

NOVEL COMPOSITION**FIELD OF THE INVENTION**

The present invention relates to pharmaceutical compositions comprising biodegradable polymer microspheres comprising triptorelin, or a pharmaceutically acceptable salt thereof, and a lactic acid polymer. The invention further relates to methods of uses of the pharmaceutical compositions described herein.

BACKGROUND

Triptorelin is a gonadotropin releasing hormone (GnRH) agonist that is a potent inhibitor of testosterone in men and estrogen in women. Triptorelin, or a pharmaceutically acceptable salt form thereof, can be used in a variety of therapeutic applications, including the treatment of prostate cancer, symptoms of prostate cancer, central precocious puberty, endometrial stromal sarcoma, uterine fibroids, breast cancer, and endometriosis. Long term treatment with triptorelin, or a pharmaceutically acceptable salt thereof, is often required for the treatment of these diseases or disorders.

Sustained release compositions can serve to reduce the number of administrations needed over the long term. However, formulating sustained release pharmaceutical compositions to have an acceptable triptorelin release profile for the specific therapeutic application is challenging, especially if the desired sustained release profile is more than 6 months, such as 10 months or more.

Accordingly, there is a need for new sustained release pharmaceutical compositions that can provide a sustained release of triptorelin, or a pharmaceutically acceptable salt thereof especially over longer periods of time, such as 10 months or more. In particular, there is a need for triptorelin 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 such as that caused by the repeated administrations associated with long term treatment, and/or syringeability and injectability issues. Patient discomfort is especially of concern for children having central precocious puberty.

SUMMARY OF THE INVENTION

The present invention relates to pharmaceutical compositions comprising biodegradable polymer microspheres comprising (a) triptorelin, or a pharmaceutically acceptable water-soluble salt thereof, and (b) a single lactic acid polymer having a lactide content of 80% or
5 more, a molecular weight (Mw) of about 30,000 g/mol to about 80,000 g/mol and a polydispersity between about 1.4 and about 2.0 as determined by gel permeation chromatography, wherein the pharmaceutical compositions provide a sustained release of the triptorelin for at least 10 months, at least 11 months or at least 12 months.

The present invention further relates to pharmaceutical compositions as described herein for
10 use in the treatment of a disease or disorder in which triptorelin, or a pharmaceutically acceptable soluble salt form thereof, has a therapeutic effect.

The present invention also relates to pharmaceutical compositions as described herein for use in the treatment of a disease or disorder in a subject, wherein the disease or disorder is prostate cancer, the symptoms of prostate cancer, central precocious puberty, endometrial
15 stromal sarcoma, uterine fibroids, breast cancer or endometriosis.

Methods of treatment of a disease or disorder using the pharmaceutical compositions as described herein are also provided.

The present invention further relates to methods of preparing triptorelin biodegradable polymer microspheres comprising

20 (a1) preparing an organic phase by dissolving the triptorelin, or a pharmaceutically acceptable soluble salt thereof, and a single lactic acid polymer or pharmaceutically acceptable salt thereof having a lactide content of 80% or more and an initial inherent viscosity of about 0.4 to about 0.8 dL/g measured at a concentration of 0.5g/dL in chloroform at 30°C, in one or more organic solvents at room temperature;

25 (a2) preparing an aqueous phase by dissolving polyvinyl alcohol and a salting-out agent in water, and cooling the aqueous phase between about 2 and about 8°C to yield a cooled aqueous phase;

(a3) mixing the organic and the cooled aqueous phase, thereby forming the microspheres, and

(a4) filtering, washing and drying the microspheres.

Also disclosed herein are the biodegradable polymer microspheres prepared by the above method, as well as pharmaceutical compositions comprising such microspheres.

The present invention also relates to kits comprising:

- 5 a) a pharmaceutical composition as described herein;
- b) optionally a vehicle for reconstitution, and
- c) a vial or syringe optionally prefilled with the pharmaceutical composition of a).

BRIEF DESCRIPTION OF THE FIGURES

Fig. 1 provides the mean plasmatic concentration (ng/mL) of triptorelin in rats after
10 administration of Composition M suspended in an aqueous vehicle or suspended in a lipid vehicle.

Fig. 2 provides the mean plasmatic concentration (ng/mL) of triptorelin in rats after administration of each of Compositions A-D.

Fig. 3 provides the mean plasmatic concentration (ng/mL) of triptorelin in rats after
15 administration of each of Compositions E-H.

Fig. 4 provides the mean plasmatic concentration (ng/mL) of triptorelin in rats after administration of each of Compositions I-L.

Fig. 5 provides the mean plasmatic concentration (ng/mL) of triptorelin in rats after administration of Compositions 1 and 2.

20 Fig. 6 provides the mean plasmatic concentration (ng/mL) of triptorelin in rats after administration of Compositions 3 and 4.

DETAILED DESCRIPTION*Definitions*

So that the present disclosure can be more readily understood, certain terms are first 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 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" 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 "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).

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 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) 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 specifically disclosed, along with each subrange between such values.

- 5 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 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,
10 or sub-range from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10.

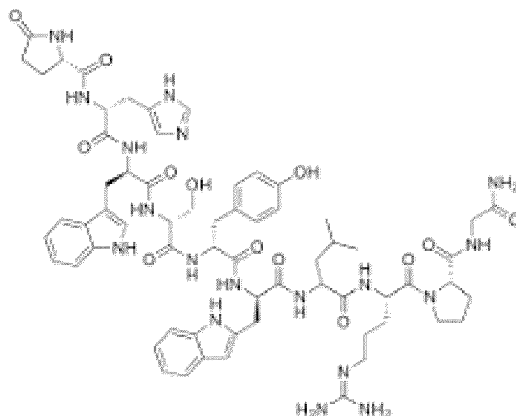
Any numerical value inherently contains certain errors necessarily resulting from the standard deviation found in their respective measurements. Additionally, all ranges disclosed herein are to be understood to encompass any and all subranges subsumed therein. For example, a stated range "1 to 10" should be considered to include any and all subranges between (and
15 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 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.
20 Where a combination is disclosed, each sub-combination of the elements 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
25 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.

The term "triptorelin," as used herein, is also known as (2S)-N-[(2S)-1-[(2S)-1-[(2S)-1-[(2S)-1-[(2R)-1-[(2S)-1-[(2S)-1-(2S)-2-[(2-amino-2-oxoethyl)carbamoyl]pyrrolidin-1-yl]-5-(diaminomethylideneamino)-1-oxopentan-2-yl]amino]-4-methyl-1-oxopentan-2-yl]amino]-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino]-3-(4-hydroxyphenyl)-1-oxopropan-2-yl]amino]-3-hydroxy-1-oxopropan-2-yl]amino]-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino]-3-(1H-imidazol-

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5-yl)-1-oxopropan-2-yl]-5-oxopyrrolidine-2-carboxamide. Triptorelin has the following structure:



The term "pharmaceutically acceptable salt" refers to relatively non-toxic, inorganic and organic acid addition salts. These salts can be prepared in situ in the administration vehicle or the dosage form manufacturing process, or by separately reacting a purified compound of the invention in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed during subsequent purification. Representative salts include those derived from hydrochloric acid, sulfuric acid, phosphoric acid, acetic acid, ascorbic acid, lactic acid, citric acid, fumaric acid, malonic acid, maleic acid, hydrobromic acid, nitric acid, tartaric acid, tosylic acid, methanesulfonic acid, aspartic acid, benzoic acid, succinic acid, oleic acid, lauric acid, glucoheptanoic acid, lactobionic acid, laurylsulfonic acid, palmitic acid, pamoic (embonic) acid, stearic acid, and valeric acid. The acid addition salts may be mono or divalent salts. The salts may be water soluble or non-water soluble. The pharmaceutically acceptable water-soluble salts include acetate, lactate, maleate, ascorbate, succinate, benzoate, tosylate, hydrochloride, hydrobromide, sulfate, bisulfate, phosphate, citrate, mesylate, tartrate, nitrate, oleate, laurate, glucoheptonate, lactobionate, laurylsulfonate salts and the like. In some aspects, the acid addition salt is acetate.

The term "biodegradable polymer," as used herein, refers to a polymer or copolymer or a mixture of polymers or 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. Examples of biodegradable polymers include, but are not limited to, lactic acid polymers. In some aspects, a biodegradable polymer, such as a

lactic acid polymer, may be degraded via hydrolysis in response to contact with bodily fluid after injection into a patient.

The term "biodegradable polymer microparticle" as used herein refers to a monolithic microparticle formed from one or more biodegradable polymers or copolymers. The
5 microparticles have an internal continuous biodegradable polymer matrix. The microparticles may be of any shape, including spherical or irregular. The term encompasses microspheres and microgranules.

The term "biodegradable polymer microgranules" as used herein refers to non-spherical irregularly shaped monolithic microparticles formed from one or more biodegradable
10 polymers or copolymers. The microgranules can have an internal continuous biodegradable polymer, e.g., lactic acid, polymer matrix.

The term "biodegradable polymer microspheres" as used herein refers to spherical or substantially spherical regularly shaped monolithic microparticles formed from one or more biodegradable polymers or copolymers. The microspheres can have an internal continuous
15 biodegradable polymer, e.g., lactic acid polymer, matrix.

Biodegradable polymer microgranules may for instance be made by a dry process e.g., extrusion and grinding. Biodegradable polymer microspheres may for instance be made by a wet process e.g., emulsion and precipitation.

The term "salting-out agent," as used herein with regard to a wet process, refers to an
20 ingredient that attracts water molecules and thereby decreases the number of water molecules available to interact with the biodegradable, e.g. lactic acid, polymer and/or triptorelin, or pharmaceutically acceptable soluble salt form.

The term "biodegradable polymer implants" as used herein refers to small cylindrical rods with a diameter of 0.2 to 10 mm and a length of 1 to 50 mm or even more, formed from one
25 or more biodegradable polymers (e.g., a single lactic acid polymer), that may be obtained by extrusion and cut to the desired length with a pelletizer.

The term "lactic acid polymer" as used herein refers to a polymer containing only lactic acid or a copolymer of lactic acid and another monomer (e.g., glycolic acid). The lactic acid polymer includes polylactic acid (also known as polylactide or PLA). The lactic acid polymer

can be poly-DL-lactic acid (also known as poly-DL-lactide). The lactic acid polymer may be linear or branched.

The copolymer of lactic acid and another monomer used in the sustained release compositions described herein may be one having a composition of lactic acid and glycolic acid (PLGA). The ratio of lactic acid:glycolic acid can be in a range of about 80:20 to 99.9:0.1, for example about 85:15 to 99:1, about 90:10 to 99:1, or about 95:5 to 99:1. The PLGA may be poly D, L-lactide-co-glycolide copolymer. The PLGA may be linear or branched.

The term “drug loading” as used herein refers to the weight ratio (presented as a percentage) of the triptorelin free base to the total mass of the biodegradable polymer microparticles i.e., as expressed by the following equation:

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

with m(triptorelin) representing the mass of the triptorelin and m(BPM) representing the mass of biodegradable polymer microparticles. A similar calculation can be done to determine the drug loading for implants.

- 15 The DvX means that X% of the volume of a biodegradable polymer microparticle sample is below the indicated diameter value e.g., a Dv50 of 80 μm means that there is 50% of the volume of the biodegradable polymer microparticle sample below 80 μm in diameter e.g. 20 μm , 30 μm , 40 μm , 50 μm , 60 μm , 70 μm , in diameter. The DvX e.g., Dv50, is determined by wet laser diffraction e.g., as described in the European pharmacopoeia V.10.8 chapter 2.9.31.
- 20 The particle size measurement 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 e.g., 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 unit
- 25 (Stirring speed 2000rpm) 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 analysed 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 purpose” may be used.
- 30 As used herein, the “inherent viscosity” of a biodegradable polymer (e.g., a lactic acid polymer) 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., a lactic acid polymer) may
5 be measured using conventional methods e.g., The Capillary Viscometer Method as described in "European Pharmacopoeia", 10.0, 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 viscosimeter.

As used herein, the "initial inherent viscosity" of a biodegradable polymer (e.g., lactic acid
10 polymer) 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 or implants.

As used herein, the "polydispersity" or "index of polydispersity (IP)" refers to the ratio M_w/M_n of a biodegradable polymer, M_w being the Weight average molecular weight (g/mol) and M_n being the Number average molecular weight (g/mol). It can be determined by Gel Permeation
15 Chromatography (GPC).

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.

20 As used herein, the terms "treat," "treated," and "treating" mean both therapeutic 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
25 limited to, alleviation of symptoms; diminishment of 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
30 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. 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, oral, topical, intramuscular, intradermal, intranasal, subcutaneous, intraocular, or intraarticular. In some aspects, the mode of administration may be parenteral administration, such as via injection, e.g. intramuscular or subcutaneous injection. In examples, the mode of administration may be intramuscular injection.

The term “therapeutically effective amount” refers to an amount of triptorelin free base that provides beneficial or desired therapeutic and/or prophylactic results. In cases where the actual formulation contains triptorelin in the form of a pharmaceutically acceptable water-soluble salt thereof, the therapeutically effective amount is expressed in “equivalent free base” or corresponds to the amount of triptorelin free base. For prophylactic use, beneficial or desired results can include, for example, one or more results such as eliminating or reducing the risk, lessening the severity, or delaying the onset of the disease, including biochemical, histological, and/or behavioural symptoms of the disease, its complications, and intermediate pathological phenotypes presenting during development of the disease. For therapeutic use, beneficial or desired results can include, for example, one or more clinical results such as decreasing one or more symptoms and pathological conditions resulting from or associated with the disease, increasing the quality of life of those suffering from the disease, decreasing the dose of other medications required to treat the disease, enhancing the effect of other medication such as via targeting, delaying the progression of the disease, and/or prolonging survival. An effective amount can be, for example, an amount sufficient to accomplish prophylactic or therapeutic treatment either directly or indirectly. An effective amount of triptorelin can be administered in one dosage or can be divided into multiple dosages, the total of such dosages being the effective amount. For example, an effective amount can be provided in two separate administrations over a period of time, that in aggregate, provide the effective amount of the formulation. For example, an effective amount can be provided in a single administration every 10, 11 or 12 months.

I. Pharmaceutical Compositions

A. Biodegradable polymer microspheres

Pharmaceutical compositions comprising biodegradable polymer microspheres comprising (a) triptorelin, or a pharmaceutically acceptable water-soluble salt thereof, and (b) a single lactic acid polymer having a lactic acid content of 80% or more, a molecular weight (Mw) of about 30,000 g/mol to about 80,000 g/mol, and a polydispersity between about 1.4 and about

2.0 as determined by gel permeation chromatography ("GPC"), wherein the pharmaceutical composition provides a sustained release of the triptorelin for at least 10 months are described herein.

In some aspects, the pharmaceutical compositions described herein have a drug loading of the triptorelin, or a pharmaceutically acceptable soluble salt form thereof (e.g., triptorelin acetate), based upon the triptorelin free base, of about 10% to about 20% (w/w), preferably about 10% to about 15% (w/w), more preferably about 12% (w/w). In some aspects, the drug loading of the triptorelin, or pharmaceutically acceptable salt thereof (e.g., triptorelin acetate), based upon triptorelin free base, is about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, or about 20%.

Drug loading can be measured using conventional methods, for example using high performance liquid chromatography (HPLC).

In some aspects, the triptorelin is present in the pharmaceutical compositions comprised herein as a pharmaceutically acceptable salt form. In some aspects, the triptorelin is present in the pharmaceutical compositions comprised herein as a pharmaceutically acceptable water-soluble salt form thereof. In some aspects, the pharmaceutically acceptable water-soluble salt form in the pharmaceutical compositions described herein is triptorelin acetate.

In some aspects, the pharmaceutical compositions described herein have a drug loading of the triptorelin acetate, based upon the triptorelin free base, of about 10% to about 20% (w/w), preferably about 10% to about 15% (w/w), more preferably about 12% (w/w). In some aspects, the drug loading of the triptorelin acetate, based upon triptorelin free base, is about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, or about 20%.

In some aspects, the biodegradable polymer microspheres of the pharmaceutical compositions described herein have a Dv50 of about 20 μm to about 80 μm , about 25 μm to about 80 μm , about 30 μm to about 80 μm , about 35 μm to about 80 μm , about 40 μm to about 80 μm , about 45 μm to about 80 μm , about 50 μm to about 80 μm , about 55 μm to about 80 μm , about 60 μm to about 80 μm , about 65 μm to about 80 μm , about 70 μm to about 80 μm , about 20 μm to about 75 μm , about 25 μm to about 75 μm , about 30 μm to about 75 μm , about 35 μm to about 75 μm , about 40 μm to about 75 μm , about 45 μm to about 75 μm , about 50 μm to about 75 μm , about 55 μm to about 75 μm , about 60 μm to about 75 μm , about 65 μm to about 75 μm , about 20 μm to about 70 μm , about 25 μm to

about 70 μm , about 30 μm to about 70 μm , about 35 μm to about 70 μm , about 40 μm to about 70 μm , about 45 μm to about 70 μm , about 50 μm to about 70 μm , about 55 μm to about 70 μm , about 60 μm to about 70 μm , about 20 μm to about 65 μm , about 25 μm to about 65 μm , about 30 μm to about 65 μm , about 35 μm to about 65 μm , about 40 μm to about 65 μm , about 45 μm to about 65 μm , about 50 μm to about 65 μm , about 55 μm to about 65 μm , about 20 μm to about 60 μm , about 25 μm to about 60 μm , about 30 μm to about 60 μm , about 35 μm to about 60 μm , about 40 μm to about 60 μm , about 45 μm to about 60 μm , about 50 μm to about 60 μm , about 20 μm to about 55 μm , about 25 μm to about 55 μm , about 30 μm to about 55 μm , about 35 μm to about 55 μm , about 40 μm to about 55 μm , about 45 μm to about 55 μm , about 20 μm to about 50 μm , about 25 μm to about 50 μm , about 30 μm to about 50 μm , about 35 μm to about 50 μm , about 40 μm to about 50 μm , about 20 μm to about 45 μm , about 25 μm to about 45 μm , about 30 μm to about 45 μm , about 35 μm to about 45 μm , about 20 μm to about 40 μm , about 25 μm to about 40 μm , about 30 μm to about 40 μm , about 20 μm to about 35 μm , about 25 μm to about 35 μm , or about 20 μm to about 30 μm . In some aspects, the biodegradable polymer microspheres of the pharmaceutical compositions described herein have a Dv_{50} of about 20 μm to about 80 μm or about 40 μm to about 60 μm . In some aspects, the biodegradable polymer microspheres of the pharmaceutical compositions described herein have a Dv_{50} of about 20 μm to about 80 μm . In some aspects, the biodegradable polymer microspheres of the pharmaceutical compositions described herein have a Dv_{50} of about 40 μm to about 60 μm .

In some aspects, the biodegradable polymer microspheres of the pharmaceutical compositions described herein comprise a lactic acid polymer having a molecular weight of about 30,000 g/mol to about 80,000 g/mol and a polydispersity between about 1.4 and about 2.0. In some aspects, the biodegradable polymer microspheres of the pharmaceutical compositions described herein comprise a lactic acid polymer having a molecular weight of about 30,000 g/mol to about 80,000 g/mol, about 30,000 g/mol to about 75,000 g/mol, about 30,000 g/mol to about 70,000 g/mol, about 30,000 g/mol to about 65,000 g/mol, about 30,000 g/mol to about 60,000 g/mol, about 30,000 g/mol to about 55,000 g/mol, about 30,000 g/mol to about 50,000 g/mol, about 30,000 g/mol to about 45,000 g/mol, about 30,000 g/mol to about 40,000 g/mol, about 35,000 g/mol to about 80,000 g/mol, about 35,000 g/mol to about 75,000 g/mol, about 35,000 g/mol to about 70,000 g/mol, about 35,000 g/mol to about 65,000 g/mol, about 35,000 g/mol to about 60,000 g/mol, about 35,000 g/mol to about 55,000 g/mol, about 35,000 g/mol to about 50,000 g/mol, about 35,000 g/mol to about 45,000 g/mol, about 40,000 g/mol to about 80,000 g/mol, about 40,000 g/mol to about 75,000 g/mol, about 40,000 to about 70,000 g/mol, about 40,000 to about 65,000 g/mol, about 40,000 to about 60,000

g/mol, about 40,000 g/mol to about 55,000 g/mol, about 40,000 g/mol to about 50,000 g/mol, about 45,000 g/mol to about 80,000 g/mol, about 45,000 g/mol to about 75,000 g/mol, about 45,000 g/mol to about 70,000 g/mol, about 45,000 g/mol to about 65,000 g/mol, about 45,000 g/mol to about 60,000 g/mol, about 45,000 g/mol to about 55,000 g/mol, about 50,000 g/mol to about 80,000 g/mol, about 50,000 g/mol to about 75,000 g/mol, about 50,000 g/mol to about 70,000 g/mol, about 50,000 g/mol to about 65,000 g/mol, about 50,000 g/mol to about 60,000 g/mol, about 55,000 g/mol to about 80,000 g/mol, about 55,000 g/mol to about 75,000 g/mol, about 55,000 g/mol to about 70,000 g/mol, about 55,000 to about 65,000 g/mol, about 60,000 g/mol to about 80,000 g/mol, about 60,000 g/mol to about 75,000 g/mol, about 60,000 g/mol to about 70,000 g/mol, about 65,000 g/mol to about 80,000 g/mol, about 65,000 g/mol to about 75,000 g/mol, or about 70,000 g/mol to about 80,000 g/mol. In some aspects, the biodegradable polymer microspheres of the pharmaceutical compositions described herein comprise a lactic acid polymer having a molecular weight of about 30,000 g/mol to about 80,000 g/mol, about 40,000 g/mol to about 65,000 g/mol, or about 45,000 g/mol to about 65,000 g/mol. In some aspects, the biodegradable polymer microspheres of the pharmaceutical compositions described herein comprise a lactic acid polymer having a molecular weight of about 30,000 g/mol to about 80,000 g/mol. In some aspects, the biodegradable polymer microspheres of the pharmaceutical compositions described herein comprise a lactic acid polymer having a molecular weight of about 40,000 g/mol to about 65,000 g/mol. In some aspects, the biodegradable polymer microspheres of the pharmaceutical compositions described herein comprise a lactic acid polymer having a molecular weight of about 45,000 g/mol to about 65,000 g/mol.

In some aspects, the biodegradable polymer microspheres of the pharmaceutical compositions described herein comprise a lactic acid polymer having a molecular weight about 30,000 g/mol to about 80,000 g/mol and a polydispersity between about 1.4 and about 2.0. In some aspects, the biodegradable polymer microspheres of the pharmaceutical compositions described herein comprise a lactic acid polymer having a polydispersity between about 1.4 and about 2.0, about 1.4 and about 1.9, about 1.4 and about 1.8, about 1.4 and about 1.7, about 1.4 and about 1.6, about 1.4 and about 1.5, about 1.5 and about 2.0, about 1.5 and about 1.9, about 1.5 and about 1.8, about 1.5 and about 1.7, about 1.5 and about 1.6, about 1.6 and about 2.0, about 1.6 and about 1.9, about 1.6 and about 1.8, about 1.6 and about 1.7, about 1.7 and about 2.0, about 1.7 and about 1.9, about 1.7 and about 1.8, about 1.8 and about 2.0, about 1.8 and about 1.9, or about 1.9 and about 2.0. In some aspects, the biodegradable polymer microspheres of the pharmaceutical compositions described herein comprise a lactic acid polymer having a polydispersity between about 1.4 and 2.0 or about 1.5 and about 1.9. In some aspects, the biodegradable polymer

microspheres of the pharmaceutical compositions described herein comprise a lactic acid polymer having a polydispersity between about 1.4 and about 2.0. In some aspects, the biodegradable polymer microspheres of the pharmaceutical compositions described herein comprise a lactic acid polymer having a polydispersity between 1.5 and about 1.9.

- 5 In some aspects, the biodegradable polymer microspheres of the pharmaceutical compositions described herein comprise a lactic acid polymer having a polydispersity of about 1.4, about 1.5, about 1.6, about 1.7, about 1.8, about 1.9, or about 2.0.

In some aspects, the molecular weight and polydispersity of the polymer are measured in the formed microspheres (rather than, e.g. in the polymer starting material). Depending on the
10 final product considered, the molecular weight and polydispersity of the polymer may be measured in the microspheres in the pharmaceutical composition or in a microsphere preparation, according to manufacturing constraints. For example, the molecular weight and polydispersity of the polymer are measured in the microspheres after irradiation.

In some aspects, the biodegradable polymer microspheres of the pharmaceutical
15 compositions described herein comprise a lactic acid polymer having an initial inherent viscosity of about 0.4 dL/g to about 0.8 dL/g. In some aspects, the initial inherent viscosity of the polymer is measured at a concentration of 0.5g/dL in chloroform at 30°C. In some aspects, the initial inherent viscosity of the polymer is measured using a Cannon-Fenske Routine size25 viscosimeter. In some aspects, the initial inherent viscosity of the polymer is measured
20 at a concentration of 0.5g/dL in chloroform at 30°C using a Cannon-Fenske Routine size25 viscosimeter. In some aspects, the biodegradable polymer microspheres of the pharmaceutical compositions described herein comprise a lactic acid polymer having an initial inherent viscosity of about 0.4 dL/g to about 0.8 dL/g, about 0.4 dL/g to about 0.7 dL/g, about 0.4 dL/g to about 0.6 dL/g, about 0.4 dL to about 0.5 dL/g, about 0.5 dL/g to about 0.8 dL/g,
25 about 0.5 dL/g to about 0.7 dL/g, about 0.5 dL/g to about 0.6 dL/g, about 0.6 dL/g to about 0.8 dL/g, about 0.6 dL/g to about 0.7 dL/g, or about 0.7 dL/g to about 0.8 dL/g. In some aspects, the biodegradable polymer microspheres of the pharmaceutical compositions described herein comprise a lactic acid polymer having an initial inherent viscosity of about 0.4 dL/g to about 0.8 dL/g or about 0.55 dL/g to about 0.75 dL/g.

- 30 In some aspects, the biodegradable polymer microspheres of the pharmaceutical compositions described herein comprise a lactic acid polymer having an initial inherent viscosity of about 0.4 dL/g, about 0.45 dL/g, about 0.5 dL/g, about 0.55 dL/g, about 0.6 dL/g, about 0.65 dL/g, about 0.7 dL/g, about 0.75 dL/g, or about 0.8 dL/g.

In some aspects, the lactic acid polymer is a single lactic acid polymer having a lactic acid content of 80% or more. In some aspects, the lactic acid polymer is a single lactic acid polymer having a lactic acid content of about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%,
5 about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%. In some aspects, the lactic acid polymer is a single lactic acid polymer having a lactic acid content of about 100% (i.e. polylactide or PLA).

In some aspects, the lactic acid polymer is a PLGA copolymer containing a molar ratio of lactide to glycolide of more than 80:20. In some aspects, the lactic acid polymer is a PLGA
10 copolymer containing a molar ratio of lactide to glycolide of 80:20, 85:15, 90:10, or 95:5.

The end groups of the lactic acid polymer are not limited. Example of possible end groups include hydroxy, ester e.g., a stearyl group or a lauryl group, acidic e.g., a carboxy group, or the like. In some aspects, the end groups of the lactic acid polymer are ester groups.

In some aspects, the lactic acid polymer is a single lactic acid polymer having a lactic acid
15 content of about 100% and is linear.

In some aspects, the pharmaceutical composition contains only a single group of biodegradable microspheres as defined herein.

B. Components of the Pharmaceutical Compositions

In some aspects, the pharmaceutical compositions described herein comprise triptorelin in
20 the form of the water-soluble acetate salt. In some aspects, the pharmaceutical compositions described herein comprise an amount of about 40 mg to about 90 mg, about 40 mg to about 85 mg, about 40 mg to about 80 mg, about 40 mg to about 75 mg, about 40 mg to about 70 mg, about 40 mg to about 65 mg, about 40 mg to about 60 mg, about 40 mg to about 55 mg, about 40 mg to about 50 mg, about 45 mg to about 90 mg, about 45 mg to about 85 mg,
25 about 45 mg to about 80 mg, about 45 mg to about 75 mg, about 45 mg to about 70 mg, about 45 mg to about 65 mg, about 45 mg to about 60 mg, about 45 mg to about 55 mg, about 50 mg to about 90 mg, about 50 mg to about 85 mg, about 50 mg to about 80 mg, about 50 mg to about 75 mg, about 50 mg to about 70 mg, about 50 mg to about 65 mg, about 50 mg to about 60 mg, about 55 mg to about 90 mg, about 55 mg to about 85 mg,
30 about 55 mg to about 80 mg, about 55 mg to about 75 mg, about 55 mg to about 70 mg, about 55 mg to about 65 mg, about 60 mg to about 90 mg, about 60 mg to about 85 mg,

about 60 mg to about 80 mg, about 60 mg to about 75 mg, about 60 mg to about 70 mg, about 65 mg to about 90 mg, about 65 mg to about 85 mg, about 65 mg to about 80 mg, about 65 mg to about 75 mg, about 70 mg to about 90 mg, about 70 mg to about 85 mg, about 70 mg to about 80 mg, about 75 mg to about 90 mg, about 75 mg to about 85 mg, or
5 about 80 mg to about 90 mg triptorelin as the free base. In some aspects, the pharmaceutical compositions described herein comprise an amount of about 40 mg to about 90 mg triptorelin as the free base. In cases where the triptorelin is present in the form of an acetate salt thereof, the amount is expressed as "equivalent free base". Thus, it is to be understood that the actual amount of the triptorelin acetate form is higher than the amount of "triptorelin as the free
10 base", due to the weight of the acetate salt.

In some aspects, the pharmaceutical compositions described herein comprise about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, or about 90 mg triptorelin as the free base. In some aspects, the pharmaceutical compositions described herein comprise about 70 mg triptorelin as the
15 free base.

In addition to the biodegradable polymer microspheres, the pharmaceutical compositions described herein may additionally comprise one or more other pharmaceutical excipients e.g., pharmaceutical excipients ordinarily comprised in the type of formulation in question e.g., diluents, surfactants, stabilisers, release modifiers, preservatives, antioxidants, buffers, anti-
20 agglomerating agents and the like.

Non limiting examples of other pharmaceutical excipients that can be included in the pharmaceutical compositions 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-oxypropylene),
25 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
30 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.

In some aspects, the pharmaceutical compositions described herein may be a composition of dried biodegradable polymer microspheres described herein ready for suspension in a liquid vehicle prior to injection. In some aspects, the pharmaceutical compositions described herein can be a ready to use suspension comprising the liquid vehicle and the biodegradable
5 polymer microspheres described herein. The liquid vehicle in the pharmaceutical compositions described herein can be an aqueous (water-based) or non-aqueous vehicle.

In some aspects, the aqueous (water-based) vehicle is predominately water. In some aspects, the aqueous (water-based) 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%,
10 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 aspects, the aqueous (water-based) vehicle can contain additional pharmaceutical excipients. The additional excipients can be used to ensure isotonicity and to improve the
15 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
20 4000.

In some aspects, non-aqueous vehicle is free from or substantially free from water e.g., a pharmaceutically acceptable liquid that comprises 0.25% (w/v) water or less, 0.1% water or less, 0.05% (w/v) water or less. In some aspects, the non-aqueous liquid is inert or substantially inert with respect to the biodegradable polymer microspheres described herein,
25 as well as with the triptorelin, or pharmaceutically acceptable soluble salt form thereof.

The water content of the non-aqueous vehicle can be measured using conventional methods e.g., The Micro Determination Method as described in "European Pharmacopoeia", 10.0, chapter 2.5.32.

In some aspects, the non-aqueous vehicle can be a pharmaceutically acceptable oil. In some
30 aspects, the oil is in a viscous liquid state at ambient temperatures (20°C - 30°C), or slightly warmer, and is both hydrophobic (immiscible with water) and lipophilic (miscible with other oils). Non limiting 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, safflower oil, cottonseed oil, ethyl oleate, and any combinations thereof.

In some aspects, the non-aqueous vehicle is a pharmaceutically acceptable oil. In some aspects, pharmaceutically acceptable oils can comprise medium chain triglycerides (MCTs). In some aspects, the MCTs are glyceride esters formed from glycerol 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 (hexanoic acid), C8 (octanoic acid), C10 (decanoic acid), C12 (dodecanoic acid). The three medium chain fatty acids from which the triglyceride is formed can all be the same e.g., all three may be medium chain fatty acids with aliphatic chains of, for example, 8 or 10 carbons 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.

In some aspects, the pharmaceutically acceptable oil is considered to essentially consist of one or more MCT if it 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% of one or more medium chain triglyceride.

In one aspect, the non-aqueous liquid is an oil essentially consisting of C8 and/or C10 medium chain triglycerides e.g., essentially consisting of C8 and C10 medium chain triglycerides e.g. consisting 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 as mentioned below. As stated above, the MCT content of the oil is measured by GC in accordance with the method set out in Ph. Eur. 2.4.22, without further conversion.

In some aspects, 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.

Pharmaceutically acceptable MCT oils are commercially available. Non limiting examples of commercially available MCT oils include MIGLYOL® 810, 812, 818, (Sasol Germany GmbH, Witten, Germany). In some aspects, the MCT oil may be MIGLYOL® 812.

In some aspects, the pharmaceutical composition is a suspension comprising the biodegradable polymer microspheres in a concentration of about 100 mg/mL to about 500 mg/mL, about 100 mg/mL to about 450 mg/mL, about 100 mg/mL to about 400 mg/mL, about 100 mg/mL to about 350 mg/mL, about 100 mg/mL to about 300 mg/mL, about 100 mg/mL to about 250 mg/mL, about 100 mg/mL to about 200 mg/mL, about 150 mg/mL to about 500 mg/mL, about 150 mg/mL to about 450 mg/mL, about 150 mg/mL to about 400 mg/mL, about 150 mg/mL to about 350 mg/mL, about 150 mg/mL to about 300 mg/mL, about 150 mg/mL to about 250 mg/mL, about 200 mg/mL to about 500 mg/mL, about 200 mg/mL to about 450 mg/mL, about 200 mg/mL to about 400 mg/mL, about 200 mg/mL to about 350 mg/mL, about 200 mg/mL to about 300 mg/mL, about 250 mg/mL to about 500 mg/mL, about 250 mg/mL to about 450 mg/mL, about 250 mg/mL to about 400 mg/mL, about 250 mg/mL to about 350 mg/mL, about 300 mg/mL to about 500 mg/mL, about 300 mg/mL to about 450 mg/mL, about 300 mg/mL to about 400 mg/mL, about 350 mg/mL to about 500 mg/mL, about 350 mg/mL to about 450 mg/mL, or about 400 mg/mL to about 500 mg/mL. In some aspects, the pharmaceutical composition is a suspension comprising the biodegradable polymer microspheres in a concentration of about 100 mg/mL to about 500 mg/mL, about 200 mg/mL to about 400 mg/mL, or about 250 mg/mL to about 350 mg/mL. In some aspects, the pharmaceutical composition is a suspension comprising the biodegradable polymer microspheres in a concentration of about 100 mg/mL to about 500 mg/mL. In some aspects, the pharmaceutical composition is a suspension comprising the biodegradable polymer microspheres in a concentration of about 200 mg/mL to about 400 mg/mL. In some aspects, the pharmaceutical composition is a suspension comprising the biodegradable polymer microspheres in a concentration of about 250 mg/mL to about 350 mg/mL.

In some aspects, the pharmaceutical composition described herein comprising the biodegradable polymer microspheres described herein or the liquid vehicle suspension comprising the biodegradable polymer microspheres can be provided in an injection device, e.g. a syringe e.g., ready for injection.

In some aspects, the pharmaceutical composition described herein can be manufactured aseptically or non-aseptically. In some aspects, the pharmaceutical composition described herein, such as the liquid vehicle suspension comprising the biodegradable polymer microspheres or the composition of dried biodegradable polymer microspheres, is sterilised. In some aspects, the pharmaceutical composition described herein is sterilised by irradiation e.g., by X-ray or gamma irradiation. In some aspects, the pharmaceutical composition described herein is sterilised by X-ray irradiation at a dose between about 25 and about 40 kGy.

- In some aspects, the pharmaceutical composition described herein in the form of a liquid vehicle suspension comprising the biodegradable polymer microspheres, has the following in vitro release profile: less than 10% of the triptorelin is released over 21 hours, less than 15% of the triptorelin is released after about 165 hours, and more than 75% of the triptorelin is released after about 330 hours, wherein the release may be measured using a USP II apparatus, including:
- introducing MCT oil suspension comprising the biodegradable polymer microspheres equivalent to 70mg of triptorelin base, in 900 mL of a 100 mM acetate buffer,
 - applying the following gradient of temperature:
 - o incubating at about 37°C for about 21 hours,
 - o applying a gradient of temperature with an increase of about 0.5°C per hour for about 46 hours,
 - o maintaining at 60 °C until 330 hours,
- wherein samples are withdrawn from the apparatus at specific time points and the drug dissolved is quantified via HPLC.

In some aspects, the in vitro release is measured using a USP II apparatus, for example with the following parameters: in 900 mL of a 100 mM acetate buffer pH 4, introducing an amount of the liquid vehicle suspension, such as MCT oil suspension, comprising the biodegradable polymer microspheres equivalent to 70mg of triptorelin base, at about 37 °C for about 21 hours with a paddle rotation at 75 rpm speed, then applying a gradient of temperature with an increase of about 0.5 °C per hour for about 46 hours, and then maintaining at 60°C for the remaining time, with the same rotation speed throughout the experiment. Samples withdrawn from the apparatus can be filtered through 0.2µm filters and quantification of the drug dissolved can be performed using the same HPLC method as described herein for the drug loading determination.

II. Medical Uses

In some aspects, there is provided the pharmaceutical compositions described herein for use as a medicament. The medicament may be for use in long term therapy e.g., long term maintenance therapy (e.g., for at least 10 months, 11 months or 12 months), for a disease and/or disorder.

In some aspects, there is provided the pharmaceutical compositions described herein for use in the prevention and/or treatment of a disease and/or disorder.

In some aspects, the pharmaceutical compositions described herein can be for use in the prevention and/or treatment of any disease and/or disorder for which triptorelin, or a
5 pharmaceutically acceptable soluble salt form thereof (e.g., triptorelin acetate), has a therapeutic effect. In some aspects, the disease or disorder is selected from prostate cancer, the symptoms of prostate cancer, central precocious puberty ("CPP"), endometrial stromal sarcoma, uterine fibroids, breast cancer or endometriosis. In some aspects, the disease or disorder is central precocious puberty.

10 Methods of treating any of the diseases or disorders (e.g., CPP) specified herein comprising the step of administering the pharmaceutical compositions described herein to a subject (e.g., a human) in need thereof are also contemplated.

In some aspects, the pharmaceutical compositions described herein are administered to a subject (e.g., a human) in need thereof that has not been previously treated for the disease
15 or disorder for which the pharmaceutical compositions are administered (e.g., CPP), i.e. the patient is a treatment-naïve patient.

In some aspects, the pharmaceutical compositions described herein are administered to a subject (e.g., a human) in need thereof that has been previously treated for the disease or disorder (e.g., CPP). In some aspects, the subject (e.g., a human) in need thereof that has
20 been previously treated for the disease or disorder for which the pharmaceutical compositions are administered (e.g., CPP), has been treated with a pre-loading dose. 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 compositions are administered (e.g., CPP), has been treated for at least one month, at least two months, at least six months, at least one year.
25 Such previous treatment may be with triptorelin or another GnRH agonist, GnRH antagonist or GnRH analog.

In some aspects, the pharmaceutical compositions described herein can be administered to a subject (e.g., a human) parenterally. In some aspects, the subject may be parenterally administered the pharmaceutical compositions described herein via intra-muscular or
30 subcutaneous injection.

The pharmaceutical compositions described herein can be administered as often as necessary e.g., depending on the sustained release period of the composition. In some aspects, the pharmaceutical compositions can be administered yearly.

5 The pharmaceutical compositions described herein provide a sustained release of the triptorelin, or pharmaceutically acceptable soluble salt thereof, comprised within the biodegradable polymer microspheres. In some aspects, the sustained release is for at least 10 months. In some aspects, the sustained release is for at least 1 year. In some aspects, the sustained release is for about 1 year.

10 In some aspects, the pharmaceutical compositions described herein provide sustained hormonal suppression over about 10, about 11 or about 12 months in a subject (e.g. human).

In some aspects, the pharmaceutical compositions described herein are administered to a subject (e.g., a human) every 10, 11, or 12 months. In some aspects, the pharmaceutical compositions described herein are administered to a subject (e.g., a human) yearly. In some aspects, the pharmaceutical compositions described herein are administered to a subject
15 (e.g., a human) once about every 52 weeks.

In some aspects, the pharmaceutical compositions described herein are administered to a subject (e.g., a human) having central precocious puberty every 10, 11, or 12 months. In some aspects, the pharmaceutical compositions described herein are administered to a subject (e.g., a human) having central precocious puberty yearly. In some aspects, the
20 pharmaceutical compositions described herein are administered to a subject (e.g., a human) having central precocious puberty once about every 52 weeks.

In some aspects, the pharmaceutical compositions described herein are administered in a dosing regimen to achieve a desired hormonal suppression as compared with a subject not administered the pharmaceutical compositions described herein. In some aspects, the
25 pharmaceutical compositions described herein are administered in a dosing regimen to achieve a desired hormonal suppression as compared with a subject prior to administration of the pharmaceutical composition. Hormonal suppression can be assessed in various ways, e.g. depending on the therapeutic indication considered.

In some aspects, the pharmaceutical composition consists of biodegradable polymer
30 microspheres comprising (a) triptorelin, or a pharmaceutically acceptable water-soluble salt thereof and (b) a single lactic acid polymer, as a suspension in liquid medium or in dried form

for suspension in a liquid medium. The inventors have found that despite using a single lactic acid polymer (i.e. not a mixture) and a water-soluble salt of triptorelin in microspheres (i.e. not implants for example), a sustained release of triptorelin over a period of at least 10 months, at least 11 months or at least 12 months, is nonetheless possible.

- 5 In some aspects, the pharmaceutical composition consists of a single group of biodegradable microspheres as defined herein. A “single group” in this context means that all microspheres have essentially the same characteristics, e.g. with regard to particle size distribution, lactic acid polymer properties, etc. The inventors have been found that despite using a single group of biodegradable microspheres, a sustained release of triptorelin over a period of at least 10
10 months, at least 11 months or at least 12 months, is nonetheless possible.

For central precocious puberty (CPP) patients, in some aspects, hormonal suppression can be characterized by LH suppression to prepubertal levels, defined as $LH \leq 5$ IU/L after GnRH or GnRH agonist stimulation. This can be measured in serum, plasma and/or blood.

- 15 In certain aspects, a pharmaceutical composition comprising microspheres of a single lactic acid polymer containing about 40 to about 90 mg triptorelin in the form of acetate salt, for suspension in a mixture of C8/C10 triglycerides (MIGLYOL® 812) may be used in the treatment of CPP patients.

- It is to be understood that in the sentence “about 40 to about 90 mg triptorelin in the form of acetate salt”, about 40 to about 90 mg triptorelin free base are present, but the actual amount
20 of the triptorelin acetate form is higher.

- In certain aspects, a pharmaceutical composition comprising microspheres of a single lactic acid polymer containing about 40 to about 90 mg triptorelin in the form of acetate salt, for suspension in a mixture of C8/C10 triglycerides (MIGLYOL® 812) may be used in the treatment of CPP patients. In examples, a pharmaceutical composition comprising
25 microspheres of poly-DL-lactic acid (DL PLA, 100:0) containing about 40 to about 90 mg triptorelin in the form of acetate salt, in a mixture of C8/C10 triglycerides (MIGLYOL® 812), may be used in the treatment of CPP patients. In examples, a pharmaceutical composition comprising microspheres of poly-DL-lactic acid (DL PLA, 100:0) with ester end groups and an initial inherent viscosity of about 0.55 to about 0.75 (as measured at a concentration of
30 g/dL in chloroform at 30°C), said microspheres containing about 40 to about 90 mg triptorelin in the form of acetate salt, in a mixture of C8/C10 triglycerides (MIGLYOL® 812), may be used in the treatment of CPP patients. In examples, a pharmaceutical composition comprising

microspheres of poly-DL-lactic acid (DL PLA, 100:0) with ester end groups, a weight average molecular weight (Mw) of about 45000 to 65000 g/mol, and a polydispersity of about 1.5 to about 1.7 as determined by GPC, said microspheres containing about 40 to about 90 mg triptorelin in the form of acetate salt, in a mixture of C8/C10 triglycerides (MIGLYOL® 812),
5 may be used in the treatment of CPP patients. In the context of these aspects, the CPP patients may be CPP patients that have been previously treated with a different therapy, e.g. another GnRH agonist therapy.

In certain aspects, a pharmaceutical composition comprising microspheres of a single lactic acid polymer containing about 70 mg triptorelin in the form of acetate salt, for suspension in
10 a mixture of C8/C10 triglycerides (MIGLYOL® 812) may be used in the treatment of CPP patients. In examples, a pharmaceutical composition comprising microspheres of poly-DL-lactic acid (DL PLA, 100:0) containing about 70 mg triptorelin in the form of acetate salt, in a mixture of C8/C10 triglycerides (MIGLYOL® 812), may be used in the treatment of CPP patients. In examples, a pharmaceutical composition comprising microspheres of poly-DL-lactic acid (DL PLA, 100:0) with ester end groups and an initial inherent viscosity of about
15 0.55 to about 0.75 (as measured at a concentration of g/dL in chloroform at 30°C), said microspheres containing about 70 mg triptorelin in the form of acetate salt, in a mixture of C8/C10 triglycerides (MIGLYOL® 812), may be used in the treatment of CPP patients. In examples, a pharmaceutical composition comprising microspheres of poly-DL-lactic acid (DL
20 PLA, 100:0) with ester end groups, a weight average molecular weight (Mw) of about 45000 to 65000 g/mol, and a polydispersity of about 1.5 to about 1.7 as determined by GPC, said microspheres containing about 70 mg triptorelin in the form of acetate salt, in a mixture of C8/C10 triglycerides (MIGLYOL® 812), may be used in the treatment of CPP patients. In the context of these aspects, the CPP patients may be CPP patients that have been previously
25 treated with a different therapy, e.g. another GnRH agonist therapy.

For prostate cancer patients, in some aspects, hormonal suppression can be characterized by testosterone suppression to castrate levels, defined as testosterone ≤ 50 ng/dL (i.e. ≤ 1.735 nmol/L). This can be measured in serum, plasma and/or blood.

In some aspects, the pharmaceutical compositions described herein provide a sustained
30 release of triptorelin with a limited burst, such as $C_{max} \leq 4$ ng/mL in a subject (e.g. human). In some aspects, a limited burst of triptorelin is observed within a few hours following administration of pharmaceutical compositions as described herein, such as an initial $C_{max} \leq 4$ ng/mL within 48h, within 24h or within 12h following administration. In some aspects, the initial C_{max} corresponds to the maximal triptorelin concentration observed during the overall

release period, such as at least 10 months, at least 11 months or at least 12 months (overall C_{max}). In some aspects, the initial C_{max} is lower than the overall C_{max}. In some preferred aspects, the overall C_{max} is ≤ 4 ng/mL in a subject (e.g. human).

5 In some aspects, the pharmaceutical compositions described herein may provide a sustained release of triptorelin above a threshold of 0.0137 ng/mL throughout a maintenance period, such as from 48h or from 1 month to 10, 11 or 12 months after administration. This threshold is associated with a 90% probability of adequate hormonal suppression (stimulated serum LH ≤ 5 IU/L) throughout the overall release period.

10 In some aspects, the pharmaceutical compositions described herein may provide a sustained release of triptorelin above a threshold of 0.0316 ng/mL throughout a maintenance period, such as from 48h or from 1 month to 10, 11 or 12 months after administration. This threshold is associated with a 95% probability of adequate hormonal suppression (stimulated serum LH ≤ 5 IU/L) throughout the overall release period.

15 In some aspects, the pharmaceutical compositions described herein may provide a sustained release of triptorelin ranging from 0.0137 ng/mL to 4 ng/mL throughout a maintenance period, such as from 48h or from 1 month to 10, 11 or 12 months after administration.

In some aspects, the pharmaceutical compositions described herein may provide a sustained release of triptorelin ranging from 0.0316 ng/mL to 4 ng/mL throughout a maintenance period, such as from 48h or from 1 month to 10, 11 or 12 months after administration.

20 In some aspects, kits comprising:
a) a pharmaceutical composition as described herein,
b) optionally a liquid vehicle for suspension, and
c) a vial or a syringe optionally prefilled with the pharmaceutical composition of a)
25 are described herein.

III. Methods of Making the Biodegradable Polymer Microspheres

Also provided are methods of preparing biodegradable polymer microspheres of triptorelin or a pharmaceutically acceptable salt thereof (e.g., triptorelin acetate) comprising

- (a1) preparing an organic phase by dissolving the triptorelin, or pharmaceutically acceptable soluble salt thereof (e.g., triptorelin acetate), and a single lactic acid polymer having a lactic acid content of 80% or more (e.g., polylactide) and an initial inherent viscosity of about 0.4 to about 0.8 dL/g measured at a concentration of 0.5g/dL in chloroform at 30°C,
5 in one or more organic solvents at room temperature;
- (a2) preparing an aqueous phase by dissolving polyvinyl alcohol and a salting-out agent in water, and cooling the aqueous phase at about 2°C to about 8°C to yield a cooled aqueous phase;
- (a3) mixing the organic and the cooled aqueous phase, thereby forming the microspheres,
10 and
- (a4) filtering, washing and drying the microspheres.

In some aspects, room temperature refers to a temperature range of about 18°C to about 25°C.

- In some aspects, the aqueous phase is cooled to about 2°C to about 7°C, about 2°C to about 6°C, about 2°C to about 5°C, about 2°C to about 4°C, about 3°C to about 8°C, about 3°C to about 7°C, about 3°C to about 6°C, about 3°C to about 5°C, about 3°C to about 4°C, about 4°C to about 8°C, about 4°C to about 7°C, about 4°C to about 6°C, about 4°C to about 5°C.
15 In some aspects, the aqueous phase is cooled to about 2°C, about 3°C, about 4°C, about 5°C, about 6°C, about 7°C, or about 8°C, preferably to about 4°C.

- 20 The one or more organic solvents used in the organic phase comprise one or more organic solvents suitable for dissolving the biodegradable polymer and/or the triptorelin, or pharmaceutically acceptable soluble salt (e.g., triptorelin acetate). Non limiting examples of the one or more organic solvents used to prepare the organic phase that may be used to dissolve the biodegradable polymer include an alcohol, e.g., methanol, ethyl acetate,
25 acetone, dimethylformamide (DMF) tetrahydrofuran (THF), acetonitrile, or halogenated hydrocarbons, e.g., dichloromethane (DCM), chloroform, hexafluoroisopropanol (HFIP), dimethylsulfoxide (DMSO), and any combination thereof. In some aspects, the one or more organic solvents in the organic phase are a mixture of dichloromethane and methanol.

- In some aspects, the dichloromethane is present in the mixture in an amount of about 50%
30 to about 100% (w/w), about 50% to about 95% (w/w), about 50% to about 90% (w/w), about 50% to about 85% (w/w), about 50% to about 80% (w/w), about 50% to about 75% (w/w), about 50% to about 70% (w/w), about 50% to about 65% (w/w), about 50% to about 60% (w/w), about 55% to about 100% (w/w), about 55% to about 95% (w/w), about 55% to about 90% (w/w), about 55% to about 85% (w/w), about 55% to about 80% (w/w), about 55% to

about 75% (w/w), about 55% to about 70% (w/w), about 55% to about 65% (w/w), about 60% to about 100% (w/w), about 60% to about 95% (w/w), about 60% to about 90% (w/w), about 60% to about 85% (w/w), about 60% to about 80% (w/w), about 60% to about 75% (w/w), about 60% to about 70% (w/w), about 65% to about 100% (w/w), about 65% to about 95% (w/w), about 65% to about 90% (w/w), about 65% to about 85% (w/w), about 65% to about 80% (w/w), about 65% to about 75% (w/w), about 70% to about 100% (w/w) to about 70% to about 95% (w/w), about 70% to about 90% (w/w), about 70% to about 85% (w/w), about 70% to about 80% (w/w), about 75% to about 100% (w/w), about 75% to about 95% (w/w), about 75% to about 90% (w/w), about 75% to about 85% (w/w), about 80% to about 100% (w/w), about 80% to about 95% (w/w), or about 80% to about 90% (w/w). In some aspects, the dichloromethane is present in the mixture in an amount of about 50% to about 100% (w/w).

In some aspects, the dichloromethane is present in the mixture in an amount of about 50%, about 55%, about 60%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95% or about 100% (w/w). In some aspects, the dichloromethane is present in the mixture in an amount of about 75% (w/w).

In some aspects, the methanol is present in the mixture in an amount of about 5% to about 50% (w/w), about 5% to about 45% (w/w), about 5% to about 40% (w/w), about 5% to about 35% (w/w), about 5% to about 30% (w/w), about 5% to about 25% (w/w), about 5% to about 20% (w/w), about 5% to about 15% (w/w), about 7.5% to about 50% (w/w), about 7.5% to about 45% (w/w), about 7.5% to about 40% (w/w), about 7.5% to about 35% (w/w), about 7.5% to about 30% (w/w), about 7.5% to about 25% (w/w), about 7.5% to about 20% (w/w), about 10% to about 50% (w/w), about 10% to about 45% (w/w), about 10% to about 40% (w/w), about 10% to about 35% (w/w), about 10% to about 30% (w/w), about 10% to about 25% (w/w), about 10% to about 20% (w/w), about 15% to about 50% (w/w), about 15% to about 45% (w/w), about 15% to about 40% (w/w), about 15% to about 35% (w/w), about 15% to about 30% (w/w), about 15% to about 25% (w/w), about 20% to about 50% (w/w), about 20% to about 45% (w/w), about 20% to about 40% (w/w), about 20% to about 35% (w/w), about 20% to about 30% (w/w), about 25% to about 50% (w/w), about 25% to about 45% (w/w), about 25% to about 40% (w/w), about 25% to about 35% (w/w), about 30% to about 50% (w/w), about 30% to about 45% (w/w), about 30% to about 40% (w/w), about 35% to about 50% (w/w), about 35% to about 45% (w/w), or about 40% to about 50% (w/w). In some aspects, the methanol is present in the mixture in an amount of about 5% to about 50%.

In some aspects, the methanol is present in the mixture in an amount of about 5%, about 7.5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%,

about 45%, or about 50% (w/w). In some aspects, the methanol is present in the mixture in an amount of about 25% (w/w).

Non limiting examples of stabilisers include polyvinyl alcohol, polyvinyl pyrrolidone, carboxymethyl cellulose sodium, dextrin, polyethylene glycol, poloxamers, poly(oxyethylene)-sorbitan-fatty acid ester, sorbitan fatty acid, lecithins, and mixtures thereof. In one aspect, the stabiliser is polyvinyl alcohol (PVA).

In some aspects, the polyvinyl alcohol in the aqueous phase is present in an amount of about 0.1% to about 10% (w/w), about 0.1% to about 9% (w/w), about 0.1% to about 8% (w/w), about 0.1% to about 7% (w/w), about 0.1% to about 6% (w/w), about 0.1% to about 5% (w/w), about 0.1% to about 4% (w/w), about 0.1% to about 3% (w/w), about 0.1% to about 2% (w/w), about 0.1% to about 1%. In some aspects, the polyvinyl alcohol in the aqueous phase is present in an amount of about 0.1% to about 10% (w/w).

In some aspects, the polyvinyl alcohol in the aqueous phase is present in an amount of about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 1.25%, about 1.5%, about 1.75%, about 2%, about 2.25%, about 2.5%, about 2.75%, about 3%, about 3.25%, about 3.5%, about 3.75%, about 4%, about 4.25%, about 4.5%, about 4.75%, about 5%, about 5.25%, about 5.5%, about 5.75%, about 6%, about 6.25%, about 6.5%, about 6.75%, about 7%, about 7.25%, about 7.5%, about 7.75%, about 8%, about 8.25%, about 8.5%, about 8.75%, about 9%, about 9.25%, about 9.5%, about 9.75%, or about 10%. In some aspects, the polyvinyl alcohol in the aqueous phase is present in an amount of about 1% (w/w).

The salting-out agent in step (a2) of the methods described herein can be a salt. In some aspects, the salt can be an alkali-metal salt, such as an alkali-metal chloride, alkali metal nitrate or alkali-metal sulfate. Non-limiting examples of suitable salts include sodium chloride (NaCl), potassium chloride (KCl). In some aspects, the salting out agent in step (a2) of the methods described herein is NaCl.

In some aspects, the salting-out agent (e.g., NaCl) in step (a2) of the methods described herein is present in an amount of about 0.1% to about 10% (w/w), about 0.1% to about 9% (w/w), about 0.1% to about 8% (w/w), about 0.1% to about 7% (w/w), about 0.1% to about 6% (w/w), about 0.1% to about 5% (w/w), about 0.1% to about 4% (w/w), about 0.1% to about 3% (w/w), about 0.1% to about 2% (w/w), about 0.1% to about 1%. In some aspects, the salting-out agent (e.g., NaCl) in step (a2) of the methods described herein is present in an amount of about 0.1% to about 10% (w/w).

In some aspects, the salting-out agent (e.g., NaCl) in step (a2) of the methods described herein is present in an amount of about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 1.25%, about 1.5%, about 1.75%, about 2%, about 2.25%, about 2.5%, about 2.75%, about 3%, about 3.25%,
5 about 3.5%, about 3.75%, about 4%, about 4.25%, about 4.5%, about 4.75%, about 5%, about 5.25%, about 5.5%, about 5.75%, about 6%, about 6.25%, about 6.5%, about 6.75%, about 7%, about 7.25%, about 7.5%, about 7.75%, about 8%, about 8.25%, about 8.5%, about 8.75%, about 9%, about 9.25%, about 9.5%, about 9.75%, or about 10%. In some aspects, the salting-out agent (e.g., NaCl) in step (a2) of the methods described herein is
10 present in an amount of about 2.5% (w/w).

In some aspects, the organic and aqueous phases of the methods described herein are mixed at a ratio of 1:50 to 1:500. 1:50 to 1:400, 1:50 to 1:300, 1:50 to 1:250, 1:50 to 1:200, 1:50 to 1:150, or 1:50 to 1:100. In some aspects, the organic and aqueous phases of the methods described herein are mixed at a ratio of about 1:100.

15 In some aspects, the organic and aqueous phases of the methods described herein are continuously mixed. In some aspects, the organic and aqueous phases of the methods described herein are simultaneously fed/pumped into and mixed in a mixing apparatus (e.g., a rotor-stator mixer).

In some aspects, the organic solvents of the methods described herein can be removed by
20 solvent evaporation or solvent extraction from the emulsion. In some aspects, the microspheres prepared by the methods described herein can be dried. In some aspects, the microspheres prepared by the methods described herein are dried in an oven.

The predetermined level of any residual solvent in the microspheres according to the present invention, especially after drying, can be a level in accordance with the guidelines from the
25 International Council for Harmonisation of Technical requirements for Pharmaceuticals or Human use ICH Q3C. In the case of DCM, the predetermined level of residual solvent can be a level of 10000 ppm or below, 5000 ppm or below, 1000 ppm or below, 600 ppm or below. In the case of methanol, the predetermined level of residual solvent may be a level of 40,000 ppm or below, 3000 ppm or below, or 500 ppm or below.

30 Sieving can be done using a sieve with a mesh size that yields the particle sizes specified hereinabove and below. In some aspects, the sieve is a 106 μ m sieve although smaller or

larger opening sizes such as 50 μm or 200 μm or any other value in the range of 75 μm to 180 μm can be used.

In some aspects, the encapsulation efficiency of the triptorelin in the microspheres prepared
5 by the methods described herein is between about 80% and about 99%, about 80% and
about 95%, about 80% and about 90%, about 85% and about 99%, about 85% and about
95%, or about 90% and about 99%. In some aspects, the encapsulation efficiency of the
triptorelin in the microspheres prepared by the methods described herein is about 80%, about
85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%,
10 about 97%, about 98%, or about 99%.

IV. The invention is further characterized by the following items:

Item 1. A pharmaceutical composition comprising biodegradable polymer
microspheres comprising (a) triptorelin, or a pharmaceutically acceptable water-
15 soluble salt thereof, and (b) a single lactic acid polymer having a lactide content of
80% or more, a molecular weight (Mw) of about 30,000 g/mol to about 80,000 g/mol
and a polydispersity between about 1.4 and about 2.0 as determined by gel
permeation chromatography, wherein the pharmaceutical composition provides a
sustained release of the triptorelin for at least 10 months.

20 Item 2. The pharmaceutical composition of item 1, wherein the pharmaceutical
composition provides a sustained release of the triptorelin for at least 11 months or
for at least 12 months.

Item 3. The pharmaceutical composition of item 1 or 2, wherein the biodegradable
polymer microspheres have a drug loading of triptorelin, or a pharmaceutically
25 acceptable water-soluble salt form thereof, based upon triptorelin free base, of about
10% to about 20% (w/w), preferably about 10% to about 15% (w/w), more preferably
about 12% (w/w).

Item 4. The pharmaceutical composition of any one of items 1 to 3, wherein the
triptorelin is present as triptorelin acetate.

- Item 5. The pharmaceutical composition of any one of items 1 to 4, wherein the biodegradable polymer microspheres have a Dv50 of about 20 μm to about 80 μm , preferably about 40 μm to about 60 μm .
- 5 Item 6. The pharmaceutical composition of any one of items 1 to 5, wherein the lactic acid polymer has a molecular weight of about 40,000 g/mol to about 65,000 g/mol and a polydispersity between about 1.5 and about 1.9.
- Item 7. The pharmaceutical composition of item 6, wherein the lactic acid polymer has a molecular weight of about 45,000 to about 65,000 g/mol.
- 10 Item 8. The pharmaceutical composition of any one of items 1 to 7, wherein the molecular weight of the lactic acid polymer is measured in the formed microspheres.
- Item 9. The pharmaceutical composition of any one of items 1 to 8, wherein the polydispersity of the lactic acid polymer is measured in the formed microspheres.
- 15 Item 10. The pharmaceutical composition of any one of items 1 to 9, wherein the lactic acid polymer has an initial inherent viscosity of about 0.4 dL/g to about 0.8 dL/g measured at a concentration of 0.5g/dL in chloroform at 30°C.
- Item 11. The pharmaceutical composition of item 10, wherein the lactic acid polymer has an initial inherent viscosity of about 0.55 dL/g to about 0.75 dL/g measured at a concentration of 0.5g/dL in chloroform at 30°C.
- 20 Item 12. The pharmaceutical composition of any one of items 1-11, wherein the biodegradable polymer microspheres have a Dv10 of about 10 μm to about 40 μm , preferably of about 15 μm to about 30 μm , a Dv50 of about 40 μm to about 60 μm and a Dv90 of about 60 μm to about 120 μm , preferably of about 80 μm to about 100 μm .
- 25 Item 13. The pharmaceutical composition of any one of items 1 to 12, wherein the lactic acid polymer is polylactic acid (PLA) or poly(lactic-co-glycolic acid) (PLGA), particularly PLA.
- Item 14. The pharmaceutical composition of any one of items 1 to 13, wherein the lactic acid polymer is selected from PLGA 85:15, PLGA 90:10, PLGA 95:5 or PLA 100:0.

- Item 15. The pharmaceutical composition of any one of items 1 to 14, wherein the lactic acid polymer is selected from PLGA 85:15 with ester end group, PLA 100:0 with carboxyl end group, or PLA 100:0 with ester end group.
- 5 Item 16. The pharmaceutical composition of any one of items 1 to 15, wherein the lactic acid polymer is DL PLA 100:0 with carboxyl end group and an initial inherent viscosity of about 0.55 to about 0.75 dL/g measured at a concentration of 0.5g/dL in chloroform at 30°C.
- 10 Item 17. The pharmaceutical composition of any one of items 1 to 12, wherein the lactic acid polymer has a lactic acid content of about 100%.
- Item 18. The pharmaceutical composition of any one of items 1 to 17, wherein the pharmaceutical composition comprises an amount of about 40 mg to about 90 mg, preferably about 70 mg triptorelin as the free base.
- 15 Item 19. The pharmaceutical composition of any one of items 1 to 18, wherein the sustained release is for at least 1 year, preferably about 1 year.
- Item 20. The pharmaceutical composition of any one of items 1 to 19, wherein the pharmaceutical composition is a suspension comprising biodegradable polymer microspheres or is a composition of dried biodegradable polymer microspheres for
20 suspension in a liquid medium.
- Item 21. The pharmaceutical composition of item 20, wherein the pharmaceutical composition is a suspension comprising the biodegradable polymer microspheres in a concentration of about 100 mg/mL to about 500 mg/mL, preferably about 200 mg/mL to about 400 mg/mL, and more preferably about 250 mg/mL to about 350 mg/mL.
- 25 Item 22. The pharmaceutical composition of item 20 or 21, wherein the suspension or liquid medium comprises a non-aqueous vehicle.
- Item 23. The pharmaceutical composition of item 22, wherein the non-aqueous vehicle comprises an oil.
- Item 24. The pharmaceutical composition of item 23, wherein the oil comprises medium
30 chain triglycerides.

Item 25. The pharmaceutical composition of any one of items 22 to 24, wherein the non-aqueous vehicle is a mixture of medium-chain triglycerides, such as a mixture of C8/C10 triglycerides.

5 Item 26. The pharmaceutical composition of items 24 or 25, wherein less than 10% of the triptorelin is released over 21 hours, less than 15% of the triptorelin is released after about 165 hours, and more than 75% of the triptorelin is released after about 330 hours, in vitro.

Item 27. The pharmaceutical composition of item 26, wherein the in vitro release is measured using a USP II apparatus, including:

10 - introducing MCT oil suspension comprising the biodegradable polymer microspheres equivalent to 70mg of triptorelin base, in 900 mL of a 100 mM acetate buffer,

- applying the following gradient of temperature:

- incubating at about 37°C for about 21 hours,
- 15 ○ applying a gradient of temperature with an increase of about 0.5°C per hour for about 46 hours,
- maintaining at 60 °C until 330 hours,

wherein samples are withdrawn from the apparatus at specific time points and the drug dissolved is quantified via HPLC.

20 Item 28. The pharmaceutical composition of item 20, wherein the liquid medium for suspension comprises an aqueous vehicle.

Item 29. The pharmaceutical composition of any one of items 1 to 28, wherein the pharmaceutical composition consists of biodegradable polymer microspheres comprising (a) triptorelin, or a pharmaceutically acceptable water-soluble salt thereof and (b) the single lactic acid polymer, as a suspension in liquid medium or in dried

25 form for suspension in a liquid medium.

Item 30. The pharmaceutical composition of any one of items 1 to 29, wherein the pharmaceutical composition consists of a single group of biodegradable polymer microspheres.

30 Item 31. The pharmaceutical composition of any one of items 1 to 30, wherein the pharmaceutical composition is sterilised by irradiation.

- Item 32. A pharmaceutical composition of any one of items 1 to 31 for use as a medicament.
- Item 33. A pharmaceutical composition of any one of items 1 to 31 for use in the treatment of a disease or disorder in which triptorelin, or a pharmaceutically acceptable soluble salt form thereof, has a therapeutic effect.
- Item 34. The pharmaceutical composition for use according to item 33, wherein the disease or disorder is selected from prostate cancer, the symptoms of prostate cancer, central precocious puberty, endometrial stromal sarcoma, uterine fibroids, breast cancer or endometriosis.
- Item 35. The pharmaceutical composition for use according to item 34, wherein the disease or disorder is central precocious puberty.
- Item 36. The pharmaceutical composition for use according to any one of items 32 to 35, wherein the pharmaceutical composition is to be administered to a subject parenterally.
- Item 37. The pharmaceutical composition for use according to item 36, wherein the pharmaceutical composition is to be parenterally administered via intramuscular or subcutaneous injection.
- Item 38. The pharmaceutical composition for use according to item 37, wherein the pharmaceutical composition is to be parenterally administered via intramuscular injection.
- Item 39. A method of treating a disease or disorder in which triptorelin, or a pharmaceutically acceptable water-soluble salt form thereof, has a therapeutic effect, comprising administering to a subject in need thereof the pharmaceutical composition of any one of items 1 to 31.
- Item 40. The method of item 39, wherein the disease or disorder is selected from prostate cancer, the symptoms of prostate cancer, central precocious puberty, endometrial stromal sarcoma, uterine fibroids, breast cancer or endometriosis.

Item 41. The method of item 40, wherein the disease or disorder is central precocious puberty.

Item 42. The method of any one of items 39 to 41, wherein the subject has not been previously treated for the disease or disorder.

5 Item 43. The method of any one of items 39 to 41, wherein the subject has been previously treated for the disease or disorder.

Item 44. The pharmaceutical composition for use according to any one of items 36 to 38 or the method of any one of items 39 to 43, wherein the subject is a human.

10 Item 45. A method of preparing triptorelin biodegradable polymer microspheres comprising

(a1) preparing an organic phase by dissolving the triptorelin, or a pharmaceutically acceptable soluble salt thereof, and a single lactic acid polymer or pharmaceutically acceptable salt thereof having a lactide content of 80% or more and an initial inherent viscosity of about 0.4 to about 0.8 dL/g measured at a concentration of 0.5g/dL in
15 chloroform at 30°C, in one or more organic solvents at room temperature;

(a2) preparing an aqueous phase by dissolving polyvinyl alcohol and a salting-out agent in water, and cooling the aqueous phase between about 2 and about 8°C to yield a cooled aqueous phase;

20 (a3) mixing the organic and the cooled aqueous phase, thereby forming the microspheres, and

(a4) filtering, washing and drying the microspheres.

Item 46. The method of item 45, wherein the one or more organic solvents in the organic phase are a mixture of dichloromethane and methanol.

25 Item 47. The method of item 46, wherein the dichloromethane is present in the mixture in an amount of about 50% to about 90% (w/w).

- Item 48. The method of item 47, wherein the dichloromethane is present in the mixture in an amount of about 75% (w/w).
- Item 49. The method of item 46, wherein the methanol is present in the mixture in an amount of about 5% to about 50% (w/w).
- 5 Item 50. The method of item 49, wherein the methanol is present in the mixture in an amount of about 25% (w/w).
- Item 51. The method of any one of items 45 to 50, wherein the polyvinyl alcohol in the aqueous phase is present in an amount of about 0.1% to about 10% (w/w).
- 10 Item 52. The method of item 51, wherein the polyvinyl alcohol in the aqueous phase is present in an amount of about 1% (w/w).
- Item 53. The method of any one of items 45 to 52, wherein the salting-out agent in the aqueous phase is present in an amount of about 0.1% to about 10% (w/w).
- Item 54. The method of item 53, wherein the salting-out agent in the aqueous phase is present in an amount of about 2.5% (w/w).
- 15 Item 55. The method of any one of items 45 to 54, wherein the salting-out agent in the aqueous phase is sodium chloride.
- Item 56. The method of any one of items 45 to 55, wherein the organic and aqueous phases are mixed at a ratio of 1:50 to 1:500.
- Item 57. The method of item 56, wherein the ratio is about 1:100.
- 20 Item 58. The method of any one of items 45 to 57, wherein the biodegradable polymer microspheres have a Dv50 of about 20 μm to about 80 μm , preferably about 40 μm to about 60 μm .
- 25 Item 59. The method of any one of items 45 to 58, wherein the encapsulation efficiency of triptorelin in the microspheres is between about 80% and about 99%, preferably between about 90% and about 99%.

Item 60. The biodegradable polymer microspheres prepared by the method of any one of items 45 to 59.

Item 61. A pharmaceutical composition comprising the biodegradable polymer microspheres of item 60.

5 Item 62. The pharmaceutical composition of item 61, wherein the biodegradable polymer microspheres are mixed with an aqueous or non-aqueous vehicle to prepare a pharmaceutical composition.

Item 63. The pharmaceutical composition of items 61 or 62, wherein the pharmaceutical composition provides a sustained release of the triptorelin for at least 10 months, at
10 least 11 months or at least 12 months.

Item 64. The pharmaceutical composition of any one of items 1 to 38 or 61 to 63, wherein the pharmaceutical composition provides a sustained release of the triptorelin with an initial C_{max} of 4 ng/mL or less within 48h, within 24h or within 12h following administration to a subject.

15 Item 65. The pharmaceutical composition of any one of items 1 to 38 or 61 to 64, wherein the pharmaceutical composition provides a sustained release of the triptorelin with an overall C_{max} of 4 ng/mL or less in a subject.

Item 66. The pharmaceutical composition of any one of items 1 to 38 or 61 to 65, wherein the pharmaceutical composition provides a sustained release of the triptorelin above a threshold of 0.0137 ng/mL throughout a maintenance period from 1 month to
20 10, 11 or 12 months after administration to a subject, preferably from 48h to 10, 11 or 12 months after administration.

Item 67. The pharmaceutical composition of any one of items 1 to 38 or 61 to 66, wherein the pharmaceutical composition provides a sustained release of the triptorelin above a threshold of 0.0316 ng/mL throughout a maintenance period from 1 month to
25 10, 11 or 12 months after administration to a subject, preferably from 48h to 10, 11 or 12 months after administration.

Item 68. The pharmaceutical composition of any one of items 64 to 67, wherein the subject is a human.

- Item 69. A kit comprising:
- a) the pharmaceutical composition of any one of items 1 to 31, 61 or 63-67;
 - b) optionally a vehicle for reconstitution, and
 - c) a vial or syringe optionally prefilled with the pharmaceutical composition of a).
- 5

While the invention has been illustrated and described with respect to illustrative embodiments and modes of practice, it will be apparent to those skilled in the art that various modifications and improvements may be made without departing from the scope and spirit of the invention. Accordingly, the invention is not to be limited by the illustrative embodiments and modes of practice.

10

EXAMPLES

Example 1: Characterizations

Gel permeation chromatography (GPC) can be performed as follows. The sample is dissolved in tetrahydrofuran (THF) and analysed in isocratic elution with THF at 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 ($I_p = Mw/Mn$) are determined based on a calibration curve using narrow molecular weight polystyrene as standards obtained from Sigma Aldrich as shown in Table 1:

15

20

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

The lactic acid content of the biodegradable polymer can be measured by using conventional methods, for example by Nuclear Magnetic Resonance (^1H NMR).

The drug loading can be measured using conventional methods, for example using high performance liquid chromatography (HPLC). The HPLC method can be as follows. An appropriate weight e.g., 20mg, of the biodegradable polymer microparticles can be weighed, dissolved in acetonitrile (ACN) and dichloromethane (DCM), and the sample can be analysed in gradient elution using a C18 column, a phosphate buffer pH 6.8/acetonitrile mobile phase and an UV detection at 280nm.

Example 2: Microsphere preparation

- 10 The following method was used to make the microspheres (Compositions A-M) listed in Table 2.
1. An appropriate amount of dichloromethane and methanol was mixed in a glass container to obtain a solution with the appropriate concentration of methanol as stated in Table 2 (column "methanol conc."). An appropriate amount of PL(G)A polymer was then dissolved in this solution to give a polymer concentration as stated in Table 2 (column "PL(G)A conc."). Following this, an appropriate amount of triptorelin acetate was weighed and added to this solution under magnetic stirring, the triptorelin acetate was added in an amount that equated to a theoretical drug load for the later formed microspheres as stated in Table 2 (column "theoretical drug load"). The solution obtained is referred to as the "organic solution". The organic solution was kept at room temperature until the mixing step 3.
 2. An appropriate amount of polyvinyl alcohol (PVA 4-88) was dissolved in an appropriate amount of deionized water to form 1% PVA 4-88 solution. An appropriate amount of NaCl was then dissolved in this 1% PVA 4-88 solution to obtain a solution with a concentration of NaCl as stated in Table 2 (column "NaCl conc."). The solution obtained is referred to as the "aqueous solution". The aqueous solution was kept at 4 °C until the mixing step 3.
 3. Mixing step. The organic solution (at room temperature) was mixed with the aqueous solution (at 4°C) by pumping the organic solution, with a flexible tube pump at a rate as indicated in Table 2 (column "organic solution rate"), into a rotor-stator equipment and by pumping the aqueous solution, using a peristaltic pump or a flowmeter at a rate as stated in Table 2 (column "aqueous solution rate"), into the same rotor-stator equipment. The two solutions were mixed in the rotor-stator chamber at a speed as stated in Table 2 (column "rotor-stator speed"). The microsphere suspension obtained by O/W emulsion was collected in a glass beaker or inox tank.

4. Microspheres ripening. The microsphere suspension was kept under magnetic stirring and under vacuum for 4 hours to evaporate the dichloromethane. The temperature at the end of the solvent evaporation step was below 15°C.
5. Microsphere filtration & washing. The microspheres were collected by filtration (20 µm) and then washed several times (to remove any triptorelin acetate and/or PVA on their surface) with an appropriate amount of a solution of 10% methanol in water.
6. Microsphere drying and sterilization. The microspheres were dried overnight (16 h) at 30 °C under vacuum in the filter, then a second drying step was performed during 2 to 7 days in an oven under vacuum at 40°C. The dried microspheres were sieved through 106 µm sieve and added, under nitrogen, into glass vials. The microspheres were then sterilized by X-ray irradiation with a dose of 25kGy.
7. The drug load was quantified via liquid chromatography after solubilization (in acetonitrile and dichloromethane) using a gradient method on a C18 column. The drug loads are shown in Table 2 (column "drug load real"). The molecular weight of the polymer in the microspheres was determined by GPC and indicated in Table 2.

Composition M is the same composition as that of Composition E, but was manufactured at a different scale. Batch size for Compositions A to L was approximately 10 g and batch size for Composition M was approximately 60 g. The manufacturing lines were different depending on the batch size, but the equipment used were equivalent.

Table 2:

Composition	Polymer nature	Drug load theoretical (%)	Methanol conc. (%)	PL(G)A conc. (%)	NaCl conc. (%)	Organic solution rate (mL/min)	Aqueous solution rate (mL/min)	Rotor stator speed (rpm)	GPC data * Mw (g/mol) Mn (g/mol) IP	Drug load real (%)	Encapsulation efficiency (%)
A	PLGA 75:25 end group ester, initial iv 0.7dL/g	13	18	10	5	5	575	5000	49700 32049 1.55	12.2	94
B	PLGA 85:15 end group ester, initial iv 0.6dL/g	13	18	10	5	5	575	5000	52634 33745 1.56	10.7	82
C	DL PLA (100:0) end group COOH, initial iv 0.21dL/g	13	18	15	5	5	575	5000	15700 10655 1.47	11.1	85
D	DL PLA (100:0) end group ester, initial iv 0.36dL/g	13	21	12	5	5	575	4000	31621 19860 1.59	10.4	80
E	DL PLA (100:0) end group ester, initial iv 0.67dL/g	13	21	11	5	5	575	5000	56653 35315 1.60	11.1	85
F	PLGA 75:25 end group ester, initial iv 0.7dL/g	13	18	10	2.5	5	575	5000	48775 30730 1.58	10.5	81
G	PLGA 75:25 end group ester, initial iv 0.7dL/g	6	10	10	5	5	575	5000	47173 30899 1.53	5.4	90
H	PLGA 75:25 end group ester, initial iv 0.7dL/g	17	20	10	5	5	550	5000	45973 29831 1.54	14.4	85
I	PLGA 75:25 end group ester, initial iv 0.7dL/g	6	21	20	5	5	500	8000	48776 31128 1.57	5.5	92

J	Mix: A (20%) + B (30%) + E (50%)	13	NA	NA	NA	5	NA	NA	NA	11.1	85
K	Mix: A (30%) + C (70%)	13	NA	NA	NA	NA	NA	NA	NA	11.3	87
L	PLGA 75:25 end group ester, initial iv 0.7dL/g (30%) + DL PLA (100:0) end group COOH, initial iv 0.21dL/g (70%)	13	22	14	5	5	750	5000	26716 13219 2.02	10.9	84
M	DL PLA (100:0) end group ester, initial iv 0.67dL/g	13	25	12	2.5	23	2300	2300	57755 36553 1.58	12.3	95

*GPC data = Gel Permeation Chromatography data, namely Mw = Weight average molecular weight (g/mol); Mn = Number average molecular weight (g/mol); IP = Index of Polydispersity (ratio Mw/Mn)

Example 3: Determination of the particle size

The particle size distributions of Compositions A to M was determined by wet laser diffraction using Malvern mastersizer 3000. Each sample was resuspended in an aqueous solution of sodium carboxymethyl cellulose (1.5% w/w) and polysorbate 80 (0.1%) and then
 5 diluted/dispersed in purified water in a hydro MV dispersion unit (stirring at 2000rpm) until reaching a stable laser obscuration of 10% to 20%. The sample was then subject 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; imaginary particle
 10 refractive index 0.001. The results for compositions A to M are shown in Table 3.

Table 3: particle size distributions

Composition	Dv10 (μm)	Dv50 (μm)	Dv90 (μm)
A	24.5	53.6	96.9
B	22.8	47.8	85.2
C	19.6	43.4	80.1
D	22.3	45.7	83.7
E	20.8	51.4	95.3
F	28.0	55.4	96.2
G	24.4	51.3	95.2
H	24.9	53.0	95.2
I	13.7	46.0	97.6
J	22.7	51.2	91.2
K	21.5	47.1	85.6
L	22.0	49.8	91.3
M	24.5	48.4	95.1

Example 4: In vivo pharmacokinetic profile of Compositions A to L in rats

The microspheres were suspended in a physiologically acceptable lipophilic vehicle (MCT) to obtain a drug suspension concentration of 45 mg/mL. The resulting suspension was
 15 intramuscularly injected, in an amount equating to a single dose of triptorelin of 39 mg/kg, into 6 males Sprague Dawley rats weighing 200-250 g (5-6 weeks old) at the day of treatment. After defined time periods, plasma samples were taken and analyzed for the triptorelin concentration. Results are shown in Table 4 and FIGs. 2-4.

20 Compositions B, D, and E were formulations comprising a single lactic acid polymer that exhibited the statistically longest observed release profile with significant triptorelin plasmatic concentrations measurable over at least 10 months. Composition E (identical to that of Composition M) provided a particularly advantageous pharmacokinetic profile.

98.0	0.56	0.29	1.94	1.04	1.08	0.63	0.58	0.15	0.63	0.69	0.64	0.59
112.0	0.16	0.08	2.21	2.12	0.62	0.29	1.29	1.09	1.11	1.05	0.24	0.15
126.0	0.03	0.00	1.21	0.31	0.33	0.11	1.74	1.51	1.01	0.75	0.06	0.08
140.0	0.00	0.00	1.20	0.42	0.30	0.10	1.08	0.69	0.85	0.20	0.04	0.07
154.0	0.00	0.00	0.79	0.13	0.28	0.08	1.16	0.83	0.81	0.18	0.00	0.01
168.0	0.00	0.00	0.48	0.21	0.16	0.06	0.61	0.30	1.05	0.60	0.00	0.00
196.0	0.00	0.00	0.30	0.07	0.21	0.32	1.09	1.01	0.81	0.57	0.00	0.00
210.0	0.00	0.00	0.60	1.00	0.06	0.04	2.43	2.17	0.59	0.41	0.00	0.00
224.0	0.00	0.00	0.10	0.01	0.03	0.03	1.27	0.91	0.36	0.07	0.00	0.00
238.0	0.00	0.00	0.04	0.02	0.02	0.02	0.61	0.16	0.26	0.09	0.00	0.00
252.0	0.00	0.00	0.06	0.04	0.01	0.01	0.56	0.10	0.57	0.63	0.00	0.00
266.0	0.00	0.00	0.04	0.03	0.00	0.00	0.55	0.33	0.22	0.04	0.00	0.00
280.0	0.00	0.00	0.01	0.01	0.00	0.00	0.51	0.36	0.29	0.05	0.00	0.00
294.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.16	0.01	0.00	0.00
308.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.20	0.00	0.00	0.00
322.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.23	0.00	0.00	0.00
336.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.24	0.00	0.00	0.00

Table 4b: in vivo results

Time (days)	Composition											
	G			H			I			J		
	Mean plasmatic concentrati on (ng/mL)	SD (ng/mL)	Mean plasmatic concentrati on (ng/mL)	SD (ng/mL)	Mean plasmatic concentrati on (ng/mL)	SD (ng/mL)	Mean plasmatic concentrati on (ng/mL)	SD (ng/mL)	Mean plasmatic concentrati on (ng/mL)	SD (ng/mL)	Mean plasmatic concentrati on (ng/mL)	SD (ng/mL)
0.0	10.57	2.30	19.67	3.70	8.66	3.82	16.56	3.75	14.29	3.90	14.23	4.79
0.0	12.15	2.85	20.04	3.63	13.14	3.37	17.41	5.48	16.72	5.90	16.24	3.79
0.1	11.64	2.75	14.72	2.95	14.15	3.13	15.84	4.36	26.99	10.73	15.78	2.95
0.2	6.10	1.94	3.84	1.07	4.67	3.21	10.91	3.41	51.27	8.16	11.36	2.00
0.3	2.36	0.63	3.00	0.32	1.06	0.49	4.50	2.57	47.19	9.88	11.45	2.34
1.0	0.60	0.10	1.65	0.17	0.10	0.02	1.17	0.39	9.36	1.49	14.71	3.60
2.0	0.57	0.13	1.30	0.14	0.13	0.03	0.76	0.22	6.23	1.53	15.61	3.27
3.0	0.55	0.10	1.10	0.12	0.18	0.05	0.58	0.15	5.25	1.17	17.79	3.53
7.0	0.44	0.24	1.80	0.25	0.62	0.43	0.69	0.14	6.22	1.57	14.78	1.60
14.0	0.34	0.09	25.24	13.00	0.31	0.18	1.12	0.45	8.44	2.71	4.92	1.57
28.0	1.53	0.99	16.85	7.84	0.73	0.32	2.28	0.47	5.23	1.17	2.11	1.67
42.0	2.48	0.58	4.05	1.41	4.88	4.40	1.74	0.42	4.65	1.41	2.24	0.37
56.0	7.41	3.42	1.84	0.82	4.03	2.12	1.11	0.48	1.69	0.61	4.82	2.40
70.0	4.01	2.03	1.21	0.69	6.70	9.13	0.98	0.25	1.26	0.50	2.41	1.30

84.0	1.59	0.52	0.58	0.18	2.99	5.22	1.14	0.81	0.90	0.38	0.95	0.30
98.0	1.00	1.07	0.52	0.28	0.50	0.31	0.80	0.44	0.71	0.16	2.97	3.55
112.0	0.16	0.08	0.11	0.04	0.09	0.07	0.48	0.06	0.56	0.36	0.91	0.68
126.0	0.04	0.03	0.05	0.06	0.02	0.02	0.61	0.27	0.44	0.25	0.35	0.12
140.0	0.01	0.01	0.01	0.01	0.00	0.01	0.65	0.29	0.42	0.16	0.27	0.11
154.0	0.00	0.00	0.00	0.00	0.00	0.00	0.62	0.24	0.30	0.15	0.24	0.10
168.0	0.00	0.00	0.00	0.00	0.00	0.00	0.23	0.13	0.16	0.18	0.09	0.05
196.0	0.00	0.00	0.00	0.00	0.00	0.00	0.28	0.12	0.06	0.04	0.05	0.03
210.0	0.00	0.00	0.00	0.00	0.00	0.00	0.38	0.51	0.03	0.03	0.02	0.01
224.0	0.00	0.00	0.00	0.00	0.00	0.00	0.16	0.08	0.06	0.05	0.00	0.00
238.0	0.00	0.00	0.00	0.00	0.00	0.00	0.10	0.02	0.02	0.01	0.00	0.00
252.0	0.00	0.00	0.00	0.00	0.00	0.00	0.11	0.03	0.01	0.02	0.00	0.00
266.0	0.00	0.00	0.00	0.00	0.00	0.00	0.15	0.18	0.01	0.02	0.00	0.00
280.0	0.00	0.00	0.00	0.00	0.00	0.00	0.09	0.04	0.00	0.01	0.00	0.00
294.0	0.00	0.00	0.00	0.00	0.00	0.00	0.09	0.03	0.00	0.00	0.00	0.00
308.0	0.00	0.00	0.00	0.00	0.00	0.00	0.09	0.03	0.00	0.00	0.00	0.00
322.0	0.00	0.00	0.00	0.00	0.00	0.00	0.07	0.04	0.00	0.00	0.00	0.00
336.0	0.00	0.00	0.00	0.00	0.00	0.00	0.06	0.03	0.00	0.00	0.00	0.00

Example 5: In vivo pharmacokinetic profile of Composition M in rats

The microspheres having the components of Composition M were suspended in a physiologically acceptable aqueous vehicle of 1.5% (w/w) sodium carboxymethyl cellulose, 4.25% (w/w) mannitol, and 0.1% (w/w) polysorbate 80 (group 1) and a physiologically acceptable lipophilic vehicle of MCT oil (group 2) to obtain a drug suspension concentration of 45 mg/mL. The resulting suspension was intramuscularly injected, in an amount equating to a single dose of triptorelin of 39 mg/kg, into 20 females Wistar 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 triptorelin concentration. Results are shown in Table 5 and FIG. 1.

Table 5: in vivo results composition M

Time (days)	Composition M in aqueous suspension		Composition M in lipidic suspension	
	mean plasmatic concentration (ng/mL)	SD (ng/mL)	mean plasmatic concentration (ng/mL)	SD (ng/mL)
0.0	15.15	3.41	8.58	4.00
0.0	14.75	2.41	9.36	4.08
0.1	9.13	1.40	7.15	3.69
0.2	4.89	0.85	3.40	0.84
0.3	3.58	0.54	2.98	0.76
1.0	1.39	0.22	1.00	0.25
2.0	0.72	0.15	0.57	0.17
3.0	0.63	0.15	0.52	0.15
7.0	0.87	0.31	0.59	0.24
14.0	0.43	0.11	0.37	0.10
28.0	0.53	0.25	0.42	0.27
42.0	0.72	0.35	0.47	0.26
56.0	0.55	0.26	0.40	0.14
70.0	0.64	0.34	0.37	0.17
85.0	0.70	0.44	0.35	0.21
98.0	0.74	0.55	0.43	0.23
112.0	0.68	0.46	0.37	0.22
126.0	0.91	0.66	0.50	0.31
140.0	1.03	0.67	0.68	0.41
155.0	0.84	0.39	0.58	0.24
168.0	0.74	0.25	0.46	0.15

181.0	0.52	0.19	0.35	0.12
195.0	0.49	0.12	0.40	0.10
209.0	0.41	0.08	0.31	0.11
223.0	0.31	0.08	0.26	0.10
237.0	0.23	0.09	0.18	0.07
251.0	0.30	0.10	0.20	0.07
265.0	0.26	0.10	0.18	0.05
279.0	0.23	0.07	0.17	0.07
293.0	0.19	0.05	0.15	0.05
307.0	0.18	0.03	0.14	0.04
321.0	0.21	0.07	0.15	0.06
335.0	0.17	0.07	0.13	0.05
349.0	0.11	0.04	0.11	0.05
363.0	0.11	0.04	0.10	0.06

Composition M in both vehicles exhibited a particularly advantageous pharmacokinetic profile.

5 Example 6 (comparative): Microspheres of triptorelin pamoate preparation

The following method was used to make the microspheres for Composition 1 (batch size approximately 10 g).

1. An appropriate amount of triptorelin pamoate was suspended in an appropriate amount of dichloromethane in a glass container. Then the suspension was mixed in a mixer equipment at 15000 rpm during 3min to obtain a suspension.
2. An appropriate amount of PLA polymer (DL PLA end group ester iv 0.5dL/g) was then dissolved in an appropriate amount of dichloromethane to give a polymer concentration of 12% in the solution. Then this solution was mixed with the previous suspension under magnetic stirring to give a theoretical drug load of 18.7% for the later formed microspheres. The suspension obtained is referred to as the "organic solution".
3. An appropriate amount of PVA 4-88 was dissolved in an appropriate amount of deionized water to form 1% PVA 4-88 solution. The solution obtained is referred to as the "aqueous solution".
4. The organic solution was mixed with the aqueous solution by pumping the organic solution, with a flexible tube pump at a rate of 5mL/min, into a rotor-stator equipment and by pumping the aqueous solution, using a peristaltic pump at a rate of

625mL/min. The two solutions were mixed in the rotor-stator chamber a speed of 2500rpm. The microsphere suspension obtained by O/W emulsion was collected in a glass beaker.

- 5 5. The microspheres were collected by filtration (1.2 μ m) and then washed several times (to remove any triptorelin pamoate and/or PVA on their surface) with an appropriate amount of water. Following this the microspheres were dried overnight (16h) at room temperature under vacuum. The dried microspheres were sieved through 106 μ m sieve.
- 10 6. The microspheres were then mixed with an aqueous diluent composed of 1.5 % of CMC Na, 4.25% of mannitol and 0.1% of polysorbate 80. The suspension was freeze dried and then sterilized by gamma irradiation with a dose of 25kGy.
7. The drug load was quantified via liquid chromatography at 14.96% (encapsulation efficiency 80%).
8. The particle size was quantified via wet laser diffraction at a Dv50 of 51.3 μ m.

15 **Example 7 (comparative): Coated microspheres of triptorelin pamoate preparation**

The following method was used to make coated microspheres (Composition 2) using the microspheres of Composition 1.

- 20 1. An appropriate amount of acetone was added in water to obtain a solution at a concentration of 9% of acetone. An appropriate amount of PLA polymer (DL PLA end group ester iv 0.5dL/g) was dissolved in an appropriate amount of the previous solution to obtain a solution at a concentration of 2% of polymer ("the coating solution").
- 25 2. An appropriate amount of microspheres of Composition 1 was used to fill a fluidized air bed for coating. The fluidized air rate applied to the microspheres was at 16L/min at room temperature.
3. The coating solution was added at 1.4L/min and atomized at 6L/min over the microspheres during 100min.
4. The microspheres were collected and sieved through 180 μ m sieve.
- 30 5. The microspheres were then mixed with an aqueous diluent composed of 1.5 % of CMC Na, 4.25% of mannitol and 0.1% of polysorbate 80. The suspension was freeze dried and then sterilized by gamma irradiation with a dose of 25kGy.
6. The drug load was quantified via liquid chromatography at 12.22% (encapsulation efficiency 65%).
7. The particle size was quantified via wet laser diffraction at a Dv50 of 75 μ m.

Example 8 (comparative): Microgranules of triptorelin pamoate preparation

The following method was used to make the microgranules (Composition 3):

1. An appropriate amount of triptorelin pamoate was mixed with an appropriate amount of PLA polymer (DL PLA end group ester iv 0.5dL/g using a planetary ball mill equipment for 3 minutes to obtain a drug loading of 18.7% of triptorelin free base.
2. The mix was then extruded manually using a single screw extruder 12/24mm. at a temperature of 110°C.
3. The extrudate was cut at 2mm using a Pelletizer, and the pellets were milled using a cryo milling equipment (annular milling). The Dv50 of the microgranules were about 250 µm. The microgranules were then mixed with an aqueous diluent composed of 1.5 % of CMC Na, 4.25% of mannitol and 0.1% of polysorbate 80 and freeze dried.
4. The microgranules were sterilized by gamma irradiation with a dose of 25kGy.

Example 9 (comparative): Implant of triptorelin acetate preparation

The following method was used to make the implant (Composition 4):

1. An appropriate amount of triptorelin acetate was mixed with an appropriate amount of PLA polymer (DL PLA end group ester iv 0.5dL/g) and an appropriate amount of sodium pamoate or pamoic acid, using a planetary ball mill equipment for 3 minutes to obtain a drug loading of 30% of triptorelin free base.
2. The mix was then extruded manually using a single screw extruder 12/24mm at a temperature of 125°C.
3. The extrudate were cut manually with a scalpel at the appropriate length (2.1cm long and 1.44mm of diameter).
4. The implants were sterilized by gamma irradiation with a dose of 25kGy

Example 10 (comparative): In vivo pharmacokinetic profile of compositions 1, 2, 3, and 4 in rats

The microspheres and microgranules of compositions 1, 2 and 3 were reconstituted using water for injection. The resulting suspension was intramuscularly injected, in an amount equating to a single dose of triptorelin of 39 mg/kg, into 10 males Sprague Dawley rats. After defined time periods, plasma samples were taken and analyzed for the triptorelin concentration. Results are shown in Tables 6 and 7 and FIGs. 5 and 6.

The implant of composition 4 was intramuscularly injected, in an amount equating to a single dose of triptorelin of 39 mg/kg, into 10 males Sprague Dawley rats. After defined time

periods, plasma samples were taken and analyzed for the triptorelin concentration. Results are shown in Table 7 and FIG 6.

Table 6:

Time (days)	Composition 1		Composition 2	
	Mean plasmatic concentration (ng/mL)	SD (ng/mL)	Mean plasmatic concentration (ng/mL)	SD (ng/mL)
0	2.2	1.6	2.7	1.4
0.04	41.0	9.6	54.5	9.5
0.25	17.1	5.3	16.6	8.9
1	11.8	3.4	16.9	3.1
3	1.0	0.6	2.0	1.2
7	0.5	0.2	0.9	0.8
14	0.7	0.6	1.2	0.8
28	1.3	1.1	2.0	1.0
42	2.3	0.8	2.4	1.1
56	1.9	0.3	1.9	0.9
70	4.4	2.3	2.5	1.0
84	3.0	1.0	2.6	1.0
98	4.6	0.5	3.2	0.9
112	8.6	7.2	3.5	0.8
126	5.5	1.6	3.4	0.6
140	6.5	3.0	3.3	0.9
154	9.9	3.5	4.0	1.0
168	5.4	1.8	3.2	1.6
182				
196	3.4	1.0	3.5	2.1
210				
224	3.6	2.1	3.7	3.0
238				
252	6.2	4.7	5.4	3.5
263			11.4	NA
266			0	0
267			0	0
268			0	0
270			0	0
280	4.1	3.3	0	0
294			0	0
308	2.6	0.7	0	0
322			0	0
336	3.9	1.3	0	0
350			0	0
364	0	0	0	0

Table 7:

Time (days)	Composition 3		Composition 4	
	Mean plasmatic concentration (ng/mL)	SD (ng/mL)	Mean plasmatic concentration (ng/mL)	SD (ng/mL)
0	0.0	0.0	0.0	0.0
0.04	336.5	64.9	198.4	19.3
0.25	134.9	23.5	323.3	55.5
0.42	84.7	12.1	225.1	68.5
1	50.5	15.4	172.8	150.1
2	45.6	8.1	19.8	6.2
3	26.6	6.9	9.7	7.0
7	12.1	4.0	2.7	1.0
14	1.8	0.7	0.9	1.1
28	1.4	1.2	0.3	0.1
42	1.2	1.1	0.2	0.1
56	0.7	0.4	0.2	0.1
70	0.8	0.5	0.2	0.1
84	0.6	0.7	0.2	0.1
98	0.5	0.5	0.2	0.2
112	0.3	0.3	0.2	0.1
126	0.2	0.2	0.2	0.1
140	0.2	0.3	0.2	0.1
154	0.2	0.2	0.2	0.1
168	0.2	0.2	0.2	0.1
182	0.1	0.1	0.2	0.1
196	0.1	0.1	0.3	0.2
210	0.1	0.1	0.2	0.1
224	0.1	0.1	0.3	0.1
238	0.1	0.1	0.5	0.2
252	0.1	0.0	0.7	0.3
266	0.2	0.1	0.7	0.2
280	0.4	0.3	0.8	0.3
294	0.4	0.3	1.0	0.8
308	0.9	0.6	2.1	1.5
322	3.1	5.5	2.6	1.4
336	2.7	4.1	3.5	3.4
350	1.6	1.2	5.0	3.5
364	2.5	1.9	2.7	1.0
378	2.1	1.1	2.5	1.4
392	2.9	2.4	2.1	0.5
406	3.2	1.3	1.1	0.8
420	6.1	6.3	2.4	3.8
434	3.0	1.5	0.4	0.5
448	9.5	7.4	0.1	0.0
462	6.7	2.7	0.0	0.0
476	3.5	0.3	0.0	NA
490	5.7	8.1	NA	NA
504	3.5	4.9	NA	NA
518	0.0	NA	NA	NA
532	0.0	NA	NA	NA

None of the compositions 1 to 4 exhibited an acceptable pharmacokinetic profile.

Example 11: Clinical Trial

5 An open-label, single-arm, multi-center, Phase 3 study on the efficacy, safety, and pharmacokinetics of a triptorelin 12-month formulation (composition M, 70 mg triptorelin, in the form of acetate salt, in MIGLYOL® 812) [the Study Formulation], in pediatric participants who are receiving gonadotropin-releasing hormone agonist therapy for central precocious puberty (CPP) is conducted.

10 This Phase 3 study enrolls pediatric participants who are already on treatment with a gonadotropin-releasing hormone agonist (GnRHa) for CPP and switch to the triptorelin 12-month Study Formulation. The study is composed of 2 parts:

- Part A assesses efficacy, safety and pharmacokinetics (PK) over 12 months (52 weeks) after the first injection of the triptorelin 12-month Study Formulation. It furthermore assesses the absence of the acute-on-chronic (AOC) phenomenon after the injection of the Study Formulation in a randomly selected subset representing approximately half the study population. Additionally, the triptorelin maximum serum concentration (C_{max}) is measured in a PK subset.
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- Part B assesses the persistence of the efficacy, safety, and PK profiles over 12 months (52 weeks) after the second injection of the Study Formulation, administered 12 months following the first injection. Similar to Part A, the absence of the AOC phenomenon is investigated after the second injection of the Study Formulation in the AOC subset. Part B also assesses the potential accumulation of triptorelin serum concentration after the second injection of the Study Formulation, evaluated on C_{max} in the PK subset and on triptorelin serum concentration at the end of the dosing interval (C_{trough}) in all participants.
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The end of treatment (EOT) occurs 52 weeks after the last injection of the Study Formulation.

Primary Objective

30 The primary objective of Part A is to evaluate the efficacy of the Study Formulation in suppressing serum LH to prepubertal levels 52 weeks after the first injection of the Study Formulation.

The endpoint is the percentage of participants with suppression of stimulated serum LH to ≤ 5 IU/L at the visit scheduled for 52 weeks after the first injection of the Study Formulation.

Study Population

The study is conducted on pediatric participants (boys and girls) diagnosed with CPP and receiving GnRHa therapy.

5 Inclusion criteria:

1. Diagnosis of central precocious puberty and currently receiving GnRHa therapy
2. Onset of development of sex characteristics (i.e., breast development in girls or testicular enlargement in boys according to the Tanner method) before the age of 8 years in girls and 9 years in boy.
- 10 3. Initially, only participants aged (a) 5 to 8 years inclusive (i.e., <9 years) are eligible. The Sponsor will determine whether participants aged (b) 2 to 4 years inclusive (i.e., <5 years) and/or (c) 9 to 10 years inclusive (i.e., <11 years) may be recruited. The Sponsor will inform all Investigators in writing when enrolment in either or both of the age ranges (b) and (c) can be initiated.
- 15 4. Candidate to receive at least 1 year of GnRHa therapy from study treatment start
5. Start of initial GnRHa therapy no later than 18 months after onset of the first signs of CPP
6. Difference (Δ) between bone age (Greulich and Pyle method) and chronological age of ≥ 1 year based on historical values at the initiation of the GnRHa therapy
- 20 7. Pubertal-type LH response (LH ≥ 6 IU/L) following a GnRH/GnRHa stimulation test, or random non stimulated serum LH > 0.5 IU/L (if considered local standard of care) based on historical values prior to the initiation of GnRHa therapy
8. Clinical evidence of puberty, defined as Tanner Staging ≥ 2 for breast development for girls and testicular volume ≥ 4 mL (cc) for boys, prior to the initiation of GnRHa therapy.
- 25 9. Negative urine pregnancy test: Although pregnancy is unlikely in this study population, all girls must have a negative urine pregnancy test at screening and should not be at risk of pregnancy throughout the study period. The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to reduce the risk for inclusion of a participant with an undetected early pregnancy.
- 30 10. Informed consent form (ICF) signed by the parent(s) or by the legal guardian (where applicable) as per local regulations.
11. Signed assent form when appropriate, as determined by participant's age and individual site and country requirements.

Exclusion Criteria:

1. Gonadotropin-independent (peripheral) precocious puberty: gonadotropin-independent gonadal or adrenal sex steroid secretion
- 5 2. Non-progressing, isolated premature thelarche prior to the initial GnRHa therapy
3. Presence of an unstable intracranial tumor or an intracranial tumor potentially requiring neurosurgery or cerebral irradiation. Participants with hamartomas not requiring surgery are eligible
4. Evidence of renal (estimated Glomerular Filtration Rate [eGFR] <60 mL/min/1.73 m² assessed by the updated Schwartz formula [CKiD U25]) or hepatic impairment (total bilirubin >1.5x ULN, alanine aminotransferase [ALT] or aspartate aminotransferase [AST] >3x ULN)
- 10 5. Any other condition or chronic illness possibly interfering with growth (e.g., renal failure, diabetes, moderate to severe scoliosis, previously treated intracranial tumor)
6. Other than GnRHa therapy, any ongoing treatment with a potential effect on serum levels of gonadotropins or sex steroids, or possibly interfering with growth (e.g., chronic steroid use [except mild topical steroids], opioids)
- 15 7. Prior or current therapy with medroxyprogesterone acetate, growth hormone, or insulin-like growth factor-1 (IGF-1)
8. Participation in any clinical study involving an investigational study treatment within 4 weeks before enrollment or within 5 half-lives of the investigational product, whichever is longer
9. Major medical or psychiatric illness that could interfere with study visits
10. Diagnosis of short stature, i.e., more than 2.25 standard deviations (SD) below the mean height-for-age
- 25 11. Known history of seizures, epilepsy, and/or central nervous system disorders that may have been associated with seizures or convulsions
12. Prior (within 2 months of study treatment start) or current use of medications that have been associated with seizures or convulsions
- 30 13. (a) Use of other medications known to cause a prolonged QT interval
(b) Mean QT interval corrected for heart rate (HR) according to Fridericia's formula (QTcF) >440 ms, history of congenital heart disease, arrhythmia, long QT syndrome, or symptoms suggestive of long QT syndrome, including syncope
(c) Family history of long QT syndrome or sudden cardiac death before the age of 50

14. Known hypersensitivity to triptorelin, leuprolide or to any of the excipients in the formulations or related compounds
15. Use of anticoagulants (heparin or coumarin derivatives)
16. Any other condition that would, in the Investigator's judgment, preclude participant's participation in the clinical study due to safety concerns or compliance with clinical study procedures.

Study Formulation, dose and mode of administration

The Study Formulation is in the form of an extended-release suspension for injection of biodegradable polymer microspheres of Composition M, comprising 70 mg triptorelin, in the form of acetate salt, in MIGLYOL® 812, for administration every 12 months (52 weeks) for 24 months (104 weeks).

Participants receive 2 intramuscular (i.m.) injections of the Study Formulation, the first one on study day 1 (i.e., Visit [V] 1) and the second injection 52 weeks later (V12).

Treatment duration

The treatment duration (treatment period) for each participant will be approximately 104 weeks. It begins with the first injection and will last until 52 weeks after the second injection.

Study duration

The study will last a maximum of 120 weeks for each participant, including a 4-week screening period, a 104-week (2-year) study treatment period, and a 12-week post-treatment period.

Example 12: Early results on two clinical trial participants

In a clinical trial according to Example 11, the first 2 participants dosed were respectively an 8.9 year-old girl (Patient A) and a 7.5-year-old girl (Patient B), both previously treated with a commercial triptorelin 3-month formulation.

One month (4 weeks) post-dose, i.e. after first administration of the Study Formulation, stimulated serum LH levels were suppressed to ≤ 5 IU/L, and even to ≤ 4 IU/L, in both Patients A and B.

Patients A and B belong to the PK subset, for which the following timepoints are defined in the protocol for measuring triptorelin serum concentration (among other parameters): 0.5, 1, 2, 4, 8, 12, 24 and 48 hours post administration of the Study Formulation (post-dose), as well as 4 weeks (1 month), 8 weeks (2 months), 12 weeks, 20 weeks, 26 weeks, 36 weeks, 5 48 weeks and 52 weeks post-dose (for Part A, i.e. after first administration of Study Formulation).

For both Patients A and B:

- 10 • throughout the first 48h post-dose, serum triptorelin levels remained below 4 ng/mL, and even below 2 ng/mL;
- an initial C_{max} of triptorelin was observed within 8h post-dose.

One month post-dose in both Patients A and B, and two months post-dose in Patient A, serum triptorelin levels were at least 4-fold above the threshold of 0.0316 ng/mL of triptorelin, associated with a 95% probability of adequate hormonal suppression (stimulated 15 serum LH $\leq$ 5 IU/L), and were below 4 ng/mL, and even below 2 ng/mL. The 2-month value for Patient B, dosed a few weeks later, was not available yet.

The first administration of Study Drug was safe and well tolerated for both Patients A and B.

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CLAIMS

1. A pharmaceutical composition comprising biodegradable polymer microspheres comprising (a) triptorelin, or a pharmaceutically acceptable water-soluble salt thereof, and (b) a single lactic acid polymer having a lactide content of 80% or more,
5 a molecular weight (Mw) of about 30,000 g/mol to about 80,000 g/mol and a polydispersity between about 1.4 and about 2.0 as determined by gel permeation chromatography, wherein the pharmaceutical composition provides a sustained release of the triptorelin for at least 10 months, at least 11 months or at least 12 months.
- 10 2. The pharmaceutical composition of claim 1, wherein the biodegradable polymer microspheres have a drug loading of triptorelin, or a pharmaceutically acceptable water-soluble salt thereof, based upon triptorelin free base, of about 10% to about 20% (w/w), preferably about 10% to about 15% (w/w), more preferably about 12% (w/w).
- 15 3. The pharmaceutical composition of claim 1 or 2, wherein the triptorelin is present as triptorelin acetate.
4. The pharmaceutical composition of any one of claims 1 to 3, wherein the biodegradable polymer microspheres have a Dv50 of about 20 μm to about 80 μm , preferably about 40 μm to about 60 μm .
- 20 5. The pharmaceutical composition of any one of claims 1 to 4, wherein the lactic acid polymer has a molecular weight of about 40,000 g/mol to about 65,000 g/mol, preferably about 45,000 to about 65,000 g/mol, and a polydispersity between about 1.5 and about 1.9.
- 25 6. The pharmaceutical composition of any one of claims 1 to 5, wherein the lactic acid polymer has an initial inherent viscosity of about 0.4 dL/g to about 0.8 dL/g, preferably about 0.55 dL/g to about 0.75 dL/g, measured at a concentration of 0.5g/dL in chloroform at 30°C.

7. The pharmaceutical composition of any one of claims 1 to 6, wherein the lactic acid polymer is polylactic acid (PLA) or poly(lactic-co-glycolic acid) (PLGA), particularly PLA.
- 5 8. The pharmaceutical composition of any one of claims 1 to 7, wherein the pharmaceutical composition comprises an amount of about 40 mg to about 90 mg, preferably about 70 mg triptorelin as the free base.
- 10 9. The pharmaceutical composition of any one of claims 1 to 8, wherein the pharmaceutical composition is a suspension comprising biodegradable polymer microspheres or is a composition of dried biodegradable polymer microspheres for suspension in a liquid medium, preferably wherein the suspension and/or liquid medium comprises a non-aqueous vehicle, wherein the non-aqueous vehicle particularly comprises an oil comprising medium chain triglycerides.
- 15 10. A pharmaceutical composition of any one of claims 1 to 9 for use in the treatment of a disease or disorder in which triptorelin, or a pharmaceutically acceptable soluble salt form thereof, has a therapeutic effect.
11. A pharmaceutical composition of any one of claims 1 to 9 for use in the treatment of a disease or disorder in a subject, wherein the disease or disorder is prostate cancer, the symptoms of prostate cancer, central precocious puberty, endometrial stromal sarcoma, uterine fibroids, breast cancer or endometriosis.
- 20 12. The pharmaceutical composition for use according to claim 10 or 11, wherein the pharmaceutical composition is to be administered to a subject parenterally, such as via intra-muscular or subcutaneous injection.
13. The pharmaceutical composition for use according to any one of claims 10 to 12, wherein the subject has been previously treated for the disease or disorder.
- 25 14. A method of preparing triptorelin biodegradable polymer microspheres comprising (a1) preparing an organic phase by dissolving the triptorelin, or a pharmaceutically acceptable soluble salt thereof, and a single lactic acid polymer or pharmaceutically acceptable salt thereof having a lactide content of 80% or more and an initial inherent viscosity of about 0.4 to about 0.8 dL/g measured at a

concentration of 0.5g/dL in chloroform at 30°C, in one or more organic solvents at room temperature;

5 (a2) preparing an aqueous phase by dissolving polyvinyl alcohol and a salting-out agent in water, and cooling the aqueous phase between about 2 and about 8°C to yield a cooled aqueous phase;

(a3) mixing the organic and the cooled aqueous phase, thereby forming the microspheres, and

(a4) filtering, washing and drying the microspheres.

15. Biodegradable polymer microspheres prepared by the method of claim 14.

10 16. A pharmaceutical composition comprising the biodegradable microspheres of claim 15.

17. A kit comprising:

- 15 a) the pharmaceutical composition of any one of claims 1 to 9 or 16;
b) optionally a vehicle for reconstitution, and
c) a vial or syringe optionally prefilled with the pharmaceutical composition of a).