TREATMENT OF TYPE 2 DIABETES OR OBESITY OR OVERWEIGHT WITH 2-[(4-{6-[(4-CYANO-2-FLUOROBENZYL)OXY]PYRIDIN-2-YL}PIPERIDIN-1-YL)METHYL]-1-[(2S)-OXETAN-2-YLMETHYL]-1H-BENZIMIDAZOLE-6-CARBOXYLIC ACID OR A PHARMACEUTICALLY SALT THEREOF

FIELD OF INVENTION

The invention provides a method for treating type 2 diabetes mellitus, obesity, or overweight or for weight management control by administering to an mammal (e.g. a human) in need thereof a pharmaceutical composition twice daily in an oral dosage form, wherein the pharmaceutical composition contains 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, or a pharmaceutically salt thereof [such as its 2-amino-2-(hydroxymethyl)propane-1,3-diol salt, also known as its tris salt]. Moreover, the invention provides oral compositions/formulations for the methods of treatment described herein.

BACKGROUND OF THE INVENTION

Diabetes mellitus is a major public health concern because of its increasing prevalence and associated health risks. The disease is characterized by high levels of blood glucose resulting from defects in insulin production, insulin action, or both. Two major forms of diabetes mellitus are recognized, Type 1 and Type 2. Type 1 diabetes mellitus (T1DM) develops when the body's immune system destroys pancreatic beta cells, the only cells in the body that make the hormone insulin that regulates blood glucose. To survive, people with Type 1 diabetes must have insulin administered by injection or a pump. Type 2 diabetes mellitus (referred to generally as T2DM) usually results from insulin resistance and insufficient production of insulin to maintain an acceptable glucose level.

Currently, various pharmacological approaches are available for treating hyperglycemia in T2DM (Hampp, C. et al. *Use of Antidiabetic Drugs in the U.S.*, 2003-2012, *Diabetes Care* 2014, 37, 1367-1374). These may be grouped into six major classes, each acting through a different primary mechanism: insulin secretagogues, biguanides, alphaglucosidase inhibitors, thiazolidinediones (TZDs), insulin and sodium-glucose linked transporter cotransporter 2 (SGLT2) inhibitors. (A) Insulin secretogogues include sulphonylureas (e.g., glipizide, glimepiride, glyburide), meglitinides (e.g., nateglidine, repaglinide), dipeptidyl peptidase IV (DPP-IV) inhibitors (e.g., sitagliptin, vildagliptin, alogliptin, dutogliptin, linagliptin, saxogliptin), and glucagon-like peptide-1 receptor (GLP-1R) agonists (e.g., liraglutide, albiglutide, exenatide, lixisenatide, dulaglutide, semaglutide), and they act on the pancreatic beta-cells to enhance secretion of insulin. Sulphonyl-ureas and meglitinides have limited efficacy and tolerability,

cause weight gain and often induce hypoglycemia. DPP-IV inhibitors have limited efficacy. Marketed GLP-1R agonists are peptides administered primarily by subcutaneous injection. Liraglutide is additionally approved for the treatment of obesity. (B) Biguanides (e.g., metformin) are thought to act primarily by decreasing hepatic glucose production. Biguanides often cause gastrointestinal disturbances and lactic acidosis, further limiting their use. (C) Inhibitors of alpha-glucosidase (e.g., acarbose) decrease intestinal glucose absorption. These agents often cause gastrointestinal disturbances and/or have limited efficacy. (D) Thiazolidinediones (e.g., pioglitazone, rosiglitazone) act on a specific receptor (peroxisome proliferator-activated receptor-gamma) in the liver, muscle and fat tissues. They regulate lipid metabolism subsequently enhancing the response of these tissues to the actions of insulin. Frequent use of these drugs may lead to weight gain and may induce edema and anemia. (E) Insulin is used in more severe cases, either alone or in combination with the above agents, and frequent use may also lead to weight gain and carries a risk of hypoglycemia. (F) sodium-glucose linked transporter cotransporter 2 (SGLT2) inhibitors (e.g., dapagliflozin, empagliflozin, canagliflozin, ertugliflozin) inhibit reabsorption of glucose in the kidneys and thereby lower glucose levels in the blood. This emerging class of drugs may be associated with ketoacidosis and urinary tract infections.

However, except for GLP-1R agonists and SGLT2 inhibitors, the drugs have limited efficacy and do not address the most important problems, the declining β-cell function and the associated obesity.

Accumulation of too much storage fat can impair movement, flexibility, and alter the appearance of the body. Both overweight and obesity can be associated to or cause health problems.

Obesity is a chronic disease that is highly prevalent in modern society and is associated with numerous medical problems including hypertension, hypercholesterolemia, and coronary heart disease. It is further highly correlated with T2DM and insulin resistance, the latter of which is generally accompanied by hyperinsulinemia or hyperglycemia, or both. In addition, T2DM is associated with a two-to-four-fold increased risk of coronary artery disease. Presently, the only treatment that treats obesity with high efficacy is bariatric surgery, but this treatment is invasive and costly. Pharmacological intervention is generally less efficacious and associated with side effects. There is therefore an obvious need for more efficacious pharmacological intervention with fewer side effects and convenient administration.

Although T2DM is most commonly associated with hyperglycemia and insulin resistance, other diseases, conditions, symptoms, and complications associated with T2DM include diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, obesity, dyslipidemia, hypertension,

hyperinsulinemia, and nonalcoholic fatty liver disease (NAFLD), cardiovascular disease, and increased risk for cancer.

NAFLD is the hepatic manifestation of metabolic syndrome, and is a spectrum of hepatic conditions encompassing steatosis, non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis and ultimately hepatocellular carcinoma. NAFLD and NASH are considered the primary fatty liver diseases as they account for the greatest proportion of individuals with elevated hepatic lipids. The severity of NAFLD/NASH is based on the presence of lipid, inflammatory cell infiltrate, hepatocyte ballooning, and the degree of fibrosis. Although not all individuals with steatosis progress to NASH, a substantial portion does.

GLP-1 is a 30 amino acid long incretin hormone secreted by the L-cells in the intestine in response to ingestion of food. GLP-1 has been shown to stimulate insulin secretion in a physiological and glucose-dependent manner, decrease glucagon secretion, inhibit gastric emptying, decrease appetite, and stimulate proliferation of beta-cells. In non-clinical experiments GLP-1 promotes continued beta-cell competence by stimulating transcription of genes important for glucose-dependent insulin secretion and by promoting beta-cell neogenesis (Meier, et al. *Biodrugs.* 2003; 17 (2): 93-102).

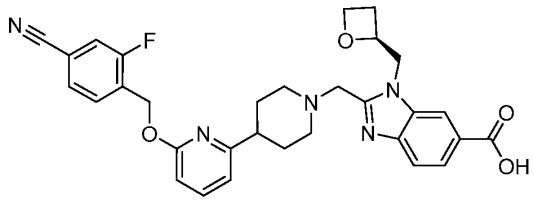
In a healthy individual, GLP-1 plays an important role regulating post-prandial blood glucose levels by stimulating glucose-dependent insulin secretion by the pancreas resulting in increased glucose absorption in the periphery. GLP-1 also suppresses glucagon secretion, leading to reduced hepatic glucose output. In addition, GLP-1 delays gastric emptying and slows small bowel motility delaying food absorption. In people with T2DM, the normal post-prandial rise in GLP-1 is absent or reduced (Vilsboll T, et al. *Diabetes*. 2001. 50; 609-613).

Holst (*Physiol. Rev.* 2007, 87, 1409) and Meier (*Nat. Rev. Endocrinol.* 2012, 8, 728) describe that GLP-1 receptor agonists, such as GLP-1, liraglutide and exendin-4, have 3 major pharmacological activities to improve glycemic control in patients with T2DM by reducing fasting and postprandial glucose (FPG and PPG): (i) increased glucose-dependent insulin secretion (improved first- and second-phase), (ii) glucagon suppressing activity under hyperglycemic conditions, (iii) delay of gastric emptying rate resulting in retarded absorption of meal-derived glucose.

There remains a need for a safe and efficacious treatment for cardiometabolic and associated diseases, such as T2DM, obesity, and overweight.

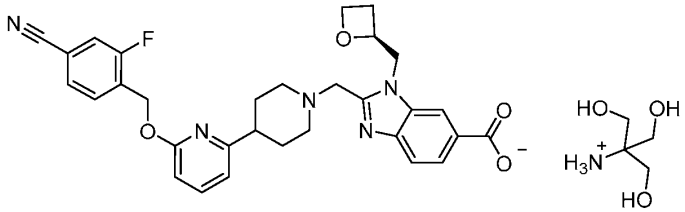
2-[(4-{6-[(4-Cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, or a pharmaceutically salt thereof [such as its 2-amino-2-(hydroxymethyl)propane-1,3-diol salt, also known as its tris salt or its tris(hydroxyethyl)methylamine salt] is a GLP-1R agonist described in U.S. Patent No.10,208,019

(see Example 4A-01 of the patent), the disclosure of which is hereby incorporated by reference herein in its entirety for all purposes.

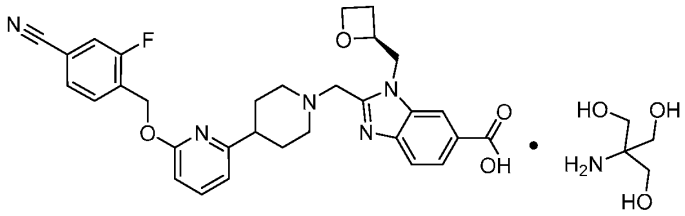


2-[(4-{6-[(4-Cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid ("Compound 1").

Tris salt of 2-[(4-{6-[(4-Cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid means a salt of Compound 1 made by using 1,3-dihydroxy-2-(hydroxymethyl)propan-2-amine. The tris is associated with the carboxylic acid moiety of Compound 1. Unless otherwise stated, when referencing the tris salt of Compound 1, the counterion and Compound 1 are in a stoichiometric ratio of about 1:1 (i.e. from 0.9:1.0 to 1.0:0.9, for example, from 0.95:1.00 to 1.00:0.95, or from 0.99:1.00 to 1.00 : 1.01). Another chemical name for tris salt of Compound 1 is 1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylate, which can also be represented, for example, by one of the following structures.



or



Tris salt of Compound 1

The novel methods of treatment and compositions/formulations described herein are directed toward this and other important ends.

SUMMARY OF THE INVENTION

The present invention provides, in part, method for treating T2DM which method includes administering to a human in need thereof a pharmaceutical composition, wherein the pharmaceutical composition is in an oral dosage form; and the pharmaceutical composition comprises 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid or a pharmaceutically salt thereof.

The present invention further provides a method for weight management control comprising administering to a human in need thereof a pharmaceutical composition, wherein the pharmaceutical composition is in an oral dosage form; and the pharmaceutical composition comprises 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid or a pharmaceutically salt thereof.

The present invention further provides an immediate-release oral pharmaceutical composition containing 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid or a pharmaceutically salt thereof. The immediate-release oral pharmaceutical composition of the invention can be used in the methods of treatment of the invention provided herein.

The present invention further provides an immediate-release oral pharmaceutical composition comprising: 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, or a pharmaceutically acceptable salt thereof; a filler; a disintegrant; and a lubricant. This immediate-release oral pharmaceutical composition of the invention can also be used in the methods of treatment of the invention provided herein.

BRIEF DESCRIPTION OF FIGURES

FIG. 1 shows a flow diagram of the preparation process of tris salt of Compound 1 immediate release tablets.

FIG. 2 shows a flow diagram of the preparation process of tris salt of Compound 1 (eqivalent to 50 mg of Compound 1) controlled release tablets.

DETAILED DESCRIPTION OF THE INVENTION

In a first aspect, the present invention provides a method for treating T2DM which method includes administering to a human in need thereof a pharmaceutical composition, wherein the pharmaceutical composition is in an oral dosage form; and the pharmaceutical composition comprises 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid (“Compound 1) or a pharmaceutically salt thereof.

In some embodiments, the pharmaceutical composition is present in an oral solution form or in a solid oral dosage form.

In some embodiments, the pharmaceutical composition is present in a solid oral dosage form, which includes, for example, tablets, capsules, caplets, sachets, powders, granules, or orally dispersible films.

In some embodiments, the pharmaceutical composition is in an immediate-release solid dosage form.

As use herein, the term "immediate release" or its abbreviated term "IR" [for example, in "immediate release tablet"] corresponds to the definition provided in European Pharmacopeia 6.0, part 01/2008: 1502 as relating to "conventional-release dosage forms" or "immediate-release dosage forms" in the form of a tablet showing a release of the active substance, which is not deliberately modified by a special formulation design and/or manufacturing method, thereby being distinct from "modify-release", "prolong-release", "delayed-release" and "pulsatile-release" dosage forms as defined in European Pharmacopeia 6.0., part 01/2008: 1502. For example, more specifically, "immediate release" or "IR" means a release quantity of the active pharmacological ingredient of at least 70%, 75%, or 80% within a defined time, such as 60 minutes, 45 minutes, or 30 minutes, as determined according to the USP release method using apparatus 2 (paddle), for example, having a Q value (30 minutes) of at least 75 %.

In some embodiments, the pharmaceutical composition is in an immediate-release tablet dosage form.

In some embodiments, the pharmaceutical composition includes one or more tablets.

In some embodiments, the pharmaceutical composition contains Compound 1 or a pharmaceutically salt thereof in an amount equivalent to about 10 mg to about 140 mg of Compound 1, for example, in an amount equivalent to about 10 mg to about 120 mg of Compound 1, about 10 mg to about 50 mg of Compound 1, about 10 mg to about 40 mg of Compound 1, about 10 mg to about 20 mg of Compound 1, about 15 mg to about 25 mg of Compound 1, about 15 mg to about 40 mg of Compound 1, about 15 mg to about 50 mg of Compound 1, about 20 mg to about 30 mg of Compound 1, about 30 mg to about 100 mg of Compound 1, about 40 mg to about 70 mg of Compound 1, about 40 mg to about 50 mg of Compound 1, about 70 mg to about 130 mg of Compound 1, about 70 mg to about 120 mg of Compound 1, about 100 mg to about 140 mg of Compound 1, about 110 mg to about 130 mg of Compound 1, about 115 mg to about 125 mg of Compound 1, or about 120 mg of Compound 1.

In some embodiments, the Compound 1 or pharmaceutically salt thereof in the pharmaceutical composition is a pharmaceutical salt of Compound 1, for example, tris salt of Compound 1.

In some embodiments, the pharmaceutical composition is administered twice daily. In some embodiments, the two daily administrations are separated by at least 4, 5, or 6 hours. In some embodiments, the two daily administrations are separated by at least 6, 7, or 8 hours. In some embodiments, the two daily administrations are separated by at least 8, 9, or 10 hours.

In some embodiments, the two daily administrations are separated by 4 to 16 hours, 8 to 16 hours, or 10 to 14 hours. In some further embodiments, the two daily administrations are separated by 11 to 13 hours, or about 12 hours.

The term "treating", as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, unless otherwise indicated, refers to the act of treating as "treating" is defined herein. The term “treating” also includes adjuvant and neo-adjuvant treatment of a subject (e.g. a human).

In some embodiments, the method for treating T2DM includes improving glycemic control.

In some embodiments, the method for treating T2DM includes reducing the fasting plasma glucose level of the human, for example, to about 126 mg/dL or lower. In some embodiments, the method treating T2DM includes reducing glycated hemoglobin (HbA1c), for example, to about 7.0 % or less, about 6.5% or less, or about 5.7% or less. In some embodiments, the method treating T2DM includes reducing the mean daily glucose level to about 157 mg/dL or less. In some embodiments, the method for treating T2DM has low or no risk of hypoglycemia.

In some embodiments, the method further includes administering to the human an additional therapeutic agent.

In some embodiments, the method is an adjunct to a reduced-calorie diet and/or increased physical activity.

In a second aspect, the invention provides a method for weight management control or for treating obesity or overweight which method includes administering to a human in need thereof a pharmaceutical composition, wherein the pharmaceutical composition is in an oral dosage form; and the pharmaceutical composition comprises 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid or a pharmaceutically salt thereof.

In some embodiments, the pharmaceutical composition is present in an oral solution form or in a solid oral dosage form.

In some embodiments, the pharmaceutical composition is present in a solid oral dosage form, which includes, for example, tablets, capsules, caplets, sachets, powders, granules, or orally dispersible films.

In some embodiments, the pharmaceutical composition is in an immediate-release solid dosage form.

In some embodiments, the pharmaceutical composition is in an immediate-release tablet dosage form.

In some embodiments, the pharmaceutical composition includes one or more tablets.

In some embodiments, the pharmaceutical composition contains Compound 1 or a pharmaceutically salt thereof in an amount equivalent to about 10 mg to about 140 mg of Compound 1, for example, in an amount equivalent to about 10 mg to about 120 mg of Compound 1, about 10 mg to about 40 mg of Compound 1, about 10 mg to about 20 mg of Compound 1, about 15 mg to about 25 mg of Compound 1, about 15 mg to about 40 mg of Compound 1, about 15 mg to about 50 mg of Compound 1, about 40 mg to about 70 mg of Compound 1, about 40 mg to about 50 mg of Compound 1, about 70 mg to about 130 mg of Compound 1, about 70 mg to about 120 mg of Compound 1, about 100 mg to about 140 mg of Compound 1, about 110 mg to about 130 mg of Compound 1, about 115 mg to about 125 mg of Compound 1, or about 120 mg of Compound 1.

In some embodiments, the Compound 1 or pharmaceutically salt thereof in the pharmaceutical composition is in an amount equivalent to about 10 mg to about 120 mg of Compound 1, about 10 mg to about 40 mg of Compound 1, about 40 mg to about 70 mg of Compound 1, about 70 mg to about 120 mg of Compound 1, or about 120 mg of Compound 1.

In some embodiments, the Compound 1 or pharmaceutically salt thereof in the pharmaceutical composition is in an amount equivalent to about 10 mg to about 100 mg of Compound 1, about 10 mg to about 40 mg of Compound 1, about 20 mg to about 100 mg of Compound 1, about 20 mg to about 80 mg of Compound 1, or about 40 mg to about 80 mg of Compound 1.

In some embodiments, the Compound 1 or pharmaceutically salt thereof in the pharmaceutical composition is a pharmaceutical salt of Compound 1, for example, tris salt of Compound 1.

In some embodiments, the pharmaceutical composition is administered twice daily. In some embodiments, the two daily administrations are separated by at least 4, 5, or 6 hours. In some embodiments, the two daily administrations are separated by at least 6, 7, or 8 hours. In some embodiments, the two daily administrations are separated by at least 8, 9, or 10 hours.

In some embodiments, the two daily administrations are separated by 4 to 16 hours, 8 to 16 hours, or 10 to 14 hours. In some further embodiments, the two daily administrations are separated by 11 to 13 hours, or about 12 hours.

In some embodiments, the weight management control includes chronic weight management control.

In some embodiments, the initial body mass index (BMI) of the human is 24 kg/m^2 or greater (the initial BMI is the BMI when the the weight the management control starts). In some embodiments, the initial BMI of the human is 24 kg/m^2 to 30 kg/m^2.

In some embodiments, the initial BMI of the human is 27 kg/m^2 or greater.

In some embodiments, the initial BMI of the human is 30 kg/m^2 or greater. In some embodiments, the initial BMI of the human is 30.0 kg/m^2 to 45 kg/m^2.

As used herein, a human with a BMI of 30 kg/m^2 or greater is obese (i.e. having obesity).

As used herein, a human with a BMI of 25.0 to 29.9 kg/m^2 is overweight (i.e. having overweight).

The term "treating", as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, unless otherwise indicated, refers to the act of treating as "treating" is defined herein. The term “treating” also includes adjuvant and neo-adjuvant treatment of a subject (e.g. a human).

In some embodiment, the treating obsesity or overweight includes weight management control.

In some embodiments, the human has at least one weight-related comorbidity (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia).

In some embodiments, the human is overweight and has at least one weight-related comorbidity (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia).

In some embodiments, the human is obesity and has at least one weight-related comorbidity (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia).

In some embodiments, the method for weight management control includes reducing the body weight of the human, for example, greater than about 3%, 4%, 5%, 6%, 7%, 8%, 9%, or 10%.

In some embodiments, the method for weight management control includes reducing the body weight of the human, for example, greater than about 10%, 15%, 20%, 25%, or 30%.

In some embodiments, the method for weight management control includes reducing the body weight of the human, for example, greater than about 3%, 4%, 5%, 6%, 7%, 8%, 9%, or 10%.

In some embodiments, the method for weight management control includes reducing the body mass index (BMI) of the human, for example, greater than about 10%, 15%, 20%, 25%, or 30%.

In some embodiments, the method further includes administering to the human an additional therapeutic agent.

In some embodiments, the method is an adjunct to a reduced-calorie diet and/or increased physical activity.

In a third aspect, the present invention provides an immediate-release oral pharmaceutical composition comprising Compound 1 or a pharmaceutically salt thereof.

In some embodiments, the Compound 1 or pharmaceutically salt thereof is tris salt Compound 1.

In some embodiments, the Compound 1 or pharmaceutically salt thereof in the pharmaceutical composition is in an amount equivalent to about 10 mg to about 140 mg of Compound 1, for example, in an amount equivalent to about 10 mg to about 120 mg of Compound 1, about 10 mg to about 40 mg of Compound 1, about 10 mg to about 20 mg of Compound 1, about 15 mg to about 25 mg of Compound 1, about 15 mg to about 40 mg of Compound 1, about 15 mg to about 50 mg of Compound 1, about 40 mg to about 70 mg of Compound 1, about 40 mg to about 50 mg of Compound 1, about 70 mg to about 130 mg of Compound 1, about 70 mg to about 120 mg of Compound 1, about 100 mg to about 140 mg of Compound 1, about 110 mg to about 130 mg of Compound 1, about 115 mg to about 125 mg of Compound 1, or about 120 mg of Compound 1.

In some embodiments, the Compound 1 or pharmaceutically salt thereof in the pharmaceutical composition is in an amount equivalent to about 10 mg to about 120 mg of Compound 1, about 10 mg to about 40 mg of Compound 1, about 40 mg to about 70 mg of Compound 1, about 70 mg to about 120 mg of Compound 1, or about 120 mg of Compound 1.

In some embodiments, the immediate-release oral dosage form is a solid oral dosage form, which includes, for example, tablets, capsules, caplets, sachets, powders, granules, orally dispersible films. In some embodiments, the immediate-release oral dosage form is a tablet form.

In some embodiments, immediate-release oral pharmaceutical composition in the third aspect can be used in the methods of the first or second aspect of the invention.

In a fourth aspect, the present invention provides an immediate-release oral pharmaceutical composition comprising:

Compound 1 or a pharmaceutically salt thereof (e.g. tris salt of Compound 1);

a filler [e.g. microcrystalline cellulose, lactose (e.g. in the form of lactose monohydrate), or a combination thereof, for example, a combination of microcrystalline cellulose and lactose monohydrate in about 2:1 weight ratio];

a disintegrant (e.g. crospovidone, starch, pregelatinized starch, carboxymethylcellulose, hydroxypropylcellulose, sodium alginate, croscarmellose sodium, or sodium starch glycolate),

and a lubricant [e.g. metallic stearate (such as magnesium stearate or sodium stearyl fumarate)].

In some embodiments, the oral pharmaceutical composition comprises microcrystalline cellulose, lactose (e.g. in the form of lactose monohydrate), sodium starch glycolate, and magnesium stearate.

In some embodiments, the oral pharmaceutical composition comprises microcrystalline cellulose, lactose (e.g. in the form of lactose monohydrate), sodium starch glycolate, and sodium stearyl fumarate.

In some embodiment, the oral pharmaceutical composition of the invention comprises:

1.0% to 35.0% by weight of Compound 1 or a pharmaceutically acceptable salt thereof (e.g. tris salt of Compound 1);

60% to 95% by weight of filler [e.g. microcrystalline cellulose, lactose (e.g. in the form of lactose monohydrate), or a combination thereof, for example, a combination of microcrystalline cellulose and lactose monohydrate in about 2:1 weight ratio];

0.2% to 2.5% by weight lubricant [e.g. metallic stearate (such as magnesium stearate or sodium stearyl fumarate)]; and

1.0% to 5.0% by weight of disintegrant (e.g. crospovidone, starch, pregelatinized starch, carboxymethylcellulose, hydroxypropylcellulose, sodium starch glycolate or croscarmellose sodium).

In some embodiment, the oral pharmaceutical composition of the invention comprises:

1.0% to 35.0% by weight of Compound 1 or a pharmaceutically acceptable salt thereof (e.g. tris salt of Compound 1);

60% to 95% by weight of filler [e.g. microcrystalline cellulose, lactose (e.g. in the form of lactose monohydrate), or a combination thereof, for example, a combination of microcrystalline cellulose and lactose monohydrate in about 2:1 weight ratio];

0.2% to 2.5% by weight lubricant [e.g. metallic stearate (such as magnesium stearate or sodium stearyl fumarate)]; and

1.0% to 5.0% by weight of disintegrant (e.g. sodium starch glycolate or croscarmellose sodium).

In some embodiment, the oral pharmaceutical composition of the invention comprises:

10.0% to 35.0% by weight of Compound 1 or a pharmaceutically acceptable salt thereof (e.g. tris salt of Compound 1);

60% to 90% by weight of filler [e.g. microcrystalline cellulose, lactose (e.g. in the form of lactose monohydrate), or a combination thereof, for example, a combination of microcrystalline cellulose and lactose monohydrate in about 2:1 weight ratio];

0.2% to 2.5% by weight lubricant [e.g. metallic stearate (such as magnesium stearate or sodium stearyl fumarate)]; and

1.0% to 5.0% by weight of disintegrant (e.g. crospovidone, starch, pregelatinized starch, carboxymethylcellulose, hydroxypropylcellulose, sodium starch glycolate or croscarmellose sodium).

In some embodiment, the oral pharmaceutical composition of the invention comprises:

1.0% to 20.0% by weight of Compound 1 or a pharmaceutically acceptable salt thereof (e.g. tris salt of Compound 1);

70% to 95% by weight of filler [e.g. microcrystalline cellulose, lactose (e.g. in the form of lactose monohydrate), or a combination thereof, for example, a combination of microcrystalline cellulose and lactose monohydrate in about 2:1 weight ratio];

0.2% to 2.0% by weight lubricant [e.g. metallic stearate (such as magnesium stearate or sodium stearyl fumarate)]; and

1.0% to 5.0% by weight of disintegrant (e.g. sodium starch glycolate or croscarmellose sodium).

In some embodiment, the oral pharmaceutical composition of the invention comprises:

1.0% to 20.0% by weight of Compound 1 or a pharmaceutically acceptable salt thereof (e.g. tris salt of Compound 1);

70% to 95% by weight of filler [e.g. microcrystalline cellulose, lactose (e.g. in the form of lactose monohydrate), or a combination thereof];

0.5% to 1.5% by weight lubricant [e.g. metallic stearate (such as magnesium stearate or sodium stearyl fumarate)]; and

2.0% to 4.0% by weight of disintegrant (e.g. sodium starch glycolate or croscarmellose sodium).

In some embodiment, the oral pharmaceutical composition of the invention comprises:

7.0% to 18.0% by weight of Compound 1 or a pharmaceutically acceptable salt thereof (e.g. tris salt of Compound 1);

75% to 90% by weight of filler [e.g. microcrystalline cellulose, lactose (e.g. in the form of lactose monohydrate), or a combination thereof];

0.5% to 1.5% by weight lubricant [e.g. metallic stearate (such as magnesium stearate or sodium stearyl fumarate)]; and

2.5% to 3.5% by weight of disintegrant (e.g. sodium starch glycolate or croscarmellose sodium).

In some embodiment, the oral pharmaceutical composition of the invention comprises:

15.0% to 35.0% by weight of Compound 1 or a pharmaceutically acceptable salt thereof (e.g. 15.0% to 35.0% by weight of tris salt of Compound 1);

60.0% to 80.0% by weight of filler [e.g. microcrystalline cellulose, lactose (e.g. in the form of lactose monohydrate), or a combination thereof];

1.5% to 2.5% by weight lubricant [e.g. metallic stearate (such as magnesium stearate or sodium stearyl fumarate)]; and

2.5% to 3.5% by weight of disintegrant (e.g. sodium starch glycolate or croscarmellose sodium).

In some embodiments, the oral pharmaceutical composition comprises:

Compound 1 or a pharmaceutically salt thereof (e.g. tris salt of Compound 1);

a filler [e.g. microcrystalline cellulose, lactose (e.g. in the form of lactose monohydrate), or a combination thereof, for example, a combination of microcrystalline cellulose and lactose monohydrate in about 2:1 weight ratio];

a disintegrant (e.g. crospovidone, starch, pregelatinized starch, carboxymethylcellulose, hydroxypropylcellulose); and

a lubricant [e.g. metallic stearate (such as magnesium stearate or sodium stearyl fumarate)].

In some embodiments, the oral pharmaceutical composition comprises microcrystalline cellulose, lactose (e.g. in the form of lactose monohydrate), crospovidone, and magnesium stearate.

In some embodiment, the oral pharmaceutical composition of the invention comprises:

1.0% to 35.0% by weight of Compound 1 or a pharmaceutically acceptable salt thereof (e.g. tris salt of Compound 1);

60% to 95% by weight of filler [e.g. microcrystalline cellulose, lactose (e.g. in the form of lactose monohydrate), or a combination thereof, for example, a combination of microcrystalline cellulose and lactose monohydrate in about 2:1 weight ratio];

0.2% to 2.5% by weight lubricant [e.g. metallic stearate (such as magnesium stearate or sodium stearyl fumarate)]; and

1.0% to 5.0% by weight of disintegrant (e.g. crospovidone,).

In some embodiment, the oral pharmaceutical composition of the invention comprises:

10.0% to 35.0% by weight of Compound 1 or a pharmaceutically acceptable salt thereof (e.g. tris salt of Compound 1);

60% to 70% by weight of filler [e.g. microcrystalline cellulose, lactose (e.g. in the form of lactose monohydrate), or a combination thereof, for example, a combination of microcrystalline cellulose and lactose monohydrate in about 2:1 weight ratio];

0.2% to 2.5% by weight lubricant [e.g. metallic stearate (such as magnesium stearate or sodium stearyl fumarate)]; and

1.0% to 5.0% by weight of disintegrant (e.g. crospovidone).

In some embodiment, the oral pharmaceutical composition of the invention comprises:

23.0% to 35.0% by weight of Compound 1 or a pharmaceutically acceptable salt thereof (e.g. 29.0% to 32.0% by weight of tris salt of Compound 1);

60% to 70% by weight of filler [e.g. microcrystalline cellulose, lactose (e.g. in the form of lactose monohydrate), or a combination thereof, for example, a combination of microcrystalline cellulose and lactose monohydrate in about 2:1 weight ratio];

1.0% to 2.5% by weight lubricant [e.g. metallic stearate (such as magnesium stearate or sodium stearyl fumarate)]; and

2.0% to 4.0% by weight of disintegrant (e.g. crospovidone).

In some embodiment, the oral pharmaceutical composition of the invention comprises:

24.0% to 33.0% by weight of Compound 1 or a pharmaceutically acceptable salt thereof (e.g. 29.0% to 32.0% by weight of tris salt of Compound 1);

62.0% to 68.0% by weight of filler [e.g. microcrystalline cellulose, lactose (e.g. in the form of lactose monohydrate), or a combination thereof, for example, a combination of microcrystalline cellulose and lactose monohydrate in about 2:1 weight ratio];

1.5% to 2.5% by weight lubricant [e.g. metallic stearate (such as magnesium stearate or sodium stearyl fumarate)]; and

2.5% to 3.5% by weight of disintegrant (e.g. crospovidone).

In some embodiments, the Compound 1 or pharmaceutically salt thereof in the pharmaceutical composition is in an amount equivalent to about 10 mg to about 140 mg of Compound 1, for example, in an amount equivalent to about 10 mg to about 120 mg of Compound 1, about 10 mg to about 40 mg of Compound 1, about 10 mg to about 20 mg of Compound 1, about 15 mg to about 25 mg of Compound 1, about 15 mg to about 40 mg of Compound 1, about 15 mg to about 50 mg of Compound 1, about 40 mg to about 70 mg of Compound 1, about 40 mg to about 50 mg of Compound 1, about 70 mg to about 130 mg of Compound 1, about 70 mg to about 120 mg of Compound 1, about 100 mg to about 140 mg of Compound 1, about 110 mg to about 130 mg of Compound 1, about 115 mg to about 125 mg of Compound 1, or about 120 mg of Compound 1.

In some embodiments, the Compound 1 or pharmaceutically salt thereof in the pharmaceutical composition is in an amount equivalent to about 10 mg to about 120 mg of

Compound 1, about 10 mg to about 40 mg of Compound 1, about 40 mg to about 70 mg of Compound 1, about 70 mg to about 120 mg of Compound 1, or about 120 mg of Compound 1.

In some embodiments, the immediate-release oral dosage form is a solid oral dosage form, which includes, for example, tablets, capsules, caplets, sachets, powders, granules, orally dispersible films. In some embodiments, the immediate-release oral dosage form is a tablet form.

In some embodiments, the tris salt of Compound 1 in the pharmaceutical composition of the present invention (or the methods of the invention) is present in a crystalline form, for example, the one disclosed in U.S. Patent No.10,208,019 (see Example 4A-01 of the patent).

In some embodiments, the Compound 1 in the pharmaceutical composition of the present invention (or the methods of the invention) is present in amorphous form of Compound 1 or in amorphous form of tris salt Compound 1. Amorphous form of Compound 1 or amorphous form of tris salt of Compound 1 can be prepared by, for example, lyophilization (freeze dry).

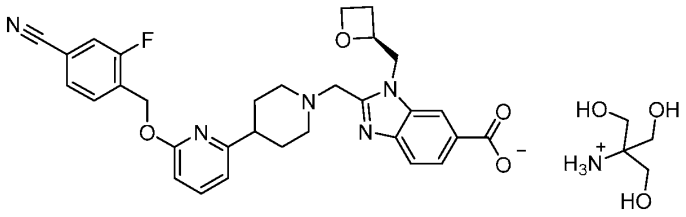
In some embodiments, the pharmaceutical composition of the present invention (including those used in the methods of the invention) is an oral solution that is prepared by using amorphous form of Compound 1 or amorphous form of tris salt of Compound 1.

In some embodiments, immediate-release oral pharmaceutical composition in the fourth aspect can be used in the methods of the first or second aspect of the invention.

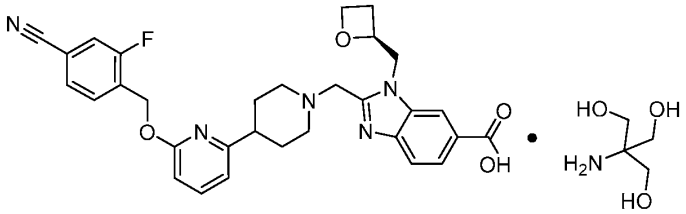
The term “about” generally means within 5%, preferably within 3%, and more preferably within 1% of a given value or range. Alternatively, the term “about” means within an acceptable standard error of the mean, when considered by one skilled in the art.

The term “tris” means 1,3-dihydroxy-2-(hydroxymethyl)propan-2-amine, also known as THAM, tromethamine, 2-amino-2-(hydroxymethyl)propane-1,3-diol, tris(hydroxymethyl)aminomethane.

Tris salt of Compound 1 means a salt of Compound 1 made using 1,3-dihydroxy-2-(hydroxymethyl)propan-2-amine. The tris is associated with the carboxylic acid moiety of Compound 1. Unless otherwise stated, when referencing the tris salt of Compound 1, the counterion and Compound 1 are in a stoichiometric ratio of about 1:1 (i.e. from 0.9:1.0 to 1.0:0.9, for example, from 0.95:1.00 to 1.00:0.95). Another chemical name for tris salt of Compound 1 is 1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylate, which can also be represented, for example, by one of the following structures.



or



Those skilled in the art would readily understand that multiple nomenclatures can be used to name a same compound (including a same salt).

Pharmaceutically acceptable salts include acid addition and base salts.

Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, adipate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulfate/sulfate, borate, camsylate, citrate, cyclamate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulfate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, pyroglutamate, saccharate, stearate, succinate, tannate, tartrate, tosylate, trifluoroacetate, 1,5-naphathalenedisulfonic acid and xinafoate salts.

Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, bis(2-hydroxyethyl)amine (diolamine), glycine, lysine, magnesium, meglumine, 2-aminoethanol (olamine), potassium, sodium, 2-Amino-2-(hydroxymethyl)propane-1,3-diol (tris or tromethamine) and zinc salts.

Hemisalts of acids and bases may also be formed, for example, hemisulfate and hemicalcium salts. For a review on suitable salts, see Handbook of Pharmaceutical Salts: Properties, Selection, and Use by Stahl and Wermuth (Wiley-VCH, 2002).

Pharmaceutically acceptable salts may be prepared by one or more of three methods:

(i) by reacting a compound with the desired acid or base;

(ii) by removing an acid- or base-labile protecting group from a suitable precursor of a compound or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid or base; or

(iii) by converting one salt of a compound to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column.

All three reactions are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the resulting salt may vary from completely ionised to almost non-ionised.

Compounds and pharmaceutically acceptable salts, may exist in unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising a compound or its salt, and one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water. For example, a hydrate crystalline form of tris salt of Compound 1 disclosed herein refers to a crystalline material/complex that includes both tris salt of Compond 1 and water (hydrate water) in the crystal lattice of the crystalline material/complex.

A currently accepted classification system for organic hydrates is one that defines isolated site, channel, or metal-ion coordinated hydrates - see Polymorphism in Pharmaceutical Solids by K. R. Morris (Ed. H. G. Brittain, Marcel Dekker, 1995). Isolated site hydrates are ones in which the water molecules are isolated from direct contact with each other by intervening organic molecules. In channel hydrates, the water molecules lie in lattice channels where they are next to other water molecules. In metal-ion coordinated hydrates, the water molecules are bonded to the metal ion.

When the solvent or water is tightly bound, the complex may have a well-defined stoichiometry independent of humidity. When, however, the solvent or water is weakly bound, as in channel solvates and hygroscopic compounds, the water/solvent content may be dependent on humidity and drying conditions. In such cases, non-stoichiometry will be the norm.

Also included within the scope of the invention are multi-component complexes (other than salts and solvates) wherein the drug and at least one other component are present in stoichiometric or non-stoichiometric amounts. Complexes of this type include clathrates (drug-host inclusion complexes) and co-crystals. The latter are typically defined as crystalline complexes of neutral molecular constituents which are bound together through non-covalent interactions, but could also be a complex of a neutral molecule with a salt. Co-crystals may be prepared by melt crystallisation, by recrystallisation from solvents, or by physically grinding the components together - see Chem Commun, 17, 1889-1896, by O. Almarsson and M. J. Zaworotko (2004). For a general review of multi-component complexes, see J Pharm Sci, 64 (8), 1269-1288, by Haleblian (August 1975).

The compounds of the invention may exist in a continuum of solid states ranging from fully amorphous to fully crystalline. The term 'amorphous' refers to a state in which the material lacks long range order at the molecular level and, depending upon temperature, may exhibit the

physical properties of a solid or a liquid. Typically such materials do not give distinctive X-ray diffraction patterns and, while exhibiting the properties of a solid, are more formally described as a liquid. Upon heating, a change from solid to liquid properties occurs which is characterised by a change of state, typically second order ('glass transition'). The term 'crystalline' refers to a solid phase in which the material has a regular ordered internal structure at the molecular level and gives a distinctive X-ray diffraction pattern with defined peaks. Such materials when heated sufficiently will also exhibit the properties of a liquid, but the change from solid to liquid is characterised by a phase change, typically first order ('melting point').

A compound may also exist in a mesomorphic state (mesophase or liquid crystal) when subjected to suitable conditions. The mesomorphic state is intermediate between the true crystalline state and the true liquid state (either melt or solution). Mesomorphism arising as the result of a change in temperature is described as 'thermotropic' and that resulting from the addition of a second component, such as water or another solvent, is described as 'lyotropic'. Compounds that have the potential to form lyotropic mesophases are described as 'amphiphilic' and consist of molecules which possess an ionic (such as $-COO^-Na^+$, $-COO^-K^+$, or $-SO_3^-Na^+$) or non-ionic (such as $-N^+(CH_3)_3$) polar head group. For more information, see Crystals and the Polarizing Microscope by N. H. Hartshorne and A. Stuart, 4th Edition (Edward Arnold, 1970).

Some compounds may exhibit polymorphism and/or one or more kinds of isomerism (e.g. optical, geometric or tautomeric isomerism). The crystalline forms of the invnetions may also be isotopically labelled. Such variation is implicit to Compound 1 or its salt defined as they are by reference to their structural features and therefore within the scope of the invention.

Compounds containing one or more asymmetric carbon atoms can exist as two or more stereoisomers. Where a compound contains an alkenyl or alkenylene group, geometric cis/trans (or Z/E) isomers are possible. Where structural isomers are interconvertible via a low energy barrier, tautomeric isomerism ('tautomerism') can occur. This can take the form of proton tautomerism in compounds containing, for example, an imino, keto, or oxime group, or so-called valence tautomerism in compounds which contain an aromatic moiety. It follows that a single compound may exhibit more than one type of isomerism.

Certain pharmaceutically acceptable salts of Compound 1 may also contain a counterion which is optically active (e.g. d-lactate or l-lysine) or racemic (e.g. dl-tartrate or dl-arginine).

Cis/trans isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallisation.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC). Alternatively, a racemic precursor containing a chiral ester may be separated by

enzymatic resolution (see, for example, Int J Mol Sci 29682-29716 by A. C. L. M. Carvaho et. al. (2015)). In the case where a compound contains an acidic or basic moiety, a salt may be formed with an optically pure base or acid such as 1-phenylethylamine or tartaric acid. The resulting diastereomeric mixture may be separated by fractional crystallization and one or both of the diastereomeric salts converted to the corresponding pure enantiomer(s) by means well known to a skilled person. Alternatively, the racemate (or a racemic precursor) may be covalently reacted with a suitable optically active compound, for example, an alcohol, amine or benzylic chloride. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization by means well known to a skilled person to give the separated diastereomers as single enantiomers with 2 or more chiral centers. Chiral compounds (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% by volume of isopropanol, typically from 2% to 20%, and from 0 to 5% by volume of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture. Chiral chromatography using sub-and supercritical fluids may be employed. Methods for chiral chromatography useful in some embodiments of the present invention are known in the art (see, for example, Smith, Roger M., Loughborough University, Loughborough, UK; Chromatographic Science Series (1998), 75 (SFC with Packed Columns), pp. 223-249 and references cited therein). In some relevant examples herein, columns were obtained from Chiral Technologies, Inc, West Chester, Pennsylvania, USA, a subsidiary of *Daicel® Chemical Industries, Ltd., Tokyo, Japan*.

When any racemate crystallises, crystals of two different types are possible. The first type is the racemic compound (true racemate) referred to above wherein one homogeneous form of crystal is produced containing both enantiomers in equimolar amounts. The second type is the racemic mixture or conglomerate wherein two forms of crystal are produced in equimolar amounts each comprising a single enantiomer. While both of the crystal forms present in a racemic mixture have identical physical properties, they may have different physical properties compared to the true racemate. Racemic mixtures may be separated by conventional techniques known to those skilled in the art - see, for example, *Stereochemistry of Organic Compounds* by E. L. Eliel and S. H. Wilen (Wiley, 1994).

Although Compound 1 and its salts have been drawn herein in a single tautomeric form, all possible tautomeric forms are included within the scope of the invention.

The present invention includes all pharmaceutically acceptable isotopically-labeled Compound 1 or a salt thereof wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number which predominates in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, nitrogen, such as ^{13}N and ^{15}N, and oxygen, such as ^{15}O, ^{17}O and ^{18}O.

Certain isotopically-labelled Compound 1 or a salt thereof, for example those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. ^{3}H, and carbon-14, i.e. ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with heavier isotopes such as deuterium, i.e. ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements.

Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

Isotopically-labeled compounds can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, e.g. D_2O, d_6-acetone, d_6-DMSO.

Administration and Dosing

Typically, a compound of the invention is administered in an amount effective to treat a condition as described herein. The compounds of the invention can be administered as compound per se, or alternatively, as a pharmaceutically acceptable salt. For administration and dosing purposes, the compound per se or pharmaceutically acceptable salt thereof will simply be referred to as the compounds of the invention.

The compounds of the invention are administered by any suitable route in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The compounds of the invention may be administered orally, rectally, vaginally, parenterally, or topically.

The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the bloodstream directly from the mouth.

The dosage regimen for the compounds of the invention and/or compositions containing said compounds is based on a variety of factors, including the type, age, weight, sex and medical condition of the patient; the severity of the condition; the route of administration; and the

activity of the particular compound employed. Multiple doses per day typically may be used to increase the total daily dose, if desired.

For oral administration, the compositions may be provided, for example, in the form of tablets containing the active ingredient for the symptomatic adjustment of the dosage to the patient.

Suitable subjects according to the invention include mammalian subjects. In one embodiment, humans are suitable subjects. Human subjects may be of either gender and at any stage of development.

Pharmaceutical Compositions

In another embodiment, the invention comprises pharmaceutical compositions. Such pharmaceutical compositions comprise a compound of the invention presented with a pharmaceutically acceptable carrier. Other pharmacologically active substances can also be present. As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Examples of pharmaceutically acceptable carriers include one or more of water, saline, phosphate buffered saline, dextrose, glycerol, ethanol and the like, as well as combinations thereof, and may include isotonic agents, for example, sugars, sodium chloride, or polyalcohols such as mannitol, or sorbitol in the composition. Pharmaceutically acceptable substances such as wetting agents or minor amounts of auxiliary substances such as wetting or emulsifying agents, preservatives or buffers, which enhance the shelf life or effectiveness of the antibody or antibody portion.

In some embodiments, pharmaceutically acceptable carriers include one or more components select from diluents/fillers, disintegrants, binders, wetting agents, and lubricants.

As used herein, the term “diluent or filler” refers to a substance that acts to dilute the active pharmacological agent to the desired dosage and/or that acts as a carrier for the active pharmacological agent. Examples of diluent or filler include mannitol, lactose (including e.g. lactose monohydrate), sucrose, maltodextrin, sorbitol, xylitol, powdered cellulose, microcrystalline cellulose, carboxymethylcellulose, carboxyethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, methylhydroxyethylcellulose, starch, sodium starch glycolate, pregelatinized starch, a calcium phosphate, a metal carbonate, a metal oxide, and/or a metal aluminosilicate.

As used herein, the term “disintegrant” refers to a substance that encourages disintegration in water (or water-containing fluid *in vivo*) of a pharmaceutical composition/formulation of the invention. Examples of disintegrant include croscarmellose sodium, carmellose calcium, crospovidone, alginic acid, sodium alginate, potassium alginate, calcium alginate, an ion exchange resin, an effervescent system based on food acids and an

alkaline carbonate component, clay, talc, starch, pregelatinized starch, sodium starch glycolate, cellulose floc, carboxymethylcellulose, hydroxypropylcellulose, calcium silicate, a metal carbonate, sodium bicarbonate, calcium citrate, and/or calcium phosphate.

As used herein, the term “binder” refers to a substance that increases the mechanical strength and/or compressibility of a pharmaceutical composition/formulation of the invention. Examples of binder include polyvinylpyrrolidone, copovidone, hydroxypropylcellulose, hydroxypropylmethylcellulose, crosslinked poly(acrylic acid), gum arabic, gum acacia, gum tragacanath, lecithin, casein, polyvinyl alcohol, gelatin, kaolin, cellulose, methylcellulose, hydroxymethylcellulose, carboxymethylcellulose, carboxymethylcellulose calcium, carboxymethylcellulose sodium, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, hydroxyethylcellulose, methylhydroxyethylcellulose, silicified microcrystalline cellulose, starch, maltodextrin, dextrins, microcrystalline cellulose, and/or sorbitol.

As used herein, the term “wetting agent” refers to a substance that increases the water permeability of a pharmaceutical composition/formulation of the invention. In another aspect, the term, “wetting agent” refers to a substance that increases dissolution of the active pharmacological agent in water (or water containing fluid *in vivo*). In yet another aspect, the term “wetting agent” refers to a substance that increases the bioavailability of the active pharmacological agent after administration of a pharmaceutical composition/formulation of the invention. Examples of wetting agent include metallic lauryl sulfate, polyethylene glycol, glycerides of fatty ester, polyoxyethylene-polyoxypropylene copolymer, polyoxyethylene-alkyl ether, metal alkyl sulfate, polyoxyethylene sorbitan fatty acid ester, polyoxyethylene castor oil derivative, sugar ester of fatty acid, polyglycolized glyceride, quaternary ammonium amine compound, lauroyl macrogol glycerides, caprylocaproyl macrogolglycerides, stearoyl macrogol glycerides, linoleoyl macrogol glycerides, oleoyl macrogol glycerides, polyethoxylated vegetable oil, polyethoxylated sterol, polyethoxylated cholesterol, polyethoxylated glycerol fatty acid ester, polyethoxylated fatty acid ester, sulfosuccinate, taurate, and/or docusate sodium.

As used herein, the term “lubricant” refers to a substance that aids in preventing sticking to the equipment of the pharmaceutical formulations/composition during processing and/or that improves powder flow of the composition/formulation during processing. Examples of lubricant include stearic acid, metallic stearate (e.g. magnesium stearate), sodium stearyl fumarate, fatty acid, fatty alcohol, fatty acid ester, glyceryl behenate, mineral oil, vegetable oil, paraffin, leucine, silica, silicic acid, talc, propylene glycol fatty acid ester, polyethylene glycol, polypropylene glycol, polyalkylene glycol, and/or sodium chloride.

In some embodiments, a composition of the invention comprises a filler [e.g. microcrystalline cellulose, lactose (e.g. in the form of lactose monohydrate), or a combination thereof], a disintegrant (e.g. croscarmellose sodium, sodium alginate, potassium alginate, or

sodium starch glycolate), and a lubricant [e.g. metallic stearate (such as magnesium stearate)]. In some embodiments, a composition of the invention comprises microcrystalline cellulose, lactose (e.g. in the form of lactose monohydrate), sodium starch glycolate, and magnesium stearate.

The compositions of this invention may be in a variety of forms. These include, for example, liquid, semi-solid and solid dosage forms, such as liquid solutions, dispersions or suspensions, tablets, pills, powders, liposomes and suppositories. The form depends on the intended mode of administration and therapeutic application.

Oral administration of a solid dose form may be, for example, presented in discrete units, such as hard or soft capsules, pills, cachets, lozenges, or tablets, each containing a predetermined amount of a pharmacological active ingredient (API, for example, Compound 1 or a pharmaceutical acceptable salt thereof such as tris salt of Compound 1). In one embodiment, the oral administration may be in tablet form. In one embodiment, the oral administration may be in capsule form. In one embodiment, the oral administration may be in a powder or granule form. In one embodiment, the oral dose form is sub-lingual, such as, for example, a lozenge. In such solid dosage forms, the compounds of the invention are ordinarily combined with one or more adjuvants. Such capsules or tablets may contain an immediate release formulation. In other embodiments, such capsules or tablets may contain a controlled release formulation. In the case of capsules, tablets, and pills, the dosage forms also may comprise buffering agents or may be prepared with enteric coatings.

In another embodiment, oral administration may be in a liquid dose form. Liquid dosage forms for oral administration include, for example, pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art (e.g., water). Such compositions also may comprise adjuvants, such as wetting, emulsifying, suspending, flavoring (e.g., sweetening), and/or perfuming agents.

Other carrier materials and modes of administration known in the pharmaceutical art may also be used. Pharmaceutical compositions of the invention may be prepared by any of the well-known techniques of pharmacy, such as effective formulation and administration procedures. The above considerations in regard to effective formulations and administration procedures are well known in the art and are described in standard textbooks. Formulation of drugs is discussed in, for example, Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania, 1975; Liberman et al., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Kibbe et al., Eds., Handbook of Pharmaceutical Excipients (3rd Ed.), American Pharmaceutical Association, Washington, 1999.

Co-administration

The compositions of the invention can be used alone, or in combination with other therapeutic agents. The invention provides any of the uses, methods or compositions as defined herein wherein the compound of any embodiment herein, or pharmaceutically acceptable salt thereof, or pharmaceutically acceptable solvate of said compound or salt, is used in combination with one or more other therapeutic agent discussed herein. This would include a pharmaceutical composition for the treatment of a disease or condition for which an agonist of the GLP-1R is indicated, comprising a composition of the invention, as defined in any of the embodiments described herein, and one or more other therapeutic agent discussed herein.

The administration of two or more compounds "in combination" means that all of the compounds are administered closely enough in time that each may generate a biological effect in the same time frame. The presence of one agent may alter the biological effects of the other compound(s). The two or more compounds may be administered simultaneously, concurrently or sequentially. Additionally, simultaneous administration may be carried out by mixing the compounds prior to administration or by administering the compounds at the same point in time but as separate dosage forms at the same or different site of administration.

The phrases "concurrent administration," "co-administration," "simultaneous administration," and "administered simultaneously" mean that the compounds are administered in combination.

In another embodiment, the invention provides methods of treatment that include administering compounds of the present invention in combination with one or more other pharmaceutical agents, wherein the one or more other pharmaceutical agents may be selected from the agents discussed herein.

In one embodiment, the compounds of this invention are administered with an anti-diabetic agent including but not limited to a biguanide (e.g., metformin), a sulfonylurea (e.g., tolbutamide, glibenclamide, gliclazide, chlorpropamide, tolazamide, acetohexamide,glyclopyramide, glimepiride, or glipizide), a thiazolidinedione (e.g., pioglitazone, rosiglitazone, or lobeglitazone), a glitazar (e.g., saroglitazar, aleglitazar, muraglitazar or tesaglitazar), a meglitinide (e.g., nateglinide, repaglinide), a dipeptidyl peptidase 4 (DPP-4) inhibitor (e.g., sitagliptin, vildagliptin, saxagliptin, linagliptin, gemigliptin, anagliptin, teneligliptin, alogliptin, trelagliptin, dutogliptin, or omarigliptin), a glitazone (e.g., pioglitazone, rosiglitazone, balaglitazone, rivoglitazone, or lobeglitazone), a sodium-glucose linked transporter 2 (SGLT2) inhibitor (e.g., empagliflozin, canagliflozin, dapagliflozin, ipragliflozin, lpragliflozin, tofogliflozin, sergliflozin etabonate, remogliflozin etabonate, or ertugliflozin), an SGLTL1 inhibitor, a GPR40 agonist (FFAR1/FFA1 agonist, e.g. fasiglifam), glucose-dependent insulinotropic peptide (GIP) and analogues thereof, an alpha glucosidase inhibitor (e.g. voglibose, acarbose, or miglitol), or

an insulin or an insulin analogue, including the pharmaceutically acceptable salts of the specifically named agents and the pharmaceutically acceptable solvates of said agents and salts.

In another embodiment, the compounds of this invention are administered with an anti-obesity agent including but not limited to peptide YY or an analogue thereof, a neuropeptide Y receptor type 2 (NPYR2) agonist, a NPYR1 or NPYR5 antagonist, a cannabinoid receptor type 1 (CB1R) antagonist, a lipase inhibitor (e.g., orlistat), a human proislet peptide (HIP), a melanocortin receptor 4 agonist (e.g., setmelanotide), a melanin concentrating hormone receptor 1 antagonist, a farnesoid X receptor (FXR) agonist (e.g. obeticholic acid), zonisamide, phentermine (alone or in combination with topiramate), a norepinephrine/dopamine reuptake inhibitor (e.g., buproprion), an opioid receptor antagonist (e.g., naltrexone), a combination of norepinephrine/dopamine reuptake inhibitor and opioid receptor antagonist (e.g., a combination of bupropion and naltrexone), a GDF-15 analog, sibutramine, a cholecystokinin agonist, amylin and analogues therof (e.g., pramlintide), leptin and analogues thereof (e.g., metroleptin), a serotonergic agent (e.g., lorcaserin), a methionine aminopeptidase 2 (MetAP2) inhibitor (e.g., beloranib or ZGN-1061), phendimetrazine, diethylpropion, benzphetamine, an SGLT2 inhibitor (e.g., empagliflozin, canagliflozin, dapagliflozin, ipragliflozin, lpragliflozin, tofogliflozin, sergliflozin etabonate, remogliflozin etabonate, or ertugliflozin), an SGLTL1 inhibitor, a dual SGLT2/SGLT1 inhibitor, a fibroblast growth factor receptor (FGFR) modulator, an AMP-activated protein kinase (AMPK) activator, biotin, a MAS receptor modulator, or a glucagon receptor agonist (alone or in combination with another GLP-1R agonist, e.g., liraglutide, exenatide, dulaglutide, albiglutide, lixisenatide, or semaglutide), including the pharmaceutically acceptable salts of the specifically named agents and the pharmaceutically acceptable solvates of said agents and salts.

In another embodiment, the compounds of this invention are administered in combination with one or more of the following: an agent to treat NASH including but not limited to PF-05221304, an FXR agonist (e.g., obeticholic acid), a PPAR α/δ agonist (e.g., elafibranor), a synthetic fatty acid−bile acid conjugate (e.g., aramchol), a caspase inhibitor (e.g., emricasan), an anti-lysyl oxidase homologue 2 (LOXL2) monoclonal antibody (e.g., simtuzumab), a galectin 3 inhibitor (e.g., GR-MD-02), a MAPK5 inhibitor (e.g., GS-4997), a dual antagonist of chemokine receptor 2 (CCR2) and CCR5 (e.g., cenicriviroc), a fibroblast growth factor 21 (FGF21) agonist (e.g., BMS-986036), a leukotriene D4 (LTD4) receptor antagonist (e.g., tipelukast), a niacin analogue (e.g., ARI 3037MO), an ASBT inhibitor (e.g., volixibat), an acetyl-CoA carboxylase (ACC) inhibitor (e.g., NDI 010976 or PF-05221304), a ketohexokinase (KHK) inhibitor, a diacylglyceryl acyltransferase 2 (DGAT2) inhibitor, a CB1 receptor antagonist, an anti-CB1R antibody, or an apoptosis signal-regulating kinase 1 (ASK1) inhibitor, including the

pharmaceutically acceptable salts of the specifically named agents and the pharmaceutically acceptable solvates of said agents and salts.

Some specific compounds that can be used in combination with the compounds of the present invention for treating diseases or disorders described herein include:

4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid, which is an example of a selective ACC inhibitor and was prepared as the free acid in Example 9 of U.S. Patent No. 8,859,577, which is the U.S. national phase of International Application No. PCT/IB2011/054119, the disclosures of which are hereby incorporated herein by reference in their entireties for all purposes. Crystal forms of 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid, including an anhydrous mono-tris form (Form 1) and a trihydrate of the mono-tris salt (Form 2), are described in International PCT Application No. PCT/IB2018/058966, the disclosure of which is hereby incorporated herein by reference in its entirety for all purposes;

(S)-2-(5-((3-Ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide, or a pharmaceutically acceptable salt thereof, and its crystalline solid forms (Form 1 and Form 2) is an example of a DGAT2 inhibitor described in Example 1 of U.S. Patent No. 10,071,992, the disclosure of which is hereby incorporated herein by reference in its entirety for all purposes;

[(1R,5S,6R)-3-{2-[(2S)-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid, or a pharmaceutically acceptable salt thereof, (including a crystalline free acid form thereof) is an example of a ketohexokinase (KHK) inhibitor and is described in Example 4 of U.S. Patent No. 9,809,579, the disclosure of which is hereby incorporated herein by reference in its entirety for all purposes; and

the FXR agonist Tropifexor or a pharmaceutically acceptable salt thereof is described in Example 1-1B of U.S. Patent No. 9,150,568, the disclosure of which is hereby incorporated herein by reference in its entirety for all purposes.

These agents and compounds of the invention can be combined with pharmaceutically acceptable vehicles such as saline, Ringer's solution, dextrose solution, and the like. The particular dosage regimen, i.e., dose, timing and repetition, will depend on the particular individual and that individual's medical history.

Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and may comprise buffers such as phosphate, citrate, and other organic acids; salts such as sodium chloride; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens, such as methyl or propyl paraben; catechol; resorcinol;

cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or Igs; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants such as TWEEN™, PLURONICS™ or polyethylene glycol (PEG).

Liposomes containing these agents and/or compounds of the invention are prepared by methods known in the art, such as described in U.S. Pat. Nos. 4,485,045 and 4,544,545. Liposomes with enhanced circulation time are disclosed in U.S. Patent No. 5,013,556. Particularly useful liposomes can be generated by the reverse phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter.

These agents and/or the compounds of the invention may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington, The Science and Practice of Pharmacy, 20th Ed., Mack Publishing (2000).

Sustained-release preparations may be used. Suitable examples of sustained-release preparations include semi-permeable matrices of solid hydrophobic polymers containing Compound 1 or a pharmaceutically acceptable salt thereof, which matrices are in the form of shaped articles, e.g., films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or 'poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and 7 ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as those used in LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), sucrose acetate isobutyrate, and poly-D-(-)-3-hydroxybutyric acid.

The formulations to be used for intravenous administration must be sterile. This is readily accomplished by, for example, filtration through sterile filtration membranes. Compounds of the invention are generally placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Suitable emulsions may be prepared using commercially available fat emulsions, such as Intralipid™, Liposyn™, Infonutrol™, Lipofundin™ and Lipiphysan™. The active ingredient may be either dissolved in a pre-mixed emulsion composition or alternatively it may be dissolved in an oil (e.g., soybean oil, safflower oil, cottonseed oil, sesame oil, corn oil or almond oil) and an emulsion formed upon mixing with a phospholipid (e.g., egg phospholipids, soybean phospholipids or soybean lecithin) and water. It will be appreciated that other ingredients may be added, for example glycerol or glucose, to adjust the tonicity of the emulsion. Suitable emulsions will typically contain up to 20% oil, for example, between 5 and 20%. The fat emulsion can comprise fat droplets between 0.1 and 1.0 μm, particularly 0.1 and 0.5 μm, and have a pH in the range of 5.5 to 8.0.

The emulsion compositions can be those prepared by mixing a compound of the invention with Intralipid™ or the components thereof (soybean oil, egg phospholipids, glycerol and water).

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulised by use of gases. Nebulised solutions may be breathed directly from the nebulising device or the nebulising device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

KITS

Another aspect of the invention provides kits comprising a pharmaceutical composition of the invention. A kit may include, in addition to a pharmaceutical composition of the invention, diagnostic or therapeutic agents. A kit may also include instructions for use in a diagnostic or therapeutic method. In some embodiments, the kit includes a pharmaceutical composition of the invention and a diagnostic agent. In other embodiments, the kit includes a pharmaceutical composition and instructions for use in a therapeutic method.

In yet another embodiment, the invention comprises kits that are suitable for use in performing the methods of treatment described herein. In one embodiment, the kit contains one or more of solid forms of the invention in quantities sufficient to carry out the methods of the invention. In another embodiment, the kit comprises one or more solid forms of the invention in quantities sufficient to carry out the methods of the invention and a container for the dosage.

EXAMPLES

The following examples illustrate the oral compositions/formulations and methods of the present invention.

Example 1. Preparation of Immediate Release (IR) Tablets

Immediate release (IR), non-film-coated tablets of tris salt of Compound 1 in dosage strengths of 1 mg, 10 mg, 50 mg, and 100 mg were prepared [the dosage strength weight expressed in milligram is the weight equivalent to Compound 1].

The compositions of these tablets are shown in Tables 1-1 to 1-4.

Table 1-1. Composition of tris salt of Compound 1 Tablet 1 mg

Name of Ingredients	Function	Unit Formula
tris salt of Compound 1	Active Ingredient	1.218 mg
Microcrystalline Cellulose	Filler	63.188mg
Lactose Monohydrate	Filler	31.594mg
Sodium Starch Glycolate	Disintegrant	3.000 mg
Magnesium Stearate	Lubricant	1.000 mg
Total Tablet Weight		100 mg

Table 1-2. Composition of tris salt of Compound 1 IR Tablet 10 mg

Name of Ingredients	Function	Unit Formula
tris salt of Compound 1	Active Ingredient	12.180 mg
Microcrystalline Cellulose	Filler	55.880 mg
Lactose Monohydrate	Filler	27.940 mg
Sodium Starch Glycolate	Disintegrant	3.000 mg
Magnesium Stearate	Lubricant	1.000 mg
Total Tablet Weight		100 mg

Table 1-3. Composition of tris salt of Compound 1 IR Tablet 50 mg

Name of Ingredients	Function	Unit Formula
tris salt of Compound 1	Active Ingredient	60.901 mg
Microcrystalline Cellulose	Filler	471.399 mg
Lactose Monohydrate	Filler	235.700 mg
Sodium Starch Glycolate	Disintegrant	24.000 mg
Magnesium Stearate	Lubricant	8.000 mg
Total Tablet Weight		800 mg

Table 1-4. Composition of tris salt of Compound 1 IR Tablet 100 mg

Name of Ingredients	Function	Unit Formula
tris salt of Compound 1	Active Ingredient	121.803 mg
Microcrystalline Cellulose	Filler	430.798 mg
Lactose Monohydrate	Filler	215.399 mg
Sodium Starch Glycolate	Disintegrant	24.000 mg
Magnesium Stearate	Lubricant	8.000 mg
Total Tablet Weight		800 mg

Process of preparing IR tablets

The following steps were carried out in preparing the IR tablets.

1. Blend approximately half of the microcrystalline cellulose.
2. Add tris salt of Compound 1 to the microcrystalline cellulose, followed by the lactose monohydrate and sodium starch glycolate, and mix.
3. Mill the blend and pass the remaining amount of microcrystalline cellulose through the mill. Blend the milled powder.
4. Add the intra-granular magnesium stearate and blend.
5. Compact and mill, then blend.
6. Add the extra-granular magnesium stearate and blend.
7. Compress using a suitable tablet press.

Example 1B. Preparation of Additional Immediate Release (IR) Tablets

Additional immediate release (IR), non-film-coated tablets of tris salt of Compound 1 in dosage strengths of 100 mg were prepared [the dosage strength weight expressed in milligram

is the weight equivalent to Compound 1]. The compositions of these tablets are shown in Tables 1-5, 1-6, and 1-7. These tablets were prepared using a process similar to that in Example 1 (the disintegrant used was sodium starch glycolate or cropovidone)

Table 1-5. Composition of tris salt of Compound 1 Direct Compression (DC) IR Tablet 100mg

Name of Ingredients	Function	Unit Formula
tris salt of Compound 1	Active Ingredient	121.803 mg
Microcrystalline Cellulose	Filler	172.132 mg
Lactose Monohydrate	Filler	86.065 mg
Sodium Starch Glycolate	Disintegrant	12.000 mg
Magnesium Stearate	Lubricant	8.000 mg
Total Tablet Weight		400 mg

Table 1-6. Composition of tris salt of Compound 1 Direct Compression (DC) IR Tablet 100mg

Name of Ingredients	Function	Unit Formula
tris salt of Compound 1	Active Ingredient	121.803 mg
Microcrystalline Cellulose	Filler	172.132 mg
Lactose Monohydrate	Filler	86.065 mg
Crospovidone	Disintegrant	12.000 mg
Magnesium Stearate	Lubricant	8.000 mg
Total Tablet Weight		400 mg

Table 1-7. Composition of tris salt of Compound 1 Direct Compression (DC) IR Tablet 100mg

Name of Ingredients	Function	Unit Formula
tris salt of Compound 1	Active Ingredient	121.803 mg
Microcrystalline Cellulose	Filler	172.132 mg
Lactose Monohydrate	Filler	86.065 mg
Crospovidone	Disintegrant	12.000 mg
Sodium Stearyl Fumarate	Lubricant	8.000 mg
Total Tablet Weight		400 mg

Example 2. Preparation of Controlled Release (CR) Tablets

A film-coated controlled release (CR) tablet of tris salt of Compund 1 in dosage strength of 50 mg was prepared [the weight expressed in milligram is the weight equivalent to Compound 1].

The compositions of this CR tablet are shown in Table 2-1.

Table 2-1. Composition of tris salt of Compound 1 CR Tablet (equivalent to 50 mg of Compound 1)

Name of Ingredients	Function	Unit Formula (mg)
Core Tablet		
tris salt of Compound 1	Active Ingredient	60.901
Polyethylene Oxide (200,000 molecular weight)	Entraining Polymer	335.099
Magnesium Stearate	Lubricant	4.000
Total Active Layer Weight		400.000
Polyethylene Oxide (5,000,000 molecular weight)	Swelling Agent	108.400
Sodium Chloride	Osmogen	60.000
Microcrystalline Cellulose	Tableting Aid	30.000
Magnesium Stearate	Lubricant	1.000
FD&C Blue Aluminum Lake #2	Colorant	0.600
Total Sweller Layer Weight		200.000
Total Bilayer Core Tablet Weight		600.000
Cellulose Acetate	Control Release	42.500
Polyethylene Glycol 3350	Control Release	7.500
Acetone[a]	Processing Aid	as required
Purified Water[a]	Processing Aid	as required
Total Osmotic Coating Weight		50.000
Total Tablet Weight		**650.000 mg**

[a] Removed during processing

Process of preparing CR tablets

The following steps were carried out in preparing the CR tablets (See Fig. 2).

Active Layer

1. Perform Blend-Mill-Blend Process of tris salt of Compound 1, Polyethylene Oxide, and a portion of the Magnesium Stearate using a 055R screen.
2. Dry granulate mixture from Step 1 by roller compaction.
3. Add the extra-granular Magnesium Stearate and blend the mixture to yield the active layer granulation.

Sweller Layer

4. Perform Blend-Mill-Blend Process of Polyethylene Oxide, Microcrystalline Cellulose, Sodium Chloride, and FD&C Blue Aluminum Lake #2 using a 055R screen.
5. Add Magnesium Stearate and blend the mixture to yield the sweller layer blend.

Bilayer Tablet

6. Compress the active layer and sweller layer into bilayer cores.
7. Film coat the bilayer cores using a suitable pan coater to produce the osmotic membrane.
8. Dry the tablets in a tray dryer to remove any residual amount of processing solvents.
9. Produce the delivery port on the active-layer face of the bilayer tablet using a suitable laser.

Example 3. A clinical study (dose guiding study) of Compound 1 (in the form of its tris salt)

This study was a randomized, double-blind (sponsor-open), parallel, placebo-controlled, multiple oral dose-escalating study of Compound 1 (in the form of its tris salt) in participants with type 2 diabetes mellitus (T2DM) on a background of metformin monotherapy.

A total of 98 participants received oral doses of Compound 1 (in the form of its tris salt) or matching placebo for 28 days, in this study. A total of approximately 12 participants were enrolled in each cohort with a randomization ration of 3:1 (9 active and 3 placebo), and 8 cohorts were enrolled in the study. Participants were admitted to the clinical research unit (CRU) on or before Day -2 and were discharged following completion of all assessments on Day 30, at principal investigator discretion. For individual participants, the total duration of participation from the Screening visit to the on-site Follow-up visit was approximately 15 weeks. A Follow-up visit and a Follow-up contact (which have been conducted by phone call) occurred 35-42 days and 56-63 days following the first dose of investigational product on Day 1, respectively. Participants who discontinued prior to completion of the study might have been replaced, at the discretion of the principal investigator and Sponsor. 92 participants completed the inpatient study.

The planned titration schemes and dosing paradigms for all Cohorts are listed in Table 2-1.

QD: once daily
BID: twice daily

Table 2-1. Titration Scheme and Dosing Paradigm (Compound 1 (in the form of its tris salt) or Matching Placebo)

Study Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Cohort 1																												
	15 mg BID IR																											
Cohort 2																												
	50 mg BID IR																											
Cohort 3																												
	20 mg BID IR			40 mg BID IR			50 mg BID IR			70 mg BID IR					70 mg BID IR													
Cohort 4																												
	20 mg BID IR		40 mg BID IR		60 mg BID IR		80 mg BID IR			100 m BID IR			120 mg BID IR		120 mg BID IR													
Cohort 5																												
	5 mg BID IR														10 mg BID IR													
Cohort 6 (Slow titration)																												
	10 mg BID IR				20 mg BID IR				40 mg BID IR				60 mg BID IR				80 mg BID IR				100 mg BID IR				120 mg BID IR			
Cohort 7																												
	50 mg QD CR							100 mg QD CR							150 mg QD CR							200 mg QD CR					
Cohort 8																												

Table 2-1. Titration Scheme and Dosing Paradigm (Compound 1 (in the form of its tris salt) or Matching Placebo)

Study Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
	10 mg QD IR		20 mg QD IR		30 mg QD IR		40 mg QD IR				60 mg QD IR				80 mg QD IR				100 mg QD IR				120 mg QD IR			

Diagnosis and Main Criteria for Inclusion: The population for this study was female participants of non-childbearing potential and/or male participants with T2DM, with an HbA1c ≥7.0% and ≤10.5%, who were taking metformin as their only anti-hyperglycemic treatment, and who were between 18 and 70 years with T2DM at the time of consent and Screening, with a body mass index (BMI) of 24.5 to 45.4 kg/m^2 and a total body weight >50 kg (110 lb). Metformin dose was required to be ≥500 mg per day and was required to be stable, for at least 2 months prior to the Screening visit and was administered in the CRU according to patient's baseline dosing regimen.

Study Treatment: Compound 1 (in the form of its tris salt) was supplied as 1 mg, 10 mg, 50 mg and 100 mg immediate release (IR) tablets or 50 mg controlled release (CR) tablets (see Examples 1 and 2) for oral administration. Matching placebo tablets (2:1, Microcrystalline Cellulose : Lactose) were also provided.

Results

Subject Disposition and Demography: A total of 98 participants were randomized and assigned to receive study treatment, and 92 participants completed the study. Of the 6 participants who discontinued from the study, 2 participants discontinued due to treatment-related treatment-emergent AEs (TEAEs): 1 participant in Compound 1 (in the form of its tris salt) 15 mg twice daily (BID) group discontinued from the study due to a moderate TEAE of headache and 1 participant in the Compound 1 (in the form of its tris salt) 50 mg BID group discontinued from the study due to moderate TEAEs of decreased appetite, nausea, vomiting and a mild TEAE of fatigue. In addition, 1 participant in the Compound 1 (in the form of its tris salt) 50 mg BID group discontinued due to withdrawal by participant, and 3 participants from the Compound 1 (in the form of its tris salt) 200 mg once daily (QD) CR group discontinued due to other reasons. All discontinuations from the study occurred in the treatment phase. Demographic characteristics and physical measurements were generally comparable across dosing groups. The 98 randomized participants consisted of 51 males (52%) and 47 females (48%). The majority of the participants were White (70, 71.4%). Sixty-one (61, 62.2%) participants were Hispanic or Latino. The mean age of all participants was 57.4 years (range: 37 to 70 years). The mean weight was 92.4 kg (range: 50.2 to 138.9 kg). The mean BMI was 32.9 kg/m^2 (range: 25.0 to 43.0 kg/m^2). The mean duration of T2DM for all participants was 9.5 years (range: 0.3 to 29.1 years), and baseline mean HbA1c for the study population was 8.3% (range: 8.01 to 8.61%).

Safety Results:

(A) Adverse Events

A total of 319 all causalities TEAEs were reported by 83 participants (84.7%) in the study, of which 262 (262/319: 82.1%) TEAEs were considered treatment-related. Two (2) participants experienced 2 severe TEAEs during the study, 1 of which occurred in the dosing period and was considered treatment-related, the other of which occurred during the follow-up period (also an SAE) and was not considered treatment-related. There were no deaths. One (1) SAE occurred in the study reporting period (not treatment-related and as previously mentioned). Another SAE, also not treatment-related, was reported in the same participant outside of the study reporting period and was not recorded in the clinical database

A total of 2 participants discontinued from study due to TEAEs, and 2 participants discontinued from study drug due to TEAEs but continued in the study. Nine (9) participants had dose reduction or temporary discontinuation due to TEAEs: 1 in the placebo group, 4 in the 50 mg BID group, 1 in the 120 mg BID group, 2 in the 120 mg BID Slow titration group and 1 in the 200 mg QD CR group.

The Compound 1 (in the form of its tris salt) 10 mg BID and 15 mg BID groups had the lowest number of all causality TEAEs with 8 and 16 events, respectively. The 120 mg BID slow titration group had the largest number of all causality TEAEs with 50 events. One (1) SAE (not treatment-related) and 2 severe TEAEs (1 was treatment-related and 1 was not) were reported in the Compound 1 (in the form of its tris salt) 120mg BID slow titration group. The placebo, 50 mg BID, 70 mg BID, 120 mg BID, 120 mg QD and 200 mg QD CR groups reported 44, 45, 31, 43, 35 and 47 TEAEs, respectively.

The most frequently reported all causalities TEAEs by system organ class (SOC) were Gastrointestinal Disorders (reported in 73.5% of all participants) and Nervous System Disorders (33.7%). The most commonly reported al causalities TEAEs by preferred term (PT) were nausea (49.0%), dyspepsia (32.7%), vomiting (26.5%), diarrhea (24.5%), headache (23.5%) and constipation (20.4%). The incidence of all causalities TEAEs in Gastrointestinal Disorders category in each dose groups were higher than the incidence in the placebo group (52.0%) with an exception of the 10 mg BID group (33.3%).

The majority of all-causalities TEAEs (294 out of 319) were mild in severity. Twenty-three (23) TEAEs were moderate, of which 18 TEAEs were considered treatment-related. Two (2) severe TEAEs were reported in the 120 mg BID slow titration group, of which 1 was considered treatment-related.

One (1) participant in the 120 mg BID group experienced mild hypoglycemia after missing a meal or snack, which was self-limited and considered treatment-related.

(B) Clinical Laboratory Evaluation

The most common laboratory abnormality, without regard to baseline abnormality, was hemoglobin A1C (%) >1.3 × upper limit of normal (ULN) (45, 48.9%), which was expected due to the eligibility criteria for the study. Other common laboratory abnormalities included activated partial thromboplastin time >1.1 × ULN (40, 40.8%), and urine glucose ≥1 mg/dL (36, 36.7%), which did not appear to be imbalanced relative to placebo.

(C) Vital Signs

The most frequently reported post-baseline vital signs that met the pre-specified criteria for categorical analysis were supine systolic blood pressure (BP) decreased ≥30 mm Hg in 39 participants, and supine diastolic BP decreased ≥20 mm Hg in 24 participants across all treatment groups. None of the participants met the pre-specified criteria for pulse rate with values of <40 bpm and >120 bpm. There were no apparent dose-related increases in the frequency of vital sign abnormalities by categorical analysis.

Pulse rate increased with Compound 1 (in the form of its tris salt) 961 treatment compared to placebo at Days 1, 14, 21 and 28, with generally greater increases observed on Day 28 compared with Day 1. Across the dosing interval from Day 1 to Day 28, mean time-matched double differences in pulse rate ranged from -6.4 to 11.8 bpm across doses of Compound 1 (in the form of its tris salt) compared to a range of -6.4 to -0.8 bpm in placebo. While these increases in pulse rate were observed, no AEs were reported related to pulse rate and there were no occurrences of pulse rate >120 bpm.

(D) ECG

A total of 5 participants reported post-baseline ECG (electrocardiogram) data meeting pre-specified criteria of aggregate QTcF (QT interval corrected for heart rate based on the Fridericia's correction formula) interval >450 and ≤480 or change from baseline >30 and ≤60, 2 of which occurred in the placebo group and 3 of which occurred in Compound 1 (in the form of its tris salt) planned treatment groups. These occurrences were self-limited and did not require intervention. No data met criteria of PR interval ≥300 msec or QRS duration ≥140 msec, and there were no apparent dose-related increases in the frequency of ECG abnormalities by categorical analysis. There were no ECG abnormalities in optional Compound 1 (in the form of its tris salt) groups (Compound 1 (in the form of its tris salt) 120 mg BID slow titration, 120 mg QD and 200 mg QD CR groups). No ECG abnormalities were reported as AEs and none of the ECG findings were reported as clinically significant by the investigator.

Ascending, multiple, oral doses of Compound 1 (in the form of its tris salt) were generally safe and well-tolerated in adult participants with T2DM. The most commonly reported all causalities TEAEs were nausea, dyspepsia, vomiting, diarrhea, headache and constipation.

There were no clinically significant adverse trends in safety laboratory tests, vital signs or ECG parameters with increasing Compound 1 (in the form of its tris salt) dose.

Pharmacokinetic Evaluations

Compound 1 (in the form of its tris salt) plasma pharmacokinetic parameters area under the plasma concentration time profile from time 0 to time 24 hours (AUC_{24}), maximum observed concentration over a 24-hour interval (C_{max}), and time for C_{max} (T_{max}) were calculated following Day 1, and multiple dose administration, were calculated for each participant and treatment, using noncompartmental analysis of concentration-time data.

C_{max}	maximum observed concentration over a 24-hour interval
Cmax1	maximum plasma concentration during the dosing interval τ1 =0 to 10 hours
T_{max}	time for C_{max}
T_{max1}	time for C_{max1}
t½	terminal half life
HbA1c	glycated hemoglobin
AUC	area under the curve
AUC24	area under the plasma concentration time profile from time 0 to time 24 hours
BMI	body mass index Body Mass Index (kg/m^2) was defined as weight (kg) / [height (cm)×0.01]^2

Following a single oral dose of Compound 1 (in the form of its tris salt) on Day 1, absorption for the IR formulation for the QD and BID regimens occurred in a median T_{max} and T_{max1} of 2.0 to 4.0 hours post dose.

Day 1 exposure based on dose normalized mean AUC_{24} values appeared to be approximately dose proportional across the BID and QD treatments for the IR formulation. On Day 28, AUC_{24} and C_{max} increased in an approximately dose-proportional manner for cohorts administered BID IR formulation treatments.

Mean C_{max} and C_{max1} values on Day 28 were reached in a median T_{max} and T_{max1} of 3 to 10 hours post dose for the BID and QD IR treatments, while absorption was slower for the CR formulation treatment (Cohort 7), with a median Tmax of 14 hours post dose. Mean t½ values across all treatments ranged between 4.7 to 8.1 hours, and no apparent trends were observed across various treatments, regimens, or doses administered. The CR formulation exhibited approximately a 50% lower exposure (AUC_{24} and C_{max}) on Day 14 compared to that observed for the IR formulations, however on Day 28 the exposure was similar to that observed for the IR

formulation treatments. Urinary recovery of Compound 1 was low, with <0.1% of the dose recovered unchanged in urine on Day 28.

FPG, MDG, HbA1C, and Body Weight Measurement

Measurements of fasting plasma glucose (FPG), 24-hour mean daily glucose (MDG), HbA1C, and body weight at baseline (at Day -1) and at Day 28 (shown as change from baselin) are shown in Tables 2-2 to 2-5.

Baseline was defined as the measurement (MDG, FPG, HbA1c, or body weight) on Day -1.

Randomized treatment represented the target dose at Day 28.

Baseline was restricted to subjects who had a non-missing value for the change from baseline to the time point of interest

Table 2-2. Summary of Baseline and Change from Baseline (CFB) for Mean Daily Glucose (mg/dL) by Randomized Treatment.

Study Day	Randomized Treatment	N	Baseline (SD)	Mean CFB (SD)
Day 28	Placebo	25	183.9 (38.30)	-20.5 (27.20)
	Compound 1 (in the form of its tris salt) 10mg BID	9	189.9 (20.64)	-53.3 (21.80)
	Compound 1 (in the form of its tris salt) 15mg BID	8	225.4 (38.78)	-85.9 (31.62)
	Compound 1 (in the form of its tris salt) 50mg BID	8	190.2 (29.39)	-48.7 (36.29)
	Compound 1 (in the form of its tris salt) 70mg BID	9	218.5 (45.89)	-101.6 (44.26)
	Compound 1 (in the form of its tris salt) 120mg BID	9	219.0 (32.42)	-105.9 (33.64)
	Compound 1 (in the form of its tris salt) 120mg BID Slow Titration	9	179.9 (36.69)	-68.6 (34.23)
	Compound 1 (in the form of its tris salt) 120mg QD	8	188.8 (24.85)	-70.9 (23.65)

Study Day	Randomized Treatment	N	Baseline (SD)	Mean CFB (SD)
	Compound 1 (in the form of its tris salt) 200mg QD Controlled Release	7	225.2 (44.80)	-102.8 (42.56)

Observed data presented. Mean Daily Glucose (MDG) was defined as $AUC_{24}/24$.

Table 2-3. Summary of Baseline and Change from Baseline (CFB) for Fasting Plasma Glucose (mg/dL) by Randomized Treatment

Study Day	Randomized Treatment	N	Baseline (SD)	Mean CFB (SD)
Day 28	Placebo	25	167.6 (32.5)	-24.8 (33.4)
	Compound 1 (in the form of its tris salt) 10mg BID	9	158.3 (23.3)	-34.3 (37.7)
	Compound 1 (in the form of its tris salt) 15mg BID	8	198.4 (33.1)	-66.6 (27.2)
	Compound 1 (in the form of its tris salt) 50mg BID	8	168.1 (34.9)	-34.5 (47.0)
	Compound 1 (in the form of its tris salt) 70mg BID	9	186.3 (32.0)	-80.6 (37.2)
	Compound 1 (in the form of its tris salt) 120mg BID	9	196.9 (26.1)	-89.7 (30.0)
	Compound 1 (in the form of its tris salt) 120mg BID Slow Titration	9	176.3 (44.0)	-75.1 (43.2)
	Compound 1 (in the form of its tris salt) 120mg QD	8	179.9 (28.5)	-48.3 (42.8)
	Compound 1 (in the form of its tris salt) 200mg QD Controlled Release	7	195.3 (37.5)	-77.3 (44.7)

Table 2-4. Baseline and Change from Baseline (CFB) for HbA1c (%) by Randomized Treatment.

Study Day	Randomized Treatment	N	Baseline (SD)	Mean CFB (SD)
Day 28	Placebo	25	8.0 (0.8)	-0.4 (0.4)
	Compound 1 (in the form of its tris salt) 10mg BID	9	8.2 (0.6)	-0.8 (0.5)
	Compound 1 (in the form of its tris salt) 15mg BID	8	8.6 (0.6)	-0.9 (0.3)
	Compound 1 (in the form of its tris salt) 50mg BID	8	8.3 (0.9)	-1.2 (0.6)

Study Day	Randomized Treatment	N	Baseline (SD)	Mean CFB (SD)
	Compound 1 (in the form of its tris salt) 70mg BID	9	8.3 (0.6)	-1.2 (0.3)
	Compound 1 (in the form of its tris salt) 120mg BID	9	8.5 (1.0)	-1.2 (0.6)
	Compound 1 (in the form of its tris salt) 120mg BID Slow Titration	9	8.2 (0.7)	-1.2 (0.5)
	Compound 1 (in the form of its tris salt) 120mg QD	8	8.2 (1.0)	-1.0 (0.6)
	Compound 1 (in the form of its tris salt) 200mg QD Controlled Release	7	8.6 (0.9)	-1.1 (0.4)

Table 2-5. Summary of Baseline and Change from Baseline (CFB) for Body Weight (Kg) by Randomized Treatment

Study Day	Randomized Treatment	N	Baseline (SD)	Mean CFB (SD)
Day 28	Placebo	25	94.26 (17.74)	-1.9 (2.3)
	Compound 1 (in the form of its tris salt) 10mg BID	9	99.90 (12.44)	-2.8 (1.8)
	Compound 1 (in the form of its tris salt) 15mg BID	8	93.60 (22.47)	-2.4 (2.0)
	Compound 1 (in the form of its tris salt) 50mg BID	8	88.24 (13.91)	-2.4 (2.3)
	Compound 1 (in the form of its tris salt) 70mg BID	9	86.08 (18.64)	-4.0 (2.0)
	Compound 1 (in the form of its tris salt) 120mg BID	9	101.34 (17.51)	-7.9 (3.5)
	Compound 1 (in the form of its tris salt) 120mg BID Slow Titration	9	88.01 (19.89)	-5.5 (2.7)
	Compound 1 (in the form of its tris salt) 120mg QD	8	84.88 (15.50)	-4.3 (3.3)
	Compound 1 (in the form of its tris salt) 200mg QD Controlled Release	7	92.29 (18.01)	-3.1 (2.1)

As shown in Tables 2-2 to 2-4, Compound 1 (in the form of its tris salt) showed robust reductions in FPG, MDG, HbA1c, and body weight at Day 28, with increasing efficacy at higher doses of 70 mg to 120 mg twice daily.

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All patents, patent applications and references referred to herein are hereby incorporated by reference in their entirety.