK4-TF6	CMC Na 1,5%, Tw80 0,1%, Mannitol 4,25%	62	282	IM
W	PK4-TF8	CMC Na 1,5%, Tw80 0,1%, Mannitol 4,25%	62	82	IM
Z	PK4-TF9	CMC Na 0,2%, Tw80 0,1%, Mannitol 4,25%	62	242	IM

The resulting suspensions were injected subcutaneously (Reference Product) or intramuscularly (TF6, 8, 9), in an amount equating to a single dose of degarelix of 50 mg/kg, into male Sprague Dawley rats weighing 200-250g (5-6 weeks old) at the day of treatment. TF5 was administered at a degarelix dose of 25 mg/kg due to technical issues. After defined time periods, plasma samples were taken and analyzed for the degarelix concentrations. Assuming dose proportionality, the measured concentrations for TF5 were multiplied by 2. Results are shown in Tables 10 to 15 and Figures 3, 4, 5 and 6 herein.

Data show that C_{max} values were lower for Test Formulations TF6, TF8 and TF9 compared to the one of Reference Product. See in particular Figure 4, which shows the same data as Figure 3 with a focus on the first 7 days post administration.

TF6 (Composition B, PLGA microgranules containing degarelix pamoate salt) showed higher plasma concentrations profile and exposure, compared to TF9 (Composition Z,

PLGA microgranules containing degarelix HCl salt), for which concentration profiles were at similar levels as the Reference Product.

TF6 (Composition B, PLGA microgranules containing degarelix pamoate salt) also showed higher plasma concentrations and exposure over the first 84 days compared to TF8 (Composition W: degarelix pamoate microparticles without PLGA).

Figure 6 shows a comparison between 2 PK groups from PK3 and PK4 studies, namely PK3-TF5 (PLGA microgranules containing degarelix acetate salt, aqueous vehicle, IM administration) and PK4-TF5 (PLGA microgranules containing degarelix pamoate salt, aqueous vehicle, IM administration). Data indicate that PK4-TF5 shows a lower C_{max} value than PK3-TF5, and that PK4-TF5 show higher plasma concentrations after about day 34, and at day 84 (C₈₄) compared to PK3-TF5.

c) PK study 5 (PK5)

Compositions C, D and E were suspended in a physiologically acceptable aqueous or oily vehicle as specified in Table 6 below.

Commercially available Firmagon® was used as Reference Product in this study. The content of 1 vial of starting dose, i.e. 120 mg lyophilizate of degarelix acetate and mannitol, was reconstituted and solubilized with water for injection to obtain a degarelix concentration of 40 mg/mL for the starting dose in animals. The content of 1 vial of maintenance dose, i.e. 80 mg lyophilizate of degarelix acetate and mannitol, was reconstituted and solubilized with water for injection to obtain a degarelix concentration of 20 mg/mL for the maintenance doses in animals. See also Table 6.

Table 6

Composition	PK group	Vehicle	Degarelix suspension concentration mg/mL	Concentration of microparticles in suspension (mg/mL)	Route of administration
	PK5-Reference product	Water for injection	40 mg/mL at Day 1 20 mg/mL at Day 28 20 mg/mL at Day 56	N/A	SC

C	PK5-TF2	MCT	62	190	IM
C	PK5-TF3	MCT	62	190	SC
C	PK5-TF4	CMC Na 1,5% Tw80 0,1% Mannitol 4,25%	62	190	IM
D	PK5-TF6	MCT	62	223	IM
E	PK5-TF7	MCT	62	144	IM

The resulting suspensions were injected intramuscularly (TF2, TF4, TF6 and TF7) or subcutaneously (Reference Product and TF3), in an amount equating to a single dose of degarelix of 50 mg/kg, into male Sprague Dawley rats weighing 200-250g (5-6 weeks old) at the day of treatment.

The Reference Product was administered at Day 1 (30 mg/kg), Day 28 (10 mg/kg) and Day 56 (10 mg/kg) subcutaneously, to mimic the starting dose and maintenance doses of the commercial product Firmagon®.

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For the Reference Product, as the animals in the Firmagon® group gained weight between the first and the last administration, and doses were administered on a mg/kg basis, degarelix concentrations were adjusted to achieve a total dose per animal over 12 weeks (84 days) equivalent to that in the Test Formulation groups. (No adjustment of concentrations of the first dose were made, while adjustments were made to the second and third doses' concentrations based on the initial animal body weight, ensuring the same total amount of degarelix per animal).

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After defined time periods, plasma samples were taken and analyzed for the degarelix concentrations. Results are shown in Tables 16 to 19 and Figures 7, 8, and 9 herein. In this Example, where Firmagon® is used as Reference Product, particular attention should be drawn to the C_{max}. Indeed, as Firmagon® is formulated for administration in 1-month intervals, it had to be administered three times, whereas the Test Formulations were administered once for a release over 3 months (12 weeks, 84 days).

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As mentioned above, the overall dose for 12 weeks was the same for Firmagon® as Reference Product and the Test Formulations (namely 50 mg/kg). However, the dose of the first administration of Firmagon (30 mg/kg) was relatively lower than the dose of

the Test Formulations (50 mg/kg). Thus, the observed burst over the first few days, including the maximal concentration (C_{max}) value, is in fact substantially lower for the Test Formulations TF2, TF3, TF4 and TF6 (when dose normalized).

- 5 TF2 (PLGA microgranules containing degarelix pamoate salt of Composition C, DL 32.9%, in oily vehicle, IM administration) showed higher plasma concentrations than TF3 (Composition C, in oily vehicle, SC administration) and TF4 (Composition C, in aqueous vehicle, IM administration). The exposure for TF2 over 84 days post administration, represented by the area under the curve (AUC), was higher than the exposure of Reference Product. The exposure (AUC) of TF3 was similar to that of the Reference Product. TF4 showed a lower AUC than TF2 and Reference Product.

TF6 (Composition D: PLGA microgranules containing degarelix pamoate salt, DL 28%, in oily vehicle, IM administration) shows a particularly advantageous PK profile.

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Both TF6 and TF7 have higher exposures than Reference Product over the first 84 days post administration.

- TF7 (Composition E: PLGA microgranules containing degarelix pamoate salt, DL 43.3%, in oily vehicle, IM administration) had a higher C_{max} value than TF6 and Reference Product. TF7 showed similar exposure to that of TF6 over the first 84 days post administration but lower sustained plasma concentration levels. These values observed for TF7 indicate that the drug loading in Composition E is likely too high.

d) PK study 8 (PK8)

- 25 Compositions F to J were suspended in a physiologically acceptable oily vehicle as specified in Table 7 below.

Table 7

Composition	PK group	Vehicle	Degarelix suspension concentration mg/mL	Concentration of microparticles in suspension (mg/mL)	Route of administration
F	PK8-TF1	MCT	62	208	IM
G	PK8-TF3	MCT	62	180	IM

H	PK8-TF4	MCT	62	208	IM
I	PK8-TF6	MCT	62	208	IM
J	PK8-TF7	MCT	62	190	IM

The resulting suspensions were intramuscularly injected, in an amount equating to a single dose of degarelix of 50 mg/kg, into male Sprague Dawley rats weighing 200-250g (5-6 weeks old) at the day of treatment. After defined time periods, plasma samples were taken and analyzed for the degarelix concentrations. Results are presented in Tables 20 to 25 and in Figures 10, 11 and 12.

TF1 (Formulation F: PLGA iv 0.42, microgranules containing degarelix pamoate salt, DL 32.3%, in oily vehicle, IM administration) shows a particularly advantageous PK profile.

TF1, TF3 and TF4 (Formulations F, G and H: all microgranules containing degarelix pamoate salt with similar DL values and PLGA initial inherent viscosity (inherent iv) varying from 0.33 to 0.50, in oily vehicle, IM administration) showed similar C_{max} , similar exposure (slightly higher for TF1), similar plasma concentrations at day 84 (C_{84}) as well as similar sustained concentration levels, indicating that the tested range of PLGA inherent viscosity is acceptable.

Considering the variability, TF1 also showed similar to slightly higher plasma levels and exposure than TF6 (Formulation I: PLGA microgranules containing degarelix pamoate salt with a ratio degarelix base to pamoate of 2.06:1, in oily vehicle, IM administration) and TF7 (Formulation J: PLGA microgranules containing degarelix pamoate salt, DL 34.3%, in oily vehicle, IM administration), indicating that the tested degarelix base to pamoate ratios and drug loadings (DL) are acceptable.

Table 8: PK3 Individual plasma concentrations (B1, B4: animals dead after day 84)

PK3	Reference Product Gonax					TF4					TF8				
	Subject_ID					Subject_ID					Subject_ID				
	B1	B2	B3	B4	B5	D1	D2	D3	D4	D5	H1	H3	H4	H5	
Nominal_time (day)	Concentration (ng/mL)														
0.02	186	248	91.0	106	57.9	147	71.6	79.9	45.9	37.4	81.0	56.3	72.8	93.8	
0.04	152	254	333	102	91.6	125	62.7	119	65.6	52.6	74.0	48.5	64.0	50.6	
0.08	225	131	96.0	336	118	173	110	147	93.2	79.3	63.0	65.4	62.7	64.9	
0.17	271	168	107	125	123	151	76.4	131	87.9	71.4	44.2	51.5	60.0	48.7	
0.33	219	69.6	65.2	108	114	132	71.8	114	70.1	61.4	36.3	56.8	52.4	47.5	
1.00	95.3	31.9	24.3	60.5	57.7	62.5	37.5	73.0	43.4	29.2	28.2	30.2	33.4	33.0	
2.00	67.8	25.6	20.3	36.4	34.1	48.3	28.3	65.0	37.1	19.3	22.2	20.0	30.0	25.7	
3.00	68.8	33.4	26.0	34.9	48.8	40.1	26.8	62.7	42.3	19.2	26.0	34.2	22.3	22.1	
7.00	70.5	47.1	26.4	54.8	45.4	40.5	24.8	74.5	59.3	44.7	35.8	48.0	28.2	46.2	
14.00	36.1	15.1	12.0	18.9	18.8	16.4	12.3	27.2	25.5	13.1	29.5	42.8	40.0	32.0	
21.00	32.3	10.7	5.34	16.4	16.6	15.7	10.4	26.0	23.5	6.41	34.9	29.4	25.1	20.3	
28.00	30.8	9.43	3.90	10.6	14.3	13.9	9.01	5.64	21.2	5.83	28.7	29.5	19.2	20.1	
35.00	23.8	6.59	3.38	5.69	10.4	11.1	7.13	22.5	13.8	5.61	23.7	24.3	17.9	17.0	
42.00	24.8	4.99	3.16	3.57	6.78	8.51	4.18	22.2	10.7	5.42	21.1	18.2	16.2	16.5	
49.00	21.0	2.56	<LLOQ	<LLOQ	3.40	11.6	5.09	14.4	5.97	13.2	19.0	17.3	15.4	12.8	
56.00	24.0	<LLOQ	<LLOQ	<LLOQ	2.64	5.33	<LLOQ	6.52	5.92	4.03	14.9	14.4	14.2	12.7	
63.00	20.7	<LLOQ	<LLOQ	<LLOQ	<LLOQ	3.90	<LLOQ	4.67	4.41	2.84	16.0	12.2	13.1	10.8	
70.00	22.1	<LLOQ	<LLOQ	<LLOQ	<LLOQ	3.15	<LLOQ	7.45	3.01	<LLOQ	15.2	10.0	12.7	11.7	
77.00	19.8	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ	2.54	<LLOQ	13.6	7.37	11.8	9.95	
84.00	15.7	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ	12.3	5.79	11.3	8.71	
91.00	---	<LLOQ	<LLOQ	---	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ	9.61	4.73	13.4	7.25	
98.00	---	<LLOQ	<LLOQ	---	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ	9.67	4.00	15.0	6.19	
105.00	---	<LLOQ	<LLOQ	---	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ	7.80	3.06	13.0	5.01	
112.00	---	<LLOQ	<LLOQ	---	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ	7.57	<LLOQ	12.6	4.24	

Table 9: PK3 Individual and Mean PK parameters

PK3	Subject_ID	Cmax (ng/mL)	AUC0-84 (day*ng/mL)	C84 (ng/mL)
Reference Product Gonax	B1	271	2670	15.7
	B2	254	784	0.00
	B3	333	490	0.00
	B4	336	918	0.00
	B5	123	1020	0.00
	Mean	263	1180	3.14
	SD	86.5	860	7.01
	CV%	32.8	73.1	224
	D1	173	1110	2.22E-14
	D2	110	659	0.00
TF4	D3	147	1650	5.33E-14
	D4	93.2	1350	1.27
	D5	79.3	751	0.00
	Mean	121	1110	0.254
	SD	38.7	413	0.568
	CV%	32.1	37.4	224
	H1	81.0	1890	12.3
	H3	65.4	1880	5.79
	H4	72.8	1640	11.3
	H5	93.8	1560	8.71
TF8	Mean	78.2	1740	9.52
	SD	12.2	167	2.92
	CV%	15.6	9.59	30.6

Table 10: PK4 individual concentrations

PK4	Reference compound Gonax commercial					TF6					TF9				
	Subject_ID					Subject_ID					Subject_ID				
	C1	C2	C3	C4	C5	F1	F2	F3	F4	F5	I1	I2	I3	I4	I5
	Concentration (ng/mL)														
Nominal_time (day)															
0.02	41.6	40.0	39.1	67.9	82.0	21.0	29.4	33.2	23.3	22.3	24.4	24.3	23.1	43.6	26.1
0.04	60.7	58.0	65.9	72.1	84.1	23.1	36.2	37.6	27.9	34.0	35.1	28.6	27.8	56.7	31.7
0.08	104	77.5	112	228	119	28.9	41.3	43.6	31.0	44.9	33.2	31.1	28.1	53.1	35.7
0.17	117	90.9	112	99.4	135	28.5	45.0	44.8	28.2	46.7	36.3	34.9	26.9	38.0	34.1
0.33	103	69.1	96.1	79.0	122	30.7	40.8	45.3	28.6	48.4	36.6	35.6	32.4	28.8	41.4
1.00	41.5	43.0	51.6	38.1	75.4	31.3	50.1	36.5	40.6	49.1	46.0	28.7	36.9	33.2	36.1
2.00	28.9	37.1	32.2	32.0	56.4	25.6	37.6	50.0	34.2	42.1	39.2	22.6	30.4	25.0	31.1
3.00	34.7	49.2	38.2	29.6	41.8	25.0	36.6	58.9	36.6	44.5	29.3	31.0	40.8	25.5	35.2
7.00	24.8	49.3	28.4	19.3	32.8	49.9	31.5	67.2	45.9	44.2	28.6	27.1	39.4	17.2	32.4
14.00	6.59	16.2	14.0	8.24	13.2	26.6	20.5	29.8	32.8	22.1	16.1	10.9	16.8	11.2	12.7
21.00	4.78	13.6	12.1	5.78	9.86	24.4	19.3	24.3	29.0	21.5	14.7	8.73	16.1	10.9	10.9
28.00	3.54	14.4	11.7	5.65	8.45	27.2	19.5	27.2	24.2	21.0	11.3	5.76	14.6	10.3	7.92
35.00	2.61	13.6	9.34	4.55	7.47	20.9	16.5	23.0	20.8	17.6	9.48	3.53	11.0	7.40	5.49
42.00	< LLOQ	8.86	6.12	3.07	4.85	19.0	16.9	18.4	17.1	16.1	8.80	3.03	9.13	5.88	4.26
49.00	< LLOQ	6.34	4.98	< LLOQ	4.24	17.2	14.0	15.5	14.4	11.9	6.67	< LLOQ	5.64	4.42	3.15
56.00	< LLOQ	4.70	4.29	3.53	3.71	13.7	10.7	11.8	11.3	9.74	4.91	< LLOQ	4.01	3.38	< LLOQ
63.00	< LLOQ	3.88	3.81	< LLOQ	3.57	15.3	9.11	11.7	10.8	9.41	3.37	< LLOQ	3.76	3.21	< LLOQ
70.00	< LLOQ	3.86	3.17	< LLOQ	2.95	13.6	7.74	9.38	8.46	7.19	< LLOQ	< LLOQ	< LLOQ	2.64	< LLOQ
77.00	< LLOQ	2.94	2.74	< LLOQ	4.49	11.2	5.88	7.99	6.77	6.93	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ

PK4	Reference compound Gonax commercial						TF6						TF9					
	Subject_ID						Subject_ID						Subject_ID					
	C1	C2	C3	C4	C5		F1	F2	F3	F4	F5		I1	I2	I3	I4	I5	
Nominal_time (day)	Concentration (ng/mL)																	
84.00	< LLOQ	2.53	< LLOQ	< LLOQ	< LLOQ		9.72	5.08	6.99	5.97	5.65		< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	
91.00	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ		8.83	4.57	6.66	4.99	4.94		< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	
98.00	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ		7.84	3.71	5.22	4.24	3.93		< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	
105.00	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ		6.88	3.17	4.66	3.55	3.37		< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	
112.00	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ		5.84	3.20	3.56	2.94	2.78		< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	
126.08	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ		4.50	< LLOQ	< LLOQ	< LLOQ	< LLOQ		< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	
140.00	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ		2.91	< LLOQ	< LLOQ	< LLOQ	< LLOQ		< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	
154.00	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ		< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ		< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	
168.00	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ		< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ		< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	

Table 11: PK4 individual and mean PK parameters

PK4 Test formulations	Subject_ID	Cmax (ng/mL)	AUC0-84 (day*ng/mL)	C84 (ng/mL)
Reference Products	C1	117	501	0.314
	C2	90.9	1120	2.53
	C3	112	893	2.37
	C4	228	567	0.509
	C5	135	912	1.49
	Mean	137	798	1.44
	SD	53.3	258	1.02
	CV%	39.0	32.3	70.9
	F1	49.9	1750	9.72
	F2	50.1	1360	5.08
TF6	F3	67.2	1880	6.99
	F4	45.9	1670	5.97
	F5	49.1	1480	5.65
	Mean	52.4	1630	6.68
	SD	8.43	209	1.83
	CV%	16.1	12.8	27.5
	I1	46.0	886	1.22
	I2	35.6	551	0.353
	I3	40.8	991	1.40
	I4	56.7	665	1.59
TF9	I5	41.4	695	0.657
	Mean	44.1	757	1.05
	SD	7.96	178	0.520
	CV%	18.0	23.4	49.8

Table 12: PK4 Individual plasma concentrations

PK4	Reference Product commercial Gonax®					TF6					TF8				
	Subject_ID					Subject_ID					Subject_ID				
	C1	C2	C3	C4	C5	F1	F2	F3	F4	F5	H1	H3	H4	H5	
Nominal_time (day)	Concentration (ng/mL)														
0.02	41.6	40.0	39.1	67.9	82.0	21.0	29.4	33.2	23.3	22.3	28.3	22.6	43.3	25.9	
0.04	60.7	58.0	65.9	72.1	84.1	23.1	36.2	37.6	27.9	34.0	27.5	35.1	52.3	24.5	
0.08	104	77.5	112	228	119	28.9	41.3	43.6	31.0	44.9	23.8	33.8	48.0	22.6	
0.17	117	90.9	112	99.4	135	28.5	45.0	44.8	28.2	46.7	22.3	33.4	32.8	21.3	
0.33	103	69.1	96.1	79.0	122	30.7	40.8	45.3	28.6	48.4	21.9	32.8	23.2	20.9	
1.00	41.5	43.0	51.6	38.1	75.4	31.3	50.1	36.5	40.6	49.1	26.3	26.8	30.1	25.7	
2.00	28.9	37.1	32.2	32.0	56.4	25.6	37.6	50.0	34.2	42.1	20.1	20.7	32.5	18.6	
3.00	34.7	49.2	38.2	29.6	41.8	25.0	36.6	58.9	36.6	44.5	22.0	25.7	33.4	20.4	
7.00	24.8	49.3	28.4	19.3	32.8	49.9	31.5	67.2	45.9	44.2	30.8	36.8	68.8	19.3	
14.00	6.59	16.2	14.0	8.24	13.2	26.6	20.5	29.8	32.8	22.1	10.7	16.9	20.1	12.1	
21.00	4.78	13.6	12.1	5.78	9.86	24.4	19.3	24.3	29.0	21.5	8.73	9.20	13.2	11.7	
28.00	3.54	14.4	11.7	5.65	8.45	27.2	19.5	27.2	24.2	21.0	10.3	10.3	13.3	10.1	
35.00	2.61	13.6	9.34	4.55	7.47	20.9	16.5	23.0	20.8	17.6	9.06	9.87	11.7	7.98	
42.00	< LLOQ	8.86	6.12	3.07	4.85	19.0	16.9	18.4	17.1	16.1	9.51	10.2	12.6	7.81	
49.00	< LLOQ	6.34	4.98	< LLOQ	4.24	17.2	14.0	15.5	14.4	11.9	7.53	8.55	12.1	7.10	
56.00	< LLOQ	4.70	4.29	3.53	3.71	13.7	10.7	11.8	11.3	9.74	7.96	8.70	10.4	5.98	
63.00	< LLOQ	3.88	3.81	< LLOQ	3.57	15.3	9.11	11.7	10.8	9.41	6.45	7.86	10.3	5.10	
70.00	< LLOQ	3.86	3.17	< LLOQ	2.95	13.6	7.74	9.38	8.46	7.19	5.80	6.12	10.1	3.53	
77.00	< LLOQ	2.94	2.74	< LLOQ	4.49	11.2	5.88	7.99	6.77	6.93	4.97	5.49	8.49	3.14	
84.00	< LLOQ	2.53	< LLOQ	< LLOQ	< LLOQ	9.72	5.08	6.99	5.97	5.65	4.24	5.23	7.69	2.69	

PK4	Reference Product commercial Gonax®					TF6					TF8				
	Subject_ID					Subject_ID					Subject_ID				
	C1	C2	C3	C4	C5	F1	F2	F3	F4	F5	H1	H3	H4	H5	
Nominal_time (day)	Concentration (ng/mL)														
91.00	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	8.83	4.57	6.66	4.99	4.94	3.42	4.54	5.98	< LLOQ	
98.00	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	7.84	3.71	5.22	4.24	3.93	2.92	4.16	5.66	< LLOQ	
105.00	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	6.88	3.17	4.66	3.55	3.37	2.93	4.04	4.94	< LLOQ	
112.00	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	5.84	3.20	3.56	2.94	2.78	2.57	3.38	5.18	< LLOQ	
126.08	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	4.50	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	2.62	3.68	< LLOQ	
140.00	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	2.91	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	
154.00	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	
168.00	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	

Table 13: PK4 Individual and Mean PK parameters

PK4	Subject_ID	C _{max} (ng/mL)	AUC ₀₋₈₄ (day*ng/mL)	C ₈₄ (ng/mL)
Reference Product	C1	117	501	0.314
	C2	90.9	1120	2.53
	C3	112	893	2.37
	C4	228	567	0.509
	C5	135	912	1.49
	Mean	137	798	1.44
	SD	53.3	258	1.02
	CV%	39.0	32.3	70.9
TF6	F1	49.9	1750	9.72
	F2	50.1	1360	5.08
	F3	67.2	1880	6.99
	F4	45.9	1670	5.97
	F5	49.1	1480	5.65
	Mean	52.4	1630	6.68
	SD	8.43	209	1.83
	CV%	16.1	12.8	27.5
TF8	H1	30.8	850	4.24
	H3	36.8	989	5.23
	H4	68.8	1380	7.69
	H5	25.9	739	2.69
	Mean	40.6	991	4.96
	SD	19.3	282	2.10
	CV%	47.7	28.4	42.3

Table 14: PK3 and PK4 Individual plasma concentrations (--- dead rat)

	PK3-TF5							PK4-TF5				
	Subject_ID							Subject_ID				
	E3	E4	E5	E6	E7	E1	E2	E3	E4	E5		
Nominal_time (day)	Concentration (ng/mL)											
0.02	896	66.7	108	2310	76.1	50.0	45.3	38.8	45.1	49.2		
0.04	335	81.2	130	2370	112	55.9	48.1	40.1	47.1	77.6		
0.08	320	114	182	1720	273							
0.17	234	122	233	661	203							
0.33	366	125	309	265	251							
1.00	272	127	274	259	260	72.2	51.0	63.8	59.5	56.5		
2.00	142	89.8	135	115	118	54.6	35.6	35.6	41.5	39.1		
3.00	89.3	95.9	94.4	76.6	81.8							
6.00						35.1	28.8	21.6	30.4	29.0		
7.00	61.8	87.1	57.2	58.4	57.7							
13.00						25.0	21.1	25.1	21.2	23.3		
14.00	32.9	48.6	40.5	32.6	43.2							
20.00						21.5	22.3	22.2	17.2	19.1		
21.00	24.0	43.1	34.8	22.4	21.8							
27.00						22.3	23.1	24.1	17.4	18.5		
28.00	24.6	34.4	33.9	22.5	21.6							
34.00						20.9	22.0	20.4	15.6	19.0		
35.00	17.7	17.1	22.9	13.8	18.8							
41.00						20.9	21.4	28.0	15.8	17.7		
42.00	15.2	9.16	15.3	10.2	18.4							
48.00						19.3	18.9	21.2	12.9	16.5		
49.00	6.05	3.84	9.53	7.26	5.23							
55.00						20.0	17.6	12.4	14.4	14.1		
56.00	12.7	3.46	10.9	10.6	13.0							
62.00						14.4	11.9	18.3	13.9	14.9		
63.00	5.93	<LLOQ	7.12	3.01	11.5							

	PK3-TF5					PK4-TF5				
	Subject_ID					Subject_ID				
	E3	E4	E5	E6	E7	E1	E2	E3	E4	E5
Nominal_time (day)	Concentration (ng/mL)									
69.00						14.0	10.4	14.8	10.6	13.7
70.00	5.42	<LLOQ	5.75	<LLOQ	9.96					
76.00						11.6	10.2	14.6	10.2	11.8
77.00	4.23	<LLOQ	4.08	<LLOQ	9.01					
83.00						10.6	7.80	10.7	7.92	11.3
84.00	3.14	<LLOQ	2.81	<LLOQ	7.98					
90.00		<LLOQ				10.6	7.84	11.3	8.22	10.7
91.00	2.53	<LLOQ	<LLOQ	<LLOQ	7.02					
97.00						8.48	6.78	8.04	7.60	8.90
98.00	<LLOQ	<LLOQ	<LLOQ	<LLOQ	5.02					
104.00						7.54	5.98	8.96	6.60	9.86
105.00	<LLOQ	<LLOQ	<LLOQ	<LLOQ	4.07					
111.00						< LLOQ	6.04	---	5.98	7.90
112.00	<LLOQ	<LLOQ	<LLOQ	<LLOQ	3.04					
125.00						5.56	< LLOQ	---	< LLOQ	6.64
140.00						< LLOQ	< LLOQ	---	< LLOQ	< LLOQ
153.00						< LLOQ	< LLOQ	---	< LLOQ	< LLOQ
167.00						< LLOQ	< LLOQ	---	< LLOQ	< LLOQ

Table 15: PK4 and PK3 Individual and mean PK parameters

Study & Test Formulation	Subject_ID	Cmax (ng/mL)	C84 (ng/mL)	AUC0-84 (day*ng/mL)
PK3 -TF5	E3	896	3.14	2180
	E4	127	0.00	2090
	E5	309	2.81	2360
	E6	2370	0.00	2090
	E7	273	7.98	2210
	Mean	795	2.79	2190
	SD	929	3.26	113
PK4-TF5	CV%	117	117	5.16
	E1	72.2	10.6	1800
	E2	51.0	7.81	1610
	E3	63.8	10.7	1740
	E4	59.5	7.96	1430
	E5	77.6	11.2	1580
	Mean	64.8	9.65	1630
	SD	10.5	1.63	144
	CV%	16.2	16.9	8.87

PK5	Reference Product Commercial Firmagon®					TF2					TF3					TF4				
	Subject_ID					Subject_ID					Subject_ID					Subject_ID				
	A1	A2	A3	A4	A5	B1	B2	B3	B4	B5	C1	C2	C3	C4	C5	D1	D2	D4	D5	
Nominal_time (day)	Concentration (ng/mL)																			
28.25	55.2	56.5	42.9	53.4	31.2	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
29.00	53.5	36.2	28.6	35.3	22.4	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
30.00	24.6	33.7	27.6	32.3	17.0	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
31.00	21.6	32.4	23.5	33.8	17.9	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
35.00	14.6	20.3	18.3	17.7	13.9	25.0	18.3	25.2	27.9	26.8	14.6	17.4	4.63	18.9	20.7	17.2	19.3	11.2	5.16	
43.00	12.0	12.1	11.3	13.3	7.27	21.9	14.3	23.5	23.1	21.0	10.1	17.0	3.81	17.3	19.1	14.1	17.5	9.06	4.71	
49.00	11.0	9.94	10.7	11.8	6.25	19.4	12.7	17.6	20.2	19.4	10.7	15.4	3.90	15.6	15.7	13.2	15.1	8.87	3.74	
56.00	9.03	8.62	9.90	10.4	5.76	15.9	15.0	16.5	17.7	15.8	9.56	14.1	3.20	15.0	15.0	11.2	12.5	6.68	3.24	
56.04	20.0	16.9	25.6	25.2	15.9	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
56.08	29.1	25.5	42.5	35.6	22.5	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
56.25	54.8	44.4	50.6	43.4	24.0	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
57.00	41.1	41.7	45.8	43.3	18.4	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
58.00	28.7	29.4	33.9	31.5	22.3	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
59.00	22.3	24.7	25.5	25.2	19.5	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
63.00	15.8	17.8	17.2	17.9	19.5	12.8	9.38	13.1	15.8	11.3	10.4	11.9	2.75	13.0	13.0	10.1	9.91	5.25	2.74	

PK5	Reference Product Commercial Firmagon®					TF2					TF3					TF4					
	Subject_ID					Subject_ID					Subject_ID					Subject_ID					
	A1	A2	A3	A4	A5	B1	B2	B3	B4	B5	C1	C2	C3	C4	C5	D1	D2	D3	D4	D5	D6
Nominal_ time (day)	Concentration (ng/mL)																				
70.00	13.3	11.8	14.2	14.0	11.1	13.1	7.75	10.6	13.4	8.69	10.3	10.1	2.26	12.5	12.0	8.41	6.91	4.72	4.20		
77.00	9.79	9.62	11.8	13.7	8.29	10.6	6.31	8.12	12.8	7.46	11.4	8.17	2.21	10.3	10.6	6.83	4.89	4.01	4.192		
84.00	8.7	7.53	10.8	12.4	6.57	8.91	6.21	7.07	9.84	5.84	9.42	6.93	1.92	9.44	8.43	5.70	3.78	3.42	3.145		
92.00	8.7	7.61	11.6	12.1	6.91	7.51	2.60	4.85	9.57	4.89	9.29	5.79	1.33	7.41	7.35	4.14	3.15	3.67	3.154		
98.00	6.52	6.55	10.0	10.9	6.23	6.52	4.89	3.92	7.75	4.10	9.89	4.06	1.29	6.78	5.75	3.47	2.36	2.81	2.109		
105.00	6.54	5.84	8.71	10.1	5.71	5.61	3.92	2.81	7.03	3.03	7.98	3.25	1.35	5.61	4.79	2.40	1.86	2.65	2.109		
112.00	5.90	5.30	8.49	9.82	4.56	4.91	4.18	2.56	6.42	2.44	9.23	3.01	1.03	4.24	3.82	2.20	1.53	2.22	2.109		
126.00	3.99	3.53	6.79	8.16	3.49	3.55	3.07	1.76	4.56	1.43	9.77	2.18	<LL	2.87	3.07	1.19	<LL	1.96	1.109		
140.00	3.53	3.11	5.41	6.03	3.13	2.73	2.60	1.33	3.51	1.09	8.70	1.82	<LL	2.22	2.34	1.13	<LL	1.70	1.109		
154.00	2.81	2.28	4.28	4.29	2.08	2.10	1.86	1.05	2.48	<LL	10.9	1.49	<LL	1.17	1.90	<LL	<LL	1.41	1.109		
168.00	1.87	1.90	2.86	3.54	1.88	2.60	2.08	<LL	1.70	<LL	4.22	1.23	<LL	<LL	1.62	<LL	<LL	1.49	1.109		

Table 17: PK5 Individual and Mean PK parameters

PK5	Subject_ID	Cmax (ng/mL)	AUC0-84 (day*ng/mL)	C84 (ng/mL)
Reference Product Firmagon	A1	65.2	1210	8.12
	A2	92.8	1450	7.53
	A3	102	1340	10.8
	A4	109	1540	12.4
	A5	80.6	1030	6.57
	Mean	89.9	1320	9.08
	SD	17.4	202	2.43
	CV%	19.4	15.3	26.7
TF2	B1	79.6	2190	8.91
	B2	87.9	1680	6.21
	B3	69.6	1970	7.07
	B4	91.1	2150	9.84
	B5	119	2300	5.84
	Mean	89.4	2060	7.57
	SD	18.5	243	1.74
	CV%	20.7	11.8	22.9
TF3	C1	132	1110	9.42
	C2	85.5	1530	6.93
	C3	45.0	384	1.92
	C4	59.5	1470	9.44
	C5	66.4	1890	8.43
	Mean	77.7	1280	7.23

PK5	Subject_ID	Cmax (ng/mL)	AUC0-84 (day*ng/mL)	C84 (ng/mL)
	SD	33.8	571	3.14
	CV%	43.4	44.7	43.4
TF4	D1	48.1	1460	5.70
	D2	43.6	1430	3.78
	D4	37.7	932	3.42
	D5	27.9	488	1.45
	Mean	39.3	1080	3.59
	SD	8.71	461	1.74
	CV%	22.1	42.8	48.5

PK5	Reference Product Firmagon®						TF6					TF7				
	Subject_ID						Subject_ID					Subject_ID				
	A1	A2	A3	A4	A5		F1	F2	F3	F4	F5	G1	G2	G3	G4	G5
Nominal_time (day)	Concentration (ng/mL)															
57.00	41.1	41.7	45.8	43.3	18.4		28.1	15.2	17.3	26.6	17.4	13.8	9.53	12.0	10.9	15.5
58.00	28.7	29.4	33.9	31.5	22.3											
59.00	22.3	24.7	25.5	25.2	19.5											
63.00	15.8	17.8	17.2	17.9	19.5											
70.00	13.3	11.8	14.2	14.0	11.1		22.0	14.0	14.7	23.4	13.4	10.2	8.22	10.2	9.91	13.3
77.00	9.79	9.62	11.8	13.7	8.29		18.7	13.2	11.9	20.3	11.6	10.8	7.34	8.86	7.18	11.4
84.00	8.12	7.53	10.8	12.4	6.57		15.0	11.2	9.90	17.4	9.81	8.22	6.18	7.30	6.25	9.72
92.00	8.14	7.61	11.6	12.1	6.91		11.7	9.65	8.44	14.8	6.87	6.54	4.85	5.49	5.53	7.26
98.00	6.52	6.55	10.0	10.9	6.23		11.2	7.97	6.65	13.7	4.86	5.35	4.55	4.67	4.23	5.54
105.00	6.54	5.84	8.71	10.1	5.71		8.63	7.67	6.25	12.6	4.81	3.96	3.68	3.38	3.40	4.81
112.00	5.90	5.30	8.49	9.82	4.56		7.67	6.93	5.35	11.3	4.12	3.67	2.99	2.76	2.93	3.76
126.00	3.99	3.53	6.79	8.16	3.49		6.11	6.69	4.41	7.37	2.42	2.61	2.56	1.60	2.23	2.27
140.00	3.53	3.11	5.41	6.03	3.13		3.86	5.48	3.25	5.45	1.51	1.64	1.73	<LLOQ	1.70	1.55
154.00	2.81	2.12	4.28	4.29	2.08		2.40	4.50	2.73	4.08	1.30	1.12	1.44	<LLOQ	1.19	1.00
168.00	1.87	1.90	2.86	3.54	1.88		1.57	3.41	1.93	3.48	<LLOQ	<LLOQ	1.39	<LLOQ	<LLOQ	<LLOQ

Table 19: PK5 Individual and Mean PK Parameters

PK5	Subject_ID	Cmax (ng/mL)	AUC0-84 (day*ng/mL)	C84 (ng/mL)
Reference product Firmagon®	A1	65.2	1210	8.12
	A2	92.8	1450	7.53
	A3	102	1340	10.8
	A4	109	1540	12.4
	A5	80.6	1030	6.57
	Mean	89.9	1320	9.08
	SD	17.4	202	2.43
	CV%	19.4	15.3	26.7
TF6	F1	116	3560	15.0
	F2	74.3	2000	11.2
	F3	90.4	2600	9.90
	F4	89.3	2900	17.4
	F5	77.8	2430	9.81
	Mean	89.5	2700	12.7
	SD	16.3	583	3.40
	CV%	18.2	21.6	26.8
TF7	G1	90.2	2590	8.22
	G2	76.8	1730	6.18
	G3	118	2640	7.30
	G4	826	2650	6.25
	G5	115	2660	9.72
	Mean	245	2460	7.53
	SD	325	408	1.48
	CV%	133	16.6	19.7

Table 20: PK8 Individual plasma concentrations

PK8	TF1					TF3					TF4				
	Subject_ID					Subject_ID					Subject_ID				
	A1	A2	A3	A4	A5	C1	C2	C4	C5	D1	D2	D3	D4	D5	
Nominal time (day)	Concentration (ng/mL)														
0.02	45.8	104	40.7	36.9	50.4	94.2	68.7	52.5	85.2	117	68.6	74.7	64.5	65.2	
0.04	110	111	79.5	62.4	51.7	106	57.4	54.6	41.6	148	76.4	78.4	43.9	91.9	
0.08	75.1	69.3	88.3	56.8	60.7	95.1	64.3	56.4	54.3	65.7	92.7	103	37.9	84.6	
0.17	61.4	62.3	86.9	50.4	53.8	93.1	54.5	64.1	56.9	56.8	66.7	66.0	49.5	71.7	
0.33	63.8	55.5	74.3	45.3	89.1	64.7	57.6	37.3	42.3	45.4	63.7	71.5	30.0	57.1	
2.00	106	66.5	74.1	41.3	74.5	61.4	60.8	39.7	41.5	46.3	69.4	75.7	28.4	56.6	
3.00	76.9	58.8	61.1	33.9	50.7	48.1	56.2	36.9	31.4	31.1	67.8	58.9	26.0	46.0	
4.00	68.8	55.9	52.6	31.5	51.8	43.1	41.1	31.3	28.9	22.3	56.7	51.5	23.7	39.9	
8.00	42.1	46.8	58.7	58.7	56.9	45.5	41.1	28.8	34.5	15.8	55.7	64.8	22.6	62.8	
15.00	27.1	30.2	37.0	29.3	34.9	31.1	28.6	23.3	24.4	12.8	38.6	42.0	19.7	42.1	
22.00	26.5	24.9	30.8	23.4	31.1	25.8	27.0	18.2	21.4	11.7	31.9	36.0	17.2	29.1	
29.00	19.3	21.5	23.8	23.9	26.9	22.6	25.3	16.9	18.8	10.2	24.2	29.4	13.2	23.9	
36.00	17.8	21.8	22.7	25.1	24.1	19.0	22.4	14.2	17.2	8.12	19.5	23.2	12.5	19.3	
43.00	17.8	19.9	18.4	23.7	25.8	17.3	21.2	11.9	14.1	7.69	17.5	18.0	10.5	17.9	
50.00	15.2	16.3	16.5	18.0	19.1	15.0	20.2	10.8	15.0	7.27	15.9	17.3	10.2	15.5	
57.00	14.8	15.6	13.8	18.4	16.7	12.7	21.2	10.4	19.7	6.17	13.1	19.6	8.63	12.7	
64.00	11.3	13.1	12.4	16.3	15.3	11.2	15.9	9.04	18.9	9.89	11.5	14.4	7.21	11.8	
71.00	9.14	12.4	8.64	11.6	11.3	9.52	12.4	8.43	11.2	6.02	9.29	10.8	6.41	9.99	
78.00	7.69	10.5	7.45	10.8	9.46	9.27	11.8	7.55	9.46	5.49	8.16	11.0	5.50	8.54	
85.00	6.63	9.10	6.05	10.6	8.11	8.12	10.1	6.94	9.09	5.82	6.98	8.79	4.62	7.34	
99.00	3.55	4.74	2.03	5.20	4.44	5.53	6.78	3.73	6.81	4.56	4.53	6.68	2.34	4.81	
113.00	2.48	3.53	1.38	5.38	2.98	4.08	4.99	2.79	5.27	3.68	2.38	4.80	1.49	3.59	
127.00	1.78	2.83	1.32	3.10	2.18	3.20	3.48	1.95	4.84	3.06	1.90	3.71	<LLOQ	2.20	
141.00	1.29	1.89	<LLOQ	2.18	1.37	2.61	2.52	1.45	3.91	2.90	1.50	3.17	<LLOQ	1.49	
155.00	<LLOQ	1.26	<LLOQ	1.62	<LLOQ	1.85	1.75	<LLOQ	3.03	2.66	1.61	2.30	<LLOQ	<LLOQ	

PK8	TF1					TF3					TF4				
	Subject_ID					Subject_ID					Subject_ID				
	A1	A2	A3	A4	A5	C1	C2	C4	C5		D1	D2	D3	D4	D5
Nominal time (day)	Concentration (ng/mL)														
169.00	<LLOQ	1.12	<LLOQ	1.31	<LLOQ	1.39	1.18	1.28	2.45		1.95	1.06	2.03	<LLOQ	<LLOQ

Table 21: PK8 Individual and Mean PK parameters

PK8 Test Formulations	Subject_ID	Cmax (ng/mL)	AUC0-84 (day*ng/mL)	C84 (ng/mL)
TF1	A1	110	1870	6.77
	A2	111	1930	9.29
	A3	88.3	2050	6.23
	A4	62.4	1960	10.6
	A5	89.1	2200	8.29
	Mean	92.3	2000	8.24
	SD	20.1	128	1.79
	CV%	21.7	6.41	21.8
TF3	C1	106	1800	8.28
	C2	68.7	2000	10.3
	C4	64.1	1300	7.02
	C5	85.2	1610	9.14
	Mean	81.0	1680	8.68
	SD	19.1	295	1.38
	CV%	23.5	17.6	15.9
TF4	D1	148	903	5.77
	D2	92.7	2020	7.14
	D3	103	2290	9.08
	D4	64.5	1070	4.74
	D5	91.9	1980	7.50
	Mean	99.9	1650	6.84
	SD	30.2	622	1.66
	CV%	30.3	37.6	24.3

Table 22: PK8 Individual concentrations

PK8	Test Formulations									
	TF1					TF6				
	Subject_ID									
	A1	A2	A3	A4	A5	F1	F2	F3	F4	F5
Nominal_time_1 (day)	Concentration (ng/mL)									
0.02	45.8	104	40.7	36.9	50.4	141	46.7	51.9	160	29.5
0.04	110	111	79.5	62.4	51.7	90.0	35.8	66.6	68.8	25.9
0.08	75.1	69.3	88.3	56.8	60.7	49.0	27.4	53.4	34.3	22.4
0.17	61.4	62.3	86.9	50.4	53.8	37.9	24.8	43.8	22.2	19.9
0.33	63.8	55.5	74.3	45.3	89.1	46.8	24.0	36.9	22.3	24.9
2.00	106	66.5	74.1	41.3	74.5	75.2	49.3	50.2	32.1	24.6
3.00	76.9	58.8	61.1	33.9	50.7	63.1	48.2	43.1	30.5	22.5
4.00	68.8	55.9	52.6	31.5	51.8	41.7	39.1	39.1	37.7	21.8
8.00	42.1	46.8	58.7	58.7	56.9	52.3	27.1	44.1	41.6	26.1
15.00	27.1	30.2	37.0	29.3	34.9	40.2	18.3	25.5	24.3	16.4
22.00	26.5	24.9	30.8	23.4	31.1	32.0	15.3	20.6	21.3	16.2
29.00	19.3	21.5	23.8	23.9	26.9	29.6	13.9	17.8	19.4	13.3
36.00	17.8	21.8	22.7	25.1	24.1	22.7	13.1	15.3	21.4	12.7
43.00	17.8	19.9	18.4	23.7	25.8	19.3	11.0	13.4	17.1	11.1
50.00	15.2	16.3	16.5	18.0	19.1	18.8	9.66	11.6	16.4	9.31
57.00	14.8	15.6	13.8	18.4	16.7	16.8	9.83	9.22	16.3	7.99
64.00	11.3	13.1	12.4	16.3	15.3	14.7	8.03	8.96	14.6	6.13
71.00	9.14	12.4	8.64	11.6	11.3	13.0	7.74	6.01	13.8	4.79
78.00	7.69	10.5	7.45	10.8	9.46	12.3	6.33	5.42	12.7	3.46
85.00	6.63	9.10	6.05	10.6	8.11	11.4	5.03	4.81	12.1	2.45
99.00	3.55	4.74	2.03	5.20	4.44	7.22	2.77	2.39	7.12	1.71
113.00	2.48	3.53	1.38	5.38	2.98	4.89	1.71	1.50	5.60	<LLOQ
127.00	1.78	2.83	1.32	3.10	2.18	3.77	1.33	<LLOQ	4.54	<LLOQ
141.00	1.29	1.89	<LLOQ	2.18	1.37	2.82	<LLOQ	<LLOQ	3.19	<LLOQ

PK8	Test Formulations									
	TF1					TF6				
	Subject_ID									
	A1	A2	A3	A4	A5	F1	F2	F3	F4	F5
Nominal_time_1 (day)	Concentration (ng/mL)									
155.00	<LLOQ	1.26	<LLOQ	1.62	<LLOQ	2.15	<LLOQ	<LLOQ	1.90	<LLOQ
169.00	<LLOQ	1.12	<LLOQ	1.31	<LLOQ	1.74	<LLOQ	<LLOQ	1.57	<LLOQ

Table 23: PK8 Individual and mean PK parameters

PK8 Test Formulations	Subject_ID	Cmax (ng/mL)	AUC0-84 (day*ng/mL)	C84 (ng/mL)
TF1	A1	110	1870	6.77
	A2	111	1930	9.29
	A3	88.3	2050	6.23
	A4	62.4	1960	10.6
	A5	89.1	2200	8.29
	Mean	92.3	2000	8.24
	Standard Deviation (SD)	20.1	128	1.79
	CV%	21.7	6.41	21.8
TF6	F1	141	2170	11.5
	F2	49.3	1190	5.20
	F3	66.6	1440	4.89
	F4	160	1690	12.2
	F5	29.5	993	2.57
	Mean	89.2	1500	7.28
	SD	57.7	459	4.31
	CV%	64.6	30.7	59.3

Table 24: PK8 individual concentrations

PK8	TF1					TF7				
	Subject_ID					Subject_ID				
	A1	A2	A3	A4	A5	G1	G2	G4	G5	
Nominal_time_1 (day)	Concentration (ng/mL)									
0.02	45.8	104	40.7	36.9	50.4	121	271	56.3	111	
0.04	110	111	79.5	62.4	51.7	80.5	56.8	62.6	156	
0.08	75.1	69.3	86.3	56.8	60.7	75.5	70.6	56.3	139	
0.17	61.4	62.3	86.9	50.4	53.8	66.3	66.5	44.2	121	
0.33	63.8	55.5	74.3	45.3	89.1	68.6	73.4	44.9	107	
2.00	106	66.5	74.1	41.3	74.5	58.9	74.7	58.9	77.5	
3.00	76.9	58.8	61.1	33.9	50.7	48.2	52.6	43.8	48.6	
4.00	68.8	55.9	52.6	31.5	51.8	37.8	53.0	40.4	47.1	
8.00	42.1	46.8	58.7	58.7	56.9	34.8	57.5	35.1	40.8	
15.00	27.1	30.2	37.0	29.3	34.9	27.8	39.2	20.2	23.0	
22.00	26.5	24.9	30.8	23.4	31.1	22.6	29.5	16.1	18.6	
29.00	19.3	21.5	23.8	23.9	26.9	20.4	23.0	13.2	13.7	
36.00	17.8	21.8	22.7	25.1	24.1	21.1	21.7	11.6	13.4	
43.00	17.8	19.9	18.4	23.7	25.8	20.3	16.4	11.4	10.6	
50.00	15.2	16.3	16.5	18.0	19.1	19.3	14.8	10.8	10.6	
57.00	14.8	15.6	13.8	18.4	16.7	17.5	12.2	9.63	9.86	
64.00	11.3	13.1	12.4	16.3	15.3	14.2	11.7	8.64	9.09	
71.00	9.14	12.4	8.64	11.6	11.3	13.0	9.40	7.87	6.66	
78.00	7.69	10.5	7.45	10.8	9.46	10.7	9.24	7.63	5.50	
85.00	6.63	9.10	6.05	10.6	8.11	10.6	7.52	6.97	5.10	
99.00	3.55	4.74	2.03	5.20	4.44	6.16	7.15	4.97	2.77	
113.00	2.48	3.53	1.38	5.38	2.98	4.75	2.26	3.94	2.12	
127.00	1.78	2.83	1.32	3.10	2.18	4.32	2.14	3.72	1.47	
141.00	1.29	1.89	<LLOQ	2.18	1.37	3.31	1.56	3.66	<LLOQ	
155.00	<LLOQ	1.26	<LLOQ	1.62	<LLOQ	2.91	1.00	2.86	<LLOQ	

PK8	TF1					TF7				
	Subject_ID					Subject_ID				
	A1	A2	A3	A4	A5	G1	G2	G4	G5	
Nominal_time_1 (day)	Concentration (ng/mL)									
169.00	<LLOQ	1.12	<LLOQ	1.31	<LLOQ	2.68	<LLOQ	2.77	<LLOQ	<LLOQ

Table 25: PK8 individual and Mean PK parameters

PK8 Test formulation	Subject_ID	Cmax (ng/mL)	AUC0-84 (day*ng/mL)	C84 (ng/mL)
TF1	A1	110	1870	6.77
	A2	111	1930	9.29
	A3	88.3	2050	6.23
	A4	62.4	1960	10.6
	A5	89.1	2200	8.29
	Mean	92.3	2000	8.24
	SD	20.1	128	1.79
	CV%	21.7	6.41	21.8
TF7	G1	121	1820	10.6
	G2	271	2010	7.74
	G4	62.6	1300	7.06
	G5	156	1470	5.16
	Mean	153	1650	7.64
	SD	87.9	323	2.26
	CV%	57.5	19.6	29.6

Example 3: Clinical trial

A Phase 2, randomized, open-label, dose-finding study of a degarelix 12-week extended-release formulation (Composition K, 200 or 300 mg degarelix, in the form of pamoate salt, in MIGLYOL® 812 N) [the Study Formulation] will be conducted in participants with locally advanced/metastatic prostate cancer. The study will evaluate the pharmacokinetics (PK), pharmacodynamics (PD), efficacy, safety, and tolerability of the Study Formulation.

The study may enroll up to 3 cohorts. Each cohort may be closed once approximately 20 participants are enrolled. At least 6 participants must be enrolled in Cohort 1 and followed up for 28 days before initiating a cohort at a higher dose level.

- **Cohort 1:** Participants will receive a single intramuscular (IM) administration of 200 mg (based on degarelix free base) of Study Formulation.

Six participants will initially be enrolled into Cohort 1 (200 mg) and enrollment will be subsequently paused. Four weeks after the Study Formulation administration to the last enrolled participant, the totality of PK, PD, and safety data from the 6 participants collected up to that point in time will be analyzed. If the safety and PK/PD data from the first 6 participants is considered adequate, enrollment in Cohort 1 will be resumed and in parallel enrollment into Cohort 2 (300 mg) will be initiated. Therefore, following initiation of Cohort 2, participants may be randomized between Cohort 1 and 2.

- **Cohort 2:** Participants will receive a single IM administration of 300 mg (based on degarelix base) of Study Formulation.

For Cohorts 1 and 2, the study consists of a screening period of up to 5 weeks; a 12-week treatment period, and up to a 12-week follow-up period including a safety follow-up (SFU) and additional PK assessment(s). After a 12-week treatment period, the participants will continue treatment with a standard of care ([SoC] i.e., non-degarelix or degarelix containing SoC) as per Investigator's discretion.

- Participants who will receive a non-degarelix containing SoC after EOT will continue in the study and undergo safety and PK assessments until Day 169, which will represent end of study (EOS) for these participants.
- Participants who will receive a degarelix-containing SoC after EOT will have a 4-week SFU and EOS at Day 113. The SFU visit, and an additional PK assessment on Day 113 will represent EOS for these participants. The

participants shall switch to a degarelix containing SoC after the EOS. If medically indicated, the participants could receive a degarelix containing SoC after EOT.

If a higher or alternative dose is deemed necessary based on the preliminary data (PK, PD, efficacy, and safety) from Cohorts 1 and 2, Cohort 3 will be initiated. Continuation of participants in Cohorts 1 and 2 will be regularly assessed based on testosterone levels and achievement of castration in each cohort.

- Cohort 3: Dose selection for this cohort will be guided by population PK/PD modeling and simulation derived from the PK and PD data from Cohorts 1 and 2 as well as safety and efficacy in these cohorts. Based on the preliminary assumptions, the provisional dose level for this cohort is: Study formulation loading dose (IM) of 400 mg (based on degarelix free base) (2 injections of 200 mg) at the study start (Day 1) followed by a maintenance dose of 200 mg (based on degarelix free base) (IM) 12 weeks after receiving the loading dose (i.e., at Day 85). The selected dose for Cohort 3 will be documented in the Sponsor Data Review Committee (DRC) proceedings.

For Cohort 3, the study consists of a screening period of up to 5 weeks; a 24-week treatment period, and a 4-week SFU period. For participants who have completed the planned study duration, the EOS will occur after the 4 week SFU period. After the treatment period, participants shall receive a SoC treatment as per Investigator's decision.

End of treatment:

Cohorts 1 and 2: the end of treatment (EOT) visit will occur 12 weeks after the Study Formulation administration (i.e., on Day 85), or earlier if premature discontinuation occurs before EOT.

Cohort 3: the EOT visit will occur 12 weeks after administration of the Study Formulation maintenance dose (i.e., on Day 169), or earlier if premature discontinuation occurs before EOT.

For all cohorts, participants who do not achieve testosterone castration levels (<50 ng/dL) at Day 29 or later, will receive a SoC as per Investigator's discretion (i.e., non-degarelix or degarelix containing SoC). Testosterone levels will be assessed locally at site to enable a timely decision. The EOT visit will occur before switching to the new therapy.

Objectives, endpoints, and estimands

The Primary, Secondary and Exploratory objectives of the study as well as estimands (endpoints, population, treatment, summary measures, intercurrent event strategy) are presented in Table 26 below.

5 Table 26

Objectives	Estimands	Ref. #
Primary Objectives		
To determine the PK of Study Formulation	• Endpoints: Degarelix plasma PK profile and PK parameters over 12 weeks after Study Formulation dosing, including but not limited to: - Maximum concentration (C_{max}) - Area under the concentration-time curve over 12 weeks (AUC_{84d}) - Concentration at 12 weeks (C_{84d}) This will be derived for each treatment period. • Population: Adult participants with histologically confirmed locally advanced/metastatic prostate cancer who are candidates for continuous ADT • Treatment: Study Formulation (IM) • Population-level summary measure: Mean, geometric mean, median, standard deviation (SD), coefficient of variation (CV), minimum (min), maximum (max), geometric CV, and 95% confidence interval (CI) of plasma concentrations over time and PK parameters • Intercurrent event strategy: Relevant events (e.g., dosing or sampling issue, co-medication) that might have an impact on a particular PK assessment will lead to exclusion of the data from the PK analysis	1
To determine the PD of Study Formulation	• Endpoint: Testosterone serum concentration profile from Day 1 to Day 85 for all cohorts and from Day 85 to Day 169 in case of Cohort 3 • Population: See Ref #1 • Treatment: See Ref #1	2

Objectives	Estimands	Ref. #
	• Population-level summary measure: Mean, median, SD, CV, min, max, 95% CI of serum testosterone concentrations over time • Intercurrent event strategy: There will be no imputation of missing data, and at each timepoint, only participants with available data will be considered	
Secondary Objectives		
To evaluate the efficacy of Study Formulation in achieving and maintaining castration	• Endpoints: - Achievement and maintenance of testosterone castration (testosterone level <50 ng/dL and <20 ng/dL) from Day 29 to Day 85 for all cohorts - Maintenance of testosterone castration (testosterone level <50 ng/dL and <20 ng/dL) from Day 29 to Day 169 for Cohort 3 • Population: See Ref #1 • Treatment: See Ref #1 • Population-level summary measures: - Percentage of participants who achieved a testosterone level <50 ng/dL and <20 ng/dL at Day 15, 22, 29, 85, and 169 (in case of Cohort 3) - Percentage of participants who maintained a testosterone level <50 ng/dL and <20 ng/dL from Day 29 to Day 85 - Percentage of participants who maintained a testosterone level <50 ng/dL and <20 ng/dL from Day 29 to Day 169 (in case of Cohort 3) • Intercurrent event strategy: The following events may lead to exclusion of the data from the analysis: - Any event (e.g., participant's withdrawal) that prevents collection of 2 or more consecutive blood samples - Other hormonal prohibited medications	3
To evaluate the efficacy of Study Formulation in terms of time to castration	• Endpoint: Time to castration (testosterone level <50 ng/dL and <20 ng/dL)	4

Objectives	Estimands	Ref. #
	• <u>Population:</u> See Ref #1 • <u>Treatment:</u> See Ref #1 • <u>Population-level summary measure:</u> - Time to reach a testosterone level <50 ng/dL - Time to reach a testosterone level <20 ng/dL Time to castration will be summarized based on cumulative incidence estimates (based on 1-KM, where KM is the Kaplan-Meier estimate) • <u>Intercurrent event strategy:</u> See Ref #3	
To assess the local tolerability at the injection site	• <u>Endpoint:</u> Investigator's assessment (4-point rating scale) of erythema, swelling, and induration at the injection site immediately after and 2 hours after Study Formulation injection • <u>Population:</u> See Ref #1 • <u>Treatment:</u> See Ref #1 • <u>Population-level summary measure:</u> Distribution of Investigator's rating (% per rating scale) at each timepoint • <u>Intercurrent event strategy:</u> The endpoint will be analyzed for any (non-null) exposure, regardless of the level of exposure	5
To assess injection site pain	• <u>Endpoint:</u> Participants' self-assessment of pain at the injection site immediately after and 2 hours after Study Formulation injection using visual analog scale (VAS) • <u>Population:</u> See Ref #1 • <u>Treatment:</u> See Ref #1 • <u>Population-level summary measure:</u> Mean, SD, 95% CI, median, Q1, Q3, min, max of the VAS score at each time point • <u>Intercurrent event strategy:</u> See Ref #5	6
To assess the safety profile of Study Formulation	• <u>Endpoints:</u> - Incidence and severity of treatment-emergent adverse events (TEAEs), related TEAEs, serious TEAEs, adverse events of special interest (AESIs), death, and TEAEs leading to treatment delay, and/or discontinuation,	7

Objectives	Estimands	Ref. #
	graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0; - Safety laboratory parameters and related severity based on NCI-CTCAE version 5.0; - Changes from baseline in vital signs, weight, and electrocardiogram (ECG). • <u>Population:</u> See Ref #1 • <u>Treatment:</u> See Ref #1 • <u>Population-level summary measure:</u> - For incidence of TEAEs: Percentages of participants with at least 1 event. For severity: Distribution of severity - For changes in laboratory values from baseline: Proportion of laboratory abnormalities and distribution of grading for laboratory abnormalities - Mean changes from baseline in parameters of vital signs, and ECG. • <u>Intercurrent event strategy:</u> See Ref #5	
To assess the serum PSA level over time	• <u>Endpoint:</u> Percentage of change of PSA over time (per scheduled timepoint) • <u>Population:</u> See Ref #1 • <u>Treatment:</u> See Ref #1 • <u>Population-level summary measure:</u> Mean change from baseline of PSA • <u>Intercurrent event strategy:</u> See Ref #5	8
To assess the change of serum LH and FSH levels over time	• <u>Endpoint:</u> Time course of changes of LH and FSH (per scheduled timepoint) • <u>Population:</u> See Ref #1 • <u>Treatment:</u> See Ref #1 • <u>Population-level summary measure:</u> Mean change from baseline of LH and FSH • <u>Intercurrent event strategy:</u> See Ref #5	9
Exploratory Objectives		

Objectives	Estimands	Ref. #
To assess the immunogenicity of Study Formulation in case of unexpected PK profile, inefficacy, and/or safety events	• Endpoint: Anti-drug antibodies (ADA) levels in Cohorts 1 and 2 (Day 1 [predose], Day 29, Day 85, and EOS) and in Cohort 3 (Day 1 [predose] and Day 29, Day 85 [predose] in the treatment period with the loading dose, Day 29, and Day 85 in the treatment period with the maintenance dose)	

Abbreviations: ADA: anti-drug antibodies; AESIs: adverse events of special interest; AUC_{84d}: area under the concentration-time curve over 12 weeks; C_{84d}: concentration at 12 weeks; CI: confidence interval; C_{max}: maximum concentration; CV: coefficient of variation; ECG: electrocardiogram; EOS: end of study; FSH: follicle-stimulating hormone; IM: intramuscular; LH: luteinizing hormone; Max: maximum; Min: minimum; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; PD: pharmacodynamic(s); PK: pharmacokinetic(s); PSA: prostate-specific antigen; SD: standard deviation; TEAEs: treatment-emergent adverse events; VAS: visual analog scale.

Study population

Participants (approximately N = 20 per cohort) with histologically confirmed locally advanced/metastatic prostate cancer who are candidates for Androgen Deprivation Therapy (ADT).

Inclusion criteria

The following inclusion criteria must be met during screening:

1. Participant with histologically confirmed locally advanced/metastatic prostate cancer
2. Signed and dated written informed consent obtained before undertaking any study-specific procedures
3. Participant judged by the Study Investigator to be candidate for continuous ADT
4. Baseline morning serum testosterone levels >150 ng/dL at screening visit
5. Age ≥18 years
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
7. Life expectancy of at least 6 months

8. Adequate bone marrow, hepatic and renal function at the screening visit:
- a. Hemoglobin ≥ 10 g/dL,
 - b. Total bilirubin ≤ 1.5 x upper limit of normal (ULN) (for participants with Gilbert's syndrome, total bilirubin ≤ 3 x ULN is allowed),
 - 5 c. AST ≤ 2.5 x ULN, and/or ALT ≤ 2.5 x ULN,
 - d. Absolute neutrophil count ≥ 1500 cell/ μ L and platelets $\geq 100,000$ cells/ μ L,
 - e. Estimated glomerular filtration rate ≥ 50 mL/min based on the Chronic Kidney Disease-Epidemiology Collaboration-creatinine (CKD-EPIcr) equation.
9. Participants must agree to use acceptable methods of contraception:
- 10 a. Sexually active men, including vasectomized men, must agree to use a condom during intercourse or to refrain from fathering a child and from donating sperm during treatment period and until 6 months following the last dose of Study Formulation.
 - b. The participant's female partner should use highly effective contraception methods (achieving a failure rate of $<1\%$ per year when used consistently and correctly), including but not limited to hormonal contraceptives (combined [estrogen- and progestogen-containing] hormonal contraception associated with inhibition of ovulation [oral, intravaginal, transdermal], progestogen-only hormonal contraception associated with inhibition of ovulation [oral, injectable, implantable]), intrauterine device (IUD), intrauterine hormone-releasing system, 20 bilateral tubal occlusion/ligation procedures and sexual abstinence during the entire study duration (only if in line with the participant's usual lifestyle). Periodic abstinence (e.g., calendar, symptothermal, post-ovulation methods) and withdrawal are not considered as highly effective methods and are not acceptable.
 - 25 c. If the female partner has undergone documented placement of an IUD or intrauterine system (IUS), a barrier method (condom with spermicidal foam/gel/film/cream/suppository) should also be used.
10. Willingness and ability to comply with scheduled visits, treatment plans, 30 laboratory tests, and other study procedures.

Exclusion criteria

Any of the following would render a participant ineligible for participation in the study:

1. Previous ADT (neoadjuvant or adjuvant hormonal therapy) for ≥ 6 months duration and < 6 months treatment-free interval before start of screening
- 5 2. Indication for androgen deprivation combination therapy
3. History of bilateral orchiectomy, adrenalectomy, or hypophysectomy
4. Received chemotherapy or cryotherapy within 8 weeks prior to the start of screening for the treatment of prostate cancer
5. Cardiovascular function:
 - 10 a. QTc interval > 450 ms (using Fridericia formula) during the screening period
 - b. Known history of torsade de pointes
 - c. Currently taking drugs with warnings/precautions for QT-interval prolongation
 - 15 d. Significant cardiovascular risk conditions: heart attack or stroke in the previous 6 months; arrhythmia; uncontrolled hypertension.
6. Use of exogenous testosterone within 6 months before the start of screening
7. Major surgery within 4 weeks before the start of screening (including surgery for prostate cancer)
- 20 8. Uncontrolled symptomatic congestive heart failure (New York Heart Association Class III IV), unstable angina pectoris, cardiac arrhythmia, or uncontrolled atrial fibrillation
9. Uncontrolled diabetes mellitus Type 1 or uncontrolled diabetes mellitus Type 2 (control with hypoglycemic agents is allowed)
- 25 10. Have been previously diagnosed with or treated for active cancer (other than prostate cancer or non-melanoma skin cancer) within the previous 2 years
11. Participation in a previous clinical study involving an investigational study treatment or any other type of medical research within 4 weeks before the start of screening or within 5 half lives of the investigational product, whichever is longer
- 30 12. Any serious medical or psychiatric illness, social situations, ongoing condition or disorder, including drug or alcohol abuse, likely to interfere with the ability to comply with protocol requirements or give informed consent as per Investigator's judgment

13. Any other condition that would, in the Investigator's judgment, preclude participation in the clinical study due to safety concerns or compliance with clinical study procedures

14. Known hypersensitivity to degarelix, or any excipients of the Study Formulation

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Study Formulation, dose and mode of administration

The Study Formulation is a 12-week extended-release formulation that consists of PLGA microgranules containing degarelix pamoate of Composition K for intramuscular (IM) injections. The intended dosage strengths are 200 and 300 mg, as single dose
10 vials containing powder for suspension for injection. Before injection, each vial of powder is suspended in an oily vehicle (Medium Chain Triglycerides, MIGLYOL® 812 N).

Cohorts 1 and 2:

Participants will receive a single IM injection of Study Formulation at a dose of 200 mg
15 (Cohort 1) or 300 mg (Cohort 2) at the study start (Day 1).

Cohort 3:

As mentioned above, dose selection for this cohort will be guided by population PK/PD modeling and simulation derived from the PK and PD data from Cohorts 1 and 2 as well as safety and efficacy in these cohorts. Based on the preliminary assumptions,
20 the provisional dose level for this cohort is: Study Formulation loading dose (IM) of 400 mg (2 injections of 200 mg) at the study start (Day 1) followed by a maintenance dose of 200 mg (IM) 12 weeks after receiving the loading dose (i.e., at Day 85).

Treatment duration

25 Cohorts 1 and 2: the treatment period consists of 84 days.

Cohort 3: the treatment period consists of 168 days.

Overall end of study:

The overall EOS is defined as the date of the last visit of the last on-study participant.

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CLAIMS

1. A pharmaceutical composition comprising degarelix in the form of a pamoate salt,
wherein the degarelix pamoate salt is contained in microparticles of a
5 biodegradable copolymer of lactide units and glycolide units (PLGA) and wherein
the microparticles contain at least 50 wt% PLGA and from about 20 wt% to about
34 wt% degarelix free base equivalents.
2. The pharmaceutical composition of claim 1, wherein the PLGA has a molar ratio of
10 lactide units to glycolide units of from about 75:25 to about 85:15.
3. The pharmaceutical composition of claim 1 or claim 2, wherein the microparticles
contain from about 55 to about 75 wt% PLGA, from about 60 to about 70 wt%
PLGA, or from about 60 to about 65 wt% PLGA.
15
4. The pharmaceutical composition of any one of the preceding claims, wherein the
initial inherent viscosity (i.v.) of the PLGA is from about 0.3 dL/g to about 0.5 dL/g,
or from about 0.35 dL/g to about 0.45 dL/g.
- 20 5. The pharmaceutical composition of any one of the preceding claims, wherein the
microparticles have a particle size distribution defined as
 - D (v,0.1) of from about 5 to about 22 μm
 - D (v,0.5) of from about 25 to about 45 μm
 - D (v,0.9) of from about 55 to about 90 μm .
- 25 6. The pharmaceutical composition of any one of the preceding claims, further
comprising a vehicle, which is an aqueous vehicle or an oily vehicle.
7. The pharmaceutical composition of any one of the preceding claims, wherein the
30 microparticles are microgranules.
8. The pharmaceutical composition of any one of the preceding claims, wherein the
microparticles contain between about 28 wt% to about 33 wt% degarelix free base
equivalents.
35

9. A pharmaceutical composition of any one of claims 1 to 8 for use in the treatment of prostate cancer.
10. The pharmaceutical composition for use according to claim 9, wherein the
5 composition is for administration once every 12 weeks.
11. The pharmaceutical composition for use according to claim 9 or claim 10, wherein degarelix is for administration in an amount of from about 200 mg to about 360 mg free base equivalents per dose, particularly about 200 mg to about 300 mg free
10 base equivalents per dose.
12. The pharmaceutical composition for use according to any one of claims 9 to 11, wherein degarelix is continuously released from the microparticles, thereby reducing and maintaining serum testosterone levels to castration levels for at least
15 12 weeks.
13. The pharmaceutical composition for use according to any one of claims 9 to 12, wherein the average degarelix plasma concentration from day 1 to day 7 post administration is less than 100 ng/mL, less than 80 ng/mL, less than 60 ng/mL, less
20 than 50 ng/mL, less than 40 ng/mL, or less than 30 ng/mL.
14. A method for the preparation of a pharmaceutical composition of any one of items 1 to 8, comprising:
- 25 (a) mixing degarelix, particularly in powder form, in the form of a pharmaceutically acceptable pamoate salt, with a biodegradable copolymer of lactide units and glycolide units (PLGA), particularly in powder form;
- (b) subjecting the mixture to progressive heating and extrusion;
- (c) pelletizing the obtained extrudate;
- 30 (d) grinding the obtained pellets at low temperature.
15. A kit comprising a device, such as a prefilled syringe, containing a pharmaceutical composition according to any one of items 1 to 8, and instructions for use.