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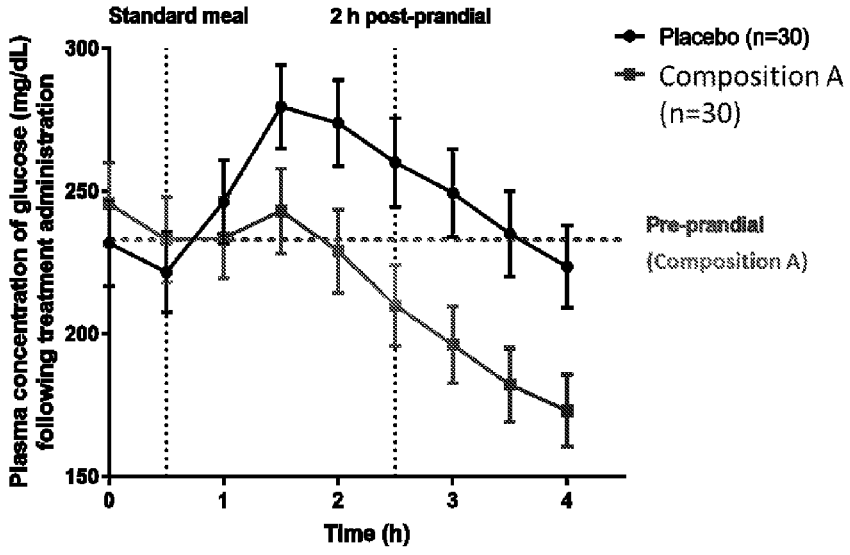


Fig. 6

(57) Abstract: Provided herein are pharmaceutical compositions that are useful for the treatment of diabetes and associated conditions, diseases, and disorders. The compositions comprise a) a dipeptidyl peptidase IV (DPPIV) inhibitor such as sitagliptin, b) a subtype 2 sodium-glucose transport (SGLT2) inhibitor such as either dapagliflozin or empagliflozin, and c) a biguanide such as metformin. The DPPIV inhibitor, SGLT2 inhibitor and biguanide are at a dose that is at about 20-75% of the lowest diabetes therapeutic dose.

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# LOW-DOSE TRIPLE COMBINATION FORMULATION

## CROSS-REFERENCE

**[0001]** This application claims the benefit of U.S. Patent Application No. 16/364,063 filed on March 25, 2019, which is incorporated by reference in its entirety.

## BACKGROUND

**[0002]** Diabetes mellitus (DM), commonly referred to as diabetes, is a group of metabolic disorders in which there are high blood sugar levels over a prolonged period. Symptoms of high blood sugar include frequent urination, increased thirst, and increased hunger. If left untreated, diabetes can cause many complications.

## SUMMARY OF THE DISCLOSURE

**[0003]** Provided herein, in certain embodiments, are pharmaceutical compositions comprising: a) a dipeptidyl peptidase IV (DPP IV) inhibitor; b) a biguanide; c) a subtype 2 sodium-glucose transport protein (SGLT2) inhibitor; and d) at least one pharmaceutically-acceptable excipient wherein (a), (b), and (c) are each at about 20% to about 75% of the lowest diabetes therapeutic dose (LDTD). Provided herein, in certain embodiments, are pharmaceutical compositions consisting essentially of: a) a DPP IV inhibitor; b) a biguanide; c) a SGLT2 inhibitor; and d) at least one pharmaceutically-acceptable excipient wherein (a), (b), and (c) are each at about 20% to about 75% of the lowest diabetes therapeutic dose (LDTD). Provided herein, in certain embodiments, are pharmaceutical compositions, comprising: a) a dipeptidyl peptidase IV (DPP IV) inhibitor; b) a biguanide; and c) a subtype 2 sodium-glucose transport protein (SGLT2) inhibitor; wherein (a) and (b) are each at about 65%-75% of the lowest diabetes therapeutic dose (LDTD), and (c) is at about 45%-55% of the lowest diabetes therapeutic dose (LDTD). Provided herein, in certain embodiments, are pharmaceutical compositions consisting essentially of: a) a DPP IV inhibitor; b) a biguanide; c) a SGLT2 inhibitor; and d) at least one pharmaceutically-acceptable excipient wherein (a) and (b) are each at about 65%-75% of the lowest diabetes therapeutic dose (LDTD), and (c) is at about 45%-55% of the lowest diabetes therapeutic dose (LDTD). In some embodiments, the DPP IV inhibitor is a gliptin. In some embodiments, the DPP IV inhibitor is selected from sitagliptin, vildagliptin, saxagliptin, linagliptin, gemigliptin, anagliptin, teneligliptin, alogliptin, trelagliptin, omarigliptin, evogliptin, gosogliptin, dutogliptin, or the pharmaceutically acceptable salt or hydrate thereof. In some embodiments, the DPP IV inhibitor is sitagliptin or the pharmaceutically acceptable salt thereof. In some embodiments, the DPP IV inhibitor is sitagliptin phosphate. In some embodiments, the biguanide is metformin or the pharmaceutically acceptable salt or hydrate thereof. In some

embodiments, the biguanide is metformin hydrochloride. In some embodiments, the metformin is formulated for immediate release. In some embodiments, the metformin is formulated for slow release. In some embodiments, the SGLT2 inhibitor is a gliflozin. In some embodiments, the SGLT2 inhibitor is inhibitor is dapagliflozin, empagliflozin, canagliflozin, ipragliflozin (ASP-1941), tofogliflozin, remogliflozin, sergliflozin, ertugliflozin, sotagliflozin, or the pharmaceutically acceptable salt, hydrate, or combinations thereof. In some embodiments, the SGLT2 inhibitor is dapagliflozin or pharmaceutically acceptable salt, hydrate, or a combination thereof. In some embodiments, the SGLT2 inhibitor is empagliflozin or pharmaceutically acceptable salt, hydrate, or a combination thereof. In some embodiments, the SGLT2 inhibitor is a dapagliflozin hydrate. In some embodiments, the SGLT2 inhibitor is dapagliflozin propanediol monohydrate. In some embodiments, the SGLT2 inhibitor is dapagliflozin compounded with (2S)-1,2-propanediol, hydrate in a ratio of about 1:1:1. In some embodiments, the dose of each (a), (b), and (c) is from about 40% to about 75% of the lowest diabetes therapeutic dose (LDTD). In some embodiments, the dose of each (a), (b), and (c) is from about 60% to about 75% of the lowest diabetes therapeutic dose (LDTD). In some embodiments, the dose of each (a), (b), and (c) is from about 65% to about 75% of the lowest diabetes therapeutic dose (LDTD). In some embodiments, the dose of each (a), (b), and (c) is about 70% of the lowest diabetes therapeutic dose (LDTD). In some embodiments, the dose of each (a), (b), and (c) is from about 40% to about 70% of the lowest diabetes therapeutic dose (LDTD). In some embodiments, the dose of each (a), (b), and (c) is from about 40% to about 60% of the lowest diabetes therapeutic dose (LDTD). In some embodiments, the dose of each (a), (b), and (c) is from about 45% to about 55% of the lowest diabetes therapeutic dose (LDTD). In some embodiments, the dose of each (a), (b), and (c) is about 50% of the lowest diabetes therapeutic dose (LDTD). In some embodiments, the DPP IV inhibitor is about 70% of the lowest diabetes therapeutic dose (LDTD) for the DPP IV inhibitor. In some embodiments, the DPP IV inhibitor is sitagliptin, and the dose of sitagliptin is about 17.5 mg. In some embodiments, the DPP IV inhibitor is about 50% of the lowest diabetes therapeutic dose (LDTD) for the DPP IV inhibitor. In some embodiments, the DPP IV inhibitor is sitagliptin, and the dose of sitagliptin is about 12.5 mg. In some embodiments, the biguanide is about 70% of the lowest diabetes therapeutic dose (LDTD) for the biguanide. In some embodiments, the biguanide is metformin hydrochloride, and the dose of metformin hydrochloride is about 350 mg. In some embodiments, the biguanide is about 50% of the lowest diabetes therapeutic dose (LDTD) for the biguanide. In some embodiments, the biguanide is metformin hydrochloride, and the dose of metformin hydrochloride is about 250 mg. In some embodiments, the SGLT2 inhibitor is about 50% of the lowest diabetes therapeutic dose (LDTD) for the SGLT2 inhibitor. In some

embodiments, the SGLT2 inhibitor is dapagliflozin, and the dose of dapagliflozin is about 2.5 mg. In some embodiments, the DPP IV inhibitor is sitagliptin, the biguanide is metformin, and the SGLT2 inhibitor is dapagliflozin. In some embodiments, the dose of sitagliptin is from about 5.0 mg to about 18.75 mg, the dose of metformin is from about 100 mg to about 375 mg, and the dose of dapagliflozin is from about 1.0 mg to about 3.75 mg. In some embodiments, the dose of sitagliptin is from about 10 mg to about 16.25 mg, the dose of metformin is from about 200 mg to about 325 mg, and the dose of dapagliflozin is from about 2.0 mg to about 3.25 mg. In some embodiments, the dose of sitagliptin is from about 10 mg to about 15 mg, the dose of metformin is from about 200 mg to about 300 mg, and the dose of dapagliflozin is from about 2 mg to about 3 mg. In some embodiments, the dose of sitagliptin is from about 11.25 mg to about 13.75 mg, the dose of metformin is from about 225 mg to about 275 mg, and the dose of dapagliflozin is from about 2.25 mg to about 2.75 mg. In some embodiments, the dose of sitagliptin is about 12.5 mg, the dose of metformin is about 250 mg, and the dose of dapagliflozin is about 2.5 mg. In some embodiments, the dose of each (a), (b), and (c) is from about 30% to about 40% of the lowest diabetes therapeutic dose (LDTD). In some embodiments, the dose of each (a), (b), and (c) is from about 30% to about 35% of the lowest diabetes therapeutic dose (LDTD). In some embodiments, the SGLT2 inhibitor is about 33% of the lowest diabetes therapeutic dose (LDTD) for the SGLT2 inhibitor. In some embodiments, the SGLT2 inhibitor is dapagliflozin, and the dose of dapagliflozin is about 1.65 mg. In some embodiments, the SGLT2 inhibitor is empagliflozin, and the dose of empagliflozin is about 3.3 mg. In some embodiments, the DPP IV inhibitor is sitagliptin, the biguanide is metformin, and the SGLT2 inhibitor is dapagliflozin or empagliflozin. In some embodiments, the dose of sitagliptin is from about 7.5 mg to about 10 mg and the dose of metformin is from about 150 mg to about 200 mg. In some embodiments, the SGLT2 inhibitor is dapagliflozin and the dose of dapagliflozin is from about 1.5 mg to about 2.0 mg. In some embodiments, the SGLT2 inhibitor is empagliflozin and the dose of empagliflozin is from about 3.0 mg to about 4.0 mg. In some embodiments, the dose of sitagliptin is about 8.25 mg and the dose of metformin is about 165 mg. In some embodiments, the SGLT2 inhibitor is dapagliflozin and the dose of dapagliflozin is about 1.65 mg. In some embodiments, the SGLT2 inhibitor is empagliflozin, and the dose of empagliflozin is about 3.3 mg. In some embodiments, the dose of each (a), (b), and (c) is from about 20% to about 30% of the lowest diabetes therapeutic dose (LDTD). In some embodiments, the dose of each (a), (b), and (c) is from about 22% to about 28% of the lowest diabetes therapeutic dose (LDTD). In some embodiments, the dose of the SGLT2 inhibitor is about 25% of the lowest diabetes therapeutic dose (LDTD) for the SGLT2 inhibitor. In some embodiments, the SGLT2 inhibitor is dapagliflozin, and the dose of dapagliflozin is about 1.25 mg. In some

embodiments, the SGLT2 inhibitor is empagliflozin, and the dose of empagliflozin is about 2.5 mg. In some embodiments, the DPP IV inhibitor is sitagliptin, the biguanide is metformin, and the SGLT2 inhibitor is dapagliflozin or empagliflozin. In some embodiments, the dose of sitagliptin is from about 5mg to about 7.5 mg and the dose of metformin is from about 100 mg to about 150 mg. In some embodiments, the SGLT2 inhibitor is dapagliflozin, and the dose of dapagliflozin is about 1.0 mg. In some embodiments, the SGLT2 inhibitor is empagliflozin, and the dose of empagliflozin is about 2.0 mg. In some embodiments, the dose of sitagliptin is about 6.25 mg and the dose of metformin is about 150 mg. In some embodiments, the SGLT2 inhibitor is dapagliflozin, and the dose of dapagliflozin is about 1.5 mg. In some embodiments, the SGLT2 inhibitor is empagliflozin, and the dose of empagliflozin is about 3.0 mg. In some embodiments, the DPP IV inhibitor is sitagliptin and the dose of sitagliptin is from about 16.25 mg to about 18.75 mg. In some embodiments, the biguanide is metformin and the dose of metformin is from about 325 mg to about 375 mg. In some embodiments, the SGLT2 inhibitor is dapagliflozin, and the dose of dapagliflozin from about 2.25 mg to about 2.75 mg. In some embodiments, the SGLT2 inhibitor is empagliflozin, and the dose of empagliflozin from about 4.5 mg to about 7.5 mg. In some embodiments, the DPP IV inhibitor is at about 70% of the lowest diabetes therapeutic dose (LDTD) for the DPP IV inhibitor. In some embodiments, the biguanide is at about 70% of the lowest diabetes therapeutic dose (LDTD) for the biguanide. In some embodiments, the SGLT2 inhibitor is at about 50% of the lowest diabetes therapeutic dose (LDTD) for the SGLT2 inhibitor. In some embodiments, the DPP IV inhibitor is sitagliptin, the biguanide is metformin, and the SGLT2 inhibitor is dapagliflozin or empagliflozin. In some embodiments, the dose of sitagliptin is about 17.5 mg, the dose of metformin is about 350 mg, and the dose of dapagliflozin is about 2.5 mg. In some embodiments, the dose of sitagliptin is about 17.5 mg, the dose of metformin is about 350 mg, and the dose of empagliflozin is about 5.0 mg. In some embodiments, the DPP IV inhibitor is sitagliptin and the dose of the sitagliptin is about 17.5 mg. In some embodiments, the biguanide is metformin and the dose of the metformin is about 350 mg. In some embodiments, the SGLT2 inhibitor is dapagliflozin and the dose of the dapagliflozin is about 2.5 mg. In some embodiments, the SGLT2 inhibitor is empagliflozin and the dose of the empagliflozin is about 5.0 mg. In some embodiments, a), (b), and (c) are provided in one formulation. In some embodiments, (a), (b), and (c) are each provided in a separate formulation. In some embodiments, two of the (a), (b), and (c) are provided in one formulation. In some embodiments, the pharmaceutical composition is in the form of pill, tablet or capsule. In some embodiments, the pharmaceutical composition is suitable for oral administration.

**[0004]** Provided herein, in certain embodiments, are methods of treating diabetes in a subject in need thereof, comprising administering any one of the pharmaceutical compositions disclosed herein. In some embodiments, the treatment results in an improvement, slowing the progression of, or delaying a metabolic disorder such as diabetes mellitus, impaired glucose tolerance, impaired fasting blood glucose, hyperglycemia, postprandial hyperglycemia, overweight, obesity, metabolic syndrome, impaired renal function, gestational diabetes, new onset diabetes after transplantation (NODAT) and complications associated therewith, and post-transplant metabolic syndrome (PTMS) and complications associated therewith. In some embodiments, the treatment results in an improvement, slowing the progression of, or delaying a metabolic disorder that is greater than that obtained with the full lowest diabetes therapeutic dose (LDTD) dose of any one of (a), (b), and (c) in the pharmaceutical composition. In some embodiments, the treatment results in greater long term tolerability and reduced risk of side effects when compared to treatment with the lowest diabetes therapeutic dose (LDTD) of any one of (a), (b), and (c) in the pharmaceutical composition. In some embodiments, the treatment is the initial or first-line treatment of diabetes. In some embodiments, the subject is not receiving any diabetes therapy prior to treatment. In some embodiments, the subject is receiving diabetes therapy prior to treatment and treatment with the formulations disclosed herein is second-line or maintenance treatment.

**[0005]** Provided herein, in certain embodiments, are pharmaceutical compositions comprising: a) a low-dose, therapeutically-effective amount of a dipeptidyl peptidase IV (DPP IV) inhibitor; b) a low-dose, therapeutically-effective amount of a biguanide; c) a low-dose, therapeutically-effective amount of a subtype 2 sodium-glucose transport protein (SGLT2) inhibitor; and d) at least one pharmaceutically-acceptable excipient, wherein (a), (b), and (c) are each at about 20-75% of the lowest diabetes therapeutic dose (LDTD). In some embodiments, the DPP IV inhibitor is sitagliptin, the biguanide is metformin, and the SGLT2 inhibitor is dapagliflozin or empagliflozin. In some embodiments, the dose of sitagliptin is from about 5.0 mg to about 18.75 mg, the dose of metformin is from about 100 mg to about 375 mg, and the dose of dapagliflozin is from about 1.0 mg to about 2.75 mg. In some embodiments, the dose of sitagliptin is from about 5.0 mg to about 18.75 mg, the dose of metformin is from about 100 mg to about 375 mg, and the dose of empagliflozin is from about 2.0 mg to about 7.5 mg. In some embodiments, (a) and (b) are each at about 65%-75% of the lowest diabetes therapeutic dose (LDTD) and (c) is at about 45%-55% of the lowest diabetes therapeutic dose (LDTD). In some embodiments, the DPP IV inhibitor is sitagliptin and the dose of sitagliptin is from about 16.25 mg to about 18.75 mg. In some embodiments, the biguanide is metformin and the dose of metformin is from about 325 mg to about 375 mg. In some embodiments, the SGLT2 inhibitor

is dapagliflozin, and the dose of dapagliflozin from about 2.25 mg to about 2.75 mg. In some embodiments, the SGLT2 inhibitor is empagliflozin, and the dose of empagliflozin from about 4.5 mg to about 7.5 mg. In some embodiments, the DPP IV inhibitor is at about 70% of the lowest diabetes therapeutic dose (LDTD) for the DPP IV inhibitor. In some embodiments, the biguanide is at about 70% of the lowest diabetes therapeutic dose (LDTD) for the biguanide. In some embodiments, the SGLT2 inhibitor is at about 50% of the lowest diabetes therapeutic dose (LDTD) for the SGLT2 inhibitor. In some embodiments, the DPP IV inhibitor is sitagliptin, the biguanide is metformin, and the SGLT2 inhibitor is dapagliflozin or empagliflozin. In some embodiments, the dose of sitagliptin is about 17.5 mg, the dose of metformin is about 350 mg, and the dose of dapagliflozin is about 2.5 mg. In some embodiments, the dose of sitagliptin is about 17.5 mg, the dose of metformin is about 350 mg, and the dose of empagliflozin is about 5.0 mg. In some embodiments, the DPP IV inhibitor is sitagliptin and the dose of the sitagliptin is about 17.5 mg. In some embodiments, the biguanide is metformin and the dose of the metformin is about 350 mg. In some embodiments, the SGLT2 inhibitor is empagliflozin and the dose of the empagliflozin is about 5.0 mg. In some embodiments, the pharmaceutical composition is suitable for oral administration. In some embodiments, the pharmaceutical composition is in the form of pill, tablet, or capsule. In some embodiments, the metformin is formulated for immediate release. In some embodiments, the metformin is formulated for slow release. In some embodiments, the pharmaceutical composition does not comprise any further additional anti-hyperglycemic or anti-diabetic agents. In some embodiments, the combination of a), b), and c) produces a synergistic effect. In some embodiments, the pharmaceutical composition produces a larger decrease in 2 hour post-prandial glucose as compared to a maximum decrease in the post-prandial glucose obtained from about 100 mg of sitagliptin. In some embodiments, the pharmaceutical composition produces a larger decrease in 2 hour post-prandial glucose as compared to a maximum decrease in the post-prandial glucose obtained from about 850 mg of metformin. In some embodiments, the pharmaceutical composition produces a larger decrease in 2 hour post-prandial glucose as compared to a maximum decrease in the post-prandial glucose obtained from about 1700 mg of metformin.

**[0006]** Provided herein, in certain embodiments, are pharmaceutical compositions, comprising: a) a low-dose, therapeutically-effective amount of a dipeptidyl peptidase IV (DPP IV) inhibitor; b) a low-dose, therapeutically-effective amount of a biguanide; c) a low-dose, therapeutically-effective amount of a subtype 2 sodium-glucose transport protein (SGLT2) inhibitor; and d) at least one pharmaceutically-acceptable excipient, wherein (a) and (b) are each at about 65%-75% of a lowest diabetes therapeutic dose (LDTD), and (c) is at about 45%-55% of the lowest diabetes therapeutic dose (LDTD). In some embodiments, the DPP IV inhibitor is sitagliptin

and a dose of sitagliptin is from about 16.25 mg to about 18.75 mg. In some embodiments, the biguanide is metformin and a dose of metformin is from about 325 mg to about 375 mg. In some embodiments, the SGLT2 inhibitor is dapagliflozin, and the dose of dapagliflozin from about 2.25 mg to about 2.75 mg. In some embodiments, the SGLT2 inhibitor is empagliflozin, and the dose of empagliflozin from about 4.5 mg to about 7.5 mg. In some embodiments, the DPP IV inhibitor is at about 70% of the lowest diabetes therapeutic dose (LDTD) for the DPP IV inhibitor. In some embodiments, the biguanide is at about 70% of the lowest diabetes therapeutic dose (LDTD) for the biguanide. In some embodiments, the SGLT2 inhibitor is at about 50% of the lowest diabetes therapeutic dose (LDTD) for the SGLT2 inhibitor. In some embodiments, the DPP IV inhibitor is sitagliptin, the biguanide is metformin, and the SGLT2 inhibitor is dapagliflozin. In some embodiments, the DPP IV inhibitor is sitagliptin, the biguanide is metformin, and the SGLT2 inhibitor is empagliflozin. In some embodiments, the dose of sitagliptin is about 17.5 mg, the dose of metformin is about 350 mg, and the dose of dapagliflozin is about 2.5 mg. In some embodiments, the DPP IV inhibitor is sitagliptin and the dose of the sitagliptin is about 17.5 mg. In some embodiments, the biguanide is metformin and the dose of the metformin is about 350 mg. In some embodiments, the SGLT2 inhibitor is dapagliflozin, and the dose of dapagliflozin is about 2.5 mg. In some embodiments, the SGLT2 inhibitor is empagliflozin, and the dose of empagliflozin is about 5.0 mg. In some embodiments, the pharmaceutical composition is suitable for oral administration. In some embodiments, the pharmaceutical composition is in the form of pill, tablet or capsule. In some embodiments, the metformin is formulated for immediate release. In some embodiments, the metformin is formulated for slow release. In some embodiments, the pharmaceutical composition does not comprise any further additional anti-hyperglycemic or anti-diabetic agents. In some embodiments, the combination of a), b), and c) produces a synergistic effect. In some embodiments, the pharmaceutical composition produces a larger decrease in 2 hour post-prandial glucose as compared to a maximum decrease in the post-prandial glucose obtained from about 100 mg of sitagliptin. In some embodiments, the pharmaceutical composition produces a larger decrease in 2 hour post-prandial glucose as compared to a maximum decrease in the post-prandial glucose obtained from about 850 mg of metformin. In some embodiments, the pharmaceutical composition produces a larger decrease in 2 hour post-prandial glucose as compared to a maximum decrease in the post-prandial glucose obtained from about 1700 mg of metformin.

**[0007]** Provided herein, in certain embodiments, are pharmaceutical compositions comprising a combination of: a) about 17.5 mg of sitagliptin; b) about 350 mg of metformin; c) about 2.5 mg of dapagliflozin; and d) at least one pharmaceutically-acceptable excipient. In some

embodiments, the combination is synergistic. In some embodiments, the pharmaceutical composition is in the form of pill, tablet, or capsule. In some embodiments, the pharmaceutical composition is suitable for oral administration. In some embodiments, the metformin is formulated for immediate release. In some embodiments, the metformin is formulated for slow release. In some embodiments, the pharmaceutical composition does not comprise any further additional anti-hyperglycemic or anti-diabetic agents. In some embodiments, the combination of a), b), and c) produces a synergistic effect. In some embodiments, the pharmaceutical composition produces a larger decrease in 2 hour post-prandial glucose as compared to a maximum decrease in the post-prandial glucose obtained from about 100 mg of sitagliptin, from about 850 mg of metformin, or from about 1700 mg of metformin.

**[0008]** Provided herein, in certain embodiments, are pharmaceutical compositions, comprising a combination of: a) about 17.5 mg of sitagliptin; b) about 350 mg of metformin; c) about 5.0 mg of empagliflozin; and d) at least one pharmaceutically-acceptable excipient. In some embodiments, the combination is synergistic. In some embodiments, the pharmaceutical composition is in the form of pill, tablet, or capsule. In some embodiments, the pharmaceutical composition is suitable for oral administration. In some embodiments, the metformin is formulated for immediate release. In some embodiments, the metformin is formulated for slow release. In some embodiments, the pharmaceutical composition does not comprise any further additional anti-hyperglycemic or anti-diabetic agents. In some embodiments, the combination of a), b), and c) produces a synergistic effect. In some embodiments, the pharmaceutical composition produces a larger decrease in 2 hour post-prandial glucose as compared to a maximum decrease in the post-prandial glucose obtained from about 100 mg of sitagliptin, from about 850 mg of metformin, or from about 1700 mg of metformin.

**[0009]** Provided herein, in certain embodiments, are synergistic, ultra-low dose, anti-diabetic drug combinations, consisting of: a) about 16.25 mg to about 18.75 mg of sitagliptin, or a salt or hydrate thereof; b) about 325 mg to about 375 mg of metformin, or a salt or hydrate thereof; c) about 2.25 mg to about 2.75 mg of dapagliflozin, or a salt or hydrate thereof; and d) at least one excipient. In some embodiments, the combination of a), b), and c) produces a synergistic effect. In some embodiments, the combination does not comprise any further additional anti-hyperglycemic or anti-diabetic agents. In some embodiments, the combination produces a larger decrease in 2 hour post-prandial glucose as compared to a maximum decrease in the post-prandial glucose obtained from 100 mg of sitagliptin, from 850 mg of metformin, or from 1700 mg of metformin.

**[0010]** Provided herein, in certain embodiments, are synergistic, ultra-low dose, anti-diabetic drug combinations, consisting of: a) about 16.25 mg to about 18.75 mg of sitagliptin, or a salt or

hydrate thereof; b) about 325 mg to about 375 mg of metformin, or a salt or hydrate thereof; c) about 4.5 mg to about 7.5 mg of empagliflozin, or a salt or hydrate thereof; and d) at least one excipient. In some embodiments, the combination of a), b), and c) produces a synergistic effect. In some embodiments, the combination does not comprise any further additional anti-hyperglycemic or anti-diabetic agents. In some embodiments, the combination produces a larger decrease in 2 hour post-prandial glucose as compared to a maximum decrease in the post-prandial glucose obtained from about 100 mg of sitagliptin, from about 850 mg of metformin, or from about 1700 mg of metformin.

**[0011]** Provided herein, in certain embodiments, are methods of treating diabetes in a subject in need thereof comprising administering the pharmaceutical composition as described herein. In some embodiments, the subject has persisting elevation of blood sugar after treatment with one or two of a DPP IV inhibitor, a biguanide, or an SGLT2 inhibitor at the LDTD or higher dose. In some embodiments, the administration of the pharmaceutical composition is an initial or first-line treatment of diabetes.

**[0012]** Provided herein, in certain embodiments, are methods of improving, slowing the progression of, or delaying a metabolic disorder, wherein the metabolic disorder comprises diabetes mellitus, impaired glucose tolerance, impaired fasting blood glucose, hyperglycemia, postprandial hyperglycemia, overweight, obesity, metabolic syndrome, impaired renal function, gestational diabetes, new onset diabetes after transplantation (NODAT) and complications associated therewith, or post-transplant metabolic syndrome (PTMS) and complications associated therewith, comprising administering to a subject in need thereof the pharmaceutical composition as described herein.

**[0013]** Provided herein, in certain embodiments, are methods of treating diabetes in a subject in need thereof, comprising administering a synergistic, ultra-low dose, anti-diabetic drug combination, consisting of: a) about 16.25 mg to about 18.75 mg of sitagliptin, or a salt or hydrate thereof; b) about 325 mg to about 375 mg of metformin, or a salt or hydrate thereof; c) about 2.25 mg to about 2.75 mg of dapagliflozin, or a salt or hydrate thereof; and d) at least one excipient. In some embodiments, the combination of a), b), and c) produces a synergistic effect. In some embodiments, the combination does not comprise any further additional anti-hyperglycemic or anti-diabetic agents. In some embodiments, the combination produces a larger decrease in 2 hour post-prandial glucose as compared to a maximum decrease in the post-prandial glucose obtained from about 100 mg of sitagliptin, from about 850 mg of metformin, or from about 1700 mg of metformin.

**[0014]** Provided herein, in certain embodiments, are methods of treating diabetes in a subject in need thereof, comprising administering a synergistic, ultra-low dose, anti-diabetic drug

combination, consisting of: a) about 16.25 mg to about 18.75 mg of sitagliptin, or a salt or hydrate thereof; b) about 325 mg to about 375 mg of metformin, or a salt or hydrate thereof; c) about 4.5 mg to about 7.5 mg of empagliflozin, or a salt or hydrate thereof; and d) at least one excipient. In some embodiments, the combination of a), b), and c) produces a synergistic effect. In some embodiments, the combination does not comprise any further additional anti-hyperglycemic or anti-diabetic agents. In some embodiments, the combination produces a larger decrease in 2 hour post-prandial glucose as compared to a maximum decrease in the post-prandial glucose obtained from about 100 mg of sitagliptin, from about 850 mg of metformin, or from about 1700 mg of metformin.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0015] Figure 1** shows non-fasting Whole blood glucose (mg/dL) post-dosing by treatment group.

**[0016] Figure 2** shows Hemoglobin A1c (%) post-dosing by treatment group. Error bars represent standard error of the mean (SEM).

**[0017] Figure 3** shows serum Creatinine (mg/dL) post-dosing by treatment group. Error bars represent standard error of the mean (SEM).

**[0018] Figure 4** shows plasma insulin (pg/mL) post-dosing by treatment group.

**[0019] Figure 5** shows the study design of the Composition A Phase I clinical trial.

**[0020] Figure 6** exemplifies a time course of the plasma concentration of glucose (mean and standard error) before and after the administration of a single dose of placebo and Composition A patients with type 2 diabetes (n=30) in a crossover study.

**[0021] Figure 7** exemplifies a time course of serum concentration of insulin (mean and standard error) before and after the administration of a single dose of placebo and Composition A in patients with type 2 diabetes (n=30) in a crossover study.

**[0022] Figure 8** exemplifies a graph of effect of single dose of sitagliptin 100 mg on plasma glucose (PG).

## DETAILED DESCRIPTION OF THE DISCLOSURE

**[0023]** Disclosed herein, in certain embodiments, are pharmaceutical compositions for the treatment of diabetes, comprising a low dose, therapeutically-effective amount of a DPP IV inhibitor (e.g., sitagliptin), a low dose, therapeutically-effective amount of a biguanide (e.g., metformin), and a low dose, therapeutically-effective amount of an SGLT2 inhibitor (e.g., dapagliflozin). In some embodiments, the dose of each component is below the lowest dose approved for the treatment of diabetes. In some embodiments, the low dose produces no or essentially no therapeutic effect as a monotherapy.

**[0024]** The present disclosure recognizes the technical effects of low-dose combination therapy set forth herein. Surprisingly, the combination of a low dose amount of a DPP IV inhibitor (e.g., sitagliptin), a low dose amount of a biguanide (e.g., metformin), and a low dose amount of an SGLT2 inhibitor (e.g., dapagliflozin) produces a therapeutic effect that is greater than the effect of any of the individual components administered as a monotherapy at the equivalent dosages. In some instances, the individual components produce no or essentially no therapeutic effect at equivalent dosages when administered as monotherapies.

**[0025]** The use of low dose amounts of each of the components results in beneficial effects, including but not limited to, avoiding or ameliorating negative side effects while retaining or improving benefits. Known side-effects of DPP IV inhibitors (e.g., sitagliptin), biguanides (e.g., metformin), and SGLT2 inhibitors (e.g., dapagliflozin) include upset stomach, nausea, and low blood sugar. Long-term side effects also include decreased absorption of vitamin B12 and lactic acidosis. Reducing these side-effects further allows for the early introduction of combination therapy to improve therapeutic effects. Described herein in one aspect are low-dose combination compositions for the treatment of diabetes, including the initial or first-line treatment of diabetes.

*Certain Terminology*

**[0026]** As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated below.

**[0027]** As used herein and in the appended claims, the singular forms “a,” “and,” and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “an agent” includes a plurality of such agents, and reference to “the composition” includes reference to one or more compositions (or to a plurality of compositions) and equivalents thereof known to those skilled in the art, and so forth. When ranges are used herein for physical properties, such as molecular weight, or chemical properties, such as chemical formulae, all combinations and sub-combinations of ranges and specific embodiments therein are intended to be included. The term “about” when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus in some embodiments, the number or numerical range varies between 1% and 10% of the stated number or numerical range. The term “comprising” (and related terms such as “comprise” or “comprises” or “having” or “including”) is not intended to exclude that in other certain embodiments, for example, an embodiment of any composition of matter, composition, method, or process, or the like, described herein, may “consist of” or “consist essentially of” the described features.

**[0028]** "Pharmaceutically acceptable salt" as used herein includes both acid and base addition salts. In some embodiments, the pharmaceutically acceptable salt of any one of the compounds described herein is the form approved for use by the US Food and Drug Administration. Preferred pharmaceutically acceptable salts of the compounds described herein are pharmaceutically acceptable acid addition salts and pharmaceutically acceptable base addition salts.

**[0029]** "Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, hydroiodic acid, hydrofluoric acid, phosphorous acid, and the like. Also included are salts that are formed with organic acids such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. and include, for example, acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Exemplary salts thus include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, nitrates, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, trifluoroacetates, propionates, caprylates, isobutyrates, oxalates, malonates, succinate suberates, sebacates, fumarates, maleates, mandelates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, phthalates, benzenesulfonates, toluenesulfonates, phenylacetates, citrates, lactates, malates, tartrates, methanesulfonates, and the like. Also contemplated are salts of amino acids, such as arginates, gluconates, and galacturonates (see, for example, Berge S.M. et al., "Pharmaceutical Salts," *Journal of Pharmaceutical Science,* 66:1-19 (1997), which is hereby incorporated by reference in its entirety). Acid addition salts of basic compounds may be prepared by contacting the free base forms with a sufficient amount of the desired acid to produce the salt according to methods and techniques with which a skilled artisan is familiar.

**[0030]** "Pharmaceutically acceptable base addition salt" refers to those salts that retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Pharmaceutically acceptable base addition salts may be formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Salts derived from inorganic bases include, but are not limited to, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, for example,

isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, diethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, *N,N*-dibenzylethylenediamine, chloroprocaine, hydrabamine, choline, betaine, ethylenediamine, ethylenedianiline, *N*-methylglucamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, *N*-ethylpiperidine, polyamine resins and the like. See Berge et al., *supra*.

**[0031]** As used herein, "hydrates" are compounds that contain either stoichiometric or non-stoichiometric amounts of water, and, in some embodiments, are formed during the process of crystallization with water. Hydrates are meant to include the hydrates of any one of the compounds described herein that is approved for use by the US Food and Drug Administration.

**[0032]** The term "acceptable" with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated.

**[0033]** The terms "administer," "administering," "administration," and the like, as used herein, refer to the methods that may be used to enable delivery of compounds or compositions to the desired site of biological action. These methods include, but are not limited to, oral routes, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intraperitoneal, intramuscular, intravascular or infusion), topical, and rectal administration. Those of skill in the art are familiar with administration techniques that can be employed with the compounds and methods described herein. In some embodiments, the compounds and compositions described herein are administered orally.

**[0034]** The term "subject," "patient" or "individual" encompasses mammals. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species. In one aspect, the mammal is a human. None of "subject," "patient," or "individual" should be construed as requiring or not requiring the intervention of a medical professional.

**[0035]** As used herein, "treatment" or "treating" or "palliating" or "ameliorating" are used interchangeably herein. These terms refer to an approach for obtaining beneficial or desired results including but not limited to anti-diabetic effect, therapeutic benefit and/or a prophylactic benefit. By "therapeutic benefit" or "anti-diabetic effect" is meant eradication or amelioration of the underlying disorder being treated. A therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder (e.g., an improvement in: hyperglycemia, polyuria, polydipsia, polyphagia, diabetic dermadromes, etc.) such that an improvement is observed in the patient, notwithstanding that the patient may still be afflicted with the underlying disorder. Also, a therapeutic benefit is achieved

with the eradication or amelioration of one or more of the complications associated with the underlying disorder (e.g., cardiovascular disease). For prophylactic benefit, the compositions may be administered to a patient at risk of developing a particular disease, or to a patient reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease may not have been made.

**[0036]** The terms "diabetes" and "diabetes mellitus" are used interchangeably herein. These terms refers to type 1 diabetes mellitus, type 2 diabetes mellitus, complications of diabetes mellitus, and of neighboring disease states. As used herein, diabetes or diabetes mellitus (DM) refers to a group of metabolic disorders in which there are high blood sugar levels over a prolonged period.

**[0037]** *Triple Compositions*

**[0038]** Described herein are pharmaceutical compositions comprising: (a) a dipeptidyl peptidase IV (DPP IV) inhibitor; (b) a biguanide; and (c) a subtype 2 sodium-glucose transport protein (SGLT2) inhibitor;

wherein (a), (b), and (c) are each at about 20% to about 75% of the lowest diabetes therapeutic dose (LDTD).

**[0039]** Described herein are pharmaceutical compositions consisting essentially of: a) a dipeptidyl peptidase IV (DPP IV) inhibitor; b) a biguanide; and c) a subtype 2 sodium-glucose transport protein (SGLT2) inhibitor;

wherein (a), (b), and (c) are each at about 20% to about 75% of the lowest diabetes therapeutic dose (LDTD).

**[0040]** Described herein are pharmaceutical compositions comprising: a) a dipeptidyl peptidase IV (DPP IV) inhibitor; b) a biguanide; and c) a subtype 2 sodium-glucose transport protein (SGLT2) inhibitor;

wherein (a) and (b) are each at about 65%-75% of the lowest diabetes therapeutic dose (LDTD), and (c) is at about 45%-55% of the lowest diabetes therapeutic dose (LDTD).

**[0041]** Described herein are pharmaceutical compositions consisting essentially of: a) a DPP IV inhibitor; b) a biguanide; and c) a SGLT2 inhibitor;

wherein (a) and (b) are each at about 65%-75% of the lowest diabetes therapeutic dose (LDTD), and (c) is at about 45%-55% of the lowest diabetes therapeutic dose (LDTD).

**[0042]** In some embodiments, the DPP IV inhibitor is a gliptin. In some embodiments, the DPP IV inhibitor is selected from sitagliptin, vildagliptin, saxagliptin, linagliptin, gemigliptin, anagliptin, teneligliptin, alogliptin, trelagliptin, omarigliptin, evogliptin, gosogliptin, dutogliptin, or the pharmaceutically acceptable salt or hydrate thereof.

**[0043]** In some embodiments, the DPP IV inhibitor is sitagliptin or the pharmaceutically acceptable salt thereof. In some embodiments, the DPP IV inhibitor is sitagliptin phosphate.

**[0044]** In some embodiments, the biguanide is metformin or the pharmaceutically acceptable salt or hydrate thereof. In some embodiments, the biguanide is metformin hydrochloride.

**[0045]** In some embodiments, the metformin is formulated for immediate release. In some embodiments, the metformin is formulated for slow release.

**[0046]** In some embodiments, the SGLT2 inhibitor is a gliflozin. In some embodiments, the SGLT2 inhibitor is inhibitor is dapagliflozin, empagliflozin, canagliflozin, ipragliflozin (ASP-1941), tofogliflozin, remogliflozin, sergliflozin, ertugliflozin, sotagliflozin, or the pharmaceutically acceptable salt, hydrate, or combinations thereof. In some embodiments, the SGLT2 inhibitor is dapagliflozin or pharmaceutically acceptable salt, hydrate, or a combination thereof. In some embodiments, the SGLT2 inhibitor is empagliflozin or pharmaceutically acceptable salt, hydrate, or a combination thereof. In some embodiments, the SGLT2 inhibitor is a dapagliflozin hydrate. In some embodiments, the SGLT2 inhibitor is dapagliflozin propanediol monohydrate. In some embodiments, the SGLT2 inhibitor is dapagliflozin compounded with (2S)-1,2-propanediol, hydrate in a ratio of about 1:1:1.

**[0047]** In some embodiments, the dose of each (a), (b), and (c) is from about 40% to about 75% of the lowest diabetes therapeutic dose (LDTD).

**[0048]** In some embodiments, the dose of each (a), (b), and (c) is from about 60% to about 75% of the lowest diabetes therapeutic dose (LDTD). In some embodiments, the dose of each (a), (b), and (c) is from about 65% to about 75% of the lowest diabetes therapeutic dose (LDTD). In some embodiments, the dose of each (a), (b), and (c) is about 70% of the lowest diabetes therapeutic dose (LDTD).

**[0049]** In some embodiments, the dose of each (a), (b), and (c) is from about 40% to about 70% of the lowest diabetes therapeutic dose (LDTD).

**[0050]** In some embodiments, the dose of each (a), (b), and (c) is from about 40% to about 60% of the lowest diabetes therapeutic dose (LDTD). In some embodiments, the dose of each (a), (b), and (c) is from about 45% to about 55% of the lowest diabetes therapeutic dose (LDTD). In some embodiments, the dose of each (a), (b), and (c) is about 50% of the lowest diabetes therapeutic dose (LDTD).

**[0051]** In some embodiments, the DPP IV inhibitor is about 70% of the lowest diabetes therapeutic dose (LDTD) for the DPP IV inhibitor. In some embodiments, the DPP IV inhibitor is sitagliptin, and the dose of sitagliptin is about 17.5 mg.

**[0052]** In some embodiments, the DPP IV inhibitor is about 50% of the lowest diabetes therapeutic dose (LDTD) for the DPP IV inhibitor. In some embodiments, the DPP IV inhibitor is sitagliptin, and the dose of sitagliptin is about 12.5 mg.

**[0053]** In some embodiments, the biguanide is about 70% of the lowest diabetes therapeutic dose (LDTD) for the biguanide. In some embodiments, the biguanide is metformin hydrochloride, and the dose of metformin hydrochloride is about 350 mg.

**[0054]** In some embodiments, the biguanide is about 50% of the lowest diabetes therapeutic dose (LDTD) for the biguanide. In some embodiments, the biguanide is metformin hydrochloride, and the dose of metformin hydrochloride is about 250 mg.

**[0055]** In some embodiments, the SGLT2 inhibitor is about 50% of the lowest diabetes therapeutic dose (LDTD) for the SGLT2 inhibitor. In some embodiments, the SGLT2 inhibitor is dapagliflozin, and the dose of dapagliflozin is about 2.5 mg.

**[0056]** In some embodiments, the DPP IV inhibitor is sitagliptin, the biguanide is metformin, and the SGLT2 inhibitor is dapagliflozin.

**[0057]** In some embodiments, the dose of sitagliptin is from about 5.0 mg to about 18.75 mg, the dose of metformin is from about 100 mg to about 375 mg, and the dose of dapagliflozin is from about 1.0 mg to about 3.75 mg. In some embodiments, the dose of sitagliptin is from about 10 mg to about 16.25 mg, the dose of metformin is from about 200 mg to about 325 mg, and the dose of dapagliflozin is from about 2.0 mg to about 3.25 mg. In some embodiments, the dose of sitagliptin is from about 10 mg to about 15 mg, the dose of metformin is from about 200 mg to about 300 mg, and the dose of dapagliflozin is from about 2 mg to about 3 mg. In some embodiments, the dose of sitagliptin is from about 11.25 mg to about 13.75 mg, the dose of metformin is from about 225 mg to about 275 mg, and the dose of dapagliflozin is from about 2.25 mg to about 2.75 mg. In some embodiments, the dose of sitagliptin is about 12.5 mg, the dose of metformin is about 250 mg, and the dose of dapagliflozin is about 2.5 mg.

**[0058]** In some embodiments, the dose of each (a), (b), and (c) is from about 30% to about 40% of the lowest diabetes therapeutic dose (LDTD). In some embodiments, the dose of each (a), (b), and (c) is from about 30% to about 35% of the lowest diabetes therapeutic dose (LDTD). In some embodiments, the SGLT2 inhibitor is about 33% of the lowest diabetes therapeutic dose (LDTD) for the SGLT2 inhibitor.

**[0059]** In some embodiments, the SGLT2 inhibitor is dapagliflozin, and the dose of dapagliflozin is about 1.65 mg. In some embodiments, the SGLT2 inhibitor is empagliflozin, and the dose of empagliflozin is about 3.3 mg.

**[0060]** In some embodiments, the DPP IV inhibitor is sitagliptin, the biguanide is metformin, and the SGLT2 inhibitor is dapagliflozin or empagliflozin.

**[0061]** In some embodiments, the dose of sitagliptin is from about 7.5 mg to about 10 mg and the dose of metformin is from about 150 mg to about 200 mg. In some embodiments, the SGLT2 inhibitor is dapagliflozin and the dose of dapagliflozin is from about 1.5 mg to about 2.0 mg. In some embodiments, the SGLT2 inhibitor is empagliflozin and the dose of empagliflozin is from about 3.0 mg to about 4.0 mg. In some embodiments, the dose of sitagliptin is about 8.25 mg and the dose of metformin is about 165 mg. In some embodiments, the SGLT2 inhibitor is dapagliflozin and the dose of dapagliflozin is about 1.65 mg. In some embodiments, the SGLT2 inhibitor is empagliflozin, and the dose of empagliflozin is about 3.3 mg.

**[0062]** In some embodiments, the dose of each (a), (b), and (c) is from about 20% to about 30% of the lowest diabetes therapeutic dose (LDTD). In some embodiments, the dose of each (a), (b), and (c) is from about 22% to about 28% of the lowest diabetes therapeutic dose (LDTD). In some embodiments, the dose of the SGLT2 inhibitor is about 25% of the lowest diabetes therapeutic dose (LDTD) for the SGLT2 inhibitor.

**[0063]** In some embodiments, the SGLT2 inhibitor is dapagliflozin, and the dose of dapagliflozin is about 1.25 mg. In some embodiments, the SGLT2 inhibitor is empagliflozin, and the dose of empagliflozin is about 2.5 mg.

**[0064]** In some embodiments, the DPP IV inhibitor is sitagliptin, the biguanide is metformin, and the SGLT2 inhibitor is dapagliflozin or empagliflozin.

**[0065]** In some embodiments, the dose of sitagliptin is from about 5mg to about 7.5 mg and the dose of metformin is from about 100 mg to about 150 mg.

**[0066]** In some embodiments, the SGLT2 inhibitor is dapagliflozin, and the dose of dapagliflozin is about 1.0 mg. In some embodiments, the SGLT2 inhibitor is empagliflozin, and the dose of empagliflozin is about 2.0 mg.

**[0067]** In some embodiments, the dose of sitagliptin is about 6.25 mg and the dose of metformin is about 150 mg.

**[0068]** In some embodiments, the SGLT2 inhibitor is dapagliflozin, and the dose of dapagliflozin is about 1.5 mg. In some embodiments, the SGLT2 inhibitor is empagliflozin, and the dose of empagliflozin is about 3.0 mg.

**[0069]** In some embodiments, the DPP IV inhibitor is sitagliptin and the dose of sitagliptin is from about 16.25 mg to about 18.75 mg.

**[0070]** In some embodiments, the biguanide is metformin and the dose of metformin is from about 325 mg to about 375 mg.

**[0071]** In some embodiments, the SGLT2 inhibitor is dapagliflozin, and the dose of dapagliflozin from about 2.25 mg to about 2.75 mg. In some embodiments, the SGLT2 inhibitor is empagliflozin, and the dose of empagliflozin from about 4.5 mg to about 7.5 mg.

**[0072]** In some embodiments, the DPP IV inhibitor is at about 70% of the lowest diabetes therapeutic dose (LDTD) for the DPP IV inhibitor.

**[0073]** In some embodiments, the biguanide is at about 70% of the lowest diabetes therapeutic dose (LDTD) for the biguanide.

**[0074]** In some embodiments, the SGLT2 inhibitor is at about 50% of the lowest diabetes therapeutic dose (LDTD) for the SGLT2 inhibitor.

**[0075]** In some embodiments, the DPP IV inhibitor is sitagliptin, the biguanide is metformin, and the SGLT2 inhibitor is dapagliflozin or empagliflozin.

**[0076]** In some embodiments, the dose of sitagliptin is about 17.5 mg, the dose of metformin is about 350 mg, and the dose of dapagliflozin is about 2.5 mg. In some embodiments, the dose of sitagliptin is about 17.5 mg, the dose of metformin is about 350 mg, and the dose of empagliflozin is about 5.0 mg.

**[0077]** In some embodiments, the DPP IV inhibitor is sitagliptin and the dose of the sitagliptin is about 17.5 mg.

**[0078]** In some embodiments, the biguanide is metformin and the dose of the metformin is about 350 mg.

**[0079]** In some embodiments, the SGLT2 inhibitor is dapagliflozin and the dose of the dapagliflozin is about 2.5 mg. In some embodiments, the SGLT2 inhibitor is empagliflozin and the dose of the empagliflozin is about 5.0 mg.

**[0080]** In some embodiments, a), (b), and (c) are provided in one formulation. In some embodiments, (a), (b), and (c) are each provided in a separate formulation. In some embodiments, two of the (a), (b), and (c) are provided in one formulation. In some embodiments, the pharmaceutical composition is in the form of pill, tablet or capsule. In some embodiments, the pharmaceutical composition is suitable for oral administration

**[0081]** In some embodiments, the pharmaceutical compositions described herein comprise at least one pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical compositions comprising (a) a DPP IV inhibitor; (b) a biguanide; and (c) an SGLT2 inhibitor described herein are essentially free of additional anti-hyperglycemic or anti-diabetic agents.

**[0082]** In some embodiments, the pharmaceutical composition comprises an anti-diabetic or anti-hyperglycemic combination of anti-diabetic active or anti-hyperglycemic agents, wherein the anti-diabetic or anti-hyperglycemic active agents consist of a DPP IV inhibitor; a biguanide; and an SGLT2 inhibitor.

**[0083]** In some embodiments, the pharmaceutical compositions disclosed herein achieve a significant anti-diabetic effect or therapeutic benefit in a subject with diabetes. In some embodiments, the pharmaceutical compositions disclosed herein achieve a significant anti-

diabetic effect or therapeutic benefit in a subject with diabetes with minimum, insignificant, or no side effects. In some embodiments, the combination of the (a) a DPP IV inhibitor; (b) a biguanide; and (c) an SGLT2 inhibitor in the composition achieves a synergistic effect.

*DPP IV Inhibitors*

**[0084]** As used herein, DPP IV inhibitors are compounds that block the enzyme dipeptidyl peptidase-4 (DPP IV) and reduce glucagon and blood glucose levels.

**[0085]** In some embodiments, the DPP IV inhibitor is a gliptin. In some embodiments, the DPP IV inhibitor is sitagliptin, vildagliptin, saxagliptin, linagliptin, gemigliptin, anagliptin, teneligliptin, alogliptin, trelagliptin, omarigliptin, evogliptin, gosogliptin, dutogliptin, or the pharmaceutically acceptable salt or hydrate thereof.

**[0086]** In some embodiments, the DPP IV inhibitor is sitagliptin, or the pharmaceutically acceptable salt or hydrate thereof. In some embodiments, the DPP IV inhibitor is sitagliptin phosphate, or a hydrate thereof. In some embodiments, the DPP IV inhibitor is vildagliptin, or the pharmaceutically acceptable salt or hydrate thereof. In some embodiments, the DPP IV inhibitor is saxagliptin, or the pharmaceutically acceptable salt or hydrate thereof. In some embodiments, the DPP IV inhibitor is linagliptin, or the pharmaceutically acceptable salt or hydrate thereof. In some embodiments, the DPP IV inhibitor is gemigliptin, or the pharmaceutically acceptable salt or hydrate thereof. In some embodiments, the DPP IV inhibitor is anagliptin, or the pharmaceutically acceptable salt or hydrate thereof. In some embodiments, the DPP IV inhibitor is teneligliptin, or the pharmaceutically acceptable salt or hydrate thereof. In some embodiments, the DPP IV inhibitor is alogliptin. In some embodiments, the DPP IV inhibitor is trelagliptin, or the pharmaceutically acceptable salt or hydrate thereof. In some embodiments, the DPP IV inhibitor is omarigliptin, or the pharmaceutically acceptable salt or hydrate thereof. In some embodiments, the DPP IV inhibitor is evogliptin, or the pharmaceutically acceptable salt or hydrate thereof. In some embodiments, the DPP IV inhibitor is gosogliptin, or the pharmaceutically acceptable salt or hydrate thereof. In some embodiments, the DPP IV inhibitor is dutogliptin, or the pharmaceutically acceptable salt or hydrate thereof.

*Biguanides*

**[0087]** As used herein, biguanides are compounds that refer to a class of drugs that function as oral antihyperglycemic drugs used for diabetes mellitus or prediabetes treatment.

**[0088]** In some embodiments, the biguanide is metformin. In some embodiments, the biguanide is metformin hydrochloride, or a hydrate thereof.

*SGLT2 inhibitors*

**[0089]** As used herein, SGLT2 inhibitors are compounds that lead to a reduction in blood glucose levels.

**[0090]** In some embodiments, the is selected from dapagliflozin, empagliflozin, canagliflozin, ipragliflozin (ASP-1941), tofogliflozin, remogliflozin, sergliflozin, ertugliflozin, sotagliflozin, or the pharmaceutically acceptable salt or hydrate thereof. In some embodiments, the SGLT2 inhibitor is dapagliflozin, or the pharmaceutically acceptable salt or hydrate thereof. In some embodiments, the SGLT2 inhibitor is empagliflozin, or the pharmaceutically acceptable salt or hydrate thereof. In some embodiments, the SGLT2 inhibitor is canagliflozin, or the pharmaceutically acceptable salt or hydrate thereof. In some embodiments, the SGLT2 inhibitor is ipragliflozin (ASP-1941), or the pharmaceutically acceptable salt or hydrate thereof. In some embodiments, the SGLT2 inhibitor is tofogliflozin, or the pharmaceutically acceptable salt or hydrate thereof. In some embodiments, the SGLT2 inhibitor is remogliflozin, or the pharmaceutically acceptable salt or hydrate thereof. In some embodiments, the SGLT2 inhibitor is sergliflozin, or the pharmaceutically acceptable salt or hydrate thereof. In some embodiments, the SGLT2 inhibitor is ertugliflozin, or the pharmaceutically acceptable salt or hydrate thereof. In some embodiments, the SGLT2 inhibitor is sotagliflozin, or the pharmaceutically acceptable salt or hydrate thereof.

**[0091]** *Lowest Diabetes Therapeutic Dose*

**[0092]** As used herein, the lowest diabetes therapeutic dose (LDTD) refers to the lowest strength dose for the single agent for diabetes approved by the US Food and Drug Administration and is not marked as "discontinued" by the Orange Book database (world-wide web at address accessdata.fda.gov/scripts/cder/ob/) as of the filing date of this application. The lowest diabetes therapeutic dose does not include the lowest manufactured dose for cases wherein the lowest diabetes therapeutic dose is not the same as the lowest manufactured dose. Furthermore, the lowest diabetes therapeutic dose does not include the dose as recommended by a physician for cases wherein the lowest diabetes therapeutic dose is not the same dose as recommended by a physician. Further, the lowest diabetes dose of the DPP IV inhibitors, biguanides, and SGLT2 inhibitors, described herein refers to the dose of the form of DPP IV inhibitors, biguanides, and SGLT2 inhibitors approved for use by the US Food and Drug Administration, which includes the free base, pharmaceutically acceptable salt, or hydrate thereof.

**[0093]** In some embodiments, the dose of the DPP IV inhibitor is from about 20% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 20% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 20% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 20% to about 60% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 20% to about 55% of the lowest diabetes therapeutic dose. In some

embodiments, the dose of the DPP IV inhibitor is from about 20% to about 50% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 20% to about 45% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 20% to about 40% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 20% to about 35% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 20% to about 30% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 20% to about 25% of the lowest diabetes therapeutic dose.

**[0094]** In some embodiments, the dose of the DPP IV inhibitor is from about 25% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 25% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 25% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 25% to about 60% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 25% to about 55% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 25% to about 50% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 25% to about 45% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 25% to about 40% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 25% to about 35% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 25% to about 30% of the lowest diabetes therapeutic dose.

**[0095]** In some embodiments, the dose of the DPP IV inhibitor is from about 30% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 30% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 30% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 30% to about 60% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 30% to about 55% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 30% to about 50% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 30% to about 45% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 30% to about 40% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 30% to about 35% of the lowest diabetes therapeutic dose.

**[0096]** In some embodiments, the dose of the DPP IV inhibitor is from about 35% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 35% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 35% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 35% to about 60% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 35% to about 55% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 35% to about 50% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 35% to about 45% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 35% to about 40% of the lowest diabetes therapeutic dose

**[0097]** In some embodiments, the dose of the DPP IV inhibitor is from about 40% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 40% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 40% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 40% to about 60% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 40% to about 55% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 40% to about 50% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 40% to about 45% of the lowest diabetes therapeutic dose.

**[0098]** In some embodiments, the dose of the DPP IV inhibitor is from about 45% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 45% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 45% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 45% to about 60% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 45% to about 55% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 45% to about 50% of the lowest diabetes therapeutic dose.

**[0099]** In some embodiments, the dose of the DPP IV inhibitor is from about 50% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 50% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 50% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 50% to

about 60% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 50% to about 55% of the lowest diabetes therapeutic dose.

**[0100]** In some embodiments, the dose of the DPP IV inhibitor is from about 55% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 55% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 55% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 55% to about 60% of the lowest diabetes therapeutic dose.

**[0101]** In some embodiments, the dose of the DPP IV inhibitor is from about 60% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 60% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 60% to about 65% of the lowest diabetes therapeutic dose.

**[0102]** In some embodiments, the dose of the DPP IV inhibitor is from about 65% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 65% to about 70% of the lowest diabetes therapeutic dose.

**[0103]** In some embodiments, the dose of the DPP IV inhibitor is from about 70% to about 75% of the lowest diabetes therapeutic dose.

**[0104]** In some embodiments, the dose of the biguanide is from about 20% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 20% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 20% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 20% to about 60% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 20% to about 55% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 20% to about 50% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 20% to about 45% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 20% to about 40% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 20% to about 35% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 20% to about 30% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 20% to about 25% of the lowest diabetes therapeutic dose.

**[0105]** In some embodiments, the dose of the biguanide is from about 25% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about

25% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 25% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 25% to about 60% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 25% to about 55% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 25% to about 50% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 25% to about 45% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 25% to about 40% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 25% to about 35% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 25% to about 30% of the lowest diabetes therapeutic dose.

**[0106]** In some embodiments, the dose of the biguanide is from about 30% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 30% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 30% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 30% to about 60% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 30% to about 55% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 30% to about 50% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 30% to about 45% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 30% to about 40% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 30% to about 35% of the lowest diabetes therapeutic dose.

**[0107]** In some embodiments, the dose of the biguanide is from about 35% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 35% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 35% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 35% to about 60% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 35% to about 55% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 35% to about 50% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 35% to about 45% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 35% to about 40% of the lowest diabetes therapeutic dose

**[0108]** In some embodiments, the dose of the biguanide is from about 40% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 40% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 40% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 40% to about 60% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 40% to about 55% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 40% to about 50% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 40% to about 45% of the lowest diabetes therapeutic dose.

**[0109]** In some embodiments, the dose of the biguanide is from about 45% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 45% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 45% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 45% to about 60% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 45% to about 55% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 45% to about 50% of the lowest diabetes therapeutic dose.

**[0110]** In some embodiments, the dose of the biguanide is from about 50% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 50% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 50% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 50% to about 60% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 50% to about 55% of the lowest diabetes therapeutic dose.

**[0111]** In some embodiments, the dose of the biguanide is from about 55% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 55% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 55% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 55% to about 60% of the lowest diabetes therapeutic dose.

**[0112]** In some embodiments, the dose of the biguanide is from about 60% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 60% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 60% to about 65% of the lowest diabetes therapeutic dose.

**[0113]** In some embodiments, the dose of the biguanide is from about 65% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 65% to about 70% of the lowest diabetes therapeutic dose.

**[0114]** In some embodiments, the dose of the biguanide is from about 70% to about 75% of the lowest diabetes therapeutic dose.

**[0115]** In some embodiments, the dose of the SGLT2 inhibitor is from about 20% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 20% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 20% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 20% to about 60% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 20% to about 55% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 20% to about 50% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 20% to about 45% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 20% to about 40% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 20% to about 35% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 20% to about 30% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 20% to about 25% of the lowest diabetes therapeutic dose.

**[0116]** In some embodiments, the dose of the SGLT2 inhibitor is from about 25% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 25% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 25% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 25% to about 60% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 25% to about 55% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 25% to about 50% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 25% to about 45% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 25% to about 40% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 25% to about 35% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 25% to about 30% of the lowest diabetes therapeutic dose.

**[0117]** In some embodiments, the dose of the SGLT2 inhibitor is from about 30% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 30% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 30% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 30% to about 60% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 30% to about 55% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 30% to about 50% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 30% to about 45% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 30% to about 40% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 30% to about 35% of the lowest diabetes therapeutic dose.

**[0118]** In some embodiments, the dose of the SGLT2 inhibitor is from about 35% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 35% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 35% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 35% to about 60% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 35% to about 55% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 35% to about 50% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 35% to about 45% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 35% to about 40% of the lowest diabetes therapeutic dose

**[0119]** In some embodiments, the dose of the SGLT2 inhibitor is from about 40% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 40% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 40% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 40% to about 60% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 40% to about 55% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 40% to about 50% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 40% to about 45% of the lowest diabetes therapeutic dose.

**[0120]** In some embodiments, the dose of the SGLT2 inhibitor is from about 45% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 45% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 45% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 45% to about 60% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 45% to about 55% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 45% to about 50% of the lowest diabetes therapeutic dose.

**[0121]** In some embodiments, the dose of the SGLT2 inhibitor is from about 50% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 50% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 50% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 50% to about 60% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 50% to about 55% of the lowest diabetes therapeutic dose.

**[0122]** In some embodiments, the dose of the SGLT2 inhibitor is from about 55% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 55% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 55% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 55% to about 60% of the lowest diabetes therapeutic dose.

**[0123]** In some embodiments, the dose of the SGLT2 inhibitor is from about 60% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 60% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 60% to about 65% of the lowest diabetes therapeutic dose.

**[0124]** In some embodiments, the dose of the SGLT2 inhibitor is from about 65% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 65% to about 70% of the lowest diabetes therapeutic dose.

**[0125]** In some embodiments, the dose of the SGLT2 inhibitor is from about 70% to about 75% of the lowest diabetes therapeutic dose.

**[0126]** In some embodiments, the dose of the DPP IV inhibitor is from about 20% to about 50% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 20% to about 45% of the lowest diabetes therapeutic dose. In some embodiments,

the dose of the DPP IV inhibitor is from about 20% to about 40% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 20% to about 35% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 20% to about 30% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 20% to about 25% of the lowest diabetes therapeutic dose.

**[0127]** In some embodiments, the dose of the DPP IV inhibitor is from about 25% to about 50% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 25% to about 45% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 25% to about 40% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 25% to about 35% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 25% to about 30% of the lowest diabetes therapeutic dose.

**[0128]** In some embodiments, the dose of the DPP IV inhibitor is from about 30% to about 50% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 30% to about 45% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 30% to about 40% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 30% to about 35% of the lowest diabetes therapeutic dose.

**[0129]** In some embodiments, the dose of the DPP IV inhibitor is from about 35% to about 50% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 35% to about 45% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 35% to about 40% of the lowest diabetes therapeutic dose.

**[0130]** In some embodiments, the dose of the DPP IV inhibitor is from about 40% to about 50% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 45% to about 50% of the lowest diabetes therapeutic dose.

**[0131]** In some embodiments, the dose of the biguanide is from about 20% to about 50% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 20% to about 45% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 20% to about 40% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 20% to about 35% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 20% to about 30% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 20% to about 25% of the lowest diabetes therapeutic dose.

**[0132]** In some embodiments, the dose of the biguanide is from about 25% to about 50% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 25% to about 45% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 25% to about 40% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 25% to about 35% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 25% to about 30% of the lowest diabetes therapeutic dose.

**[0133]** In some embodiments, the dose of the biguanide is from about 30% to about 50% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 30% to about 45% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 30% to about 40% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 30% to about 35% of the lowest diabetes therapeutic dose.

**[0134]** In some embodiments, the dose of the biguanide is from about 35% to about 50% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 35% to about 45% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 35% to about 40% of the lowest diabetes therapeutic dose.

**[0135]** In some embodiments, the dose of the biguanide is from about 40% to about 50% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 45% to about 50% of the lowest diabetes therapeutic dose.

**[0136]** In some embodiments, the dose of the SGLT2 inhibitor is from about 20% to about 50% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 20% to about 45% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 20% to about 40% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 20% to about 35% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 20% to about 30% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 20% to about 25% of the lowest diabetes therapeutic dose.

**[0137]** In some embodiments, the dose of the SGLT2 inhibitor is from about 25% to about 50% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 25% to about 45% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 25% to about 40% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 25% to

about 35% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 25% to about 30% of the lowest diabetes therapeutic dose.

**[0138]** In some embodiments, the dose of the SGLT2 inhibitor is from about 30% to about 50% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 30% to about 45% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 30% to about 40% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 30% to about 35% of the lowest diabetes therapeutic dose.

**[0139]** In some embodiments, the dose of the SGLT2 inhibitor is from about 35% to about 50% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 35% to about 45% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 35% to about 40% of the lowest diabetes therapeutic dose.

**[0140]** In some embodiments, the dose of the SGLT2 inhibitor is from about 40% to about 50% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 45% to about 50% of the lowest diabetes therapeutic dose.

**[0141]** In some embodiments, the dose of each of the DPP IV inhibitor, the biguanide, and the SGLT2 inhibitor is from about 20% to about 40% of the lowest diabetes therapeutic dose.

**[0142]** In some embodiments, the dose of each of the DPP IV inhibitor, the biguanide, and the SGLT2 inhibitor is from about 20% to about 30% of the lowest diabetes therapeutic dose.

**[0143]** In some embodiments, the dose of the DPP IV inhibitor is about 20%, about 21%, about 22, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, or about 30% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is about 25% of the lowest diabetes therapeutic dose. In some embodiments, the DPP IV inhibitor is sitagliptin. In some embodiments, the dose of sitagliptin is about 5.0, about 5.25, about 5.5, about 5.75, about 6.0, about 6.25, about 6.5, about 6.75, about 7.0, about 7.25, or about 7.5 mg.

**[0144]** In some embodiments, the dose of the biguanide inhibitor is about 20%, about 21%, about 22, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, or about 30% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is about 25% of the lowest diabetes therapeutic dose. In some embodiments, the biguanide is metformin or metformin hydrochloride. In some embodiments, the dose of metformin or metformin hydrochloride is about 100, about 105, about, 110, about 115, about 120, about 125, about 130, about 135, about 140, about 145, or about 150 mg.

**[0145]** In some embodiments, the dose of the SGLT2 inhibitor is about 20%, about 21%, about 22, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, or about 30% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is about 25% of the lowest diabetes therapeutic dose. In some embodiments, the SGLT2 inhibitor is dapagliflozin. In some embodiments, the SGLT2 inhibitor is dapagliflozin. In some embodiments, the dose of dapagliflozin is about 1.0, about 1.1, about 1.2, about 1.3, about 1.4, or about 1.5 mg. In some embodiments, the SGLT2 inhibitor is empagliflozin. In some embodiments, the dose of empagliflozin is about 2.0, about 2.1, about 2.2, about 2.3, about 2.4, about 2.5, about 2.6, about 2.7, about 2.8, about 2.9, or about 3.0 mg.

**[0146]** In some embodiments, the lowest diabetes therapeutic dose (LDTD) and the corresponding proposed dose and proposed dose range for the following compounds are as described in Table 1.

**Table 1.**

| Agent | Lowest Diabetes Therapeutic Dose (LDTD) (mg) | Proposed Dose (mg) 25% LDTD | Proposed Dose Range 20% - 30% LDTD (mg) |
|---|---|---|---|
| sitagliptin | 25 | 6.25 | 5.0 – 7.5 |
| vildagliptin | 50 | 12.5 | 10 – 15 |
| saxagliptin | 2.5 | 0.625 | 0.5 – 0.75 |
| linagliptin | 5.0 | 1.25 | 1.0 – 1.5 |
| alogliptin | 6.25 | 1.5625 | 1.25 – 1.875 |
| metformin | 500 | 125 | 100 – 150 |
| dapagliflozin | 5.0 | 1.25 | 1.0 – 1.5 |
| empagliflozin | 10.0 | 2.5 | 2.0 – 3.0 |
| canagliflozin | 100 | 25 | 20 – 30 |
| ertugliflozin | 5.0 | 1.25 | 1.0 – 1.5 |

**[0147]** In some embodiments, the pharmaceutical composition comprises: (a) sitagliptin as a DPP IV inhibitor; (b) metformin as a biguanide; and (c) dapagliflozin as an SGLT2 inhibitor. In some embodiments, the pharmaceutical composition comprises: (a) sitagliptin as a DPP IV inhibitor; (b) metformin as a biguanide; and (c) empagliflozin as an SGLT2 inhibitor. In some embodiments, the dose of sitagliptin is from about 5 mg to about 7.5 mg, the dose of metformin is from about 100 mg to about 150 mg, and the dose of dapagliflozin is from about 1.0 mg to about 1.5 mg. In some embodiments, the dose of sitagliptin is from about 5 mg to about 7.5 mg,

the dose of metformin is from about 100 mg to about 150 mg, and the dose of empagliflozin is from about 2.0 mg to about 3.0 mg.

**[0148]** In some embodiments, the dose of each of (a) a DPP IV inhibitor; (b) a biguanide; and (c) an SGLT2 inhibitor is about 25% of the lowest diabetes therapeutic dose (LDTD) for each of (a), (b), and (c). In some embodiments, the dose of sitagliptin is about 6.25 mg, the dose of metformin is about 125 mg, and the dose of dapagliflozin is about 1.25 mg. In some embodiments, the dose of sitagliptin is about 6.25 mg, the dose of metformin is about 125 mg, and the dose of empagliflozin is about 2.5 mg. In some embodiments, the metformin is metformin hydrochloride.

**[0149]** In some embodiments, the dose of each of the DPP IV inhibitor, the biguanide, and the SGLT2 inhibitor is from about 30% to about 40% of the lowest diabetes therapeutic dose.

**[0150]** In some embodiments, the dose of the DPP IV inhibitor is about 30%, about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, or about 40% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is about 33% of the lowest diabetes therapeutic dose. In some embodiments, the DPP IV inhibitor is sitagliptin. In some embodiments, the dose of sitagliptin is about 7.5, about 7.75, about 8.0, about 8.25, about 8.5, about 8.75, about 9.0, about 9.25, about 9.5, about 9.75, or about 10 mg.

**[0151]** In some embodiments, the dose of the biguanide inhibitor is about 30%, about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, or about 40% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is about 33% of the lowest diabetes therapeutic dose. In some embodiments, the biguanide is metformin or metformin hydrochloride. In some embodiments, the dose of metformin or metformin hydrochloride is about 150, about 155, about 160, about 165, about 170, about 175, about 180, about 185, about 190, about 195, or about 200 mg.

**[0152]** In some embodiments, the dose of the SGLT2 inhibitor is about 30%, about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, or about 40% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is about 33% of the lowest diabetes therapeutic dose. In some embodiments, the SGLT2 inhibitor is dapagliflozin. In some embodiments, the dose of dapagliflozin is about 1.5, about 1.55, about 1.6, about 1.65, about 1.7, about 1.75, about 1.8, about 1.85, about 1.9, about 1.95, or about 2.0 mg. In some embodiments, the SGLT2 inhibitor is empagliflozin. In some embodiments, the dose of empagliflozin is about 3.0, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, or about 4.0 mg.

**[0153]** In some embodiments, the lowest diabetes therapeutic dose (LDTD) and the corresponding proposed dose and proposed dose range for the following compounds are as described in Table 2.

**Table 2.**

| Agent | Lowest Diabetes Therapeutic Dose (LDTD) (mg) | Proposed Dose (mg) 33% LDTD | Proposed Dose Range 30% - 40% LDTD (mg) |
|---|---|---|---|
| sitagliptin | 25 | 8.25 | 7.5 – 10 |
| vildagliptin | 50 | 16.5 | 15 – 20 |
| saxagliptin | 2.5 | 0.825 | 0.75 – 1 |
| linagliptin | 5.0 | 1.65 | 1.5 – 2 |
| alogliptin | 6.25 | 2.0625 | 1.875 – 2.5 |
| metformin | 500 | 165 | 150 – 200 |
| dapagliflozin | 5.0 | 1.65 | 1.5 – 2.0 |
| empagliflozin | 10.0 | 3.3 | 3.0 – 4.0 |
| canagliflozin | 100 | 33 | 30 – 40 |
| ertugliflozin | 5.0 | 1.65 | 1.5 – 2.0 |

**[0154]** In some embodiments, the pharmaceutical composition comprises: (a) sitagliptin as a DPP IV inhibitor; (b) metformin as a biguanide; and (c) dapagliflozin as an SGLT2 inhibitor. In some embodiments, the pharmaceutical composition comprises: (a) sitagliptin as a DPP IV inhibitor; (b) metformin as a biguanide; and (c) empagliflozin as an SGLT2 inhibitor. In some embodiments, the dose of sitagliptin is from about 7.5 mg to about 10 mg, the dose of metformin is from about 150 mg to about 200 mg, and the dose of dapagliflozin is from about 1.5 mg to about 2.0 mg. In some embodiments, the dose of sitagliptin is from about 7.5 mg to about 10 mg, the dose of metformin is from about 150 mg to about 200 mg, and the dose of empagliflozin is from about 3.0 mg to about 4.0 mg.

**[0155]** In some embodiments, the dose of each of (a) a DPP IV inhibitor; (b) a biguanide; and (c) an SGLT2 inhibitor is about 33% of the lowest diabetes therapeutic dose (LDTD) for each of (a), (b), and (c). In some embodiments, the dose of sitagliptin is about 8.25 mg, the dose of metformin is about 165 mg, and the dose of dapagliflozin is about 1.65 mg. In some embodiments, the metformin is metformin hydrochloride. In some embodiments, the dose of sitagliptin is about 8.25 mg, the dose of metformin is about 165 mg, and the dose of empagliflozin is about 3.3 mg.

**[0156]** In some embodiments, the dose of the DPP IV inhibitor is from about 40% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 40% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 40% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 40% to about 60% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 40% to about 55% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 40% to about 50% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 40% to about 45% of the lowest diabetes therapeutic dose.

**[0157]** In some embodiments, the dose of the DPP IV inhibitor is from about 45% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 45% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 45% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 45% to about 60% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 45% to about 55% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 45% to about 50% of the lowest diabetes therapeutic dose.

**[0158]** In some embodiments, the dose of the DPP IV inhibitor is from about 50% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 50% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 50% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 50% to about 60% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 50% to about 55% of the lowest diabetes therapeutic dose.

**[0159]** In some embodiments, the dose of the DPP IV inhibitor is from about 55% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 55% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 55% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 55% to about 60% of the lowest diabetes therapeutic dose.

**[0160]** In some embodiments, the dose of the DPP IV inhibitor is from about 60% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 60% to about 70% of the lowest diabetes therapeutic dose. In some embodiments,

the dose of the DPP IV inhibitor is from about 60% to about 65% of the lowest diabetes therapeutic dose.

**[0161]** In some embodiments, the dose of the DPP IV inhibitor is from about 65% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 65% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is from about 70% to about 75% of the lowest diabetes therapeutic dose.

**[0162]** In some embodiments, the dose of the biguanide is from about 40% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 40% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 40% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 40% to about 60% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 40% to about 55% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 40% to about 50% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 40% to about 45% of the lowest diabetes therapeutic dose.

**[0163]** In some embodiments, the dose of the biguanide is from about 45% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 45% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 45% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 45% to about 60% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 45% to about 55% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 45% to about 50% of the lowest diabetes therapeutic dose.

**[0164]** In some embodiments, the dose of the biguanide is from about 50% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 50% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 50% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 50% to about 60% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 50% to about 55% of the lowest diabetes therapeutic dose.

**[0165]** In some embodiments, the dose of the biguanide is from about 55% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 55% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of

the biguanide is from about 55% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 55% to about 60% of the lowest diabetes therapeutic dose.

**[0166]** In some embodiments, the dose of the biguanide is from about 60% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 60% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 60% to about 65% of the lowest diabetes therapeutic dose.

**[0167]** In some embodiments, the dose of the biguanide is from about 65% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 65% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is from about 70% to about 75% of the lowest diabetes therapeutic dose.

**[0168]** In some embodiments, the dose of the SGLT2 inhibitor is from about 40% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 40% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 40% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 40% to about 60% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 40% to about 55% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 40% to about 50% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 40% to about 45% of the lowest diabetes therapeutic dose.

**[0169]** In some embodiments, the dose of the SGLT2 inhibitor is from about 45% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 45% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 45% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 45% to about 60% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 45% to about 55% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 45% to about 50% of the lowest diabetes therapeutic dose.

**[0170]** In some embodiments, the dose of the SGLT2 inhibitor is from about 50% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 50% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 50% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 50% to

about 60% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 50% to about 55% of the lowest diabetes therapeutic dose.

**[0171]** In some embodiments, the dose of the SGLT2 inhibitor is from about 55% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 55% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 55% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 55% to about 60% of the lowest diabetes therapeutic dose.

**[0172]** In some embodiments, the dose of the SGLT2 inhibitor is from about 60% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 60% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 60% to about 65% of the lowest diabetes therapeutic dose.

**[0173]** In some embodiments, the dose of the SGLT2 inhibitor is from about 65% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 65% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 70% to about 75% of the lowest diabetes therapeutic dose.

**[0174]** In some embodiments, the dose of the SGLT2 inhibitor is from about 40% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 40% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 40% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 40% to about 60% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 40% to about 55% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 40% to about 50% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 40% to about 45% of the lowest diabetes therapeutic dose.

**[0175]** In some embodiments, the dose of the SGLT2 inhibitor is from about 45% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 45% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 45% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 45% to about 60% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 45% to about 55% of the lowest diabetes therapeutic dose. In

some embodiments, the dose of the SGLT2 inhibitor is from about 45% to about 50% of the lowest diabetes therapeutic dose.

**[0176]** In some embodiments, the dose of the SGLT2 inhibitor is from about 50% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 50% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 50% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 50% to about 60% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 50% to about 55% of the lowest diabetes therapeutic dose.

**[0177]** In some embodiments, the dose of the SGLT2 inhibitor is from about 55% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 55% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 55% to about 65% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 55% to about 60% of the lowest diabetes therapeutic dose.

**[0178]** In some embodiments, the dose of the SGLT2 inhibitor is from about 60% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 60% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 60% to about 65% of the lowest diabetes therapeutic dose.

**[0179]** In some embodiments, the dose of the SGLT2 inhibitor is from about 65% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 65% to about 70% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is from about 70% to about 75% of the lowest diabetes therapeutic dose.

**[0180]** In some embodiments, the dose of each of the DPP IV inhibitor, the biguanide, and the SGLT2 inhibitor is from about 40% to about 60% of the lowest diabetes therapeutic dose.

**[0181]** In some embodiments, the dose of each of the DPP IV inhibitor, the biguanide, and the SGLT2 inhibitor is from about 40% to about 50% of the lowest diabetes therapeutic dose.

**[0182]** In some embodiments, the dose of each of the DPP IV inhibitor, the biguanide, and the SGLT2 inhibitor is from about 50% to about 60% of the lowest diabetes therapeutic dose.

**[0183]** In some embodiments, the dose of each of the DPP IV inhibitor, the biguanide, and the SGLT2 inhibitor is from about 45% to about 55% of the lowest diabetes therapeutic dose.

**[0184]** In some embodiments, the dose of the DPP IV inhibitor is about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about

50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, or about 60% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is about 50% of the lowest diabetes therapeutic dose. In some embodiments, the DPP IV inhibitor is sitagliptin. In some embodiments, the dose of sitagliptin is about 10, about 10.25, about 10.5, about 10.75, about 11, about 11.25, about 11.5, about 11.75, about 12, about 12.25, about 12.5, about 12.75, about 13, about 13.25, about 13.5, about 13.75, about 14, about 14.25, about 14.5, about 14.75, or about 15 mg.

**[0185]** In some embodiments, the dose of the biguanide inhibitor is about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, or about 60% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is about 50% of the lowest diabetes therapeutic dose. In some embodiments, the biguanide is metformin or metformin hydrochloride. In some embodiments, the dose of metformin or metformin hydrochloride is about 200, about 205, about 210, about 215, about 220, about 225, about 230, about 235, about 240, about 245, about 250, about 255, about 260, about 265, about 270, about 275, about 280, about 285, about 290, about 295, or about 300 mg.

**[0186]** In some embodiments, the dose of the SGLT2 inhibitor is about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, or about 60% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is about 50% of the lowest diabetes therapeutic dose. In some embodiments, the SGLT2 inhibitor is dapagliflozin. In some embodiments, the dose of dapagliflozin is about 2.0, about 2.1, about 2.2, about 2.3, about 2.4, about 2.5, about 2.6, about 2.7, about 2.8, about 2.9, or about 3.0 mg. In some embodiments, the dose of dapagliflozin is about 2.0, about 2.25, about 2.5, about 2.75, or about 3.0 mg. In some embodiments, the SGLT2 inhibitor is empagliflozin. In some embodiments, the dose of empagliflozin is about 4.0, about 4.1, about 4.2, about 4.3, about 4.4, about 4.5, about 4.6, about 4.7, about 4.8, about 4.9, about 5.0, about 5.1, about 5.2, about 5.3, about 5.4, about 5.5, about 5.6, about 5.7, about 5.8, about 5.9, or about 6.0 mg.

**[0187]** In some embodiments, the lowest diabetes therapeutic dose (LDTD) and the corresponding proposed dose and proposed dose range for the following compounds are as described in Table 3.

**Table 3.**

| Agent | Lowest Diabetes Therapeutic Dose (LDTD) (mg) | Proposed Dose (mg) 50% LDTD | Proposed Dose Range 40% - 60% LDTD (mg) | Proposed Dose Range 45% - 55% LDTD (mg) |
|---|---|---|---|---|
| sitagliptin | 25 | 12.5 | 10 – 15 | 11.25 – 12.5 |
| vildagliptin | 50 | 25 | 20 – 30 | 22.5 – 27.5 |
| saxagliptin | 2.5 | 1.25 | 1 – 1.5 | 1.125 – 1.375 |
| linagliptin | 5.0 | 2.5 | 2 – 3 | 2.25 – 2.75 |
| alogliptin | 6.25 | 3.125 | 2.5 – 3.75 | 2.8125 – 3.4375 |
| metformin | 500 | 250 | 200 – 300 | 225 – 275 |
| dapagliflozin | 5.0 | 2.5 | 2 – 3 | 2.25 – 2.75 |
| empagliflozin | 10.0 | 5.0 | 4.0 – 6.0 | 4.5 – 5.5 |
| canagliflozin | 100 | 50 | 40 – 50 | 45 – 55 |
| ertugliflozin | 5.0 | 2.5 | 2 – 3 | 2.25 – 2.75 |

**[0188]** In some embodiments, the pharmaceutical composition comprises: (a) sitagliptin as a DPP IV inhibitor; (b) metformin as a biguanide; and (c) dapagliflozin as an SGLT2 inhibitor. In some embodiments, the dose of sitagliptin is from about 10 mg to about 15 mg, the dose of metformin is from about 200 mg to about 300 mg, and the dose of dapagliflozin is from about 2.0 to about 3.0 mg. In some embodiments, the dose of sitagliptin is from about 10 mg to about 15 mg, the dose of metformin is from about 200 mg to about 300 mg, and the dose of empagliflozin is from about 4.0 to about 6.0 mg.

**[0189]** In some embodiments, the dose of sitagliptin is from about 11.25 mg to about 12.5 mg, the dose of metformin is from about 225 mg to about 275 mg, and the dose of dapagliflozin is from about 2.25 to about 2.75 mg. In some embodiments, the dose of sitagliptin is from about 11.25 mg to about 12.5 mg, the dose of metformin is from about 225 mg to about 275 mg, and the dose of empagliflozin is from about 4.5 to about 5.5 mg.

**[0190]** In some embodiments, the dose of each of (a) a DPP IV inhibitor; (b) a biguanide; and (c) an SGLT2 inhibitor is about 50% of the lowest diabetes therapeutic dose (LDTD) for each of (a), (b), and (c). In some embodiments, the dose of sitagliptin is about 12.5 mg, the dose of metformin is about 250 mg, and the dose of dapagliflozin is about 2.5 mg. In some embodiments, the dose of sitagliptin is about 12.5 mg, the dose of metformin is about 250 mg, and the dose of empagliflozin is about 5.0 mg. In some embodiments, the metformin is metformin hydrochloride.

**[0191]** In some embodiments, the dose of the DPP IV inhibitor is from about 60% to about 75% of the lowest diabetes therapeutic dose.

**[0192]** In some embodiments, the dose of the DPP IV inhibitor is about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, or about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the DPP IV inhibitor is about 70% of the lowest diabetes therapeutic dose. In some embodiments, the DPP IV inhibitor is sitagliptin. In some embodiments, the dose of sitagliptin is about 15, about 15.25, about 15.5, about 15.75, about 16, about 16.25, about 16.5, about 16.75, about 17, about 17.25, about 17.5, about 17.75, about 18, about 18.25, about 18.5, or about 18.75 mg.

**[0193]** In some embodiments, the dose of the biguanide is from about 60% to about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide inhibitor is about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, or about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the biguanide is about 70% of the lowest diabetes therapeutic dose. In some embodiments, the biguanide is metformin or metformin hydrochloride. In some embodiments, the dose of metformin or metformin hydrochloride is about 300, about 305, about 310, about 315, about 320, about 325, about 330, about 335, about 340, about 345, about 350, about 355, about 360, about 365, about 370, or about 375 mg.

**[0194]** In some embodiments, the dose of the SGLT2 inhibitor is from about 60% to about 75% of the lowest diabetes therapeutic dose.

**[0195]** In some embodiments, the dose of the SGLT2 inhibitor is about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, or about 75% of the lowest diabetes therapeutic dose. In some embodiments, the dose of the SGLT2 inhibitor is about 70% of the lowest diabetes therapeutic dose. In some embodiments, the SGLT2 inhibitor is dapagliflozin. In some embodiments, the dose of dapagliflozin is about 3.0, about 3.05, about 3.10, about 3.15, 3.20, about 3.25, about 3.30, about 3.35, about 3.40, about 3.45, about 3.5, about 3.55, about 3.60, about 3.65, about 3.70, or about 3.75 mg. In some embodiments, the SGLT2 inhibitor is empagliflozin. In some embodiments, the dose of empagliflozin is about 6.0, about 6.1, about 6.2, about 6.3, about 6.4, about 6.5, about 6.6, about 6.7, about 6.8, about 6.9, about 7.0, about 7.1, about 7.2, about 7.3, about 7.4, or about 7.5 mg.

**[0196]** In some embodiments, the lowest diabetes therapeutic dose (LDTD) and the corresponding proposed dose and proposed dose range for the following compounds are as described in Table 4.

**Table 4.**

| Agent | Lowest Diabetes Therapeutic Dose (LDTD) (mg) | Proposed Dose (mg) 70% LDTD | Proposed Dose Range 60% - 75% LDTD (mg) | Proposed Dose Range 60% - 70% LDTD (mg) |
|---|---|---|---|---|
| sitagliptin | 25 | 17.5 | 15 – 18.75 | 15 – 17.5 |
| vildagliptin | 50 | 35 | 30 – 37.5 | 30 – 35 |
| saxagliptin | 2.5 | 1.75 | 1.5 – 1.875 | 1.5 – 1.75 |
| linagliptin | 5.0 | 3.5 | 3 – 3.75 | 3 – 3.5 |
| alogliptin | 6.25 | 4.375 | 3.75 – 4.6875 | 3.75 – 4.375 |
| metformin | 500 | 350 | 300 – 375 | 300 – 350 |
| dapagliflozin | 5.0 | 3.5 | 3.0 – 3.75 | 3.0 – 3.5 |
| empagliflozin | 10.0 | 7.0 | 6.0 – 7.5 | 6.0 – 7.0 |
| canagliflozin | 100 | 70 | 60 – 75 | 60 – 70 |
| ertugliflozin | 5.0 | 3.5 | 3.0 – 3.75 | 3.0 – 3.5 |

**[0197]** In some embodiments, the pharmaceutical composition comprises: (a) sitagliptin as a DPP IV inhibitor; (b) metformin as a biguanide; and (c) dapagliflozin as an SGLT2 inhibitor. In some embodiments, the pharmaceutical composition comprises: (a) sitagliptin as a DPP IV inhibitor; (b) metformin as a biguanide; and (c) empagliflozin as an SGLT2 inhibitor. In some embodiments, the dose of sitagliptin is from about 15 mg to about 18.75 mg, the dose of metformin is from about 300 mg to about 375 mg, and the dose of dapagliflozin is from about 3.0 mg to about 3.75 mg. In some embodiments, the dose of sitagliptin is from about 15 mg to about 17.5 mg, the dose of metformin is from about 300 mg to about 350 mg, and the dose of empagliflozin is from about 6.0 mg to about 7.5 mg.

**[0198]** In some embodiments, the dose of sitagliptin is from about 15 mg to about 17.5 mg, the dose of metformin is from about 300 mg to about 350 mg, and the dose of dapagliflozin is from about 3.0 mg to about 3.5 mg. In some embodiments, the dose of sitagliptin is from about 15 mg to about 17.5 mg, the dose of metformin is from about 300 mg to about 350 mg, and the dose of empagliflozin is from about 6.0 mg to about 7.0 mg.

**[0199]** In some embodiments, the dose of (a) a DPP IV inhibitor; (b) a biguanide; and (c) an SGLT2 inhibitor is about 70% of the lowest diabetes therapeutic dose (LDTD) for each of (a),

(b), and (c). In some embodiments, the dose of sitagliptin is about 17.5 mg, the dose of metformin is about 350 mg, and the dose of dapagliflozin is about 3.5 mg. In some embodiments, the dose of sitagliptin is about 17.5 mg, the dose of metformin is about 350 mg, and the dose of empagliflozin is about 7.0 mg. In some embodiments, metformin is metformin hydrochloride.

**[0200]** In some embodiments, the dose of (a) a DPP IV inhibitor; (b) a biguanide; and (c) an SGLT2 inhibitor is about 70% of the lowest diabetes therapeutic dose (LDTD) for each of (a) and (b), and about 50% of the lowest diabetes therapeutic dose (LDTD) for (c).

**[0201]** In some embodiments, the lowest diabetes therapeutic dose (LDTD) and the corresponding proposed dose and proposed dose range for the following compounds are as described in Table 5.

**Table 5.**

| Agent | Lowest Diabetes Therapeutic Dose (LDTD) (mg) | Proposed Dose (mg) (% LDTD) | Proposed Dose Range (% LDTD) (mg) |
|---|---|---|---|
| sitagliptin | 25 | 17.5 (70) | 16.25 – 18.75 (65-75) |
| vildagliptin | 50 | 35 (70) | 32.5 – 37.5 (65-75) |
| saxagliptin | 2.5 | 1.75 (70) | 1.625 – 1.875 (65-75) |
| linagliptin | 5.0 | 3.5 (70) | 3.25 – 3.75 (65-75) |
| alogliptin | 6.25 | 4.375 (70) | 4.0625 – 4.6875 (65-75) |
| metformin | 500 | 350 (70) | 325 – 375 (65-75) |
| dapagliflozin | 5.0 | 2.5 (50) | 2.25 – 2.75 (45-55) |
| empagliflozin | 10.0 | 5.0 (50) | 4.5 – 5.5 (45-55) |
| canagliflozin | 100 | 50 (50) | 45 – 55 (45-55) |
| ertugliflozin | 5.0 | 2.5 (50) | 2.25 – 2.75 (45-55) |

**[0202]** In some embodiments, the pharmaceutical composition comprises: (a) sitagliptin as a DPP IV inhibitor; (b) metformin as a biguanide; and (c) dapagliflozin as an SGLT2 inhibitor. In some embodiments, the pharmaceutical composition comprises: (a) sitagliptin as a DPP IV inhibitor; (b) metformin as a biguanide; and (c) empagliflozin as an SGLT2 inhibitor. In some embodiments, the dose of sitagliptin is from about 1.625 mg to about 18.75 mg, the dose of metformin is from about 325 mg to about 375 mg, and the dose of dapagliflozin is from about 2.25 mg to about 2.75 mg.

**[0203]** In some embodiments, the dose of sitagliptin is from about 1.625 mg to about 18.75 mg and the dose of metformin is from about 325 mg to about 375 mg. In some embodiments, the

dose of sitagliptin is from about 1.625 mg to about 18.75 mg and the dose of dapagliflozin is from about 2.25 mg to about 2.75 mg. In some embodiments, the dose of metformin is from about 325 mg to about 375 mg and the dose of dapagliflozin is from about 2.25 mg to about 2.75 mg.

**[0204]** In some embodiments, the dose of sitagliptin is from about 1.625 mg to about 18.75 mg, the dose of metformin is from about 325 mg to about 375 mg, and the dose of empagliflozin is from about 4.5 mg to about 5.5 mg.

**[0205]** In some embodiments, the dose of sitagliptin is from about 1.625 mg to about 18.75 mg and the dose of empagliflozin is from about 4.5 mg to about 5.5 mg. In some embodiments, the dose of metformin is from about 325 mg to about 375 mg and the dose of empagliflozin is from about 4.5 mg to about 5.5 mg.

**[0206]** In some embodiments, the dose of sitagliptin is about 17.5 mg, the dose of metformin is about 350 mg, and the dose of dapagliflozin is about 2.5 mg. In some embodiments, the dose of sitagliptin is about 17.5 mg and the dose of metformin is about 350 mg. In some embodiments, the dose of sitagliptin is about 17.5 mg and the dose of dapagliflozin is about 2.5 mg. In some embodiments, the dose of metformin is about 350 mg and the dose of dapagliflozin is about 2.5 mg.

**[0207]** In some embodiments, the dose of sitagliptin is about 17.5 mg, the dose of metformin is about 350 mg, and the dose of empagliflozin is about 5.0 mg. In some embodiments, the dose of sitagliptin is about 17.5 mg and the dose of metformin is about 350 mg. In some embodiments, the dose of sitagliptin is about 17.5 mg and the dose of empagliflozin is about 5.0 mg. In some embodiments, the dose of metformin is about 350 mg and the dose of empagliflozin is about 5.0 mg.

*Formulations*

**[0208]** In some embodiments, the DPP IV inhibitor, biguanide, and SGLT2 inhibitor are provided in one formulation. In some embodiments, the DPP IV inhibitor, biguanide, and SGLT2 inhibitor are each provided in a separate formulation. In some embodiments, two of the DPP IV inhibitor, biguanide, and SGLT2 inhibitor are provided in one formulation. In some embodiments, the DPP IV inhibitor and biguanide are provided in one formulation. In some embodiments, the DPP IV inhibitor and SGLT2 inhibitor are provided in one formulation. In some embodiments, the biguanide and SGLT2 inhibitor are provided in one formulation. In some embodiments, the pharmaceutical composition is in the form of a pill, a tablet, or a capsule. In some embodiments, the pharmaceutical composition is in the form of a pill. In some embodiments, the pharmaceutical composition is in the form of a tablet. In some embodiments,

the pharmaceutical composition is in the form of a capsule. In some embodiments, the pharmaceutical composition is suitable for oral administration.

**[0209]** Other suitable formulations include, but are not limited to, those suitable for rectal, topical, buccal, parenteral (e.g., subcutaneous, intramuscular, intradermal, or intravenous), vaginal, or aerosol administration, although the most suitable form of administration in any given case will depend on the degree and severity of the condition being treated and on the nature of the particular compound being used. For example, disclosed compositions may be formulated as a unit dose.

**[0210]** Exemplary pharmaceutical compositions may be used in the form of a pharmaceutical preparation, for example, in solid, semisolid, or liquid form, which includes one or more of a disclosed compound, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external, enteral, or parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The active object compound is included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of the disease.

**[0211]** For preparing solid compositions such as tablets, the principal active ingredient may be mixed with a pharmaceutical carrier, e.g., conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g., water, to form a solid preformulation composition containing a homogeneous mixture of a disclosed compound or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills, and capsules.

**[0212]** In solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the subject composition is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, acetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9)

lubricants, such a talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills, the compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

**[0213]** A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the subject composition moistened with an inert liquid diluent. In some embodiments, capsules are prepared by encapsulating tablets in hard-gelatin capsules (e.g., over-encapsulation). Tablets, and other solid dosage forms, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art.

*Methods of Treatment*

**[0214]** The pharmaceutical compositions described herein are useful for treating a metabolic disorder in a subject in need thereof. The pharmaceutical compositions described herein are useful for treating diabetes in a subject in need thereof.

**[0215]** The high incidence of therapeutic failure is a major contributor to the high rate of long-term hyperglycemia-associated complications or chronic damages (including microvascular complications such as diabetic nephropathy, retinopathy or neuropathy, and macrovascular complications such as coronary heart disease, cerebrovascular disease, and peripheral vascular disease) in patients with type 2 diabetes. Therefore, there is an unmet medical need for methods, medicaments, and pharmaceutical compositions with a good efficacy with regard to glycemic control, with regard to disease-modifying properties and with regard to reduction of cardiovascular morbidity and mortality while at the same time showing an improved safety profile.

**[0216]** In some embodiments, the treatment or methods of the present disclosure result in one or more of the following:

i. preventing, slowing progression of, delaying, or treating a metabolic disorder;
ii. preventing, slowing progression of, delaying, or treating diabetes;
iii. improving glycemic control and/or for reducing of fasting plasma glucose, of postprandial plasma glucose, of continuously measured blood glucose, and/or of glycosylated hemoglobin HbA1c;

iv. preventing, slowing, delaying or reversing progression from impaired glucose tolerance, impaired fasting blood glucose, and/or insulin resistance from metabolic syndrome and/or type 2 diabetes mellitus;

v. preventing, slowing progression of, delaying or treating of a condition or disorder selected from the group consisting of vascular and non-vascular complications of diabetes mellitus;

vi. preventing, slowing progression of, delaying, or treating impairment of renal function;

vii. preventing, slowing progression of, delaying, or treating impaired renal function;

viii. preventing, slowing progression of, delaying, or treating retinal vascular disease;

ix. reducing body weight and/or body fat or preventing an increase in body weight and/or body fat or facilitating a reduction in body weight and/or body fat;

x. preventing or treating the degeneration of pancreatic beta cells and/or for improving and/or restoring the functionality of pancreatic beta cells and/or restoring the functionality of pancreatic insulin secretion;

xi. preventing, slowing, delaying or treating diseases or conditions attributed to an abnormal accumulation of ectopic fat;

xii. maintaining and/or improving the insulin sensitivity and/or for treating or preventing hyperinsulinemia and/or insulin resistance,

xiii. preventing, slowing progression of, delaying, or treating new onset diabetes after transplantation (NODAT) and/or post-transplant metabolic syndrome (PTMS);

xiv. preventing, delaying, or reducing NODAT and/or PTMS associated complications including microvascular and macrovascular diseases and events, graft rejection, infection, and death;

xv. treating hyperuricemia and hyperuricemia associated conditions;

xvi. treating or preventing kidney stones; and/or

xvii. treating hyponatremia.

**[0217]** In some embodiments, the treatment results in slowing progression of, delaying or treating a metabolic disorder, in particular of type 2 diabetes mellitus.

**[0218]** In some embodiments, the treatment results in an improvement in glycemic control in a patient in need thereof, in particular in patients with type 2 diabetes mellitus.

**[0219]** In some embodiments, the treatment results in an improvement in glycemic control in a patient with insufficient glycemic control despite monotherapy with an antidiabetic drug or despite combination therapy with two antidiabetic drugs.

**[0220]** In some embodiments, the treatment results in glucose lowering effects, effects on insulin levels, or combinations thereof. In some embodiments, the treatment results in glucose

lowering effects, effects on insulin levels, or combinations thereof without any adverse events or low incidence of adverse evidence.

**[0221]** In some embodiments, the treatment results in glucose lowering effects at about 0.5 hour, about 1 hour, about 1.5 hours, about 2 hours, about 2.5 hours, about 3 hours, about 3.5 hours, about 4 hours, about 4.5 hours, about 5 hours, about 5.5 hours, about 6 hours, or more than about 6 hours following treatment. In some embodiments, the glucose lowering effects is determined by measuring primary endpoints, secondary endpoints, tertiary endpoints, or combinations thereof.

**[0222]** In some embodiments, the primary and secondary endpoints are the mean absolute change in plasma glucose and serum insulin, respectively at a certain time post-prandial from pre-prandial following the administration of a single dose of the treatment. In some embodiments, the primary and secondary endpoints are the mean absolute change in plasma glucose and serum insulin, respectively at about 0.5 hour, about 1 hour, about 1.5 hours, about 2 hours, about 2.5 hours, about 3 hours, about 3.5 hours, about 4 hours, about 4.5 hours, about 5 hours, about 5.5 hours, about 6 hours, or more than about 6 hours post-prandial from pre-prandial following the administration of a single dose of the treatment. In some embodiments, the primary and secondary endpoints are the mean absolute change in plasma glucose and serum insulin, respectively at about 2 hours post-prandial from pre-prandial following the administration of a single dose of the treatment. In some embodiments, the primary endpoint and secondary endpoint are compared to plasma glucose, serum insulin, or combinations thereof pre-prandial.

**[0223]** In some embodiments, the tertiary endpoints are determined as the area under the concentration time curve (AUC) of plasma glucose, serum insulin, or combinations thereof post-dose. In some embodiments, the tertiary endpoints are determined as the area under the concentration time curve (AUC) of plasma glucose, serum insulin, or combinations thereof post-meal. In some embodiments, the tertiary endpoints are determined as about 0.5 hour, about 1 hour, about 1.5 hours, about 2 hours, about 2.5 hours, about 3 hours, about 3.5 hours, about 4 hours, about 4.5 hours, about 5 hours, about 5.5 hours, about 6 hours, about 6.5 hours, about 7 hours, about 7.5 hours, about 8 hours, or more than about 8 hours of the AUC of plasma glucose, serum insulin, or combinations thereof post-dose. In some embodiments, the tertiary endpoints are determined as about 0.5 hour, about 1 hour, about 1.5 hours, about 2 hours, about 2.5 hours, about 3 hours, about 3.5 hours, about 4 hours, about 4.5 hours, about 5 hours, about 5.5 hours, about 6 hours, about 6.5 hours, about 7 hours, about 7.5 hours, about 8 hours, or more than about 8 hours of the AUC of plasma glucose, serum insulin, or combinations thereof post-meal. In

some embodiments, the tertiary endpoints are compared to plasma glucose, serum insulin, or combinations thereof pre-prandial.

**[0224]** In some embodiments, treatment using compositions described herein (e.g., Composition A) results in a glucose lowering effect. In some embodiments, treatment using compositions described herein (e.g., Composition A) results in a glucose lowering effect by at least or about 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or more than 95% as compared to no treatment, placebo treatment, or treatment with one or two active agents of the composition. In some embodiments, the treatment results in post-prandial plasma glucose being lowered by at least or about 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or more than 95% as compared to no treatment, placebo treatment, or treatment with one or two active agents of the composition. In some embodiments, the treatment results in the about 0.5 hour, about 1 hour, about 1.5 hours, about 2 hours, about 2.5 hours, about 3 hours, about 3.5 hours, about 4 hours, about 4.5 hours, about 5 hours, about 5.5 hours, about 6 hours, about 6.5 hours, about 7 hours, about 7.5 hours, about 8 hours, or more than about 8 hours post-prandial plasma glucose being lowered at least or about 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or more than 95% as compared to no treatment, placebo treatment, or treatment with one or two active agents of the composition. In some embodiments, the treatment results in the about 0.5 hour to about 6 hours, about 1 hour to about 5 hours, or about 2 hours to about 4 hours post-prandial plasma glucose being lowered by at least or about 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or more than 95% as compared to no treatment, placebo treatment, or treatment with one or two active agents of the composition. In some embodiments, the glucose lowering effects of the treatment is compared pre-prandial.

**[0225]** In some embodiments, treatment using compositions described herein (e.g., Composition A) results in increased insulin levels. In some embodiments, the treatment using compositions described herein (e.g., Composition A) results in increased insulin levels by at least or about 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or more than 95% as compared to no treatment, placebo treatment, or treatment with one or two active agents of the composition. In some embodiments, the treatment results in post-prandial insulin levels being increased by at least or about 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or more than 95% as compared to no treatment, placebo treatment, or treatment with one or two active agents of the composition. In some embodiments, the treatment results in the about 0.5 hour, about 1 hour, about 1.5 hours, about 2 hours, about 2.5 hours, about 3 hours, about 3.5 hours, about 4 hours, about 4.5 hours, about 5 hours, about 5.5 hours, about 6 hours, about 6.5 hours, about 7 hours, about 7.5 hours, about 8 hours, or more than about 8 hours post-

prandial insulin levels being increased by at least or about 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or more than 95% as compared to no treatment, placebo treatment, or treatment with one or two active agents of the composition. In some embodiments, the treatment results in the about 0.5 hour to about 6 hours, about 1 hour to about 5 hours, or about 2 hours to about 4 hours post-prandial insulin levels being increased by at least or about 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or more than 95% as compared to no treatment, placebo treatment, or treatment with one or two active agents of the composition. In some embodiments, the increased insulin levels of the treatment is compared pre-prandial.

**[0226]** In some embodiments, the treatment using compositions described herein (e.g., Composition A) results in plasma glucose levels, insulin levels, or combinations thereof returning to pre-prandial levels at a faster rate as compared to no treatment, placebo treatment, or treatment with one or two active agents of the composition. In some embodiments, the treatment using compositions described herein (e.g., Composition A) results in plasma glucose levels, insulin levels, or combinations thereof returning to pre-prandial levels at least or about 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or more than 95% faster as compared to no treatment, placebo treatment, or treatment with one or two active agents of the composition.

**[0227]** In some embodiments, the treatment results in slowing or delaying progression from impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), insulin resistance and/or metabolic syndrome to type 2 diabetes mellitus.

**[0228]** In some embodiments, the method results in prevention, slowing progression of, delaying or treatment of a condition or disorder from the group consisting of complications of diabetes mellitus.

**[0229]** In some embodiments, the treatment results in a reduction in the weight or prevention of an increase of the weight in a patient in need thereof.

**[0230]** In some embodiments, the method results in efficacious treatment of metabolic disorders, such as diabetes mellitus, impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), and/or hyperglycemia, with good pharmacological and/or pharmacokinetic and/or physicochemical properties.

**[0231]** In some embodiments, the method results in efficacious treatment of metabolic disorders, such as diabetes mellitus, impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), and/or hyperglycemia, with greater long term tolerability and reduced risk of side effects (e.g., low blood sugar, pancreatic cancer, hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions

including Stevens-Johnson syndrome; hepatic enzyme elevations; acute pancreatitis, including fatal and nonfatal hemorrhagic and necrotizing pancreatitis; worsening renal function, including acute renal failure (sometimes requiring dialysis); severe and disabling arthralgia; constipation; vomiting; headache; myalgia; pain in extremity; back pain; pruritus; and/or pemphigoid, joint pain, lactic acidosis, vitamin B12 and folic acid deficiency, nasopharyngitis, upper respiratory tract infection).

**[0232]** In some embodiments, treatment results in improved treatment of diabetes that is greater than the treatment obtained with the full lowest diabetic therapeutic dose of any one of the DPP IV inhibitor, the biguanide, and the SGLT2 inhibitor in the pharmaceutical composition.

**[0233]** In some embodiments, treatment results in improved treatment of diabetes that is greater than the treatment obtained with the full lowest diabetic therapeutic dose of the DPP IV inhibitor in the pharmaceutical composition. In some embodiments, treatment results in improved treatment of diabetes that is greater than the treatment obtained with the full lowest diabetic therapeutic dose of the biguanide in the pharmaceutical composition. In some embodiments, treatment results in improved treatment of diabetes that is greater than the treatment obtained with the full lowest diabetic therapeutic dose of the SGLT2 inhibitor in the pharmaceutical composition.

**[0234]** In some embodiments, treatment results in greater long term tolerability and reduced risk of side effects when compared to treatment with the full lowest diabetic therapeutic dose of any one of the DPP IV inhibitor, the biguanide, and the SGLT2 inhibitor in the pharmaceutical composition. In some embodiments, the treatment results in greater long term tolerability and reduced risk of side effects when compared to treatment with the full lowest diabetic therapeutic dose of the DPP IV inhibitor in the pharmaceutical composition. In some embodiments, the treatment results in greater long term tolerability and reduced risk of side effects when compared to treatment with the full lowest diabetic therapeutic dose of the biguanide in the pharmaceutical composition. In some embodiments, the treatment results in greater long term tolerability and reduced risk of side effects when compared to treatment with the full lowest diabetic therapeutic dose of the SGLT2 inhibitor in the pharmaceutical composition.

**[0235]** In some embodiments, treatment results in an improvement in diabetes and/or associated conditions that is greater than or equal to the improvement obtained with the combination of any two of the DPP IV inhibitor, the biguanide, and the SGLT2 inhibitor in the pharmaceutical composition. In some embodiments, treatment results in an improvement in diabetes and/or associated conditions that is greater than or equal to the improvement obtained with a combination of any two of the DPP IV inhibitor, the biguanide, and the SGLT2 inhibitor

in the pharmaceutical composition, wherein the dose of each the DPP IV inhibitor, the biguanide, and the SGLT2 inhibitor is about 25% of the lowest diabetic therapeutic dose. In some embodiments, treatment results in an improvement in diabetes and/or associated conditions that is greater than or equal to the improvement obtained with a combination of any two of the DPP IV inhibitor, the biguanide, and the SGLT2 inhibitor in the pharmaceutical composition, wherein the dose of each the DPP IV inhibitor, the biguanide, and the SGLT2 inhibitor is about 33% of the lowest diabetic therapeutic dose. In some embodiments, treatment results in an improvement in diabetes and/or associated conditions that is greater than or equal to the improvement obtained with a combination of any two of the DPP IV inhibitor, the biguanide, and the SGLT2 inhibitor in the pharmaceutical composition, wherein the dose of each the DPP IV inhibitor, the biguanide, and the SGLT2 inhibitor is about 50% of the lowest diabetic therapeutic dose. In some embodiments, treatment results in an improvement in diabetes and/or associated conditions that is greater than or equal to the improvement obtained with a combination of any two of the DPP IV inhibitor, the biguanide, and the SGLT2 inhibitor in the pharmaceutical composition, wherein the dose of each the DPP IV inhibitor, the biguanide, and the SGLT2 inhibitor is about 70% of the lowest diabetic therapeutic dose. In some embodiments, treatment results in an improvement in diabetes and/or associated conditions that is greater than or equal to the improvement obtained with a combination of any two of the DPP IV inhibitor, the biguanide, and the SGLT2 inhibitor in the pharmaceutical composition, wherein the dose of the DPP IV inhibitor and the biguanide are about 70% of the lowest diabetic therapeutic dose for each of the DPP IV inhibitor and the biguanide, and the dose of the SGLT2 inhibitor is about 50% of the lowest diabetic therapeutic dose for the SGLT2 inhibitor.

**[0236]** In some embodiments, the treatment results in greater long term tolerability and reduced risk of side effects when compared to treatment with a combination of any two of the DPP IV inhibitor, the biguanide, and the SGLT2 inhibitor in the pharmaceutical composition, wherein the dose of each the DPP IV inhibitor, the biguanide, and the SGLT2 inhibitor is about 50% of the lowest diabetic therapeutic dose.

**[0237]** In some embodiments, the treatment is the initial or first-line treatment of diabetes. In some embodiments, the subject has a very mild elevation of blood sugar prior to treatment. In some embodiments, the subject is not on any previous diabetic therapy prior to treatment. In some embodiments, the subject has a very mild elevation of blood sugar prior to treatment and is not on any previous diabetic therapy prior to treatment. In some embodiments, the subject has persisting elevation of blood sugar after treatment with one or two of a DPP IV inhibitor, a biguanide, or a SGLT2 inhibitor at the LDTD or higher dose.

**[0238]** This present disclosure recognizes that the use of the DPP IV inhibitor in the pharmaceutical compositions disclosed herein in some embodiments provides beneficial therapeutic effects, which include, but are not limited to, significant reduction in blood sugar, significant reduction in blood sugar among subjects with mild elevation in blood sugar, greater long term tolerability, and reduced risk of side effects.

**[0239]** It is also recognized herein that in some embodiments, the triple low-dose combination formulation described herein comprising a DPP IV inhibitor, a biguanide, and an SGLT2 inhibitor provides reductions in blood sugar greater than the LDTD of each individual drug given singly. For example, in some embodiments, a triple combination formulation comprising 70% DPP IV inhibitor, 50% biguanide, and 70% SGLT2 inhibitor provides reductions in blood sugar greater than, or substantially greater than, the LDTD of the DPP IV inhibitor, or the LDTD of biguanide, or the LDTD of the SGLT2 inhibitor, given singly. As another example, in some embodiments, a triple combination formulation comprising 50% DPP IV inhibitor, 50% biguanide, and 50% SGLT2 inhibitor provides reductions in blood sugar greater than, or substantially greater than, the LDTD of the DPP IV inhibitor, or the LDTD of biguanide or the LDTD of the SGLT2 inhibitor, given singly.

**[0240]** It is also recognized herein that in some embodiments, the triple low-dose combination formulation described herein comprising a DPP IV inhibitor, a biguanide, and an SGLT2 inhibitor provides reductions in blood sugar greater than twice the LDTD of each individual drug given singly. For example, in some embodiments, a triple combination formulation comprising 70% DPP IV inhibitor, 50% biguanide, and 70% SGLT2 inhibitor provides reductions in blood sugar greater than, or substantially greater than twice the LDTD of each individual drug given singly. As another example, in some embodiments, a triple combination formulation comprising 50% DPP IV inhibitor, 50% biguanide, and 50% SGLT2 inhibitor provides reductions in blood sugar greater than, or substantially greater than twice the LDTD of each individual drug given singly.

**[0241]** Additional Embodiments

**[0242]** Embodiments includes embodiment 1 to 92 following.

**[0243]** Embodiment 1. A pharmaceutical composition comprising:

a) a dipeptidyl peptidase IV (DPP IV) inhibitor;

b) a biguanide; and

c) a subtype 2 sodium-glucose transport protein (SGLT2) inhibitor;

wherein (a), (b), and (c) are each at about 20-75% of the lowest diabetes therapeutic dose (LDTD).

**[0244]** Embodiment 2. The pharmaceutical composition of Embodiment 1, wherein the DPP IV inhibitor is a gliptin.

**[0245]** Embodiment 3. The pharmaceutical composition of Embodiment 1 or 2, wherein the DPP-IV inhibitor is sitagliptin, vildagliptin, saxagliptin, linagliptin, gemigliptin, anagliptin, teneligliptin, alogliptin, trelagliptin, omarigliptin, evogliptin, gosogliptin, dutogliptin, or the pharmaceutically acceptable salt or hydrate thereof.

**[0246]** Embodiment 4. The pharmaceutical composition of any one of Embodiments 1-3, wherein the DPP IV inhibitor is sitagliptin or the pharmaceutically acceptable salt thereof.

**[0247]** Embodiment 5. The pharmaceutical composition of Embodiment 4, wherein the DPP IV inhibitor is sitagliptin phosphate.

**[0248]** Embodiment 6. The pharmaceutical composition of any one of Embodiments 1-5, wherein the biguanide is metformin or the pharmaceutically acceptable salt or hydrate thereof

**[0249]** Embodiment 7. The pharmaceutical composition of Embodiment 6, wherein the biguanide is metformin hydrochloride.

**[0250]** Embodiment 8. The pharmaceutical composition of Embodiment 6 or 7, wherein the metformin is formulated for immediate release.

**[0251]** Embodiment 9. The pharmaceutical composition of Embodiment 6 or 7, wherein the metformin is formulated for slow release.

**[0252]** Embodiment 10. The pharmaceutical composition of any one of Embodiments 1-9, wherein the SGLT2 inhibitor is a gliflozin.

**[0253]** Embodiment 11. The pharmaceutical composition of Embodiment 10, wherein the SGLT2 inhibitor is dapagliflozin, empagliflozin, canagliflozin, ipragliflozin (ASP-1941), tofogliflozin, remogliflozin, sergliflozin, ertugliflozin, sotagliflozin, or the pharmaceutically acceptable salt, hydrate, or combinations thereof.

**[0254]** Embodiment 12. The pharmaceutical composition of Embodiment 11, wherein the SGLT2 inhibitor is dapagliflozin or pharmaceutically acceptable salt, hydrate, or a combination thereof.

**[0255]** Embodiment 13. The pharmaceutical composition of Embodiment 12, wherein the SGLT2 inhibitor is a dapagliflozin hydrate.

**[0256]** Embodiment 14. The pharmaceutical composition of Embodiment 13, wherein the SGLT2 inhibitor is dapagliflozin propanediol monohydrate.

**[0257]** Embodiment 15. The pharmaceutical composition of any one of Embodiments 1-14, wherein the dose of each (a), (b), and (c) is from about 40% to about 75% of the lowest diabetes therapeutic dose (LDTD).

**[0258]** Embodiment 16. The pharmaceutical composition of any one of Embodiments 1-14, wherein the dose of each (a), (b), and (c) is from about 60% to about 75% of the lowest diabetes therapeutic dose (LDTD).

**[0259]** Embodiment 17. The pharmaceutical composition of any one of Embodiments 1-14, wherein the dose of each (a), (b), and (c) is from about 65% to about 75% of the lowest diabetes therapeutic dose (LDTD).

**[0260]** Embodiment 18. The pharmaceutical composition of any one of Embodiments 1-14, wherein the dose of each (a), (b), and (c) is from about 40% to about 70% of the lowest diabetes therapeutic dose (LDTD).

**[0261]** Embodiment 19. The pharmaceutical composition of any one of Embodiments 1-14, wherein the dose of each (a), (b), and (c) is from about 40% to about 60% of the lowest diabetes therapeutic dose (LDTD).

**[0262]** Embodiment 20. The pharmaceutical composition of any one of Embodiments 1-14, wherein the dose of each (a), (b), and (c) is from about 45% to about 55% of the lowest diabetes therapeutic dose (LDTD).

**[0263]** Embodiment 21. The pharmaceutical composition of any one of Embodiments 1-18, wherein the DPP IV inhibitor is about 70% of the lowest diabetes therapeutic dose (LDTD) for the DPP IV inhibitor.

**[0264]** Embodiment 22. The pharmaceutical composition of Embodiment 18, wherein the DPP IV inhibitor is sitagliptin, and the dose of sitagliptin is about 17.5 mg.

**[0265]** Embodiment 23. The pharmaceutical composition of any one of Embodiments 1-15 or 18-20, wherein the DPP IV inhibitor is about 50% of the lowest diabetes therapeutic dose (LDTD) for the DPP IV inhibitor.

**[0266]** Embodiment 24. The pharmaceutical composition of Embodiment 23, wherein the DPP IV inhibitor is sitagliptin, and the dose of sitagliptin is about 12.5 mg.

**[0267]** Embodiment 25. The pharmaceutical composition of any one of Embodiments 1-18, wherein the biguanide is about 70% of the lowest diabetes therapeutic dose (LDTD) for the biguanide.

**[0268]** Embodiment 26. The pharmaceutical composition of Embodiment 25, wherein the biguanide is metformin hydrochloride, and the dose of metformin hydrochloride is about 350 mg.

**[0269]** Embodiment 27. The pharmaceutical composition of any one of Embodiments 1-15 or 18-24, wherein the biguanide is about 50% of the lowest diabetes therapeutic dose (LDTD) for the biguanide.

**[0270]** Embodiment 28. The pharmaceutical composition of Embodiment 27, wherein the biguanide is metformin hydrochloride, and the dose of metformin hydrochloride is about 250 mg.

**[0271]** Embodiment 29. The pharmaceutical composition of any one of Embodiments 1-15 or 18-28, wherein the SGLT2 inhibitor is about 50% of the lowest diabetes therapeutic dose (LDTD) for the SGLT2 inhibitor.

**[0272]** Embodiment 30. The pharmaceutical composition of Embodiment 29, wherein the SGLT2 inhibitor is dapagliflozin, and the dose of dapagliflozin is about 2.5 mg.

**[0273]** Embodiment 31. The pharmaceutical composition of Embodiment 1, wherein the DPP IV inhibitor is sitagliptin, the biguanide is metformin, and the SGLT2 inhibitor is dapagliflozin or empagliflozin.

**[0274]** Embodiment 32. The pharmaceutical composition of Embodiment 31, wherein the dose of sitagliptin is from about 5.0 mg to about 18.75 mg, the dose of metformin is from about 100 mg to about 375 mg, and the dose of dapagliflozin is from about 1.0 mg to about 3.75 mg.

**[0275]** Embodiment 33. The pharmaceutical composition of Embodiment 31, wherein the dose of sitagliptin is from about 5.0 mg to about 18.75 mg, the dose of metformin is from about 100 mg to about 375 mg, and the dose of empagliflozin is from about 2.0 mg to about 7.5 mg.

**[0276]** Embodiment 34. The pharmaceutical composition of Embodiment 31, wherein the dose of sitagliptin is from about 10 mg to about 16.25 mg, the dose of metformin is from about 200 mg to about 325 mg, and the dose of dapagliflozin is from about 2.0 mg to about 3.25 mg.

**[0277]** Embodiment 35. The pharmaceutical composition of Embodiment 31, wherein the dose of sitagliptin is from about 10 mg to about 15 mg, the dose of metformin is from about 200 mg to about 300 mg, and the dose of dapagliflozin is from about 2 mg to about 3 mg.

**[0278]** Embodiment 36. The pharmaceutical composition of Embodiment 31, wherein the dose of sitagliptin is from about 11.25 mg to about 13.75 mg, the dose of metformin is from about 225 mg to about 275 mg, and the dose of dapagliflozin is from about 2.25 mg to about 2.75 mg.

**[0279]** Embodiment 37. The pharmaceutical composition of Embodiment 31, wherein the dose of sitagliptin is about 12.5 mg, the dose of metformin is about 250 mg, and the dose of dapagliflozin is about 2.5 mg.

**[0280]** Embodiment 38. The pharmaceutical composition of any one of Embodiments 1-11, wherein the dose of each (a), (b), and (c) is from about 30% to about 40% of the lowest diabetes therapeutic dose (LDTD).

**[0281]** Embodiment 39. The pharmaceutical composition of any one of Embodiments 1-11, wherein the dose of each (a), (b), and (c) is from about 30% to about 35% of the lowest diabetes therapeutic dose (LDTD).

**[0282]** Embodiment 40. The pharmaceutical composition of Embodiment 38 or 39, wherein the SGLT2 inhibitor is about 33% of the lowest diabetes therapeutic dose (LDTD) for the SGLT2 inhibitor.

**[0283]** Embodiment 41. The pharmaceutical composition of Embodiment 40, wherein the SGLT2 inhibitor is dapagliflozin, and the dose of dapagliflozin is about 1.65 mg.

**[0284]** Embodiment 42. The pharmaceutical composition of Embodiment 40, wherein the SGLT2 inhibitor is empagliflozin, and the dose of empagliflozin is about 3.3 mg.

**[0285]** Embodiment 43. The pharmaceutical composition of Embodiment 38, wherein the DPP IV inhibitor is sitagliptin, the biguanide is metformin, and the SGLT2 inhibitor is dapagliflozin or empagliflozin.

**[0286]** Embodiment 44. The pharmaceutical composition of Embodiment 43, wherein the dose of sitagliptin is from about 7.5 mg to about 10 mg and the dose of metformin is from about 150 mg to about 200 mg.

**[0287]** Embodiment 45. The pharmaceutical composition of Embodiment 44, wherein the SGLT2 inhibitor is dapagliflozin and the dose of dapagliflozin is from about 1.5 mg to about 2.0 mg.

**[0288]** Embodiment 46. The pharmaceutical composition of Embodiment 44, wherein the SGLT2 inhibitor is empagliflozin and the dose of empagliflozin is from about 3.0 mg to about 4.0 mg.

**[0289]** Embodiment 47. The pharmaceutical composition of Embodiment 40, wherein the dose of sitagliptin is about 8.25 mg and the dose of metformin is about 165 mg.

**[0290]** Embodiment 48. The pharmaceutical composition of Embodiment 44, wherein the SGLT2 inhibitor is dapagliflozin and the dose of dapagliflozin is about 1.65 mg.

**[0291]** Embodiment 49. The pharmaceutical composition of Embodiment 44, wherein the SGLT2 inhibitor is empagliflozin, and the dose of empagliflozin is about 3.3 mg.

**[0292]** Embodiment 50. The pharmaceutical composition of any one of Embodiments 1-11, wherein the dose of each (a), (b), and (c) is from about 20% to about 30% of the lowest diabetes therapeutic dose (LDTD).

**[0293]** Embodiment 51. The pharmaceutical composition of any one of Embodiments 1-11, wherein the dose of each (a), (b), and (c) is from about 22% to about 28% of the lowest diabetes therapeutic dose (LDTD).

**[0294]** Embodiment 52. The pharmaceutical composition of Embodiment 50 or 51, wherein the dose of the SGLT2 inhibitor is about 25% of the lowest diabetes therapeutic dose (LDTD) for the SGLT2 inhibitor.

**[0295]** Embodiment 53. The pharmaceutical composition of Embodiment 52, wherein the SGLT2 inhibitor is dapagliflozin, and the dose of dapagliflozin is about 1.25 mg.

**[0296]** Embodiment 54. The pharmaceutical composition of Embodiment 52, wherein the SGLT2 inhibitor is empagliflozin, and the dose of empagliflozin is about 2.5 mg.

**[0297]** Embodiment 55. The pharmaceutical composition of Embodiment 51, wherein the DPP IV inhibitor is sitagliptin, the biguanide is metformin, and the SGLT2 inhibitor is dapagliflozin or empagliflozin.

**[0298]** Embodiment 56. The pharmaceutical composition of Embodiment 55, wherein the dose of sitagliptin is from about 5mg to about 7.5 mg and the dose of metformin is from about 100 mg to about 150 mg.

**[0299]** Embodiment 57. The pharmaceutical composition of Embodiment 56, wherein the SGLT2 inhibitor is dapagliflozin, and the dose of dapagliflozin is about 1.0 mg.

**[0300]** Embodiment 58. The pharmaceutical composition of Embodiment 56, wherein the SGLT2 inhibitor is empagliflozin, and the dose of empagliflozin is about 2.0 mg.

**[0301]** Embodiment 59. The pharmaceutical composition of Embodiment 55, wherein the dose of sitagliptin is about 6.25 mg and the dose of metformin is about 150 mg.

**[0302]** Embodiment 60. The pharmaceutical composition of Embodiment 59, wherein the SGLT2 inhibitor is dapagliflozin, and the dose of dapagliflozin is about 1.5 mg.

**[0303]** Embodiment 61. The pharmaceutical composition of Embodiment 59, wherein the SGLT2 inhibitor is empagliflozin, and the dose of empagliflozin is about 3.0 mg.

**[0304]** Embodiment 62. The pharmaceutical composition of any one of Embodiments 1-61, wherein (a), (b), and (c) are provided in one formulation.

**[0305]** Embodiment 63. The pharmaceutical composition of any one of Embodiments 1-61, wherein (a), (b), and (c) are each provided in a separate formulation.

**[0306]** Embodiment 64. The pharmaceutical composition of any one of Embodiments 1-61, wherein two of the (a), (b), and (c) are provided in one formulation.

**[0307]** Embodiment 65. The pharmaceutical composition of any one of Embodiments 1-64, wherein the pharmaceutical composition is suitable for oral administration.

**[0308]** Embodiment 66. The pharmaceutical composition of any one of Embodiments 1-65, wherein the pharmaceutical composition is in the form of pill, tablet or capsule.

**[0309]** Embodiment 67. A pharmaceutical composition comprising:

a) a dipeptidyl peptidase IV (DPP IV) inhibitor;

b) a biguanide; and

c) a subtype 2 sodium-glucose transport protein (SGLT2) inhibitor;

wherein (a) and (b) are each at about 65%-75% of the lowest diabetes therapeutic dose (LDTD), and (c) is at about 45%-55% of the lowest diabetes therapeutic dose (LDTD).

**[0310]** Embodiment 68. The pharmaceutical composition of Embodiment 67, wherein the DPP IV inhibitor is sitagliptin and the dose of sitagliptin is from about 16.25 mg to about 18.75 mg.

**[0311]** Embodiment 69. The pharmaceutical composition of Embodiment 67, wherein the biguanide is metformin and the dose of metformin is from about 325 mg to about 375 mg.

**[0312]** Embodiment 70. The pharmaceutical composition of Embodiment 67, wherein the SGLT2 inhibitor is dapagliflozin, and the dose of dapagliflozin from about 2.25 mg to about 2.75 mg.

**[0313]** Embodiment 71. The pharmaceutical composition of Embodiment 67, wherein the SGLT2 inhibitor is empagliflozin, and the dose of empagliflozin from about 4.5 mg to about 7.5 mg.

**[0314]** Embodiment 72. The pharmaceutical composition of Embodiment 67, wherein the DPP IV inhibitor is at about 70% of the lowest diabetes therapeutic dose (LDTD) for the DPP IV inhibitor.

**[0315]** Embodiment 73. The pharmaceutical composition of Embodiment 67 or 71, wherein the biguanide is at about 70% of the lowest diabetes therapeutic dose (LDTD) for the biguanide.

**[0316]** Embodiment 74. The pharmaceutical composition of any one of Embodiments 67 or 72-73, wherein the SGLT2 inhibitor is at about 50% of the lowest diabetes therapeutic dose (LDTD) for the SGLT2 inhibitor.

**[0317]** Embodiment 75. The pharmaceutical composition of any one of Embodiments 67 or 72-74, wherein the DPP IV inhibitor is sitagliptin, the biguanide is metformin, and the SGLT2 inhibitor is dapagliflozin or empagliflozin.

**[0318]** Embodiment 76. The pharmaceutical composition of Embodiment 75, wherein the dose of sitagliptin is about 17.5 mg, the dose of metformin is about 350 mg, and the dose of dapagliflozin is about 2.5 mg.

**[0319]** Embodiment 77. The pharmaceutical composition of Embodiment 75, wherein the dose of sitagliptin is about 17.5 mg, the dose of metformin is about 350 mg, and the dose of empagliflozin is about 5.0 mg.

**[0320]** Embodiment 78. The pharmaceutical composition of any one of Embodiments 67 or 72-74, wherein the DPP IV inhibitor is sitagliptin and the dose of the sitagliptin is about 17.5 mg.

**[0321]** Embodiment 79. The pharmaceutical composition of any one of Embodiments 67 or 72-74, wherein the biguanide is metformin and the dose of the metformin is about 350 mg.

**[0322]** Embodiment 80. The pharmaceutical composition of any one of Embodiments 67 or 72-74, wherein the SGLT2 inhibitor is dapagliflozin and the dose of the dapagliflozin is about 2.5 mg.

**[0323]** Embodiment 81. The pharmaceutical composition of any one of Embodiments 67 or 72-74, wherein the SGLT2 inhibitor is empagliflozin and the dose of the empagliflozin is about 5.0 mg.

**[0324]** Embodiment 82. The pharmaceutical composition of any one of Embodiments 67-82, wherein (a), (b), and (c) are provided in one formulation.

**[0325]** Embodiment 83. The pharmaceutical composition of any one of Embodiments 67-82, wherein (a), (b), and (c) are each provided in a separate formulation.

**[0326]** Embodiment 84. The pharmaceutical composition of any one of Embodiments 67-82, wherein two of the (a), (b), and (c) are provided in one formulation.

**[0327]** Embodiment 85. The pharmaceutical composition of any one of Embodiments 67-84, wherein the pharmaceutical composition is suitable for oral administration.

**[0328]** Embodiment 86. The pharmaceutical composition of any one of Embodiments 67-85, wherein the pharmaceutical composition is in the form of pill, tablet or capsule.

**[0329]** Embodiment 87. The pharmaceutical composition of any one of Embodiments 67-86, wherein the metformin is formulated for immediate release.

**[0330]** Embodiment 88. The pharmaceutical composition of any one of Embodiments 67-86, wherein the metformin is formulated for slow release.

**[0331]** Embodiment 89. A method of treating diabetes in a subject in need thereof comprising administering the pharmaceutical composition of any one of Embodiments 1-88.

**[0332]** Embodiment 90. The method of Embodiment 89, wherein the subject has persisting elevation of blood sugar after treatment with one or two of a DPP IV inhibitor, a biguanide, or an SGLT2 inhibitor at the LDTD or higher dose.

**[0333]** Embodiment 91. The method of Embodiment 89, wherein the administration of the pharmaceutical composition is an initial or first-line treatment of diabetes.

**[0334]** Embodiment 92. A method of improving, slowing the progression of, or delaying a metabolic disorder such as diabetes mellitus, impaired glucose tolerance, impaired fasting blood glucose, hyperglycemia, postprandial hyperglycemia, overweight, obesity, metabolic syndrome, impaired renal function, gestational diabetes, new onset diabetes after transplantation (NODAT) and complications associated therewith, and post-transplant metabolic syndrome (PTMS) and complications associated therewith, comprising administering to a subject in need thereof the pharmaceutical composition of any one of Embodiments 1-88.

**[0335]** The disclosure will be further understood by the following non-limiting examples.

## EXAMPLES

**[0336]** The examples set forth below are provided to give those of ordinary skill in the art with a complete disclosure and description of how to make and use the claimed embodiments, and are not intended to limit the scope of what is disclosed herein. Modifications that are obvious to persons of skill in the art are intended to be within the scope of the following claims.

**[0337] Example 1: Study of the effects of a combination of a DPP IV inhibitor, a biguanide, and an SGLT2 inhibitor on Whole Blood Glucose (WBG), Glycated Hemoglobin (HbA1c), Insulin, and Creatinine levels.**

**[0338] Study design**: A Zucker rat model of diet induced diabetes (Zucker Diabetic Fatty Rats) was used. The study was a parallel randomized study. 10 animals were used in each of 4 treatment groups. The treatment included 21 days of treatment.

**[0339] Main study outcomes**: Glucose (measured at multiple time points before and during treatment); HbA1c (before and at the end of the treatment period); Insulin (before and at the end of the treatment period); Creatinine (before and at the end of the treatment period).

**Table 6**. Treatment groups and doses in ultra-low-dose glucose-lowering drug combinations

| Group | Test Article | | Human Dose Level | Animal Dose Level | Animal Concentration | Animal Volume |
|---|---|---|---|---|---|---|
| | | | (mg) | (mg/kg) | (mg/mL) | (mL/kg) |
| 1 | Vehicle | Metformin | 0 | 0 | 0 | 10 |
| 2 | Composition A | Sitagliptin | 17.5 | 1.545 | 0.1545 | 10 |
| | | Dapagliflozin | 2.5 | 0.220 | 0.0220 | |
| | | Metformin | 350 | 30.833 | 3.0833 | |
| 3 | Composition B | Sitagliptin | 17.5 | 1.545 | 0.1545 | 10 |
| | | Empagliflozin | 5.0 | 0.440 | 0.0440 | |
| | | Metformin | 350 | 30.833 | 3.0833 | |
| 4 | 1K-MET | Metformin | 1000 | 88.095 | 8.8095 | 10 |

**[0340]** Ten Zucker Diabetic Fatty (ZDF) rats were randomly allocated to each of the four different treatment groups (Table 6). Whole blood glucose measurements were made from 4 days before dosing, then daily until for 8 days, then at reduced frequency. Measurements of HbA1c and creatinine were made the day prior to dosing, then at days 9 and 21. Insulin measurements were made the day prior to dosing then on day 20. A clinical chemistry sample from one animal in the vehicle group on day 9 was not available so there is a missing measurement for creatinine and HbA1c on that day

**[0341] Methods**

**[0342]** *Statistical Analysis*

**[0343]** Whole blood glucose, HbA1c and Creatinine were each analyzed using a linear mixed mode (proc mixed in SAS/STAT 14.2). For WBC, unstructured, autoregressive, exchangeable and Toeplitz correlation structures for repeated measurements across the study were compared using Akaike Information Criterion and Bayesian Information Criterion. The Toeplitz correlation structure was selected as the best fitting structure. For HbA1c and Creatinine an exchangeable structure was used as there were only two measurements. Denominator degrees of freedom were calculated using the between-within subject method. The model included coefficients for baseline measurement (the closest measurement preceding dosing), type of drug treatment, time and an interaction between drug treatment and time. Marginal means (with 95% confidence intervals) for the measurement at each period for each drug were estimated, and an overall marginal mean (with 95% confidence interval) for measurements across time was estimated using weights that reflect the differing amounts of time in each measurement period (assuming each measurement represented all time since the preceding measurement). A likelihood ratio test of overall differences between treatment was initially used, if significant ($p<0.05$) then we tested for differences between each combination of treatments.

**[0344]** For Insulin, a baseline measure and a measurement at day 20 was available, so the ANCOVA approach (linear regression with the baseline value as a covariate) was used to test for differences in this measurement between treatments. The interaction between baseline value and treatment was tested but there was no evidence of an interaction, therefore the main effects were retained.

**[0345]** To test for robustness of the linear mixed model and ANCOVA models a bootstrapped 95% CI (percentile method) for the weighted marginal mean of measurements across the entire study period or single outcome measurement using 2000 replicates was estimated. The bootstrap sampling was done on individual animal (using complete measurements), with stratification by treatment type.

**[0346] Results**

**[0347]** It was found that there is an overall difference among treatments for the primary outcome WBG ($p<0.001$, Table 7), and the secondary outcomes of HbA1c ($p<0.0001$, Table 8), Insulin ($p<0.0001$, Table 9), and Serum Creatinine ($p<0.0001$, Table 10).

**[0348] Table 7**. Number of available measurements for analysis by outcome, timing, and treatment

**Table 7**.

| Outcome | Days from dosing | Vehicle | Composition A | Composition B | 1K-MET |
|---|---|---|---|---|---|
| Serum Creatinine | 9 | 9 | 10 | 10 | 10 |

| Outcome | Days from dosing | Vehicle | Composition A | Composition B | 1K-MET |
|---|---|---|---|---|---|
| | 21 | 10 | 10 | 10 | 10 |
| Whole Blood Glucose | 1 | 10 | 10 | 10 | 10 |
| | 2 | 10 | 10 | 10 | 10 |
| | 3 | 10 | 10 | 10 | 10 |
| | 4 | 10 | 10 | 10 | 10 |
| | 5 | 10 | 10 | 10 | 10 |
| | 6 | 10 | 10 | 10 | 10 |
| | 7 | 10 | 10 | 10 | 10 |
| | 8 | 10 | 10 | 10 | 10 |
| | 12 | 10 | 10 | 10 | 10 |
| | 14 | 10 | 10 | 10 | 10 |
| | 16 | 10 | 10 | 10 | 10 |
| | 19 | 10 | 10 | 10 | 10 |
| | 21 | 10 | 10 | 10 | 10 |
| HbA1c | 9 | 9 | 10 | 10 | 10 |
| | 21 | 10 | 10 | 10 | 10 |
| Insulin | 20 | 10 | 10 | 10 | 10 |

**Table 8**. Effects of combinations of glucose lowering medications on whole blood glucose (mg/dL)

| Comparison | Level | Estimate (95% CI) | P-value |
|---|---|---|---|
| Overall difference between treatments | | | <.0001 |
| Overall level in WBG after dosing (95% CI) | Vehicle | 418.3 (397.4 - 439.2) | |
| | Composition A | 213.2 (192.3 - 234.0) | |
| | Composition B | 371.5 (350.7 - 392.4) | |
| | 1K-MET | 442.7 (421.8 - 463.5) | |
| Pairwise comparisons | Vehicle vs Composition A | -205.2 (-234.7 - -175.6) | <.0001 |
| | Vehicle vs Composition B | -46.8 (-76.3 - -17.3) | 0.0026 |
| | Vehicle vs 1K-MET | 24.4 (-5.2 - 53.9) | 0.1035 |
| | Composition A vs 1K-MET | 229.5 (200.0 - 259.0) | <.0001 |
| | Composition B vs Composition A | -158.4 (-187.9 - -128.9) | <.0001 |

| Comparison | Level | Estimate (95% CI) | P-value |
|---|---|---|---|
| | Composition B vs 1K-MET | 71.1 (41.6 - 100.7) | <.0001 |

**Table 9.** Effects of combinations of glucose lowering medications on HbA1c (%)

| Comparison | Level | Estimate (95% CI) | P-value |
|---|---|---|---|
| Overall difference between treatments | | | <.0001 |
| Overall level in WBG after dosing (95% CI) | Vehicle | 6.86 (6.63 - 7.10) | |
| | Composition A | 4.75 (4.53 - 4.98) | |
| | Composition B | 5.83 (5.61 - 6.06) | |
| | 1K-MET | 6.52 (6.29 - 6.75) | |
| Pairwise comparisons | Vehicle vs Composition A | -2.11 (-2.44 - -1.78) | <.0001 |
| | Vehicle vs Composition B | -1.03 (-1.36 - -0.70) | <.0001 |
| | Vehicle vs 1K-MET | -0.35 (-0.68 - -0.01) | 0.0410 |
| | Composition A vs 1K-MET | 1.76 (1.44 - 2.08) | <.0001 |
| | Composition B vs Composition A | -1.08 (-1.40 - -0.76) | <.0001 |
| | Composition B vs 1K-MET | 0.68 (0.36 - 1.00) | 0.0001 |

**[0349]** For WBG, Composition A ($p<0.0001$) and Composition B ($p=0.0026$) groups were significantly lower across the post-dose measurement period. Composition A lowered WBG by 205 mg/dL relative to the vehicle, and Composition B lowered WBG by 47 mg/dL relative to the vehicle. There was significant interaction between time and treatment ($p<0.0001$), with WBG increasing by small amount in most of the treatments except for Composition B (**FIG. 1**). Composition B had a similar WBG to other treatments immediately after dosing (day 1), but then declined and stayed lower for the remainder of the study period.

**[0350]** Evidence of differences among study groups was found in HbA1c throughout the study ($p<0.0001$, Table 9), with Composition A ($p<0.0001$) and Composition B ($p<0.0001$) having lower HbA1c than the vehicle, and all the other drug combinations ($p<0.001$). The estimated overall level of HbA1c in the Composition A group (4.75) estimated to be 1.1% absolutely lower than Composition B (5.83, $p<0.0001$). The HbA1c level over the time-course of the study varied between treatments (**FIG. 2**, interaction: $p<0.0001$). The HbA1c in the Composition A group stayed approximately the same as at baseline. HbA1c increased in Composition B over time but not as much as the other treatments.

**[0351]** Insulin measurements were significantly different among treatments ($p<0.0001$, Table 10) with Composition A ($p<0.0001$) and Composition B ($p=0.0054$) having higher insulin levels

at 20 days than the vehicle, and no evidence of a difference between the vehicle and 1K-MET (p=0.2955). The Composition A group achieved an estimated average of 10,186 (pg/mL) by day 20, which is significantly greater (p<0.0001) than Composition B (5259 pg/mL).

**Table 10.** Effects of combinations of glucose lowering medications on Insulin (pg/mL)

| Comparison | Level | Estimate (95% CI) | P-value |
|---|---|---|---|
| Overall difference between treatments | | | <.0001 |
| Overall level in WBG after dosing (95% CI) | Vehicle | 2947 (1822 - 4072) | |
| | Composition A | 10186 (9062 - 11310) | |
| | Composition B | 5259 (4138 - 6380) | |
| | 1K-MET | 3879 (2757 - 5001) | |
| Pairwise comparisons | Vehicle vs Composition A | 7239 (5644 - 8834) | <.0001 |
| | Vehicle vs Composition B | 2312 (723 - 3901) | 0.0053 |
| | Vehicle vs 1K-MET | 932 (-660 - 2524) | 0.2445 |
| | Composition A vs 1K-MET | -6307 (-7892 - -4722) | <.0001 |
| | Composition B vs Composition A | 4927 (3341 - 6514) | <.0001 |
| | Composition B vs 1K-MET | -1380 (-2965 - 206) | 0.0865 |

**[0352]** There was significant (p<0.0001) difference in average Creatinine levels between treatment groups. Creatinine levels in the Composition A (p<0.0001) and Composition B (p=0.0082) groups were lower than the vehicle group. The Composition A group had a significantly lower (p<0.001) level of creatinine (0.69 mg/dL) than the Composition B group (0.75 mg/dL). Creatinine levels were similar throughout the study in the Composition A and Composition B groups, with levels increasing in the other study groups (**FIG. 3**).

**Table 11.** Effects of combinations of glucose lowering medications on Creatinine (mg/dL)

| Comparison | Level | Estimate (95% CI) | P-value |
|---|---|---|---|
| Overall difference between treatments | | | <.0001 |
| Overall level in WBG after dosing (95% CI) | Vehicle | 0.78 (0.76 - 0.79) | |
| | Composition A | 0.69 (0.68 - 0.70) | |
| | Composition B | 0.75 (0.74 - 0.76) | |
| | 1K-MET | 0.79 (0.77 - 0.80) | |
| Pairwise comparisons | Vehicle vs Composition A | -0.09 (-0.10 - -0.07) | <.0001 |
| | Vehicle vs Composition B | -0.03 (-0.04 - -0.01) | 0.0082 |
| | Vehicle vs 1K-MET | 0.01 (-0.01 - 0.03) | 0.2565 |

| Comparison | Level | Estimate (95% CI) | P-value |
|---|---|---|---|
| | Composition A vs 1K-MET | 0.10 (0.08 - 0.12) | <.0001 |
| | Composition B vs Composition A | -0.06 (-0.08 - -0.04) | <.0001 |
| | Composition B vs 1K-MET | 0.04 (0.02 - 0.06) | 0.0003 |

**Table 12** Estimates of outcome by treatment with bootstrap medians and confidence intervals

| Measure | Vehicle | Composition A | Composition B | 1K-MET |
|---|---|---|---|---|
| Whole blood glucose (mg/dL) | 418.6 (399.8 - 439.4) | 213.3 (186.7 - 238.5) | 372.5 (334.7 - 400.8) | 443.4 (419.8 - 465.0) |
| HbA1c (%) | 6.86 (6.60 - 7.11) | 4.75 (4.56 - 4.95) | 5.85 (5.50 - 6.12) | 6.53 (6.24 - 6.82) |
| Insulin (pg/m) | 2920 (2119 - 3828) | 10176 (8675 - 11747) | 5240 (4084 - 6531) | 3867 (2914 - 4874) |
| Creatinine (mg/dL) | 0.78 (0.76 - 0.79) | 0.69 (0.67 - 0.70) | 0.75 (0.74 - 0.76) | 0.79 (0.77 - 0.80) |

**[0353]** Both of the Composition A and Composition B groups showed lower WBC, HbA1c, reatinine, and higher insulin levels relative to the control group. The 1K-MET group, on the other hand, showed essentially no difference for all the measurements compared to the control.

**[0354]** ULD Compositions A and B reduced blood glucose and HbA1c suggesting a potential therapeutic effect at ultra-low doses. ULD Compositions A and B prevented or reduced the fall in insulin suggesting preserved pancreatic beta-cell function at ultra-low doses. Similarly, ULD Compositions A and B prevented or reduced the increase in creatinine suggesting preserved renal function at ultra-low doses. The effects of triple ULD combinations that included an SGLT-2 antagonist were greater than those of a ULD combination that did not include an SGLT-2 antagonist, suggesting drug-specific treatment benefits. The effects of triple ULD combinations that included an SGLT-2 antagonist were greater than those of standard-dose metformin. The effects of Composition A on all outcomes were greater than Composition B, indicating differences in the effects of ULD dapagliflozin compared with ULD empagliflozin

**[0355] Example 2. Analysis of Glucose and Insulin Profiles in Patients with Type 2 Diabetes**

**[0356]** The purpose of this study was to evaluate the pharmacodynamics (glucose-lowering effects) and tolerability of Composition A in patients with diabetes mellitus.

**[0357]** In the present study, thirty adult patients with type 2 diabetes (23 females and 7 males), either treatment naïve, previously treated or currently treated with only one glucose lowering therapeutic class excluding insulin and glucagon like peptide-1 analogues, were randomized to

receive either placebo or Composition A comprising 350 mg of metformin, 17.5 mg of sitagliptin, and 2.5 mg of dapagliflozin in a 3 treatment, 3 sequence, 3 period, crossover study, with one week washout in between periods as shown in **Fig 5**. The primary and secondary endpoints were the mean absolute change in plasma glucose and serum insulin respectively at 2 hour (h) post-prandial from pre-prandial following the administration of a single dose of the treatments. The tertiary outcomes were the 120-minutes and 210-minutes of the area under the concentration-time curve (AUC) of plasma glucose and serum insulin post-meal, and the 120-minutes and 240-minutes of the area under the concentration-time curve (AUC) of plasma glucose and serum insulin post-dose. An ad hoc analysis was performed to determine the differences between the study groups in the mean absolute change in plasma glucose and serum insulin from pre-prandial at the following time points after the administration of a single dose of the study treatments: 1, 1.5, 2, 2.5, 3, 3.5 and 4 h.

**[0358]** Participating patients withheld taking any glucose-lowering therapy 24 h prior to the screening visit and for 7 days prior to the study visits and until the study exit. During the study visits, blood samples were collected from the participants before the administration of a single dose of the randomized treatment and at the following times after treatment administration: 0.5, 1, 1.5, 2, 2.5, 3, 3.5 and 4 h. Participants consumed a standard meal (550 kcal; composed of 55% carbohydrate, 15% protein, and 30% fat) immediately after the 0.5 h blood collection. Measurement of plasma glucose and serum insulin were performed on all samples by validated methods. Plasma glucose was measured.

**[0359] Methods**

**[0360]** *Statistical Analysis*

**[0361]** Data for each treatment group were pooled. A one-way analysis of variance (ANOVA) was performed to examine the differences between treatments in the primary (mean absolute change in plasma glucose at 2 h post-prandial from pre-prandial) and secondary endpoint (mean absolute change in serum insulin at 2 h post-prandial from pre-prandial) using SPSS version 17.0. Post hoc multiple pairwise comparisons were performed using the Tukey test. The $AUC_{120min}$ and $AUC_{210min}$ of glucose and insulin post-meal and the $AUC_{120min}$ and $AUC_{240min}$ post-dose were calculated using the standard trapezoidal method. WinNonlin version 8.2 was used to compare pairs of the study treatments and to estimate the sequence and period effects. An ad hoc analysis using R Statistical Programming version 3.6.1 was performed to determine the differences between the study groups in the mean absolute change in plasma glucose and serum insulin from pre-prandial concentrations (0.5 h collection time point) at the following time points after the administration of a single dose of the study treatments: 1, 1.5, 2, 2.5, 3, 3.5 and 4 h. A p-value $< 0.05$ was considered statistically significant.

**[0362] Results**

**[0363]** The baseline characteristics are summarized in **Table 13**. Thirty patients with type 2 diabetes were recruited in the present study. Baseline plasma glycated hemoglobin (HBA1c) and fasting plasma glucose in the participating patients ranged from ≥6.1% to ≤11.9 % and >119 to 260 mg/dL, respectively (**Table 13**).

**Table 13.** Demographics and characteristics of the study population at screening

| Subject ID | Gender (M / F) | Age (y) | Body weight (kg) | Height (cm) | BMI ($kg/m^2$) | Duration of type 2 diabetes (y) | $HBA_{1c}$ (%) | FPG (mg/dL) | eGFR (mL/min/1.73 $m^2$) |
|---|---|---|---|---|---|---|---|---|---|
| S-01 | F | 59 | 64 | 148 | 29.2 | 3 | 10.7 | 180 | 137 |
| S-02 | M | 47 | 76 | 161 | 29.3 | 6 | 7.5 | 199 | 145 |
| S-03 | F | 44 | 75 | 147 | 34.7 | 4 | 11.9 | 206 | 196 |
| S-04 | F | 48 | 115 | 148 | 52.5 | 19 | 8.4 | 169 | 125 |
| S-05 | F | 53 | 59 | 148 | 26.9 | 2 | 11.6 | 198 | 151 |
| S-06 | F | 52 | 45 | 142 | 22.3 | 1 | 8.1 | 129 | 72 |
| S-07 | M | 56 | 51 | 158 | 20.4 | 3 | 9.3 | 188 | 157 |
| S-08 | M | 62 | 76 | 161 | 29.3 | 2 | 7 | 139 | 92 |
| S-09 | F | 45 | 50 | 135 | 27.4 | 2 | 8.4 | 190 | 142 |
| S-10 | M | 43 | 74 | 170 | 25.6 | 3 | 6.5 | 157 | 73 |
| S-11 | F | 35 | 66 | 160 | 25.8 | 1 | 8.5 | 221 | 156 |
| S-12 | F | 59 | 52 | 154 | 21.9 | 1 | 7.1 | 159 | 107 |
| S-13 | F | 46 | 54 | 156 | 22.2 | 2 | 10.3 | 219 | 148 |
| S-14 | F | 48 | 60 | 149.5 | 26.9 | 2 | 11 | 190 | 48 |
| S-15 | F | 46 | 64 | 152 | 27.7 | 10 | 7.9 | 149 | 132 |
| S-16 | F | 53 | 60 | 157 | 24.3 | 3 | 10.9 | 235 | 183 |
| S-17 | F | 50 | 71 | 156 | 29.2 | 9 | 10.5 | 240 | 165 |
| S-18 | F | 54 | 51 | 141 | 25.7 | 6 | 7.9 | 157 | 120 |
| S-19 | F | 55 | 54 | 152 | 23.4 | 1 | 11.2 | 223 | 97 |
| S-20 | M | 46 | 105 | 167 | 37.7 | 5 | 6.1 | 120 | 108 |
| S-21 | F | 43 | 58 | 150.5 | 25.6 | 3 | 9.1 | 160 | 180 |
| S-22 | M | 45 | 65 | 170 | 22.5 | 2 | 8.2 | 240 | 60 |
| S-23 | F | 43 | 104 | 161 | 40.1 | 3 | 10.3 | 234 | 112 |
| S-24 | F | 42 | 82 | 161 | 31.6 | 6 | 9.1 | 180 | 94 |
| S-25 | F | 41 | 103 | 155 | 42.9 | 1 | 6.6 | 119 | 129 |
| S-26 | F | 45 | 77 | 152 | 33.3 | 1 | 8.3 | 141 | 59 |
| S-27 | F | 51 | 55 | 149 | 24.8 | 1 | 10.1 | 260 | 132 |
| S-28 | F | 39 | 70 | 156 | 28.8 | 6 | 11.5 | 219 | 106 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| S-29 | M | 54 | 66 | 165.5 | 24.1 | 3 | 8.2 | 199 | 79 |
| S-30 | F | 58 | 87 | 150.5 | 38.4 | 10 | 8.5 | 216 | 83 |
| Summary | 23 F (77%) 7 M (23%) | 48.7 ± 6.6 | 69.6 ± 18.1 | 154.4 ± 8.3 | 29.2 ± 7.2 | 4.0 ± 3.9 | 9.0 ± 1.7 | 188.1 ± 39.5 | 119.0 ± 39.6 |
| a. Summary presented as number (percentage) or mean ± SD. BMI= body mass index, eGFR= estimated glomerular filtration rate, FPG= fasting plasma glucose, $HBA_{1c}$= glycated hemoglobin. | | | | | | | | | |

**[0364]** In terms of efficacy, there was an overall statistically significant difference among treatments for the primary endpoint ($p<0.05$, **Table 14**), and the secondary endpoint ($p<0.05$, **Table 15**), and the tertiary outcomes ($p<0.05$, **Table 16**).

**Table 14.** The effect of a single dose of the study treatments on the 2 hour post-prandial plasma glucose (2 h PPG) from pre-prandial in patients with type 2 diabetes (n=30)

| **Comparison** | **Treatment** | **Estimate (95% CI)** | **p-value** |
|---|---|---|---|
| Pre-prandial plasma glucose (95% CI) | Placebo | 221.6 (192.8, 250.4) | |
| | Composition A | 233.1 (202.5, 263.6) | |
| 2 h PPG (95% CI) | Placebo | 260.13 (228.4, 291.9) | |
| | Composition A | 209.9 (180.8, 239.1) | |
| Pairwise comparison (Tukey Test) | Composition A vs Placebo | -61.7 (-77.9, -45.4) | $5.0 \times 10^{-9*}$ |

*Statistically significant

**Table 15.** The effect of a single dose of the study treatments on the 2 hour post-prandial serum insulin from pre-prandial in patients with type 2 diabetes (n=30).

| **Comparison** | **Treatment** | **Estimate (95% CI)** | **P-value** |
|---|---|---|---|
| Pre-prandial serum insulin (95% CI) | Placebo | 12.3 (9.8, 14.7) | |
| | Composition A | 14.5 (11.2, 17.78) | |
| 2 h post-prandial serum insulin (95% CI) | Placebo | 28.7 (22.9, 34.6) | |
| | Composition A | 26.8 (20.6, 33.0) | |
| Pairwise comparison (Tukey Test) Measurement 1 | Composition A vs Placebo | -4.1 (-6.2, 14.5) | 0.6 |

*Statistically significant

**Table 16.** The tertiary endpoints following the administration of a single dose of the study treatments in patients with type 2 diabetes (n=30).

| Comparison | Treatment | Mean ± SD | P-value |
|---|---|---|---|
| **Area under the concentration-time curve of plasma glucose (mg.h/dL)** | | | |
| $AUC_{0-120}$ post-meal | Placebo | 520.3 ± 159.7 | |
| | Composition A | 463.6 ± 157.3 | |
| Pairwise comparison | Composition A vs. Placebo | | 0.002** |
| AUC0-210 post-meal | Placebo | 883.5 ± 281.3 | |
| | Composition A | 748.6 ± 263.8 | |
| Pairwise comparison | Composition A vs. Placebo | | 0.00005* |
| $AUC_{0-120}$ post-dose | Placebo | 500.2 ± 157.8 | |
| | Composition A | 473.6 ± 158.0 | |
| Pairwise comparison | Composition A vs. Placebo | | 0.1 |
| $AUC_{0-240}$ post-dose | Placebo | 996.8 ± 320.4 | |
| | Composition A | 868.2 ± 302.3 | |
| Pairwise comparison | Composition A vs. Placebo | | 0.0003* |
| **Area under the concentration-time curve (AUC) of serum insulin (µIU.h/L)** | | | |
| $AUC_{0-120}$ post-meal | Placebo | 51.6 ± 24.8 | |
| | Composition A | 49.9 ± 29.2 | |
| Pairwise comparison | Composition A vs. Placebo | | 0.3 |
| $AUC_{0-210}$ post-meal | Placebo | 87.4 ± 41.0 | |
| | Composition A | 83.2 ± 47.03 | |
| Pairwise comparison | Composition A vs. Placebo | | 0.2 |
| $AUC_{0-120}$ post-dose | Placebo | 43.3 ± 20.8 | |
| | Composition A | 43.9 ± 26.1 | |

| | | | |
|---|---|---|---|
| Pairwise comparison | Composition A vs. Placebo | | 0.7 |
| $AUC_{0-240}$ post-dose | Placebo | 93.9 ± 44.0 | |
| | Composition A | 90.7 ± 51.4 | |
| Pairwise comparison | Composition A vs. Placebo | | 0.3 |

*Statistically significant p-value < 0.05

**[0365]** In terms of safety and tolerability, no adverse events were associated with the administration of a single dose of either placebo or Composition A in patients with type 2 diabetes (n=30).

**[0366]** *Effect on Plasma Glucose*

**[0367]** *Time course of plasma glucose*: The time course of plasma glucose following a single dose of Composition A and placebo is presented in **Fig. 6**. In the placebo group, plasma glucose increased after the standard meal, as would be expected, by a mean of 58 mg/dL over the pre-prandial concentration, achieving its peak at the 1.5 h time point (1 h post-prandial), then plasma glucose started to decrease gradually returning to approximately the pre-prandial concentration at the 4 h collection time point. By contrast, in the Composition A group, plasma glucose has slightly and insignificantly increased by a mean of 10.1 mg/dL (achieved at the 1.5 h collection time point) over the pre-prandial concentration, then plasma glucose decreased steadily until the last collection time point (4 h). By contrast to placebo, in the Composition A group, plasma glucose stayed above the pre-prandial concentration for approximately 45 minutes in the Composition A, then remained below the pre-prandial concentrations for the rest of the collection time points (2, 2.5, 3, 3.5 and 4 h).

**[0368]** *Primary endpoint*: The primary endpoint was the mean absolute change in the 2 h post-prandial plasma glucose (2 h PPG) from pre-prandial. Composition A significantly reduced the plasma concentrations of glucose at this endpoint compared to placebo (**Table 14** and **Fig. 6**). The difference in the mean absolute change in the 2 h PPG from pre-prandial between the Composition A and placebo groups was -61.7 mg/dL, which is statistically significant ($p=5.0 \times 10^{-9}$, **Table 14**).

**[0369]** *Ad hoc analysis*: Composition A achieved significantly lower plasma glucose over the entire 1-4 h sampling window compared to placebo as seen in **Table 17**. The differences in the mean absolute change in plasma glucose from pre-prandial at the 1 to 4 h post-dose time points between the Composition A and placebo groups were statistically significant (**Table 17**). Over this time interval (1-4 h post-dose), the differences in the mean absolute change in plasma

glucose from pre-prandial between the Composition A and placebo groups ranged from -24.1 to -64.7 mg/dL (**Table 17**). The glucose-lowering effects of Composition A peaked at the 2.5 h collection time point and was maintained until the last sampling collection time point (**Table 17**).

**Table 17.** The effect of a single dose of the study treatments on the absolute change in plasma glucose from pre-prandial in patients with type 2 diabetes (n=30).

| **Plasma glucose (mg/dL)** | | |
|---|---|---|
| Collection time points post-dose | Overall p-value | Composition A vs Placebo |
| 1 h | $1.0 \times 10^{-5*}$ | -24.1 (-35.4, -12.9; 0.000005*) |
| 1.5 h | $2.1 \times 10^{-12*}$ | -47.9 (-61.2, -34.7; 0.0000000*) |
| 2 h | $1.1 \times 10^{-12*}$ | -56.4 (-71.8, -40.9; 0.0000000*) |
| 2.5 h | $1.2 \times 10^{-13*}$ | -61.7 (-77.9, -45.4; 0.0000000*) |
| 3 h | $1.1 \times 10^{-13*}$ | -64.7 (-82.5 -46.8; 0.0000000*) |
| 3.5 h | $9.1 \times 10^{-14*}$ | -64.4 (-83.04703 -45.8; 0.0000000*) |
| 4 h | $1.4 \times 10^{-12*}$ | -61.9 (-81.8, -41.9; 0.0000000*) |

*Statistically significant

**[0370]** *Effect on Serum Insulin*

**[0371]** *Time course of serum insulin*: The time course of serum insulin in the Composition A and placebo groups was by and large similar as seen in **Fig. 7**. In both groups, serum insulin increased and decreased to somewhat similar concentrations following the standard meal (**Fig. 7**). Of note, in both groups, serum insulin did not recover to the pre-prandial concentrations by the 4 h time point.

**[0372]** *Secondary endpoint*: The secondary endpoint was the mean absolute change in the 2 h post-prandial serum insulin from pre-prandial. Composition A had no effect on serum insulin at this time point compared to placebo (p=0.6, **Table 15** and **Fig. 7**).

**[0373]** *Ad hoc analysis*: The difference in the mean absolute change in serum insulin from pre-prandial between the Composition A and placebo groups are seen in **Table 18**.

**Table 18.** The effect of a single dose of the study treatments on the absolute change in serum insulin from pre-prandial in patients with type 2 diabetes (n=30).

| **Serum insulin (µIU/mL)** | | |
|---|---|---|
| Collection | Overall p- | Composition A vs Placebo |

| time points post-dose | value | |
|---|---|---|
| 1 h | 0.2 | -0.09 (-7.4, 7.2; 1.0) |
| 1.5 h | 0.03* | -5.1 (-13.6, 3.4; 0.3) |
| 2 h | 0.0004* | -5.0 (-15.0, 5.0; 0.5) |
| 2.5 h | $1.7x10^{-5}$ * | -4.1 (-14.5, 6.3; 0.6) |
| 3 h | $2.0x10^{-7}$ * | -4.6 (-13.5, 4.4; 0.5) |
| 3.5 h | $1.5x10^{-6}$ * | -2.6 (-9.6, 4.4; 0.6) |
| 4 h | $3.1x10^{-6}$ * | -4.6 (-10.6, 1.3; 0.2) |

*Statistically significant

**[0374]** *Tertiary outcomes*: Composition A achieved significantly lower area under the concentration-time curve (AUC) of plasma glucose over the entire blood sampling window compared to placebo. *See* **Table 16**. Composition A achieved area under the concentration-time curve (AUC) of serum insulin similar to placebo. *See* **Table 16**.

**[0375]** The data shows that Composition A has significant glucose-lowering effects and were not associated with any adverse events following a single dose administration in male and female patients with type 2 diabetes.

**[0376] Example 3. Comparator Analysis**

**[0377]** Time course of plasma glucose following single dose of monotherapy based on published studies was compared to Composition A.

**[0378] Table 23** shows percentage change in plasma glucose from pre-prandial adjusted for placebo at various doses of single monotherapies as compared to Composition A.

**Table 23.** Percentage Change

| | **At 2 h PPG** | **Maximum** |
|---|---|---|
| Sitagliptin 100 mg | -6.3 | -20.3[a] |
| Acarbose 100 mg | -5.3 | -24.5[b] |
| Metformin 850 mg | -9.4 | Same as 2 h |
| Metformin 1700 mg | -21.9 | Same as 2 h |
| Composition A | -28.8 | |

a. Maximum achieved at 1.5 h post-prandial
b. Maximum achieved at 1 h post-prandial

**[0379]** As seen in **Fig. 8**, difference in mean 2 h post prandial glucose (PPG) vs placebo (180 min) is ~1 mmol/L. Baseline (fasting PG) was much lower compared to Composition A (drug-naïve in sitagliptin 100 mg). Maximum difference between sitagliptin and placebo is at 120 min post-dose (90 min post-meal) of ~ 1.5 mmol/L. Maximum PPG and serum insulin were achieved at ~ 1 h post-dose (0.5 h post-meal).

**[0380]** While preferred embodiments of the present disclosure have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the disclosure. It should be understood that various alternatives to the embodiments of the disclosure described herein may be employed in practicing the disclosure. It is intended that the following claims define the scope of the disclosure and that methods and structures within the scope of these claims and their equivalents be covered thereby.

## CLAIMS

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising:

a) a low-dose, therapeutically-effective amount of a dipeptidyl peptidase IV (DPP IV) inhibitor;

b) a low-dose, therapeutically-effective amount of a biguanide;

c) a low-dose, therapeutically-effective amount of a subtype 2 sodium-glucose transport protein (SGLT2) inhibitor; and

d) at least one pharmaceutically-acceptable excipient,

wherein (a), (b), and (c) are each at about 20-75% of the lowest diabetes therapeutic dose (LDTD).

2. The pharmaceutical composition of claim 1, wherein the DPP IV inhibitor is sitagliptin, the biguanide is metformin, and the SGLT2 inhibitor is dapagliflozin or empagliflozin.
3. The pharmaceutical composition of claim 2, wherein the dose of sitagliptin is from about 5.0 mg to about 18.75 mg, the dose of metformin is from about 100 mg to about 375 mg, and the dose of dapagliflozin is from about 1.0 mg to about 2.75 mg.
4. The pharmaceutical composition of claim 2, wherein the dose of sitagliptin is from about 5.0 mg to about 18.75 mg, the dose of metformin is from about 100 mg to about 375 mg, and the dose of empagliflozin is from about 2.0 mg to about 7.5 mg.
5. The pharmaceutical composition of claim 1, wherein (a) and (b) are each at about 65%-75% of the lowest diabetes therapeutic dose (LDTD) and (c) is at about 45%-55% of the lowest diabetes therapeutic dose (LDTD).
6. The pharmaceutical composition of claim 5, wherein the DPP IV inhibitor is sitagliptin and the dose of sitagliptin is from about 16.25 mg to about 18.75 mg.
7. The pharmaceutical composition of claim 5, wherein the biguanide is metformin and the dose of metformin is from about 325 mg to about 375 mg.
8. The pharmaceutical composition of claim 5, wherein the SGLT2 inhibitor is dapagliflozin, and the dose of dapagliflozin from about 2.25 mg to about 2.75 mg.
9. The pharmaceutical composition of claim 5, wherein the SGLT2 inhibitor is empagliflozin, and the dose of empagliflozin from about 4.5 mg to about 7.5 mg.
10. The pharmaceutical composition of claim 5, wherein the DPP IV inhibitor is at about 70% of the lowest diabetes therapeutic dose (LDTD) for the DPP IV inhibitor.
11. The pharmaceutical composition of claim 5, wherein the biguanide is at about 70% of the lowest diabetes therapeutic dose (LDTD) for the biguanide.

12. The pharmaceutical composition of claim 5, wherein the SGLT2 inhibitor is at about 50% of the lowest diabetes therapeutic dose (LDTD) for the SGLT2 inhibitor.
13. The pharmaceutical composition of claim 5, wherein the DPP IV inhibitor is sitagliptin, the biguanide is metformin, and the SGLT2 inhibitor is dapagliflozin or empagliflozin.
14. The pharmaceutical composition of claim 13, wherein the dose of sitagliptin is about 17.5 mg, the dose of metformin is about 350 mg, and the dose of dapagliflozin is about 2.5 mg.
15. The pharmaceutical composition of claim 13, wherein the dose of sitagliptin is about 17.5 mg, the dose of metformin is about 350 mg, and the dose of empagliflozin is about 5.0 mg.
16. The pharmaceutical composition of claim 5, wherein the DPP IV inhibitor is sitagliptin and the dose of the sitagliptin is about 17.5 mg.
17. The pharmaceutical composition of claim 5, wherein the biguanide is metformin and the dose of the metformin is about 350 mg.
18. The pharmaceutical composition of claim 5, wherein the SGLT2 inhibitor is dapagliflozin and the dose of the dapagliflozin is about 2.5 mg.
19. The pharmaceutical composition of claim 5, wherein the SGLT2 inhibitor is empagliflozin and the dose of the empagliflozin is about 5.0 mg.
20. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is suitable for oral administration.
21. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is in the form of pill, tablet, or capsule.
22. The pharmaceutical composition of claim 1, wherein the metformin is formulated for immediate release.
23. The pharmaceutical composition of claim 1, wherein the metformin is formulated for slow release.
24. The pharmaceutical composition of any of claims 1-23, wherein the pharmaceutical composition does not comprise any further additional anti-hyperglycemic or anti-diabetic agents.
25. The pharmaceutical composition of any of claims 1-23, wherein the combination of a), b), and c) produces a synergistic effect.
26. The pharmaceutical composition of any of claims 1-25, wherein the pharmaceutical composition produces a larger decrease in 2 hour post-prandial glucose as compared to a maximum decrease in the post-prandial glucose obtained from about 100 mg of sitagliptin.
27. The pharmaceutical composition of any of claims 1-25, wherein the pharmaceutical composition produces a larger decrease in 2 hour post-prandial glucose as compared to a maximum decrease in the post-prandial glucose obtained from about 850 mg of metformin.

28. The pharmaceutical composition of any of claims 1-25, wherein the pharmaceutical composition produces a larger decrease in 2 hour post-prandial glucose as compared to a maximum decrease in the post-prandial glucose obtained from about 1700 mg of metformin.

29. A pharmaceutical composition, comprising:

a) a low-dose, therapeutically-effective amount of a dipeptidyl peptidase IV (DPP IV) inhibitor;

b) a low-dose, therapeutically-effective amount of a biguanide;

c) a low-dose, therapeutically-effective amount of a subtype 2 sodium-glucose transport protein (SGLT2) inhibitor; and

d) at least one pharmaceutically-acceptable excipient,

wherein (a) and (b) are each at about 65%-75% of a lowest diabetes therapeutic dose (LDTD), and (c) is at about 45%-55% of the lowest diabetes therapeutic dose (LDTD).

30. The pharmaceutical composition of claim 29, wherein the DPP IV inhibitor is sitagliptin and a dose of sitagliptin is from about 16.25 mg to about 18.75 mg.

31. The pharmaceutical composition of claim 29, wherein the biguanide is metformin and a dose of metformin is from about 325 mg to about 375 mg.

32. The pharmaceutical composition of claim 29, wherein the SGLT2 inhibitor is dapagliflozin, and the dose of dapagliflozin from about 2.25 mg to about 2.75 mg.

33. The pharmaceutical composition of claim 29, wherein the SGLT2 inhibitor is empagliflozin, and the dose of empagliflozin from about 4.5 mg to about 7.5 mg.

34. The pharmaceutical composition of claim 29, wherein the DPP IV inhibitor is at about 70% of the lowest diabetes therapeutic dose (LDTD) for the DPP IV inhibitor.

35. The pharmaceutical composition of claim 29, wherein the biguanide is at about 70% of the lowest diabetes therapeutic dose (LDTD) for the biguanide.

36. The pharmaceutical composition of claim 29, wherein the SGLT2 inhibitor is at about 50% of the lowest diabetes therapeutic dose (LDTD) for the SGLT2 inhibitor.

37. The pharmaceutical composition of claim 29, wherein the DPP IV inhibitor is sitagliptin, the biguanide is metformin, and the SGLT2 inhibitor is dapagliflozin.

38. The pharmaceutical composition of claim 29, wherein the DPP IV inhibitor is sitagliptin, the biguanide is metformin, and the SGLT2 inhibitor is empagliflozin.

39. The pharmaceutical composition of claim 37, wherein the dose of sitagliptin is about 17.5 mg, the dose of metformin is about 350 mg, and the dose of dapagliflozin is about 2.5 mg.

40. The pharmaceutical composition of claim 29, wherein the DPP IV inhibitor is sitagliptin and the dose of the sitagliptin is about 17.5 mg.

41. The pharmaceutical composition of claim 29, wherein the biguanide is metformin and the dose of the metformin is about 350 mg.
42. The pharmaceutical composition of claim 29, wherein the SGLT2 inhibitor is dapagliflozin, and the dose of dapagliflozin is about 2.5 mg.
43. The pharmaceutical composition of claim 29, wherein the SGLT2 inhibitor is empagliflozin, and the dose of empagliflozin is about 5.0 mg.
44. The pharmaceutical composition of any one of claims 29-43, wherein the pharmaceutical composition is suitable for oral administration.
45. The pharmaceutical composition of any one of claims 29-43, wherein the pharmaceutical composition is in the form of pill, tablet or capsule.
46. The pharmaceutical composition of any one of claims 31-45, wherein the metformin is formulated for immediate release.
47. The pharmaceutical composition of any one of claims 31-45, wherein the metformin is formulated for slow release.
48. The pharmaceutical composition of any of claims 29-47, wherein the pharmaceutical composition does not comprise any further additional anti-hyperglycemic or anti-diabetic agents.
49. The pharmaceutical composition of any of claims 29-47, wherein the combination of a), b), and c) produces a synergistic effect.
50. The pharmaceutical composition of any of claims 29-49, wherein the pharmaceutical composition produces a larger decrease in 2 hour post-prandial glucose as compared to a maximum decrease in the post-prandial glucose obtained from about 100 mg of sitagliptin.
51. The pharmaceutical composition of any of claims 29-49, wherein the pharmaceutical composition produces a larger decrease in 2 hour post-prandial glucose as compared to a maximum decrease in the post-prandial glucose obtained from about 850 mg of metformin.
52. The pharmaceutical composition of any of claims 29-49, wherein the pharmaceutical composition produces a larger decrease in 2 hour post-prandial glucose as compared to a maximum decrease in the post-prandial glucose obtained from about 1700 mg of metformin.
53. A pharmaceutical composition, comprising a combination of:
    a) about 17.5 mg of sitagliptin;
    b) about 350 mg of metformin;
    c) about 2.5 mg of dapagliflozin; and
    d) at least one pharmaceutically-acceptable excipient.
54. The pharmaceutical composition of claim 53, wherein the combination is synergistic.

55. The pharmaceutical composition of claim 53 or 54, wherein the pharmaceutical composition is in the form of pill, tablet, or capsule.
56. The pharmaceutical composition of claim 53 or 54, wherein the pharmaceutical composition is suitable for oral administration.
57. The pharmaceutical composition of any one of claims 53-56, wherein the metformin is formulated for immediate release.
58. The pharmaceutical composition of any one of claims 53-56, wherein the metformin is formulated for slow release.
59. The pharmaceutical composition of any of claims 53-58, wherein the pharmaceutical composition does not comprise any further additional anti-hyperglycemic or anti-diabetic agents.
60. The pharmaceutical composition of any of claims 53-58, wherein the combination of a), b), and c) produces a synergistic effect.
61. The pharmaceutical composition of any of claims 53-60, wherein the pharmaceutical composition produces a larger decrease in 2 hour post-prandial glucose as compared to a maximum decrease in the post-prandial glucose obtained from about 100 mg of sitagliptin, from about 850 mg of metformin, or from about 1700 mg of metformin.
62. A pharmaceutical composition, comprising a combination of:
    a) about 17.5 mg of sitagliptin;
    b) about 350 mg of metformin;
    c) about 5.0 mg of empagliflozin; and
    d) at least one pharmaceutically-acceptable excipient.
63. The pharmaceutical composition of claim 62, wherein the combination is synergistic.
64. The pharmaceutical composition of claim 62 or 63, wherein the pharmaceutical composition is in the form of pill, tablet, or capsule.
65. The pharmaceutical composition of claim 62 or 63, wherein the pharmaceutical composition is suitable for oral administration.
66. The pharmaceutical composition of any one of claims 62-65, wherein the metformin is formulated for immediate release.
67. The pharmaceutical composition of any one of claims 62-65, wherein the metformin is formulated for slow release.
68. The pharmaceutical composition of any of claims 62-67, wherein the pharmaceutical composition does not comprise any further additional anti-hyperglycemic or anti-diabetic agents.

69. The pharmaceutical composition of any of claims 62-67, wherein the combination of a), b), and c) produces a synergistic effect.
70. The pharmaceutical composition of any of claims 62-69, wherein the pharmaceutical composition produces a larger decrease in 2 hour post-prandial glucose as compared to a maximum decrease in the post-prandial glucose obtained from about 100 mg of sitagliptin, from about 850 mg of metformin, or from about 1700 mg of metformin.
71. A synergistic, ultra-low dose, anti-diabetic drug combination, consisting of:
    a) about 16.25 mg to about 18.75 mg of sitagliptin, or a salt or hydrate thereof;
    b) about 325 mg to about 375 mg of metformin, or a salt or hydrate thereof;
    c) about 2.25 mg to about 2.75 mg of dapagliflozin, or a salt or hydrate thereof; and
    d) at least one excipient.
72. The combination of claim 71, wherein the combination of a), b), and c) produces a synergistic effect is synergistic.
73. The combination of claim 71, wherein the combination does not comprise any further additional anti-hyperglycemic or anti-diabetic agents.
74. The combination of claim 71, wherein the combination produces a larger decrease in 2 hour post-prandial glucose as compared to a maximum decrease in the post-prandial glucose obtained from 100 mg of sitagliptin, from 850 mg of metformin, or from 1700 mg of metformin.
75. A synergistic, ultra-low dose, anti-diabetic drug combination, consisting of:
    a) about 16.25 mg to about 18.75 mg of sitagliptin, or a salt or hydrate thereof;
    b) about 325 mg to about 375 mg of metformin, or a salt or hydrate thereof;
    c) about 4.5 mg to about 7.5 mg of empagliflozin, or a salt or hydrate thereof; and
    d) at least one excipient.
76. The combination of claim 75, wherein the combination of a), b), and c) produces a synergistic effect is synergistic.
77. The combination of claim 75, wherein the combination does not comprise any further additional anti-hyperglycemic or anti-diabetic agents.
78. The combination of claim 75, wherein the combination produces a larger decrease in 2 hour post-prandial glucose as compared to a maximum decrease in the post-prandial glucose obtained from about 100 mg of sitagliptin, from about 850 mg of metformin, or from about 1700 mg of metformin.
79. A method of treating diabetes in a subject in need thereof comprising administering the pharmaceutical composition of any one of claims 1-70.

80. The method of claim 79, wherein the subject has persisting elevation of blood sugar after treatment with one or two of a DPP IV inhibitor, a biguanide, or an SGLT2 inhibitor at the LDTD or higher dose.

81. The method of claim 79, wherein the administration of the pharmaceutical composition is an initial or first-line treatment of diabetes.

82. A method of improving, slowing the progression of, or delaying a metabolic disorder, wherein the metabolic disorder comprises diabetes mellitus, impaired glucose tolerance, impaired fasting blood glucose, hyperglycemia, postprandial hyperglycemia, overweight, obesity, metabolic syndrome, impaired renal function, gestational diabetes, new onset diabetes after transplantation (NODAT) and complications associated therewith, or post-transplant metabolic syndrome (PTMS) and complications associated therewith, comprising administering to a subject in need thereof the pharmaceutical composition of any one of claims 1-70.

83. A method of treating diabetes in a subject in need thereof, comprising administering a synergistic, ultra-low dose, anti-diabetic drug combination, consisting of:
    a) about 16.25 mg to about 18.75 mg of sitagliptin, or a salt or hydrate thereof;
    b) about 325 mg to about 375 mg of metformin, or a salt or hydrate thereof;
    c) about 2.25 mg to about 2.75 mg of dapagliflozin, or a salt or hydrate thereof; and
    d) at least one excipient.

84. The method of claim 83, wherein the combination of a), b), and c) produces a synergistic effect is synergistic.

85. The method of claim 83, wherein the combination does not comprise any further additional anti-hyperglycemic or anti-diabetic agents.

86. The method of claim 83, wherein the combination produces a larger decrease in 2 hour post-prandial glucose as compared to a maximum decrease in the post-prandial glucose obtained from about 100 mg of sitagliptin, from about 850 mg of metformin, or from about 1700 mg of metformin.

87. A method of treating diabetes in a subject in need thereof, comprising administering a synergistic, ultra-low dose, anti-diabetic drug combination, consisting of:
    a) about 16.25 mg to about 18.75 mg of sitagliptin, or a salt or hydrate thereof;
    b) about 325 mg to about 375 mg of metformin, or a salt or hydrate thereof;
    c) about 4.5 mg to about 7.5 mg of empagliflozin, or a salt or hydrate thereof; and
    d) at least one excipient.

88. The method of claim 87, wherein the combination of a), b), and c) produces a synergistic effect is synergistic.

89. The method of claim 87, wherein the combination does not comprise any further additional anti-hyperglycemic or anti-diabetic agents.

90. The method of claim 87, wherein the combination produces a larger decrease in 2 hour post-prandial glucose as compared to a maximum decrease in the post-prandial glucose obtained from about 100 mg of sitagliptin, from about 850 mg of metformin, or from about 1700 mg of metformin.

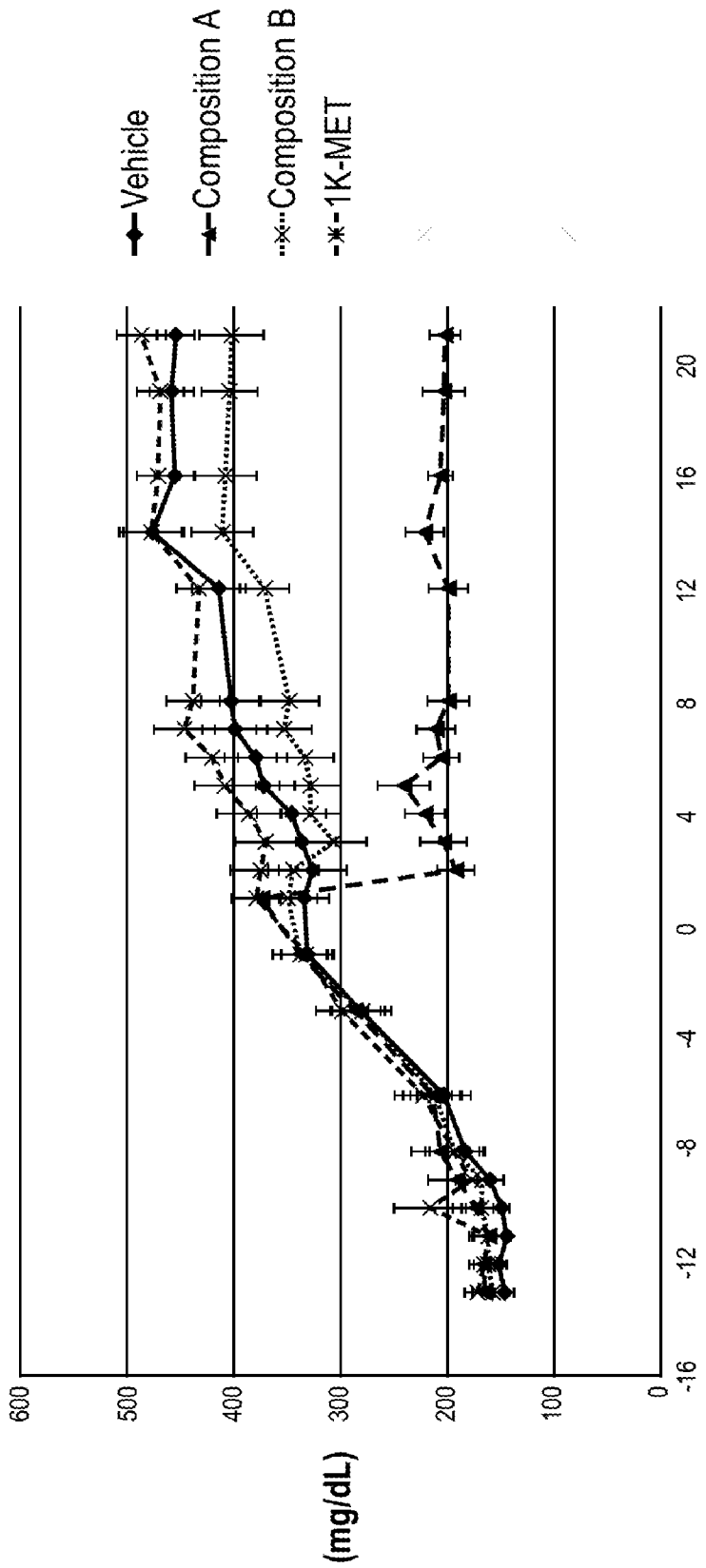
Vehicle
Composition A
Composition B
1K-MET
600
500
400
300
200
100
0
(mg/dL)
-16
-12
-8
-4
0
4
8
12
16
20
Study Day

Fig. 1

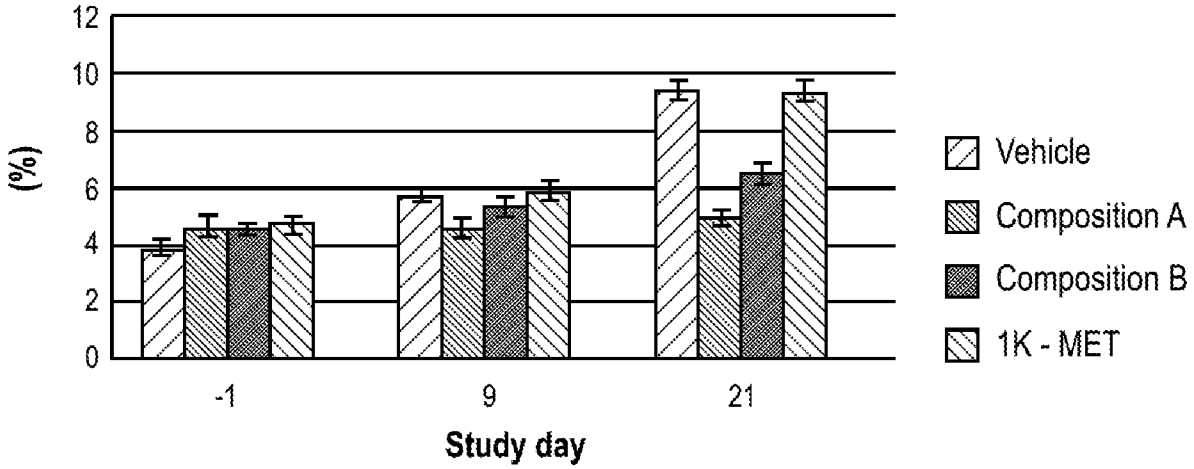
12
10
8
6
4
2
0
(%)
-1
9
21
Study day
Vehicle
Composition A
Composition B
1K - MET

Fig. 2

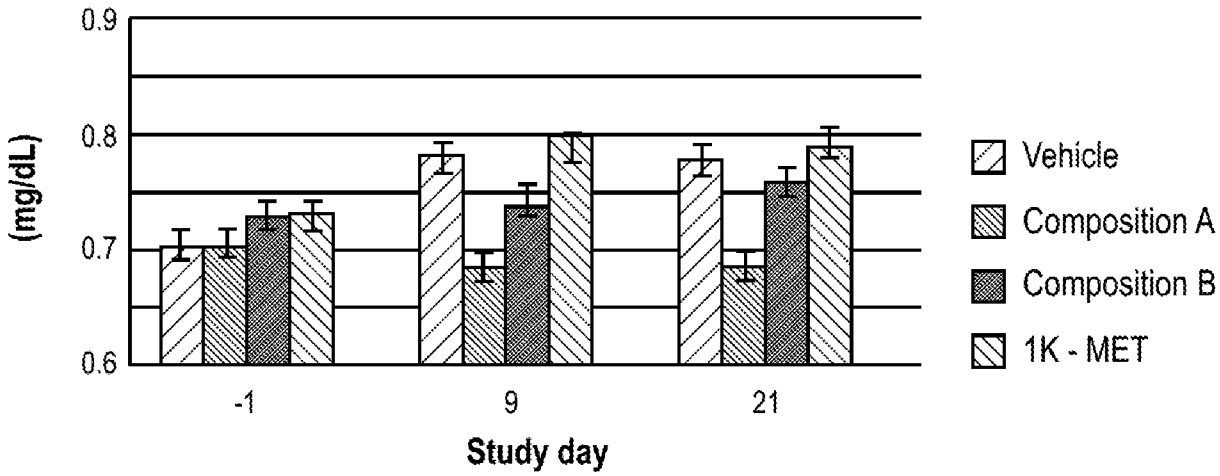
0.9
0.8
0.7
0.6
(mg/dL)
-1
9
21
Study day
Vehicle
Composition A
Composition B
1K - MET

Fig. 3

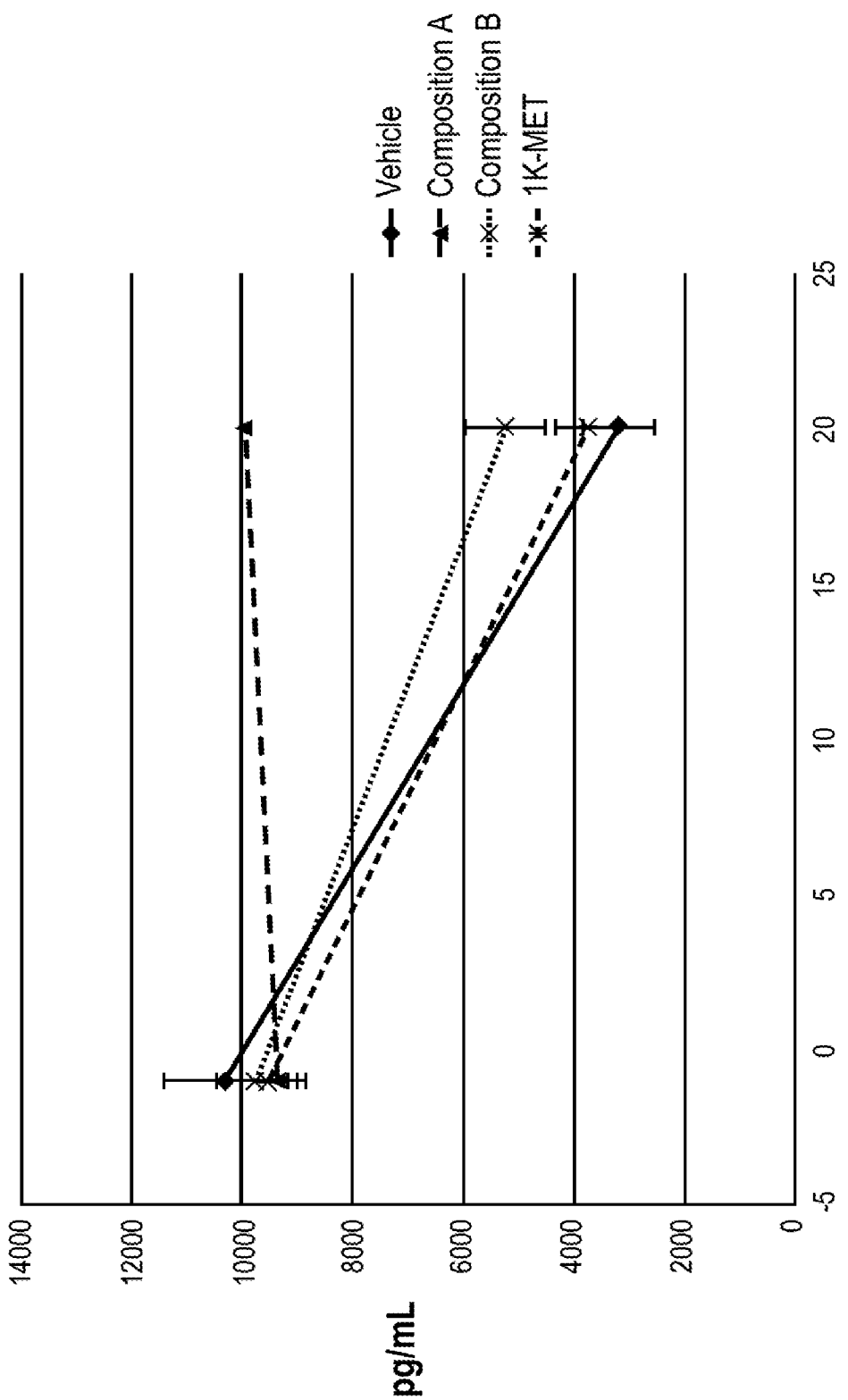
Vehicle
Composition A
Composition B
1K-MET
pg/mL
14000
12000
10000
8000
6000
4000
2000
0
-5
0
5
10
15
20
25
Study day

Fig. 4

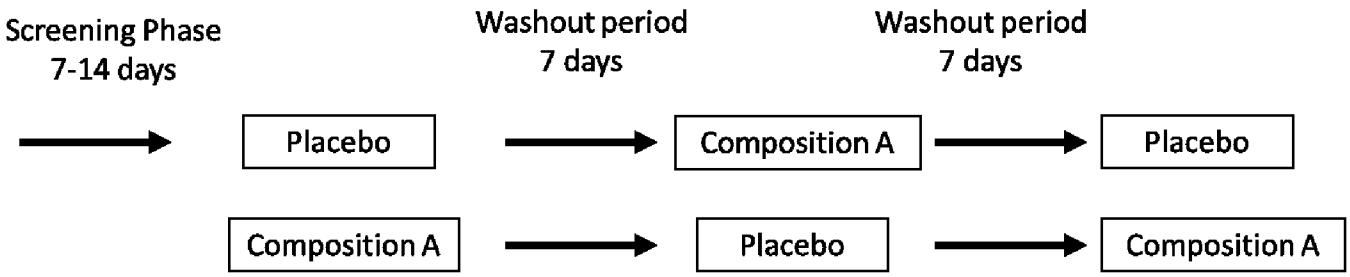
Screening Phase
7-14 days
Washout period
7 days
Washout period
7 days
Placebo
Composition A
Placebo
Composition A
Placebo
Composition A

Fig .5

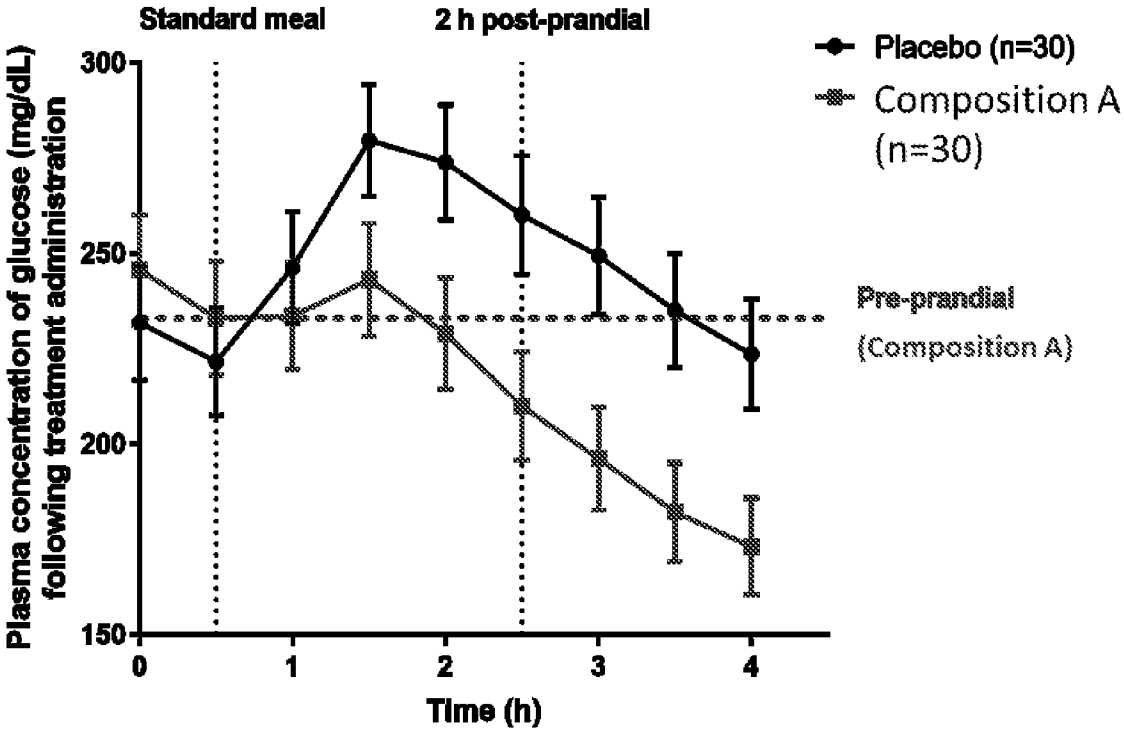
Standard meal
2 h post-prandial
Placebo (n=30)
Composition A (n=30)
Pre-prandial (Composition A)
Plasma concentration of glucose (mg/dL) following treatment administration
300
250
200
150
0
1
2
3
4
Time (h)

Fig. 6

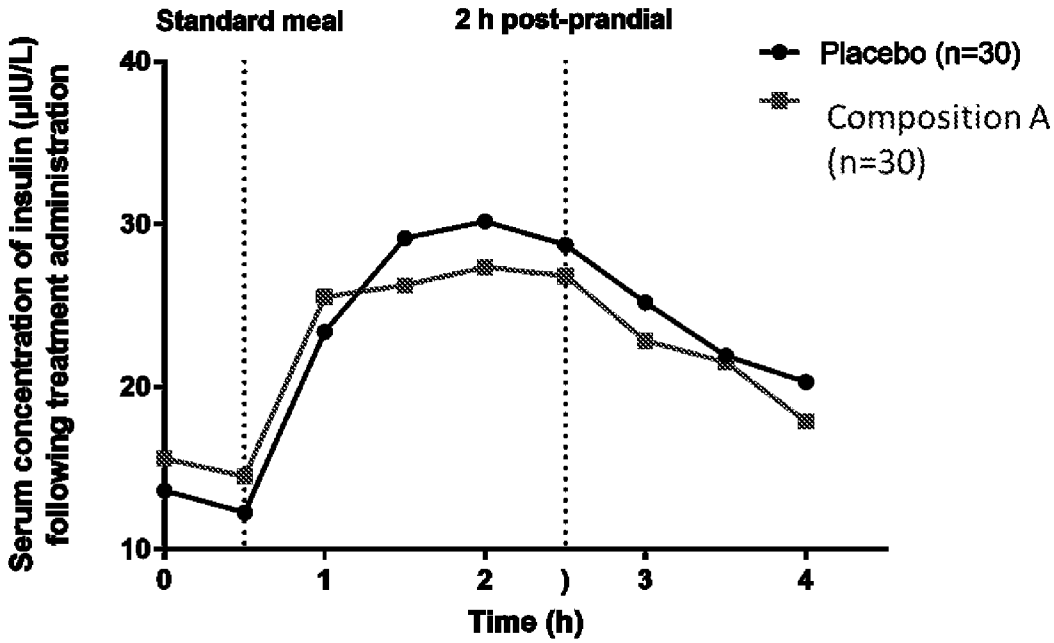
Standard meal
2 h post-prandial
Placebo (n=30)
Composition A (n=30)
Serum concentration of insulin (µIU/L) following treatment administration
40
30
20
10
0
1
2
)
3
4
Time (h)

Fig. 7

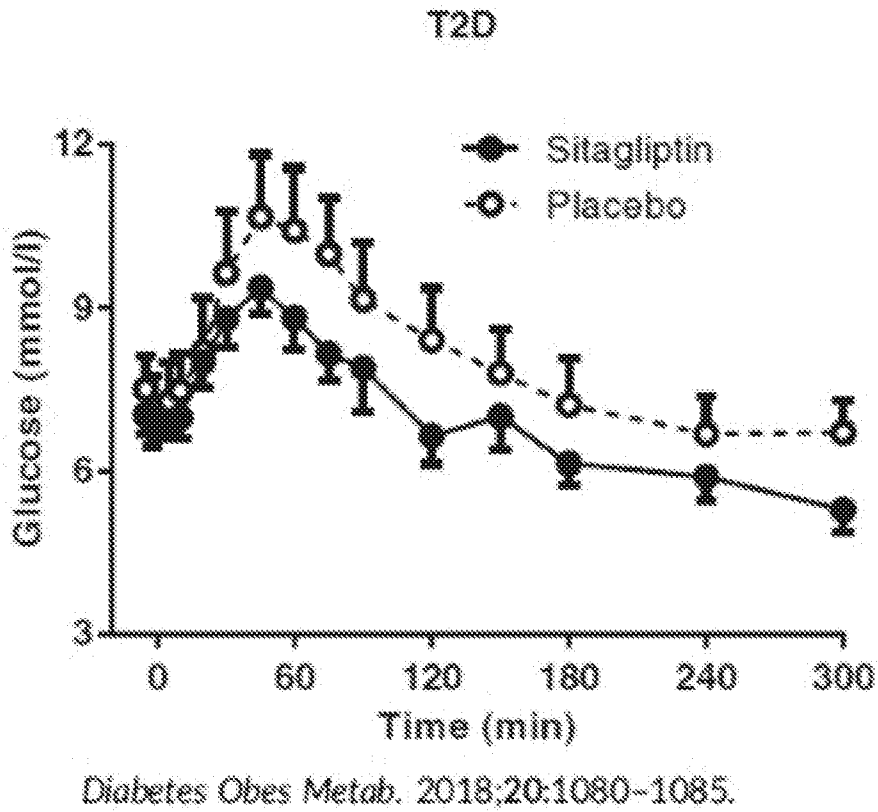
T2D
Sitagliptin
Placebo
Glucose (mmol/l)
12
9
6
3
0
60
120
180
240
300
Time (min)
Diabetes Obes Metab. 2018;20:1080–1085.

Fig. 8