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(54) Title: COMPOSITIONS COMPRISING PGI2-RECEPTOR AGONISTS AND PROCESSES FOR THE PREPARATION THEREOF

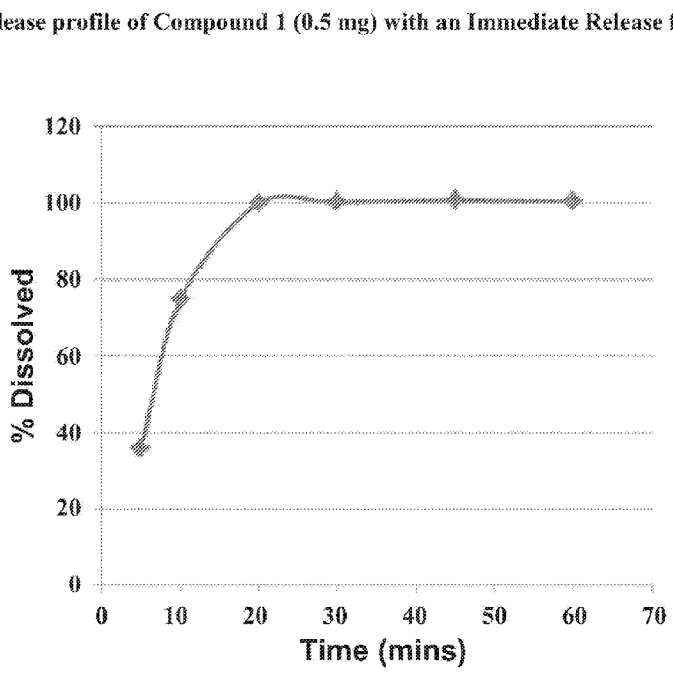

FIGURE 1

(57) Abstract: Provided herein in some embodiments are pharmaceutical compositions comprising a prostacyclin (PGI2) receptor agonist selected from 2-(((1r,4r)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, as disclosed herein. In some embodiments the pharmaceutical compositions comprise a compound selected from 2-(((1r,4r)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1), and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, the composition having a release rate by weight of the compound in an aqueous medium that is one or more of release rates (a), (b) and (c) as disclosed herein. The compositions of the present invention are useful in the treatment of PGI2 related disorders, such as those disclosed herein.

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[Continued on next page]

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COMPOSITIONS COMPRISING PGI2-RECEPTOR AGONISTS AND PROCESSES FOR THE PREPARATION THEREOF

The present invention relates in some embodiments to methods of using, and compositions comprising a prostacyclin (PGI2) receptor agonist selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof. The compositions of the present invention are useful in the treatment of, for example: pulmonary arterial hypertension (PAH); idiopathic PAH; familial PAH; PAH associated with: a collagen vascular disease, a congenital heart disease, portal hypertension, HIV infection, ingestion of a drug or toxin, hereditary hemorrhagic telangiectasia, splenectomy, pulmonary veno-occlusive disease (PVOD) or pulmonary capillary hemangiomatosis (PCH); PAH with significant venous or capillary involvement; platelet aggregation; coronary artery disease; myocardial infarction; transient ischemic attack; angina; stroke; ischemia-reperfusion injury; restenosis; atrial fibrillation; blood clot formation in an angioplasty or coronary bypass surgery individual or in an individual suffering from atrial fibrillation; atherothrombosis; asthma or a symptom thereof; a diabetic-related disorder such as diabetic peripheral neuropathy, diabetic nephropathy or diabetic retinopathy; glaucoma or other disease of the eye with abnormal intraocular pressure; hypertension; inflammation; psoriasis; psoriatic arthritis; rheumatoid arthritis; Crohn's disease; transplant rejection; multiple sclerosis; systemic lupus erythematosus (SLE); ulcerative colitis; atherosclerosis; acne; type 1 diabetes; type 2 diabetes; sepsis; and chronic obstructive pulmonary disorder (COPD).

BACKGROUND OF THE INVENTION

PGI2 is a lipid molecule derived from arachidonic acid through the cyclooxygenase pathway. It is a potent vasodilator, antiproliferative, anti-thrombotic and antiplatelet agent that mediates its effects as an agonist of a G protein-coupled receptor (PGI2 receptor; *e.g.,* human PGI2 receptor, GenBank® Accession No. NP_000951 and alleles thereof). It is known that the binding of PGI2 (or other such agonists) to the PGI2 receptor leads to coupling with the Gs protein and increased intracellular cAMP levels. (See, *e.g.,* Zhang *et al,* Arch. Biochem. Biophys, 2006, 454:80-88).

PAH is a life-threatening disease characterized by a progressive pulmonary vasculopathy leading to right ventricular hypertrophy. Right heart failure occurs if left untreated. Prostacyclin, which has vasodilatory and antiproliferative effects on the pulmonary vasculature has been found to be low in patients with PAH compared with normal controls. Exogenous administration of prostacyclin or an analog of prostacyclin (*i.e.,* an agonist of the PGI2 receptor) has become an important strategy in the treatment of PAH. (See, *e.g.,* Tuder *et al,* Am. *J.* Respir. Crit. Care. Med, 1999, 159:1925-1932; Humbert

et al, J. Am. Coll. Cardiol, 2004, 43:13S-24S; Rosenzweig, Expert Opin. Emerging Drugs, 2006, 11:609-619; McLaughlin *et al,* Circulation, 2006, 114:1417-1431; Rosenkranz, Clin. Res. Cardiol, 2007, 96:527-541; Driscoll *et al,* Expert Opin. Pharmacother, 2008, 9:.2 65-81).

Trepostinil and iloprost are FDA-approved analogs of prostacyclin which, like prostacyclin, are not orally-active. Beraprost is an orally-active analog of prostacyclin approved for the treatment of PAH in Japan, but it has failed registration for the treatment of PAH in Europe and in the US. Of the three FDA-approved drugs, prostacyclin is the best studied in PAH patients. The approximate annual cost of treating PAH with these drugs is $25,000 to $200,000 depending on the dose. At present, many experts consider intravenous prostacyclin to be the most reliable agent for managing the sickest PAH patients. Due to the short half-life of prostacyclin, intravenous treatment is complicated by the need for a continuous infusion. Patients are at risk for potentially fatal rebound pulmonary hypertension if the infusion is abruptly disrupted, as well as significant risk of catheter-related complications including sepsis. (See, *e.g.,* Rosenzweig, Expert Opin. Emerging Drugs, 2006, 11:609-619; Naeije *et al,* Expert Opin. Pharmacother, 2007, 8:2247-2265; Strauss *et al,* Clin. Chest. Med, 2007, 28:127-142; Driscoll *et al,* Expert Opin. Pharmacother, 2008, 9:65-81).

Orally available, non-prostanoid PGI2-receptor agonists that provide clinical benefits similar to currently available PGI2-receptor agonists have the potential to improve the standard of care for PAH. The compositions of the present invention comprise the PGI2-receptor agonist, Compound 1, a novel, non-prostanoid, oral drug candidate discovered by Arena Pharmaceuticals, Inc, and intended for the treatment of PAH. Compound 1 was disclosed in PCT publication WO2009/117095, which is incorporated herein by reference in its entirety. Various synthetic routes to Compound 1, its related salts, prodrugs, crystalline forms, and intermediates, have been reported in PCT publication WO 2011/037613, which is incorporated herein by reference in its entirety. 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) is disclosed in WO 2009/117095 (incorporated by reference herein in its entirety).

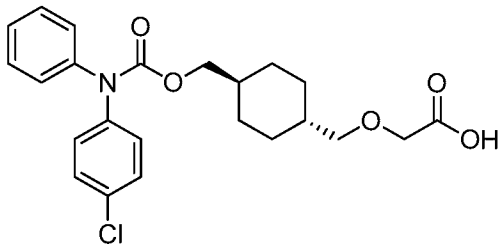
Compound 1 has the potential to improve treatment for PAH by providing patients with an oral, once-daily option targeting the PGI2 receptor. In view of the potency of Compound 1, side effects that are associated with this class of compounds may be observed in patients. Examples of such side effects include nausea and headaches.

Compound 1 has a long plasma half-life (~24 hours). Unlike many active compounds, an extended-release formulation of Compound 1 is not necessary to achieve once daily dosing. However, side effects (such as nausea and headaches) are associated with the class of compounds that target the IP receptor, and Compound 1 is a particularly potent IP receptor agonist. There is evidence of a dose-response relationship for some drugs targeting the prostacyclin receptor. However, the relationship

between drug plasma levels and hemodynamic parameters is unknown. Understanding the relationship between plasma levels and clinical response can help to define therapeutic dose levels. Accordingly, it is desirable to develop new pharmaceutical compositions that modify the release of Compound 1 to balance once daily dosing with improved pharmacokinetics, and to develop treatment regimens with Compound 1 that account for blood plasma levels, in order to optimize treatment for patients with life-threatening disorders.

SUMMARY

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid, having the structure:



(Compound 1),

and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, the composition having a release rate by weight of the compound in an aqueous medium that is one or more of release rates (a), (b) and (c), wherein:

(a) about 15% to about 35% by weight of the compound is released over the first two hours in the aqueous medium;

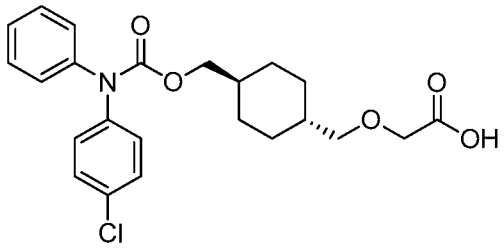
(b) about 24% to about 59% by weight of the compound is released over the first four hours in the aqueous medium; and/or

(c) about 43% to about 96% by weight of the compound is released over the first eight hours in the aqueous medium.

In some embodiments, the release rate is measured with USP Apparatus 1 (baskets) at 80 to 120 rpm in 400 to 600 mL of an aqueous medium at a pH of 6.3 to 7.3 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.04 to 0.06 M.

In some embodiments, the release rate is measured with USP Apparatus 2 (paddle) at 40 to 60 rpm in 400 to 600 mL of an aqueous medium at a pH of 6.3 to 7.3 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.04 to 0.06 M.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid, having the structure:



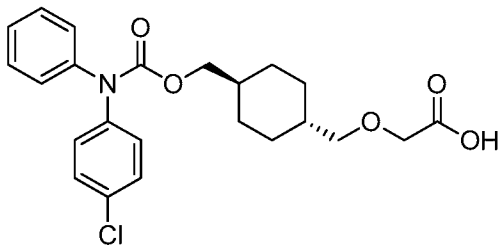
(Compound 1),

and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, the composition having a release rate by weight of the compound in an aqueous medium that is release rate (a), wherein:

(a) about 15% to about 35% by weight of the compound is released over the first two hours in the aqueous medium,

wherein the release rate is measured with USP Apparatus 1 (baskets) at 80 to 120 rpm in 400 to 600 mL of an aqueous medium at a pH of 6.3 to 7.3 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.04 to 0.06 M.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid, having the structure:



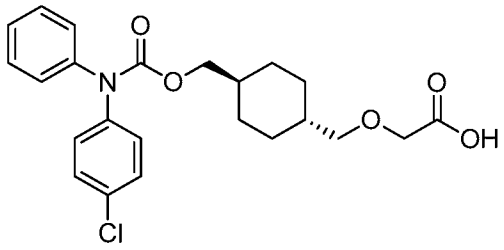
(Compound 1),

and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, the composition having a release rate by weight of the compound in an aqueous medium that is release rate (b), wherein:

(b) about 24% to about 59% by weight of the compound is released over the first four hours in the aqueous medium,

wherein the release rate is measured with USP Apparatus 1 (baskets) at 80 to 120 rpm in 400 to 600 mL of an aqueous medium at a pH of 6.3 to 7.3 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.04 to 0.06 M.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid, having the structure:



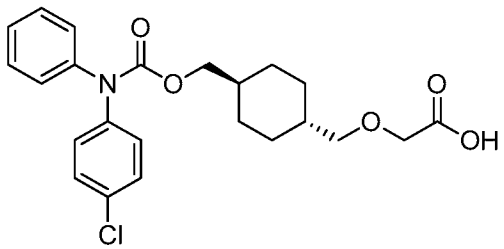
(Compound 1),

and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, the composition having a release rate by weight of the compound in an aqueous medium that is release rate (c), wherein:

(c) about 43% to about 96% by weight of the compound is released over the first eight hours in the aqueous medium,

wherein the release rate is measured with USP Apparatus 1 (baskets) at 80 to 120 rpm in 400 to 600 mL of an aqueous medium at a pH of 6.3 to 7.3 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.04 to 0.06 M.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid, having the structure:



(Compound 1),

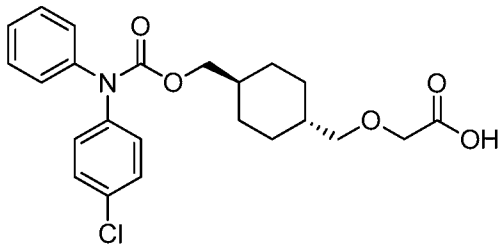
and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, the composition having release rates by weight of the compound in an aqueous medium that are release rates (a) and (b), wherein:

(a) about 15% to about 35% by weight of the compound is released over the first two hours in the aqueous medium; and

(b) about 24% to about 59% by weight of the compound is released over the first four hours in the aqueous medium,

wherein the release rate is measured with USP Apparatus 1 (baskets) at 80 to 120 rpm in 400 to 600 mL of an aqueous medium at a pH of 6.3 to 7.3 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.04 to 0.06 M.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid, having the structure:



(Compound 1),

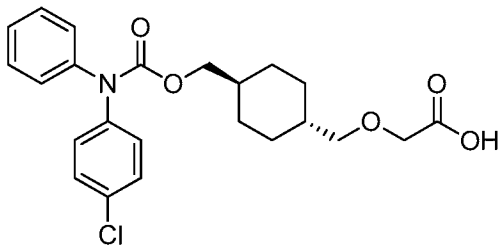
and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, the composition having release rates by weight of the compound in an aqueous medium that are release rates (a) and (c), wherein:

(a) about 15% to about 35% by weight of the compound is released over the first two hours in the aqueous medium; and

(c) about 43% to about 96% by weight of the compound is released over the first eight hours in the aqueous medium,

wherein the release rate is measured with USP Apparatus 1 (baskets) at 80 to 120 rpm in 400 to 600 mL of an aqueous medium at a pH of 6.3 to 7.3 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.04 to 0.06 M.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid, having the structure:



(Compound 1),

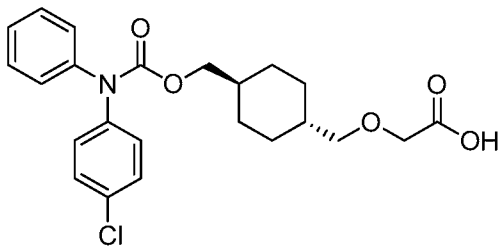
and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, the composition having a release rate by weight of the compound in an aqueous medium that are release rates (b) and (c), wherein:

(b) about 24% to about 59% by weight of the compound is released over the first four hours in the aqueous medium; and

(c) about 43% to about 96% by weight of the compound is released over the first eight hours in the aqueous medium,

wherein the release rate is measured with USP Apparatus 1 (baskets) at 80 to 120 rpm in 400 to 600 mL of an aqueous medium at a pH of 6.3 to 7.3 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.04 to 0.06 M.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid, having the structure:



(Compound 1),

and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, the composition having a release rate by weight of the compound in an aqueous medium that are release rates (a), (b) and (c), wherein:

(a) about 15% to about 35% by weight of the compound is released over the first two hours in the aqueous medium;

(b) about 24% to about 59% by weight of the compound is released over the first four hours in the aqueous medium; and

(c) about 43% to about 96% by weight of the compound is released over the first eight hours in the aqueous medium,

wherein the release rate is measured with USP Apparatus 1 (baskets) at 80 to 120 rpm in 400 to 600 mL of an aqueous medium at a pH of 6.3 to 7.3 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.04 to 0.06 M.

In some embodiments provided herein is a composition having a release rate by weight of the compound as disclosed herein in an aqueous medium, wherein the release rate is the release rate measured with USP Apparatus 1 (baskets) at 100 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.05 M.

In some embodiments provided herein is a composition having a release rate by weight of the compound as disclosed herein in an aqueous medium, wherein the release rate is the release rate measured

USP Apparatus 2 (paddle) at 50 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.05 M.

In some embodiments provided herein is a composition as disclosed herein, wherein the composition is a tablet. In some embodiments provided herein is a composition as disclosed herein, wherein the composition is in a tablet produced using wet granulation.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, wherein the composition comprises an excipient comprising hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C, wherein the excipient is present in an amount equal to about 40% to about 60% by weight.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, wherein the composition comprises an excipient comprising hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C, wherein the excipient is present in an amount equal to about 40% to about 60% by weight.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, wherein the composition comprises a first excipient and a second excipient, wherein the first excipient comprises hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C and the second excipient comprises hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C.

In some embodiments provided herein is a process for preparing a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, as disclosed herein, wherein the process comprises mixing the compound, ethanol, a first excipient comprising hydroxypropyl methylcellulose having a

viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C, and a second excipient comprising hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C, to form the composition.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, wherein the composition comprises a first excipient and a second excipient, wherein the first excipient comprises a copolymer comprising (a) a first polyoxyethylene chain; (b) a poly(propylene oxide) chain bonded to the first polyoxyethylene chain; and (c) a second polyoxyethylene chain bonded to the poly(propylene oxide) chain; and the second excipient comprises an ester of a polyalcohol and a fatty acid.

In some embodiments provided herein is a pharmaceutical composition prepared by the process comprising:

curing a mixture comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, a first excipient, and a second excipient, wherein the first excipient comprises a copolymer comprising (a) a first polyoxyethylene chain; (b) a poly(propylene oxide) chain bonded to the first polyoxyethylene chain; and (c) a second polyoxyethylene chain bonded to the poly(propylene oxide) chain, and the second excipient comprises an ester of a polyalcohol and a fatty acid, to form the composition.

In some embodiments provided herein is a process for preparing a pharmaceutical composition, the process comprising:

curing a mixture comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, a first excipient, and a second excipient, wherein the first excipient comprises a copolymer comprising (a) a first polyoxyethylene chain; (b) a poly(propylene oxide) chain bonded to the first polyoxyethylene chain; and (c) a second polyoxyethylene chain bonded to the poly(propylene oxide) chain, and the second excipient comprises an ester of a polyalcohol and a fatty acid, to form the composition.

In some embodiments, provided herein is a method for the treatment of a PGI2 receptor mediated disorder in an individual, comprising: administering to the individual in need thereof a dose of Compound 1 or a pharmaceutically acceptable salt, solvate, or hydrate thereof sufficient to achieve in the individual a blood plasma concentration of Compound 1 of at least about 2.5 ng/mL.

In some embodiments, provided herein is a method for the treatment of pulmonary arterial hypertension (PAH) in an individual, comprising: administering to the individual in need thereof a dose of Compound 1 sufficient to achieve in the individual a blood plasma concentration of Compound 1 of at least about 2.5 ng/mL.

In some embodiments, provided herein is a method for the treatment of a PGI2 receptor mediated disorder in an individual, comprising: administering to the individual in need thereof a dose of Compound 1 or a pharmaceutically acceptable salt, solvate, or hydrate thereof sufficient to achieve in the individual a blood plasma concentration of Compound 1 of at least about 5 ng/mL.

In some embodiments, provided herein is a method for the treatment of pulmonary arterial hypertension (PAH) in an individual, comprising: administering to the individual in need thereof a dose of Compound 1 sufficient to achieve in the individual a blood plasma concentration of Compound 1 of at least about 5 ng/mL.

In some embodiments, provided herein is a method for the treatment of pulmonary arterial hypertension (PAH) in an individual, comprising: administering to the individual in need thereof a dose of Compound 1; determining the blood plasma level of Compound 1 in the individual; and increasing the dose of Compound 1 if the individual does not have at least a threshold blood plasma level.

In some embodiments, provided herein is a method for the treatment of pulmonary arterial hypertension (PAH) in an individual, comprising: administering to the individual in need thereof a dose of Compound 1; determining the blood plasma level of Compound 1 in the individual; and discontinuing administration of Compound 1 to the individual if the individual does not have at least a threshold blood plasma level.

In some embodiments, provided herein is a method for the treatment of pulmonary arterial hypertension (PAH) in an individual, comprising: administering to the individual in need thereof a dose of Compound 1; determining the blood plasma level of Compound 1 in the individual; and continuing to administer Compound 1 to the individual if the individual has at least a threshold blood plasma level or discontinuing administration of Compound 1 to the individual if the individual does not have at least a threshold blood plasma level.

In some embodiments, provided herein is a method for the treatment of pulmonary arterial hypertension (PAH) in an individual, comprising: administering to the individual in need thereof a maximum tolerated dose of Compound 1; determining the blood plasma level of Compound 1 in the individual; and discontinuing administration of Compound 1 to the individual if the individual does not have at least a threshold blood plasma level at the maximum tolerated dose.

In some embodiments, provided herein is a method for the treatment of pulmonary arterial hypertension (PAH) in an individual, comprising: administering to the individual in need thereof a

maximum tolerated dose of Compound 1; determining the blood plasma level of Compound 1 in the individual; and continuing to administer Compound 1 to the individual if the individual has at least a threshold blood plasma level at the maximum tolerated dose or discontinuing administration of Compound 1 to the individual if the individual does not have at least a threshold blood plasma level at the maximum tolerated dose.

In some embodiments, provided herein is a method for the treatment of pulmonary arterial hypertension (PAH) in an individual, comprising: administering to the individual in need thereof a dose of Compound 1; determining the blood plasma level of Compound 1 in the individual; and increasing the dose of Compound 1 to the individual until a threshold blood plasma level is reached.

In some embodiments, provided herein is a method for selecting a dose of Compound 1 for an individual with pulmonary arterial hypertension (PAH), comprising: determining the blood plasma level of Compound 1 in the individual; and increasing the dose of Compound 1 to the individual until a threshold blood plasma level is reached.

In some embodiments, provided herein is a method for selecting a dose of Compound 1 for an individual with pulmonary arterial hypertension (PAH), comprising: determining the blood plasma level of Compound 1 in the individual; and maintaining the dose of Compound 1 to the individual if a threshold blood plasma level has been reached.

In some embodiments, provided herein is a method for selecting a dose of Compound 1 for an individual with pulmonary arterial hypertension (PAH), comprising: determining the blood plasma level of Compound 1 in the individual; and decreasing the dose of Compound 1 to the individual if a threshold blood plasma level has been exceeded.

In some embodiments, the blood plasma concentration of Compound 1 is at least, or at least about, 3.0, 3.1, 3.2, 3.25, 3.3, 3.4, 3.5, 3.6, 3.7, 3.75, 3.8, 3.9, 4.0, 4.1, 4.2, 4.25, 4.3, 4.4, 4.5, 4.6, 4.7, 4.75, 4.8, 4.9, 5.0, 5.1, 5.2, 5.25, 5.3, 5.4, 5.5, 5.6, 5.7, 5.75, 5.8, 5.9, 6.0, 6.1, 6.2, 6.25, 6.3, 6.4, 6.5, 6.6, 6.7, 6.75, 6.8, 6.9, 7.0, 7.1, 7.2, 7.25, 7.3, 7.4, 7.5, 7.6, 7.7, 7.75, 7.8, 7.9, 8.0, 8.1, 8.2, 8.25, 8.3, 8.4, 8.5, 8.6, 8.7, 8.75, 8.8, 8.9, 9.0, 9.1, 9.2, 9.25, 9.3, 9.4, 9.5, 9.6, 9.7, 9.75, 9.8, 9.9, or 10 ng/mL.

In some embodiments, the blood plasma concentration of Compound 1 is, or is about 3.0, 3.1, 3.2, 3.25, 3.3, 3.4, 3.5, 3.6, 3.7, 3.75, 3.8, 3.9, 4.0, 4.1, 4.2, 4.25, 4.3, 4.4, 4.5, 4.6, 4.7, 4.75, 4.8, 4.9, or 5.0 ng/mL.

In some embodiments, the threshold blood plasma level of Compound 1 is selected from, or from about: 1, 1.1, 1.2, 1.25, 1.3, 1.4, 1.5, 1.6, 1.7, 1.75, 1.8, 1.9, 2, 2.1, 2.2, 2.25, 2.3, 2.4, 2.5, 2.6, 2.7, 2.75, 2.8, 2.9, 3, 3.1, 3.2, 3.25, 3.3, 3.4, 3.5, 3.6, 3.7, 3.75, 3.8, 3.9, 4, 4.1, 4.2, 4.25, 4.3, 4.4, 4.5, 4.6, 4.7, 4.75, 4.8, 4.9, 5, 5.1, 5.2, 5.25, 5.3, 5.4, 5.5, 5.6, 5.7, 5.75, 5.8, 5.9, 6, 6.25, 6.5, 6.75, 7, 7.25, 7.5, 7.75, 8, 8.25, 8.5, 8.75, 9, 9.25, 9.5, 9.75, and 10 ng/ml.

In some embodiments, the therapeutically effective amount of Compound 1 is selected from, or from about, 0.01 mg, 0.02 mg, 0.025 mg, 0.03 mg, 0.04 mg, 0.05 mg, 0.06 mg, 0.065 mg, 0.07 mg, 0.075 mg, 0.08 mg, 0.09 mg, 0.1 mg, 0.12 mg, 0.15 mg, 0.16 mg, 0.2 mg, 0.25 mg, 0.3 mg, 0.35 mg, 0.4 mg, 0.45 mg, 0.5 mg, 0.55 mg, 0.6 mg, 0.65 mg, 0.7 mg, 0.75 mg, 0.8 mg, 0.85 mg, 0.9 mg, 0.95 mg, 1.0 mg, 1.05 mg, 1.1 mg, 1.15 mg. 1.2 mg, 1.25 mg, 1.3 mg, 1.35 mg. 1.4 mg, 1.45, and 1.5 mg daily.

In some embodiments, the therapeutically effective amount of Compound 1 is a starting dose selected from, or from about, 0.01, 0.02, 0.025, 0.03, 0.04, 0.05, 0.06, 0.07, 0.075, 0.08, 0.09, and 0.1 mg daily.

In some embodiments, the therapeutically effective amount of Compound 1 is a highest tolerated dose selected from, or from about, 0.4 mg, 0.45 mg, 0.5 mg, 0.55 mg, 0.6 mg, 0.65 mg, 0.7 mg, 0.75 mg, 0.8 mg, 0.85 mg, 0.9 mg, 0.95 mg, 1.0 mg, and 1.05 mg, 1.1 mg, 1.15 mg. 1.2 mg, 1.25 mg, 1.3 mg, 1.35 mg. 1.4 mg, 1.45, and 1.5 mg daily.

In some embodiments, the therapeutically effective amount of Compound 1 is a maximum dose selected from, or from about, 0.4 mg, 0.45 mg, 0.5 mg, 0.55 mg, 0.6 mg, 0.65 mg, 0.7 mg, 0.75 mg, 0.8 mg, 0.85 mg, 0.9 mg, 0.95 mg, 1.0 mg, 1.05 mg, 1.1 mg, 1.15 mg. 1.2 mg, 1.25 mg, 1.3 mg, 1.35 mg. 1.4 mg, 1.45, and 1.5 mg daily.

In some embodiments, the therapeutically effective amount of Compound 1 is a maximum tolerated dose selected from, or from about, 0.4 mg, 0.45 mg, 0.5 mg, 0.55 mg, 0.6 mg, 0.65 mg, 0.7 mg, 0.75 mg, 0.8 mg, 0.85 mg, 0.9 mg, 0.95 mg, 1.0 mg 1.05 mg, 1.1 mg, 1.15 mg. 1.2 mg, 1.25 mg, 1.3 mg, 1.35 mg. 1.4 mg, 1.45, and 1.5 mg daily.

In some embodiments, the therapeutically effective amount of Compound 1 is a maintenance dose selected from, or from about, 0.01 mg, 0.02 mg, 0.025 mg, 0.03 mg, 0.04 mg, 0.05 mg, 0.06 mg, 0.065 mg, 0.07 mg, 0.075 mg, 0.08 mg, 0.09 mg, 0.1 mg, 0.12 mg, 0.15 mg, 0.16 mg, 0.2 mg, 0.25 mg, 0.3 mg, 0.35 mg, 0.4 mg, 0.45 mg, 0.5 mg, 0.55 mg, 0.6 mg, 0.65 mg, 0.7 mg, 0.75 mg, 0.8 mg, 0.85 mg, 0.9 mg, 0.95 mg, 1.0 mg, 1.05 mg, 1.1 mg, 1.15 mg. 1.2 mg, 1.25 mg, 1.3 mg, 1.35 mg. 1.4 mg, 1.45, and 1.5 mg daily.

In some embodiments, the threshold blood plasma level is a peak blood plasma level.

In some embodiments, the threshold blood plasma level is a trough blood plasma level.

In some embodiments, the threshold blood plasma level is a peak blood plasma level and a trough blood plasma level.

In some embodiments, the threshold blood plasma level is: a peak blood plasma level of, of about, of at least, or of at least about, 3.0, 3.1, 3.2, 3.25, 3.3, 3.4, 3.5, 3.6, 3.7, 3.75, 3.8, 3.9, 4.0, 4.1, 4.2, 4.25, 4.3, 4.4, 4.5, 4.6, 4.7, 4.75, 4.8, 4.9, 5.0, 5.1, 5.2, 5.25, 5.3, 5.4, 5.5, 5.6, 5.7, 5.75, 5.8, 5.9, 6.0, 6.1, 6.2, 6.25, 6.3, 6.4, 6.5, 6.6, 6.7, 6.75, 6.8, 6.9, 7.0, 7.1, 7.2, 7.25, 7.3, 7.4, 7.5, 7.6, 7.7, 7.75, 7.8, 7.9, 8.0,

8.1, 8.2, 8.25, 8.3, 8.4, 8.5, 8.6, 8.7, 8.75, 8.8, 8.9, 9.0, 9.1, 9.2, 9.25, 9.3, 9.4, 9.5, 9.6, 9.7, 9.75, 9.8, 9.9, or 10 ng/mL; and a trough blood plasma level of, of about, of at least, or of at least about, 2.0, 2.1, 2.2, 2.25, 2.3, 2.4, 2.5, 2.6, 2.7, 2.75, 2.8. 2.9, 3.0, 3.1, 3.2, 3.25, 3.3, 3.4, 3.5, 3.6, 3.7, 3.75, 3.8, 3.9, 4.0, 4.1, 4.2, 4.25, 4.3, 4.4, 4.5, 4.6, 4.7, 4.75, 4.8, 4.9, 5.0, 5.1, 5.2, 5.25, 5.3, 5.4, 5.5, 5.6, 5.7, 5.75, 5.8, 5.9, 6.0, 6.1, 6.2, 6.25, 6.3, 6.4, 6.5, 6.6, 6.7, 6.75, 6.8, 6.9, 7.0, 7.1, 7.2, 7.25, 7.3, 7.4, 7.5, 7.6, 7.7, 7.75, 7.8, 7.9, 8.0, 8.1, 8.2, 8.25, 8.3, 8.4, 8.5, 8.6, 8.7, 8.75, 8.8, 8.9, 9.0, 9.1, 9.2, 9.25, 9.3, 9.4, 9.5, 9.6, 9.7, 9.75, 9.8, 9.9, or 10 ng/mL.

In some embodiments, the threshold blood plasma level is: a peak blood plasma level of, of about, or of at least about, 2.5 ng/mL; and a trough blood plasma level of, of about, or of at least of about, 2.5 ng/mL.

In some embodiments, the threshold blood plasma level is: a peak blood plasma level of, of about, or of at least about, 5 ng/mL; and a trough blood plasma level of, of about, or of at least of about, 2.5 ng/mL.

In some embodiments, the threshold blood plasma level is: a peak blood plasma level of, or of about, 5 ng/mL; and a trough blood plasma level of, or of about, 2.5 ng/mL.

In some embodiments, Compound 1 is in a pharmaceutical composition having a release rate by weight of the compound in an aqueous medium that is one or more of release rates (a), (b) and (c), where: (a) about 15% to about 35% by weight of the compound is released over the first two hours in the aqueous medium; (b) about 24% to about 59% by weight of the compound is released over the first four hours in the aqueous medium; and/or (c) about 43% to about 96% by weight of the compound is released over the first eight hours in the aqueous medium, where the release rate is measured with USP Apparatus 1 (baskets) at 80 to 120 rpm in 400 to 600 mL of an aqueous medium at a pH of 6.3 to 7.3 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.04 to 0.06 M.

In some embodiments, Compound 1 is in a pharmaceutical composition having a release rate release rate by weight of the compound in an aqueous medium that is one or more of release rates (a), (b) and (c), where: (a) less than or equal to about 40% by weight of the compound is released over the first two hours in the aqueous medium; (b) about 40% to about 60% by weight of the compound is released over the first five hours in the aqueous medium; and/or (c) more than or equal to about 80% by weight of the compound is released over the first fourteen hours in the aqueous medium, where the release rate is measured with USP Apparatus 1 (baskets) at 80 to 120 rpm in 400 to 600 mL of an aqueous medium at a pH of 6.3 to 7.3 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.04 to 0.06 M.

In some embodiments, the pharmaceutical composition comprises a first excipient and a second excipient, where the first excipient comprises hydroxypropyl methylcellulose having a viscosity of about

2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C and the second excipient comprises hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C.

In some embodiments, the pharmaceutical composition comprises a first excipient and a second excipient, where the first excipient comprises a release modifier having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C and the second excipient comprises a release modifier having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C.

In some embodiments, the pharmaceutical composition has a release rate selected from: (a); (b); (c); (a) and (b); (a) and (c); (b) and (c); (a), (b) and (c).

In some embodiments, the first excipient is present in an amount equal to about 5% to about 45% by weight and the second excipient is present in an amount equal to about 5% to about 45% by weight.

In some embodiments, the first excipient is present in an amount equal to about 5% to about 45% by weight and the second excipient is present in an amount equal to about 5% to about 45% by weight.

In some embodiments, the first excipient is present in an amount equal to about 10% to about 40% by weight and the second excipient is present in an amount equal to about 10% to about 40% by weight.

In some embodiments, the first excipient is present in an amount equal to about 12.5% to about 37.5% by weight and the second excipient is present in an amount equal to about 12.5% to about 37.5% by weight.

In some embodiments, the first excipient is present in an amount equal to about 25% by weight and the second excipient is present in an amount equal to about 25% by weight.

In some embodiments, the release rate is the release rate measured with USP Apparatus 1 (baskets) at 100 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C.

In some embodiments, the aqueous medium comprises sodium phosphate at a concentration of 0.05 M.

In some embodiments, the release rate is the release rate measured with USP Apparatus 2 (paddle) at 50 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C.

In some embodiments, the aqueous medium comprises sodium phosphate at a concentration of 0.05 M.

In some embodiments, the pharmaceutical composition is a tablet comprising a core and a coating.

In some embodiments, the core comprises hydroxypropyl methylcellulose.

In some embodiments, the coating does not comprise hydroxypropyl methylcellulose.

In some embodiments, the therapeutically effective amount of Compound 1 is selected from: about 0.01 % to about 1 % by weight of the composition; about 0.01 % to about 0.6 % by weight of the composition; about 0.02 % to about 0.3 % by weight of the composition; about 0.03 % to about 0.2 % by weight of the composition; about 0.04 % to about 0.12% by weight of the composition; about 0.04 % to about 0.1% by weight of the composition; about 0.04 % to about 0.1% by weight of the composition; about 0.05 % to about 0.08% by weight of the composition; about 0.06 % by weight of the composition; about 0.01 mg to about 1 mg.

In some embodiments, the therapeutically effective amount of Compound 1 is suitable for administration to an individual once daily.

In some embodiments, the pharmaceutical composition comprises about 0.05% by weight of Compound 1; about 25% by weight of hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C; and about 25% by weight of hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C.

In some embodiments, the pharmaceutical composition comprises about 0.05 mg of Compound 1; about 25 mg of hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C; and about 25 mg of hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C.

In some embodiments, the pharmaceutical composition comprises about 0.01 mg to about 0.8 mg of Compound 1; about 5 mg to about 45 mg of hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C; and about 5 mg to about 45 mg of hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C.

In some embodiments, the pharmaceutical composition comprises about 0.01 mg to about 0.8 mg of Compound 1; about 25 mg of hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C; and about 25 mg of hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C.

In some embodiments, the pharmaceutical composition comprises about 0.01 mg to about 0.8 mg of Compound 1; about 25 mg of hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C; and about 25 mg of hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA

seconds when present in an amount of about 2% in water at 20° C; about 25mg of Methocel™ K4M Premium CR; and about 25 mg of Methocel™ K100 Premium LVCR.

In some embodiments, the pharmaceutical composition is storage-stable.

In some embodiments, the pharmaceutical composition is a tablet.

In some embodiments, the tablet contains 0.05 mg, 0.25 mg, or 0.4 mg of Compound 1.

In some embodiments, the pharmaceutical composition is a capsule.

In some embodiments, the release rate of Compound 1 after storage of the pharmaceutical composition at 40°C and 75% RH for at least about one month does not vary at any given dissolution time point equal or greater than 2 hours by more than about 20% of the release rate of the compound prior to storage, where the release rate after storage and prior to storage are each measured with USP Apparatus 1 (baskets) at 100 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C, where the aqueous medium comprises sodium phosphate at a concentration of 0.05 M.

In some embodiments, the pharmaceutical composition comprises a first excipient and a second excipient, where the first excipient comprises a copolymer comprising (a) a first polyoxyethylene chain; (b) a poly(propylene oxide) chain bonded to the first polyoxyethylene chain; and (c) a second polyoxyethylene chain bonded to the poly(propylene oxide) chain; and the second excipient comprises an ester of a polyalcohol and a fatty acid.

In some embodiments, the first excipient comprises Poloxamer 188.

In some embodiments, the second excipient comprises glycerol monostearate and has a monoester content of at least about 90%.

In some embodiments, the second excipient comprises glycerol monostearate and has a monoester content of at least about 95%.

In some embodiments, the pharmaceutical composition is a cured composition.

In some embodiments, the ratio by weight of the first excipient to the second excipient is selected from: about 70:30 to about 10:90; about 50:50 to about 30:70; about 70:30; about 50:50; about 40:60; and about 30:70.

In some embodiments, the release rate is the release rate measured with USP Apparatus 2 (paddle) at 50 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C.

In some embodiments, the aqueous medium comprises sodium phosphate at a concentration of 0.05 M.

In some embodiments, the compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof is 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1).

In some embodiments, the compound is 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1).

In some embodiments, the pharmaceutical composition exhibits peaks in the PXRD spectrum having the following 2θ values: 19.7°, 20.2°, 20.7°, 22.6°, 23.1°, and 23.7°.

In some embodiments, provided herein is a method for the treatment of a PGI2 receptor-mediated disorder in an individual, comprising: administering to the individual in need thereof a starting dose of Compound 1 where the starting dose is an amount equivalent to 0.05 mg of Compound 1 daily for about one week; provided that the individual tolerates the starting dose, administering an increased dose for about one week, where the increased dose is an amount equivalent to 0.05 mg greater than the starting dose, provided that the individual tolerates the increased dose, further increasing the dose.

Some embodiments further comprise repeating the cycle of administering the increased dose for a period of about one week and then further increasing the dose, so long as the patient tolerates the further increased dose, until an optimized dose is administered.

In some embodiments, provided herein is a method for the treatment of pulmonary arterial hypertension (PAH) in an individual, comprising: administering to the individual in need thereof a starting dose of Compound 1 where the starting dose is an amount equivalent to 0.05 mg of Compound 1 daily for about one week; provided that the individual tolerates the starting dose, administering an increased dose for about one week, where the increased dose is an amount equivalent to 0.05 mg greater than the starting dose, provided that the individual tolerates the increased dose, further increasing the dose.

Some embodiments further comprise repeating the cycle of administering the increased dose for a period of about one week and then further increasing the dose, so long as the patient tolerates the further increased dose, until an optimized dose is administered.

In some embodiments, Compound 1 is titrated over about, or at least about, 9 weeks.

In some embodiments, Compound 1 is titrated over about, or at least about, 16 weeks.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the release profile of Compound 1 with an immediate-release formulation.

Figure 2 shows a flowchart of an example of process for manufacturing a modified-release pharmaceutical composition comprising Compound 1 ("API" in the flowchart).

Figure 3 shows dissolution profiles for a capsule containing Compound 1 with varying ratios of Gelucire® 50/13:Kolliphor® RH40. An immediate release (IR) composition profile (left-most plot) is also shown for comparison.

Figure 4 shows dissolution profiles for a capsule containing Compound 1 with Gelucire® 50/13 : Kolliphor® RH40 in a 75:25 ratio at various storage times.

Figures 5A, **5B**, and **5C** shows a dissolution profiles for a 0.04 mg capsule of Compound 1 in Gelucire® 50/13, (i) initially (time = 0), **Figure 5A**; (ii) after curing for 18 hours at 40°C, **Figure 5B**; and (iii) after storage at 40°C and 75% RH for two weeks, **Figure 5C**.

Figure 6 shows a dissolution profile for a capsule containing Compound 1 in 50:50 Poloxamer 188:food grade GMS (i) uncured (T = 0), (ii) after curing at 50°C for 18 hours, (iii) after storage at 40°C and 75% RH for one week post-curing, (iv) after storage at 40°C and 75% RH for two weeks post-curing, and (v) after storage at 40°C and 75% RH for four weeks post-curing.

Figure 7A shows a comparison of Powder X-Ray Diffraction (PXRD) spectra of a capsule containing Poloxamer 188 and food grade GMS in a 50:50 ratio by weight (i) before curing, and (ii) after curing at 50°C for 18 hours. The solid line in Figure **7A** relates to 0.04 mg of Compound 1 in 50:50 Poloxamer-GMS, 18hrs, 50°C; and the dashed line in Figure **7A** relates to 0.04 mg of Compound 1 in 50:50 Poloxamer-GMS, T=0.

Figure 7B shows a Powder X-Ray Diffraction spectrum of a capsule comprising Poloxamer 188 and research grade GMS in a 50:50 ratio by weight (i) before curing, and (ii) after curing at 50°C for 18 hours. Powder X-Ray Diffraction spectrum of a capsule comprising Poloxamer 188 and research grade GMS in a 50:50 ratio by weight (i) before curing, and (ii) after curing at 50°C for 18 hours. Also shown for comparison is (iii) a PXRD spectrum of a capsule comprising Poloxamer 188 and food grade GMS in a 50:50 ratio by weight after curing at 50°C for 18 hours.

Figure 7C shows three Powder X-Ray Diffraction spectra of capsules comprising Poloxamer 188 and research grade GMS in a 50:50 ratio by weight (i) before curing ("uncured"), (ii) after partial curing at 47.5°C for 10 hours ("partially cured"), and (iii) after curing at 50°C for 18 hours ("fully cured").

Figure 8 shows release profiles of a pharmaceutical composition containing Poloxamer 188 and food grade GMS in a 70:30 ratio by weight, and 0.5 mg of Compound 1.

Figure 9 shows release profiles of a pharmaceutical composition containing Poloxamer 188 and food grade GMS in a 50:50 ratio by weight, and 0.5 mg of Compound 1.

Figure 10 shows release profiles of a pharmaceutical composition containing Poloxamer 188 and food grade GMS in a 30:70 ratio by weight, and 0.5 mg of Compound 1.

Figure 11A shows release profiles of the following compositions: (**A**) Immediate release composition containing 0.03 mg of Compound 1; (**B**) Composition containing Poloxamer 188 and food grade GMS in a 50:50 ratio by weight, and 0.03 mg of Compound 1; (**C**) Composition containing Poloxamer 188 and food grade GMS in a 40:60 ratio by weight, and 0.03 mg of Compound 1; (**D**)

Composition containing Poloxamer 188 and food grade GMS in a 30:70 ratio by weight, and 0.03 mg of Compound 1.

Figure 11B shows a release profile for a composition containing Poloxamer 188 and food grade GMS in a 30:70 ratio by weight, and 0.12 mg of Compound 1.

Figure 12 shows dissolution profiles for a tablet comprising Compound 1 (0.05 mg), Methocel K4M Premium CR (25 mg), and Methocel 100 Premium LVCR (25 mg). The points for each plot represent mean values; (a) diamonds: initial dissolution profile; (b) squares: profile after storage at 40°C and 75% RH for 6 months.

Figure 13 shows dissolution profiles for a tablet comprising Compound 1 (0.5 mg), Methocel K4M Premium CR (25 mg), and Methocel 100 Premium LVCR (25 mg). The points for each plot represent mean values; (a) diamonds: initial dissolution profile; (b) squares: profile after storage at 40°C and 75% RH for 6 months.

Figure 14 shows dissolution profiles for: (a) (diamonds) a tablet comprising Compound 1 (0.05 mg), Methocel K4M Premium CR (25 mg), and Methocel 100 Premium LVCR (25 mg); (b) (squares) a tablet comprising Compound 1 (0.5 mg), Methocel K4M Premium CR (25 mg), and Methocel 100 Premium LVCR (25 mg); and (c) (triangles) a capsule comprising Compound 1 (0.03 mg), and Poloxamer 188 and food grade GMS in a ratio of 30:70 of Poloxamer 188 to food grade GMS. The points for each plot represent mean values. All three dissolution profiles were determined after storage at 40°C and 75% RH for 6 months. Profiles (a) and (b) were determined using USP 1 (Baskets) at 100 rpm. Profile (c) was determined using USP 2 (Paddles) at 50 rpm.

Figure 15 shows the mean plasma concentration of Compound 1 measured pre-dose and at 4 hours post-dose in the clinical trial described in Example 8.

Figure 16 shows a scatter plot of C_{max} and the last Compound 1 dose level in patients as described in Example 8.

Figure 17 shows change in PVR as a function of Compound 1 plasma levels as described in Example 8.

Figure 18 shows change in 6MWD as a function of Compound 1 plasma levels as described in Example 8.

Figure 19 shows change in BNP as a function of Compound 1 plasma levels as described in Example 8.

DETAILED DESCRIPTION OF THE INVENTION

Compound 1 is a potent IP receptor agonist. Due to the low doses of Compound 1 needed for therapeutic purposes, a solid oral dosage form (such as a tablet) would require extensive formulation

development to achieve content uniformity. A liquid-in-hard gelatin capsule was therefore developed with an immediate-release formulation for initial clinical studies with Compound 1. However, the immediate-release capsule formulation had a high C_{max} and peak-trough fluctuation, which can affect tolerability and patient compliance. To mitigate these concerns, the dosage amount for the immediate-release capsule formulation was reduced and administered twice daily.

Modified-release capsule formulations were developed for subsequent clinical studies to achieve once daily dosing while addressing shortcomings of the immediate-release formulation. These modified-release capsule formulations demonstrated a desirable combination of properties—balancing once daily dosing with a stable release profile and improved pharmacokinetics. Modified-release tablet formulations were also developed to achieve content uniformity and further improve stability and manufacturing processes. Described herein are such modified-release formulations of Compound 1. As described herein, efficacy for Compound 1 better correlates with peak and trough plasma levels than dosing.

DEFINITIONS

For clarity and consistency, the following definitions will be used throughout this patent document.

The term "agonist" as used herein refers to a moiety that interacts with and activates a G-protein-coupled receptor, for instance PGI2, and can thereby initiate a physiological or pharmacological response characteristic of that receptor. For example, an agonist may activate an intracellular response upon binding to a receptor, or enhance GTP binding to a membrane.

The term "in need of treatment" and the term "in need thereof" when referring to treatment are used interchangeably and refer to a judgment made by a caregiver (*e.g.* physician, nurse, nurse practitioner, *etc.* in the case of humans; veterinarian in the case of animals, including non-human mammals) that an individual or animal requires or will benefit from treatment. This judgment is made based on a variety of factors that are in the realm of a caregiver's expertise, but that includes the knowledge that the individual or animal is ill, or will become ill, as the result of a disease, condition or disorder that is treatable by the compounds of the invention. Accordingly, the compounds of the invention can be used in a protective or preventive manner; or compounds of the invention can be used to alleviate, inhibit or ameliorate the disease, condition or disorder.

The term "individual" refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

The term "modulate or modulating" refers to an increase or decrease in the amount, quality, response or effect of a particular activity, function or molecule.

The term "composition" refers to a compound, including but not limited to, salts, solvates, and hydrates of a compound of the present invention, in combination with at least one additional component.

The term "pharmaceutical composition" refers to a composition comprising at least one active ingredient, such as a compound as described herein; including but not limited to, salts, solvates, and hydrates of compounds of the present invention, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

The term "hydroxypropyl methylcellulose", which may be also referred to as "hypromellose", refers to a propylene glycol ether of methylcellulose. The hydroxypropyl methylcellulose is available in varying degrees of viscosity. As an example, the hydroxypropyl methylcellulose may be a hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C. As an example, the hydroxypropyl methylcellulose may be Methocel K4M Premium CR. As an example, the hydroxypropyl methylcellulose may be a hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C. As an example, the hydroxypropyl methylcellulose may be Methocel K100 Premium LVCR.

The term "copolymer comprising (a) a first polyoxyethylene chain; (b) a poly(propylene oxide) chain bonded to the first polyoxyethylene chain; and (c) a second polyoxyethylene chain bonded to the poly(propylene oxide) chain" refers to a poly(ethylene oxide)-block-poly(propylene oxide)-block-poly(ethylene oxide) block copoplymer.

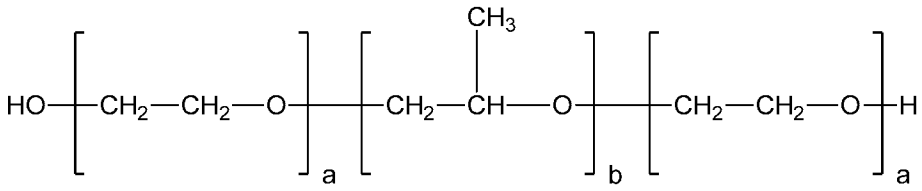
The term "polyoxyethylene oil" as used herein refers to a class of excipients comprising or consisting essentially of either a single compound or a mixture of compounds obtained from the reaction of varying amounts of ethylene oxide with one or more glycerides derived from one or more hydroxyl substituted fatty acids. Examples of hydroxyl substituted fatty acids include ricinoleic acid. Examples of glycerides derived from one or more hydroxyl substituted fatty acids include castor oil. Examples of polyoxyethylene oils include Kolliphor® RH40 (previously known as Cremophor® RH40) (BASF, Mount Olive, NJ).

The term "stearoyl polyoxylglycerides" means a mixture of monoesters, diesters, and triesters of glycerol, and monoesters and diesters of polyethylene glycols with a nominal mean relative molecular weight between 300 and 4000. Examples of stearoyl polyoxylglycerides include stearoyl polyoxyl-32 glycerides such as Gelucire® 50/13 (Gattefosse, France) and Acconon® C-50 (ABITEC, USA).

The term "Poloxamer" as used herein refers to an excipient comprising a copolymer comprising (a) a first polyoxyethylene chain; (b) a poly(propylene oxide) chain bonded to the first polyoxyethylene

chain; and (c) a second polyoxyethylene chain bonded to the poly(propylene oxide) chain. In some embodiments, the copolymer has an average molecular weight of about 17500 or less, such as between about 7680 and about 9510. In some embodiments, the excipient consists essentially of the copolymer. In some embodiments, the excipient is the copolymer.

In some embodiments, the copolymer is represented by the chemical structure below:



wherein the values in the copolymer for variable a at each occurrence are independently from 1 to about 141, such as from about 64 to about 141, such as from about 80 to about 101, or such as from 1 to about 101: and wherein the values in the copolymer for variable b are from 1 to about 56, such as from about 27 to about 56, such as from about 37 to about 44. Poloxamers are known or can be prepared by methods in the art. A number of poloxamers are commercially available. Representative examples of a Poloxamer include, but are not limited to, Poloxamer 124 (Pluronic® L44NF), Poloxamer 188 (Pluronic® F68NF), Poloxamer 237 (Pluronic® F87NF), Poloxamer 338 (Pluronic® F108NF), Poloxamer 407 (Pluronic® F127NF) and the like.

In some embodiments, the values in the copolymer for variable a and for variable b are as follows:

	a	b
In Poloxamer 188	about 80	about 27
In Poloxamer 237	about 64	about 37
In Poloxamer 338	about 141	about 44
In Poloxamer 407	about 101	about 56

The term "glycerol monostearate" – also referred to as "glyceryl monostearate" or "GMS" - as used herein refers to an excipient comprising the monoester of glycerol and stearic acid.

The term "monoester content", also referred to as the "monoglyceride content", is the amount, as a mole percentage, of the monoester of glycerol and stearic acid in the excipient relative to the sum of the amounts of the monoester, the diester of glycerol and stearic acid, the triester of glycerol and stearic acid, and glycerol, in the excipient. Various forms of glycerol monostearate (GMS) are commercially available. "Research grade" GMS has a monoester content that is lower than "NF" grade GMS. NF grade GMS has a monoester content that is lower than that of "food grade" GMS. In some embodiments, the compositions of the invention comprise food grade GMS. As used herein, "food grade" GMS has a monoester content of at least about 95%. Representative examples of commercially available GMS

include, but are not limited to, Myverol™ 18-04 K, Myverol™ 18-06 K, Myverol™ 18-06 PK, Myverol™ 18-04 K, and the like.

The term "cured composition" as used herein refers to a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, the first excipient, and the second excipient that are cured together.

The term "therapeutically effective amount" refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician or caregiver or by an individual, which includes one or more of the following:

(1) preventing the disease, for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease;

(2) inhibiting the disease, for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (*i.e.,* arresting further development of the pathology and/or symptomatology); and

(3) ameliorating the disease, for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (*i.e.,* reversing the pathology and/or symptomatology).

The term "an amount equivalent to", followed by the recitation of an amount of Compound 1 (such as, for example 0.01 mg of Compound 1) refers to the amount of a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof that is equivalent to the recited amount of Compound 1.

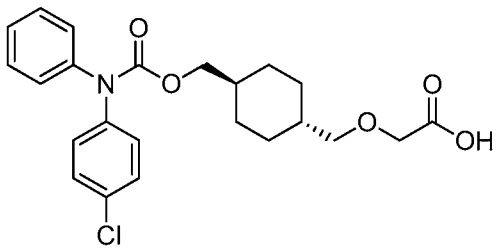
The term "% by weight", when referring to an amount of a component that is present in a composition – such as Compound 1, or such as an excipient – refers to the amount of that component as a % by weight of the composition.

The term "release rate", also referred to as a "dissolution rate" herein, with reference to a compound, refers to the percentage amount of that compound that is released in an aqueous medium over a specified time period. As an example, the recitation "a release rate by weight of the compound in an aqueous medium that is release rate (a), wherein (a) about 15% to about 35% by weight of the compound is released over the first two hours" means that the percentage by weight of the compound that is released over the first two hours is about 15% to about 35% by weight of the initial amount of the compound. The

term "release profile", also referred to as a "dissolution profile" herein, with reference to a compound, refers to a plot showing the percentage amount of that compound that is released in an aqueous medium over time. The aqueous medium may be an aqueous medium as described herein.

COMPOSITIONS AND PROCESSES OF MANUFACTURE

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid, having the structure:



(Compound 1),

and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, the composition having a release rate by weight of the compound in an aqueous medium that is one or more of release rates (a), (b) and (c), wherein:

(a) about 15% to about 35% by weight of the compound is released over the first two hours in the aqueous medium;

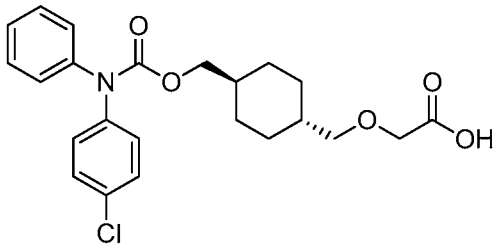
(b) about 24% to about 59% by weight of the compound is released over the first four hours in the aqueous medium; and/or

(c) about 43% to about 96% by weight of the compound is released over the first eight hours in the aqueous medium.

In some embodiments, the release rate is measured with USP Apparatus 1 (baskets) at 80 to 120 rpm in 400 to 600 mL of an aqueous medium at a pH of 6.3 to 7.3 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.04 to 0.06 M.

In some embodiments, the release rate is measured with USP Apparatus 2 (paddle) at 40 to 60 rpm in 400 to 600 mL of an aqueous medium at a pH of 6.3 to 7.3 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.04 to 0.06 M.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid, having the structure:



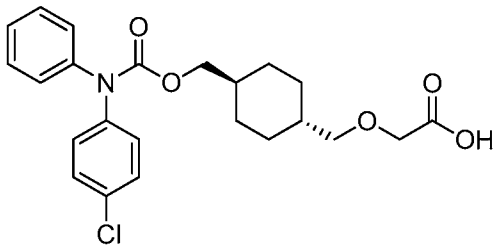
(Compound 1),

and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, the composition having a release rate by weight of the compound in an aqueous medium that is release rate (a), wherein:

(a) about 15% to about 35% by weight of the compound is released over the first two hours in the aqueous medium,

wherein the release rate is measured with USP Apparatus 1 (baskets) at 80 to 120 rpm in 400 to 600 mL of an aqueous medium at a pH of 6.3 to 7.3 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.04 to 0.06 M.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid, having the structure:



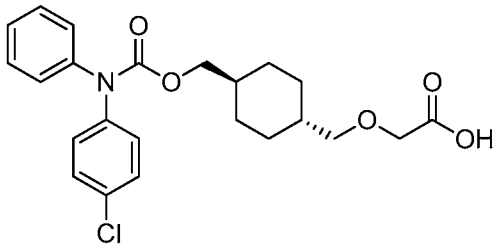
(Compound 1),

and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, the composition having a release rate by weight of the compound in an aqueous medium that is release rate (b), wherein:

(b) about 24% to about 59% by weight of the compound is released over the first four hours in the aqueous medium,

wherein the release rate is measured with USP Apparatus 1 (baskets) at 80 to 120 rpm in 400 to 600 mL of an aqueous medium at a pH of 6.3 to 7.3 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.04 to 0.06 M.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid, having the structure:



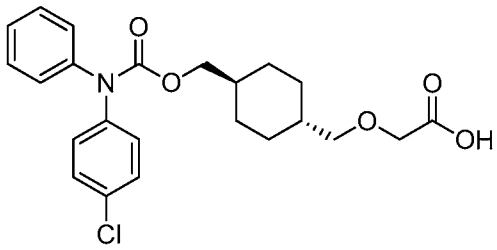
(Compound 1),

and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, the composition having a release rate by weight of the compound in an aqueous medium that is release rate (c), wherein:

(c) about 43% to about 96% by weight of the compound is released over the first eight hours in the aqueous medium,

wherein the release rate is measured with USP Apparatus 1 (baskets) at 80 to 120 rpm in 400 to 600 mL of an aqueous medium at a pH of 6.3 to 7.3 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.04 to 0.06 M.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid, having the structure:



(Compound 1),

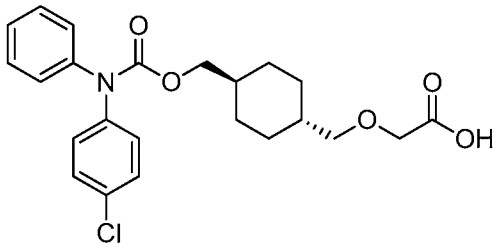
and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, the composition having release rates by weight of the compound in an aqueous medium that are release rates (a) and (b), wherein:

(a) about 15% to about 35% by weight of the compound is released over the first two hours in the aqueous medium; and

(b) about 24% to about 59% by weight of the compound is released over the first four hours in the aqueous medium,

wherein the release rate is measured with USP Apparatus 1 (baskets) at 80 to 120 rpm in 400 to 600 mL of an aqueous medium at a pH of 6.3 to 7.3 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.04 to 0.06 M.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid, having the structure:



(Compound 1),

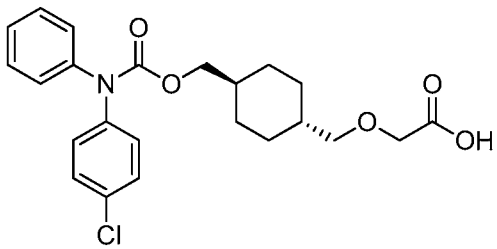
and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, the composition having release rates by weight of the compound in an aqueous medium that are release rates (a) and (c), wherein:

(a) about 15% to about 35% by weight of the compound is released over the first two hours in the aqueous medium; and

(c) about 43% to about 96% by weight of the compound is released over the first eight hours in the aqueous medium,

wherein the release rate is measured with USP Apparatus 1 (baskets) at 80 to 120 rpm in 400 to 600 mL of an aqueous medium at a pH of 6.3 to 7.3 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.04 to 0.06 M.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid, having the structure:



(Compound 1),

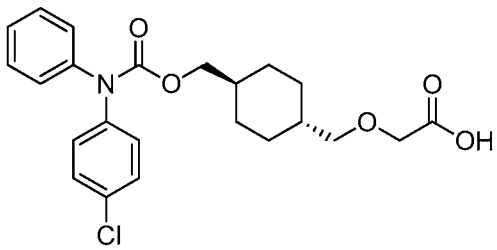
and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, the composition having a release rate by weight of the compound in an aqueous medium that are release rates (b) and (c), wherein:

(b) about 24% to about 59% by weight of the compound is released over the first four hours in the aqueous medium; and

(c) about 43% to about 96% by weight of the compound is released over the first eight hours in the aqueous medium,

wherein the release rate is measured with USP Apparatus 1 (baskets) at 80 to 120 rpm in 400 to 600 mL of an aqueous medium at a pH of 6.3 to 7.3 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.04 to 0.06 M.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid, having the structure:



(Compound 1),

and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, the composition having a release rate by weight of the compound in an aqueous medium that are release rates (a), (b) and (c), wherein:

(a) about 15% to about 35% by weight of the compound is released over the first two hours in the aqueous medium;

(b) about 24% to about 59% by weight of the compound is released over the first four hours in the aqueous medium; and

(c) about 43% to about 96% by weight of the compound is released over the first eight hours in the aqueous medium,

wherein the release rate is measured with USP Apparatus 1 (baskets) at 80 to 120 rpm in 400 to 600 mL of an aqueous medium at a pH of 6.3 to 7.3 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.04 to 0.06 M.

In some embodiments provided herein is a composition having a release rate by weight of the compound as disclosed herein in an aqueous medium, wherein the release rate is the release rate measured with USP Apparatus 1 (baskets) at 100 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.05 M.

In some embodiments provided herein is a composition having a release rate by weight of the compound as disclosed herein in an aqueous medium, wherein the release rate is the release rate measured USP Apparatus 2 (paddle) at 50 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.05 M.

In some embodiments provided herein is a composition as disclosed herein, wherein the composition is a tablet.

In some embodiments provided herein is a composition as disclosed herein, wherein the composition is a capsule.

In some embodiments provided herein is a composition having one or more of release rates (a), (b) and (c) as disclosed herein, wherein the composition comprises one or more excipients selected from the group consisting of (1) ethers of cellulose, such as hydroxypropyl methylcellulose, (2) esters of cellulose, (3) cellulose acetate, (4) ethyl cellulose, (5) polyvinyl acetate, (6) neutral copolymers based on ethylacrylate and methylmethacrylate, (7) copolymers of acrylic and methacrylic acid esters with quaternary ammonium groups, (8) pH-insensitive ammonio methacrylic acid copolymers, (9) polyethylene oxides, (10) polyvinylpyrrolidone, (11) polysaccharides of natural origin such as xanthan gum and locust bean gum, (12) polyethylene glycol, (13) polypropylene glycol, (14) castor oil, (15) triacetin, (16) tributyl citrate, (17) tri-ethyl citrate, (18) acetyl tri-n-butyl citrate, (19) diethyl phthalate, (20) dibutyl sebacate, (21) acetylated mono- and di-glycerides, and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (1) and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (2) and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (3) and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (4) and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (5) and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (6) and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (7) and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (8) and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (9) and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (10) and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (11) and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (12) and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (13) and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (14) and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (1), (2), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (1), (3), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (1), (4), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (1), (5), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (1), (6), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (1),

(7), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (1), (8), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (1), (9), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (1), (10), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (1), (11), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (1), (12), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (1), (13), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (1), (14), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (2), (3), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (2), (4), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (2), (5), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (2), (6), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (2), (7), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (2), (8), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (2), (9), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (2), (10), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (2), (11), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (2), (12), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (2), (13), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (2), (14), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (3), (4), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (3), (5), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (3), (6), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (3), (7), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (3), (8), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (3), (9), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (3), (10), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (3), (11), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (3), (12), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (3), (13), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (3), (14), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (4), (5), and mixtures thereof. In some embodiments, the excipients are

selected from the group consisting of (4), (6), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (4), (7), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (4), (8), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (4), (9), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (4), (10), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (4), (11), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (4), (12), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (4), (13), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (4), (14), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (5), (6), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (5), (7), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (5), (8), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (5), (9), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (5), (10), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (5), (11), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (5), (12), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (5), (13), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (5), (14), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (6), (7), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (6), (8), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (6), (9), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (6), (10), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (6), (11), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (6), (12), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (6), (13), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (6), (14), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (7), (8), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (7), (9), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (7), (10), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (7), (11), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (7), (12), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (7), (13), and mixtures

thereof. In some embodiments, the excipients are selected from the group consisting of (7), (14), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (8), (9), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (8), (10), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (8), (11), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (8), (12), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (8), (13), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (8), (14), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (9), (10), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (9), (11), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (9), (12), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (9), (13), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (9), (14), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (10), (11), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (10), (12), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (10), (13), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (10), (14), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (11), (12), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (11), (13), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (11), (14), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (12), (13), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (12), (14), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (13), (14), and mixtures thereof.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1r,4r)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, wherein the composition comprises an excipient comprising hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount

equivalent to a therapeutically effective amount of Compound 1, wherein the composition comprises an excipient comprising hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C, wherein the excipient is present in an amount equal to about 40% to about 60% by weight. In some embodiments, the composition comprises an excipient comprising hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C, wherein the excipient is present in an amount equal to about 45% to about 55% by weight. In some embodiments, the composition comprises an excipient comprising hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C, wherein the excipient is present in an amount equal to about 50 % by weight.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, wherein the composition comprises an excipient comprising hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, wherein the composition comprises an excipient comprising hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C, wherein the excipient is present in an amount equal to about 40% to about 60% by weight. In some embodiments, the composition comprises an excipient comprising hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C, wherein the excipient is present in an amount equal to about 45% to about 55% by weight. In some embodiments, the composition comprises an excipient comprising hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C, wherein the excipient is present in an amount equal to about 50% by weight.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, wherein the composition comprises a first excipient and a second excipient, wherein the first excipient comprises hydroxypropyl

methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C and the second excipient comprises hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C.

In some embodiments provided herein is a process for preparing a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, as disclosed herein, wherein the process comprises mixing the compound, ethanol, a first excipient comprising hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C, and a second excipient comprising hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, wherein the composition comprises a first excipient and a second excipient, wherein the first excipient comprises hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C and the second excipient comprises hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C,

wherein the composition has a release rate by weight of the compound in an aqueous medium that is release rate (a), wherein:

(a) about 15% to about 35% by weight of the compound is released over the first two hours in the aqueous medium,

wherein the release rate is measured with USP Apparatus 1 (baskets) at 80 to 120 rpm in 400 to 600 mL of an aqueous medium at a pH of 6.3 to 7.3 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.04 to 0.06 M.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, wherein the composition comprises a

first excipient and a second excipient, wherein the first excipient comprises hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C and the second excipient comprises hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C,

wherein the composition has a release rate by weight of the compound in an aqueous medium that is release rate (b), wherein:

(b) about 24% to about 59% by weight of the compound is released over the first four hours in the aqueous medium,

wherein the release rate is measured with USP Apparatus 1 (baskets) at 80 to 120 rpm in 400 to 600 mL of an aqueous medium at a pH of 6.3 to 7.3 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.04 to 0.06 M.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, wherein the composition comprises a first excipient and a second excipient, wherein the first excipient comprises hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C and the second excipient comprises hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C,

wherein the composition has a release rate by weight of the compound in an aqueous medium that is release rate (c), wherein:

(c) about 43% to about 96% by weight of the compound is released over the first eight hours in the aqueous medium,

wherein the release rate is measured with USP Apparatus 1 (baskets) at 80 to 120 rpm in 400 to 600 mL of an aqueous medium at a pH of 6.3 to 7.3 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.04 to 0.06 M.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, wherein the composition comprises a first excipient and a second excipient, wherein the first excipient comprises hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present

in an amount of about 2% in water at 20° C and the second excipient comprises hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C,

wherein the composition has release rates by weight of the compound in an aqueous medium that are release rates (a) and (b), wherein:

(a) about 15% to about 35% by weight of the compound is released over the first two hours in the aqueous medium; and

(b) about 24% to about 59% by weight of the compound is released over the first four hours in the aqueous medium,

wherein the release rate is measured with USP Apparatus 1 (baskets) at 80 to 120 rpm in 400 to 600 mL of an aqueous medium at a pH of 6.3 to 7.3 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.04 to 0.06 M.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, wherein the composition comprises a first excipient and a second excipient, wherein the first excipient comprises hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C and the second excipient comprises hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C,

wherein the composition has release rates by weight of the compound in an aqueous medium that are release rates (a) and (c), wherein:

(a) about 15% to about 35% by weight of the compound is released over the first two hours in the aqueous medium; and

(c) about 43% to about 96% by weight of the compound is released over the first eight hours in the aqueous medium,

wherein the release rate is measured with USP Apparatus 1 (baskets) at 80 to 120 rpm in 400 to 600 mL of an aqueous medium at a pH of 6.3 to 7.3 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.04 to 0.06 M.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, wherein the composition comprises a

first excipient and a second excipient, wherein the first excipient comprises hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C and the second excipient comprises hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C,

wherein the composition has release rates by weight of the compound in an aqueous medium that are release rates (b) and (c), wherein:

(b) about 24% to about 59% by weight of the compound is released over the first four hours in the aqueous medium; and

(c) about 43% to about 96% by weight of the compound is released over the first eight hours in the aqueous medium,

wherein the release rate is measured with USP Apparatus 1 (baskets) at 80 to 120 rpm in 400 to 600 mL of an aqueous medium at a pH of 6.3 to 7.3 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.04 to 0.06 M.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, wherein the composition comprises a first excipient and a second excipient, wherein the first excipient comprises hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C and the second excipient comprises hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C,

wherein the composition has release rates by weight of the compound in an aqueous medium that are release rates (a), (b) and (c), wherein:

(a) about 15% to about 35% by weight of the compound is released over the first two hours in the aqueous medium;

(b) about 24% to about 59% by weight of the compound is released over the first four hours in the aqueous medium; and

(c) about 43% to about 96% by weight of the compound is released over the first eight hours in the aqueous medium,

wherein the release rate is measured with USP Apparatus 1 (baskets) at 80 to 120 rpm in 400 to 600 mL of an aqueous medium at a pH of 6.3 to 7.3 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.04 to 0.06 M.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, wherein the composition comprises a first excipient and a second excipient, wherein the first excipient comprises hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C and the second excipient comprises hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C, wherein the first excipient is present in an amount equal to about 5% to about 45% by weight and the second excipient is present in an amount equal to about 5% to about 45% by weight. In some embodiments, the first excipient is present in an amount equal to about 10% to about 40% by weight and the second excipient is present in an amount equal to about 10% to about 40% by weight. In some embodiments, the first excipient is present in an amount equal to about 12.5% to about 37.5% by weight and the second excipient is present in an amount equal to about 12.5% to about 37.5% by weight. In some embodiments, the first excipient is present in an amount equal to about 25% by weight and the second excipient is present in an amount equal to about 25% by weight.

In some embodiments provided herein is a composition having a release rate by weight of the compound as disclosed herein in an aqueous medium, wherein the release rate is the release rate measured with USP Apparatus 1 (baskets) at 100 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C. In some embodiments, the aqueous medium comprises sodium phosphate at a concentration of 0.05 M.

In some embodiments provided herein is a composition as disclosed herein, wherein the composition is a tablet. In some embodiments, the tablet comprises a core and a coating. In some embodiments, the core comprises one or more excipients selected from the group consisting of (1) ethers of cellulose, such as hydroxypropyl methylcellulose, (2) esters of cellulose, (3) cellulose acetate, (4) ethyl cellulose, (5) polyvinyl acetate, (6) neutral copolymers based on ethylacrylate and methylmethacrylate, (7) copolymers of acrylic and methacrylic acid esters with quaternary ammonium groups, (8) pH-insensitive ammonio methacrylic acid copolymers, (9) polyethylene oxides, (10) polyvinylpyrrolidone, (11) polysaccharides of natural origin such as xanthan gum and locust bean gum, (12) polyethylene glycol, (13) polypropylene glycol, (14) castor oil, (15) triacetin, (16) tributyl citrate, (17) tri-ethyl citrate, (18) acetyl tri-n-butyl citrate, (19) diethyl phthalate, (20) dibutyl sebacate, (21) acetylated mono- and di-glycerides, and mixtures thereof. In some embodiments, the core comprises hydroxypropyl methylcellulose. In some embodiments, the coating does not comprise hydroxypropyl methylcellulose. In some embodiments, the coating does not comprise an excipient selected from the group consisting of (1)

ethers of cellulose, such as hydroxypropyl methylcellulose, (2) esters of cellulose, (3) cellulose acetate, (4) ethyl cellulose, (5) polyvinyl acetate, (6) neutral copolymers based on ethylacrylate and methylmethacrylate, (7) copolymers of acrylic and methacrylic acid esters with quaternary ammonium groups, (8) pH-insensitive ammonio methacrylic acid copolymers, (9) polyethylene oxides, (10) polyvinylpyrrolidone, (11) polysaccharides of natural origin such as xanthan gum and locust bean gum, (12) polyethylene glycol, (13) polypropylene glycol, (14) castor oil, (15) triacetin, (16) tributyl citrate, (17) tri-ethyl citrate, (18) acetyl tri-n-butyl citrate, (19) diethyl phthalate, (20) dibutyl sebacate, (21) acetylated mono- and di-glycerides, and mixtures thereof. In some embodiments provided herein is a tablet having one or more of release rates (a), (b) and (c) as disclosed herein, wherein the tablet comprises one or more excipients selected from the group consisting of (1) ethers of cellulose, such as hydroxypropyl methylcellulose, (2) esters of cellulose, (3) cellulose acetate, (4) ethyl cellulose, (5) polyvinyl acetate, (6) neutral copolymers based on ethylacrylate and methylmethacrylate, (7) copolymers of acrylic and methacrylic acid esters with quaternary ammonium groups, (8) pH-insensitive ammonio methacrylic acid copolymers, (9) polyethylene oxides, (10) polyvinylpyrrolidone, (11) polysaccharides of natural origin such as xanthan gum and locust bean gum, (12) polyethylene glycol, (13) polypropylene glycol, (14) castor oil, (15) triacetin, (16) tributyl citrate, (17) tri-ethyl citrate, (18) acetyl tri-n-butyl citrate, (19) diethyl phthalate, (20) dibutyl sebacate, (21) acetylated mono- and di-glycerides, and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (1) and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (2) and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (3) and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (4) and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (5) and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (6) and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (7) and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (8) and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (9) and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (10) and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (11) and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (12) and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (13) and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (14) and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (1), (2), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (1), (3), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of

(1), (4), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (1), (5), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (1), (6), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (1), (7), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (1), (8), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (1), (9), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (1), (10), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (1), (11), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (1), (12), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (1), (13), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (1), (14), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (2), (3), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (2), (4), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (2), (5), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (2), (6), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (2), (7), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (2), (8), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (2), (9), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (2), (10), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (2), (11), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (2), (12), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (2), (13), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (2), (14), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (3), (4), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (3), (5), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (3), (6), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (3), (7), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (3), (8), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (3), (9), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (3), (10), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (3), (11), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (3), (12), and mixtures thereof. In some embodiments, the

excipients are selected from the group consisting of (3), (13), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (3), (14), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (4), (5), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (4), (6), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (4), (7), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (4), (8), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (4), (9), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (4), (10), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (4), (11), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (4), (12), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (4), (13), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (4), (14), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (5), (6), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (5), (7), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (5), (8), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (5), (9), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (5), (10), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (5), (11), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (5), (12), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (5), (13), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (5), (14), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (6), (7), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (6), (8), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (6), (9), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (6), (10), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (6), (11), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (6), (12), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (6), (13), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (6), (14), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (7), (8), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (7), (9), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (7),

(10), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (7), (11), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (7), (12), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (7), (13), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (7), (14), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (8), (9), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (8), (10), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (8), (11), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (8), (12), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (8), (13), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (8), (14), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (9), (10), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (9), (11), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (9), (12), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (9), (13), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (9), (14), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (10), (11), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (10), (12), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (10), (13), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (10), (14), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (11), (12), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (11), (13), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (11), (14), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (12), (13), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (12), (14), and mixtures thereof. In some embodiments, the excipients are selected from the group consisting of (13), (14), and mixtures thereof. In some embodiments, the core comprises hydroxypropyl methylcellulose and the coating does not comprise hydroxypropyl methylcellulose. In some embodiments, the core comprises a first excipient and a second excipient, wherein the first excipient comprises hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C and the second excipient comprises hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA

seconds when present in an amount of about 2% in water at 20° C, and the coating does not comprise hydroxypropyl methylcellulose.

In some embodiments, the tablet has a circular cross-section with a diameter of about 1/4 to about 1/3 inch. In some embodiments, the tablet has a circular cross-section with a diameter of about 1/4 inch. In some embodiments, the tablet has a circular cross-section with a diameter of about 1/3 inch.

In some embodiments, the tablet has a circular cross-section with a diameter of about 6.35 mm to about 8.46 mm. In some embodiments, the tablet has a circular cross-section with a diameter of about 6.35 mm. In some embodiments, the tablet has a circular cross-section with a diameter of about 8.46 mm.

In some embodiments, the oral form has content uniformity (*e.g.*, for Compound 1). In some embodiments, the content uniformity is as measured by a content uniformity test in the International Phamacopoeia (IP), British Pharmacopoeia (BP), United States Pharmacopoeia (USP), or European Pharmacopoeia (Ph. Eur.), which are each incorporated herein by reference. In some embodiments, the oral form has a relative standard deviation that is less than, or is less than about, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or 0.5% content. In some embodiments, the oral form has no value that falls outside a range, for example 75-125%, 80-125%, 85-120%, 85-115%, 90-120%, 90-110%, or 95-105% content. In some embodiments, the oral form has no less than, or less than about, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 99.5% content. In some embodiments, the oral form has no more than, or more than about, 100.5%, 101%, 102%, 103%, 104%, 105%, 110%, 115%, 120%, or 125% content.

In some embodiments, the tablet has a hardness of about 5 kp to about 9 kp. In some embodiments, the tablet has a hardness of about 6 kp to about 8 kp. In some embodiments, the tablet has a hardness of about 7 kp.

In some embodiments, the tablet has a core weight of about 95 mg to about 105 mg. In some embodiments, the tablet has a core weight of about 97.5 mg to about 102.5 mg. In some embodiments, the tablet has a core weight of about 99 mg to about 101 mg. In some embodiments, the tablet has a core weight of about 100 mg.

In some embodiments, the tablet has a coating of about 3 mg to about 5 mg. In some embodiments, the tablet has a core weight of about 3.5 mg to about 4.5 mg. In some embodiments, the tablet has a core weight of about 4 mg.

In some embodiments, the tablet has a total weight of about 98 mg to about 110 mg. In some embodiments, the tablet has a total weight of about 101 mg to about 107 mg. In some embodiments, the tablet has a total weight of about 104 mg.

In some embodiments, the therapeutically effective amount of Compound 1 in the composition is about 0.01 % to about 1 % by weight, such as about 0.01 % to about 0.6 % by weight, such as about 0.02 % to about 0.3 % by weight, such as about 0.03 % to about 0.2 % by weight, such as about 0.04 % to about 0.12 % by weight, such as about 0.04 % to about 0.1 % by weight, such as about 0.05 % to about 0.08 % by weight, such as about 0.06 % by weight. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.025 %. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.03 % by weight. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.04 %. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.05 % by weight. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.06 % by weight. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.1 %. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.2 %. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.25 %. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.3 % by weight. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.35 %. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.4 %. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.5 % by weight. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.6 %. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.7 %. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.75 %. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.8 %. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.9 %. In some embodiments, the therapeutically effective amount of Compound 1 is about 1.0 %.

In some embodiments, the therapeutically effective amount of Compound 1 in the composition is about 0.01 mg to about 1.5 mg, such as about 0.01 to about 1.45 mg, such as about 0.01 to about 1.2 mg, such as about 0,01 to about 1.0 mg, such as about 0.01 to about 0.8 mg, such as about 0.01 mg to about 0.6 mg, such as about 0.02 to about 0.3 mg, such as about 0.03 to about 0.2 mg, such as about 0.04 to about 0.12 mg, such as about 0.04 to about 0.1 mg, such as about 0.05 to about 0.08 mg, such as about 0.06 mg.

In some embodiments provided herein is a pharmaceutical composition according to any of the embodiments described herein, wherein the therapeutically effective amount of Compound 1 is selected from, or from about, 0.01 mg, 0.02 mg, 0.025 mg, 0.03 mg, 0.04 mg, 0.05 mg, 0.06 mg, 0.065 mg, 0.07 mg, 0.075 mg, 0.08 mg, 0.09 mg, 0.1 mg, 0.12 mg, 0.15 mg, 0.16 mg, 0.2 mg, 0.25 mg, 0.3 mg, 0.35 mg,

0.4 mg, 0.45 mg, 0.5 mg, 0.55 mg, 0.6 mg, 0.65 mg, 0.7 mg, 0.75 mg, 0.8 mg, 0.85 mg, 0.9 mg, 0.95 mg, and 1.0 mg daily.

In some embodiments provided herein is a pharmaceutical composition according to any of the embodiments described herein, wherein the therapeutically effective amount of Compound 1 selected from 0.01 mg, 0.02 mg, 0.025 mg, 0.03 mg, 0.04 mg, 0.05 mg, 0.06 mg, 0.065 mg, 0.07 mg, 0.075 mg, 0.08 mg, 0.09 mg, 0.1 mg, 0.12 mg, 0.15 mg, 0.16 mg, 0.2 mg, 0.25 mg, 0.3 mg, 0.35 mg, 0.4 mg, 0.45 mg, 0.5 mg, 0.55 mg, 0.6 mg, 0.65 mg, 0.7 mg, 0.75 mg, 0.8 mg, 0.85 mg, 0.9 mg, 0.95 mg, and 1.0 mg daily.

In some embodiments, the therapeutically effective amount of Compound 1 is about 0.018 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.025 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.01 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.02 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.025 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.03 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.04 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.05 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.06 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.065 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.07 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.075 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.08 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.09 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.1 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.12 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.15 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.16 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.2 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.25 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.3 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.35 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.4 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.45 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.5 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.55 mg. In some

embodiments, the therapeutically effective amount of Compound 1 is about 0.6 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.65 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.7 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.75 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.8 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.85 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.9 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 0.95 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 1.0 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 1,1 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 1.2 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 1.25 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 1.3 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 1.35 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 1.4 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 1.45 mg. In some embodiments, the therapeutically effective amount of Compound 1 is about 1.5 mg.

In some embodiments, the therapeutically effective amount of Compound 1 is a starting dose.

In some embodiments provided herein is a pharmaceutical composition according to any of the embodiments described herein, wherein the therapeutically effective amount of Compound 1 is a starting dose selected from 0.01, 0.02, 0.025, 0.03, 0.04, 0.05, 0.06, 0.07, 0.075, 0.08, 0.09, or 0.1 mg daily. In some embodiments, the therapeutically effective amount of Compound 1 is a starting dose and is about 0.01 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a starting dose and is about 0.02 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a starting dose and is about 0.025 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a starting dose and is about 0.03 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a starting dose and is about 0.04 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a starting dose and is about 0.05 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a starting dose and is about 0.06 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a starting dose and is about 0.07 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a starting dose and is about 0.075 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a starting dose and is about 0.08 mg. In some embodiments, the therapeutically effective amount of Compound 1 is

a starting dose and is about 0.09 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a starting dose and is about 0.1 mg.

In some embodiments, the therapeutically effective amount of Compound 1 is a highest tolerated dose.

In some embodiments provided herein is a pharmaceutical composition according to any of the embodiments described herein, wherein the therapeutically effective amount of Compound 1 is a highest tolerated dose selected from 0.4 mg, 0.45 mg, 0.5 mg, 0.55 mg, 0.6 mg, 0.65 mg, 0.7 mg, 0.75 mg, 0.8 mg, 0.85 mg, 0.9 mg, 0.95 mg, and 1.0 mg daily. In some embodiments the therapeutically effective amount of Compound 1 is a highest tolerated dose and is about 0.4 mg. In some embodiments the therapeutically effective amount of Compound 1 is a highest tolerated dose and is about 0.45 mg. In some embodiments the therapeutically effective amount of Compound 1 is a highest tolerated dose and is about 0.5 mg. In some embodiments the therapeutically effective amount of Compound 1 is a highest tolerated dose and is about 0.55 mg. In some embodiments the therapeutically effective amount of Compound 1 is a highest tolerated dose and is about 0.6 mg. In some embodiments the therapeutically effective amount of Compound 1 is a highest tolerated dose and is about 0.65 mg. In some embodiments the therapeutically effective amount of Compound 1 is a highest tolerated dose and is about 0.7 mg. In some embodiments the therapeutically effective amount of Compound 1 is a highest tolerated dose and is about 0.75 mg. In some embodiments the therapeutically effective amount of Compound 1 is a highest tolerated dose and is about 0.8 mg. In some embodiments the therapeutically effective amount of Compound 1 is a highest tolerated dose and is about 0.85 mg. In some embodiments the therapeutically effective amount of Compound 1 is a highest tolerated dose and is about 0.9 mg. In some embodiments the therapeutically effective amount of Compound 1 is a highest tolerated dose and is about 0.95 mg. In some embodiments the therapeutically effective amount of Compound 1 is a highest tolerated dose and is about 1.0 mg.

In some embodiments, the therapeutically effective amount of Compound 1 is a maximum dose.

In some embodiments provided herein is a pharmaceutical composition according to any of the embodiments described herein, wherein the therapeutically effective amount of Compound 1 is a maximum dose selected from 0.4 mg, 0.45 mg, 0.5 mg, 0.55 mg, 0.6 mg, 0.65 mg, 0.7 mg, 0.75 mg, 0.8 mg, 0.85 mg, 0.9 mg, 0.95 mg, and 1.0 mg daily. In some embodiments the therapeutically effective amount of Compound 1 is a maximum dose and is about 0.4 mg. In some embodiments the therapeutically effective amount of Compound 1 is a maximum dose and is about 0.45 mg. In some embodiments the therapeutically effective amount of Compound 1 is a maximum dose and is about 0.5 mg. In some embodiments the therapeutically effective amount of Compound 1 is a maximum dose and is about 0.55 mg. In some embodiments the therapeutically effective amount of Compound 1 is a maximum dose and is about 0.6 mg. In some embodiments the therapeutically effective amount of Compound 1 is a

maximum dose and is about 0.65 mg. In some embodiments the therapeutically effective amount of Compound 1 is a maximum dose and is about 0.7 mg. In some embodiments the therapeutically effective amount of Compound 1 is a maximum dose and is about 0.75 mg. In some embodiments the therapeutically effective amount of Compound 1 is a maximum dose and is about 0.8 mg. In some embodiments the therapeutically effective amount of Compound 1 is a maximum dose and is about 0.85 mg. In some embodiments the therapeutically effective amount of Compound 1 is a maximum dose and is about 0.9 mg. In some embodiments the therapeutically effective amount of Compound 1 is a maximum dose and is about 0.95 mg. In some embodiments the therapeutically effective amount of Compound 1 is a maximum dose and is about 1.0 mg.

In some embodiments, the therapeutically effective amount of Compound 1 is a maximum tolerated dose.

In some embodiments provided herein is a pharmaceutical composition according to any of the embodiments described herein, wherein the therapeutically effective amount of Compound 1 is a maximum tolerated dose selected from 0.4 mg, 0.45 mg, 0.5 mg, 0.55 mg, 0.6 mg, 0.65 mg, 0.7 mg, 0.75 mg, 0.8 mg, 0.85 mg, 0.9 mg, 0.95 mg, and 1.0 mg daily. In some embodiments the therapeutically effective amount of Compound 1 is a maximum tolerated dose and is about 0.4 mg. In some embodiments the therapeutically effective amount of Compound 1 is a maximum tolerated dose and is about 0.45 mg. In some embodiments the therapeutically effective amount of Compound 1 is a maximum tolerated dose and is about 0.5 mg. In some embodiments the therapeutically effective amount of Compound 1 is a maximum tolerated dose and is about 0.55 mg. In some embodiments the therapeutically effective amount of Compound 1 is a maximum tolerated dose and is about 0.6 mg. In some embodiments the therapeutically effective amount of Compound 1 is a maximum tolerated dose and is about 0.65 mg. In some embodiments the therapeutically effective amount of Compound 1 is a maximum tolerated dose and is about 0.7 mg. In some embodiments the therapeutically effective amount of Compound 1 is a maximum tolerated dose and is about 0.75 mg. In some embodiments the therapeutically effective amount of Compound 1 is a maximum tolerated dose and is about 0.8 mg. In some embodiments the therapeutically effective amount of Compound 1 is a maximum tolerated dose and is about 0.85 mg. In some embodiments the therapeutically effective amount of Compound 1 is a maximum tolerated dose and is about 0.9 mg. In some embodiments the therapeutically effective amount of Compound 1 is a maximum tolerated dose and is about 0.95 mg. In some embodiments the therapeutically effective amount of Compound 1 is a maximum tolerated dose and is about 1.0 mg.

In some embodiments, the therapeutically effective amount of Compound 1 is a maintenance dose.

In some embodiments provided herein is a pharmaceutical composition according to any of the embodiments described herein, wherein the therapeutically effective amount of Compound 1 is a maintenance dose selected from 0.01 mg, 0.02 mg, 0.025 mg, 0.03 mg, 0.04 mg, 0.05 mg, 0.06 mg, 0.065 mg, 0.07 mg, 0.075 mg, 0.08 mg, 0.09 mg, 0.1 mg, 0.12 mg, 0.15 mg, 0.16 mg, 0.2 mg, 0.25 mg, 0.3 mg, 0.35 mg, 0.4 mg, 0.45 mg, 0.5 mg, 0.55 mg, 0.6 mg, 0.65 mg, 0.7 mg, 0.75 mg, 0.8 mg, 0.85 mg, 0.9 mg, 0.95 mg, and 1.0 mg daily. In some embodiments, the therapeutically effective amount of Compound 1 is a maintenance dose and is about 0.01 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a maintenance dose and is about 0.02 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a maintenance dose and is about 0.025 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a maintenance dose and is about 0.03 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a maintenance dose and is about 0.04 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a maintenance dose and is about 0.05 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a maintenance dose and is about 0.06 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a maintenance dose and is about 0.065 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a maintenance dose and is about 0.07 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a maintenance dose and is about 0.075 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a maintenance dose and is about 0.08 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a maintenance dose and is about 0.09 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a maintenance dose and is about 0.1 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a maintenance dose and is about 0.12 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a maintenance dose and is about 0.15 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a maintenance dose and is about 0.16 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a maintenance dose and is about 0.2 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a maintenance dose and is about 0.25 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a maintenance dose and is about 0.3 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a maintenance dose and is about 0.35 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a maintenance dose and is about 0.4 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a maintenance dose and is about 0.45 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a maintenance dose and is about 0.5 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a maintenance dose and is about 0.55 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a

maintenance dose and is about 0.6 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a maintenance dose and is about 0.65 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a maintenance dose and is about 0.7 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a maintenance dose and is about 0.75 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a maintenance dose and is about 0.8 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a maintenance dose and is about 0.85 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a maintenance dose and is about 0.9 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a maintenance dose and is about 0.95 mg. In some embodiments, the therapeutically effective amount of Compound 1 is a maintenance dose and is about 1.0 mg.

In some embodiments, the starting dose is for a patient. In some embodiments, the starting dose is for a patient population. In some embodiments, the highest tolerated dose is for a patient. In some embodiments, the highest tolerated dose is for a patient population. In some embodiments, the maximum dose is for a patient. In some embodiments, the maximum dose is for a patient population. In some embodiments, the maximum tolerated dose is for a patient. In some embodiments, the maximum tolerated dose is for a patient population. In some embodiments, the maintenance dose is for a patient. In some embodiments, the maintenance dose is for a patient population.

In some embodiments, the starting dose of Compound 1 is selected from, or from about, 0.01, 0.02, 0.025, 0.03, 0.04, 0.05, 0.06, 0.07, 0.075, 0.08, 0.09, or 0.1 mg once daily. In some embodiments, the starting dose of Compound 1 is 0.01 mg once daily. In some embodiments, the starting dose of Compound 1 is 0.02 mg once daily. In some embodiments, the starting dose of Compound 1 is 0.05 mg once daily. In some embodiments, the starting dose of Compound 1 is 0.06 mg once daily.

In some embodiments, the dose of Compound 1 is increased at weekly intervals by 0.05 mg once daily to the highest tolerated dose up to 0.8 mg once daily.

In some embodiments, the dose of Compound 1 is increased at weekly intervals. In some embodiments, the dose of Compound 1 is increased at bimonthly intervals.

In some embodiments, the dose of Compound 1 is increased by an amount selected from, or from about, 0.02 mg, 0.05 mg, 0.75 mg and 0.1 mg once daily.

In some embodiments, the dose of Compound 1 is increased at weekly intervals by an amount selected from, or from about, 0.02 mg, 0.05 mg, 0.75 mg, and 0.1 mg once daily.

In some embodiments, the highest tolerated dose of Compound 1 is selected from, or from about, 0.4 mg, 0.45 mg, 0.5 mg, 0.55 mg, 0.6 mg, 0.65 mg, 0.7 mg, 0.75 mg, 0.8 mg, 0.85 mg, 0.9 mg, 0.95 mg, and 1.0 mg once daily. In some embodiments, the maximum dose of Compound 1 is 0.6 mg once daily. In some embodiments, the maximum dose of Compound 1 is 0.75 mg once daily. In some embodiments, the

maximum dose of Compound 1 is 0.8 mg once daily. In some embodiments, the highest tolerated dose of Compound 1 is from 0.4 to 1.0 mg once daily. In some embodiments, the highest tolerated dose of Compound 1 is from 0.6 to 1.0 mg once daily. In some embodiments, the highest tolerated dose of Compound 1 is from 0.6 to 0.8 mg once daily. In some embodiments, the highest tolerated dose of Compound 1 is from 0.65 to 1.0 mg once daily. In some embodiments, the highest tolerated dose of Compound 1 is from 0.65 to 0.8 mg once daily. In some embodiments, the highest tolerated dose of Compound 1 is greater than 0.4 mg daily. In some embodiments, the highest tolerated dose of Compound 1 is greater than 0.6 mg daily. In some embodiments, the highest tolerated dose of Compound 1 is greater than 0.8 mg daily. In some embodiments, the highest tolerated dose of Compound 1 is greater than 1.0 mg daily.

In some embodiments, the maximum dose of Compound 1 is selected from, or from about, 0.4 mg, 0.45 mg, 0.5 mg, 0.6 mg, 0.65 mg, 0.7 mg, 0.75 mg, 0.8 mg, 0.85 mg, 0.9 mg, 0.95 mg, and 1.0 mg once daily. In some embodiments, the maximum dose of Compound 1 is 0.6 mg once daily. In some embodiments, the maximum dose of Compound 1 is 0.75 mg once daily. In some embodiments, the maximum dose of Compound 1 is 0.8 mg once daily. In some embodiments, the highest tolerated dose of Compound 1 is from 0.4 to 1.0 mg once daily. In some embodiments, the maximum dose of Compound 1 is from 0.6 to 1.0 mg daily. In some embodiments, the maximum dose of Compound 1 is from 0.6 to 0.8 mg once daily. In some embodiments, the maximum dose of Compound 1 is from 0.65 to 1.0 mg once daily. In some embodiments, the maximum dose of Compound 1 is from 0.65 to 0.8 mg once daily. In some embodiments, the maximum dose of Compound 1 is greater than 0.4 mg daily. In some embodiments, the maximum dose of Compound 1 is greater than 0.6 mg daily. In some embodiments, the maximum dose of Compound 1 is greater than 0.8 mg daily. In some embodiments, the maximum dose of Compound 1 is greater than 1.0 mg daily.

In some embodiments, the maximum tolerated dose of Compound 1 is selected from, or from about, 0.4 mg, 0.45 mg, 0.5 mg, 0.6 mg, 0.65 mg, 0.7 mg, 0.75 mg, 0.8 mg, 0.85 mg, 0.9 mg, 0.95 mg, and 1.0 mg once daily. In some embodiments, the maximum tolerated dose of Compound 1 is 0.6 mg once daily. In some embodiments, the maximum tolerated dose of Compound 1 is 0.75 mg once daily. In some embodiments, the maximum tolerated dose of Compound 1 is 0.8 mg once daily. In some embodiments, the maximum tolerated dose of Compound 1 is 0.75 mg once daily. In some embodiments, the maximum tolerated dose of Compound 1 is 0.8 mg once daily. In some embodiments, the maximum tolerated dose of Compound 1 is from 0.4 to 1.0 mg once daily. In some embodiments, the maximum tolerated dose of Compound 1 is from 0.6 to 1.0 mg once daily. In some embodiments, the maximum tolerated dose of Compound 1 is from 0.6 to 0.8 mg once daily. In some embodiments, the maximum tolerated dose of Compound 1 is from 0.65 to 1.0 mg once daily. In some embodiments, the maximum

tolerated dose of Compound 1 is from 0.65 to 0.8 mg once daily. In some embodiments, the maximum tolerated dose of Compound 1 is greater than 0.4 mg daily. In some embodiments, the maximum tolerated dose of Compound 1 is greater than 0.6 mg daily. In some embodiments, the maximum tolerated dose of Compound 1 is greater than 0.8 mg daily. In some embodiments, the maximum tolerated dose of Compound 1 is greater than 1.0 mg daily.

In some embodiments, the maximum dose of Compound 1 in a dosage form is selected from, or from about, 0.4 mg, 0.45 mg, 0.5 mg, 0.6 mg, 0.65 mg, 0.7 mg, 0.75 mg, 0.8 mg, 0.85 mg, 0.9 mg, 0.95 mg, and 1.0 mg. In some embodiments, the maximum dose of Compound 1 in a dosage form is 0.6 mg. In some embodiments, the maximum dose of Compound 1 in a dosage form is 0.75 mg. In some embodiments, the maximum dose of Compound 1 in a dosage form is 0.8 mg. In some embodiments, the maximum dose of Compound 1 is from 0.4 to 1.0 mg daily. In some embodiments, the maximum dose of Compound 1 is from 0.6 to 1.0 mg daily. In some embodiments, the maximum dose of Compound 1 is from 0.6 to 0.8 mg daily. In some embodiments, the maximum dose of Compound 1 is from 0.65 to 1.0 mg daily. In some embodiments, the maximum dose of Compound 1 is from 0.65 to 0.8 mg daily. In some embodiments, the maximum dose of Compound 1 is greater than 0.4 mg daily. In some embodiments, the maximum dose of Compound 1 is greater than 0.6 mg daily. In some embodiments, the maximum dose of Compound 1 is greater than 0.8 mg daily. In some embodiments, the maximum dose of Compound 1 is greater than 1.0 mg daily.

In some embodiments, the maintenance dose of Compound 1 is selected from, or from about, 0.01 mg, 0.02 mg, 0.025 mg, 0.03 mg, 0.04 mg, 0.05 mg, 0.06 mg, 0.065 mg, 0.07 mg, 0.075 mg, 0.08 mg, 0.09 mg, 0.1 mg, 0.12 mg, 0.15 mg, 0.16 mg, 0.2 mg, 0.25 mg, 0.3 mg, 0.35 mg, 0.4 mg, 0.45 mg, 0.5 mg, 0.55 mg, 0.6 mg, 0.65 mg, 0.7 mg, 0.75 mg, 0.8 mg, 0.85 mg, 0.9 mg, 0.95 mg, and 1.0 mg daily. In some embodiments, the maintenance dose of Compound 1 is from 0.4 to 1.0 mg once daily. In some embodiments, the maintenance dose of Compound 1 is from 0.6 to 1.0 mg once daily. In some embodiments, the maintenance dose of Compound 1 is from 0.6 to 0.8 mg once daily. In some embodiments, the maintenance dose of Compound 1 is from 0.65 to 1.0 mg once daily. In some embodiments, the maintenance dose of Compound 1 is from 0.65 to 0.8 mg once daily. In some embodiments, the maintenance dose of Compound 1 is determined by tolerability. In some embodiments, the maintenance dose of Compound 1 is greater than 0.4 mg daily. In some embodiments, the maintenance dose of Compound 1 is greater than 0.6 mg daily. In some embodiments, the maintenance dose of Compound 1 is greater than 0.8 mg daily. In some embodiments, the maintenance dose of Compound 1 is greater than 1.0 mg daily.

In some embodiments, Compound 1 is administered in an amount sufficient to achieve in the patient a blood plasma concentration of Compound 1 of about 2 ng/mL. In some embodiments,

Compound 1 is administered in an amount sufficient to achieve in the patient a blood plasma concentration of Compound 1 of about 2.5 ng/mL. Compound 1 is administered in an amount sufficient to achieve in the patient a blood plasma concentration of Compound 1 of about 2.75 ng/mL.

In some embodiments, Compound 1 is administered in an amount sufficient to achieve in the patient a blood plasma concentration of Compound 1 of about 3 ng/mL. In some embodiments, Compound 1 is administered in an amount sufficient to achieve in the patient a blood plasma concentration of Compound 1 of at least about 3 ng/mL, such as about 3.1 ng/mL, about 3.2 ng/mL, about 3.3 ng/mL, about 3.4 ng/mL, about 3.5 ng/mL, about 3.6 ng/mL, about 3.7 ng/mL, about 3.8 ng/mL, or about 3.9 ng/mL.

In some embodiments, Compound 1 is administered in an amount sufficient to achieve in the patient a blood plasma concentration of Compound 1 of about 4 ng/mL. In some embodiments, Compound 1 is administered in an amount sufficient to achieve in the patient a blood plasma concentration of Compound 1 of at least about 4 ng/mL, such as about 4.1 ng/mL, about 4.2 ng/mL, about 4.3 ng/mL, about 4.4 ng/mL, about 4.5 ng/mL, about 4.6 ng/mL, about 4.7 ng/mL, about 4.8 ng/mL, or about 4.9 ng/mL.

In some embodiments, Compound 1 is administered in an amount sufficient to achieve in the patient a blood plasma concentration of Compound 1 of about 5 ng/mL. In some embodiments, Compound 1 is administered in an amount sufficient to achieve in the patient a blood plasma concentration of Compound 1 of at least about 5 ng/mL, such as about 5.1 ng/mL, about 5.2 ng/mL, about 5.3 ng/mL, about 5.4 ng/mL, about 5.5 ng/mL, about 5.6 ng/mL, about 5.7 ng/mL, about 5.8 ng/mL, or about 5.9 ng/mL.

In some embodiments, Compound 1 is administered in an amount sufficient to achieve in the patient a blood plasma concentration of Compound 1 of between about 3 ng/mL and about 5 ng/mL. In some embodiments, Compound 1 is administered in an amount sufficient to achieve in the patient a blood plasma concentration of Compound 1 of between about 3.5 ng/mL and about 5 ng/mL. In some embodiments, Compound 1 is administered in an amount sufficient to achieve in the patient a blood plasma concentration of Compound 1 of between about 4 ng/mL and about 5 ng/mL. In some embodiments, Compound 1 is administered in an amount sufficient to achieve in the patient a blood plasma concentration of Compound 1 of between about 4.5 ng/mL and about 5 ng/mL. In some embodiments, Compound 1 is administered in an amount sufficient to achieve in the patient a blood plasma concentration of Compound 1 of between about 3 ng/mL and about 4.5 ng/mL. In some embodiments, Compound 1 is administered in an amount sufficient to achieve in the patient a blood plasma concentration of Compound 1 of between about 3 ng/mL and about 4 ng/mL. In some embodiments, Compound 1 is administered in an amount sufficient to achieve in the patient a blood

plasma concentration of Compound 1 of between about 3 ng/mL and about 3.5 ng/mL. In some embodiments, Compound 1 is administered in an amount sufficient to achieve in the patient a blood plasma concentration of Compound 1 of between about 3.5 ng/mL and about 5.0 ng/mL. In some embodiments, Compound 1 is administered in an amount sufficient to achieve in the patient a blood plasma concentration of Compound 1 of between about 3.5 ng/mL and about 4.5 ng/mL. In some embodiments, Compound 1 is administered in an amount sufficient to achieve in the patient a blood plasma concentration of Compound 1 of between about 3.5 ng/mL and about 4.0 ng/mL.

In some embodiments, Compound 1 is administered in an amount sufficient to achieve in the patient a blood plasma concentration of Compound 1at or above the binding affinity concentration. In some embodiments, Compound 1 is administered in an amount sufficient to achieve in the patient a blood plasma concentration of Compound 1at or above 3.4 nM.

In some embodiments, the dose of Compound 1 for an individual is selected based on a correlation with a blood plasma level in the individual. In some embodiments, the dose of Compound 1 administered to an individual is that which corresponds to at least a threshold blood plasma level in the individual. In some embodiments, Compound 1 is administered in an amount that reaches at least a threshold blood plasma level in an individual. In some embodiments, Compound 1 is titrated in an individual until at least a threshold blood plasma level is reached in the individual.

In some embodiments, Compound 1 is titrated in an individual over about, or over at least about, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 weeks.

In some embodiments, the administration of Compound 1 is continued if the individual has at least a threshold blood plasma level of Compound 1 at a starting dose. In some embodiments, the administration of Compound 1 is continued if the individual has at least a threshold blood plasma level of Compound 1 at the highest tolerated dose. In some embodiments, the administration of Compound 1 is continued if the individual has at least a threshold blood plasma level of Compound 1 at the maximum dose. In some embodiments, the administration of Compound 1 is continued if the individual has at least a threshold blood plasma level of Compound 1 at the maximum tolerated dose. In some embodiments, the administration of Compound 1 is continued if the individual has at least a threshold blood plasma level of Compound 1 at the maintenance dose.

In some embodiments, the administration of Compound 1 is discontinued if the individual does not have at least a threshold blood plasma level of Compound 1 at the starting dose. In some embodiments, the administration of Compound 1 is discontinued if the individual does not have at least a threshold blood plasma level of Compound 1 at the highest tolerated dose. In some embodiments, the administration of Compound 1 is discontinued if the individual does not have at least a threshold blood plasma level of Compound 1 at the maximum dose. In some embodiments, the administration of

Compound 1 is discontinued if the individual does not have at least a threshold blood plasma level of Compound 1 at the maximum tolerated dose. In some embodiments, the administration of Compound 1 is discontinued if the individual does not have at least a threshold blood plasma level of Compound 1 at the maintenance dose.

In some embodiments, the threshold blood plasma concentration in an individual is, or is about, 1, 1.1, 1.2, 1.25, 1.3, 1.4, 1.5, 1.6, 1.7, 1.75, 1.8, 1.9, 2, 2.1, 2.2, 2.25, 2.3, 2.4, 2.5, 2.6, 2.7, 2.75, 2.8, 2.9, 3, 3.1, 3.2, 3.25, 3.3, 3.4, 3.5, 3.6, 3.7, 3.75, 3.8, 3.9, 4, 4.1, 4.2, 4.25, 4.3, 4.4, 4.5, 4.6, 4.7, 4.75, 4.8, 4.9, 5, 5.1, 5.2, 5.25, 5.3, 5.4, 5.5, 5.6, 5.7, 5.75, 5.8, 5.9, 6, 6.25, 6.5, 6.75, 7, 7.25, 7.5, 7.75, 8, 8.25, 8.5, 8.75, 9, 9.25, 9.5, 9.75, or 10 ng/ml.

One of skill in the art will recognize that the term "plasma concentration" is a type of "plasma level."

In some embodiments, in a patient who receives a dose of Compound 1 that cannot be tolerated, the dose of Compound 1 is reduced to the previous tolerated dose. In some embodiments, the previous tolerated dose is the maximum tolerated dose for the patient.

In some embodiments, the amount of Compound 1 is adjusted to account for a difference in bioequivalence between an immediate-release form and an extended-release form. For example, in some embodiments, 0.8 mg of Compound 1 in an extended-release dosage form is provided to equate two 0.3 mg immediate-release dosage forms of Compound 1, where the extended-release dosage form has less than 100% bioequivalence with the immediate-release dosage forms.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, wherein the composition comprises a first excipient and a second excipient, wherein the first excipient comprises a copolymer comprising (a) a first polyoxyethylene chain; (b) a poly(propylene oxide) chain bonded to the first polyoxyethylene chain; and (c) a second polyoxyethylene chain bonded to the poly(propylene oxide) chain; and the second excipient comprises an ester of a polyalcohol and a fatty acid.

In some embodiments provided herein is a pharmaceutical composition prepared by the process comprising:

curing a mixture comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, a first excipient, and a second excipient, wherein the first excipient comprises a copolymer comprising (a) a first polyoxyethylene chain; (b) a poly(propylene oxide) chain bonded to the first polyoxyethylene chain; and (c) a second polyoxyethylene

chain bonded to the poly(propylene oxide) chain, and the second excipient comprises an ester of a polyalcohol and a fatty acid,

to form the composition.

In some embodiments provided herein is a process for preparing a pharmaceutical composition, the process comprising:

curing a mixture comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, a first excipient, and a second excipient, wherein the first excipient comprises a copolymer comprising (a) a first polyoxyethylene chain; (b) a poly(propylene oxide) chain bonded to the first polyoxyethylene chain; and (c) a second polyoxyethylene chain bonded to the poly(propylene oxide) chain, and the second excipient comprises an ester of a polyalcohol and a fatty acid, to form the composition.

In some embodiments of the compositions provided herein, the release rate is one or more of the release rates (a), (b) and/or (c) disclosed herein.

In some embodiments, the release rate is the release rate measured with USP Apparatus 1 (baskets) at 100 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C.

In some embodiments, the release rate is the release rate measured with USP Apparatus 1 (baskets) at 100 rpm in 500 mL of an aqueous medium at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.05 M.

USP Apparatus 1 (BASKETS) is described, for example, in the United States Pharmacopeial Convention, February 1, 2012, Chapter <711> ("Dissolution"), incorporated by reference herein in its entirety. *See* http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/revisions/m99470-gc_711.pdf. The USP Apparatus 1 (baskets) assembly consists of the following: a vessel, which may be covered, made of glass or other inert, transparent material; a motor; a metallic drive shaft; and a cylindrical basket. The materials should not sorb, react, or interfere with the specimen being tested. The vessel is partially immersed in a suitable water bath of any convenient size or heated by a suitable device such as a heating jacket. The water bath or heating device permits holding the temperature inside the vessel at 37 ± 0.5° during the test and keeping the bath fluid in constant, smooth motion. No part of the assembly, including the environment in which the assembly is placed, contributes significant motion, agitation, or vibration beyond that due to the smoothly rotating stirring element. An apparatus that permits observation of the specimen and stirring element during the test is preferable. The vessel is cylindrical, with a hemispherical bottom and with one of the following dimensions and capacities: for a nominal capacity of 1 L, the height is 160 mm to 210 mm and its inside diameter is 98 mm to 106 mm; for a nominal capacity of 2 L, the height is 280 mm to 300 mm and its inside diameter is 98 mm to 106 mm; and for a nominal capacity of 4

L, the height is 280 mm to 300 mm and its inside diameter is 145 mm to 155 mm. Its sides are flanged at the top. A fitted cover may be used to retard evaporation. If a cover is used, it provides sufficient openings to allow ready insertion of the thermometer and withdrawal of specimens. The shaft is positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel and rotates smoothly and without significant wobble that could affect the results. The vertical center line of the blade passes through the axis of the shaft so that the bottom of the blade is flush with the bottom of the shaft. A distance of 25 ± 2 mm between the bottom of the blade and the inside bottom of the vessel is maintained during the test. The metallic or suitably inert, rigid blade and shaft comprise a single entity. A suitable two-part detachable design may be used provided the assembly remains firmly engaged during the test.

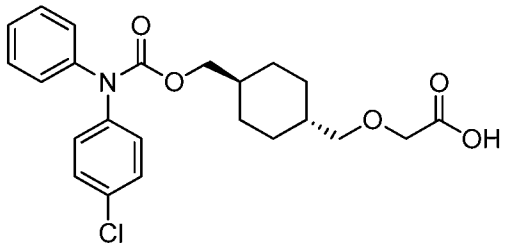
A speed-regulating device is used that allows the shaft rotation speed to be selected and maintained at the specified rate within ±4%. Shaft and basket components of the stirring element are fabricated of stainless steel, type 316, or other inert material. A basket having a gold coating of about 0.0001 inch (2.5 μm) thick may be used. A dosage unit is placed in a dry basket at the beginning of each test. The distance between the inside bottom of the vessel and the bottom of the basket is maintained at 25 ± 2 mm during the test.

USP Apparatus 2 (Paddle Apparatus) is described, for example, in the United States Pharmacopeial Convention, February 1, 2012, Chapter <711> ("Dissolution"), incorporated by reference herein in its entirety. *See* http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/revisions/m99470-gc_711.pdf. The assembly from Apparatus 1 is used, except that a paddle formed from a blade and a shaft is used as the stirring element. The shaft is positioned so that its axis is not more than 2 mm from the vertical axis of the vessel at any point and rotates smoothly without significant wobble that could affect the results. The vertical center line of the blade passes through the axis of the shaft so that the bottom of the blade is flush with the bottom of the shaft. A distance of 25±2 mm between the bottom of the blade and the inside bottom of the vessel is maintained during the test. The metallic or suitably inert, rigid blade and shaft comprise a single entity. A suitable two-part detachable design may be used provided the assembly remains firmly engaged during the test. The paddle blade and shaft may be coated with a suitable coating so as to make them inert. The dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started. A small, loose piece of nonreactive material, such as not more than a few turns of wire helix, may be attached to dosage units that would otherwise float. Other validated sinker devices may be used.

Where water or a specified rate medium with a pH of less than 6.8 is specified as the medium, the same medium may be used with the addition of purified pepsin that results in an activity of 750,000 Units

or less per 1000 mL. For media with a pH of 6.8 or greater, pancreatin can be added to produce not more than 1750 USP Units of protease activity per 1000 mL.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid, having the structure:



(Compound 1),

and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, the composition having a release rate by weight of the compound in an aqueous medium that is one or more of release rates (a), (b) and (c), wherein:

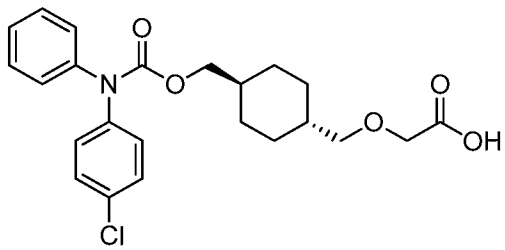
(a) about 15% to about 35% by weight of the compound is released over the first two hours in the aqueous medium;

(b) about 24% to about 59% by weight of the compound is released over the first four hours in the aqueous medium; and/or

(c) about 43% to about 96% by weight of the compound is released over the first eight hours in the aqueous medium,

wherein the release rate is measured with USP Apparatus 1 (baskets) at 80 to 120 rpm in 400 to 600 mL of an aqueous medium at a pH of 6.3 to 7.3 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.04 to 0.06 M.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid, having the structure:



(Compound 1),

and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, the composition having a release rate by weight of the compound in an aqueous medium that is one or more of release rates (a), (b) and (c), wherein:

(a) less than or equal to about 40% by weight of the compound is released over the first two hours in the aqueous medium;

(b) about 40% to about 60% by weight of the compound is released over the first five hours in the aqueous medium; and/or

(c) more than or equal to about 80% by weight of the compound is released over the first fourteen hours in the aqueous medium,

wherein the release rate is measured with USP Apparatus 1 (baskets) at 80 to 120 rpm in 400 to 600 mL of an aqueous medium at a pH of 6.3 to 7.3 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.04 to 0.06 M.

In some embodiments, the composition has release rate (a). In some embodiments, the composition has release rate (b). In some embodiments, the composition has release rate (c). In some embodiments, the composition has release rates (a) and (b). In some embodiments, the composition has release rates (a) and (c). In some embodiments, the composition has release rates (b) and (c). In some embodiments, the composition has release rates (a), (b) and (c).

In some embodiments, the release rate is the release rate measured with USP Apparatus 1 (baskets) at 100 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C.

In some embodiments, the aqueous medium comprises sodium phosphate at a concentration of 0.05 M.

In some embodiments, the release rate is the release rate measured with USP Apparatus 2 (paddle) at 50 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C, wherein the aqueous medium comprises sodium phosphate at a concentration of 0.05 M.

In some embodiments, the composition is a tablet.

In some embodiments, the composition is a capsule.

In some embodiments, the pharmaceutical composition is a tablet.

In some embodiments, the pharmaceutical composition is a capsule.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, wherein the composition comprises a first excipient and a second excipient, wherein the first excipient comprises hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present

in an amount of about 2% in water at 20° C and the second excipient comprises hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, wherein the composition comprises a first excipient and a second excipient, wherein the first excipient comprises a release modifier having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C and the second excipient comprises a release modifier having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, wherein the composition comprises a first excipient and a second excipient, wherein the first excipient comprises hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C and the second excipient comprises hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C,

wherein the composition has a release rate by weight of the compound in an aqueous medium that is one or more of release rates (a), (b) and (c), wherein:

(a) about 15% to about 35% by weight of the compound is released over the first two hours in the aqueous medium;

(b) about 24% to about 59% by weight of the compound is released over the first four hours in the aqueous medium; and/or

(c) about 43% to about 96% by weight of the compound is released over the first eight hours in the aqueous medium,

wherein the release rate is measured with USP Apparatus 1 (baskets) at 80 to 120 rpm in 400 to 600 mL of an aqueous medium at a pH of 6.3 to 7.3 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.04 to 0.06 M.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount

equivalent to a therapeutically effective amount of Compound 1, wherein the composition comprises a first excipient and a second excipient, wherein the first excipient comprises a release modifier having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C and the second excipient comprises a release modifier having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C, wherein the composition has a release rate by weight of the compound in an aqueous medium that is one or more of release rates (a), (b) and (c), wherein:

(a) less than or equal to about 40% by weight of the compound is released over the first two hours in the aqueous medium;

(b) about 40% to about 60% by weight of the compound is released over the first five hours in the aqueous medium; and/or

(c) more than or equal to about 80% by weight of the compound is released over the first fourteen hours in the aqueous medium,

wherein the release rate is measured with USP Apparatus 1 (baskets) at 80 to 120 rpm in 400 to 600 mL of an aqueous medium at a pH of 6.3 to 7.3 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.04 to 0.06 M.

In some embodiments, the composition has release rate (a). In some embodiments, the composition has release rate (b). In some embodiments, the composition has release rate (c). In some embodiments, the composition has release rates (a) and (b). In some embodiments, the composition has release rates (a) and (c). In some embodiments, the composition has release rates (b) and (c). In some embodiments, the composition has release rates (a), (b) and (c).

In some embodiments, the composition is a tablet.

In some embodiments, the pharmaceutical composition is a tablet.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, wherein the composition comprises a first excipient and a second excipient, wherein the first excipient comprises hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C and the second excipient comprises hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C, wherein the first excipient is present in an amount equal to about 5% to about 45% by weight and the second excipient is present in an amount equal to about 5% to about 45% by weight.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, wherein the composition comprises a first excipient and a second excipient, wherein the first excipient comprises a release modifier having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C and the second excipient comprises a release modifier having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C, wherein the first excipient is present in an amount equal to about 5% to about 45% by weight and the second excipient is present in an amount equal to about 5% to about 45% by weight.

In some embodiments, the first excipient is present in an amount equal to about 10% to about 40% by weight and the second excipient is present in an amount equal to about 10% to about 40% by weight.

In some embodiments, the first excipient is present in an amount equal to about 12.5% to about 37.5% by weight and the second excipient is present in an amount equal to about 12.5% to about 37.5% by weight.

In some embodiments, the first excipient is present in an amount equal to about 25% by weight and the second excipient is present in an amount equal to about 25% by weight.

In some embodiments, the composition has a release rate by weight of the compound in an aqueous medium that is one or more of release rates (a), (b) and (c), wherein:

(a) about 15% to about 35% by weight of the compound is released over the first two hours in the aqueous medium;

(b) about 24% to about 59% by weight of the compound is released over the first four hours in the aqueous medium; and/or

(c) about 43% to about 96% by weight of the compound is released over the first eight hours in the aqueous medium,

wherein the release rate is measured with USP Apparatus 1 (baskets) at 80 to 120 rpm in 400 to 600 mL of an aqueous medium at a pH of 6.3 to 7.3 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.04 to 0.06 M.

In some embodiments, the release rate is the release rate measured with USP Apparatus 1 (baskets) at 100 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C.

In some embodiments, the aqueous medium comprises sodium phosphate at a concentration of 0.05 M.

In some embodiments, the release rate is the release rate measured with USP Apparatus 2 (paddle) at 50 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C.

In some embodiments, the aqueous medium comprises sodium phosphate at a concentration of 0.05 M.

In some embodiments, the composition is a tablet.

In some embodiments, the pharmaceutical composition is a tablet.

In some embodiments, the tablet comprises a core and a coating.

In some embodiments, the core comprises hydroxypropyl methylcellulose.

In some embodiments, the coating does not comprise hydroxypropyl methylcellulose.

In some embodiments, the core comprises a first excipient and a second excipient, wherein the first excipient comprises hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C and the second excipient comprises hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C, and the coating does not comprise hydroxypropyl methylcellulose.

In some embodiments, the therapeutically effective amount of Compound 1 is about 0.01 % to about 1 % by weight of the composition.

In some embodiments, the therapeutically effective amount of Compound 1 is about 0.01 % to about 0.6 % by weight of the composition.

In some embodiments, the therapeutically effective amount of Compound 1 is about 0.02 % to about 0.3 % by weight of the composition.

In some embodiments, the therapeutically effective amount of Compound 1 is about 0.03 % to about 0.2 % by weight of the composition.

In some embodiments, the therapeutically effective amount of Compound 1 is about 0.04 % to about 0.12% by weight of the composition.

In some embodiments, the therapeutically effective amount of Compound 1 is about 0.04 % to about 0.1% by weight of the composition.

In some embodiments, the therapeutically effective amount of Compound 1 is about 0.04 % to about 0.1% by weight of the composition.

In some embodiments, the therapeutically effective amount of Compound 1 is about 0.05 % to about 0.08% by weight of the composition.

In some embodiments, the therapeutically effective amount of Compound 1 is about 0.06 % by weight of the composition.

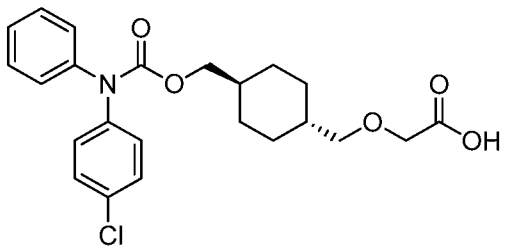
In some embodiments, the therapeutically effective amount of Compound 1 is about 0.01 mg to about 1 mg.

In some embodiments, the compound is 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1).

In some embodiments, the therapeutically effective amount of Compound 1 is suitable for administration to a subject once daily.

In some embodiments, the therapeutically effective amount of Compound 1 is suitable for administration to a patient once daily.

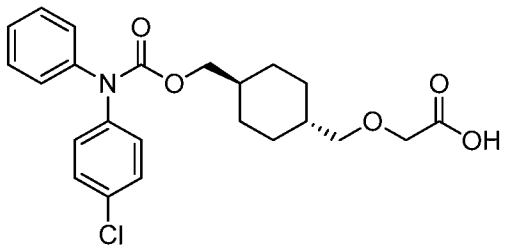
In some embodiments provided herein is a pharmaceutical composition comprising 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid, having the structure:



(Compound 1),

wherein the composition comprises about 0.05% by weight of Compound 1; about 25% by weight of hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C; and about 25% by weight of hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C.

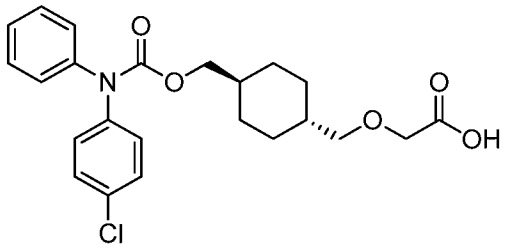
In some embodiments provided herein is a pharmaceutical composition comprising 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid, having the structure:



(Compound 1),

wherein the composition comprises about 0.05 mg of Compound 1; about 25 mg of hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C; and about 25 mg of hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C.

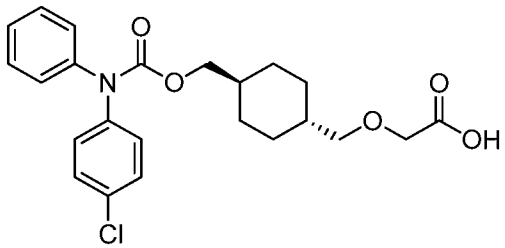
In some embodiments provided herein is a pharmaceutical composition comprising 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid, having the structure:



(Compound 1),

wherein the composition comprises about 0.01 mg to about 0.8 mg of Compound 1; about 5 mg to about 45 mg of hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C; and about 5 mg to about 45 mg of hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C.

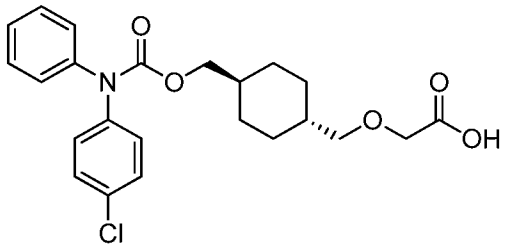
In some embodiments provided herein is a pharmaceutical composition comprising 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid, having the structure:



(Compound 1),

wherein the composition comprises about 0.01 mg to about 0.6 mg of Compound 1; about 5 mg to about 45 mg of hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C; and about 5 mg to about 45 mg of hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C.

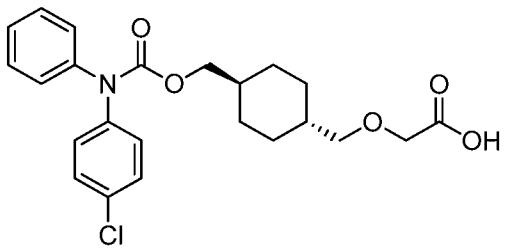
In some embodiments provided herein is a pharmaceutical composition comprising 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid, having the structure:



(Compound 1),

wherein the composition comprises about 0.01 mg to about 0.8 mg of Compound 1; about 25 mg of hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C; and about 25 mg of hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C.

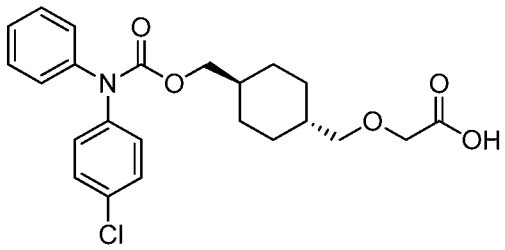
In some embodiments provided herein is a pharmaceutical composition comprising 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid, having the structure:



(Compound 1),

wherein the composition comprises about 0.01 mg to about 0.6 mg of Compound 1; about 25 mg of hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C; and about 25 mg of hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C.

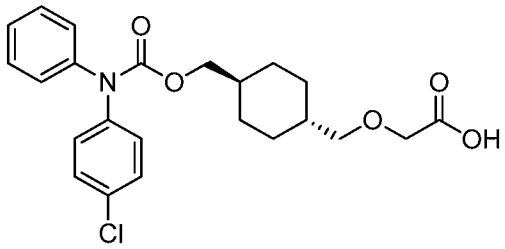
In some embodiments provided herein is a pharmaceutical composition comprising 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid, having the structure:



(Compound 1),

wherein the composition comprises about 0.01 mg to about 0.8 mg of Compound 1; about 25 mg of hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C; and about 25 mg of hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C; about 25mg of Methocel™ K4M Premium CR; and about 25 mg of Methocel™ K100 Premium LVCR.

In some embodiments provided herein is a pharmaceutical composition comprising 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid, having the structure:



(Compound 1),

wherein the composition comprises about 0.01 mg to about 0.6 mg of Compound 1; about 25 mg of hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C; and about 25 mg of hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C; about 25mg of Methocel™ K4M Premium CR; and about 25 mg of Methocel™ K100 Premium LVCR.

In some embodiments provided herein is a process for preparing a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, comprising mixing the compound with a first excipient comprising hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C, and a second excipient comprising hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C, and optionally an additional pharmaceutically acceptable excipient, to form the pharmaceutical composition.

In some embodiments provided herein is a process for preparing a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, comprising mixing the compound with a first excipient comprising a release modifier having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C, and a second excipient comprising a release modifier having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C, and optionally an additional pharmaceutically acceptable excipient, to form the pharmaceutical composition.

In some embodiments provided herein is a process for preparing a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-

chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, wherein the process comprises mixing the compound, ethanol, a first excipient comprising hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C, and a second excipient comprising hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C, to form the composition.

In some embodiments, the pharmaceutical composition is a tablet.

In some embodiments provided herein is a pharmaceutical composition wherein the composition is storage-stable.

In some embodiments, the storage-stable composition is a pharmaceutical composition wherein the composition is a tablet.

In some embodiments, the storage-stable composition is a pharmaceutical composition wherein the composition is a capsule.

In some embodiments, the storage-stable composition is a pharmaceutical composition wherein the release rate of the compound after storage of the composition at 40°C and 75% RH for at least about one month does not vary at any given dissolution time point equal or greater than 2 hours by more than about 20% of the release rate of the compound prior to storage, wherein the release rate after storage and prior to storage are each measured with USP Apparatus 1 (baskets) at 100 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C, wherein the aqueous medium comprises sodium phosphate at a concentration of 0.05 M.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, wherein the composition comprises a first excipient and a second excipient, wherein the first excipient comprises a copolymer comprising (a) a first polyoxyethylene chain; (b) a poly(propylene oxide) chain bonded to the first polyoxyethylene chain; and (c) a second polyoxyethylene chain bonded to the poly(propylene oxide) chain; and the second excipient comprises an ester of a polyalcohol and a fatty acid.

In some embodiments, the pharmaceutical composition is a composition.

In some embodiments, the first excipient comprises Poloxamer 188.

In some embodiments, the second excipient comprises glycerol monostearate and has a monoester content of at least about 90%.

In some embodiments, the second excipient comprises glycerol monostearate and has a monoester content of at least about 95%.

In some embodiments, the composition is a cured composition.

In some embodiments provided herein is a pharmaceutical composition prepared by the process comprising:

curing a mixture comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, a first excipient, and a second excipient, wherein the first excipient comprises a copolymer comprising (a) a first polyoxyethylene chain; (b) a poly(propylene oxide) chain bonded to the first polyoxyethylene chain; and (c) a second polyoxyethylene chain bonded to the poly(propylene oxide) chain, and the second excipient comprises an ester of a polyalcohol and a fatty acid, to form the composition.

In some embodiments, the first excipient comprises Poloxamer 188 and the second excipient comprises glycerol monostearate and has a monoester content of at least about 90%.

In some embodiments, the first excipient comprises Poloxamer 188 and the second excipient comprises glycerol monostearate and has a monoester content of at least about 95%.

In some embodiments, the curing of a mixture is performed at a temperature of about 45°C to about 55°C.

In some embodiments, the curing of a mixture is performed for about 12 hours to about 36 hours at a temperature of about 50°C to about 55°C.

In some embodiments, the ratio by weight of the first excipient to the second excipient is from about 70:30 to about 10:90.

In some embodiments, the ratio by weight of the first excipient to the second excipient is about 50:50 to about 30:70.

In some embodiments, the ratio by weight of the first excipient to the second excipient is about 70:30.

In some embodiments, the ratio by weight of the first excipient to the second excipient is about 50:50.

In some embodiments, the ratio by weight of the first excipient to the second excipient is about 40:60.

In some embodiments, the ratio by weight of the first excipient to the second excipient is about 30:70.

In some embodiments, the composition has a release rate by weight of the compound in an aqueous medium that is one or more of release rates (a), (b) and (c), wherein:

(a) about 15% to about 35% of the compound is released over the first two hours in the aqueous medium;

(b) about 24% to about 59% of the compound is released over the first four hours in the aqueous medium; and/or

(c) about 43% to about 96% of the compound is released over the first eight hours in the aqueous medium.

In some embodiments, the composition has release rate (a).

In some embodiments, the composition has release rate (b).

In some embodiments, the composition has release rate (c).

In some embodiments, the composition has release rates (a) and (b).

In some embodiments, the composition has release rates (a) and (c).

In some embodiments, the composition has release rates (b) and (c).

In some embodiments, the composition has release rates (a), (b) and (c).

In some embodiments, the composition is a capsule.

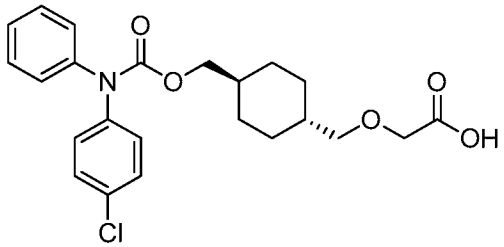
In some embodiments, the release rate is the release rate measured with USP Apparatus 2 (paddle) at 50 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C.

In some embodiments, the aqueous medium comprises sodium phosphate at a concentration of 0.05 M.

In some embodiments, the compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof is 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1).

In some embodiments, the composition exhibits peaks in the PXRD spectrum having the following 2θ values: 19.7°, 20.2°, 20.7°, 22.6°, 23.1°, and 23.7°.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid, having the structure:



(Compound 1),

and pharmaceutically acceptable salts, solvates, and hydrates thereof, in an amount equivalent to a therapeutically effective amount of Compound 1, the composition having a release rate by weight of the compound in an aqueous medium that is one or more of release rates (a), (b) and (c), wherein:

(a) about 15% to about 35% by weight of the compound is released over the first two hours in the aqueous medium;

(b) about 24% to about 59% by weight of the compound is released over the first four hours in the aqueous medium; and/or

(c) about 43% to about 96% by weight of the compound is released over the first eight hours in the aqueous medium,

wherein the release rate is measured with USP Apparatus 1 (baskets) at 80 to 120 rpm in 400 to 600 mL of an aqueous medium at a pH of 6.3 to 7.3 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.04 to 0.06 M,

wherein the composition comprises a first excipient and a second excipient, wherein the first excipient comprises a copolymer comprising (a) a first polyoxyethylene chain; (b) a poly(propylene oxide) chain bonded to the first polyoxyethylene chain; and (c) a second polyoxyethylene chain bonded to the poly(propylene oxide) chain; and the second excipient comprises an ester of a polyalcohol and a fatty acid.

In some embodiments of the pharmaceutical compositions disclosed herein, the first excipient comprises Poloxamer 188.

In some embodiments of the pharmaceutical compositions disclosed herein, the second excipient comprises glycerol monostearate and has a monoester content of at least about 50%. In some embodiments, the second excipient comprises glycerol monostearate and has a monoester content of at least about 60%, such as at least about 70%, such as at least about 75%, such as at least about 80%, such as at least about 90%, such as at least about 95%, such as at least about 96%, such as at least about 97%, such as at least about 98%, such as at least about 99%.

In some embodiments of the pharmaceutical compositions disclosed herein, the ratio by weight of the first excipient to the second excipient is about 30:70.

In some embodiments of the pharmaceutical compositions disclosed herein, the first excipient comprises Poloxamer 188 and the second excipient comprises glycerol monostearate and has a monoester content of at least about 90%, wherein the ratio by weight of the first excipient to the second excipient is about 30:70.

In some embodiments of the pharmaceutical compositions disclosed herein, the first excipient comprises Poloxamer 188 and the second excipient comprises glycerol monostearate and has a monoester

content of at least about 95%, wherein the ratio by weight of the first excipient to the second excipient is about 30:70.

In some embodiments, the pharmaceutical composition is a dosage form composed of a size 4 gelatin capsule, such as a white opaque, hard gelatin capsule. In some embodiments, the pharmaceutical composition is a dosage form composed of a size 2 gelatin capsule, such as a white opaque, hard gelatin capsule. In some embodiments, the pharmaceutical composition is a dosage form composed of a size 4 HPMC capsule. In some embodiments, the pharmaceutical composition is a dosage form composed of a size 2 HPMC capsule.

In some embodiments of the pharmaceutical compositions disclosed herein, the compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof is 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1).

In some embodiments of the pharmaceutical compositions disclosed herein, the compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof is a pharmaceutically acceptable salt of 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1).

In some embodiments, the therapeutically effective amount of Compound 1 is suitable for administration to a subject, such as a patient, once daily.

In some embodiments, the therapeutically effective amount of Compound 1 is suitable for administration to a subject, such as a patient, twice daily.

In some embodiments, the pharmaceutical composition contains a release modifier. In some embodiments, the release modifier is hydroxypropyl methylcellulose. For example, in some embodiments, the release modifier is hydroxypropyl methylcellulose K4M CR and/or hydroxypropyl methylcellulose K100 LVCR. In some embodiments, the release modifier is a resin. For example, in some embodiments, the release modifier is an ethylene oxide resin (such as Polyox® resin). In some embodiments, the release modifier is another excipient known in the pharmaceutical art to modify release of an active agent.

In some embodiments, the pharmaceutical composition contains a filler. For example, in some embodiments, the pharmaceutical composition contains microcrystalline cellulose. In some embodiments, the filler is another excipient known in the pharmaceutical art. In some embodiments, the pharmaceutical composition contains a glidant. For example, in some embodiments, the pharmaceutical composition contains silicon dioxide. In some embodiments, the glidant is another excipient known in the pharmaceutical art. In some embodiments, the pharmaceutical composition contains a lubricant. For

example, in some embodiments, the pharmaceutical composition contains magnesium stearate. In some embodiments, the lubricant is another excipient known in the pharmaceutical art. In some embodiments, the pharmaceutical composition contains a film coating. For example, in some embodiment, the pharmaceutical composition contains Opadry®. In some embodiments, the film coating is another excipient known in the pharmaceutical art.

In some embodiments, the pharmaceutical composition is in the form of, for example, granules, spheroids or pellets in a capsule or in any other suitable dosage form. In some embodiments, the pharmaceutical composition is in the form of a capsule, such as a hard gelatin capsule. In some embodiments, the pharmaceutical composition is in the form of a tablet.

In addition to the above ingredients, the pharmaceutical composition may further comprise suitable quantities of other materials, e.g. stabilizers, diluents, lubricants, binders, granulating aids, colorants, flavorants and glidants that are conventional in the pharmaceutical art.

In some embodiments, the pharmaceutical composition herein comprises Compound 1; hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C; and hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C, the composition comprising about 0.01% to about 1% of Compound 1 as a % by weight of the composition, such as about 0.02% to about 0.5 %, such as about 0.03% to about 0.4 %, such as about 0.05% to about 0.2 %, such as about 0.03%, about 0.5 %, about 0.1%, 0.2% or 0.5%, of Compound 1 as a % by weight of the composition.

In some embodiments, the pharmaceutical composition comprises about 0.03% by weight of Compound 1; about 5% to about 45% by weight of hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C (the first excipient); and about 5% to about 45% by weight of hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C (the second excipient). In some embodiments, the composition comprises about 0.03% by weight of Compound 1; about 10% to about 40% by weight of the first excipient; and about 10% to about 40% by weight of the second excipient. In some embodiments, the composition comprises about 0.03% by weight of Compound 1; about 12.5% to about 37.5% by weight of the first excipient; and about 12.5% to about 37.5% by weight of the second excipient. In some embodiments, the composition comprises about 0.03% by weight of Compound 1; about 25% by weight of hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C; and about 25% by weight of hydroxypropyl methylcellulose

having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C.

In some embodiments, the pharmaceutical composition comprises about 0.05% by weight of Compound 1; about 5% to about 45% by weight of hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C (the first excipient); and about 5% to about 45% by weight of hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C (the second excipient). In some embodiments, the composition comprises about 0.05% by weight of Compound 1; about 10% to about 40% by weight of the first excipient; and about 10% to about 40% by weight of the second excipient. In some embodiments, the composition comprises about 0.05% by weight of Compound 1; about 12.5% to about 37.5% by weight of the first excipient; and about 12.5% to about 37.5% by weight of the second excipient. In some embodiments, the composition comprises about 0.05% by weight of Compound 1; about 25% by weight of hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C; and about 25% by weight of hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C.

In some embodiments, the pharmaceutical composition comprises about 0.1% by weight of Compound 1; about 5% to about 45% by weight of hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C (the first excipient); and about 5% to about 45% by weight of hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C (the second excipient). In some embodiments, the composition comprises about 0.1% by weight of Compound 1; about 10% to about 40% by weight of the first excipient; and about 10% to about 40% by weight of the second excipient. In some embodiments, the composition comprises about 0.1% by weight of Compound 1; about 12.5% to about 37.5% by weight of the first excipient; and about 12.5% to about 37.5% by weight of the second excipient. In some embodiments, the composition comprises about 0.1% by weight of Compound 1; about 25% by weight of hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C; and about 25% by weight of hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C.

In some embodiments, the pharmaceutical composition herein comprises about 0.03 mg of Compound 1; about 25 mg of hydroxypropyl methylcellulose having a viscosity of about 2300 mPA

seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C; and about 25 mg of hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C.

In some embodiments, the pharmaceutical composition herein comprises about 0.05 mg of Compound 1; about 25 mg of hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C; and about 25 mg of hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C.

In some embodiments, the pharmaceutical composition herein comprises about 0.1 mg of Compound 1; about 25 mg of hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C; and about 25 mg of hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C.

In some embodiments, the pharmaceutical composition herein comprises an amount equivalent to about 0.01 mg to about 0.6 mg, such as about 0.02 to about 0.3 mg, such as about 0.03 to about 0.2 mg, such as about 0.04 to about 0.12 mg, such as about 0.04 to about 0.1 mg, such as about 0.05 to about 0.08 mg, such as about 0.06 mg. of Compound 1; about 5 mg to about 45 mg, such as about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, or about 40 mg, of hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C; and about 5 mg to about 45 mg, such as about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, or about 40 mg, of hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C.

In some embodiments, the pharmaceutical composition herein comprises about 0.01 mg to about 0.6 mg, such as about 0.02 to about 0.3 mg, such as about 0.03 to about 0.2 mg, such as about 0.04 to about 0.12 mg, such as about 0.04 to about 0.1 mg, such as about 0.05 to about 0.08 mg, such as about 0.06 mg. of Compound 1; about 25 mg of hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C; and about 25 mg of hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C.

In some embodiments, the pharmaceutical composition herein comprises about 0.01 mg to about 0.6 mg, such as about 0.02 to about 0.3 mg, such as about 0.03 to about 0.2 mg, such as about 0.04 to about 0.12 mg, such as about 0.04 to about 0.1 mg, such as about 0.05 to about 0.08 mg, such as about

0.06 mg. of Compound 1; about 25 mg of Methocel™ K4M Premium CR; and about 25 mg of Methocel™ K100 Premium LVCR.

In some embodiments, the pharmaceutical composition herein comprises Compound 1; Poloxamer 188; and food grade glycerol monostearate; the composition comprising about 0.0066% to about 0.666% of Compound 1 as a % by weight of the composition.

In some embodiments, the pharmaceutical composition herein comprises Compound 1; Poloxamer 188; and food grade glycerol monostearate; the composition comprising about 0.0066% to about 0.4% of Compound 1 as a % by weight of the composition.

In some embodiments, the pharmaceutical composition herein comprises Compound 1; Poloxamer 188; and food grade glycerol monostearate; the composition comprising about 0.0133% to about 0.2% of Compound 1 as a % by weight of the composition.

In some embodiments, the pharmaceutical composition herein comprises Compound 1; Poloxamer 188; and food grade glycerol monostearate; the composition comprising about 0.02% to about 0.133% of Compound 1 as a % by weight of the composition.

In some embodiments, the pharmaceutical composition herein comprises Compound 1; Poloxamer 188; and food grade glycerol monostearate; the composition comprising about 0.0266% to about 0.066% of Compound 1 as a % by weight of the composition.

In some embodiments, the pharmaceutical composition herein comprises Compound 1; Poloxamer 188; and food grade glycerol monostearate; the composition comprising about 0.0333% to about 0.066% of Compound 1 as a % by weight of the composition.

In some embodiments, the pharmaceutical composition herein comprises Compound 1; Poloxamer 188; and food grade glycerol monostearate; the composition comprising about 0.04% of Compound 1 as a % by weight of the composition.

In some embodiments, the pharmaceutical composition herein comprises Compound 1; Poloxamer 188; and glycerol monostearate having a monoester content of at least about 90%; the composition comprising about 0.0066% to about 0.666% of Compound 1 as a % by weight of the composition.

In some embodiments, the pharmaceutical composition herein comprises Compound 1; Poloxamer 188; and glycerol monostearate having a monoester content of at least about 90%; the composition comprising about 0.0066% to about 0.4% of Compound 1 as a % by weight of the composition.

In some embodiments, the pharmaceutical composition herein comprises Compound 1; Poloxamer 188; and glycerol monostearate having a monoester content of at least about 90%; the

composition comprising about 0.0133% to about 0.2% of Compound 1 as a % by weight of the composition.

In some embodiments, the pharmaceutical composition herein comprises Compound 1; Poloxamer 188; and glycerol monostearate having a monoester content of at least about 90%; the composition comprising about 0.02% to about 0.133% of Compound 1 as a % by weight of the composition.

In some embodiments, the pharmaceutical composition herein comprises Compound 1; Poloxamer 188; and glycerol monostearate having a monoester content of at least about 90%; the composition comprising about 0.0266% to about 0.066% of Compound 1 as a % by weight of the composition.

In some embodiments, the pharmaceutical composition herein comprises Compound 1; Poloxamer 188; and glycerol monostearate having a monoester content of at least about 90%; the composition comprising about 0.0333% to about 0.066% of Compound 1 as a % by weight of the composition.

In some embodiments, the pharmaceutical composition herein comprises Compound 1; Poloxamer 188; and glycerol monostearate having a monoester content of at least about 90%; the composition comprising about 0.04% of Compound 1 as a % by weight of the composition.

In some embodiments, the pharmaceutical composition herein comprises Compound 1; Poloxamer 188; and glycerol monostearate having a monoester content of at least about 95%; the composition comprising about 0.0066% to about 0.666% of Compound 1 as a % by weight of the composition.

In some embodiments, the pharmaceutical composition herein comprises Compound 1; Poloxamer 188; and glycerol monostearate having a monoester content of at least about 95%; the composition comprising about 0.0066% to about 0.4% of Compound 1 as a % by weight of the composition.

In some embodiments, the pharmaceutical composition herein comprises Compound 1; Poloxamer 188; and glycerol monostearate having a monoester content of at least about 95%; the composition comprising about 0.0133% to about 0.2% of Compound 1 as a % by weight of the composition.

In some embodiments, the pharmaceutical composition herein comprises Compound 1; Poloxamer 188; and glycerol monostearate having a monoester content of at least about 95%; the composition comprising about 0.02% to about 0.133% of Compound 1 as a % by weight of the composition.

In some embodiments, the pharmaceutical composition herein comprises Compound 1; Poloxamer 188; and glycerol monostearate having a monoester content of at least about 95%; the composition comprising about 0.0266% to about 0.066% of Compound 1 as a % by weight of the composition.

In some embodiments, the pharmaceutical composition herein comprises Compound 1; Poloxamer 188; and glycerol monostearate having a monoester content of at least about 95%; the composition comprising about 0.0333% to about 0.066% of Compound 1 as a % by weight of the composition.

In some embodiments, the pharmaceutical composition herein comprises Compound 1; Poloxamer 188; and glycerol monostearate having a monoester content of at least about 95%; the composition comprising about 0.04% of Compound 1 as a % by weight of the composition.

In some embodiments, the pharmaceutical composition herein comprises an amount equivalent to about 0.01 mg to about 0.6 mg, such as about 0.02 to about 0.3 mg, such as about 0.03 to about 0.2 mg, such as about 0.04 to about 0.12 mg, such as about 0.04 to about 0.1 mg, such as about 0.05 to about 0.08 mg, such as about 0.06 mg. of Compound 1; about 45 mg to about 135 mg, such as about 45 mg, about 60 mg, about 75 mg, about 90 mg, about 105 mg, about 120 mg, or about 135 mg, of food grade GMS; and about 105 mg to about 15 mg, such as about 105 mg, about 90 mg, about 75 mg, about 60 mg, about 45 mg, about 30 mg, or about 15 mg, of Poloxamer 188. In some embodiments, the composition herein comprises about 0.01 mg, about 0.02 mg, about 0.03 mg, about 0.04 mg, about 0.05 mg, about 0.06 mg, about 0.07 mg, about 0.08 mg, about 0.09 mg, about 0.1 mg, about 0.12 mg, about 0.2 mg, about 0.3 mg, or about 0.5 mg, or about 0.6 mg, of Compound 1; about 45 mg to about 135 mg, such as about 60 mg, about 75 mg, about 90 mg, about 105 mg, about 120 mg, or about 135 mg, of food grade GMS; and about 105 mg to about 15 mg, such as about 105 mg, about 90 mg, about 75 mg, about 60 mg, about 45 mg, about 30 mg, or about 15 mg, of Poloxamer 188.

In some embodiments, the pharmaceutical composition herein comprises about 0.01 mg to about 0.6 mg, such as about 0.02 to about 0.3 mg, such as about 0.03 to about 0.2 mg, such as about 0.04 to about 0.12 mg, such as about 0.04 to about 0.1 mg, such as about 0.05 to about 0.08 mg, such as about 0.06 mg. of Compound 1; about 75 mg of Poloxamer 188; and about 75 mg of food grade glycerol monostearate.

In some embodiments, the pharmaceutical composition herein comprises about 0.01 mg to about 0.6 mg, such as about 0.02 to about 0.3 mg, such as about 0.03 to about 0.2 mg, such as about 0.04 to about 0.12 mg, such as about 0.04 to about 0.1 mg, such as about 0.05 to about 0.08 mg, such as about 0.06 mg. of Compound 1; about 45 mg of Poloxamer 188; and about 105 mg of food grade glycerol monostearate.

In some embodiments, the pharmaceutical composition herein comprises about 0.01 mg to about 0.6 mg, such as about 0.02 to about 0.3 mg, such as about 0.03 to about 0.2 mg, such as about 0.04 to about 0.12 mg, such as about 0.04 to about 0.1 mg, such as about 0.05 to about 0.08 mg, such as about 0.06 mg. of Compound 1; about 105 mg of Poloxamer 188; and about 45 mg of food grade glycerol monostearate.

In some embodiments, the pharmaceutical composition herein comprises about 0.01 mg to about 0.6 mg, such as about 0.02 to about 0.3 mg, such as about 0.03 to about 0.2 mg, such as about 0.04 to about 0.12 mg, such as about 0.04 to about 0.1 mg, such as about 0.05 to about 0.08 mg, such as about 0.06 mg. of Compound 1; about 75 mg of Poloxamer 188; and about 75 mg of glycerol monostearate having a monoester content of at least about 90%.

In some embodiments, the pharmaceutical composition herein comprises about 0.01 mg to about 0.6 mg, such as about 0.02 to about 0.3 mg, such as about 0.03 to about 0.2 mg, such as about 0.04 to about 0.12 mg, such as about 0.04 to about 0.1 mg, such as about 0.05 to about 0.08 mg, such as about 0.06 mg. of Compound 1; about 45 mg of Poloxamer 188; and about 105 mg of glycerol monostearate having a monoester content of at least about 90%.

In some embodiments, the pharmaceutical composition herein comprises about 0.01 mg to about 0.6 mg, such as about 0.02 to about 0.3 mg, such as about 0.03 to about 0.2 mg, such as about 0.04 to about 0.12 mg, such as about 0.04 to about 0.1 mg, such as about 0.05 to about 0.08 mg, such as about 0.06 mg. of Compound 1; about 105 mg of Poloxamer 188; and about 45 mg of glycerol monostearate having a monoester content of at least about 90%.

In some embodiments, the pharmaceutical composition herein comprises about 0.01 mg to about 0.6 mg, such as about 0.02 to about 0.3 mg, such as about 0.03 to about 0.2 mg, such as about 0.04 to about 0.12 mg, such as about 0.04 to about 0.1 mg, such as about 0.05 to about 0.08 mg, such as about 0.06 mg. of Compound 1; about 75 mg of Poloxamer 188; and about 75 mg of glycerol monostearate having a monoester content of at least about 95%.

In some embodiments, the pharmaceutical composition herein comprises about 0.01 mg to about 0.6 mg, such as about 0.02 to about 0.3 mg, such as about 0.03 to about 0.2 mg, such as about 0.04 to about 0.12 mg, such as about 0.04 to about 0.1 mg, such as about 0.05 to about 0.08 mg, such as about 0.06 mg. of Compound 1; about 45 mg of Poloxamer 188; and about 105 mg of glycerol monostearate having a monoester content of at least about 95%.

In some embodiments, the pharmaceutical composition herein comprises about 0.01 mg to about 0.6 mg, such as about 0.02 to about 0.3 mg, such as about 0.03 to about 0.2 mg, such as about 0.04 to about 0.12 mg, such as about 0.04 to about 0.1 mg, such as about 0.05 to about 0.08 mg, such as about

0.06 mg. of Compound 1; about 105 mg of Poloxamer 188; and about 45 mg of glycerol monostearate having a monoester content of at least about 95%.

In some embodiments, the pharmaceutical composition herein comprises about 0.01 mg to about 0.6 mg, such as about 0.02 to about 0.3 mg, such as about 0.03 to about 0.2 mg, such as about 0.04 to about 0.12 mg, such as about 0.04 to about 0.1 mg, such as about 0.05 to about 0.08 mg, such as about 0.06 mg. of Compound 1; about 75 mg of Poloxamer 188; and about 75 mg of Myverol™ 18-04 K.

In some embodiments, the pharmaceutical composition herein comprises about 0.01 mg to about 0.6 mg, such as about 0.02 to about 0.3 mg, such as about 0.03 to about 0.2 mg, such as about 0.04 to about 0.12 mg, such as about 0.04 to about 0.1 mg, such as about 0.05 to about 0.08 mg, such as about 0.06 mg. of Compound 1; about 45 mg of Poloxamer 188; and about 105 mg of Myverol™ 18-04 K.

In some embodiments, the pharmaceutical composition herein comprises about 0.01 mg to about 0.6 mg, such as about 0.02 to about 0.3 mg, such as about 0.03 to about 0.2 mg, such as about 0.04 to about 0.12 mg, such as about 0.04 to about 0.1 mg, such as about 0.05 to about 0.08 mg, such as about 0.06 mg. of Compound 1; about 105 mg of Poloxamer 188; and about 45 mg of Myverol™ 18-04 K.

In some embodiments, the pharmaceutical composition herein comprises about 0.03 mg of Compound 1; about 75 mg of Poloxamer 188; and about 75 mg of food grade glycerol monostearate.

In some embodiments, the pharmaceutical composition herein comprises about 0.03 mg of Compound 1; about 45 mg of Poloxamer 188; and about 105 mg of food grade glycerol monostearate.

In some embodiments, the pharmaceutical composition herein comprises about 0.03 mg of Compound 1; about 105 mg of Poloxamer 188; and about 45 mg of food grade glycerol monostearate.

In some embodiments, the pharmaceutical composition herein comprises about 0.03 mg of Compound 1; about 75 mg of Poloxamer 188; and about 75 mg of glycerol monostearate having a monoester content of at least about 90%.

In some embodiments, the pharmaceutical composition herein comprises about 0.03 mg of Compound 1; about 45 mg of Poloxamer 188; and about 105 mg of glycerol monostearate having a monoester content of at least about 90%.

In some embodiments, the pharmaceutical composition herein comprises about 0.03 mg of Compound 1; about 105 mg of Poloxamer 188; and about 45 mg of glycerol monostearate having a monoester content of at least about 90%.

In some embodiments, the pharmaceutical composition herein comprises about 0.03 mg of Compound 1; about 75 mg of Poloxamer 188; and about 75 mg of glycerol monostearate having a monoester content of at least about 95%.

In some embodiments, the pharmaceutical composition herein comprises about 0.03 mg of Compound 1; about 45 mg of Poloxamer 188; and about 105 mg of glycerol monostearate having a monoester content of at least about 95%.

In some embodiments, the pharmaceutical composition herein comprises about 0.03 mg of Compound 1; about 105 mg of Poloxamer 188; and about 45 mg of glycerol monostearate having a monoester content of at least about 95%.

In some embodiments, the pharmaceutical composition herein comprises about 0.03 mg of Compound 1; about 75 mg of Poloxamer 188; and about 75 mg of Myverol™ 18-04 K.

In some embodiments, the pharmaceutical composition herein comprises about 0.03 mg of Compound 1; about 45 mg of Poloxamer 188; and about 105 mg of Myverol™ 18-04 K.

In some embodiments, the pharmaceutical composition herein comprises about 0.03 mg of Compound 1; about 105 mg of Poloxamer 188; and about 45 mg of Myverol™ 18-04 K.

In some embodiments, the pharmaceutical composition herein comprises about 0.5 mg of Compound 1; about 75 mg of Poloxamer 188; and about 75 mg of food grade glycerol monostearate.

In some embodiments, the pharmaceutical composition herein comprises about 0.5 mg of Compound 1; about 45 mg of Poloxamer 188; and about 105 mg of food grade glycerol monostearate.

In some embodiments, the pharmaceutical composition herein comprises about 0.5 mg of Compound 1; about 105 mg of Poloxamer 188; and about 45 mg of food grade glycerol monostearate.

In some embodiments, the pharmaceutical composition herein comprises about 0.5 mg of Compound 1; about 75 mg of Poloxamer 188; and about 75 mg of glycerol monostearate having a monoester content of at least about 90%.

In some embodiments, the pharmaceutical composition herein comprises about 0.5 mg of Compound 1; about 45 mg of Poloxamer 188; and about 105 mg of glycerol monostearate having a monoester content of at least about 90%.

In some embodiments, the pharmaceutical composition herein comprises about 0.5 mg of Compound 1; about 105 mg of Poloxamer 188; and about 45 mg of glycerol monostearate having a monoester content of at least about 90%.

In some embodiments, the pharmaceutical composition herein comprises about 0.5 mg of Compound 1; about 75 mg of Poloxamer 188; and about 75 mg of glycerol monostearate having a monoester content of at least about 95%.

In some embodiments, the pharmaceutical composition herein comprises about 0.5 mg of Compound 1; about 45 mg of Poloxamer 188; and about 105 mg of glycerol monostearate having a monoester content of at least about 95%.

In some embodiments, the pharmaceutical composition herein comprises about 0.5 mg of Compound 1; about 105 mg of Poloxamer 188; and about 45 mg of glycerol monostearate having a monoester content of at least about 95%.

In some embodiments, the pharmaceutical composition herein comprises about 0.5 mg of Compound 1; about 75 mg of Poloxamer 188; and about 75 mg of Myverol™ 18-04 K.

In some embodiments, the pharmaceutical composition herein comprises about 0.5 mg of Compound 1; about 45 mg of Poloxamer 188; and about 105 mg of Myverol™ 18-04 K.

In some embodiments, the pharmaceutical composition herein comprises about 0.5 mg of Compound 1; about 105 mg of Poloxamer 188; and about 45 mg of Myverol™ 18-04 K.

In some embodiments, the pharmaceutical composition herein comprises about 0.12 mg of Compound 1; about 75 mg of Poloxamer 188; and about 75 mg of food grade glycerol monostearate.

In some embodiments, the pharmaceutical composition herein comprises about 0.12 mg of Compound 1; about 45 mg of Poloxamer 188; and about 105 mg of food grade glycerol monostearate.

In some embodiments, the pharmaceutical composition herein comprises about 0.12 mg of Compound 1; about 105 mg of Poloxamer 188; and about 45 mg of food grade glycerol monostearate.

In some embodiments, the pharmaceutical composition herein comprises about 0.12 mg of Compound 1; about 75 mg of Poloxamer 188; and about 75 mg of glycerol monostearate having a monoester content of at least about 90%.

In some embodiments, the pharmaceutical composition herein comprises about 0.12 mg of Compound 1; about 45 mg of Poloxamer 188; and about 105 mg of glycerol monostearate having a monoester content of at least about 90%.

In some embodiments, the pharmaceutical composition herein comprises about 0.12 mg of Compound 1; about 105 mg of Poloxamer 188; and about 45 mg of glycerol monostearate having a monoester content of at least about 90%.

In some embodiments, the pharmaceutical composition herein comprises about 0.12 mg of Compound 1; about 75 mg of Poloxamer 188; and about 75 mg of glycerol monostearate having a monoester content of at least about 95%.

In some embodiments, the pharmaceutical composition herein comprises about 0.12 mg of Compound 1; about 45 mg of Poloxamer 188; and about 105 mg of glycerol monostearate having a monoester content of at least about 95%.

In some embodiments, the pharmaceutical composition herein comprises about 0.12 mg of Compound 1; about 105 mg of Poloxamer 188; and about 45 mg of glycerol monostearate having a monoester content of at least about 95%.

In some embodiments, the pharmaceutical composition herein comprises about 0.12 mg of Compound 1; about 75 mg of Poloxamer 188; and about 75 mg of Myverol™ 18-04 K.

In some embodiments, the pharmaceutical composition herein comprises about 0.12 mg of Compound 1; about 45 mg of Poloxamer 188; and about 105 mg of Myverol™ 18-04 K.

In some embodiments, the pharmaceutical composition herein comprises about 0.12 mg of Compound 1; about 105 mg of Poloxamer 188; and about 45 mg of Myverol™ 18-04 K.

In any of the embodiments wherein the composition comprises glycerol monostearate having a monoester content of at least about 95%, the glycerol monostearate may have a monoester content that is at least about 96%, such as at least about 97%, such as at least about 98%, such as at least about 99%.

In some embodiments, provided herein is a pharmaceutical composition having a release rate by weight of the compound in an aqueous medium that is one or more of the release rates (a), (b) and/or (c) disclosed herein, wherein the composition comprises a first excipient and a second excipient, wherein the first excipient comprises hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C and the second excipient comprises hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C, wherein the ratio by weight of the first excipient to the second excipient is about 50:50, wherein the release rate is the release rate measured with USP Apparatus 1 (baskets) at 100 rpm in 500 mL of an aqueous medium at a temperature of 37°C ± 0.5 °C at a pH of about 6.8, wherein the aqueous medium comprises sodium phosphate at a concentration of 0.05 M.

In some embodiments, provided herein is a pharmaceutical composition having a release rate by weight of the compound in an aqueous medium that is one or more of the release rates (a), (b) and/or (c) disclosed herein, wherein the composition comprises a first excipient and a second excipient, wherein the first excipient comprises hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C and the second excipient comprises hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C, wherein the first excipient is present in an amount equal to about 25% by weight and the second excipient is present in an amount equal to about 25% by weight, wherein the release rate is the release rate measured with USP Apparatus 1 (baskets) at 100 rpm in 500 mL of an aqueous medium at a temperature of 37°C ± 0.5 °C at a pH of about 6.8, wherein the aqueous medium comprises sodium phosphate at a concentration of 0.05 M.

In some embodiments, provided herein is a pharmaceutical composition having a release rate by weight of Compound 1 in an aqueous medium that is one or more of release rates (a), (b) and (c) herein, wherein the composition comprises a first excipient and a second excipient, wherein the first excipient is

Poloxamer 188 and the second excipient is glycerol monostearate and has a monoester content of at least about 95%, wherein the ratio by weight of the first excipient to the second excipient is about 30:70, wherein the release rate is the release rate measured with USP Apparatus 2 (paddle) at 50 rpm in 500 mL of an aqueous medium at a temperature of 37°C ± 0.5 °C at a pH of about 6.8. In some embodiments, the aqueous medium is an aqueous medium comprising sodium phosphate at a concentration of 0.05 M.

In some embodiments, the present invention is directed to a process for the preparation of a pharmaceutical composition comprising Compound 1. The process in one embodiment comprises:

mixing a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof with a first excipient as disclosed herein, a second excipient as disclosed herein, and optionally an additional pharmaceutically acceptable excipient, to form the pharmaceutical composition.

In some embodiments, the pharmaceutical compositions herein are in the form of a capsule. In some embodiments, the pharmaceutical compositions herein are in the form of a tablet.

In some embodiments of the pharmaceutical compositions and/or the processes disclosed herein, the mixture comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, a first excipient as disclosed herein, and a second excipient as disclosed herein, may be formed in any order. For example, in some embodiments, formation of the mixture of the compound and the two excipients may comprise mixing the two excipients to form an initial mixture. The mixing of the two excipients may comprise melting the two excipients together. The initial mixture may be subsequently mixed with the compound to form the mixture of the compound and the two excipients.

In some embodiments provided herein is a pharmaceutical composition prepared by the process comprising:

curing a mixture comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, a first excipient, and a second excipient, wherein the first excipient comprises a copolymer comprising (a) a first polyoxyethylene chain; (b) a poly(propylene oxide) chain bonded to the first polyoxyethylene chain; and (c) a second polyoxyethylene chain bonded to the poly(propylene oxide) chain, and the second excipient comprises an ester of a polyalcohol and a fatty acid, to form the composition.

In some embodiments provided herein is a process for preparing a pharmaceutical composition, the process comprising:

curing a mixture comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, a first excipient, and a second excipient, wherein the first excipient comprises a copolymer comprising (a) a first polyoxyethylene chain; (b) a poly(propylene oxide) chain bonded to the first polyoxyethylene chain; and (c) a second polyoxyethylene chain bonded to the poly(propylene oxide) chain, and the second excipient comprises an ester of a polyalcohol and a fatty acid, to form the composition.

In some embodiments of the pharmaceutical composition and/or the process disclosed herein, curing a mixture is performed at a temperature of about 40°C to about 70°C, such as about 45°C to about 70°C, such as about 45°C to about 65°C, such as about 45°C to about 60°C, such as about 45°C to about 55°C, such as about 50°C to about 55°C, such as about 45°C, about 46°C, about 47°C, about 48°C, about 49°C, about 50°C, about 51°C, about 52°C, about 53°C, about 54°C, or about 55°C. The temperature at which curing the mixture is performed is also referred to as the curing temperature. The time for which curing the mixture at the curing temperature is performed is also referred to as the curing time. In some embodiments curing the mixture is performed for about 10 hours to about one week. In some embodiments curing the mixture is performed for about 10 hours to about 48 hours, such as for about 12 hours to about 36 hours, such as for about 16 hours to about 24 hours, such as for about 18 hours. In some embodiments curing the mixture is performed at a temperature of about 40°C to about 70°C, such as about 50°C to about 60°C, such as about 50°C or about 55°C, for about 10 hours to about 48 hours, such as for about 12 hours to about 36 hours, such as for about 16 hours to about 24 hours, such as for about 18 hours. In some embodiments curing the mixture is performed at a temperature of about 50°C for about 18 hours. In some embodiments curing the mixture is performed at a temperature of about 55°C for about 36 hours. In some embodiments curing the mixture is performed at a temperature of about 50°C to about 60°C, such as about 50°C or about 55°C, for about 10 hours to about 48 hours, such as for about 12 hours to about 36 hours, such as for about 16 hours to about 24 hours, such as for about 18 hours. In some embodiments curing the mixture is performed at a temperature of about 50°C for about 18 hours. In some embodiments curing the mixture is performed at a temperature of about 55°C for about 36 hours.

In some embodiments of the pharmaceutical compositions disclosed herein, at least one of the first excipient and the second excipient has a melting point of about 45°C to about 70°C. In some embodiments of the pharmaceutical compositions disclosed herein, at least one of the first excipient and the second excipient has a melting point of about 45°C to about 65°C. In some embodiments of the pharmaceutical compositions disclosed herein, at least one of the first excipient and the second excipient has a melting point of about 45°C to about 60°C. In some embodiments of the pharmaceutical compositions disclosed herein, at least one of the first excipient and the second excipient has a melting

point of about 45°C to about 55°C. In some embodiments of the pharmaceutical compositions disclosed herein, at least one of the first excipient and the second excipient has a melting point of about 50°C to about 60°C. In some embodiments of the pharmaceutical compositions disclosed herein, at least one of the first excipient and the second excipient has a melting point of about 50°C to about 55°C. In some embodiments of the pharmaceutical compositions disclosed herein, at least one of the first excipient and the second excipient has a melting point that is about 45°C, about 46°C, about 47°C, about 48°C, about 49°C, about 50°C, about 51°C, about 52°C, about 53°C, about 54°C, about 55°C, about 56°C, about 57°C, about 58°C, about 59°C, or about 60°C. In some embodiments, the first excipient and the second excipient each have a melting point that is independently about 45°C, about 46°C, about 47°C, about 48°C, about 49°C, about 50°C, about 51°C, about 52°C, about 53°C, about 54°C, or about 55°C.

In some embodiments of the pharmaceutical compositions disclosed herein, the composition is a cured composition. In some embodiments, the cured composition is a composition in which the compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, the first excipient, and the second excipient are cured together at a curing temperature as disclosed herein. In some embodiments, the cured composition is prepared by a process comprising curing the mixture as disclosed herein.

In some embodiments, curing the mixture results in a change in the Powder X-Ray Diffraction (PXRD) spectrum. In some embodiments, the pharmaceutical composition comprises the compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof; Poloxamer 188; and glycerol monostearate; wherein the composition exhibits peaks in the PXRD spectrum having the following 2θ values: 19.7°, 20.2°, 20.7°, 21.6°, 22.6°, 23.1° and 23.7°. In some embodiments, the composition exhibits peaks in the PXRD spectrum having the following 2θ values: 19.7°, 20.2°, 20.7°, 22.6°, 23.1° and 23.7°. Each of the PXRD peak values reported above values may vary by ± 0.2 2θ. In some embodiments of the composition having peaks in the PXRD spectrum as disclosed herein, the composition comprises glycerol monostearate having a monoester content of at least about 90%, such as at least about 95%. In some embodiments of the composition having peaks in the PXRD spectrum as disclosed herein, the composition comprises Poloxamer 188 and glycerol monostearate having a monoester content of at least about 90%, such as at least about 95%, in a ratio of Poloxamer 188:glycerol monostearate by weight that is about 70:30 to 10:90, such as 60:40 to about 20:80, such as about 50:50 to about 30:70, such as about 50:50, such as about 40:60, such as about 30:70.

In some embodiments, wherein the first excipient comprises a copolymer comprising (a) a first polyoxyethylene chain; (b) a poly(propylene oxide) chain bonded to the first polyoxyethylene chain; and

(c) a second polyoxyethylene chain bonded to the poly(propylene oxide) chain, the first excipient consists essentially of the copolymer.

In some embodiments, wherein the first excipient comprises Poloxamer 188, the first excipient consists essentially of Poloxamer 188.

In some embodiments, wherein the first excipient comprises a copolymer as defined herein, the first excipient is the copolymer.

In some embodiments, wherein the first excipient comprises Poloxamer 188, the first excipient is Poloxamer 188.

In some embodiments, wherein the second excipient comprises glycerol monostearate, the second excipient consists essentially of glycerol monostearate. For example, in some embodiments wherein the second excipient comprises glycerol monostearate and has a monoester content of at least about 50%, the second excipient consists essentially of glycerol monostearate and has a monoester content of at least about 50%. For example, in some embodiments wherein the second excipient comprises glycerol monostearate and has a monoester content of at least about 60%, such as at least about 70%, such as at least about 75%, such as at least about 80%, such as at least about 90%, such as at least about 95%, such as at least about 96%, such as at least about 97%, such as at least about 98%, such as at least about 99%, the second excipient consists essentially of glycerol monostearate and has a monoester content of at least about 60%, such as at least about 70%, such as at least about 75%, such as at least about 80%, such as at least about 90%, such as at least about 95%, such as at least about 96%, such as at least about 97%, such as at least about 98%, such as at least about 99%.

In some embodiments, wherein the second excipient comprises glycerol monostearate, the second excipient is glycerol monostearate. For example, in some embodiments wherein the second excipient comprises glycerol monostearate and has a monoester content of at least about 50%, the second excipient is glycerol monostearate having a monoester content of at least about 50%. For example, in some embodiments wherein the second excipient comprises glycerol monostearate and has a monoester content of at least about 60%, such as at least about 70%, such as at least about 75%, such as at least about 80%, such as at least about 90%, such as at least about 95%, such as at least about 96%, such as at least about 97%, such as at least about 98%, such as at least about 99%, the second excipient is glycerol monostearate having a monoester content of at least about 60%, such as at least about 70%, such as at least about 75%, such as at least about 80%, such as at least about 90%, such as at least about 95%, such as at least about 96%, such as at least about 97%, such as at least about 98%, such as at least about 99%.

In some embodiments provided herein is a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, a first excipient,

and a second excipient, wherein the first excipient comprises a copolymer comprising (a) a first polyoxyethylene chain; (b) a poly(propylene oxide) chain bonded to the first polyoxyethylene chain; and (c) a second polyoxyethylene chain bonded to the poly(propylene oxide) chain, and the second excipient comprises an ester of a polyalcohol and a fatty acid.

In some embodiments the present invention relates to a storage-stable pharmaceutical composition comprising compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof, as disclosed herein. "Storage-stable" as used herein means that the release rate of the compound is substantially the same after storage of the composition at 40°C and 75% RH. In some embodiments of the storage-stable composition, the release rate of the compound is substantially the same after storage at 40°C and 75% RH for at least about one month. In some embodiments of the storage-stable composition, the release rate of the compound is substantially the same after storage at 40°C and 75% RH for at least about six months. In some embodiments of the storage-stable composition, the release rate of the compound is substantially the same after storage at 25°C and 60% RH for at least about two years.

In some embodiments, the release rate of the compound after storage of the composition at 40°C and 75% RH for at least about one month does not vary at any given dissolution time point by more than about 20% of the release rate of the compound prior to storage. In some embodiments, the release rate of the compound after storage of the composition at 40°C and 75% RH for at least about one month does not vary at any given dissolution time point by more than about 20% of the release rate of the compound prior to storage, wherein the release rate after storage and prior to storage are each measured with USP Apparatus 1 (baskets) at 100 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C, wherein the aqueous medium comprises sodium phosphate at a concentration of 0.05 M. In some embodiments, the release rate of the compound after storage of the composition at 40°C and 75% RH for at least about one month does not vary at any given dissolution time point equal or greater than 2 hours by more than about 20% of the release rate of the compound prior to storage, wherein the release rate after storage and prior to storage are each measured with USP Apparatus 1 (baskets) at 100 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C, wherein the aqueous medium comprises sodium phosphate at a concentration of 0.05 M. In some embodiments, the release rate of the compound after storage of the composition at 40°C and 75% RH for at least about one month does not vary at any given dissolution time point equal or greater than 2 hours by more than about 10% of the release rate of the compound prior to storage, wherein the release rate after storage and prior to storage are each measured with USP Apparatus 1 (baskets) at 100 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C, wherein the aqueous medium comprises sodium phosphate at a

concentration of 0.05 M. In some embodiments, the release rate of the compound after storage of the composition at 40°C and 75% RH for at least about one month does not vary at any given dissolution time point by more than about 20% of the release rate of the compound prior to storage, wherein the release rate after storage and prior to storage are each measured with USP Apparatus 2 (paddle) at 50 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C, wherein the aqueous medium comprises sodium phosphate at a concentration of 0.05 M. In some embodiments, the release rate of the compound after storage of the composition at 40°C and 75% RH for at least about one month does not vary at any given dissolution time point equal or greater than 2 hours by more than about 20% of the release rate of the compound prior to storage, wherein the release rate after storage and prior to storage are each measured with USP Apparatus 2 (paddle) at 50 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C, wherein the aqueous medium comprises sodium phosphate at a concentration of 0.05 M. In some embodiments, the release rate of the compound after storage of the composition at 40°C and 75% RH for at least about one month does not vary at any given dissolution time point equal or greater than 2 hours by more than about 10% of the release rate of the compound prior to storage, wherein the release rate after storage and prior to storage are each measured with USP Apparatus 2 (paddle) at 50 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C, wherein the aqueous medium comprises sodium phosphate at a concentration of 0.05 M.

In some embodiments, the release rate of the compound after storage of the composition at 40°C and 75% RH for at least about six months does not vary at any given dissolution time point by more than about 20% of the release rate of the compound prior to storage. In some embodiments, the release rate of the compound after storage of the composition at 40°C and 75% RH for at least about six months does not vary at any given dissolution time point by more than about 20% of the release rate of the compound prior to storage, wherein the release rate after storage and prior to storage are each measured with USP Apparatus 1 (baskets) at 100 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C, wherein the aqueous medium comprises sodium phosphate at a concentration of 0.05 M. In some embodiments, the release rate of the compound after storage of the composition at 40°C and 75% RH for at least about six months does not vary at any given dissolution time point equal or greater than 2 hours by more than about 20% of the release rate of the compound prior to storage, wherein the release rate after storage and prior to storage are each measured with USP Apparatus 1 (baskets) at 100 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C, wherein the aqueous medium comprises sodium phosphate at a concentration of 0.05 M. In some embodiments, the release rate of the compound after storage of the composition at 40°C and 75% RH for at least about six months does not vary at any given dissolution time point equal or greater than 2 hours by more than about 10% of the release rate of the compound prior to storage, wherein the release rate after storage and prior to storage

are each measured with USP Apparatus 1 (baskets) at 100 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C, wherein the aqueous medium comprises sodium phosphate at a concentration of 0.05 M. In some embodiments, the release rate of the compound after storage of the composition at 40°C and 75% RH for at least about six months does not vary at any given dissolution time point by more than about 20% of the release rate of the compound prior to storage, wherein the release rate after storage and prior to storage are each measured with USP Apparatus 2 (paddle) at 50 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C, wherein the aqueous medium comprises sodium phosphate at a concentration of 0.05 M. In some embodiments, the release rate of the compound after storage of the composition at 40°C and 75% RH for at least about six months does not vary at any given dissolution time point equal or greater than 2 hours by more than about 20% of the release rate of the compound prior to storage, wherein the release rate after storage and prior to storage are each measured with USP Apparatus 2 (paddle) at 50 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C, wherein the aqueous medium comprises sodium phosphate at a concentration of 0.05 M. In some embodiments, the release rate of the compound after storage of the composition at 40°C and 75% RH for at least about six months does not vary at any given dissolution time point equal or greater than 2 hours by more than about 10% of the release rate of the compound prior to storage, wherein the release rate after storage and prior to storage are each measured with USP Apparatus 2 (paddle) at 50 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C, wherein the aqueous medium comprises sodium phosphate at a concentration of 0.05 M.

In some embodiments, the release rate of the compound after storage of the composition at 25°C and 60 RH for at least about two years does not vary at any given dissolution time point by more than about 20% of the release rate of the compound prior to storage. In some embodiments, the release rate of the compound after storage of the composition at 25°C and 60 RH for at least about two years does not vary at any given dissolution time point by more than about 20% of the release rate of the compound prior to storage, wherein the release rate after storage and prior to storage are each measured with USP Apparatus 1 (baskets) at 100 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C, wherein the aqueous medium comprises sodium phosphate at a concentration of 0.05 M. In some embodiments, the release rate of the compound after storage of the composition at 25°C and 60 RH for at least about two years does not vary at any given dissolution time point equal or greater than 2 hours by more than about 10% of the release rate of the compound prior to storage, wherein the release rate after storage and prior to storage are each measured with USP Apparatus 1 (baskets) at 100 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C, wherein the aqueous medium comprises sodium phosphate at a concentration of 0.05 M. In some embodiments, the release rate of the compound after storage of the composition at 25°C and 60 RH for at least about two years does not vary

at any given dissolution time point equal or greater than 2 hours by more than about 10% of the release rate of the compound prior to storage, wherein the release rate after storage and prior to storage are each measured with USP Apparatus 1 (baskets) at 100 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C, wherein the aqueous medium comprises sodium phosphate at a concentration of 0.05 M. In some embodiments, the release rate of the compound after storage of the composition at 25°C and 60 RH for at least about two years does not vary at any given dissolution time point by more than about 20% of the release rate of the compound prior to storage, wherein the release rate after storage and prior to storage are each measured with USP Apparatus 2 (paddle) at 50 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C, wherein the aqueous medium comprises sodium phosphate at a concentration of 0.05 M. In some embodiments, the release rate of the compound after storage of the composition at 25°C and 60 RH for at least about two years does not vary at any given dissolution time point equal or greater than 2 hours by more than about 20% of the release rate of the compound prior to storage, wherein the release rate after storage and prior to storage are each measured with USP Apparatus 2 (paddle) at 50 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C, wherein the aqueous medium comprises sodium phosphate at a concentration of 0.05 M. In some embodiments, the release rate of the compound after storage of the composition at 25°C and 60 RH for at least about two years does not vary at any given dissolution time point equal or greater than 2 hours by more than about 10% of the release rate of the compound prior to storage, wherein the release rate after storage and prior to storage are each measured with USP Apparatus 2 (paddle) at 50 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C, wherein the aqueous medium comprises sodium phosphate at a concentration of 0.05 M.

In some embodiments, the release rates disclosed herein are release rates as determined by HPLC.

In some embodiments, provided herein is a composition which is any of the tablet formulations disclosed herein, such as the tablet formulations disclosed in Table 4.

In some embodiments provided herein is an ester of Compound 1. In some embodiments provided herein is 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid, ethanol ester. In some embodiments provided herein is 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid, ethylene glycol ester. In some embodiments provided herein is 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid, glycerol ester. In some embodiments provided herein is 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid, polyethylene glycol ester.

In some embodiments provided herein is 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid, propylene glycol ester.

An example of a manufacturing process suitable for the pharmaceutical compositions disclosed herein is shown in Figure 2.

A compound or composition provided herein can be formulated into pharmaceutical compositions using techniques well known to those in the art. Suitable pharmaceutically-acceptable carriers, outside those mentioned herein, are known in the art; for example, see Remington, *The Science and Practice of Pharmacy*, 20th Edition, 2000, Lippincott Williams & Wilkins, (Editors: Gennaro *et al.*).

Certain compounds described herein can be asymmetric (e.g., having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present invention that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically active starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis.

Resolution of racemic mixtures of compounds can be carried out by any of numerous methods known in the art. An example method includes fractional recrystallization (for example, diastereomeric salt resolution) using a "chiral resolving acid" which is an optically active, salt-forming organic acid. Suitable resolving agents for fractional recrystallization methods are, for example, optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids such as β-camphorsulfonic acid. Other resolving agents suitable for fractional crystallization methods include stereoisomerically pure forms of β-methylbenzylamine (e.g., S and R forms, or diastereomerically pure forms), 2-phenylglycinol, norephedrine, ephedrine, N-methylephedrine, cyclohexylethylamine, 1,2-diaminocyclohexane, and the like.

Resolution of racemic mixtures can also be carried out by elution on a column packed with an optically active resolving agent (e.g., dinitrobenzoylphenylglycine). Suitable elution solvent composition can be determined by one skilled in the art.

Compounds described herein can also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include tritium and deuterium.

Compounds described herein can also include tautomeric forms, such as keto-enol tautomers. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution.

It is appreciated that certain features disclosed herein, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment.

Conversely, various features which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination.

INDICATIONS AND METHODS OF TREATMENT

The compositions disclosed herein are useful in the treatment of diseases and disorders related to modulation of PGI2 receptor activity, and in the amelioration of symptoms thereof. Accordingly, some embodiments of the present invention relate to a method of modulating the activity of a PGI2 receptor by contacting the receptor with a composition according to any of the embodiments described herein.

In some embodiments provided herein is a method of agonizing a PGI2 receptor by contacting the receptor with composition according to any of the embodiments described herein.

In some embodiments provided herein is a method for the treatment of a PGI2 receptor mediated disorder in an individual, comprising administering to the individual in need thereof, a composition according to any of the embodiments described herein.

In some embodiments provided herein is a composition according to any of the embodiments described herein, for use in a method of treatment of the human or animal body by therapy.

In some embodiments provided herein is a composition according to any of the embodiments described herein, for use in a method of modulating the activity of a PGI2 receptor.

In some embodiments provided herein is a composition according to any of the embodiments described herein, for use in a method of agonizing a PGI2 receptor.

In some embodiments provided herein is a composition according to any of the embodiments described herein, for use in a method of treatment of a PGI2 receptor mediated disorder.

The compositions disclosed herein are useful in the treatment of other diseases and disorders related to modulation of PGI2 receptor activity, and in the amelioration of symptoms thereof, without limitation, these include the following:

1. Pulmonary Arterial Hypertension (PAH)

Pulmonary arterial hypertension (PAH) has a multifactorial pathobiology. Vasoconstriction, remodeling of the pulmonary vessel wall, and thrombosis contribute to increased pulmonary vascular resistance in PAH (Humbert et al, J. Am. Coll. Cardiol, 2004, 43:13S-24S.)

The pharmaceutical compositions of the present invention disclosed herein are useful in the treatment of pulmonary arterial hypertension (PAH) and symptoms thereof. PAH shall be understood to encompass the following forms of pulmonary arterial hypertension described in the 2003 World Health Organization (WHO) clinical classification of pulmonary arterial hypertension: idiopathic PAH (IPAH); familial PAH (FPAH); PAH associated with other conditions (APAH), such as PAH associated with

collagen vascular disease, PAH associated with congenital systemic-to-pulmonary shunts, PAH associated with portal hypertension, PAH associated with HIV infection, PAH associated with drugs or toxins, or PAH associated with Other; and PAH associated with significant venous or capillary involvement.

Idiopathic PAH refers to PAH of undetermined cause.

Familial PAH refers to PAH for which hereditary transmission is suspected or documented.

PAH associated with collagen vascular disease shall be understood to encompass PAH associated with scleroderma, PAH associated with CREST (calcinosis cutis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasias) syndrome, PAH associated with systemic lupus erythematosus (SLE), PAH associated with rheumatoid arthritis, PAH associated with Takayasu's arteritis, PAH associated with polymyositis, and PAH associated with dermatomyositis.

PAH associated with congenital systemic-to-pulmonary shunts shall be understood to encompass PAH associated with atrial septic defect (ASD), PAH associated with ventricular septic defect (VSD) and PAH associated with patent ductus arteriosus.

PAH associated with drugs or toxins shall be understood to encompass PAH associated with ingestion of aminorex, PAH associated with ingestion of a fenfluramine compound (e.g., PAH associated with ingestion of fenfluramine or PAH associated with ingestion of dexfenfluramine), PAH associated with ingestion of certain toxic oils (e.g., PAH associated with ingestion of rapeseed oil), PAH associated with ingestion of pyrrolizidine alkaloids (e.g., PAH associated with ingestion of bush tea) and PAH associated with ingestion of monocrotaline.

PAH associated with Other shall be understood to encompass PAH associated with a thyroid disorder, PAH associated with glycogen storage disease, PAH associated with Gaucher disease, PAH associated with hereditary hemorrhagic telangiectasia, PAH associated with a hemoglobinopathy, PAH associated with a myeloproliferative disorder, and PAH associated with splenectomy.

PAH associated with significant venous or capillary involvement shall be understood to encompass PAH associated with pulmonary veno-occlusive disease (PVOD) and PAH associated with pulmonary capillary hemangiomatosis (PCH).

(See, e.g., Simonneau et al, J. Am. Coll. Cardiol, 2004, 43:5S-12S; McGoon et al, Chest, 2004, 126:14S-34S; Rabinovitch, Annu. Rev. Pathol. Mech. Dis, 2007, 2:369-399; McLaughlin et al, Circulation, 2006, 114:1417-1431; Strauss et al, Clin. Chest. Med, 2007, 28:127-142; Taichman et al, Clin. Chest. Med, 2007, 28:1-22.)

Evidence for the association of PAH with scleroderma and the beneficial effect of an agonist of the PGI2 receptor on PAH is given by Badesch et al. (Badesch et al, Ann. Intern. Med, 2000, 132:425-434). Evidence for the association of PAH with the collagen vascular diseases mixed connective tissue

disease (MCTD), systemic lupus erythematosus (SLE), Sjögren's syndrome and CREST syndrome and the beneficial effect of an agonist of the PGI2 receptor on PAH is given by Humbert et al. (Eur. Respir. J, 1999, 13:1351-1356). Evidence for the association of PAH with CREST syndrome and the beneficial effect of an agonist of the PGI2 receptor on PAH is given by Miwa et al. (Int. Heart J, 2007, 48:417-422). Evidence for the association of PAH with SLE and the beneficial effect of an agonist of the PGI2 receptor on PAH is given by Robbins et al. (Chest, 2000, 117:14-18). Evidence for the association of PAH with HIV infection and the beneficial of an agonist of the PGI2 receptor on PAH is given by Aguilar et al. (Am. J. Respir. Crit. Care Med, 2000, 162:1846-1850). Evidence for the association of PAH with congenital heart defects (including ASD, VSD and patent ductus arteriosus) and the beneficial effect of an agonist of the PGI2 receptor on PAH is given by Rosenzweig et al. (Circulation, 1999, 99:1858-1865). Evidence for the association of PAH with fenfluramine and with dexfenfluramine, anorexigens, is given by Archer et al. (Am. J. Respir. Crit. Care Med, 1998, 158:1061-1067). Evidence for the association of PAH with hereditary hemorrhagic telangiectasia is given by McGoon et al. (Chest, 2004, 126:14-34). Evidence for the association of PAH with splenectomy is given by Hoeper et al. (Ann. Intern. Med, 1999, 130:506-509). Evidence for the association of PAH with portal hypertension and the beneficial effect of an agonist of the PGI2 receptor on PAH is given by Hoeper et al. (Eur. Respir. J, 2005, 25:502-508).

Symptoms of PAH include dyspnea, angina, syncope and edema (McLaughlin et al, Circulation, 2006, 114:1417-1431). The pharmaceutical compositions of the present invention disclosed herein are useful in the treatment of symptoms of PAH.

In some embodiments provided herein is a method for the treatment of pulmonary arterial hypertension (PAH) in an individual, comprising administering to the individual in need thereof, a composition according to any of the embodiments described herein.

In some embodiments provided herein is a method for the treatment of idiopathic PAH in an individual, comprising administering to the individual in need thereof, a composition according to any of the embodiments described herein.

In some embodiments provided herein is a method for the treatment of familial PAH in an individual, comprising administering to the individual in need thereof, a composition according to any of the embodiments described herein.

In some embodiments provided herein is a method for the treatment of PAH associated with a collagen vascular disease in an individual, comprising administering to the individual in need thereof, a composition according to any of the embodiments described herein.

In some embodiments provided herein is a method for the treatment of PAH associated with a collagen vascular disease selected from: scleroderma, CREST syndrome, systemic lupus erythematosus (SLE), rheumatoid arthritis, Takayasu's arteritis, polymyositis, and dermatomyositis in an individual,

comprising administering to the individual in need thereof, a composition according to any of the embodiments described herein.

In some embodiments provided herein is a method for the treatment of PAH associated with a congenital heart disease in an individual, comprising administering to the individual in need thereof, a composition according to any of the embodiments described herein.

In some embodiments provided herein is a method for the treatment of PAH associated with a congenital heart disease selected from: atrial septic defect (ASD), ventricular septic defect (VSD) and patent ductus arteriosus in an individual, comprising administering to the individual in need thereof, a composition according to any of the embodiments described herein.

In some embodiments provided herein is a method for the treatment of PAH associated with portal hypertension in an individual, comprising administering to the individual in need thereof, a composition according to any of the embodiments described herein.

In some embodiments provided herein is a method for the treatment of PAH associated with HIV infection in an individual, comprising administering to the individual in need thereof, a composition according to any of the embodiments described herein.

In some embodiments provided herein is a method for the treatment of PAH associated with ingestion of a drug or toxin in an individual, comprising administering to the individual in need thereof, a composition according to any of the embodiments described herein.

In some embodiments provided herein is a method for the treatment of PAH associated with hereditary hemorrhagic telangiectasia in an individual, comprising administering to the individual in need thereof, a composition according to any of the embodiments described herein.

In some embodiments provided herein is a method for the treatment of PAH associated with splenectomy in an individual, comprising administering to the individual in need thereof, a composition according to any of the embodiments described herein.

In some embodiments provided herein is a method for the treatment of PAH associated with significant venous or capillary involvement in an individual, comprising administering to the individual in need thereof, a composition according to any of the embodiments described herein.

In some embodiments provided herein is a method for the treatment of PAH associated with pulmonary veno-occlusive disease (PVOD) in an individual, comprising administering to the individual in need thereof, a composition according to any of the embodiments described herein.

In some embodiments provided herein is a method for the treatment of PAH associated with pulmonary capillary hemangiomatosis (PCH) in an individual, comprising administering to the individual in need thereof, a composition according to any of the embodiments described herein.

In some embodiments provided herein is a composition according to any of the embodiments described herein, for use in a method of treatment of PAH.

In some embodiments provided herein is a composition according to any of the embodiments described herein, for use in a method of treatment of idiopathic PAH.

In some embodiments provided herein is a composition according to any of the embodiments described herein, for use in a method of treatment of familial PAH.

In some embodiments provided herein is a composition according to any of the embodiments described herein, for use in a method of treatment of PAH associated with a collagen vascular disease.

In some embodiments provided herein is a composition according to any of the embodiments described herein, for use in a method of treatment of PAH associated with a collagen vascular disease selected from: scleroderma, CREST syndrome, systemic lupus erythematosus (SLE), rheumatoid arthritis, Takayasu's arteritis, polymyositis, and dermatomyositis.

In some embodiments provided herein is a composition according to any of the embodiments described herein, for use in a method of treatment of PAH associated with a congenital heart disease.

In some embodiments provided herein is a composition according to any of the embodiments described herein, for use in a method of treatment of PAH associated with a congenital heart disease selected from: atrial septic defect (ASD), ventricular septic defect (VSD) and patent ductus arteriosus.

In some embodiments provided herein is a composition according to any of the embodiments described herein, for use in a method of treatment of PAH associated with portal hypertension.

In some embodiments provided herein is a composition according to any of the embodiments described herein, for use in a method of treatment of PAH associated with HIV infection.

In some embodiments provided herein is a composition according to any of the embodiments described herein, for use in a method of treatment of PAH associated with ingestion of a drug or toxin.

In some embodiments provided herein is a composition according to any of the embodiments described herein, for use in a method of treatment of PAH associated with hereditary hemorrhagic telangiectasia.

In some embodiments provided herein is a composition according to any of the embodiments described herein, for use in a method of treatment of PAH associated with splenectomy.

In some embodiments provided herein is a composition according to any of the embodiments described herein, for use in a method of treatment of PAH associated with significant venous or capillary involvement.

In some embodiments provided herein is a composition according to any of the embodiments described herein, for use in a method of treatment of PAH associated with pulmonary veno-occlusive disease (PVOD).

In some embodiments provided herein is a composition according to any of the embodiments described herein, for use in a method of treatment of PAH associated with pulmonary capillary hemangiomatosis (PCH).

2. Antiplatelet Therapies (Conditions related to platelet aggregation)

Antiplatelet agents (antiplatelets) are prescribed for a variety of conditions. For example, in coronary artery disease they are used to help prevent myocardial infarction or stroke in patients who are at risk of developing obstructive blood clots (e.g., coronary thrombosis).

In a myocardial infarction ("MI" or "heart attack"), the heart muscle does not receive enough oxygen-rich blood as a result of a blockage in the coronary blood vessels. If taken while an attack is in progress or immediately afterward (preferably within 30 min), antiplatelets can reduce the damage to the heart.

A transient ischemic attack ("TIA" or "mini-stroke") is a brief interruption of oxygen flow to the brain due to decreased blood flow through arteries, usually due to an obstructing blood clot. Antiplatelet drugs have been found to be effective in preventing TIAs.

Angina is a temporary and often recurring chest pain, pressure or discomfort caused by inadequate oxygen-rich blood flow (ischemia) to some parts of the heart. In patients with angina, antiplatelet therapy can reduce the effects of angina and the risk of myocardial infarction.

Stroke is an event in which the brain does not receive enough oxygen-rich blood, usually due to blockage of a cerebral blood vessel by a blood clot. In high-risk patients, taking antiplatelets regularly has been found to prevent the formation of blood clots that cause first or second strokes.

Angioplasty is a catheter based technique used to open arteries obstructed by a blood clot. Whether or not stenting is performed immediately after this procedure to keep the artery open, antiplatelets can reduce the risk of forming additional blood clots following the procedure(s).

Coronary bypass surgery is a surgical procedure in which an artery or vein is taken from elsewhere in the body and grafted to a blocked coronary artery, rerouting blood around the blockage and through the newly attached vessel. After the procedure, antiplatelets can reduce the risk of secondary blood clots.

Atrial fibrillation is the most common type of sustained irregular heart rhythm (arrhythmia). Atrial fibrillation affects about two million Americans every year. In atrial fibrillation, the atria (the heart's upper chambers) rapidly fire electrical signals that cause them to quiver rather than contract normally. The result is an abnormally fast and highly irregular heartbeat. When given after an episode of atrial fibrillation, antiplatelets can reduce the risk of blood clots forming in the heart and traveling to the brain (embolism).

There is evidence that a PGI2 receptor agonist will inhibit platelet aggregation and thus be a potential treatment as an antiplatelet therapy (see, e.g., Moncada et al, Lancet, 1977, 1:18-20). It has been shown that genetic deficiency of the PGI2 receptor in mice leads to an increased propensity towards thrombosis (Murata et al, Nature, 1997, 388:678-682).

PGI2 receptor agonists can be used to treat, for example, claudication or peripheral artery disease as well as cardiovascular complications, arterial thrombosis, atherosclerosis, vasoconstriction caused by serotonin, ischemia-reperfusion injury, and restenosis of arteries following angioplasty or stent placement. (See, e.g., Fetalvero et al, Prostaglandins Other Lipid Mediat, 2007, 82:109-118; Arehart et al, Curr. Med. Chem, 2007, 14:2161-2169; Davi et al, N. Engl. J. Med, 2007, 357:2482-2494; Fetalvero et al, Am. J. Physiol. Heart. Circ. Physiol, 2006, 290:H1337-H1346; Murata et al, Nature, 1997, 388:678-682; Wang et al, Proc. Natl. Acad. Sci. USA, 2006, 103:14507-14512; Xiao et al, Circulation, 2001, 104:2210-2215; McCormick et al, Biochem. Soc. Trans, 2007, 35:910-911; Arehart et al, Circ. Res, 2008, Mar 6 Epub ahead of print.)

PGI2 receptor agonists can also be used alone or in combination with thrombolytic therapy, for example, tissue-type plasminogen activator (t-PA), to provide cardioprotection following MI or postischemic myocardial dysfunction or protection from ischemic injury during percutaneous coronary intervention, and the like, including complications resulting therefrom. PGI2 receptor agonists can also be used in antiplatelet therapies in combination with, for example, alpha-tocopherol (vitamin E), echistatin (a disintegrin) or, in states of hypercoagulability, heparin. (See, e.g., Chan, J. Nutr, 1998, 128:1593-1596; Mardla et al, Platelets, 2004, 15:319-324; Bernabei et al, Ann. Thorac. Surg, 1995, 59:149-153; Gainza et al, J. Nephrol, 2006, 19:648-655.)

The PGI2 receptor agonists disclosed herein provide beneficial improvement in microcirculation to patients in need of antiplatelet therapy by antagonizing the vasoconstrictive products of the aggregating platelets in, for example and not limited to the indications described above. Accordingly, in some embodiments, the present invention provides methods for reducing platelet aggregation in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof as disclosed herein. In further embodiments, the present invention provides methods for treating coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, or a symptom of any of the foregoing in a patient in need of the treatment, comprising administering to the patient a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-

chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof as disclosed herein.

In further embodiments, the present invention provides methods for reducing risk of blood clot formation in an angioplasty or coronary bypass surgery patient, or a patient suffering from atrial fibrillation, comprising administering to the patient a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof as disclosed herein at a time where such risk exists.

In some embodiments provided herein is a method for the treatment of platelet aggregation in an individual, comprising administering to the individual in need thereof, a composition according to any of the embodiments described herein.

In some embodiments provided herein is a method for the treatment of: coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, ischemia-reperfusion injury, restenosis or atrial fibrillation in an individual, comprising administering to the individual in need thereof, a composition according to any of the embodiments described herein.

In some embodiments provided herein is a method for reducing the risk of blood clot formation in an angioplasty or coronary bypass surgery individual comprising administering to the individual in need thereof, a composition according to any of the embodiments described herein.

In some embodiments provided herein is a method for reducing the risk of blood clot formation in an individual suffering from atrial fibrillation comprising administering to the individual in need thereof, a composition according to any of the embodiments described herein.

In some embodiments provided herein is a composition according to any of the embodiments described herein, for use in a method of treatment of platelet aggregation.

In some embodiments provided herein is a composition according to any of the embodiments described herein, for use in a method of treatment of: coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, ischemia-reperfusion injury, restenosis or atrial fibrillation.

In some embodiments provided herein is a composition according to any of the embodiments described herein, for use in a method for the treatment of blood clot formation in an angioplasty or coronary bypass surgery individual.

In some embodiments provided herein is a composition according to any of the embodiments described herein, for use in a method for the treatment of blood clot formation in an individual suffering from atrial fibrillation.

3. Atherosclerosis

Atherosclerosis is a complex disease characterized by inflammation, lipid accumulation, cell death and fibrosis. It is the leading cause of mortality in many countries, including the United States. Atherosclerosis, as the term is used herein, shall be understood to encompass disorders of large and medium-sized arteries that result in the progressive accumulation within the intima of smooth muscle cells and lipids.

It has been shown that an agonist of the PGI2 receptor can confer protection from atherosclerosis, such as from atherothrombosis (Arehart et al, Curr. Med. Chem, 2007, 14:2161-2169; Stitham et al, Prostaglandins Other Lipid Mediat, 2007, 82:95-108; Fries et al, Hematology Am. Soc. Hematol. Educ. Program, 2005, :445-451; Egan et al, Science, 2004, 306:1954-1957; Kobayashi et al, J. Clin. Invest, 2004, 114:784-794; Arehart et al, Circ. Res, 2008, Mar 6 Epub ahead of print).

It has been shown that defective PGI2 receptor signaling appears to accelerate atherothrombosis in humans, i.e. that an agonist of the PGI2 receptor can confer protection from atherothrombosis in humans (Arehart et al, Circ. Res, 2008, Mar 6 Epub ahead of print).

The pharmaceutical compositions of the present invention disclosed herein are useful in the treatment of atherosclerosis, and the treatment of the symptoms thereof. Accordingly, in some embodiments, the present invention provides methods for treating atherosclerosis in a patient in need of the treatment, comprising administering to the patient a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof as disclosed herein. In further embodiments, methods are provided for treating a symptom of atherosclerosis in a patient in need of the treatment, comprising administering to the patient a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof as disclosed herein.

In some embodiments provided herein is a method for the treatment of atherosclerosis in an individual, comprising administering to the individual in need thereof, a composition according to any of the embodiments described herein.

In some embodiments provided herein is a method for the treatment of atherothrombosis in an individual, comprising administering to the individual in need thereof, a composition according to any of the embodiments described herein.

In some embodiments provided herein is a composition according to any of the embodiments described herein, for use in a method of treatment of atherosclerosis.

In some embodiments provided herein is a composition according to any of the embodiments described herein, for use in a method of treatment of atherothrombosis.

4. Asthma

Asthma is a lymphocyte-mediated inflammatory airway disorder characterized by airway eosinophilia, increased mucus production by goblet cells, and structural remodeling of the airway wall. The prevalence of asthma has dramatically increased worldwide in recent decades. It has been shown that genetic deficiency of the PGI2 receptor in mice augments allergic airway inflammation (Takahashi et al, Br J Pharmacol, 2002, 137:315-322). It has been shown that an agonist of the PGI2 receptor can suppress not only the development of asthma when given during the sensitization phase, but also the cardinal features of experimental asthma when given during the challenge phase (Idzko et al, J. Clin. Invest, 2007, 117:464-472; Nagao et al, Am. J. Respir. Cell Mol. Biol, 2003, 29:314-320), at least in part through markedly interfering with the function of antigen-presenting dendritic cells within the airways (Idzko et al, J. Clin. Invest, 2007, 117:464-472; Zhou et al, J. Immunol, 2007, 178:702-710; Jaffar et al, J. Immunol, 2007, 179:6193-6203; Jozefowski et al, Int. Immunopharmacol, 2003, 3:865-878). These cells are crucial for both the initiation and the maintenance phases of allergic asthma, as depletion of airway dendritic cells during secondary challenge in sensitized mice abolished all characteristic features of asthma, an effect that could be completely restored by adoptive transfer of wild-type dendritic cells (van Rijt et al, J. Exp. Med, 2005, 201:981-991). It has also been shown that an agonist of the PGI2 receptor can inhibit proinflammatory cytokine secretion by human alveolar macrophages (Raychaudhuri et al, J. Biol. Chem, 2002, 277:33344-33348). The pharmaceutical compositions of the present invention disclosed herein are useful in the treatment of asthma, and the treatment of the symptoms thereof. Accordingly, in some embodiments, the present invention provides methods for treating asthma in a patient in need of the treatment, comprising administering to the patient a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof as disclosed herein. In further embodiments, methods are provided for treating a symptom of asthma in a patient in need of the treatment, comprising administering to the patient a pharmaceutical composition comprising a compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof as disclosed herein. In some embodiments provided herein is a method for the treatment of asthma in an individual, comprising administering to the individual in need thereof, a composition according to any of the embodiments described herein.

In some embodiments provided herein is a method for the treatment of a symptom of asthma in an individual, comprising administering to the individual in need thereof, a composition according to any of the embodiments described herein.

In some embodiments provided herein is a composition according to any of the embodiments described herein, for use in a method of treatment of asthma.

In some embodiments provided herein is a composition according to any of the embodiments described herein, for use in a method of treatment of a symptom of asthma.

5. Diabetic-Related Pathologies

Although hyperglycemia is the major cause for the pathogenesis of diabetic complications such as diabetic peripheral neuropathy (DPN), diabetic nephropathy (DN) and diabetic retinopathy (DR), enhanced vasoconstriction and platelet aggregation in diabetic patients has also been implicated to play a role in disease progression (Cameron et al, Naunyn Schmiedebergs Arch. Pharmacol, 2003, 367:607-614). Agonists of the PGI2 receptor promote vasodilation and inhibit platelet aggregation. Improving microvascular blood flow is able to benefit diabetic complications (Cameron, Diabetologia, 2001, 44:1973-1988).

It has been shown that an agonist of the PGI2 receptor can prevent and reverse motor and sensory peripheral nerve conduction abnormalities in streptozotocin-diabetic rats (Cotter et al, Naunyn Schmiedebergs Arch. Pharmacol, 1993, 347:534-540). Further evidence for the beneficial effect of an agonist of the PGI2 receptor in the treatment of diabetic peripheral neuropathy is given by Hotta et al. (Diabetes, 1996, 45:361-366), Ueno et al. (Jpn. J. Pharmacol, 1996, 70:177-182), Ueno et al. (Life Sci, 1996, 59:PL105-PL110), Hotta et al. (Prostaglandins, 1995, 49:339-349), Shindo et al. (Prostaglandins, 1991, 41:85-96), Okuda et al. (Prostaglandins, 1996, 52:375-384), and Koike et al. (FASEB J, 2003, 17:779-781). Evidence for the beneficial effect of an agonist of the PGI2 receptor in the treatment of diabetic nephropathy is given by Owada et al. (Nephron, 2002, 92:788-796) and Yamashita et al. (Diabetes Res. Clin. Pract, 2002, 57:149-161). Evidence for the beneficial effect of an agonist of the PGI2 receptor in the treatment of diabetic retinopathy is given by Yamagishi et al. (Mol. Med, 2002, 8:546-550), Burnette et al. (Exp. Eye Res, 2006, 83:1359-1365), and Hotta et al. (Diabetes, 1996, 45:361-366). It has been shown that an agonist of the PGI2 receptor can reduce increased tumor necrosis factor-α (TNF-α) levels in diabetic patients, implying that an agonist of the PGI2 receptor may contribute to the prevention of progression in diabetic complications (Fujiwara et al, Exp. Clin. Endocrinol. Diabetes, 2004, 112:390-394).

In some embodiments provided herein is a method for the treatment of a diabetic-related disorder in an individual, comprising administering to the individual in need thereof, a composition according to any of the embodiments described herein.

In some embodiments provided herein is a method for the treatment of diabetic peripheral neuropathy in an individual, comprising administering to the individual in need thereof, a composition according to any of the embodiments described herein.

In some embodiments provided herein is a method for the treatment of diabetic nephropathy in an individual, comprising administering to the individual in need thereof, a composition according to any of the embodiments described herein.

In some embodiments provided herein is a method for the treatment of diabetic retinopathy in an individual, comprising administering to the individual in need thereof, a composition according to any of the embodiments described herein.

In some embodiments provided herein is a composition according to any of the embodiments described herein, for use in a method of treatment of a diabetic-related disorder.

In some embodiments provided herein is a composition according to any of the embodiments described herein, for use in a method of treatment of diabetic peripheral neuropathy.

In some embodiments provided herein is a composition according to any of the embodiments described herein, for use in a method of treatment of diabetic nephropathy.

In some embodiments provided herein is a composition according to any of the embodiments described herein, for use in a method of treatment of diabetic retinopathy.

6. Glaucoma

Evidence that topical administration of an agonist of the PGI2 receptor can result in a decrease in intraocular pressure (IOP) in rabbits and dogs and thereby have beneficial effect in the treatment of glaucoma is given by Hoyng et al. (Hoyng et al, Invest. Ophthalmol. Vis. Sci, 1987, 28:470-476).

In some embodiments provided herein is a method for the treatment of glaucoma or other disease of the eye with abnormal intraocular pressure in an individual, comprising administering to the individual in need thereof, a composition according to any of the embodiments described herein.

In some embodiments provided herein is a composition according to any of the embodiments described herein, for use in a method of treatment of glaucoma or other disease of the eye with abnormal intraocular pressure.

7. Hypertension

Agonists of the PGI2 receptor have been shown to have activity for regulation of vascular tone, for vasodilation, and for amelioration of pulmonary hypertension (see, e.g., Strauss et al, Clin Chest Med, 2007, 28:127-142; Driscoll et al, Expert Opin. Pharmacother, 2008, 9:65-81). Evidence for a beneficial effect of an agonist of the PGI2 receptor in the treatment of hypertension is given by Yamada et al. (Peptides, 2008, 29:412-418). Evidence that an agonist of the PGI2 receptor can protect against cerebral

ischemia is given by Dogan et al. (Gen. Pharmacol, 1996, 27:1163-1166) and Fang et al. (J. Cereb. Blood Flow Metab, 2006, 26:491-501).

In some embodiments provided herein is a method for the treatment of hypertension in an individual, comprising administering to the individual in need thereof, a composition according to any of the embodiments described herein.

In some embodiments provided herein is a method for the treatment of hypertension intended to confer protection against cerebral ischemia in an individual, comprising administering to the individual in need thereof, a composition according to any of the embodiments described herein.

In some embodiments provided herein is a composition according to any of the embodiments described herein, for use in a method of treatment of hypertension.

In some embodiments provided herein is a composition according to any of the embodiments described herein, for use in a method of treatment of hypertension intended to confer protection against cerebral ischemia.

8. Anti-Inflammation Therapies

Anti-inflammation agents are prescribed for a variety of conditions. For example, in an inflammatory disease they are used to interfere with and thereby reduce an underlying deleterious There is evidence that a PGI2 receptor agonist can inhibit inflammation and thus be a potential treatment as an anti-inflammation therapy. It has been shown that an agonist of the PGI2 receptor can inhibit pro-inflammatory cytokine and chemokine (interleukin-12 (IL-12), tumor necrosis factor-α (TNF-α), IL-1α, IL-6, macrophage inflammatory protein-1alpha (MIP-1α), monocyte chemoattractant protein-1 (MCP-1)) production and T cell stimulatory function of dendritic cells (Jozefowski et al, Int. Immunopharmacol, 2003, 865-878; Zhou et al, J. Immunol, 2007, 178:702-710; Nagao et al, Am. J. Respir. Cell Mol. Biol, 2003, 29:314-320; Idzko et al, J. Clin. Invest, 2007, 117:464-472). It has been shown that an agonist of the PGI2 receptor can inhibit pro-inflammatory cytokine (TNF-α, IL-1β, IL-6, granulocyte macrophage stimulating factor (GM-CSF)) production by macrophages (Raychaudhuri et al, J. Biol. Chem, 2002, 277:33344-33348; Czeslick et al, Eur. J. Clin. Invest, 2003, 33:1013-1017; Di Renzo et al, Prostaglandin Leukot. Essent. Fatty Acids, 2005, 73:405-410; Shinomiya et al, Biochem. Pharmacol, 2001, 61:1153-1160). It has been shown that an agonist of the PGI2 receptor can stimulate anti-inflammatory cytokine (IL-10) production by dendritic cells (Jozefowski et al, Int. Immunopharmacol, 2003, 865-878; Zhou et al, J. Immunol, 2007, 178:702-710). It has been shown that an agonist of the PGI2 receptor can stimulate anti-inflammatory cytokine (IL-10) production by macrophages (Shinomiya et al, Biochem. Pharmacol, 2001, 61:1153-1160). It has been shown that an agonist of the PGI2 receptor can inhibit a chemokine (CCL17)-induced chemotaxis of leukocytes ($CD4^+$ Th2 T cells) (Jaffar et al, J. Immunol, 2007, 179:6193-6203). It has been shown that an agonist of the PGI2 receptor can confer protection from atherosclerosis,

such as from atherothrombosis (Arehart et al, Curr. Med. Chem, 2007, 14:2161-2169; Stitham et al, Prostaglandins Other Lipid Mediat, 2007, 82:95-108; Fries et al, Hematology Am. Soc. Hematol. Educ. Program, 2005, :445-451; Egan et al, Science, 2004, 306:1954-1957; Kobayashi et al, J. Clin. Invest, 2004, 114:784-794; Arehart et al, Circ. Res, 2008, Mar 6 Epub ahead of print). It has been shown that an agonist of the PGI2 receptor can attenuate asthma (Idzko et al, J. Clin. Invest, 2007, 117:464-472; Jaffar et al, J. Immunol, 2007, 179:6193-6203; Nagao et al, Am. J. Respir. Cell. Mol. Biol, 2003, 29:314-320). It has been shown that an agonist of the PGI2 receptor can decrease TNF-α production in type 2 diabetes patients (Fujiwara et al, Exp. Clin. Endocrinol. Diabetes, 2004, 112:390-394; Goya et al, Metabolism, 2003, 52:192-198). It has been shown that an agonist of the PGI2 receptor can inhibit ischemia-reperfusion injury (Xiao et al, Circulation, 2001, 104:2210-2215). It has been shown that an agonist of the PGI2 receptor can inhibit restenosis (Cheng et al, Science, 2002, 296:539-541). It has been shown that an agonist of the PGI2 receptor can attenuate pulmonary vascular injury and shock in a rat model of septic shock (Harada et al, Shock, 2008, Feb 21 Epub ahead of print). It has been shown that an agonist of the PGI2 receptor can reduce the serum levels of TNF-α in vivo in patients with rheumatoid arthritis, and this is associated with improvement in the clinical course of the disease (Gao et al, Rheumatol. Int, 2002, 22:45-51; Boehme et al, Rheumatol. Int, 2006, 26:340-347).

The pharmaceutical compositions of the present invention disclosed herein provide beneficial reduction of inflammation. The pharmaceutical compositions of the present invention disclosed herein provide beneficial reduction of a deleterious inflammatory response associated with an inflammatory disease. Accordingly, in some embodiments, the present invention provides methods for reducing inflammation in a patient in need thereof, comprising administering to the patient a pharmaceutical composition as disclosed herein. In some embodiments, the present invention provides methods for decreasing IL-12, TNF-α, IL-1α, IL-1β, IL-6, MIP-1α or MCP-1 production in a patient in need thereof, comprising administering to the patient a pharmaceutical composition as disclosed herein. In some embodiments, the present invention provides methods for decreasing TNF-α production in a patient in need thereof, comprising administering to the patient a pharmaceutical composition as disclosed herein. In some embodiments, the present invention provides methods for increasing IL-10 production in a patient in need thereof, comprising administering to the patient a pharmaceutical composition as disclosed herein. In some embodiments, the present invention provides methods for reducing a deleterious inflammatory response associated with an inflammatory disease in a patient in need thereof, comprising administering to the patient a pharmaceutical composition as disclosed herein. In some embodiments, the present invention provides methods for treating an inflammatory disease or a symptom thereof in a patient in need of the treatment comprising administering to the patient a pharmaceutical composition as disclosed herein. In some embodiments, the present invention provides methods for treating an

inflammatory disease or a symptom thereof in a patient in need of the treatment comprising administering to the patient a pharmaceutical composition as disclosed herein. In some embodiments, the present invention provides methods for treating an inflammatory disease or a symptom thereof in a patient in need of the treatment comprising administering to the patient a pharmaceutical composition as disclosed herein, wherein the inflammatory disease is selected from the group consisting of psoriasis, psoriatic arthritis, rheumatoid arthritis, Crohn's disease, transplant rejection, multiple sclerosis, systemic lupus erythematosus (SLE), ulcerative colitis, ischemia-reperfusion injury, restenosis, atherosclerosis, acne, diabetes (including type 1 diabetes and type 2 diabetes), sepsis, chronic obstructive pulmonary disease (COPD), and asthma.

In some embodiments provided herein is a method for the treatment of inflammation in an individual, comprising administering to the individual in need thereof, a composition according to any of the embodiments described herein.

In some embodiments provided herein is a method for the treatment of an inflammatory disease in an individual, comprising administering to the individual in need thereof, a composition according to any of the embodiments described herein.

In some embodiments provided herein is a method for the treatment of an inflammatory disease selected from: psoriasis, psoriatic arthritis, rheumatoid arthritis, Crohn's disease, transplant rejection, multiple sclerosis, systemic lupus erythematosus (SLE), ulcerative colitis, ischemia-reperfusion injury, restenosis, atherosclerosis, acne, type 1 diabetes, type 2 diabetes, sepsis, chronic obstructive pulmonary disorder (COPD) and asthma in an individual, comprising administering to the individual in need thereof, a composition according to any of the embodiments described herein.

In some embodiments provided herein is a composition according to any of the embodiments described herein, for use in a method of treatment of inflammation.

In some embodiments provided herein is a composition according to any of the embodiments described herein, for use in a method of treatment of an inflammatory disease.

In some embodiments provided herein is a composition according to any of the embodiments described herein, for use in a method of treatment of an inflammatory disease selected from: psoriasis, psoriatic arthritis, rheumatoid arthritis, Crohn's disease, transplant rejection, multiple sclerosis, systemic lupus erythematosus (SLE), ulcerative colitis, ischemia-reperfusion injury, restenosis, atherosclerosis, acne, type 1 diabetes, type 2 diabetes, sepsis, chronic obstructive pulmonary disorder (COPD) and asthma.

The dose when using the compositions of the present invention can vary within wide limits and as is customary and is known to the physician, it is to be tailored to the individual conditions in each individual case. It depends, for example, on the nature and severity of the illness to be treated, on the

condition of the patient, on the compound employed or on whether an acute or chronic disease state is treated or prophylaxis conducted or on whether further active compounds are administered in addition to the pharmaceutical composition as disclosed herein. Multiple doses may be administered during the day, especially when relatively large amounts are deemed to be needed, for example 2, 3 or 4 doses. Depending on the individual and as deemed appropriate from the patient's physician or caregiver it may be necessary to deviate upward or downward from the doses described herein.

The amount of active ingredient, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will ultimately be at the discretion of the attendant physician or clinician. In general, one skilled in the art understands how to extrapolate in vivo data obtained in a model system, typically an animal model, to another, such as a human. In some circumstances, these extrapolations may merely be based on the weight of the animal model in comparison to another, such as a mammal, preferably a human, however, more often, these extrapolations are not simply based on weights, but rather incorporate a variety of factors. Representative factors include the type, age, weight, sex, diet and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized, on whether an acute or chronic disease state is being treated or prophylaxis conducted or on whether further active compounds are administered in addition to the compounds of the present invention and as part of a drug combination. The dosage regimen for treating a disease condition with the compounds and/or compositions of this invention is selected in accordance with a variety factors as cited above. Thus, the actual dosage regimen employed may vary widely and therefore may deviate from a preferred dosage regimen and one skilled in the art will recognize that dosage and dosage regimen outside these typical ranges can be tested and, where appropriate, may be used in the methods of this invention.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations. The daily dose can be divided, especially when relatively large amounts are administered as deemed appropriate, into several, for example 2, 3 or 4 part administrations. If appropriate, depending on individual behavior, it may be necessary to deviate upward or downward from the daily dose indicated.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation.

The compositions disclosed herein are not intended for use in humans only, but in non-human mammals as well. Recent advances in the area of animal health-care mandate that consideration be given for the use of active agents, such as Compound 1, for the treatment of a PGI2-receptor associated disease or disorder in companionship animals (e.g., cats, dogs, etc.) and in livestock animals (e.g., horses, cows, etc.). Those of ordinary skill in the art are readily credited with understanding the utility of such compounds in such settings.

COMBINATION THERAPY

In some embodiments, the at least one compound according to any of the compound embodiments disclosed herein is administered in combination with at least one known pharmaceutical agent. Administration of the at least one compound and the at least one known pharmaceutical agent can occur simultaneously or sequentially by the same or different routes of administration.

In some embodiments, the at least one known pharmaceutical agent is administered to the patient prior to initiation of the administration of the at least one compound. In some embodiments, the at least one known pharmaceutical agent is administered for at least one week, or at least two weeks, or at least three weeks, or at least one month, or at least two months, or at least three months prior to initiation of the administration of the at least one compound.

The suitability of a particular route of administration employed for a particular known pharmaceutical agent will depend on the known pharmaceutical agent itself (*e.g.*, whether it can be administered orally or topically without decomposition prior to entering the blood stream) and the subject being treated. Particular routes of administration for the known pharmaceutical agents or ingredients are known to those of ordinary skill in the art.

The amount of known pharmaceutical agent administered can be determined based on the specific agent used, the subject being treated, the severity and stage of disease and the amount(s) of the at least one compound and any optional additional known pharmaceutical agents concurrently administered to the patient. The at least one known pharmaceutical agent, when employed in combination with at least one compound according to any of the compounds embodiment disclosed herein, may be used, for example, in those amounts indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

In some embodiments, the dose of the at least one known pharmaceutical agent is reduced when used in combination with the at least one compound according to any of the compound embodiments disclosed herein. In some embodiments, the dose is not reduced.

Some embodiments of the present invention include a method of producing a pharmaceutical composition for “combination therapy” comprising admixing at least one compound according to any of

the compound embodiments disclosed herein together with at least one known pharmaceutical agent as described herein and a pharmaceutically acceptable carrier.

In some embodiments, the at least one known pharmaceutical agent is an oral disease-specific PAH therapy. In some embodiments, the oral disease-specific PAH therapy is chosen from an ERA and/or an agent acting on the NO pathway including the following: a PDE-5 inhibitor and a sGC stimulator.

In some embodiments, the subject had been receiving a stable dose of oral disease-specific PAH therapy for least three months prior to initiation of administration of the at least one compound described herein.

In some embodiments, the at least one known pharmaceutical agent is chosen from vasodilators (including calcium channel blockers), digoxin, spironolactone, and L-arginine supplementation. In some embodiments, the subject had been receiving a stable dose of the at least one known pharmaceutical agent for least one month prior to initiation of administration of the at least one compound described herein. In some embodiments, the dose of the spironolactone and/or the digoxin were held or reduced.

In some embodiments, the at least one known pharmaceutical is a diuretic.

In some embodiments, the at least one known pharmaceutical agent is a PDE-5 inhibitor.

In some embodiments, the at least one known pharmaceutical agent is for supportive therapy, such as diuretics, antihypertensives, antithrombotic agents, beta blocking agents, and cardiac medications.

In some embodiments, the at least one known pharmaceutical agent is a PAH disease-specific medication chosen from ambrisentan, bosentan, macitentan, riociguat, sildenafil, sildenafil citrate, and tadalafil.

In some embodiments, the at least one known pharmaceutical agent is an antithrombotic agent chosen from acenocoumarol, acetylsalicylic acid, warfarin, enoxaparin sodium, apixaban, dalteparin, heparin sodium, nadroparin calcium, sulodexide, and ticagrelor.

In some embodiments, the at least one known pharmaceutical agent is an agent acting on the renin-angiotensin system chosen from enalapril, lisinopril, valsartan, hyzaar, perindopril arginine, ramipril, and zestoretic.

In some embodiments, the at least one known pharmaceutical agent is a beta blocking agent chosen from bisoprolol, nebivolol, bisoprolol fumarate, metoprolol, metoprolol succinate, and nadolol.

In some embodiments, the at least one known pharmaceutical agent is a calcium channel blocker chosen from nifedipine, felodipine, verapamil, amlodipine, amlodipine besilate, and diltiazem.

In some embodiments, the at least one known pharmaceutical agent is an agent for cardiac therapy chosen from digoxin, ivabradine, norepinephrine, amiodarone, amiodarone hydrochloride, atropine, dobutamine, epinephrine, trimetazidine, and trimetazidine hydrochloride.

In some embodiments, the at least one compound according to any of the compound embodiments disclosed herein is not administered in combination with intravenous inotropes.

In some embodiments, the at least one compound according to any of the compound embodiments disclosed herein is not administered in combination the chronic administration (such as >30 days) of a prostacyclin or prostacyclin analogue.

In some embodiments, the at least one known pharmaceutical agent is not a cAMP-elevating agent, or a cGMP-elevating agent, such as a soluble guanylate cyclase (sGC) stimulators such as riociguat.

In some embodiments, the at least one known pharmaceutical agent is not riociguat, vericiguat, ataciguat, nelociguat, lificiguat, IW-1701, IW-1973, IWP-051, IWP-121, IWP-427, IWP-953, BAY-60-2770, A-344905, A-350619, A-778935, BI-684067, BI-703704, BAY-41-2272, or BAY-41-8543.

In some embodiments, the at least one known pharmaceutical agent is not a prostanoid, such as treprostinil or iloprost.

In some embodiments, the at least one known pharmaceutical agent is not a prostacyclin receptor agonist.

HYDRATES AND SOLVATES

The term "hydrate" as used herein means a compound or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of water bound by non-covalent intermolecular forces. The term "solvate" as used herein means a compound or a salt, thereof, that further includes a stoichiometric or non-stoichiometric amount of a solvent bound by non-covalent intermolecular forces. Preferred solvents are volatile, non-toxic, and/or acceptable for administration to humans in trace amounts.

It is understood that when the phrase "pharmaceutically acceptable salts, solvates, and hydrates" or the phrase "pharmaceutically acceptable salt, solvate, or hydrate" is used when referring to compounds described herein, it embraces pharmaceutically acceptable solvates and/or hydrates of the compounds, pharmaceutically acceptable salts of the compounds, as well as pharmaceutically acceptable solvates and/or hydrates of pharmaceutically acceptable salts of the compounds. It is also understood that when the phrase "pharmaceutically acceptable solvates and hydrates" or the phrase "pharmaceutically acceptable solvate or hydrate" is used when referring to salts described herein, it embraces pharmaceutically acceptable solvates and/or hydrates of such salts.

It will be apparent to those skilled in the art that the compositions described herein may comprise, as the active component, either a compound described herein or a pharmaceutically acceptable salt or as a pharmaceutically acceptable solvate or hydrate thereof. Moreover, various hydrates and solvates of the compounds described herein and their salts will find use as intermediates in the manufacture of

pharmaceutical compositions. Typical procedures for making and identifying suitable hydrates and solvates, outside those mentioned herein, are well known to those in the art; see for example, pages 202-209 of K.J. Guillory, "Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids," in: Polymorphism in Pharmaceutical Solids, ed. Harry G. Britain, Vol. 95, Marcel Dekker, Inc, New York, 1999. Accordingly, one aspect of the present invention is directed to methods of administering pharmaceutical composition comprising hydrates and solvates of compounds described herein and/or their pharmaceutical acceptable salts, that can be isolated and characterized by methods known in the art, such as, thermogravimetric analysis (TGA), TGA-mass spectroscopy, TGA-Infrared spectroscopy, powder X-ray diffraction (XRPD), Karl Fisher titration, high resolution X-ray diffraction, and the like. There are several commercial entities that provide quick and efficient services for identifying solvates and hydrates on a routine basis. Example companies offering these services include Wilmington PharmaTech (Wilmington, DE), Avantium Technologies (Amsterdam) and Aptuit (Greenwich, CT).

CRYSTALLINE FORMS

Polymorphism is the ability of a substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice. Polymorphs show the same properties in the liquid or gaseous state but they behave differently in the solid state.

Besides single-component polymorphs, drugs can also exist as salts and other multicomponent crystalline phases. For example, solvates and hydrates may contain an API host and either solvent or water molecules, respectively, as guests. Analogously, when the guest compound is a solid at room temperature, the resulting form is often called a cocrystal. Salts, solvates, hydrates, and cocrystals may show polymorphism as well. Crystalline phases that share the same API host, but differ with respect to their guests, may be referred to as pseudopolymorphs of one another.

Solvates contain molecules of the solvent of crystallization in a definite crystal lattice. Solvates, in which the solvent of crystallization is water, are termed hydrates. Because water is a constituent of the atmosphere, hydrates of drugs may be formed rather easily and may be thermodynamically favored over anhydrous polymorphs.

By way of example, Stahly recently published a polymorph screen of 245 compounds consisting of a "wide variety of structural types" that revealed about 90% of the compounds exhibited multiple solid forms. Overall, approximately half the compounds were polymorphic, often having one to three forms. About one-third of the compounds formed hydrates, and about one-third formed solvates. Data from cocrystal screens of 64 compounds showed that 60% formed cocrystals other than hydrates or solvates (G. P. Stahly, Crystal Growth & Design (2007), 7(6), 1007-1026).

Crystalline forms can be identified by their unique solid state signatures with respect to, for example, differential scanning calorimetry (DSC), X-ray powder diffraction (PXRD), and other solid state methods. Further characterization with respect to water or solvent content of the crystalline forms of the present invention can be gauged by any of the following methods for example, thermogravimetric analysis (TGA), DSC and the like. For DSC, it is known that the temperatures corresponding to thermal events observed will depend upon sample purity, the rate of temperature change, as well as sample preparation technique and the particular instrument employed.

A crystalline form of Compound 1 and of certain salts thereof is disclosed in WO 2009/117095 (incorporated by reference herein in its entirety). In some embodiments, the pharmaceutical compositions disclosed herein comprise Compound 1 in a crystalline form having a PXRD spectrum with 2θ peak values as disclosed in WO 2009/117095.

PXRD may also be used to analyze the effect of curing on the pharmaceutical compositions disclosed herein. PXRD spectra disclosed herein were obtained with a Phillips X'Pert PRO MPD powder diffractometer using Cu-Kα radiation. For PXRD purposes, the composition is reduced to powder using a razor blade. The powder was then loaded onto a sample plate and smoothed flat using weighing paper and a spatula.

Figure 7a discloses a Powder X-Ray Diffraction spectra of a capsule comprising Poloxamer 188 and food grade GMS in a 50:50 ratio by weight (i) before curing, and (ii) after curing at 50°C for 18 hours. Prior to curing, the Poloxamer 188 PXRD spectrum includes peaks at 2θ values of about 19.3° and about 23.5°, while the food grade GMS PXRD spectrum includes a broad peak at a 2θ value of about 21.6°. The PXRD spectrum of the pharmaceutical composition after curing for 18 hours shows (a) a 21.6° 2θ peak of reduced intensity relative to prior to curing, and (b) peaks at 2θ values of 19.7°, 20.2°, 20.7°, 22.6°, 23.1° and 23.7° peaks. Each of the PXRD peak values reported above values may vary by ± 0.2 2θ.

Figure 7b shows a Powder X-Ray Diffraction spectra of a capsule comprising Poloxamer 188 and research grade GMS in a 50:50 ratio by weight (i) before curing, and (ii) after curing at 50°C for 18 hours. The 2θ values of the PXRD peaks of the pharmaceutical composition after curing for 18 hours do not substantially differ from the 2θ values of the Poloxamer 188 PXRD and of the research grade GMS PXRD prior to curing.

Under certain conditions, curing is partial, as indicated by the resulting PXRD. Figure 7c shows three Powder X-Ray Diffraction spectra of capsules comprising Poloxamer 188 and research grade GMS in a 50:50 ratio by weight (i) before curing ("uncured"), (ii) after partial curing at 47.5°C for 10 hours ("partially cured"), and (iii) after curing at 50°C for 18 hours ("fully cured"). Referring to (ii), following

partial curing, peaks at 2θ values of 20.2°, 20.7° appear. A peak at a 2θ value of 21.6°, also present in (i), is still visible in (ii).

OTHER UTILITIES

Other uses of the disclosed compositions will become apparent to those skilled in the art based upon, *inter alia*, a review of this disclosure.

As will be recognized, the steps of the methods of the present invention need not be performed any particular number of times or in any particular sequence. Additional objects, advantages and novel features of this invention will become apparent to those skilled in the art upon examination of the following examples thereof, which are intended to be illustrative and not intended to be limiting.

EXAMPLES

The pharmaceutical compositions disclosed herein and their preparation are further illustrated by the following examples. The following examples are provided to further define the invention without, however, limiting the invention to the particulars of these examples. The compounds described herein, *supra* and *infra*, are named according to the CS ChemDraw Ultra Version 7.0.1, AutoNom version 2.2, CS ChemDraw Ultra Version 9.0.7, or CS ChemDraw Ultra Version 12.0. In certain instances, common names are used and it is understood that these common names would be recognized by those skilled in the art.

Preparation of Liquid-filled Hard-gelatin Capsules.

In selecting excipients for Compound 1, several factors were taken into consideration with the ultimate goal of choosing excipients suitable for later-stage formulation development. Criteria based on solubility, compatibility, viscosity, and stability are outlined below. In addition, selected excipients should preferably have proven safety profiles and USP/NF monographs to allow for compendial release testing. Furthermore, these excipients should have precedence in being commercially used in other products and be produced in quantities sufficient for late-stage clinical trials and commercialization.

Comparative Example 1.

Immediate-release formulation.

Immediate-release formulations may be prepared, for example, in a manner analogous to that described in Figure 2. A suitable excipient for immediate-release (IR) formulations is Kolliphor® RH40. An immediate-release (IR) formulation containing Kolliphor® RH40 in which Compound 1 is present in the amounts of 0.01 mg, 0.02 mg, 0.03 mg, 0.04 mg, or 0.1 mg is described in the following Table 1:

Table 1

	mg/capsule

Component	Grade	Function	0.01 mg	0.02 mg	0.03 mg	0.04 mg	0.1 mg
Compound 1		Drug substance	0.01	0.02	0.03	0.04	0.10
Polyoxyl 40 hydrogenated castor oil (Kolliphor® RH40)	USP/NF	Excipient	148.46	148.45	148.44	148.43	148.37
Butylated hydroxytoluene (BHT)	USP/NF	Antioxidant	0.03	0.03	0.03	0.03	0.03
Colloidal silicon dioxide	USP/NF	Thickening agent	1.50	1.50	1.50	1.50	1.50
Fill weight			150.00	150.00	150.00	150.00	150.00
Hard-gelatin capsule[a] (white, Licaps®)	Capsugel® internal	Capsule shell	38.00	38.00	38.00	38.00	38.00
Total capsule target weight[b]			188.00	188.00	188.00	188.00	188.00

[a] Approximate weight. Based on capsule specification.

[b] Theoretical total weight calculated by combining fill and empty capsule weights together.

Figure 1 shows a release profile for an immediate release capsule having 0.5 mg of Compound 1; 0.03 mg BHT; 1.50 mg silicon dioxide; and 147.97 mg Kolliphor® RH40.

Example 1. Modified-release Compositions - Capsules

A desirable feature of a modified-release composition is a stable release profile, i.e., in which the release rate of the drug does not vary substantially over time. For example, a desirable feature is a release rate that does not vary substantially over a time period during which the drug is in storage. Accordingly, various combinations of excipients were tested with the goal of obtaining a composition having a release rate of Compound 1 that would be stable over time.

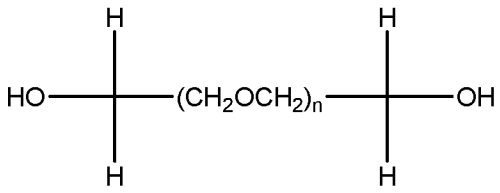
An example of a suitable composition is a composition in the form of a capsule. An example of hard-gelatin capsule is shown in Table 2.

Table 2

Size 2 Licaps® Specifications	
Weight (mg)	61 ± 4
Capacity (mL)	0.33
Length of capsule body (mm)	15.27 ± 0.46
Length of capsule cap (mm)	8.94 ± 0.46
External diameter of capsule body (mm)	6.07
External diameter of capsule cap (mm)	6.35
Overall closed length (mm)	18.0 ± 0.3

Example 2: Preparation of Capsules containing Modified Release Compositions containing Gelucire® 50/13.

Gelucire® 50/13, having a melting point of about 50°C and hydrophilic-lipophilic balance of 13 (also known as Stearoyl polyoxyl-32 glycerides, hydrogenated palm oil PEG-32 esters, PEG glyceryl stearate, and stearoyl polyoxylglycerides) is an excipient prepared via the reaction of hydrogenated palm oil with PEG 1500. Its composition is about 20% mono-, di- & tri-glycerides, about 72% mono- and di-fatty acid esters of PEG 1500, and about 8% PEG 1500, wherein PEG 1500 as used herein refers to the following:



(n = between about 28 and about 36)

PEG 1500.

Modified-release compositions containing Gelucire® 50/13 that were tested were analogous to the one described in Table 1 of comparative Example 1, except that in this Example 2, (a) Gelucire® 50/13 was used, in increasing amounts, in addition to Kolliphor® RH40, and (b) colloidal silicon dioxide was not required as a thickening agent in the compositions of this Example. Colloidal silicon dioxide was present at a level of about 1% w/w in the composition of Table 1 to minimize the potential of capsule leakage for the Kolliphor® RH40 capsules. Since Gelucire® 50/13 is a wax at ambient temperatures, the use of colloidal silicon dioxide was not required in the modified-release compositions of this Example 2.

The resulting release profiles are shown in Figure 3. Unless otherwise specified, the release profiles for capsules were measured using USP Apparatus 2 (paddle). As Figure 3 clearly shows, Gelucire® 50/13 modifies the release rate of Compound 1 relative an immediate release composition. In particular, the release rates were substantially reduced from an immediate release composition (left-most plot in Figure 3) to the composition having a 50:50 ratio of Gelucire® 50/13 to Kolliphor® RH40 (second plot from the left in Figure 3 – data points are indicated with circles). The release rate was further reduced from the composition having a 80:20 ratio of Gelucire® 50/13 to Kolliphor® RH40 to the composition having a 90:10 ratio (for the latter data points are indicated with squares in Figure 3).

The release profile was found to change following storage over time. In particular, as shown in Figure 4, the release rate of Compound 1 significantly increased after storage at 40°C and 75% RH over time. Similarly, a composition of 0.04 mg of Compound 1 in Gelucire® 50/13 exhibited a rapid increase in release rate of Compound 1 after storage at 40°C and 75% RH for two weeks, as shown in Figure 5.

In view of the change in the release profile of the composition over time various factors were considered in an attempt to stabilize the release rate of compositions containing Gelucire® 50/13. These included:

- improving the mixing of the components of the composition;
- adding Gelucire® 50/13 directly as a solid to melted Kolliphor RH40;
- utilizing only previously unheated raw materials;
- evaluating the impact of the following additives upon dissolution: BHT, SiO_2, TiO_2, Talc, & HMPC;
- evaluating the effect of varying cure time & temperature;
- preheating the fill medium of the capsule at 70 to 80°C to eliminate any "trace" solids

None of these attempts were successful in overcoming the problem of the increase in the release rate of Compound 1 after storage.

The following excipients were then evaluated for their release properties and stability of the release rate over time:

- Poloxamer 188
- PEG6000
- HPMC E5
- Gelucire 44/14
- Gelucire 43/01
- HMPC K4M
- Compritol 888 ATO
- Precirol ATO 5
- HPMC E50
- Geleol
- Glycerol Monostearate (GMS)
- Stearic Acid
- Beeswax
- Cetyl Alcohol
- Stearyl Alcohol
- Poloxamer 407
- Poloxamer 338
- Cetostearyl Alcohol
- Carboxymethylcellulose (CMC)

Following this evaluation, Poloxamer 188 and GMS were chosen for further study.

Example 3: Preparation and Testing of Capsules Containing Modified-Release Compositions Containing Poloxamer 188 and Food Grade GMS.

Table 3a below shows three exemplary embodiments of the composition, Capsules A, B and C. The capsules differ in the ratios of the two excipients Poloxamer 188 and food grade GMS. Capsule A has a Poloxamer 188:food grade GMS ratio of 70:30. Capsule B has a Poloxamer 188:food grade GMS ratio of 50:50. Capsule C has a Poloxamer 188:food grade GMS ratio of 30:70.

Table 3a

			mg/capsule		
Component	**Grade**	**Function**	**Capsule A**	**Capsule B**	**Capsule C**
Compound 1		Drug substance	0.030	0.030	0.030
Glycerol Monostearate (GMS)	Food Grade	Excipient	104.979	74.985	44.991
Poloxamer 188	NF	Excipient	44.991	74.985	104.979
Fill weight			150.000	150.000	150.000
Hard-gelatin capsule[a] (white, Licaps®)	Capsugel® internal	Capsule shell	38.00	38.00	38.00
Total capsule target weight[b]			188.00	188.00	188.00

a. Approximate weight. Based on capsule specification.

b. Theoretical total weight calculated by combining fill and empty capsule weights together.

The pharmaceutical composition was in a size 4 gelatin capsule without sealing. No additional coatings were applied. No silicon dioxide was added to the composition. Since the composition was a hard wax at room temperature, it was not necessary to take measures to avoid leaking such as adding silicon dioxide and/or performing band-sealing. The capsules of Table 3a were prepared according to a manufacturing process as disclosed herein, such as the process schematically shown in Figure 2. Similarly, capsules analogous to the capsule of Table 3a, having a total of fill weight of 150.000 mg, may be prepared analogously according to a manufacturing process as disclosed herein. In such capsules the weight of Compound 1 may be, for example, about 0.01 mg, about 0.02 mg, about 0.03 mg, about 0.04 mg, about 0.05 mg, about 0.06 mg, about 0.07 mg, about 0.08 mg, about 0.09 mg, about 0.1 mg, 0.12 mg, about 0.2 mg, about 0.3 mg, or about 0.5 mg, or about 0.6 mg of Compound 1, and the Poloxamer 188:glycerol monostearate ratio by weight is about 70:30 to 10:90, such as 60:40 to about 20:80, such as about 50:50 to about 30:70, such as about 50:50, such as about 40:60, such as about 30:70.

An exemplary preparation of a capsule containing 0.12 mg of Compound 1 is as follows:

419.66g of Myverol™ 18-04 K and 179.86 g of Poloxamer 188 are weighed into a 1L stainless steel beaker. The beaker is placed onto a hot plate stirrer and covered with a heating mantle and foil. An overhead stirrer with a 2'' 4 blade impeller is placed into the stainless steel beaker approximately 1cm from the bottom of the beaker. The hotplate is set for 90°C and the hotplate and heating mantle are adjusted until a constant temperature of 90±5°C is maintained. The beaker is purged with nitrogen gas. Purging and heating are maintained overnight to melt the mixture. The overhead stirrer is set to 270 rpm and stirring is initiated. The hotplate temperature is adjusted to a constant temperature of 72.5 ± 2.5°C. 0.4800g of Compound 1 are weighed in a tare boat and added directly into the vortex of the stainless steel beaker to form a mixture. The 1L stainless steel beaker is purged with nitrogen gas and covered with aluminum foil. The overhead stirrer is set to 270 rpm and the contents are stirred for a minimum of 30 minutes. A vacuum oven (previously left overnight to reach the desired temperature) is adjusted to a temperature of 72.5°C± 2.5°C. The stainless-steel beaker is transferred into the oven. The mixture is de-gassed for a minimum of 2 hours.

The beaker is placed back onto the hot plate stirrer, purged with nitrogen and stirred at 270 rpm adjusting the hotplate temperature to a constant value of 72.5 ± 2.5°. Based on a trial weighing, the volume of an Autorep E pipette is set to dispense 150mg of the mixture. The mixture is transferred from the beaker to a size 4, white opaque capsule using the Autorep pipette and a pre-warmed, primed Teflon-wrapped pipette tip. The transfer is repeated until the desired number of capsules is filled. Once the mixture in each capsule is congealed, each capsule cap is pressed onto the body of the capsule until it locks into place.

A zip lock bag containing the capsules is transferred into an oven pre-set at 50°C. The capsules are laid flat and spread evenly and kept in the oven for 36 hours – 38 hours.

Capsules containing various ratios of Poloxamer 188 to food grade GMS by weight were found to be cured in separate runs at the following conditions:
Composition containing Poloxamer 188 and food grade GMS in a 70:30 ratio by weight

Run	Temperature	Time(s)
1	47.5°C	18 hrs
2	50°C	27 hrs
3a	52.5°C	18 hrs
3b	52.5°C	39 hrs
3c	52.5°C	10 hrs

4a	55°C	27 hrs
4b	55°C	10 hrs

Composition containing Poloxamer 188 and food grade GMS in a 50:50 ratio by weight

Run	Temperature	Time(s)
1	40°C	1 week
2a	50°C	18 hrs
2b	50°C	39 hrs
3	52.5°C	27 hrs
4a	55°C	18 hrs
4b	55°C	39 hrs

Composition containing Poloxamer 188 and food grade GMS in a 30:70 ratio by weight

Run	Temperature	Time(s)
1	50°C	27 hrs
2a	52.5°C	18 hrs
2b	52.5°C	39 hrs
2c	52.5°C	10 hrs
3a	55°C	27 hrs
3b	55°C	10 hrs

Figure 6 shows release profiles for 0.04 mg of Compound 1 in a capsule containing Poloxamer 188 and food grade GMS in a 50:50 ratio by weight. Curing the pharmaceutical composition stabilized the release profile, as shown by the fact that the release profile following curing for 18 hours was different from the initial release profile (lowest plot in the figure) and remained substantially the same at one week, two weeks, and four weeks post-curing (Figure 6, remaining four plots in the figure). This is also shown in the following Table 3b. The table shows that the % of Compound 1 released remained substantially the same for compositions following curing for 18 hours and compositions stored subsequently over varying periods of time.

Table 3b. Release rate (percentage of Compound 1 released over time) at T=0 (pre-curing), 18 hrs (curing), 1 week (storage), 2 weeks (storage) and 4 weeks (storage)

Time (min)	T=0	18 hrs (50°C)	1 wk (40°C)	2 wks (40°C)	4 wks (40°C)
30	11.0	14.3	11.1	10.8	7.3
60	18.3	21.8	22.6	18.3	17.7
120	30.1	39.9	40.1	36.8	37.4

Time (min)	T=0	18 hrs (50°C)	1 wk (40°C)	2 wks (40°C)	4 wks (40°C)
180	39.6	56.3	59.2	52.9	54.6
240	48.8	72.6	71.8	67.4	70.3
360	64.1	89.2	88.4	83.3	87.5
480	72.7	93.5	92.2	90.3	90.9
600	79.8	95.7	96.2	93.8	93.2
720	83.1	96.9	95.3	93.7	95.0
735	84.6	95.6	96.1	94.3	94.3

For the curing to be effective in stabilizing the release profile, food grade glycerol monostearate (food grade GMS) was found to be suitable. When research grade GMS, which has a lower monoester content, was used, curing was not as effective in stabilizing the release profile.

The release profiles of pharmaceutical compositions containing Poloxamer 188 and food grade GMS in a 70:30 ratio, a 50:50 ratio, and a 30:70 ratio by weight, each with 0.5 mg of Compound 1, are shown in Figures 8, 9, and 10, respectively. Figures 8-10 shows that the respective compositions provided a release of Compound 1 at a slower rate than the immediate-release composition shown in Figure 1 in the left-most plot of Figure 3. The compositions of Figures 8-10 also provided a release of Compound 1 at a rate that was substantially the same after storage at 40°C and 75% RH for about one month, unlike the modified-release compositions of Figures 4 and 5.

Further examples of release rates (% by weight) are shown in Tables 3c – 3p. All release profiles disclosed in Tables 3c-3p were measured with USP Apparatus 2 (paddle) at 50 rpm in 500 mL of aqueous sodium phosphate at a concentration of 0.05 M (pH = 6.8). The values in a given table relate to capsules obtained from the same batch. Values shown represent mean values over a number of dissolution tests ("n" in each table) in each case.

Table 3c – % of Compound 1 that is released for size 4 capsule containing 0.03 mg of Compound 1 and Poloxamer 188:food grade GMS 70:30 (ratio by weight) – total weight of Poloxamer 188 plus food grade GMS = 149.97 mg

	20*	30*	45*	60*	90*	120*
mean value (n = 6) of % of Compound 1 released	14.8	36.1	65.4	83.8	95.5	98.4
%RSD**	44.8	38.3	29.7	24.4	15.8	9.6

*time in minutes
**RSD as a percentage of mean value of % of Compound 1 released

Table 3d – % of Compound 1 that is released for size 4 capsule containing 0.5mg of Compound 1 and Poloxamer 188:food grade GMS 70:30 (ratio by weight) – total weight of Poloxamer 188 plus food grade GMS = 149.5 mg

	30*	60*	120*
mean value (n = 4) of % of Compound 1 released	13.8	60.2	92.1
%RSD**	42.4	8.5	8.5

*time in minutes
**RSD as a percentage of mean value of % of Compound 1 released

Table 3e – % of Compound 1 that is released for size 4 capsule containing 0.5 mg of Compound 1 and Poloxamer 188:food grade GMS 70:30 (ratio by weight) – total weight of Poloxamer 188 plus food grade GMS = 149.5 mg

	30*	60*	120*
mean value (n = 4) of % of Compound 1 released	17.7	56.9	95.1
%RSD**	79.1	31.5	6.7

*time in minutes
**RSD as a percentage of mean value of % of Compound 1 released

Table 3f – % of Compound 1 that is released for size 4 capsule containing 0.5mg of Compound 1 and Poloxamer 188:food grade GMS 70:30 (ratio by weight) – total weight of Poloxamer 188 plus food grade GMS = 149.5 mg

	30*	60*	120*
mean value (n = 4) of % of Compound 1 released	19.3	61.9	98.1
%RSD**	74.7	42.7	2.5

*time in minutes
**RSD as a percentage of mean value of % of Compound 1 released

Table 3g-1 – Storage Time = 0: % of Compound 1 that is released for size 4 capsule containing 0.5mg of Compound 1 and Poloxamer 188:food grade GMS 70:30 (ratio by weight) – total weight of Poloxamer 188 plus food grade GMS = 149.5 mg

	30*	45*	60*
mean value (n = 4) of % of Compound 1 released	33.0	64.2	86.0
%RSD**	56.4	32.4	19.6

*time in minutes
**RSD as a percentage of mean value of % of Compound 1 released

Table 3g-2 – Storage Time = 2 weeks: % of Compound 1 that is released for size 4 capsule containing 0.5mg of Compound 1 and Poloxamer 188:food grade GMS 70:30 (ratio by weight) – total weight of Poloxamer 188 plus food grade GMS = 149.5 mg

	30*	45*	60*
mean value (n = 4) of % of Compound 1 released	33.0	64.2	86.0
%RSD**	56.4	32.4	19.6

	30*	45*	60*
mean value (n = 4) of % of Compound 1 released	34.8	67.9	89.4
%RSD**	52.3	24.6	9.2

Table 3h – % of Compound 1 that is released for size 4 capsule containing 0.03mg of Compound 1 and Poloxamer 188:food grade GMS 50:50 (ratio by weight) – total weight of Poloxamer188 plus food grade GMS = 149.97 mg

	60*	120*	180*	240*	300*	360*	480*
mean value (n = 6) of % of Compound 1 released	17.9	35.9	51.7	67.9	83.6	92.3	98.1
%RSD**	11.7	7.1	6.8	5.0	6.2	6.3	4.3

*time in minutes
**RSD as a percentage of mean value of % of Compound 1 released

Table 3i– % of Compound 1 that is released for size 4 capsule containing 0.5 mg of Compound 1 and Poloxamer 188:food grade GMS 50:50 (ratio by weight) – total weight of Poloxamer 188 plus food grade GMS = 149.5 mg

	30*	60*	120*	180*	240*	360*	480*
mean value (n = 4) of % of Compound 1 released	7.5	21.1	41.1	58.9	75.3	94.3	100.0
%RSD**	25.6	8.1	5.7	5.3	5.0	3.2	1.0

*time in minutes
**RSD as a percentage of mean value of % of Compound 1 released

Table 3j– % of Compound 1 that is released for size 4 capsule containing 0.5 mg of Compound 1 and Poloxamer 188:food grade GMS 50:50 (ratio by weight) – total weight of Poloxamer 188 plus food grade GMS = 149.5 mg

	30*	60*	120*	180*	240*	360*	480*
mean value (n = 4) of % of Compound 1 released	7.8	19.5	38.6	56.8	72.9	90.7	97.4

%RSD**	17.1	8.3	7.5	5.3	3.6	2.0	1.7

*time in minutes
**RSD as a percentage of mean value of % of Compound 1 released

Table 3k– % of Compound 1 that is released for size 4 capsule containing 0.03mg of Compound 1 and Poloxamer 188:food grade GMS 50:50 (ratio by weight) – total weight of Poloxamer 188 plus food grade GMS = 149.97 mg

	30*	60*	120*	180*	240*	360*	480*
mean value (n = 6) of % of Compound 1 released	8.5	18.0	39.3	58.6	75.2	91.4	98.3
%RSD**	80.5	11.1	10.1	7.3	5.2	2.5	3.8

*time in minutes
**RSD as a percentage of mean value of % of Compound 1 released

Table 3l– % of Compound 1 that is released for size 4 capsule containing 0.5mg of Compound 1 and Poloxamer 188:food grade GMS 50:50 (ratio by weight) – total weight of Poloxamer 188 plus food grade GMS = 149.5 mg

	30*	60*	120*	180*	240*	360*	480*
mean value (n = 4) of % of Compound 1 released	9.9	22.2	42.9	61.5	76.9	92.2	96.7
%RSD**	12.4	8.6	10.5	8.9	5.9	4.0	2.1

*time in minutes
**RSD as a percentage of mean value of % of Compound 1 released

Table 3m – % of Compound 1 that is released for size 4 capsule containing 0.03mg of Compound 1 and Poloxamer 188:food grade GMS 30:70 (ratio by weight) – total weight of Poloxamer 188 plus food grade GMS = 149.97 mg

	60*	120*	180*	240*	360*	480*	600*	720*	840*
mean value (n = 6) of % of Compound 1 released	15.3	27.4	38.4	49.0	70.1	85.9	93.5	97.6	99.0
%RSD**	8.8	8.7	3.5	4.0	3.5	2.2	1.9	0.9	1.0

*time in minutes
**RSD as a percentage of mean value of % of Compound 1 released

Table 3n – % of Compound 1 that is released for size 4 capsule containing 0.5mg of Compound 1 and Poloxamer 188:food grade GMS 30:70 (ratio by weight) – total weight of Poloxamer 188 plus food grade GMS = 149.5 mg

	30*	60*	120*	180*	240*	360*	480*	600*	720*	735*
mean value (n = 4) of % of Compound 1 released	7.9	15.5	26.9	37.9	48.8	68.7	83.4	90.6	94.7	95.7

%RSD**	14.7	5.1	5.6	5.7	6.0	5.2	2.6	2.0	1.9	1.5

*time in minutes
**RSD as a percentage of mean value of % of Compound 1 released

Table 3o – % of Compound 1 that is released for size 4 capsule containing 0.5mg of Compound 1 and Poloxamer 188:food grade GMS 30:70 (ratio by weight) – total weight of Poloxamer 188 plus food grade GMS = 149.5 mg

	30*	60*	120*	180*	240*	360*	480*	600*	720*	735*
mean value (n = 4) of % of Compound 1 released	5.6	13.3	25.5	37.7	49.7	71.2	84.0	89.7	93.1	94.8
%RSD**	17.5	6.7	7.4	5.9	4.7	3.4	1.2	0.7	0.8	1.2

*time in minutes
**RSD as a percentage of mean value of % of Compound 1 released

Table 3p – % of Compound 1 that is released for size 4 capsule containing 0.5mg of Compound 1 and Poloxamer 188:food grade GMS 30:70 (ratio by weight) – total weight of Poloxamer 188 plus food grade GMS = 149.5 mg

	30*	60*	120*	180*	240*	360*	480*	600*	720*	735*
mean value (n = 4) of % of Compound 1 released	7.3	14.3	26.1	38.5	51.1	74.3	87.0	92.3	95.0	96.1
%RSD**	7.7	8.1	5.4	5.2	7.4	10.0	7.7	4.9	2.9	2.2

*time in minutes
**RSD as a percentage of mean value of % of Compound 1 released

Table 3q – % of Compound 1 that is released for size 4 capsule containing 0.5mg of Compound 1 and Poloxamer 188:food grade GMS 30:70 (ratio by weight) – total weight of Poloxamer 188 plus food grade GMS = 149.5 mg

	30*	60*	120*	180*	240*	360*	480*	600*	720*	735*
mean value (n = 4) of % of Compound 1 released	6.2	13.7	27.3	40.3	52.5	74.2	85.5	91.5	93.4	94.5
%RSD**	18.6	9.6	6.7	9.2	9.8	10.7	7.7	6.4	4.3	3.5

*time in minutes
**RSD as a percentage of mean value of % of Compound 1 released

Table 3r – % of Compound 1 that is released for size 4 capsule containing 0.03 mg of Compound 1 and Poloxamer 188:food grade GMS 30:70 (ratio by weight) – total weight of Poloxamer 188 plus food grade GMS = 149.97 mg

	60*	120*	180*	240*	360*	480*	600*	720*	840*
mean value (n = 6) of % of Compound 1 released	11	23	33	43	62	77	87	91	95

%RSD**	2.4	1.7	1.9	2.3	2.8	3.5	2.8	3.6	2.7

*time in minutes
**RSD as a percentage of mean value of % of Compound 1 released

Table 3s-1 – Storage time = 0: % of Compound 1 that is released for size 4 capsule containing 0.03 mg of Compound 1 and Poloxamer 188:food grade GMS 30:70 (ratio by weight) – total weight of Poloxamer 188 plus food grade GMS = 149.97 mg

	60*	120*	180*	240*	360*	480*	600*
mean value (n = 6) of % of Compound 1 released	16.7	27.5	38.3	50.3	72.3	88.7	96.0
%RSD**	5.5	5.8	5.8	5.5	6.2	4.3	3.2

Table 3s-2 – Storage time = 2 weeks: % of Compound 1 that is released for size 4 capsule containing 0.03 mg of Compound 1 and Poloxamer 188:food grade GMS 30:70 (ratio by weight) – total weight of Poloxamer 188 plus food grade GMS = 149.97 mg

	60*	120*	180*	240*	360*	480*	600*
mean value (n = 6) of % of Compound 1 released	16.0	27.7	39.7	52.2	74.6	89.4	96.7
%RSD**	2.3	4.6	3.6	4.3	4.0	3.0	2.1

Example 4. Modified-release Compositions – Tablets

An example of a suitable composition is a composition in the form of a tablet. Examples of modified-release tablets at various doses of Compound 1 are shown in Table 4.

Table 4

Ingredient	**% (w/w)**	**mg /tablet**	**% (w/w)**	**mg /tablet**	**% (w/w)**	**mg /tablet**
Compound 1	0.00	0.00	0.05	0.05	0.10	0.10
HPMC (Methocel K4M Premium CR)	25.00	25.00	25.00	25.00	25.00	25.00
HPMC (Methocel K100 Premium LVCR)	25.00	25.00	25.00	25.00	25.00	25.00
Microcrystalline cellulose (Avicel PH102)	30.00	30.00	30.00	30.00	30.00	30.00
Mannitol (Pearlitol 100SD)	18.75	18.75	18.70	18.70	18.65	18.65
Silicon dioxide	0.25	0.25	0.25	0.25	0.25	0.25
Magnesium stearate	1.00	1.00	1.00	1.00	1.00	1.00
Total (core tablet)	100.00	100.00	100.00	100.00	100.00	100.00
Ethanol for preparing wet granulation liquid [a]	15.00	-	15.00	-	15.00	-
Ethanol for rinsing the container [a]	5.00	-	5.00	-	5.00	-
Total amount of ethanol used	20.00	-	20.00	-	20.00	-
Opadry II Orange 89F130009	-	4.00	-	4.00	-	4.00

[a] Essentially removed during processing

Table 4 (Continued)

Ingredient	% (w/w)	mg/tablet	% (w/w)	mg/tablet
Compound 1	0.20	0.20	0.50	0.50
HPMC (Methocel K4M Premium CR)	25.00	25.00	25.00	25.00
HPMC (Methocel K100 Premium LVCR)	25.00	25.00	25.00	25.00
Microcrystalline cellulose (Avicel PH102)	30.00	30.00	30.00	30.00
Mannitol (Pearlitol 100SD)	18.55	18.55	18.25	18.25
Silicon dioxide	0.25	0.25	0.25	0.25
Magnesium stearate	1.00	1.00	1.00	1.00
Total (core tablet)	100.00	100.00	100.00	100.00
Ethanol for preparing wet granulation liquid [a]	15.00	-	15.00	-
Ethanol for rinsing the container [a]	5.00	-	5.00	-
Total amount of ethanol used	20.00	-	20.00	-
Opadry II Orange 89F130009		4.00		4.00

[a] Essentially removed during processing

Table 4 (Continued)

Component	Grade	Function	Unit Formula (mg)		
Core			0.05 mg active	0.25 mg active	0.40 mg active
Compound 1		Drug substance	0.05	0.25	0.40
Ethyl Alcohol[a]	USP	Vehicle	0.00	0.00	0.00
Hydroxypropyl methylcellulose K4M CR	Ph.Eur./USP	Release modifier	25.00	25.00	25.00
Hydroxypropyl methylcellulose K100 LVCR	Ph.Eur./USP	Release modifier	25.00	25.00	25.00
Microcrystalline cellulose (Avicel PH102)	Ph.Eur./USP	Filler	30.00	30.00	30.00
Mannitol (Pearlitol 100 SD)	Ph.Eur./USP	Filler	18.70	18.50	18.35
Colloidal silicon dioxide	Ph.Eur./USP	Glidant	0.25	0.25	0.25
Magnesium stearate	Ph.Eur./USP	Lubricant	1.00	1.00	1.00
		Tablet core	100.00	100.00	100.0
Film coating					
Opadry® II Orange 89F130009[b]	Colorcon specification	Color film coat	4.00	4.00	4.00
Purified water[a]	USP	Processing aid/solvent	0.00	0.00	0.00
		Film coating	4.00	4.00	4.00
		Total	104.00	104.00	104.00

[a] Wet granulation fluid, essentially removed during processing.
[b] Manufactured by Colorcon; refer to Section 3.2.P.4 and DMF 721 for detailed information and qualitative composition.

Suppliers and grades for various components of the tablet are shown in Table 5.

Table 5

Component	Manufacturer	Supplier Grade
Compound 1	Arena	Internal
Ethanol	Pharma-Aaper	200 Proof
Hydroxypropyl Methylcellulose	The Dow Company	Methocel K4M Premium CR
Hydroxypropyl Methylcellulose	The Dow Company	Methocel K100 Premium LVCR
Microcrystalline Cellulose	FMC Biopolymer	Avicel PH102
Mannitol	Roquette	Pearlitol 100SD
Silicon dioxide	Evonik	Aerosil® 200 Pharma
Magnesium stearate	Mallinckrodt	Hyqual 5712 vegetable
Opadry II Orange	Colorcon	89F130009

Example 5. Preparation of Modified-release Tablets

An exemplary process for the preparation of modified-release tablets is as follows.

A wet granulation liquid is prepared as follows. Ethanol is weighed out and added into a beaker. A 4-blade propeller is attached to an IKA RW20 overhead mixer and lowered into the beaker. Compound 1 is weighed out and slowly added to the beaker, mixing until dissolved.

Granulation is prepared as follows. Hydroxypropyl methylcellulose (Methocel K4M CR) is weighed out and sieved through a Comil with R045 screen. Sieved powder is added to the processing bowl of the high shear mixer. The impeller speed is set to 100 rpm. Mixing is started and the wet granulation liquid is immediately poured through the top port within 1-2 min. Mixing speed is increased to 250 rpm and continue mixing for 2 min after addition was complete. Half of rinse ethanol is weighed out to rinse the beaker used for preparing the wet granulation liquid. The impeller speed is set to 250 rpm and the chopper speed to 1000 rpm. Mixing is started and the rinse liquid is immediately poured through the top port within 1 min. Mixing is continued for 2 min after addition is complete. The remaining half of rinse ethanol is weighed out to rinse the beaker used for preparing the wet granulation liquid for the 2nd time. The impeller speed is set to 250 rpm and the chopper speed to 1000 rpm. Mixing is started and the rinse liquid is immediately poured through the top port within 1 min. Mixing is continued for 2 min after addition is complete. Wet granules are discharged.

Drying is performed in an oven overnight at 40°C (±5°C). In-process testing is performed to determine residual ethanol level.

Milling, blending and lubrication are performed as follows. The ingredients are sieved through the Comil with R045 screen & round-bar impeller at 1500 rpm by the following order: Mannitol, Methocel K100 LVCR, dried granules, silicon dioxide, and microcrystalline cellulose. Milled granules and excipients are added into a V-blender. The V-blender is set to 24 rpm and blending is performed for

10 min. The powder blend is discharged and sieving through the Comil again is performed again. Sieved powder blend is added back into the V-blender. The V-blender is set to 24 rpm and blending is performed for 10 min. Magnesium stearate is sieved through a 20-mesh screen. Magnesium stearate is added into the V-blender. The V-blender is set to 24 rpm and blending is performed for 5 min. The final powder blend is discharged.

Compression of the final blend is performed on a rotary tablet press using 1/4" plain, round concave tooling to achieve target tablet weight of 100 mg and target hardness of 7 kp.
Color film coating is performed as follows. Purified water is added to a beaker. Opadry II Orange is added and mixing is performed for approximately 45 minutes until the solids are homogeneously dispersed. Coating suspension is applied until the predetermined amount of suspension is sprayed.

Examples of preparations of modified-release tablets are as follows:

(a) A 0.5 kg blend of Compound 1 0.5 mg with 40% HPMC K4M CR was prepared. Twelve tablets were compressed at 100-mg target tablet size and 7-kP target hardness and the release profile was determined. The release rate of the tablets was found to be faster than that of the modified-release capsule.

(b) A 0.5 kg batch of Compound 1 powder blend with 40% HPMC K4M and 10% HPMC K100 LVCR by wet granulation was prepared. Twelve tablets at 100-mg target tablet size and 7-kp target hardness were compressed and the release profile was determined. The release rate of the tablets was found to be faster than that of the modified-release capsule at time points < 6 hrs but slower than that of the modified-release capsule at time points ≥ 6 hrs.

(c) A 0.5 kg batch of Compound 1 powder blend with 30% HPMC K4M and 20% HPMC K100 LVCR by wet granulation was prepared. Twelve tablets at 100-mg target tablet size and 7-kp target hardness were compressed and the release profile was determined. The release rate of the tablets was found to be slightly faster than that of the modified-release capsule.

(d) Compound 1 0.5 mg XR orange film-coated tablets were manufactured. Powder blend with 30% HPMC K4M and 25% HPMC K100 LVCR was prepared by wet granulation using ethanol as the wet granulation solvent at 0.5-g scale. The powder blend was compressed to produce 100-mg core tablets. Core tablets were film-coated with Opadry II Orange 89F130009 to achieve a weight gain of $\geq$ 4%. The composition and amounts dispensed are shown in the table below:

Ingredient	% (w/w)	Amount per Tablet (mg)	Target Amount In Powder blend (g)	Amount Dispensed (g)	Stages added
Compound 1	0.50	0.50	2.50	2.50	

HPMC K4M CR	30.00	30.00	150.00	150.00	Wet
HPMC K100 LVCR	25.00	25.00	125.00	125.00	Milling & blending with dried granules
Microcrystalline cellulose	30.00	30.00	150.00	150.00	
Mannitol (Pearlitol 100SD)	13.25	13.25	66.25	66.25	
Silicon dioxide	0.25	0.25	1.25	1.25	
Magnesium stearate	1.00	1.00	5.00	5.00	Lubrication
Total (core tablet)	**100.00**	**100.00**	**500.00**	**500.00**	-
EtOH for preparing API	15.00	-	75.00	75.00	Wet granulation
EtOH for rinsing the container*	5.00	-	25.00	25.10	
Total amount of EtOH used	**20.00**	-	**100.00**	**100.10**	

* Essentially removed during processing

(e) An analogous procedure to d) was used to manufacture tablets having 0.05 mg Compound 1 (the amount of mannitol used was 0.45 mg more than in d)). The composition and amounts dispensed are shown in the table below:

Ingredient	**% (w/w)**	**Amount per Tablet (mg)**	**Target Amount In Powder blend (g)**	**Amount Dispensed (g)**	**Stages added**
Compound 1	0.05	0.05	0.25	0.25	Wet granulation
HPMC K4M CR	30.00	30.00	150.00	150.00	
HPMC K100 LVCR	25.00	25.00	125.00	125.00	Milling & blending with dried granules
Microcrystalline cellulose	30.00	30.00	150.00	150.00	
Mannitol (Pearlitol 100SD)	13.70	13.70	68.50	68.50	
Silicon dioxide	0.25	0.25	1.25	1.25	
Magnesium stearate	1.00	1.00	5.00	5.00	Lubrication
Total (core tablet)	**100.00**	**100.00**	**500.00**	**500.00**	-
EtOH for preparing API	15.00	-	75.00	75.00	Wet granulation
EtOH for rinsing the container*	5.00	-	25.00	25.38	
Total amount of EtOH used	**20.00**	-	**100.00**	**100.38**	

* Essentially removed during processing

(f) Compound 1 0.05 mg XR orange film-coated tablets were manufactured. Powder blend was prepared by wet granulation using ethanol as the wet granulation solvent at 0.5-kg scale. The powder blend was compressed to produce 100-mg core tablets at target 7 kp hardness. Approximately 380 g of 100-mg core tablets were produced. Core tablets were film-coated with Opadry II Orange 89F130009, resulting in an actual weight gain of 4.43%.

The composition and amounts dispensed are shown in the table below:

Ingredient	% (w/w)	Amount per Tablet (mg)	Target Amount In Powder blend (g)	Amount Dispensed (g)	Stages added
Compound 1	0.05	0.05	0.25	0.25	Wet granulation
HPMC K4M CR	25.00	25.00	125.00	125.00	
HPMC K100 LVCR	25.00	25.00	125.00	125.00	Milling & blending with dried granules
Microcrystalline cellulose	30.00	30.00	150.00	150.00	
Mannitol (Pearlitol 100SD)	18.70	18.70	93.50	93.50	
Silicon dioxide	0.25	0.25	1.25	1.25	
Magnesium stearate	1.00	1.00	5.00	5.00	Lubrication
Total (core tablet)	**100.00**	**100.00**	**500.00**		-
EtOH for preparing API	15.00	-	75.00	75.00	Wet granulation
EtOH for rinsing the container*	5.00	-	25.00	25.00	
Total amount of EtOH used	**20.00**	-	**100.00**	**100.00**	

* Essentially removed during processing

(g) An analogous procedure to f) was used to manufacture tablets having 0.5 mg Compound 1 (the amount of mannitol used was 0.45 mg less than in f)): The composition and amounts dispensed are shown in the table below:

Ingredient	% (w/w)	Amount per Tablet (mg)	Target Amount In Powder blend (g)	Amount Dispensed (g)	Stages added
Compound 1	0.50	0.50	2.50	2.50	Wet granulation
HPMC K4M CR	25.00	25.00	125.00	125.00	
HPMC K100 LVCR	25.00	25.00	125.00	125.00	Milling & blending with dried granules
Microcrystalline cellulose (Avicel PH102)	30.00	30.00	150.00	150.00	
Mannitol (Pearlitol 100SD)	18.25	18.25	91.25	91.30	
Silicon dioxide	0.25	0.25	1.25	1.25	
Magnesium stearate	1.00	1.00	5.00	5.00	Lubrication
Total (core tablet)	**100.00**	**100.00**	**500.00**		-
EtOH for preparing API solution*	15.00	-	75.00	75.00	Wet granulation
EtOH for rinsing the container*	5.00	-	25.00	25.00	
Total amount of EtOH used	**20.00**	-	**100.00**	**100.00**	

* Essentially removed during processing

Example 6. Release Profiles

The release profiles for modified-release tablets were measured using USP Apparatus 1 (baskets).

Exemplary release profiles are shown in Figures 12-14. It is readily seen that in all three cases the release rate is substantially relative to that of the immediate-release formulation of Figure 1. The release profile did not change significantly following storage over time. In particular, each of Figures 12 and 13 shows the initial release profile and the release profile after storage at 40°C and 75% RH for six months. In each figure, at any time point equal to or greater than 2 hours, the percentage by weight of compound released in the initial release profile was found to be within 10 % of the percentage by weight of compound released in the release profile after storage.

Examples of release rates (% by weight) are shown in Tables 6a – 6d. All release profiles disclosed in Tables 6a – 6d were measured with USP Apparatus 1 (baskets) at 100 rpm in 500 mL of aqueous sodium phosphate at a concentration of 0.05 M (pH = 6.8). The values in a given table relate to tablets obtained from the same batch. Values shown represent mean values over a number of dissolution tests ("n" in each table) in each case.

Table 6a – Initial release profile: % of Compound 1 that is released for a tablet containing 0.05 mg of Compound 1, 25 mg of Methocel K4M Premium CR and 25 mg of Methocel K100 Premium LVCR.

	60*	120*	180*	240*	360*	480*	600*	840*
mean value (n = 6) of % of Compound 1 released	6.9	25.3	35.8	45.1	62	74.8	86.6	100.4
%RSD**	1.7	2	3.3	3.9	5.7	6.9	5.3	2

*time in minutes
**RSD as a percentage of mean value of % of Compound 1 released

Table 6b – Initial release profile: % of Compound 1 that is released for a tablet containing 0.5 mg of Compound 1, 25 mg of Methocel K4M Premium CR and 25 mg of Methocel K100 Premium LVCR.

	60*	120*	180*	240*	360*	480*	600*	840*
mean value (n = 6) of % of Compound 1 released	17.9	27.3	36.9	45.5	61.1	74.2	84.8	98.1
%RSD**	1.2	1.2	1.6	1.9	3.2	4	3.9	2.8

*time in minutes
**RSD as a percentage of mean value of % of Compound 1 released

Table 6c – Release profile after storage at 40°C and 75% RH for 6 months: % of Compound 1 that is released for a tablet containing 0.05 mg of Compound 1, 25 mg of Methocel K4M Premium CR and 25 mg of Methocel K100 Premium LVCR.

	60*	120*	180*	240*	360*	480*	600*	840*

mean value (n = 6) of % of Compound 1 released	17	27.1	36.9	45.4	61.1	75.8	86.9	100
%RSD**	2.3	2.5	3.2	4.3	5.1	3.7	2.5	1.4

*time in minutes
**RSD as a percentage of mean value of % of Compound 1 released

Table 6d – Release profile after storage at 40°C and 75% RH for 6 months: % of Compound 1 that is released for a tablet containing 0.5 mg of Compound 1, 25 mg of Methocel K4M Premium CR and 25 mg of Methocel K100 Premium LVCR.

	60*	120*	180*	240*	360*	480*	600*	840*
mean value (n = 6) of % of Compound 1 released	6.8	24.3	33	41.3	55.5	67.9	79.4	94.7
%RSD**	2.4	2.8	4.3	5.6	7.5	8.3	6.7	4.3

*time in minutes
**RSD as a percentage of mean value of % of Compound 1 released

Example 7. Clinical Trials

A. An open-label, fixed sequence, non-randomized study in two cohorts of healthy male and non-pregnant, non-lactating female subjects was conducted. Two cohorts with twelve subjects in each were enrolled to ensure data in ten evaluable subjects per cohort.

Each subject in Cohort 1 received each of the following regimens, in the fasted state, in a sequential manner over four treatment periods:

- Regimen A (0.03 mg immediate-release Compound 1): 1 × 0.03 mg Compound 1 immediate-release capsule.
- Regimen B (0.06 mg modified-release Compound 1): 1 × 0.06 mg Compound 1 modified-release tablet as disclosed herein.
- Regimen C (0.12 mg modified-release Compound 1): 2 × 0.06 mg Compound 1 modified-release tablets as disclosed herein.
- Regimen D (0.18 mg modified-release Compound 1) 3 × 0.06 mg Compound 1 modified-release tablets as disclosed herein.

Subjects in Cohort 1 were considered evaluable if they received both 0.06 mg and 0.12 mg Compound 1 modified-release tablet doses and the reference Compound 1 immediate-release capsule.

Each subject in Cohort 2 received each of the following regimens, in the fasted state, in a sequential manner over three treatment periods:

- Regimen E (0.2 mg selexipag): 1 × selexipag (Uptravi®) 200 μg film-coated tablet.
- Regimen F (0.4 mg selexipag): 2 × selexipag (Uptravi®) 200 μg film-coated tablets.
- Regimen G (0.6 mg selexipag): 3 × selexipag (Uptravi®) 200 μg film-coated tablets.

Subjects in Cohort 2 were considered evaluable if they received both the 0.2 mg and 0.4 mg doses of selexipag.

Subjects received each regimen in the morning of Day 1, following an overnight fast of a minimum of 8 hours. PK samples were taken from subjects at 72 hours post-dose. There was a minimum washout period of 7 days between each administration of investigational medicinal product (IMP) (i.e., selexipag film-coated tablet(s), Compound 1 immediate-release capsule(s), and/or Compound 1 modified-release tablet(s)).

For Cohort 1, subjects received Regimens A, B and C in a sequential manner at consecutive treatment periods. Subjects who tolerated the IMP in all prior regimens continued in the study to receive the final dose (Regimen D); subjects who did not tolerate the IMP were considered to have completed the study and did not receive the final dose.

For Cohort 2, subjects received Regimens E and F in a sequential manner at consecutive treatment periods. Subjects who tolerated the IMP in all prior regimens continued in the study to receive the final dose (Regimen G); subjects who did not tolerate the IMP were considered to have completed the study and did not receive the final dose.

Pharmacokinetic Assessments:

Venous blood samples were withdrawn at regular time intervals. Plasma concentration data for Compound 1 and the selexipag parent and active metabolite were analyzed using appropriate non-compartmental techniques to obtain estimates of one or more of the following parameters:

- T_{lag}
- T_{max}
- C_{max}
- C_{12}
- C_{24}
- $AUC_{(0\text{-}last)}$
- $AUC_{(0\text{-}inf)}$
- AUC%extrap
- lambda-z
- T1/2el
- CL/F
- Frel: relative bioavailability of 0.06 mg Compound 1 tablets compared to the reference 0.03 mg Compound 1 capsule

Pharmacodynamic Assessments:

Platelet aggregation was assessed for Regimen C and optional Regimen D in Cohort 1, and Regimen F and optional Regimen G in Cohort 2.

The following comparisons were estimated for Compound 1 and selexipag:

- Platelet aggregation (% change from baseline) versus time.
- Platelet aggregation versus plasma concentration.
- Effect maxima (E_{max}) and area under the effect curve (AUEC) for platelet aggregation (% change from baseline).

One or more of the above pharmacokinetic parameters were determined at one or more of the following time points: pre-dose and (referring to hours after administration): 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36, 48, and 72 hours.

One or more of the above pharmacodynamic parameters were determined at one or more of the following time points: pre-dose and (referring to hours after administration): 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36, 48, and 72 hours.

Pharmacokinetic results showed that the modified-release tablet reduced the C_{max} and increased T_{max} while substantially maintaining similar total plasma concentrations. The most common treatment-emergent adverse events were similar to those seen in single ascending dose studies of Compound 1.

Following single oral administration of 0.06, 0.12 and 0.18 mg of the modified-release tablets of Compound 1, median T_{max} occurred between approximately 4 and 10 hours. The geometric mean half-life ranged from approximately 19 to 23 hours across all dose levels.

Systemic exposure (C_{max} and AUC) to Compound 1 following oral administration of the modified-release tablet formulation of Compound 1 increased in a slightly higher than dose-proportional manner.

Plasma concentrations at 24 hours post-dose were higher following administration of the modified-release tablet formulation of Compound 1, with an increase in line with the dose increase, compared to the immediate release-formulation.

Dose-adjusted peak plasma exposure (C_{max}/D) measures were lower for the modified-release compared to the immediate-release formulation [geometric mean ratios (GMRs) ranged from 28.7–41.2%]. Dose-adjusted total plasma exposure (AUC/D) measures ranged from similar to somewhat lower for modified-release compared to the immediate-release formulation (GMRs ranged from 63.3–97.9%). Relative bioavailability based on individual dose-adjusted peak plasma concentrations (C_{max}) was statistically significantly lower for 0.06, 0.12 and 0.18 mg of the modified-release tablet formulation of Compound 1 than the immediate-release capsule. Relative bioavailability based on individual dose-adjusted ratios of AUC(0-last) was statistically significantly lower than 0.06 and 0.12 mg of the modified-release tablet formulation of Compound 1, while 0.18 mg of the modified-release tablet formulation of

Compound 1 demonstrated similar dose-adjusted total exposure (AUC(0-last)) compared to 0.03 mg of the immediate release capsule. Relative bioavailability based on individual dose-adjusted ratios of AUC(0-inf) showed a similar trend to AUC(0-last).

Overall, the modified-release tablet formulation of Compound 1 offers improved performance over the immediate-release capsule formulation for once daily dosing by extending drug exposure and minimizing C_{max}.

B. A second open-label, non-randomized pharmacokinetic study was conducted in healthy subjects. Fasted (cohort 1; n=19) or fed state (cohort 2, n=18) subjects received a modified-release tablet formulation of Compound 1 in a dose escalation sequence over 25 days (once daily dosing started at 0.06 mg and was slowly titrated, depending upon individual subject tolerability, by additional 0.06 mg dose increments every 5 days up to 0.3 mg once daily).

Two cohorts were enrolled to ensure data in 12 evaluable subjects per cohort.

Each subject received a once daily dose of the modified-release Compound 1 for 5 days, with up to four sequential dose escalations every 5 days:

- Regimen A (0.06 mg modified-release Compound 1): 1 × 0.06 mg Compound 1 modified-release tablet for 5 days
- Regimen B (0.12 mg modified-release Compound 1): 2 × 0.06 mg Compound 1 modified-release tablet for 5 days
- Regimen C (0.18 mg modified-release Compound 1): 3 × 0.06 mg Compound 1 modified-release tablet for 5 days
- Regimen D (0.24 mg modified-release Compound 1): 4 × 0.06 mg Compound 1 modified-release tablet for 5 days
- Regimen E (0.30 mg modified-release Compound 1): 5 × 0.06 mg Compound 1 modified-release tablet for 5 days

Dose-dependent plasma exposure measures were observed for the modified-release tablet formulation given once daily, with low peak-trough fluctuation and little effect of food seen across dose levels. Somewhat higher mean plasma exposure measures were observed in females compared to males.

Accumulation index (5 days of dosing at 0.60 mg) was approximately 2.1-fold ($AUC_{(0-24)}$) in both the fed and fasted state. Exposure in the fed and fasted states was similar after single administration and at steady state; however, T_{max} was delayed in the fed state. Peak exposure was significantly higher in female subjects than in male subjects, with an increase of greater than 42% for C_{max} at steady state. However, differences in $AUC_{(0-24)}$ at steady state did not indicate a significant increase.

The modified-release tablet formulation of Compound 1 offered improved pharmacokinetic performance over both immediate-release capsules of Compound 1 and selexipag immediate-release

tablet formulations by providing once daily dosing with extended drug exposure and low peak-trough fluctuation.

Example 8. Clinical Trial

A 22-week randomized, double-blind, placebo-controlled study with a dose titration period of up to 9 weeks was conducted. Sixty-one patients were randomized 2:1 Compound 1 to placebo. Right Heart Catheterization (RHC) measurements were obtained prior to study Day 1 of the dose titration period and at Week 22. The following values were obtained and recorded: pulmonary artery pressure (PAP) (systolic, diastolic, and mean), heart rate (HR), right atrial pressure (RAP), pulmonary capillary wedge pressure (PCWP) right ventricular pressure (RVP) and cardiac output (CO), pulmonary vascular resistance (PVR), arterial and mixed venous oxygen saturation (FiO2) (if applicable). Systemic vascular resistance (SVR) was estimated from blood pressure measurements. The 6-minute walk test (6MWD) was conducted according to the modified guidelines issued by the American Thoracic Society. *See* Am J Respir Crit Care Med 166:111–117, 2002.

Primary efficacy endpoints for the study were: a) change from baseline in PVR after 22 weeks of treatment, and b) change from baseline in 6 MWD after 22 weeks of treatment.

Compound 1 was administered as a capsule in 0.01, 0.02, 0.03, 0.04, and 0.10 mg dose strengths. The formulation was supplied as a liquid-filled, size 4, hard-gelatin capsule containing Compound 1, polyoxyl 40 hydrogenated castor oil (Kolliphor® RH40) NF, butylated hydroxytoluene (BHT)NF, and colloidal silicon dioxide NF.

The starting dose of Compound 1 was 0.01 mg twice daily. The dose of Compound 1 was titrated according to patient tolerability. If the initial dose was tolerated (0.01 mg twice daily), then the dose was increased once a week in the following fashion: 0.02 mg twice daily, 0.03 mg twice daily, 0.04 mg twice daily, 0.06 mg twice daily, 0.08 mg, 0.1 mg twice daily, 0.2 mg twice daily and 0.3 mg twice daily. The dose was optionally escalated to a possible maximum total daily dose of 0.6 mg (0.3 mg twice daily), pending tolerability. If a dose was not tolerated, Compound 1 was optionally decreased to the previous dose level. If the initial dose of 0.01 mg twice daily was not tolerated, dosing was optionally decreased to 0.01 mg once daily. Compound 1 daily maintenance doses were titrated as high as 0.6 mg, and the most common dose was 0.4 mg. A scatter plot of C_{max} at the highest Compound 1 dose level is provided in Figure 16.

Subjects received concomitant oral disease-specific PAH therapy only if the dose remained stable for at least 3 months prior to the start of screening. This therapy consisted of the following: ERA and/or an agent acting on the NO pathway including the following: a PDE-5 inhibitor and a sGC stimulator.

Subjects were instructed to continue the same dose and regimen of these medications for the duration of the study.

The use of the following therapies, which may affect PAH, was also permitted if the subject was on a stable dose for 1 month prior to screening and the dose remained unchanged through the duration of the study: vasodilators (including calcium channel blockers), digoxin, spironolactone, and L-arginine supplementation.

Doses of spironolactone and digoxin were held or reduced, if necessary, to protect the subject's safety. Doses were not allowed to be increased in the month before Day 1 and during the controlled study.

Diuretics were prescribed as clinically indicated throughout the study.

Additionally, the use of PDE-5 inhibitor as needed for erectile dysfunction (ED) was permitted as long as the subject had not taken a dose within 48 hours of any baseline or study-related efficacy assessment. In addition, the subject must not have taken more than 8 sildenafil tablets, 6 vardenafil, or 4 tadalafil tablets per month for ED.

Previous administration of a prostacyclin or prostacyclin analogue was not permitted if treatment was stopped for a safety or tolerability issue. In addition, intravenous inotropes within 1 month of screening were not permitted.

All subjects were taking PAH disease-specific medication. The majority of subjects were taking an ERA or PDE-5 inhibitor during the study for the treatment of PAH. Most subjects were on supportive therapy during the study.

Compound 1 plasma levels were measured both pre-dose and at 4 hours post-dose. The mean concentration of Compound 1 over time is shown in Figure 15. Mean pre-dose and 4 hours post-dose plasma concentrations continued to rise during the 9-week dose titration period. Thereafter, mean steady-state pre-dose and 4-hours post-dose plasma concentrations were maintained throughout the 13-week maintenance period. Overall, the observed mean pre-dose and 4-hours post-dose plasma levels of Compound 1 appear similar to those previously observed in healthy human subjects when administered the same dose regimen.

Compound 1 achieved the primary endpoint with a statistically significant change from baseline in pulmonary vascular resistance (PVR) compared to placebo. Compound 1 also demonstrated numerical improvement in 6-minute walk distance (6MWD). There was a strong and positive correlation between the 4 hour post-dose plasma concentrations of Compound 1 and percent change from baseline in PVR and 6MWD. PVR decreased by 163.9 $dyn \cdot s \cdot cm^{-5}$ from baseline to Week 22 in patients receiving Compound 1, compared with an increase in PVR of 0.7 $dyn \cdot s \cdot cm^{-5}$ in patients receiving placebo ($p=0.02$). There was no significant correlation between PVR percentage change and Compound 1 dose. Over the 22-week

study period, there was a significant correlation between Compound 1 plasma levels and improvements in PVR (Figure 17; p=0.004).

Least-squares mean 6MWD increased by 36.2 m for Compound 1 compared with 29.4 m for the placebo group, but this was not significantly different. There was a significant correlation between Compound 1 plasma levels and improvements in 6MWD (Figure 18; p=0.0037).

Patients treated with Compound 1 had a numerically greater mean reduction in BNP from baseline to Week 22 versus placebo, although this difference was not significantly different. There was a significant correlation between Compound 1 plasma levels and improvements in BNP (Figure 19; p=0.047).

Adverse events observed in the study were consistent with other prostacyclin treatments for the management of PAH. The distribution of maintenance doses for patients receiving Compound 1 was as follows: 0.02 mg (n=1), 0.03 mg (n=1), 0.04 mg (n=0), 0.06 mg (n=3), 0.08 mg (n=3), 0.12 mg (n=5), 0.16 mg (n=4), 0.2 mg (n=6), 0.4 mg (n=12), and 0.6 mg (n=5).

Example 9. Clinical Trial

A randomized, double-blind, placebo-controlled study with Compound 1 will be conducted. Subjects will be randomized 1:1 to receive Compound 1 or placebo, in addition to their standard of care or PAH-specific background therapy, as applicable.

On Day 1, investigational medicinal product (IMP) (Compound 1 or placebo, according to randomization) will be initiated at a dose of 0.05 mg once daily for the first week of treatment. During each subsequent week of a 16-week dose titration period, the dose of IMP will be increased in 0.05 mg increments to a dose of 0.8 mg once daily or until the highest tolerated dose is achieved.

If the highest tolerated dose of IMP is achieved prior to Week 16, the subject will remain on that dose until the completion of the dose titration period. Decreases in IMP dose (in 0.05 mg increments) will be allowed at any time during the dose titration period to manage AEs and attain the highest tolerated dose. Background PAH therapies (regimen and doses) must remain stable throughout the dose titration period.

For subjects whose highest tolerated dose during the dose titration period is less than 0.8 mg, and for subjects who did not reach the 0.8 mg once daily, further increases in IMP dose (in increments of 0.05 mg per week) will be permitted during the treatment period (up to a maximum dose of 1.45 mg once daily), according to investigator discretion. No IMP dose increases will be allowed within 6 weeks prior to a protocol-specified efficacy evaluation. IMP dose decreases will be allowed at any time during the treatment period to manage tolerability and AEs.

Inclusion criteria to be eligible for enrollment into the study may include:

- Diagnosis of symptomatic WHO Group 1 PAH classified by one of the following subgroups:
  - Idiopathic pulmonary arterial hypertension (IPAH);
  - Heritable pulmonary arterial hypertension (HPAH);
  - Drugs and toxins induced based on prior exposure to legal drugs, chemicals, and toxins
  - PAH associated with:
    - Connective tissue disease (CTD)
    - Human Immunodeficiency Virus (HIV) infection
    - Congenital systemic-pulmonary shunt (must have undergone surgical correction at least 1 year prior to screening).
- WHO/ New York Heart Association (NYHA) functional class II to IV symptoms.
- If on PAH-specific background therapy, subject is on stable therapy with either an endothelin receptor antagonist (ERA) and/or an agent acting on the nitric oxide (NO) pathway, a phosphodiesterase type 5 (PDE5) inhibitor or a soluble guanylate cyclase (sGC) stimulator.
- Has a 6MWD of ≥50 meters on two consecutive tests.
- If the subject is taking the following concomitant medications that may affect PAH, the subject must be on a stable dose for at least 30 days prior to the start of screening and the dosage maintained throughout the study.
  - Vasodilators (including calcium channel blockers, digoxin, or L-arginine supplementation);
  - If the subject is taking anticoagulants, anticoagulation status must be maintained/stable in the therapeutic range for at least 30 days prior to the start of screening.

Exclusion criteria to be eligible for enrollment into the study may include: use of intravenous (i.v.) inotropes including, but not limited to, levosimendan, dopamine, dobutamine, dopexamine, epinephrine, isoprenaline (isoproterenol), norepinephrine (noradrenaline), milrinone, or amrinone, within 30 days prior to screening.

Investigational medicinal product (IMP) (i.e., Compound 1 and matching placebo) will be supplied as 0.05, 0.25, and 0.4 mg extended release (XR) tablets for oral administration.

The starting dose of IMP will be 0.05 mg once daily for 1 week. During the 16-week dose titration period, up-titration of IMP will occur in 0.05 mg increments each week to a dose of 0.8 mg once daily or until the highest tolerated dose is achieved. The dose of IMP may be further increased during the treatment period (up to a maximum of 1.45 mg once daily), according to investigator discretion.

The primary endpoint is the time (in days) from randomization to the first adjudicated clinical failure event in randomized subjects, including:

• Death (all causes)

- Hospital admission for worsening PAH, as a result of any of the following:
  - Non-elective hospitalization caused by clinical conditions directly related to PAH and/or right heart failure;
  - Need for i.v. diuretics;
  - Lung and/or heart transplant;
  - Atrial septostomy;
  - Initiation of parenteral (i.v. infusion or subcutaneous injection) therapy with a prostacyclin;
- Disease progression, defined as:
  - Worsening of symptoms of right heart failure and the addition or increase in dose of a PAH disease-specific therapy or initiation of chronic oxygen therapy (i.e., requires oxygen for >24 hours with the intent of long term use); or
  - A decrease in 6MWD of at least two assessments of 6MWD performed at two consecutive visits and worsening in WHO functional class for subjects with WHO functional class I/II/III.
- Unsatisfactory long-term clinical response, defined as:
  - Receiving randomized treatment for at least 6 months; and
  - Failure to improve at least 10% or 20 meters from baseline in 6MWD, at two consecutive visits; and
  - Failure to maintain or improve WHO functional class status.

Secondary endpoints will include:

- Change from baseline in N-terminal pro b-type natriuretic peptide (NT-proBNP)
- Change from baseline in 6MWD measured at trough (i.e., prior to dose of IMP)
- Change from baseline in WHO functional class
- Time to all-cause hospitalization during the study period
- Time to all-cause mortality during the study period
- Change from baseline in heart rate recovery measurements following assessment of 6MWD
- Change from baseline in proportion of subjects who achieve three, versus two, one, or none of the following (at specified time points):
  - NT-proBNP level <300 pg/mL
  - 6MWD >440 meters
  - WHO functional class II status or better
- Change from baseline in REVEAL risk score (at specified time points)
- Changes from baseline in HRQoL measures (where validated)

Plasma samples for pharmacokinetic (PK) assessments will be obtained at Day 1 (baseline) and at each subsequent clinic visit through the end of study visit.

Example 10. Clinical Trial

A multicenter, randomized, double-blind, placebo-controlled study with Compound 1 will be conducted.

On Day 1, investigational medicinal product (IMP) (Compound 1 or placebo, according to randomization) will be initiated at a dose of 0.05 mg once daily for the first week of treatment. During each subsequent week of a 16-week dose titration period, the dose of IMP will be increased in 0.05 mg increments to a dose of 0.8 mg once daily or until the highest tolerated dose is achieved.

If the highest tolerated dose of IMP is achieved prior to Week 16, the subject will remain on that dose until the completion of the dose titration period. Decreases in IMP dose (in 0.05 mg increments) will be allowed at any time during the dose titration period to manage AEs and attain the highest tolerated dose. Background PAH therapies (regimen and doses) must remain stable throughout the dose titration period.

During the treatment period, further increases in IMP dose may be implemented through to the Week 22.

Inclusion criteria may include:

- Diagnosis of symptomatic WHO Group 1 PAH classified by one of the following subgroups:
    - Idiopathic pulmonary arterial hypertension (IPAH)
    - Heritable pulmonary arterial hypertension (HPAH)
    - Drugs and toxins induced based on prior exposure to legal drugs, chemicals, and toxins
    - PAH associated with:
        - Connective tissue disease (CTD)
        - Human Immunodeficiency Virus (HIV) infection
        - Congenital systemic-pulmonary shunt (must have undergone surgical correction at least 1 year prior to screening)
- WHO/ New York Heart Association (NYHA) functional class II to IV symptoms
- Naïve to PAH disease-specific therapy (i.e., nitric oxide, endothelin receptor antagonists, PDE-5 inhibitors, soluble guanylate cyclase stimulators, or prostacyclin receptor agonists). Previous use of nitric oxide or prostacyclin for acute vasodilator testing during cardiac catheterization is permitted
- Has a 6MWD of ≥50 meters on two consecutive tests.

- If the subject is taking the following concomitant medications that may affect PAH, the subject must be on a stable dose for at least 30 days prior to the start of screening and the dosage maintained throughout the study.
    - Vasodilators (including calcium channel blockers, digoxin, or L-arginine supplementation);
    - If the subject is taking anticoagulants, anticoagulation status must be maintained/stable in the therapeutic range for at least 30 days prior to the start of screening.

Exclusion Criteria may include: use of intravenous (i.v.) inotropes including, but not limited to, levosimendan, dopamine, dobutamine, dopexamine, epinephrine, isoprenaline (isoproterenol), norepinephrine (noradrenaline), milrinone or amrinone, within 30 days prior to screening.

IMP (i.e., Compound 1 and matching placebo) will be supplied as 0.05, 0.25, and 0.4 mg extended release (XR) tablets for oral administration. During the dose titration period, the starting dose of IMP will be 0.05 mg once daily for 1 week. Up-titration of IMP will occur in 0.05 mg increments each week to a dose of 0.8 mg once daily or until the highest tolerated dose is achieved.

Total planned duration of treatment is 32 weeks, including a 4-week run-in period (for ambrisentan and tadalafil), a 16-week titration period, and a 12-week treatment period.

Efficacy will be assessed by evaluation of CPET parameters, measurement of hemodynamics during right heart catheterization (RHC), measurement of NT-proBNP, WHO/NYHA functional class assessments, measurement of 6MWD, and evaluation of HRQoL measures using the SF-36 and the PAH-Symptoms and Impact (PAH-SYMPACT®) Questionnaires. Time to the first event is evaluated in all randomized subjects during the study.

The endpoints are the change from baseline in peak VO2 after 28 weeks of treatment. Other endpoints will include:

- Changes from baseline to Week 28 in the following parameters:
    - PVR
    - NT-proBNP
    - VE/VC02 slope
    - 6MWD
    - WHO/NYHA functional class
    - Time to first all-cause hospitalization
    - Time to first protocol-defined clinical failure event
    - Change in PAH-SYMPACT®

Exploratory endpoints will include, but will not be limited to, the following:

- The proportion of subjects with improvement in risk category for peak VO2 and VE/VCO2 slope criteria (defined in the European Society of Cardiology [ESC]/European Respiratory Society [ERS] Guidelines for the diagnosis and treatment of pulmonary hypertension)
- Correlation of plasma concentrations with improvements in CPET parameters and 6MWD
- Change from baseline in heart rate recovery (HHR) measurements following assessment of 6MWD
- Change in REVEAL risk score
- The proportion of subjects who achieve three, versus two, one, or none of the following:
  - NT-proBNP level <300 pg/mL
  - 6MWD >440 meters
  - WHO functional class II status
- The proportion of subjects with change in risk category for PAH according to ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension
- Changes from baseline to Week 28 in additional CPET parameters
- Changes from baseline to Week 28 in additional RHC parameter

Plasma samples for pharmacokinetic (PK) assessments will be obtained pre-dose and post-dose at Day 1 (baseline), Week 16, and Week 28.

Those skilled in the art will recognize that various modifications, additions, and substitutions to the illustrative examples set forth herein can be made without departing from the spirit of the invention and are, therefore, considered within the scope of the invention.

CLAIMS

1. A method for the treatment of a PGI2 receptor mediated disorder in an individual, comprising:

administering to the individual in need thereof a dose of Compound 1 or a pharmaceutically acceptable salt, solvate, or hydrate thereof sufficient to achieve in the individual a blood plasma concentration of Compound 1 of at least about 2.5 ng/mL.

2. A method for the treatment of pulmonary arterial hypertension (PAH) in an individual, comprising:

administering to the individual in need thereof a dose of Compound 1 sufficient to achieve in the individual a blood plasma concentration of Compound 1 of at least about 2.5 ng/mL.

3. A method for the treatment of a PGI2 receptor mediated disorder in an individual, comprising:

administering to the individual in need thereof a dose of Compound 1 or a pharmaceutically acceptable salt, solvate, or hydrate thereof sufficient to achieve in the individual a blood plasma concentration of Compound 1 of at least about 5 ng/mL.

4. A method for the treatment of pulmonary arterial hypertension (PAH) in an individual, comprising:

administering to the individual in need thereof a dose of Compound 1 sufficient to achieve in the individual a blood plasma concentration of Compound 1 of at least about 5 ng/mL.

5. A method for the treatment of pulmonary arterial hypertension (PAH) in an individual, comprising:

administering to the individual in need thereof a dose of Compound 1;

determining the blood plasma level of Compound 1 in the individual; and

increasing the dose of Compound 1 if the individual does not have at least a threshold blood plasma level.

6. A method for the treatment of pulmonary arterial hypertension (PAH) in an individual, comprising:

administering to the individual in need thereof a dose of Compound 1;

determining the blood plasma level of Compound 1 in the individual; and

discontinuing administration of Compound 1 to the individual if the individual does not have at least a threshold blood plasma level.

7. A method for the treatment of pulmonary arterial hypertension (PAH) in an individual, comprising:

administering to the individual in need thereof a dose of Compound 1;

determining the blood plasma level of Compound 1 in the individual; and

continuing to administer Compound 1 to the individual if the individual has at least a threshold blood plasma level

or discontinuing administration of Compound 1 to the individual if the individual does not have at least a threshold blood plasma level.

8. A method for the treatment of pulmonary arterial hypertension (PAH) in an individual, comprising:

administering to the individual in need thereof a maximum tolerated dose of Compound 1;

determining the blood plasma level of Compound 1 in the individual; and

discontinuing administration of Compound 1 to the individual if the individual does not have at least a threshold blood plasma level at the maximum tolerated dose.

9. A method for the treatment of pulmonary arterial hypertension (PAH) in an individual, comprising:

administering to the individual in need thereof a maximum tolerated dose of Compound 1;

determining the blood plasma level of Compound 1 in the individual; and

continuing to administer Compound 1 to the individual if the individual has at least a threshold blood plasma level at the maximum tolerated dose or

discontinuing administration of Compound 1 to the individual if the individual does not have at least a threshold blood plasma level at the maximum tolerated dose.

10. A method for the treatment of pulmonary arterial hypertension (PAH) in an individual, comprising:

administering to the individual in need thereof a dose of Compound 1;

determining the blood plasma level of Compound 1 in the individual; and

increasing the dose of Compound 1 to the individual until a threshold blood plasma level is reached.

11. A method for selecting a dose of Compound 1 for an individual with pulmonary arterial hypertension (PAH), comprising:

determining the blood plasma level of Compound 1 in the individual; and

increasing the dose of Compound 1 to the individual until a threshold blood plasma level is reached.

12. A method for selecting a dose of Compound 1 for an individual with pulmonary arterial hypertension (PAH), comprising:

determining the blood plasma level of Compound 1 in the individual; and

maintaining the dose of Compound 1 to the individual if a threshold blood plasma level has been reached.

13. A method for selecting a dose of Compound 1 for an individual with pulmonary arterial hypertension (PAH), comprising:

determining the blood plasma level of Compound 1 in the individual; and

decreasing the dose of Compound 1 to the individual if a threshold blood plasma level has been exceeded.

14. The method of any one of the preceding claims, wherein the blood plasma concentration of Compound 1 is at least, or at least about, 3.0, 3.1, 3.2, 3.25, 3.3, 3.4, 3.5, 3.6, 3.7, 3.75, 3.8, 3.9, 4.0, 4.1, 4.2, 4.25, 4.3, 4.4, 4.5, 4.6, 4.7, 4.75, 4.8, 4.9, 5.0, 5.1, 5.2, 5.25, 5.3, 5.4, 5.5, 5.6, 5.7, 5.75, 5.8, 5.9, 6.0, 6.1, 6.2, 6.25, 6.3, 6.4, 6.5, 6.6, 6.7, 6.75, 6.8, 6.9, 7.0, 7.1, 7.2, 7.25, 7.3, 7.4, 7.5, 7.6, 7.7, 7.75, 7.8, 7.9, 8.0, 8.1, 8.2, 8.25, 8.3, 8.4, 8.5, 8.6, 8.7, 8.75, 8.8, 8.9, 9.0, 9.1, 9.2, 9.25, 9.3, 9.4, 9.5, 9.6, 9.7, 9.75, 9.8, 9.9, or 10 ng/mL.

15. The method of any one of the preceding claims, wherein the blood plasma concentration of Compound 1 is, or is about 3.0, 3.1, 3.2, 3.25, 3.3, 3.4, 3.5, 3.6, 3.7, 3.75, 3.8, 3.9, 4.0, 4.1, 4.2, 4.25, 4.3, 4.4, 4.5, 4.6, 4.7, 4.75, 4.8, 4.9, or 5.0 ng/mL.

16. The method of any one of the preceding claims, wherein the threshold blood plasma level of Compound 1 is selected from, or from about: 1, 1.1, 1.2, 1.25, 1.3, 1.4, 1.5, 1.6, 1.7, 1.75, 1.8, 1.9, 2, 2.1, 2.2, 2.25, 2.3, 2.4, 2.5, 2.6, 2.7, 2.75, 2.8, 2.9, 3, 3.1, 3.2, 3.25, 3.3, 3.4, 3.5, 3.6, 3.7, 3.75, 3.8, 3.9, 4, 4.1, 4.2, 4.25, 4.3, 4.4, 4.5, 4.6, 4.7, 4.75, 4.8, 4.9, 5, 5.1, 5.2, 5.25, 5.3, 5.4, 5.5, 5.6, 5.7, 5.75, 5.8, 5.9, 6, 6.25, 6.5, 6.75, 7, 7.25, 7.5, 7.75, 8, 8.25, 8.5, 8.75, 9, 9.25, 9.5, 9.75, and 10 ng/ml.

17. The method of any one of the preceding claims, wherein the therapeutically effective amount of Compound 1 is selected from, or from about, 0.01 mg, 0.02 mg, 0.025 mg, 0.03 mg, 0.04 mg, 0.05 mg, 0.06 mg, 0.065 mg, 0.07 mg, 0.075 mg, 0.08 mg, 0.09 mg, 0.1 mg, 0.12 mg, 0.15 mg, 0.16 mg, 0.2 mg, 0.25 mg, 0.3 mg, 0.35 mg, 0.4 mg, 0.45 mg, 0.5 mg, 0.55 mg, 0.6 mg, 0.65 mg, 0.7 mg, 0.75 mg, 0.8 mg, 0.85 mg, 0.9 mg, 0.95 mg, 1.0 mg, 1.05 mg, 1.1 mg, 1.15 mg. 1.2 mg, 1.25 mg, 1.3 mg, 1.35 mg. 1.4 mg, 1.45, and 1.5 mg daily.

18. The method of any one of the preceding claims, wherein the therapeutically effective amount of Compound 1 is a starting dose selected from, or from about, 0.01, 0.02, 0.025, 0.03, 0.04, 0.05, 0.06, 0.07, 0.075, 0.08, 0.09, and 0.1 mg daily.

19. The method of any one of the preceding claims, wherein the therapeutically effective amount of Compound 1 is a highest tolerated dose selected from, or from about, 0.4 mg, 0.45 mg, 0.5 mg, 0.55 mg, 0.6 mg, 0.65 mg, 0.7 mg, 0.75 mg, 0.8 mg, 0.85 mg, 0.9 mg, 0.95 mg, 1.0 mg, and 1.05 mg, 1.1 mg, 1.15 mg. 1.2 mg, 1.25 mg, 1.3 mg, 1.35 mg. 1.4 mg, 1.45, and 1.5 mg daily.

20. The method of any one of the preceding claims, wherein the therapeutically effective amount of Compound 1 is a maximum dose selected from, or from about, 0.4 mg, 0.45 mg, 0.5 mg, 0.55 mg, 0.6 mg, 0.65 mg, 0.7 mg, 0.75 mg, 0.8 mg, 0.85 mg, 0.9 mg, 0.95 mg, 1.0 mg, 1.05 mg, 1.1 mg, 1.15 mg. 1.2 mg, 1.25 mg, 1.3 mg, 1.35 mg. 1.4 mg, 1.45, and 1.5 mg daily.

21. The method of any one of the preceding claims, wherein the therapeutically effective amount of Compound 1 is a maximum tolerated dose selected from, or from about, 0.4 mg, 0.45 mg,

0.5 mg, 0.55 mg, 0.6 mg, 0.65 mg, 0.7 mg, 0.75 mg, 0.8 mg, 0.85 mg, 0.9 mg, 0.95 mg, 1.0 mg 1.05 mg, 1.1 mg, 1.15 mg. 1.2 mg, 1.25 mg, 1.3 mg, 1.35 mg. 1.4 mg, 1.45, and 1.5 mg daily.

22. The method of any one of the preceding claims, wherein the therapeutically effective amount of Compound 1 is a maintenance dose selected from, or from about, 0.01 mg, 0.02 mg, 0.025 mg, 0.03 mg, 0.04 mg, 0.05 mg, 0.06 mg, 0.065 mg, 0.07 mg, 0.075 mg, 0.08 mg, 0.09 mg, 0.1 mg, 0.12 mg, 0.15 mg, 0.16 mg, 0.2 mg, 0.25 mg, 0.3 mg, 0.35 mg, 0.4 mg, 0.45 mg, 0.5 mg, 0.55 mg, 0.6 mg, 0.65 mg, 0.7 mg, 0.75 mg, 0.8 mg, 0.85 mg, 0.9 mg, 0.95 mg, 1.0 mg, 1.05 mg, 1.1 mg, 1.15 mg. 1.2 mg, 1.25 mg, 1.3 mg, 1.35 mg. 1.4 mg, 1.45, and 1.5 mg daily.

23. The method of any one of the preceding claims, wherein the threshold blood plasma level is a peak blood plasma level.

24. The method of any one of the preceding claims, wherein the threshold blood plasma level is a trough blood plasma level.

25. The method of any one of the preceding claims, wherein the threshold blood plasma level is a peak blood plasma level and a trough blood plasma level.

26. The method of any one of the preceding claims, wherein the threshold blood plasma level is:

a peak blood plasma level of, of about, of at least, or of at least about, 3.0, 3.1, 3.2, 3.25, 3.3, 3.4, 3.5, 3.6, 3.7, 3.75, 3.8, 3.9, 4.0, 4.1, 4.2, 4.25, 4.3, 4.4, 4.5, 4.6, 4.7, 4.75, 4.8, 4.9, 5.0, 5.1, 5.2, 5.25, 5.3, 5.4, 5.5, 5.6, 5.7, 5.75, 5.8, 5.9, 6.0, 6.1, 6.2, 6.25, 6.3, 6.4, 6.5, 6.6, 6.7, 6.75, 6.8, 6.9, 7.0, 7.1, 7.2, 7.25, 7.3, 7.4, 7.5, 7.6, 7.7, 7.75, 7.8, 7.9, 8.0, 8.1, 8.2, 8.25, 8.3, 8.4, 8.5, 8.6, 8.7, 8.75, 8.8, 8.9, 9.0, 9.1, 9.2, 9.25, 9.3, 9.4, 9.5, 9.6, 9.7, 9.75, 9.8, 9.9, or 10 ng/mL; and

a trough blood plasma level of, of about, of at least, or of at least about, 2.0, 2.1, 2.2, 2.25, 2.3, 2.4, 2.5, 2.6, 2.7, 2.75, 2.8. 2.9, 3.0, 3.1, 3.2, 3.25, 3.3, 3.4, 3.5, 3.6, 3.7, 3.75, 3.8, 3.9, 4.0, 4.1, 4.2, 4.25, 4.3, 4.4, 4.5, 4.6, 4.7, 4.75, 4.8, 4.9, 5.0, 5.1, 5.2, 5.25, 5.3, 5.4, 5.5, 5.6, 5.7, 5.75, 5.8, 5.9, 6.0, 6.1, 6.2, 6.25, 6.3, 6.4, 6.5, 6.6, 6.7, 6.75, 6.8, 6.9, 7.0, 7.1, 7.2, 7.25, 7.3, 7.4, 7.5, 7.6, 7.7, 7.75, 7.8, 7.9, 8.0, 8.1, 8.2, 8.25, 8.3, 8.4, 8.5, 8.6, 8.7, 8.75, 8.8, 8.9, 9.0, 9.1, 9.2, 9.25, 9.3, 9.4, 9.5, 9.6, 9.7, 9.75, 9.8, 9.9, or 10 ng/mL.

27. The method of any one of the preceding claims, wherein the threshold blood plasma level is:

a peak blood plasma level of, of about, or of at least about, 2.5 ng/mL; and
a trough blood plasma level of, of about, or of at least of about, 2.5 ng/mL.

28. The method of any one of the preceding claims, wherein the threshold blood plasma level is:
a peak blood plasma level of, of about, or of at least about, 5 ng/mL; and
a trough blood plasma level of, of about, or of at least of about, 2.5 ng/mL.

29. The method of any one of the preceding claims, wherein the threshold blood plasma level is:
a peak blood plasma level of, or of about, 5 ng/mL; and
a trough blood plasma level of, or of about, 2.5 ng/mL.

30. The method of any one of the preceding claims, wherein Compound 1 is in a pharmaceutical composition having a release rate by weight of the compound in an aqueous medium that is one or more of release rates (a), (b) and (c), wherein:
(a) about 15% to about 35% by weight of the compound is released over the first two hours in the aqueous medium;
(b) about 24% to about 59% by weight of the compound is released over the first four hours in the aqueous medium; and/or
(c) about 43% to about 96% by weight of the compound is released over the first eight hours in the aqueous medium,
wherein the release rate is measured with USP Apparatus 1 (baskets) at 80 to 120 rpm in 400 to 600 mL of an aqueous medium at a pH of 6.3 to 7.3 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.04 to 0.06 M.

31. The method of any one of the preceding claims, wherein Compound 1 is in a pharmaceutical composition having a release rate release rate by weight of the compound in an aqueous medium that is one or more of release rates (a), (b) and (c), wherein:
(a) less than or equal to about 40% by weight of the compound is released over the first two hours in the aqueous medium;
(b) about 40% to about 60% by weight of the compound is released over the first five hours in the aqueous medium; and/or
(c) more than or equal to about 80% by weight of the compound is released over the first fourteen hours in the aqueous medium,

wherein the release rate is measured with USP Apparatus 1 (baskets) at 80 to 120 rpm in 400 to 600 mL of an aqueous medium at a pH of 6.3 to 7.3 at a temperature of 37°C ± 0.5 °C, comprising sodium phosphate at a concentration of 0.04 to 0.06 M.

32. The method of any one of the preceding claims, wherein the pharmaceutical composition comprises a first excipient and a second excipient, wherein the first excipient comprises hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C and the second excipient comprises hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C.

33. The method of any one of the preceding claims, wherein the pharmaceutical composition comprises a first excipient and a second excipient, wherein the first excipient comprises a release modifier having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C and the second excipient comprises a release modifier having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C.

34. The method of any one of the preceding claims, wherein the pharmaceutical composition has a release rate selected from:

(a);

(b);

(c);

(a) and (b);

(a) and (c);

(b) and (c);

(a), (b) and (c).

35. The method of any one of the preceding claims, wherein the first excipient is present in an amount equal to about 5% to about 45% by weight and the second excipient is present in an amount equal to about 5% to about 45% by weight.

36. The method of any one of the preceding claims, wherein the first excipient is present in an amount equal to about 5% to about 45% by weight and the second excipient is present in an amount equal to about 5% to about 45% by weight.

37. The method of any one of the preceding claims, wherein the first excipient is present in an amount equal to about 10% to about 40% by weight and the second excipient is present in an amount equal to about 10% to about 40% by weight.

38. The method of any one of the preceding claims, wherein the first excipient is present in an amount equal to about 12.5% to about 37.5% by weight and the second excipient is present in an amount equal to about 12.5% to about 37.5% by weight.

39. The method of any one of the preceding claims, wherein the first excipient is present in an amount equal to about 25% by weight and the second excipient is present in an amount equal to about 25% by weight.

40. The method of any one of the preceding claims, wherein the release rate is the release rate measured with USP Apparatus 1 (baskets) at 100 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C.

41. The method of any one of the preceding claims, wherein the aqueous medium comprises sodium phosphate at a concentration of 0.05 M.

42. The method of any one of the preceding claims, wherein the release rate is the release rate measured with USP Apparatus 2 (paddle) at 50 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C.

43. The method of any one of the preceding claims, wherein the aqueous medium comprises sodium phosphate at a concentration of 0.05 M.

44. The method of any one of the preceding claims, wherein the pharmaceutical composition is a tablet comprising a core and a coating.

45. The method of any one of the preceding claims, wherein the core comprises hydroxypropyl methylcellulose.

46. The method of any one of the preceding claims, wherein the coating does not comprise hydroxypropyl methylcellulose.

47. The method of any one of the preceding claims, wherein the therapeutically effective amount of Compound 1 is selected from:

about 0.01 % to about 1 % by weight of the composition;
about 0.01 % to about 0.6 % by weight of the composition;
about 0.02 % to about 0.3 % by weight of the composition;
about 0.03 % to about 0.2 % by weight of the composition;
about 0.04 % to about 0.12% by weight of the composition;
about 0.04 % to about 0.1% by weight of the composition;
about 0.04 % to about 0.1% by weight of the composition;
about 0.05 % to about 0.08% by weight of the composition;
about 0.06 % by weight of the composition;
about 0.01 mg to about 1 mg.

48. The method of any one of the preceding claims, wherein the therapeutically effective amount of Compound 1 is suitable for administration to an individual once daily.

49. The method of any one of the preceding claims, wherein the pharmaceutical composition comprises about 0.05% by weight of Compound 1; about 25% by weight of hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C; and about 25% by weight of hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C.

50. The method of any one of the preceding claims, wherein the pharmaceutical composition comprises about 0.05 mg of Compound 1; about 25 mg of hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C; and about 25 mg of hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C.

51. The method of any one of the preceding claims, wherein the pharmaceutical composition comprises about 0.01 mg to about 0.8 mg of Compound 1; about 5 mg to about 45 mg of hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800

mPA seconds when present in an amount of about 2% in water at 20° C; and about 5 mg to about 45 mg of hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C.

52. The method of any one of the preceding claims, wherein the pharmaceutical composition comprises about 0.01 mg to about 0.8 mg of Compound 1; about 25 mg of hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C; and about 25 mg of hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C.

53. The method of any one of the preceding claims, wherein the pharmaceutical composition comprises about 0.01 mg to about 0.8 mg of Compound 1; about 25 mg of hydroxypropyl methylcellulose having a viscosity of about 2300 mPA seconds to about 3800 mPA seconds when present in an amount of about 2% in water at 20° C; and about 25 mg of hydroxypropyl methylcellulose having a viscosity of about 75 mPA seconds to about 120 mPA seconds when present in an amount of about 2% in water at 20° C; about 25mg of Methocel™ K4M Premium CR; and about 25 mg of Methocel™ K100 Premium LVCR.

54. The method of any one of the preceding claims, wherein the pharmaceutical composition is storage-stable.

55. The method of any one of the preceding claims, wherein the pharmaceutical composition is a tablet.

56. The method of any one of the preceding claims, wherein the tablet contains 0.05 mg, 0.25 mg, or 0.4 mg of Compound 1.

57. The method of any one of the preceding claims, wherein the pharmaceutical composition is a capsule.

58. The method of any one of the preceding claims, wherein the release rate of Compound 1 after storage of the pharmaceutical composition at 40°C and 75% RH for at least about one month does not vary at any given dissolution time point equal or greater than 2 hours by more than about 20% of the release rate of the compound prior to storage, wherein the release rate after

storage and prior to storage are each measured with USP Apparatus 1 (baskets) at 100 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C, wherein the aqueous medium comprises sodium phosphate at a concentration of 0.05 M.

59. The method of any one of the preceding claims, wherein the pharmaceutical composition comprises a first excipient and a second excipient, wherein the first excipient comprises a copolymer comprising (a) a first polyoxyethylene chain; (b) a poly(propylene oxide) chain bonded to the first polyoxyethylene chain; and (c) a second polyoxyethylene chain bonded to the poly(propylene oxide) chain; and the second excipient comprises an ester of a polyalcohol and a fatty acid.

60. The method of any one of the preceding claims, wherein the first excipient comprises Poloxamer 188.

61. The method of any one of the preceding claims, wherein the second excipient comprises glycerol monostearate and has a monoester content of at least about 90%.

62. The method of any one of the preceding claims, wherein the second excipient comprises glycerol monostearate and has a monoester content of at least about 95%.

63. The method of any one of the preceding claims, wherein the pharmaceutical composition is a cured composition.

64. The method of any one of the preceding claims, wherein the ratio by weight of the first excipient to the second excipient is selected from:

about 70:30 to about 10:90;
about 50:50 to about 30:70;
about 70:30;
about 50:50;
about 40:60; and
about 30:70.

65. The method of any one of the preceding claims, wherein the release rate is the release rate measured with USP Apparatus 2 (paddle) at 50 rpm in 500 mL of an aqueous medium at a pH of 6.8 at a temperature of 37°C ± 0.5 °C.

66. The method of any one of the preceding claims, wherein the aqueous medium comprises sodium phosphate at a concentration of 0.05 M.

67. The method of any one of the preceding claims, wherein the compound selected from 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof is 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1).

68. The method of any one of the preceding claims, wherein the compound is 2-(((1*r*,4*r*)-4-(((4-chlorophenyl)(phenyl)carbamoyloxy)methyl)cyclohexyl)methoxy)acetic acid (Compound 1).

69. The method of any one of the preceding claims, wherein the pharmaceutical composition exhibits peaks in the PXRD spectrum having the following 2θ values: 19.7°, 20.2°, 20.7°, 22.6°, 23.1°, and 23.7°.

70. A method for the treatment of a PGI2 receptor-mediated disorder in an individual, comprising:

administering to the individual in need thereof a starting dose of Compound 1 wherein the starting dose is an amount equivalent to 0.05 mg of Compound 1 daily for about one week;

provided that the individual tolerates the starting dose, administering an increased dose for about one week, wherein the increased dose is an amount equivalent to 0.05 mg greater than the starting dose,

provided that the individual tolerates the increased dose, further increasing the dose.

71. The method of any one of the preceding claims, further comprising repeating the cycle of administering the increased dose for a period of about one week and then further increasing the dose, so long as the patient tolerates the further increased dose, until an optimized dose is administered.

72. A method for the treatment of pulmonary arterial hypertension (PAH) in an individual, comprising:

administering to the individual in need thereof a starting dose of Compound 1 wherein the starting dose is an amount equivalent to 0.05 mg of Compound 1 daily for about one week;

provided that the individual tolerates the starting dose, administering an increased dose for about one week, wherein the increased dose is an amount equivalent to 0.05 mg greater than the starting dose,

provided that the individual tolerates the increased dose, further increasing the dose.

73. The method of any one of the preceding claims, further comprising repeating the cycle of administering the increased dose for a period of about one week and then further increasing the dose, so long as the patient tolerates the further increased dose, until an optimized dose is administered.

74. The method of any one of the preceding claims, wherein Compound 1 is titrated over about, or at least about, 9 weeks.

75. The method of any one of the preceding claims, wherein Compound 1 is titrated over about, or at least about, 16 weeks.

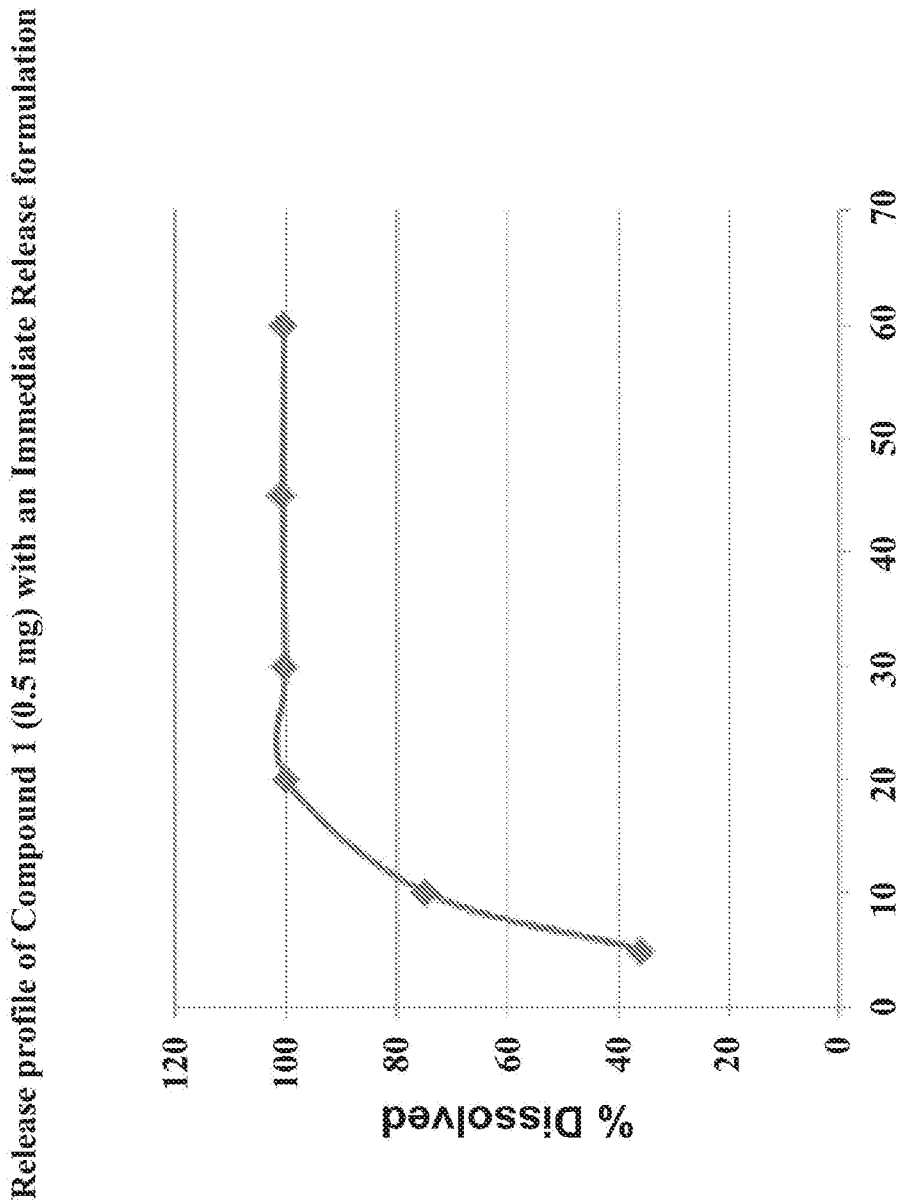

Release profile of Compound 1 (0.5 mg) with an Immediate Release formulation
% Dissolved
120
100
80
60
40
20
0
0
10
20
30
40
50
60
70
Time (mins)

FIGURE 1

Flowchart of Example of Process for Manufacturing a Modified Release Composition Comprising Compound 1 ("API" in the flowchart)

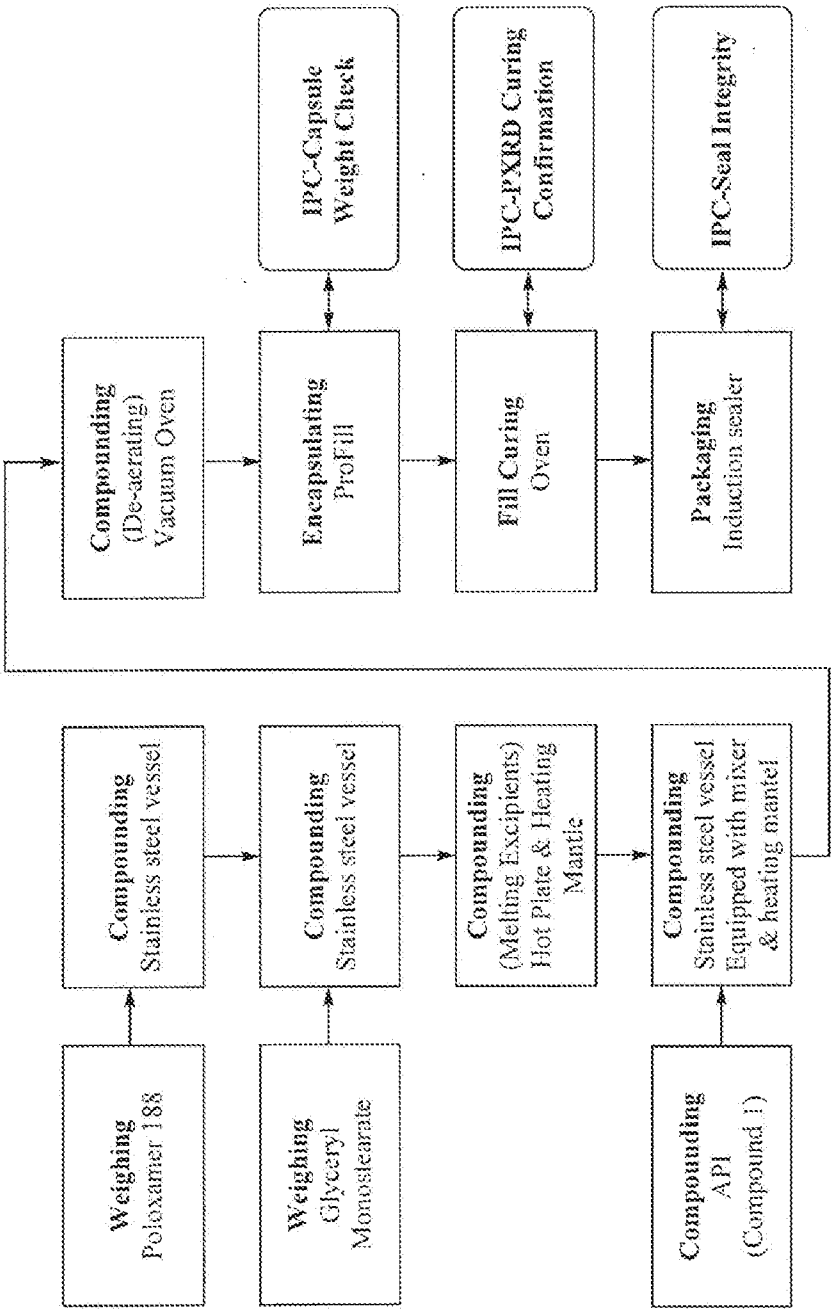
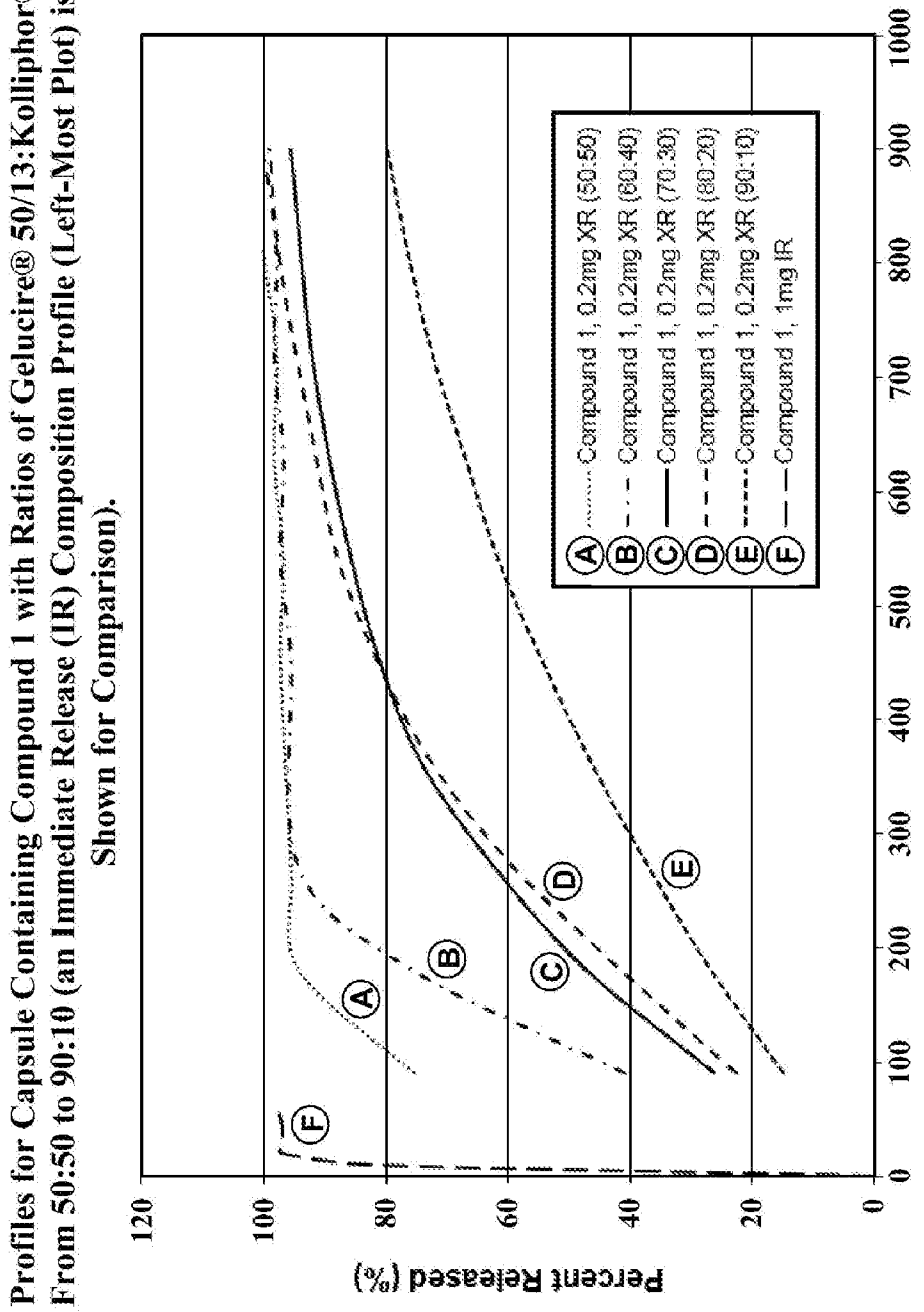


FIGURE 2



Dissolution Profiles for Capsule Containing Compound 1 with Ratios of Gelucire® 50/13:Kolliphor® RH40 Varying From 50:50 to 90:10 (an Immediate Release (IR) Composition Profile (Left-Most Plot) is also Shown for Comparison).

FIGURE 3

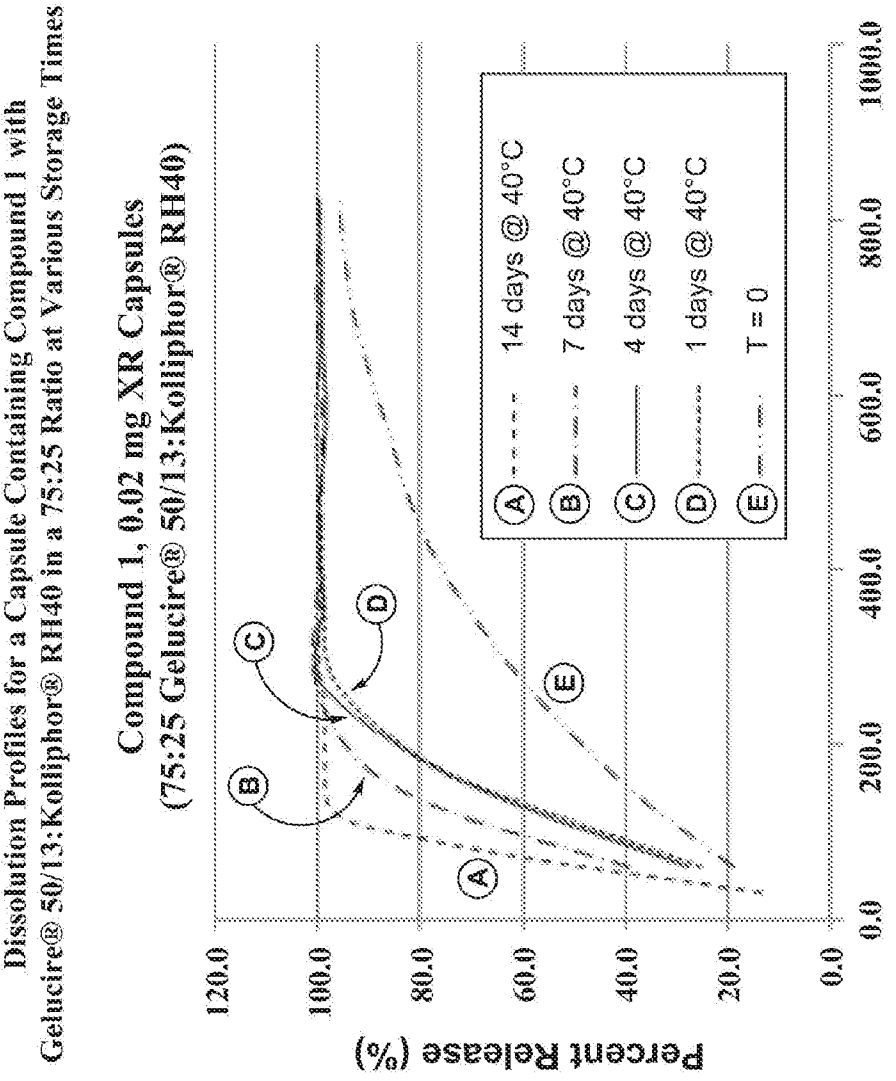

Dissolution Profiles for a Capsule Containing Compound 1 with
Gelucire® 50/13:Kolliphor® RH40 in a 75:25 Ratio at Various Storage Times
Compound 1, 0.02 mg XR Capsules
(75:25 Gelucire® 50/13:Kolliphor® RH40)
Percent Release (%)
120.0
100.0
80.0
60.0
40.0
20.0
0.0
0.0
200.0
400.0
600.0
800.0
1000.0
Time (min)
A - - - - - 14 days @ 40°C
B — · — · — 7 days @ 40°C
C ——— 4 days @ 40°C
D ——— 1 days @ 40°C
E — · — · — T = 0

FIGURE 4

Dissolution Profiles for 0.04 mg Capsule of Compound 1 in Gelucire® 50/13,
(i) initially (time = 0) Figure 5A;
(ii) after 18 hours at 40°C, Figure 5B; and
(iii) after storage at 40°C and 75% RH for two weeks, Figure 5C.

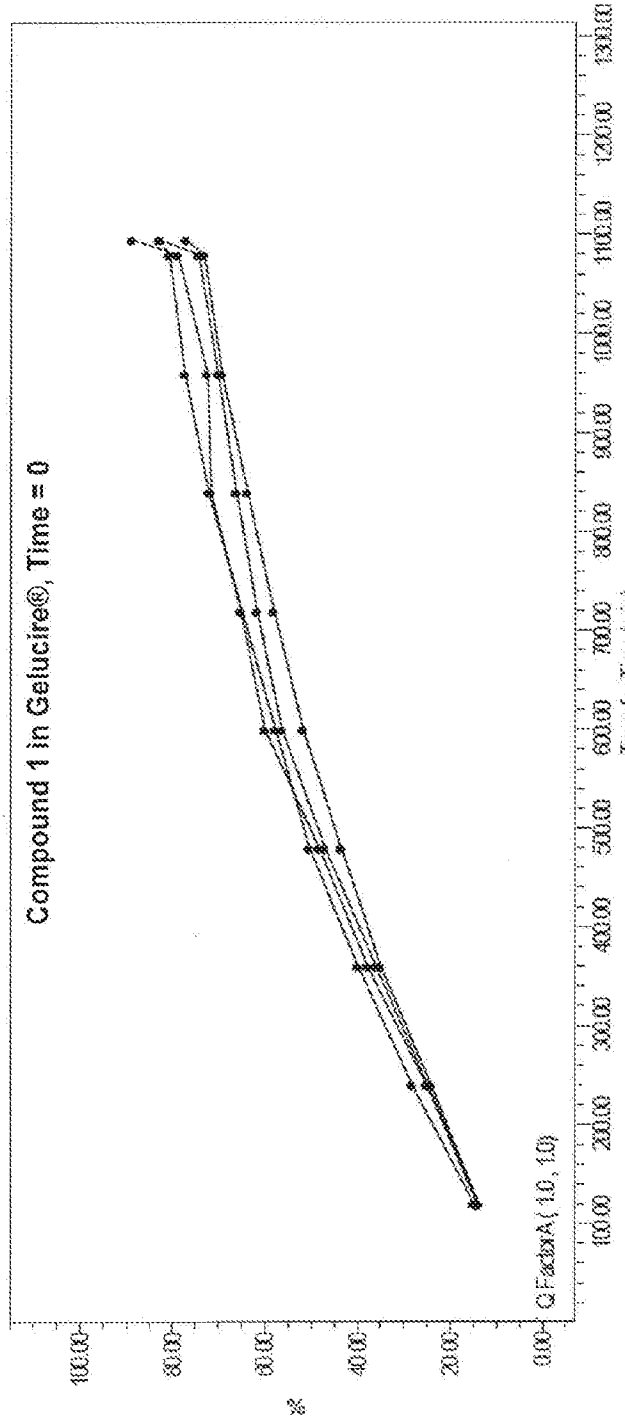


FIGURE 5A

Dissolution Profiles for 0.04 mg Capsule of Compound 1 in Gelucire® 50/13,
(i) initially (time = 0) Figure 5A;
(ii) after 18 hours at 40°C, Figure 5B; and
(iii) after storage at 40°C and 75% RH for two weeks, Figure 5C.

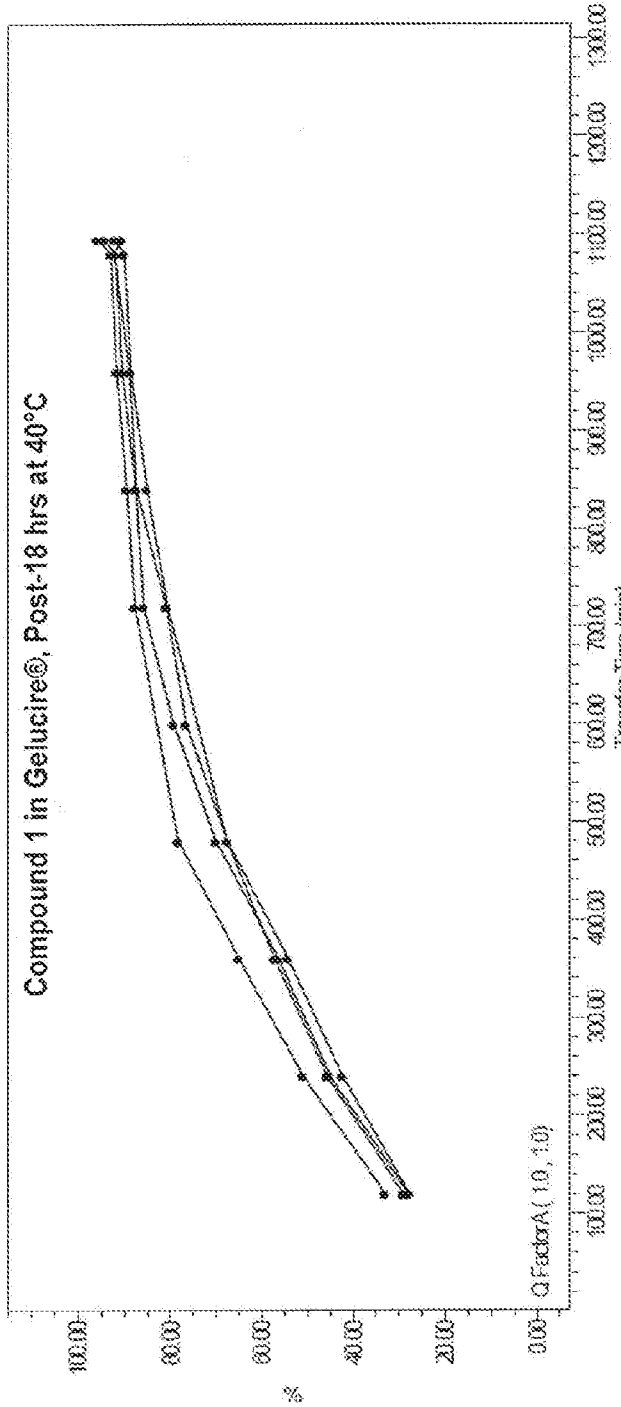


FIGURE 5B

Dissolution Profiles for 0.04 mg Capsule of Compound 1 in Gelucire® 50/13,
(i) initially (time = 0) Figure 5A;
(ii) after 18 hours at 40°C, Figure 5B; and
(iii) after storage at 40°C and 75% RH for two weeks, Figure 5C.

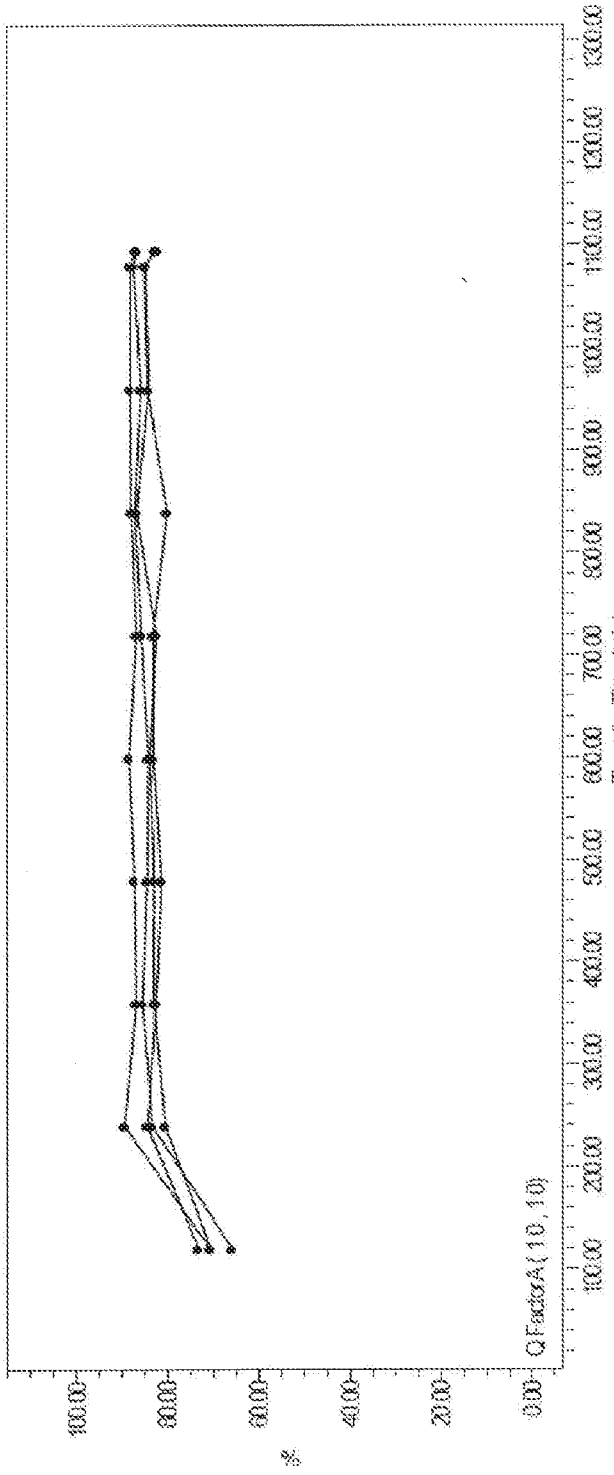


FIGURE 5C

Dissolution Profile for a Capsule Containing Compound 1 in 50:50 Poloxamer 188:Food Grade GMS, (i) uncured (T = 0 in the figure), (ii) after curing at 50°C for 18 hours, (iii) after storage at 40°C and 75% RH for one week post-curing, (iv) after storage at 40°C and 75% RH for two weeks post-curing, and (v) after storage at 40°C and 75% RH for four weeks post-curing.

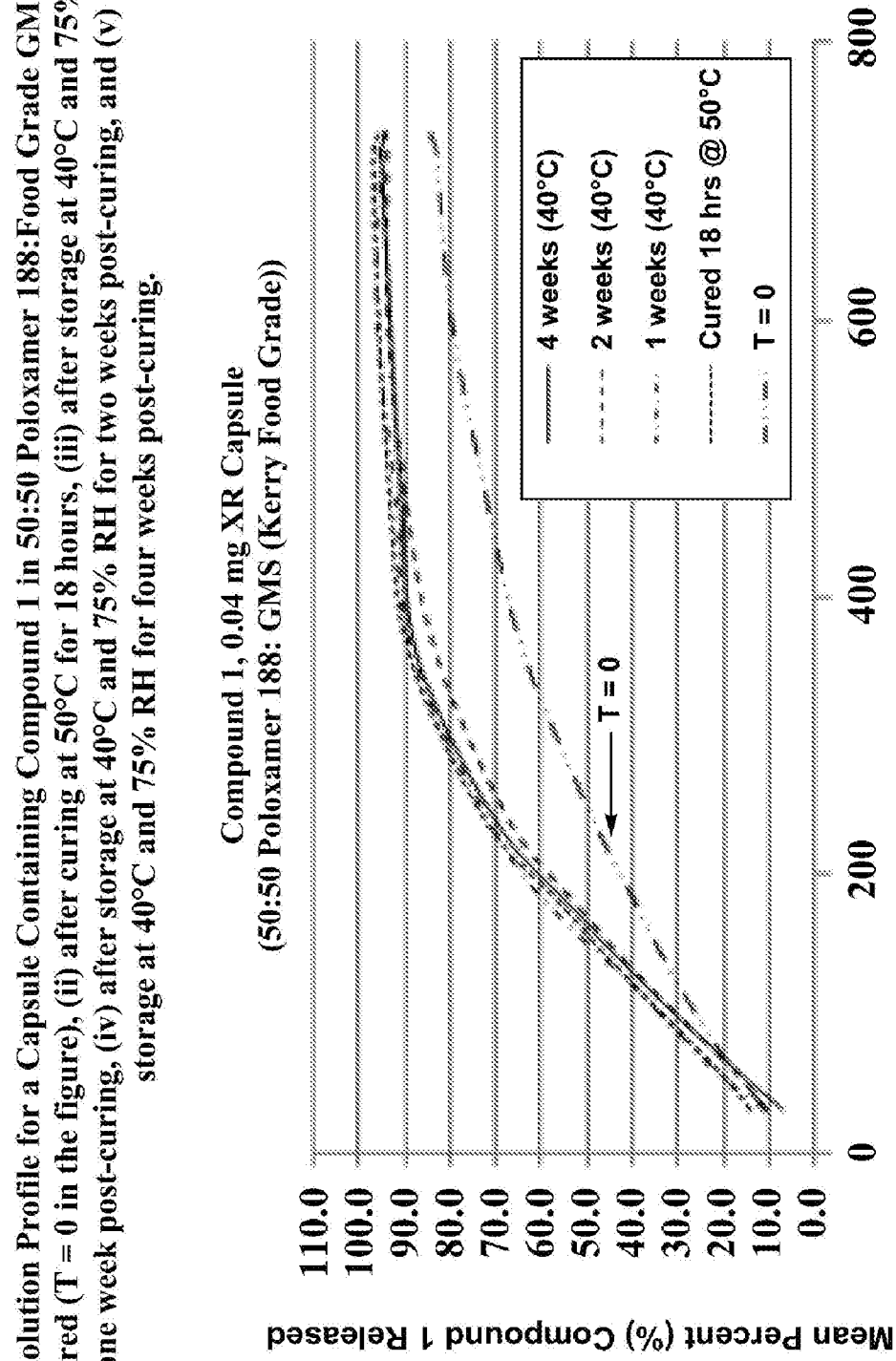


FIGURE 6

Comparison of Powder X-Ray Diffraction (PXRD) spectra of a capsule containing Poloxamer 188 and food grade GMS in a 50:50 Ratio by weight (i) before curing ("T=0", dashed line), and (ii) after curing at 50°C for 18 hours (solid line).

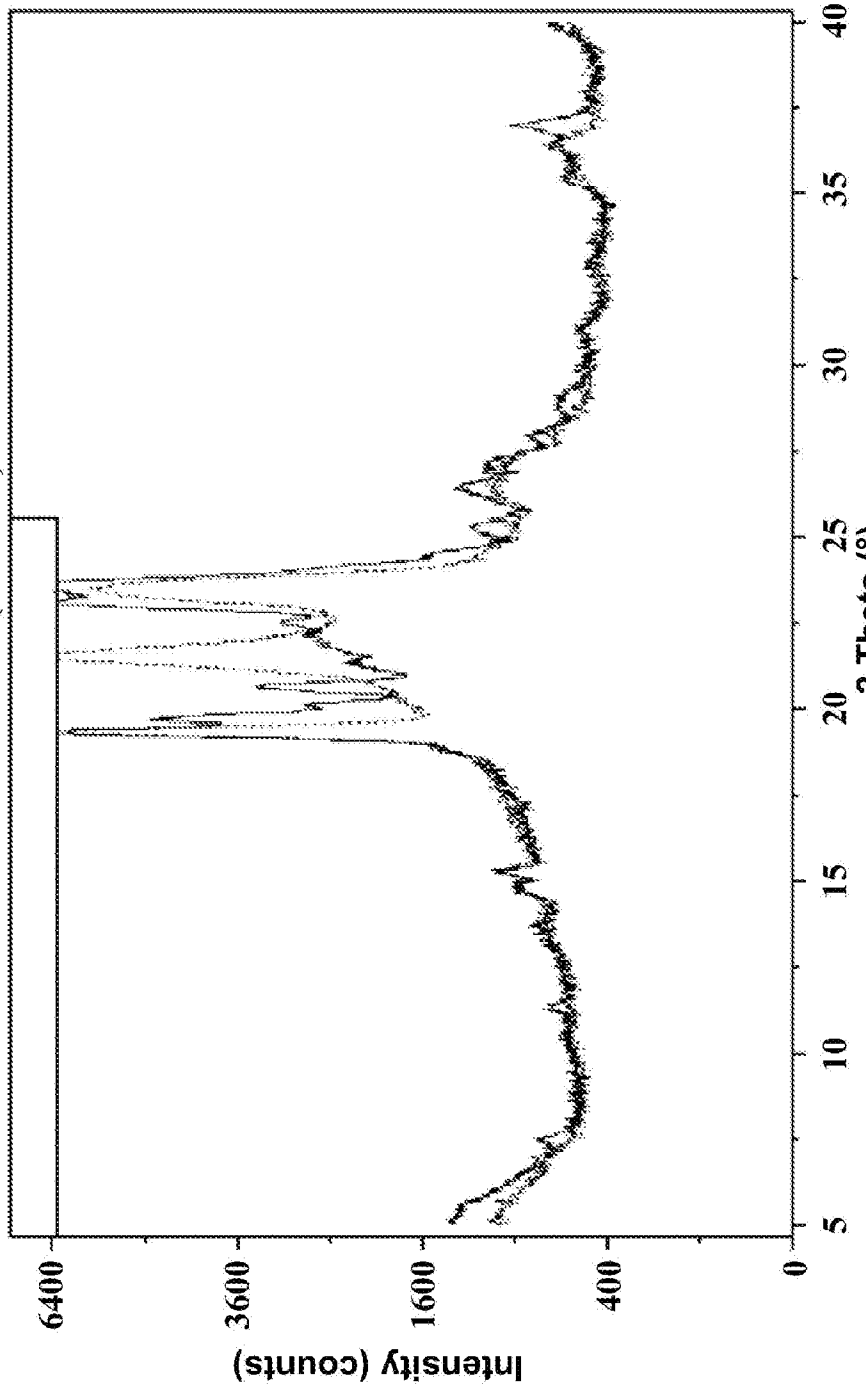


FIGURE 7A

Powder X-Ray Diffraction spectrum of a capsule comprising Poloxamer 188 and research grade GMS in a 50:50 Ratio by weight (i) before curing, and (ii) after curing at 50°C for 18 hours. Also shown for comparison is (iii) a PXRD spectrum of a capsule comprising Poloxamer 188 and food grade GMS in a 50:50 Ratio by weight after curing at 50°C for 18 hours.

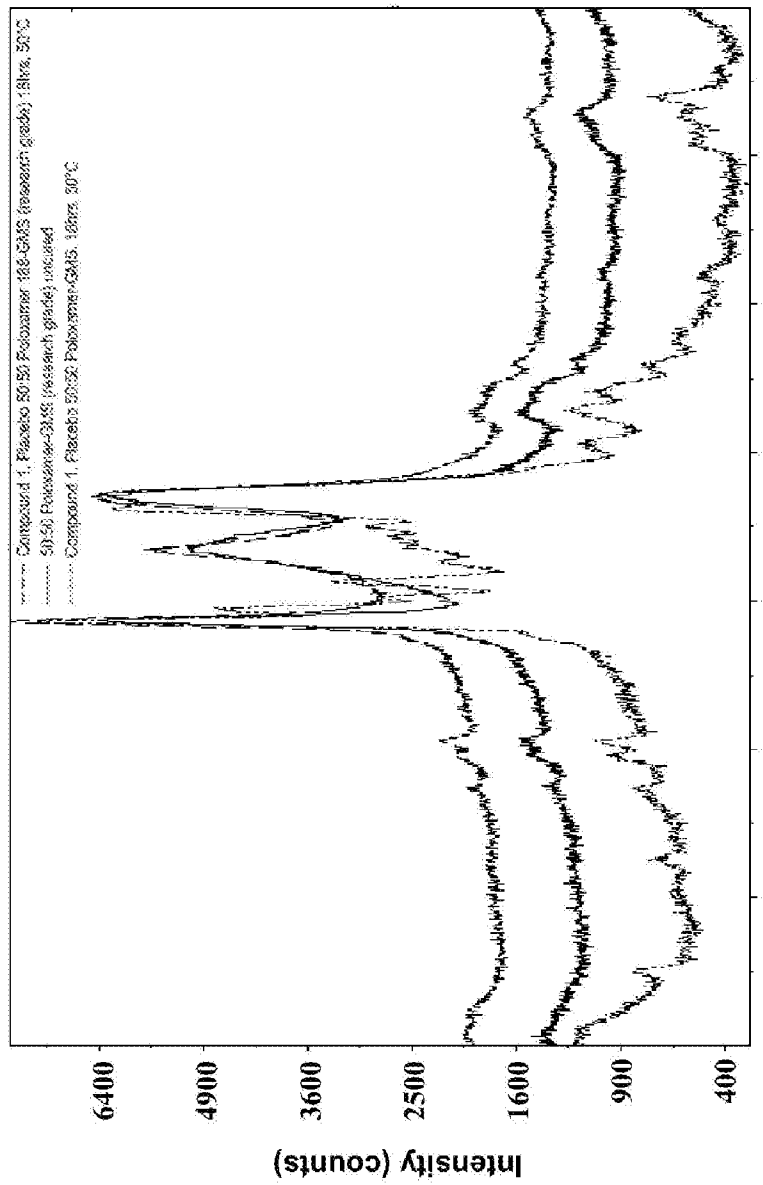


FIGURE 7B

Powder X-Ray Diffraction spectra of capsules comprising Poloxamer 188 and research grade GMS in a 50:50 Ratio by weight (i) before curing ("uncured"), (ii) after partial curing at 47.5°C for 10 hours ("partially cured"), and (iii) after curing at 50°C for 18 hours ("fully cured")

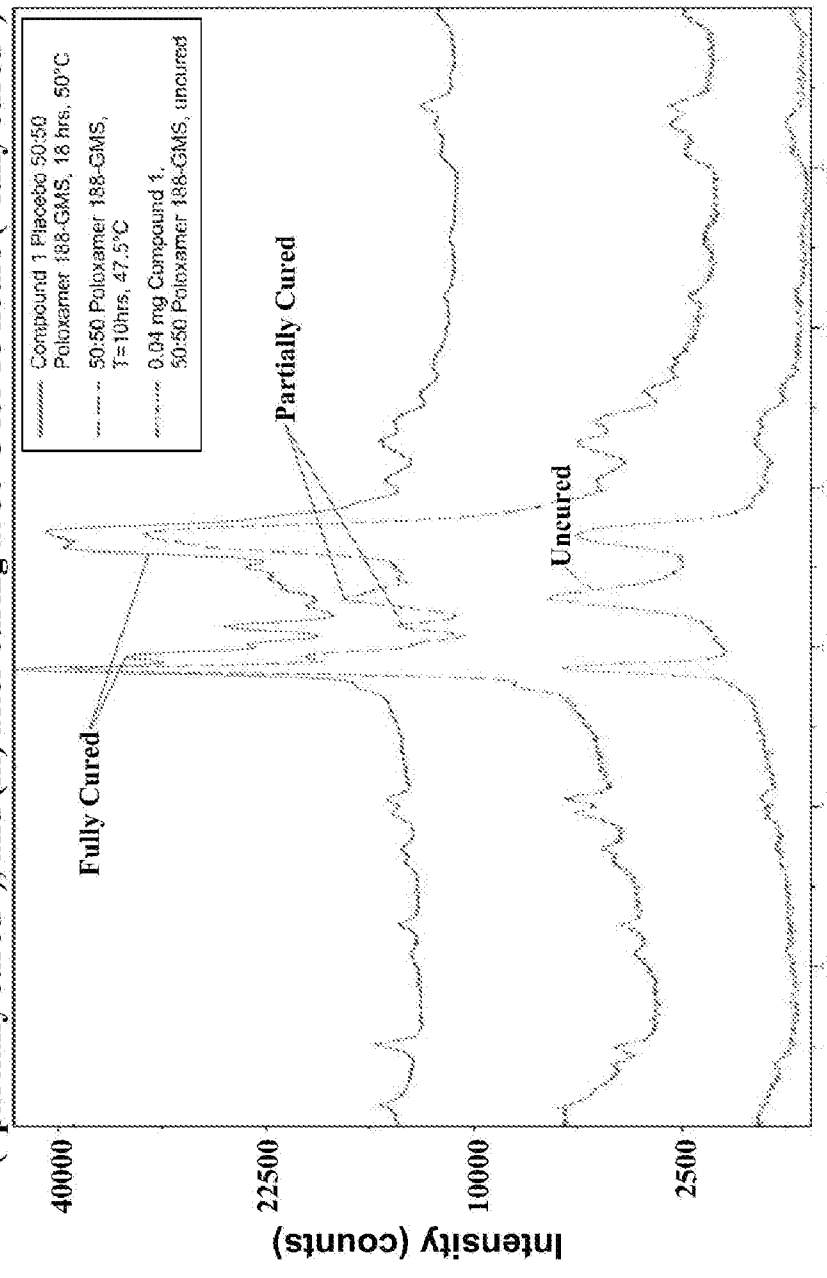


FIGURE 7C

Release Profile of Pharmaceutical Composition Containing Poloxamer 188 and Food Grade GMS in a 70:30 Ratio by weight, and 0.5 mg of Compound 1 (a) after curing at 50°C for 18 hours (diamonds), and (b) after storage at 40°C and 75% RH for one month (squares).

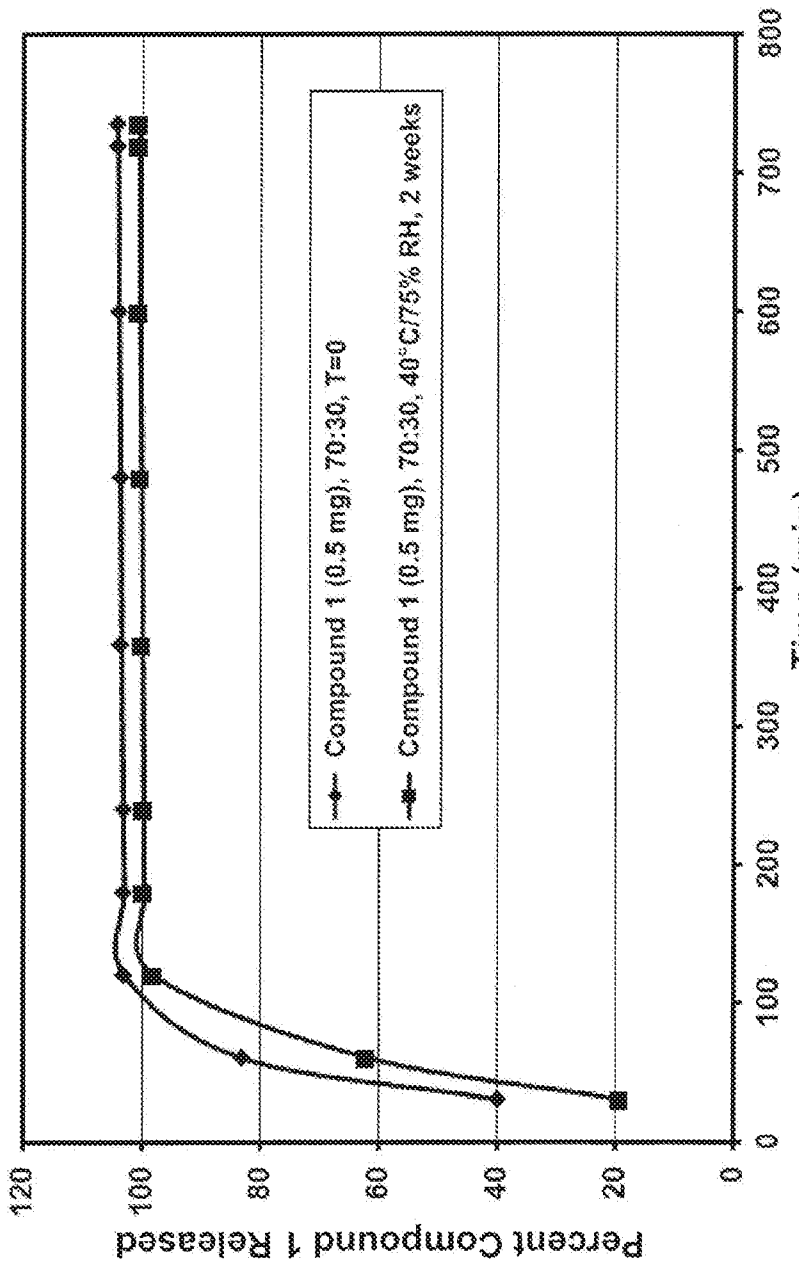
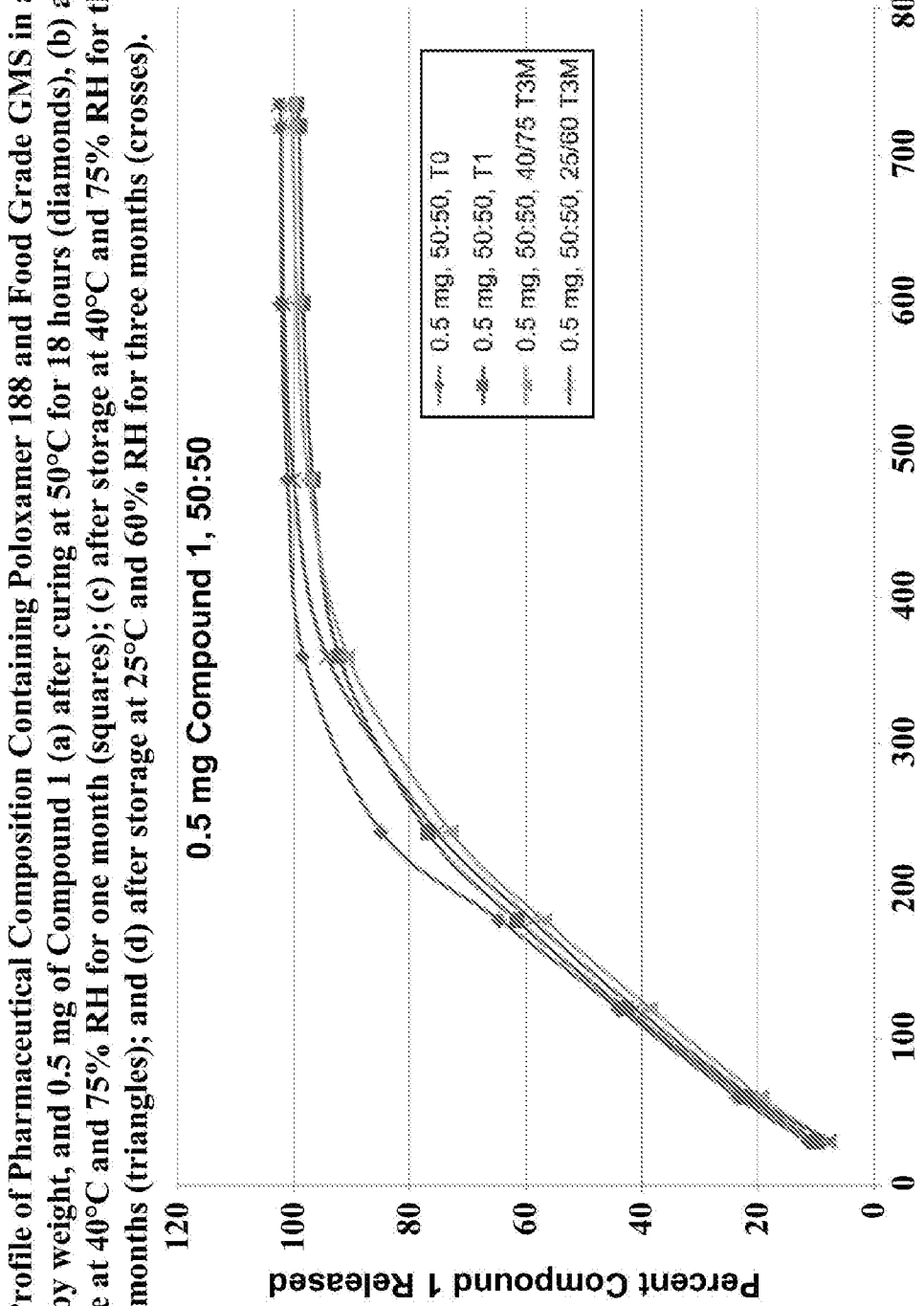


FIGURE 8



Release Profile of Pharmaceutical Composition Containing Poloxamer 188 and Food Grade GMS in a 50:50 Ratio by weight, and 0.5 mg of Compound 1 (a) after curing at 50°C for 18 hours (diamonds), (b) after storage at 40°C and 75% RH for one month (squares); (c) after storage at 40°C and 75% RH for three months (triangles); and (d) after storage at 25°C and 60% RH for three months (crosses).

FIGURE 9

Release Profile of Pharmaceutical Composition Containing Poloxamer 188 and Food Grade GMS in a 30:70 Ratio by weight, and 0.5 mg of Compound 1 (a) after curing at 50°C for 18 hours (diamonds), (b) after storage at 40°C and 75% RH for one month (squares); (c) after storage at 25°C and 60% RH for three months (triangles); and (d) after storage at 40°C and 75% RH for three months (crosses).

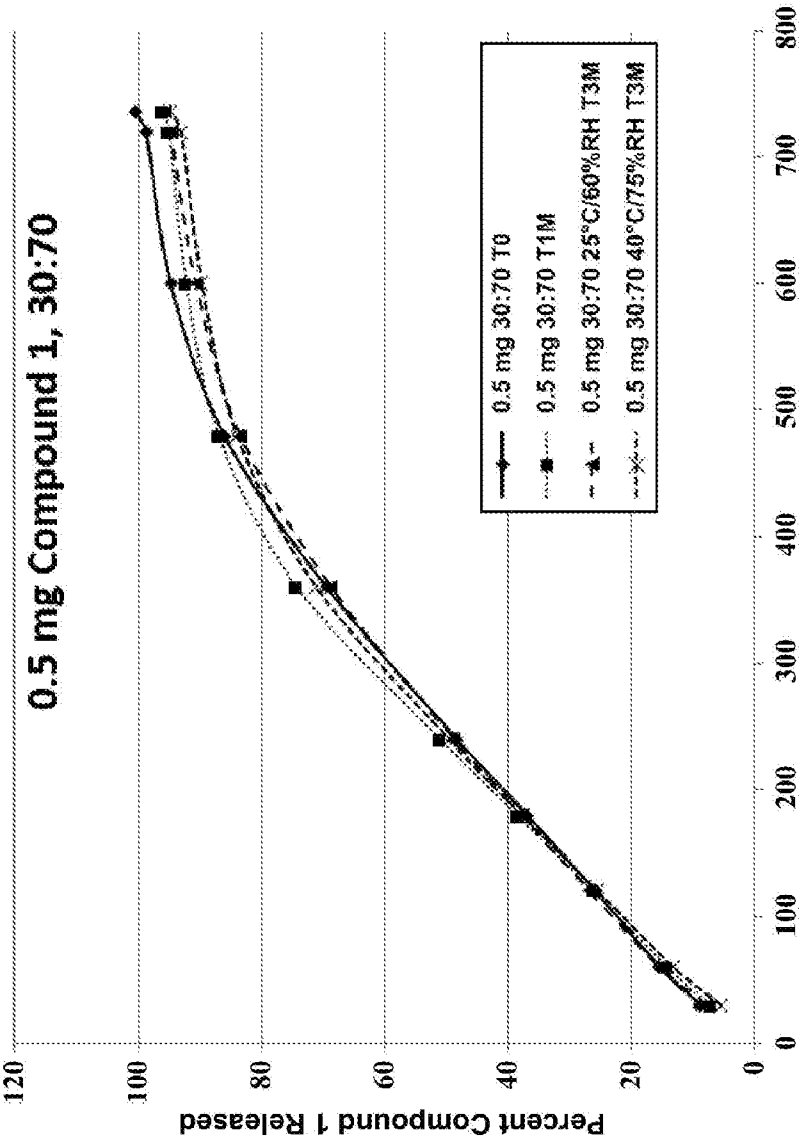


FIGURE 10

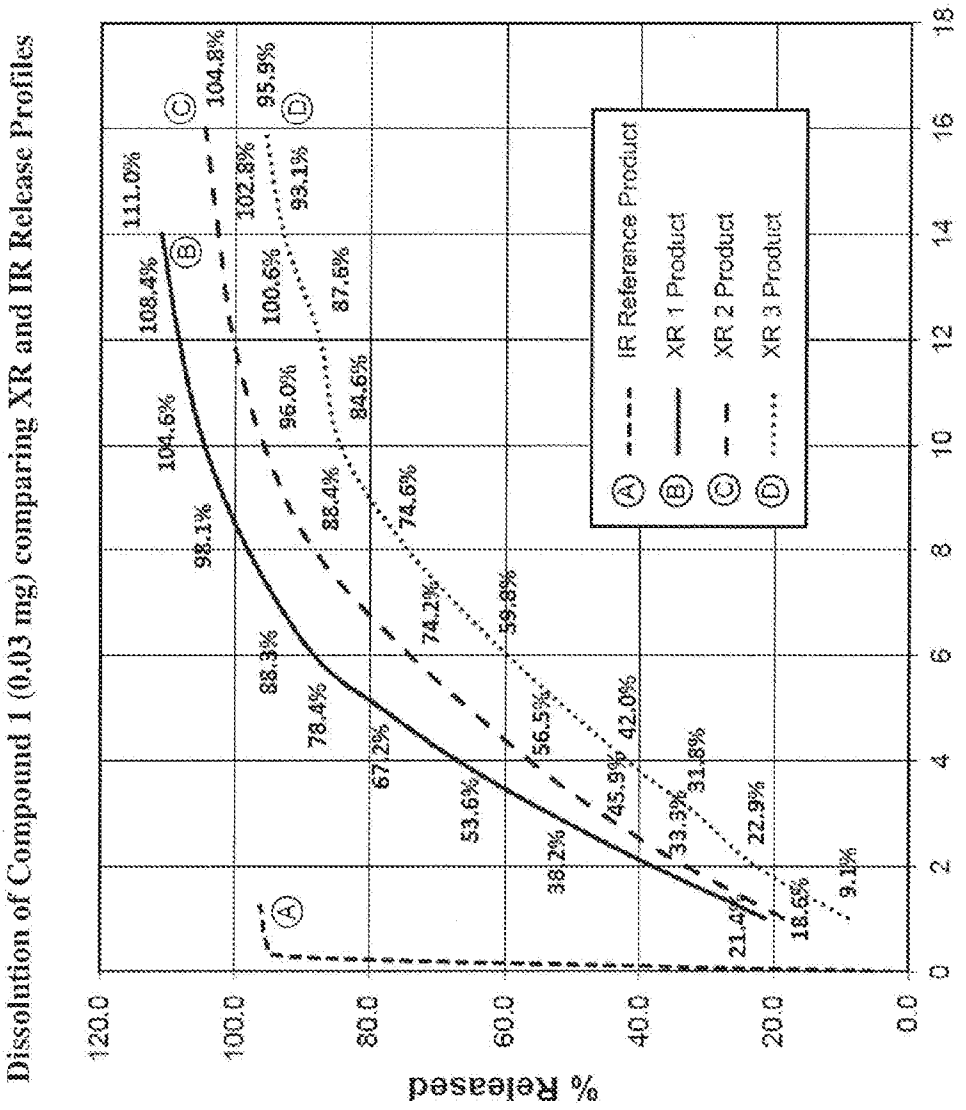

Dissolution of Compound 1 (0.03 mg) comparing XR and IR Release Profiles
% Released
Time (hrs)
IR Reference Product
XR 1 Product
XR 2 Product
XR 3 Product
A
B
C
D
120.0
100.0
80.0
60.0
40.0
20.0
0.0
0
2
4
6
8
10
12
14
16
18
111.0%
108.4%
104.6%
98.1%
88.3%
78.4%
67.2%
53.6%
38.2%
21.4%
104.8%
102.8%
96.0%
88.4%
74.2%
56.5%
45.9%
33.3%
18.6%
95.9%
93.1%
84.6%
74.6%
59.8%
42.0%
31.8%
22.9%
9.1%
100.6%
87.6%

FIGURE 11A

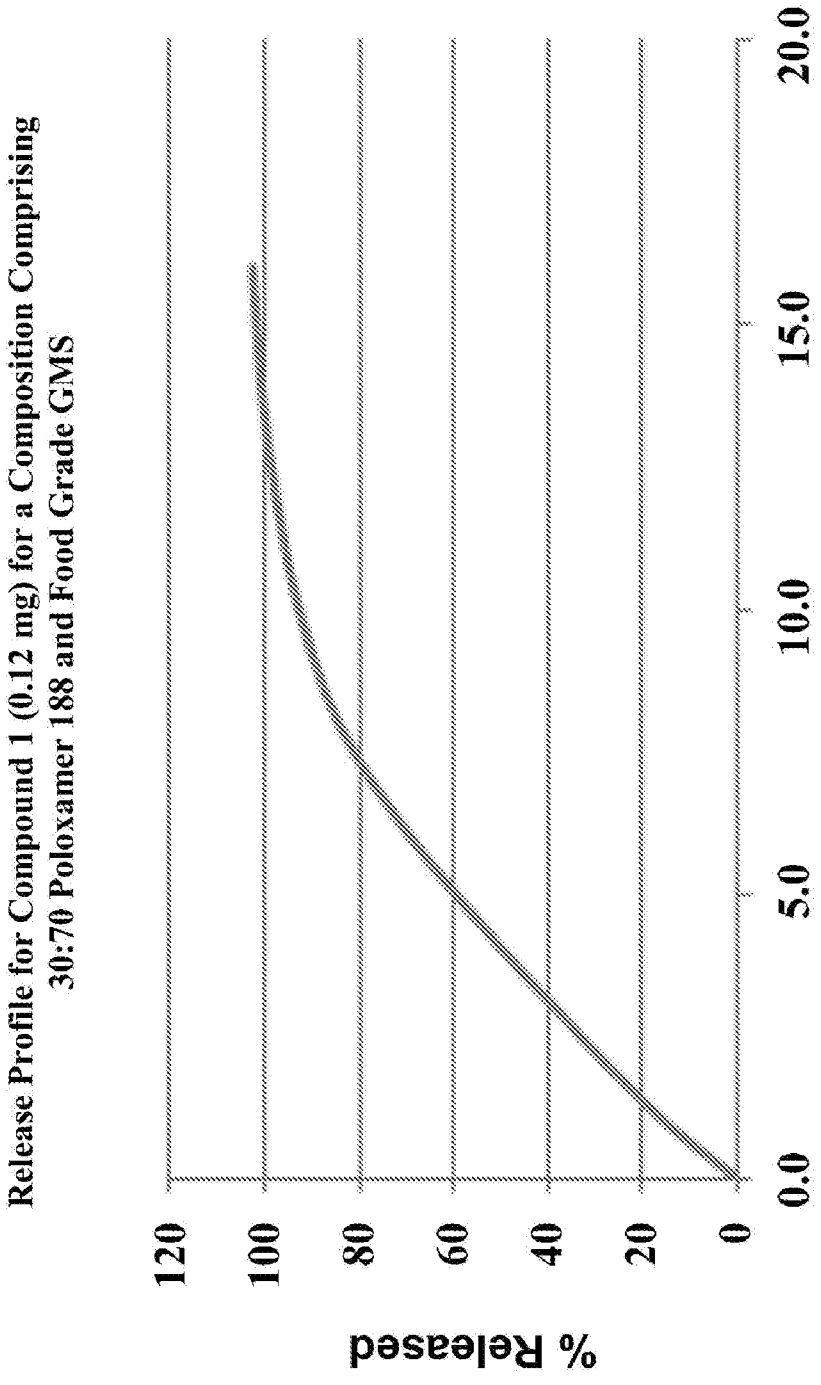

Release Profile for Compound 1 (0.12 mg) for a Composition Comprising
30:70 Poloxamer 188 and Food Grade GMS
% Released
120
100
80
60
40
20
0
0.0
5.0
10.0
15.0
20.0
Time (hrs)

FIGURE 11B

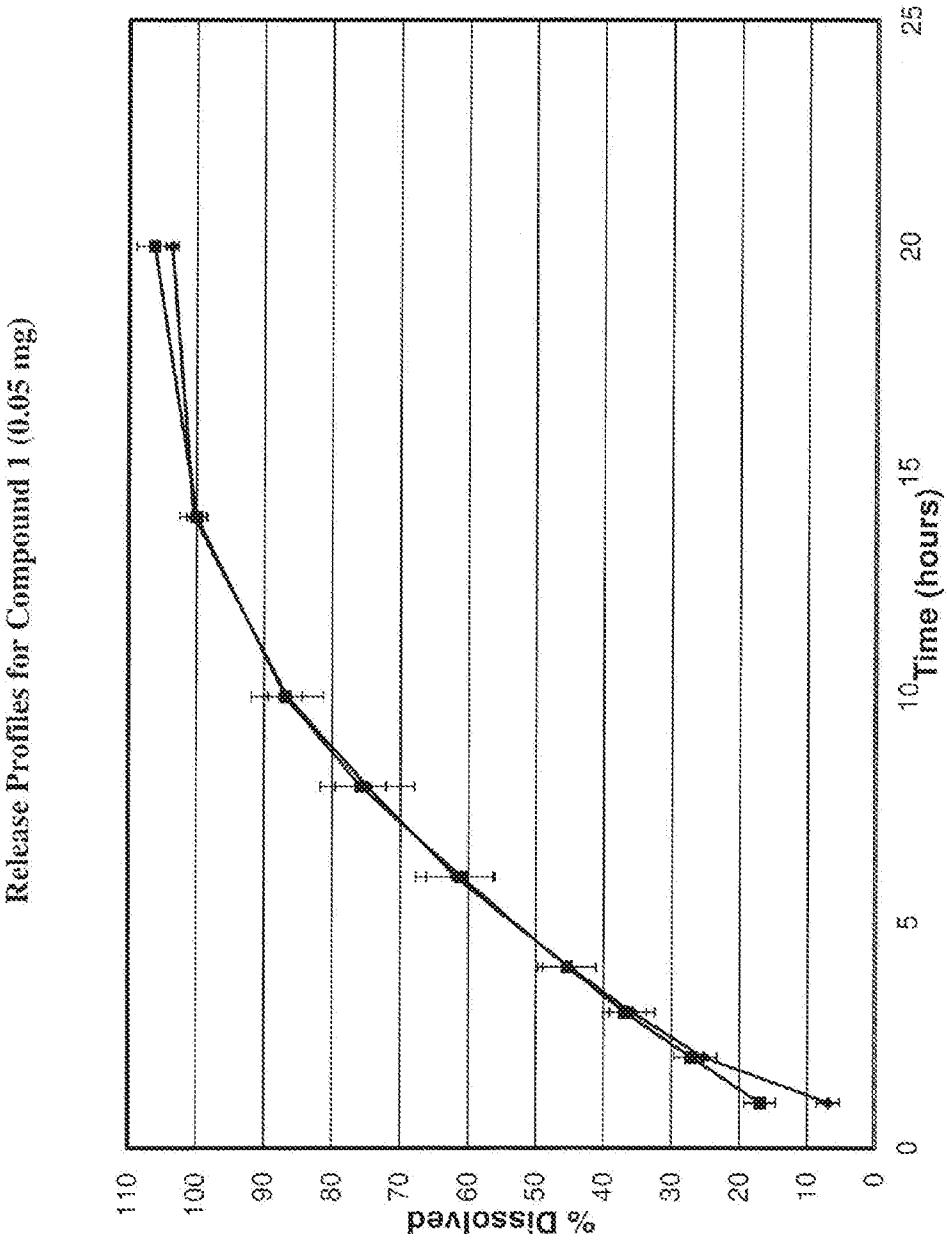

Release Profiles for Compound 1 (0.05 mg)
% Dissolved
0
10
20
30
40
50
60
70
80
90
100
110
0
5
10
15
20
25
Time (hours)

FIGURE 12

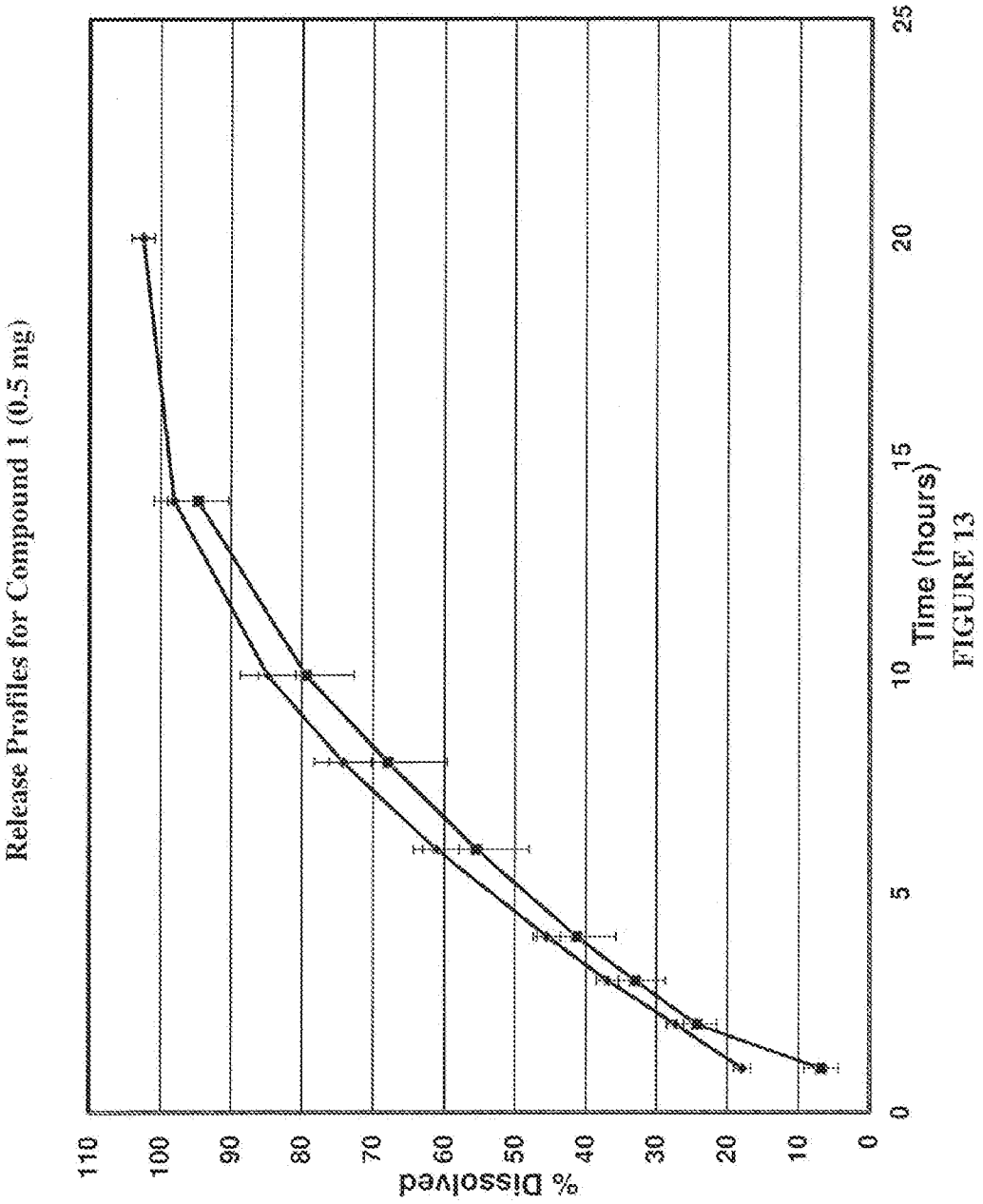

Release Profiles for Compound 1 (0.5 mg)
% Dissolved
110
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
Time (hours)

FIGURE 13

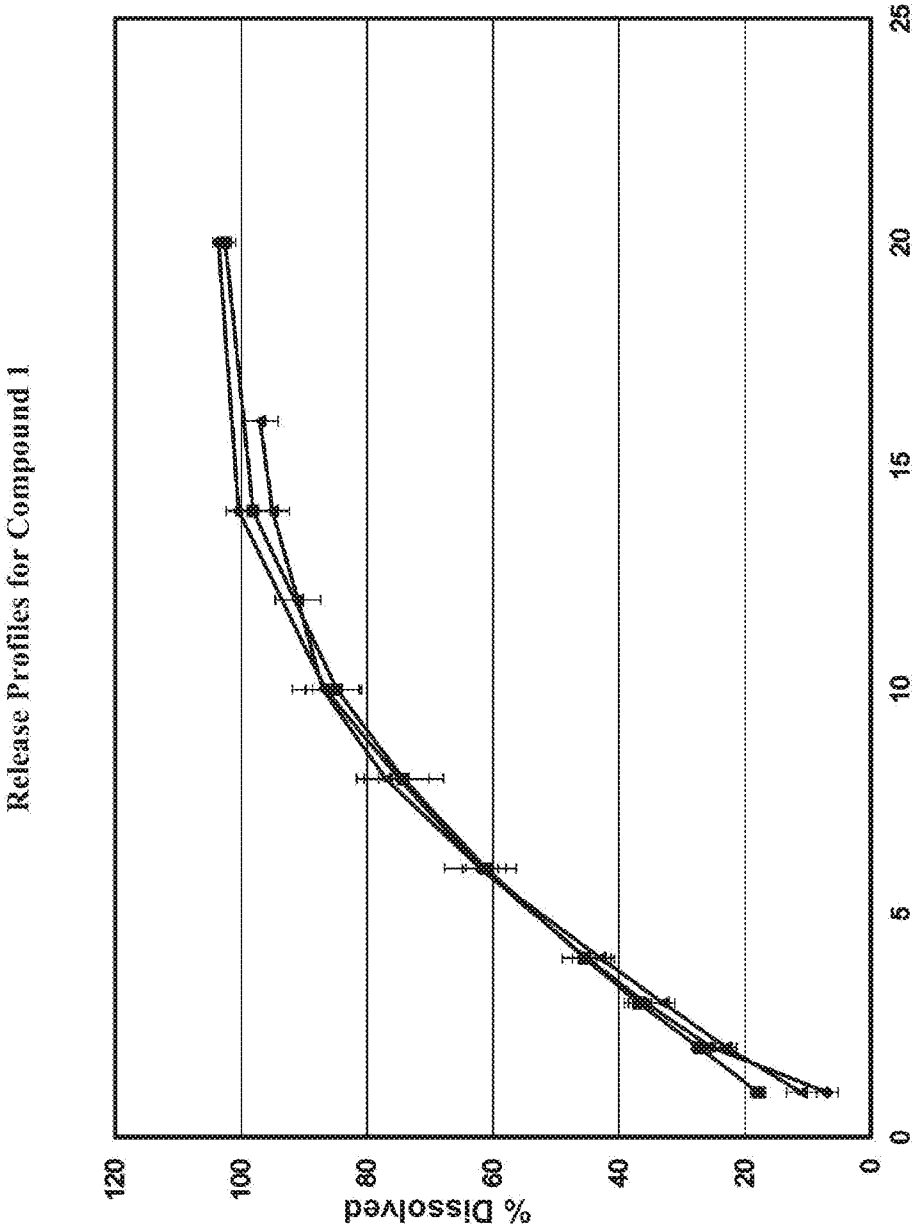

Release Profiles for Compound 1
% Dissolved
120
100
80
60
40
20
0
0
5
10
15
20
25
Time point (hours)

FIGURE 14

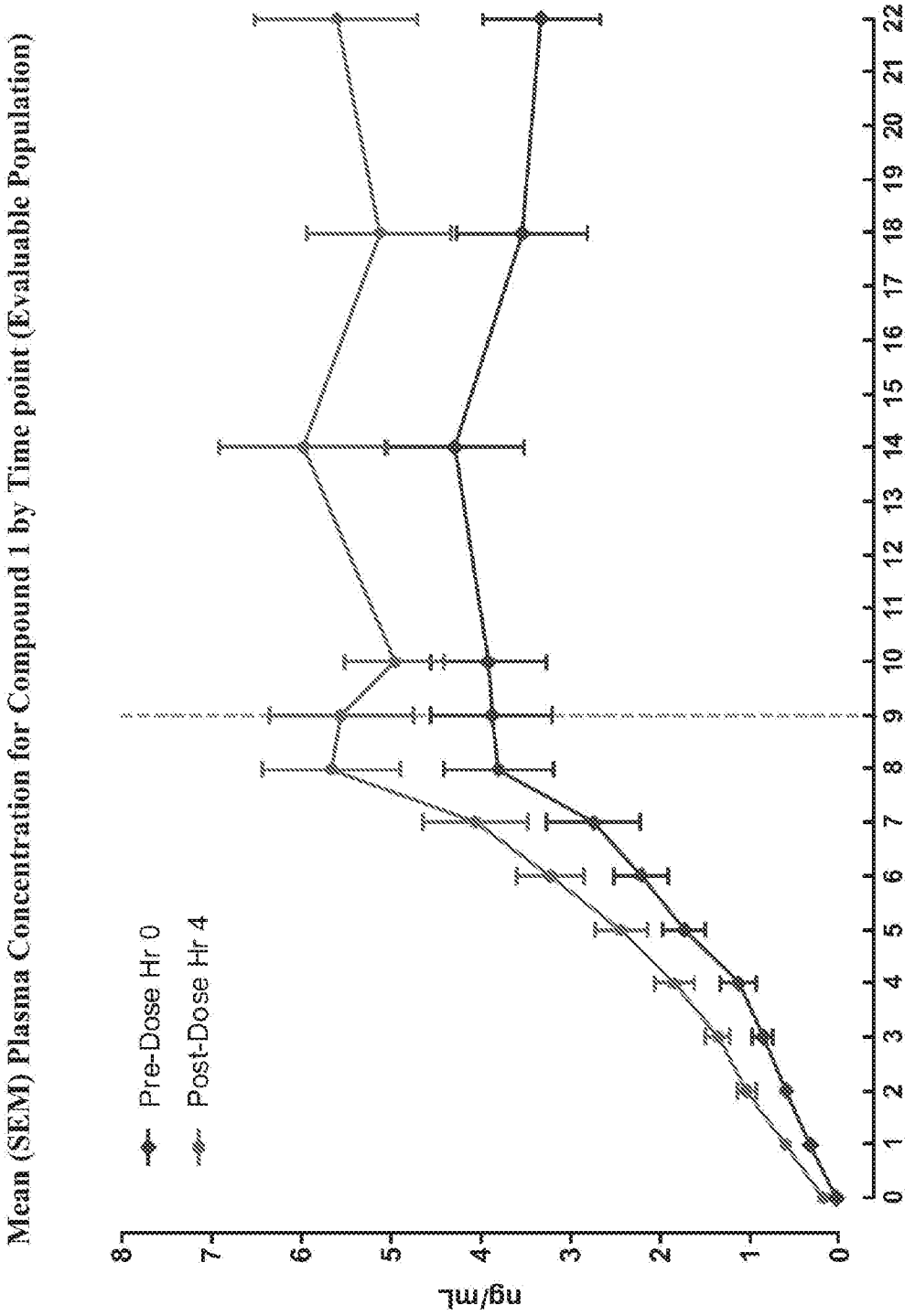

Mean (SEM) Plasma Concentration for Compound 1 by Time point (Evaluable Population)
Pre-Dose Hr 0
Post-Dose Hr 4
ng/mL
0
1
2
3
4
5
6
7
8
Weeks
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22

FIGURE 15

Figure 16

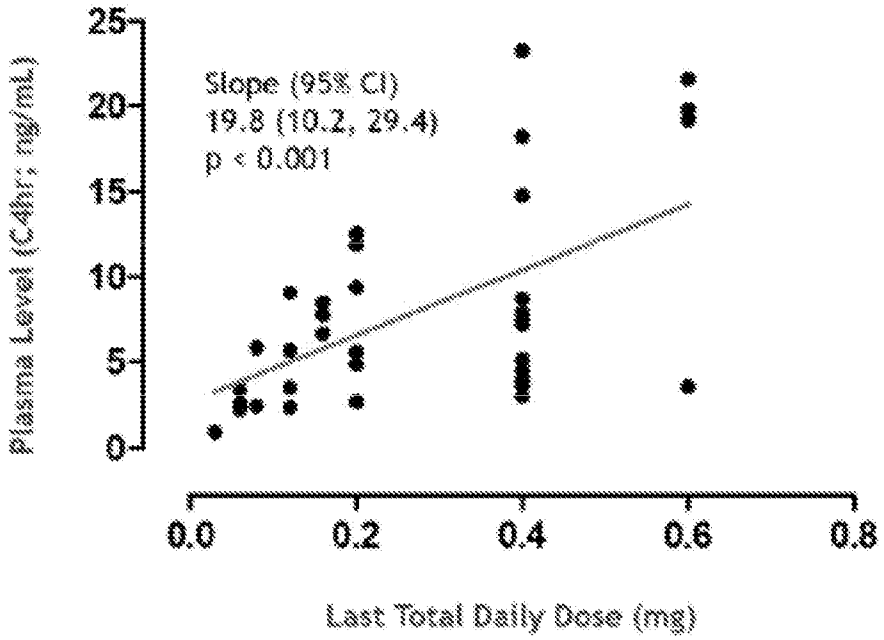

Plasma Level (C4hr; ng/mL)
25
20
15
10
5
0
Slope (95% CI)
19.8 (10.2, 29.4)
p < 0.001
0.0
0.2
0.4
0.6
0.8
Last Total Daily Dose (mg)

Figure 17

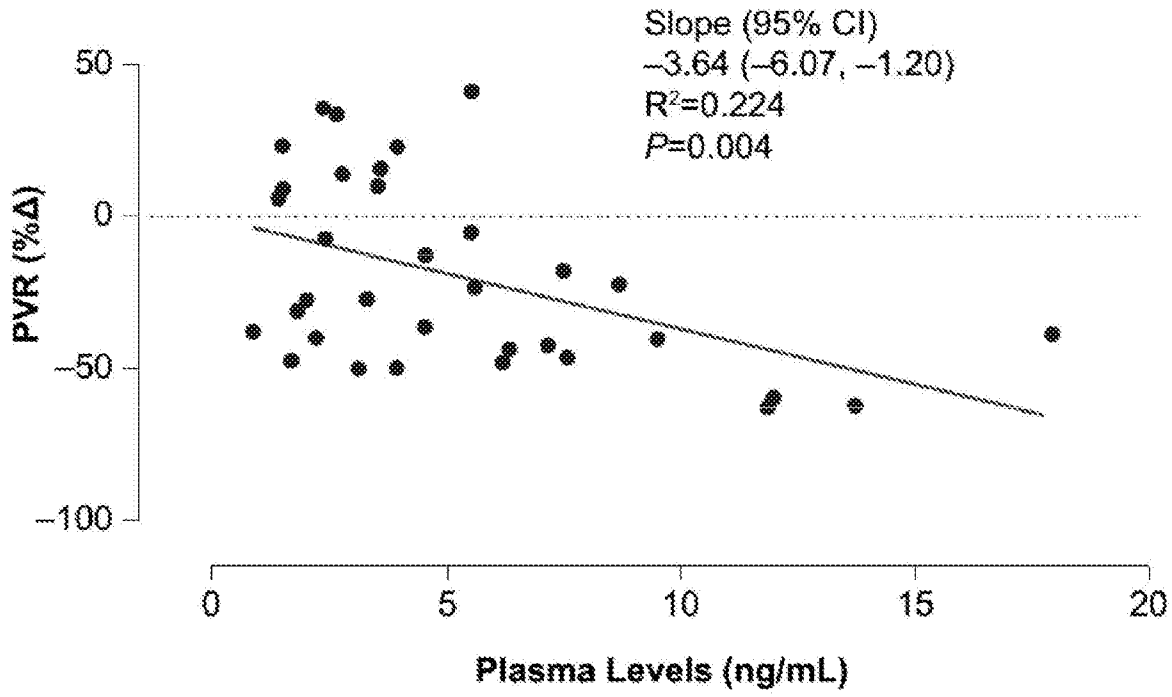

Slope (95% CI)
–3.64 (–6.07, –1.20)
R²=0.224
P=0.004
50
0
–50
–100
PVR (%Δ)
0
5
10
15
20
Plasma Levels (ng/mL)

Figure 18

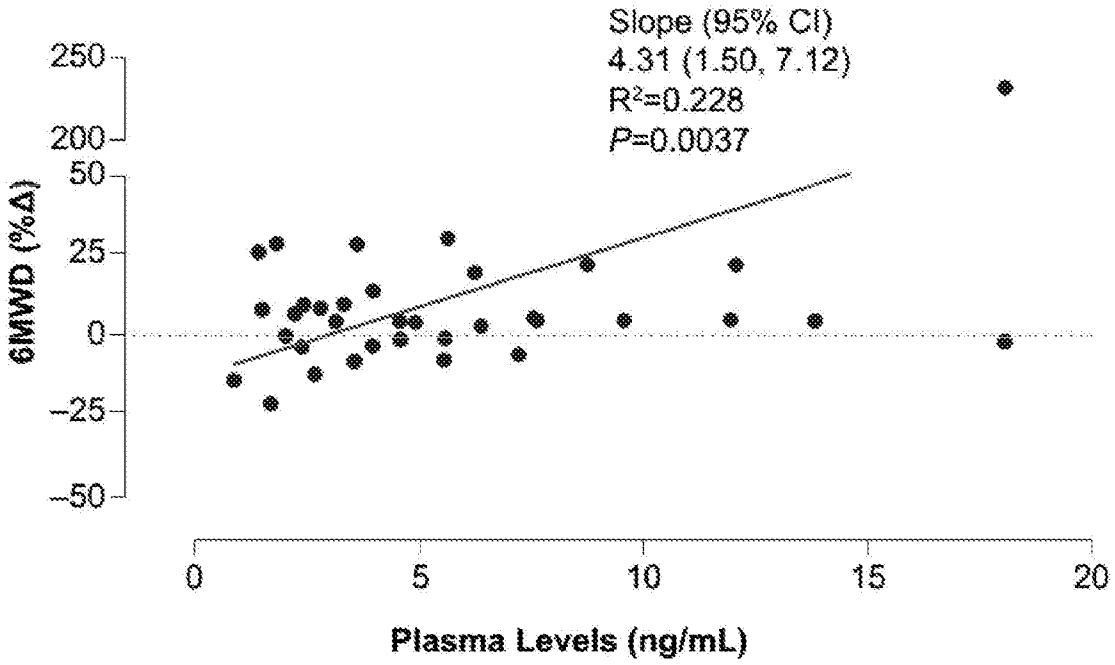
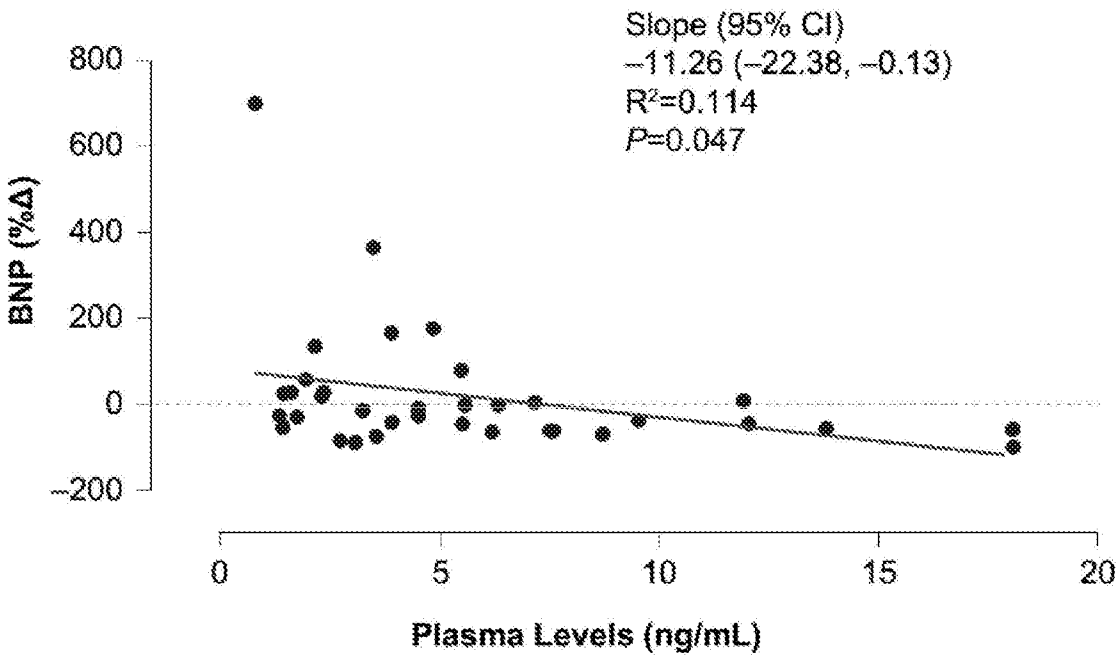

Slope (95% CI)
4.31 (1.50, 7.12)
R²=0.228
P=0.0037
250
200
50
25
0
−25
−50
6MWD (%Δ)
0
5
10
15
20
Plasma Levels (ng/mL)

Figure 19


Slope (95% CI)
−11.26 (−22.38, −0.13)
R²=0.114
P=0.047
BNP (%Δ)
800
600
400
200
0
−200
0
5
10
15
20
Plasma Levels (ng/mL)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/033727

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/27 A61K9/20 A61P9/02 A61K9/48
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2016/065103 A1 (ARENA PHARM INC) 28 April 2016 (2016-04-28) claims 1,11-20,29,31,33-42; examples	1-29,47, 48, 54-57, 67-75
A	EP 2 857 015 A1 (ARENA PHARM INC [US]) 8 April 2015 (2015-04-08) cited in the application claims	1-75
X,P	WO 2018/160882 A1 (ARENA PHARM INC [US]) 7 September 2018 (2018-09-07) claims; examples	1-75

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 October 2019	15/10/2019

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Pacreu Largo, Marta

1

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/033727

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	GRUNDY J ET AL: "Clinical Pharmacokinetic Performance of a Ralinepag Extended-Release Tablet", JOURNAL OF HEART AND LUNG TRANSPLANTATION, vol. 38, no. 4, April 2019 (2019-04), XP085631260, ISSN: 1053-2498, DOI: 10.1016/J.HEALUN.2019.01.504 abstract -----	1-4, 17-22, 47,48, 55,67,68

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2019/033727

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