METHOD OF USING A GIP/GLP1 CO-AGONIST FOR DIABETES

The present invention provides methods of treating type 2 diabetes (T2D) using a novel dosing regimen of a GIP/GLP-1 co-agonist compound (hereafter GIP:GLP-1 Peptide) having a GIP:GLP-1 receptor agonist potency ratio that is about 2.5 to about 10:1 GIP to GLP-1. Furthermore, the present invention provides methods of treating T2D using a novel dosing regimen of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio that is about 2.5:1 to about 5:1 GIP to GLP-1. Also, the present invention provides methods of inducing T2D remission using a novel dosing regimen of a GIP:GLP-1 Peptide. The present invention also provides methods of treating obesity using a novel dosing regimen of a GIP:GLP-1 Peptide.

Over the past several decades, the prevalence of diabetes has continued to rise. T2DM is the most common form of diabetes accounting for approximately 90% of all diabetes. T2DM is characterized by high blood glucose levels associated mainly with insulin resistance. T2D is epidemic. Long-term consequences of T2D translate into enormous human suffering and economic costs; however, much of the morbidity associated with long-term microvascular and neuropathic complications can be substantially reduced by interventions that achieve glucose levels close to the nondiabetic range. Although new classes of medications and numerous combinations have been demonstrated to lower glycemia, it is reported that current-day management generally fails to achieve and maintain the glycemic levels most likely to provide optimal healthcare status for people with diabetes. *The Medical Management of Hyperglycemia inType 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy,* DIABETES CARE, VOLUME 32: 193-203; , NUMBER 1, JANUARY 2009. The American Diabetes Association guidelines recommend to use HbA1c in the range of 5.7 to 6.1% (39-47 mmol/mol) as the prediabetes level. (39–47 mmol/mol). *American Diabetes Association*, Diabetes Care. 2018 January; 41 (Supplement 1): S55-S64. There is a significant need for a treatment method to enable patients with T2D to reach their glycemic treatment goals.

It is well-known that GLP1 treatments are associated with nausea, vomiting, and/or diarrhea. For example, one study reported that all GLP-1 receptor agonist dosing

regimens significantly increased the incidence of gastrointestinal adverse events. Diabetes Technol Ther. 2015 Jan;17(1):35-42.

Although endogenous GIP exerts strong insulinotropic effects in healthy subjects, the severe reduction in insulinotropic effect of GIP and the GIP-dependent enhancement of postprandial glucagon response have discouraged development of GIP-based therapies for T2D. Seino, *et.al., GIP and GLP-1, the two incretin hormones: Similarities and differences;* Journal of Diabetes Investigation, Volume 1 Issue 1/2 (February/April 2010) (8-23) p 16.

Also, previous clinical trials of a GIP/GLP1 co-agonist compound having a balanced GIP/GLP1 potency have been performed and found that tolerability at high doses was limited by gastrointestinal adverse events. Portron, A. et al. "Pharmacodynamics, pharmacokinetics, safety and tolerability of the novel dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 agonist RG7697 after single subcutaneous administration in healthy subjects." Diabetes Obes. Metab. 2017;19:1446-1453. Finan, B. et al. "Unimolecular dual incretins maximize metabolic benefits in rodents, monkeys, and humans." Sci Trans Med. 2013; 5(209):209ra151. The dose limitation associated with gastrointestinal adverse events may prevent dosing to the desired effective dose, may compromise patient compliance with treatment, and may limit the effectiveness of the treatment regimen.

While treatments for T2D include GLP-1 receptor agonists, there are currently no approved T2D treatments reporting GIP/GLP receptor co-agonism. Furthermore, there are no available treatments having a ratio that is about 2.5:1 to about 10:1 GIP to GLP-1 receptor agonist potency to treat T2D.

One GIP/GLP-1 receptor co-agonist having a potency ratio of about 3.6:1 GIP:GLP-1 is known as tirzepatide. In a Phase II clinical trial, tirzepatide treatment using once weekly subcutaneous doses including a 15 mg dose provided dramatic reduction of HbA1c, remission of diabetes for many patients after 26 weeks, and dramatic improvement in weight control.

Obesity is a complex medical disorder resulting in excessive accumulation of adipose tissue mass. Today obesity is a global public health concern that is associated with undesired health outcomes and morbidities. Desired treatments for patients with obesity strive to reduce excess body weight, improve obesity-related co-morbidities, and

maintain long-term weight reduction. Available treatments for obesity are particularly unsatisfactory for patients with severe obesity. Successful treatment of obesity is associated with alleviation or prevention of T2D. There is a need for alternative treatment options to induce therapeutic weight loss in patients in need of such treatment. Compounds having a ratio that is about 2.5:1 to about 10:1 GIP receptor agonist potency to GLP-1 receptor agonist potency are useful for significantly improving weight management, and can prevent the manifestation of T2D in formerly obese patients susceptible to T2D.

WO2016/111971 describes peptides stated to have GLP-1 and GIP activity. WO2013/164483 also discloses compounds stated to have GLP-1 and GIP activity. US9474780 generally describes compositions containing a GIP/GLP1 co-agonist, administered by parenteral routes, and generally discloses a wide dosage range up to about 30 mg per person per week. US9474780 discloses the use of GIP/GLP1 co-agonists for treating diabetes, obesity, and other conditions. US9474780 describes and claims tirzepatide.

The present invention provides novel dosing regimens of a GIP:GLP-1 Peptide for use in the aforementioned therapies (glycemic control/diabetes, obesity) that include one or more titration doses and a maintenance dose. More specifically, the present invention provides novel dosing regimens that include a titration dose and a maintenance dose wherein the titration dose is about 50% of the maintenance dose and is administered about once weekly for a minimum of about 2 weeks before administration of the maintenance dose. In another aspect, the dosing regimen comprises three titration doses: the first being about 25% of the maintenance dose, the second being about 50% of the maintenance dose and the third being about 75% of the maintenance dose, and a maintenance dose wherein each titration dose is administered about once weekly for a minimum of about 2 weeks before the administration of the next higher dose. In yet a third embodiment, the dosing regimen comprises five titration doses: the first being about 17% of the maintenance dose, the second being about 33% of the maintenance dose, the third being about 50% of the maintenance dose, the fourth being about 66% of the maintenance dose and the fifth being about 83% of the maintenance dose wherein each titration dose is administered about once weekly for a minimum of about 2 weeks before the administration of the next higher dose. Further embodiments are dosing regimens as above where each titration

dose is administered about once weekly for about 4 weeks before the administration of the next higher dose begins.

In an embodiment, GIP:GLP-1 Peptides of the present invention have a receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 of about 2.5:1 to about 10:1 GIP to GLP-1. In an embodiment, GIP:GLP-1 Peptides of the present invention have a receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 of about 2.5:1 to about 5:1 GIP to GLP-1. In an embodiment, GIP:GLP-1 Peptides of the present invention have a receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 of about 2.5:1 to about 3.5:1 GIP to GLP-1.. In an embodiment, GIP:GLP-1 Peptides of the present invention have a receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 of about 2.5:1 to about 10:1 GIP to GLP-1. In an embodiment, GIP:GLP-1 Peptides of the present invention have a receptor agonist potency ratio as measured after a 60 minute incubation at 37C using a casein cAMP assay normalized against GIP and GLP-1 of about 2.5:1 to about 10:1 GIP to GLP-1.

Accordingly, the present invention provides a method of treating type 2 diabetes in a patient in need thereof, comprising: administering a titration dose of a GIP:GLP-1 Peptide for about two weeks and thereafter administering a maintenance dose of that GIP:GLP-1 Peptide wherein the titration dose is about 50% of the maintenance dose and wherein the GIP:GLP-1 Peptide has a receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 GIP to GLP-1.

The present invention further provides a method of improving glycemic control in a patient in need thereof, comprising: administering a titration dose of a GIP:GLP-1 Peptide for about two weeks and thereafter administering a maintenance dose of that GIP:GLP-1 Peptide wherein the titration dose is about 50% of the maintenance dose and wherein the GIP:GLP-1 Peptide has a receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 GIP to GLP-1.

Furthermore, the present invention provides a method of improving weight management in a patient in need thereof, comprising: administering a titration dose of a GIP:GLP-1 Peptide for about two weeks and thereafter administering a maintenance dose of that GIP:GLP-1 Peptide wherein the titration dose is about 50% of the maintenance dose and wherein the GIP:GLP-1 Peptide has a receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 GIP to GLP-1.

Furthermore, the present invention provides a method of treating chronic kidney disease in a patient in need thereof, comprising: administering a titration dose of a GIP:GLP-1 Peptide for about two weeks and thereafter administering a maintenance dose of that GIP:GLP-1 Peptide wherein the titration dose is about 50% of the maintenance dose and wherein the GIP:GLP-1 Peptide has a receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 GIP to GLP-1.

Furthermore, the present invention provides a method of treating atherosclerosis in a patient in need thereof, comprising: administering a titration dose of a GIP:GLP-1 Peptide for about two weeks and thereafter administering a maintenance dose of that GIP:GLP-1 Peptide wherein the titration dose is about 50% of the maintenance dose and wherein the GIP:GLP-1 Peptide has a receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 GIP to GLP-1.

Furthermore, the present invention provides a method of treating NAFLD in a patient in need thereof, comprising: administering a titration dose of a GIP:GLP-1 Peptide for about two weeks and thereafter administering a maintenance dose of that GIP:GLP-1 Peptide wherein the titration dose is about 50% of the maintenance dose and wherein the GIP:GLP-1 Peptide has a receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 GIP to GLP-1.

Furthermore, the present invention provides a method of treating NASH in a patient in need thereof, comprising: administering a titration dose of a GIP:GLP-1 Peptide for about two weeks and thereafter administering a maintenance dose of that GIP:GLP-1 Peptide wherein the titration dose is about 50% of the maintenance dose and wherein the

GIP:GLP-1 Peptide has a receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 GIP to GLP-1.

Furthermore, the present invention provides a method of curing diabetes, inducing remission or regression of diabetes or preventing diabetes in a patient in need thereof, comprising: administering a titration dose of a GIP:GLP-1 Peptide for about two weeks and thereafter administering a maintenance dose of that GIP:GLP-1 Peptide wherein the titration dose is about 50% of the maintenance dose and wherein the GIP:GLP-1 Peptide has a receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 GIP to GLP-1.

A further embodiment of the present invention are the methods above wherein three titration doses (about 25%, about 50% and about 75% of the maintenance dose) are administered starting with the 25% dose and wherein each titration dose is administered for about two weeks before the administration of the next higher dose begins. A further embodiment of the present invention are the methods above wherein five titration doses (about 17%, about 33%, about 50%, about 66% and about 83% of the maintenance dose) are administered starting with the 17% dose and wherein each titration dose is administered for about two weeks before the administration of the next higher dose. A further embodiment of the present invention are the methods above where the titration dose or doses are administered for about four weeks before the administration of the next higher dose begins.

Another aspect of the present invention are methods described above for treating type 2 diabetes, improving glycemic control, improving weight management, treating chronic kidney disease, treating NAFLD, treating NASH and to cure diabetes, induce remission or regression of diabetes, or prevent diabetes wherein the GIP:GLP-1 Peptide has a GIP:GLP-1 receptor agonist potency ratio that is about 2.5:1 to about 5:1 as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1. A further aspect of the present invention are methods described above for treating type 2 diabetes, improving glycemic control, improving weight management, treating chronic kidney disease, treating NAFLD, treating NASH or to cure diabetes, induce remission or regression of diabetes, or prevent diabetes wherein the GIP:GLP-1

Peptide has a GIP:GLP-1 receptor agonist potency ratio that is about 2.5:1 to about 3.5:1 as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1.

A further aspect of the present invention are the methods described above for treating type 2 diabetes, improving glycemic control, improving weight management, treating chronic kidney disease, treating NAFLD, treating NASH or to cure diabetes, induce remission or regression of diabetes, or prevent diabetes wherein the GIP:GLP-1 Peptide is a compound of SEQ ID NO: 3, or a pharmaceutically acceptable salt thereof. Another aspect of the present invention are the methods described above for treating type 2 diabetes, improving glycemic control, improving weight management, treating chronic kidney disease, treating NAFLD, treating NASH or to cure diabetes, induce remission or regression of diabetes, or prevent diabetes wherein the GIP:GLP-1 Peptide is a compound of SEQ ID NO: 3, or a pharmaceutically acceptable salt thereof, and wherein the compound of SEQ ID NO: 3, or a pharmaceutically acceptable salt thereof, has a GIP:GLP-1 receptor agonist potency ratio that is about 2.5:1 to about 5:1 as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1. Another aspect of the present invention are the methods described above for treating type 2 diabetes, improving glycemic control, improving weight management, treating chronic kidney disease, treating NAFLD, treating NASH or to cure diabetes, induce remission or regression of diabetes, or prevent diabetes wherein the GIP:GLP-1 Peptide is a compound of SEQ ID NO: 3, or a pharmaceutically acceptable salt thereof, and wherein the compound of SEQ ID NO: 3, or a pharmaceutically acceptable salt thereof, has a GIP:GLP-1 receptor agonist potency ratio that is about 2.5:1 to about 3.5:1 as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1.

In an embodiment 1(a), the present invention provides a method of treating type 2 diabetes in a patient in need thereof, comprising:

a) administering to said patient a titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the titration dose is about 50% of the maintenance dose.

In embodiment 1(b), the present invention provides a method of treating type 2 diabetes in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 25% of the maintenance dose, the second titration dose is about 50% of the maintenance dose and the third titration dose is about 75% of the maintenance dose.

In embodiment 1(c), the present invention provides a method of treating type 2 diabetes in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a fourth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

e) administering to said patient a fifth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

f) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 17% of the maintenance dose, the second titration dose is about 33% of the maintenance dose, the third titration dose is about 50% of the maintenance dose, the fourth titration is about 66% of the maintenance dose and the fifth titration dose is about 83% of the maintenance dose.

In an embodiment 1(a1), the present invention provides a method of treating type 2 diabetes in a patient in need thereof, comprising:

a) subcutaneiously administering to said patient a titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 about once weekly for a minimum of about two weeks; and thereafter

b) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the titration dose is about 50% of the maintenance dose.

In embodiment 1(b1), the present invention provides a method of treating type 2 diabetes in a patient in need thereof, comprising:

a) subcutaneously administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 about once weekly for a minimum of about two weeks; and thereafter

b) subcutaneously administering to said patient a second titration dose of that GIP:GLP-1 Peptide about once weekly for a minimum of about two weeks; and thereafter

c) subcutaneously administering to said patient a third titration dose of that GIP:GLP-1 Peptide about once weekly for a minimum of about two weeks; and thereafter

d) subcutaneously administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 25% of the maintenance dose, the second titration dose is about 50% of the maintenance dose and the third titration dose is about 75% of the maintenance dose.

In embodiment 1(c1), the present invention provides a method of treating type 2 diabetes in a patient in need thereof, comprising:

a) subcutaneously administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 about once weekly for a minimum of about two weeks; and thereafter

b) subcutaneously administering to said patient a second titration dose of that GIP:GLP-1 Peptide about once weekly for a minimum of about two weeks; and thereafter

c) subcutaneously administering to said patient a third titration dose of that GIP:GLP-1 Peptide about once weekly for a minimum of about two weeks; and thereafter

d) subcutaneously administering to said patient a fourth titration dose of that GIP:GLP-1 Peptide about once weekly for a minimum of about two weeks; and thereafter

e) subcutaneously administering to said patient a fifth titration dose of that GIP:GLP-1 Peptide about once weekly for a minimum of about two weeks; and thereafter

f) subcutaneously administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 17% of the maintenance dose, the second titration dose is about 33% of the maintenance dose, the third titration dose is about 50% of the maintenance dose, the fourth titration is about 66% of the maintenance dose and the fifth titration dose is about 83% of the maintenance dose.

In an embodiment 2(a), the present invention provides a method of improving glycemic control in a patient in need thereof, comprising:

a) administering to said patient a titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the titration dose is about 50% of the maintenance dose.

In an embodiment 2(a), the present invention provides a method of improving glycemic control in a patient in need thereof, comprising:

a) administering to said patient a titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the titration dose is about 50% of the maintenance dose.

In embodiment 2(b), the present invention provides a method of improving glycemic control in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 25% of the maintenance dose, the second titration dose is about 50% of the maintenance dose and the third titration dose is about 75% of the maintenance dose.

In embodiment 2(c), the present invention provides a method of improving glycemic control in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a fourth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

e) administering to said patient a fifth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

f) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 17% of the maintenance dose, the second titration dose is about 33% of the maintenance dose, the third titration dose is about 50% of the maintenance dose, the fourth titration is about 66% of the maintenance dose and the fifth titration dose is about 83% of the maintenance dose.

In an embodiment 3(a), the present invention provides a method of improving weight management in a patient in need thereof, comprising:

a) administering to said patient a titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide; wherein the titration dose is about 50% of the maintenance dose.

In embodiment 3(b), the present invention provides a method of improving weight management in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 25% of the maintenance dose, the second titration dose is about 50% of the maintenance dose and the third titration dose is about 75% of the maintenance dose.

In embodiment 3(c), the present invention provides a method of improving weight management in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a fourth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

e) administering to said patient a fifth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

f) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 17% of the maintenance dose, the second titration dose is about 33% of the maintenance dose, the third titration dose is about 50% of the maintenance dose, the fourth titration is about 66% of the maintenance dose and the fifth titration dose is about 83% of the maintenance dose.

In an embodiment 4(a), the present invention provides a method of treating chronic kidney disease in a patient in need thereof, comprising:

a) administering to said patient a titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1

that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the titration dose is about 50% of the maintenance dose.

In embodiment 4(b), the present invention provides a method of treating chronic kidney disease in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 25% of the maintenance dose, the second titration dose is about 50% of the maintenance dose and the third titration dose is about 75% of the maintenance dose.

In embodiment 4(c), the present invention provides a method of treating chronic kidney disease in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a fourth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

e) administering to said patient a fifth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

f) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 17% of the maintenance dose, the second titration dose is about 33% of the maintenance dose, the third titration dose is about 50% of the maintenance dose, the fourth titration is about 66% of the maintenance dose and the fifth titration dose is about 83% of the maintenance dose.

In an embodiment 5(a), the present invention provides a method of treating NAFLD in a patient in need thereof, comprising:

a) administering to said patient a titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the titration dose is about 50% of the maintenance dose.

In embodiment 5(b), the present invention provides a method of treating NAFLD in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 25% of the maintenance dose, the second titration dose is about 50% of the maintenance dose and the third titration dose is about 75% of the maintenance dose.

In embodiment 5(c), the present invention provides a method of treating NAFLD in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a fourth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

e) administering to said patient a fifth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

f) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 17% of the maintenance dose, the second titration dose is about 33% of the maintenance dose, the third titration dose is about 50% of the maintenance dose, the fourth titration is about 66% of the maintenance dose and the fifth titration dose is about 83% of the maintenance dose.

In an embodiment 6(a), the present invention provides a method of treating NASH in a patient in need thereof, comprising:

a) administering to said patient a titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the titration dose is about 50% of the maintenance dose.

In embodiment 6(b), the present invention provides a method of treating NASH in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 25% of the maintenance dose, the second titration dose is about 50% of the maintenance dose and the third titration dose is about 75% of the maintenance dose.

In embodiment 6(c), the present invention provides a method of treating NASH in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a fourth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

e) administering to said patient a fifth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

f) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 17% of the maintenance dose, the second titration dose is about 33% of the maintenance dose, the third titration dose is about 50% of the

maintenance dose, the fourth titration is about 66% of the maintenance dose and the fifth titration dose is about 83% of the maintenance dose.

In an embodiment 7(a), the present invention provides a method of curing diabetes, inducing remission or regression of diabetes, or preventing diabetes in a patient in need thereof, comprising: to cure diabetes, induce remission or regression of diabetes, or prevent diabetes

a) administering to said patient a titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the titration dose is about 50% of the maintenance dose.

In embodiment 7(b), the present invention provides a method of curing diabetes, inducing remission or regression of diabetes, or preventing diabetes in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 25% of the maintenance dose, the second titration dose is about 50% of the maintenance dose and the third titration dose is about 75% of the maintenance dose.

In embodiment 7(c), the present invention provides a method of curing diabetes, inducing remission or regression of diabetes, or preventing diabetes in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a fourth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

e) administering to said patient a fifth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

f) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 17% of the maintenance dose, the second titration dose is about 33% of the maintenance dose, the third titration dose is about 50% of the maintenance dose, the fourth titration is about 66% of the maintenance dose and the fifth titration dose is about 83% of the maintenance dose.

In embodiment 8, the titration doses of embodiments 1(a)-(c), 2(a)-(c), 3(a)-(c), 4(a)-(c), 5(a)-(c), 6(a)-(c) or 7(a)-(c) are each administered for about four weeks before the administration of the next higher dose begins. Thus, for example, the present invention provides in embodiment 1(d) a method of treating type 2 diabetes in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for about four weeks; and thereafter

b) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the titration dose is about 50% of the maintenance dose.

The present invention thus further provides in embodiment 1(e), a method of treating type 2 diabetes in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for about four weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for about four weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for about four weeks; and thereafter

d) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 25% of the maintenance dose, the second titration dose is about 50% of the maintenance dose and the third titration dose is about 75% of the maintenance dose.

The present invention thus further provides in embodiment 1(f), a method of treating type 2 diabetes in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for about four weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for about four weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for about four weeks; and thereafter

d) administering to said patient a fourth titration dose of that GIP:GLP-1 Peptide for about four weeks; and thereafter

e) administering to said patient a fifth titration dose of that GIP:GLP-1 Peptide for about four weeks; and thereafter

f) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 17% of the maintenance dose, the second titration dose is about 33% of the maintenance dose, the third titration dose is about 50% of the maintenance dose, the fourth titration is about 66% of the maintenance dose and the fifth titration dose is about 83% of the maintenance dose.

In embodiment 9, the GIP:GLP-1 Peptide of embodiments 1(a)-(c), 2(a)-(c), 3(a)-(c), 4(a)-(c), 5(a)-(c), 6(a)-(c), 7(a)-(c) or 8 is a compound of SEQ ID NO: 3, or a pharmaceutically acceptable salt thereof. Thus, for example, the present invention provides in embodiment 1(g) a method of treating type 2 diabetes in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 wherein the GIP:GLP-1 Peptide is a compound of SEQ ID NO: 3 for about four weeks; and thereafter

b) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the titration dose is about 50% of the maintenance dose.

The present invention thus further provides in embodiment 1(h), a method of treating type 2 diabetes in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 wherein the GIP:GLP-1 Peptide is a compound of SEQ ID NO: 3 for about four weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for about four weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for about four weeks; and thereafter

d) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 25% of the maintenance dose, the second titration dose is about 50% of the maintenance dose and the third titration dose is about 75% of the maintenance dose.

The present invention thus further provides in embodiment 1(i), a method of treating type 2 diabetes in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and

GLP-1 that is about 2.5:1 to about 10:1 wherein the GIP:GLP-1 Peptide is a compound of SEQ ID NO: 3 for about four weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for about four weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for about four weeks; and thereafter

d) administering to said patient a fourth titration dose of that GIP:GLP-1 Peptide for about four weeks; and thereafter

e) administering to said patient a fifth titration dose of that GIP:GLP-1 Peptide for about four weeks; and thereafter

f) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 17% of the maintenance dose, the second titration dose is about 33% of the maintenance dose, the third titration dose is about 50% of the maintenance dose, the fourth titration is about 66% of the maintenance dose and the fifth titration dose is about 83% of the maintenance dose.

In embodiment 10, the GIP:GLP-1 Peptide of embodiments 1(a)-(c), 2(a)-(c), 3(a)-(c), 4(a)-(c), 5(a)-(c), 6(a)-(c), 7(a)-(c), 8 or 9 has a receptor agonist potency ratio that is 2.5:1 to about 5:1 GIP to GLP-1.

In embodiment 11, the GIP:GLP-1 Peptide of embodiments 1(a)-(c), 2(a)-(c), 3(a)-(c), 4(a)-(c), 5(a)-(c), 6(a)-(c), 7(a)-(c), 8, 9 or 10 has a receptor agonist potency ratio that is 2.5:1 to about 3.5:1 GIP to GLP-1.

In an embodiment 12(a), the present invention provides the use of a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating type 2 diabetes in a patient in need thereof, comprising:

a) administering to said patient a titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the titration dose is about 50% of the maintenance dose.

In an embodiment 12(b), the present invention provides the use of a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating type 2 diabetes in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 25% of the maintenance dose, the second titration dose is about 50% of the maintenance dose and the third titration dose is about 75% of the maintenance dose.

In an embodiment 12(c), the present invention provides the use of a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating type 2 diabetes in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a fourth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

e) administering to said patient a fifth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

f) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 17% of the maintenance dose, the second titration dose is about 33% of the maintenance dose, the third titration dose is about 50% of the maintenance dose, the fourth titration is about 66% of the maintenance dose and the fifth titration dose is about 83% of the maintenance dose.

In an embodiment 13(a), the present invention provides the use of a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for improving glycemic control in a patient in need thereof, comprising:

a) administering to said patient a titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the titration dose is about 50% of the maintenance dose.

In an embodiment 13(b), the present invention provides the use of a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for improving glycemic control in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 25% of the maintenance dose, the second titration dose is about 50% of the maintenance dose and the third titration dose is about 75% of the maintenance dose.

In an embodiment 13(c), the present invention provides the use of a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for improving glycemic control in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a fourth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

e) administering to said patient a fifth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

f) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 17% of the maintenance dose, the second titration dose is about 33% of the maintenance dose, the third titration dose is about 50% of the maintenance dose, the fourth titration is about 66% of the maintenance dose and the fifth titration dose is about 83% of the maintenance dose.

In an embodiment 14(a), the present invention provides the use of a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for improving weight management in a patient in need thereof, comprising:

a) administering to said patient a titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the titration dose is about 50% of the maintenance dose.

In an embodiment 14(b), the present invention provides the use of a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for improving weight management in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 25% of the maintenance dose, the second titration dose is about 50% of the maintenance dose and the third titration dose is about 75% of the maintenance dose.

In an embodiment 14(c), the present invention provides the use of a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for improving weight management in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and

GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a fourth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

e) administering to said patient a fifth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

f) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 17% of the maintenance dose, the second titration dose is about 33% of the maintenance dose, the third titration dose is about 50% of the maintenance dose, the fourth titration is about 66% of the maintenance dose and the fifth titration dose is about 83% of the maintenance dose.

In an embodiment 15(a), the present invention provides the use of a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating chronic kidney disease in a patient in need thereof, comprising:

a) administering to said patient a titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the titration dose is about 50% of the maintenance dose.

In an embodiment 15(b), the present invention provides the use of a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating chronic kidney disease in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 25% of the maintenance dose, the second titration dose is about 50% of the maintenance dose and the third titration dose is about 75% of the maintenance dose.

In an embodiment 15(c), the present invention provides the use of a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating chronic kidney disease in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a fourth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

e) administering to said patient a fifth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

f) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 17% of the maintenance dose, the second titration dose is about 33% of the maintenance dose, the third titration dose is about 50% of the maintenance dose, the fourth titration is about 66% of the maintenance dose and the fifth titration dose is about 83% of the maintenance dose.

In an embodiment 16(a), the present invention provides the use of a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating NAFLD in a patient in need thereof, comprising:

a) administering to said patient a titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the titration dose is about 50% of the maintenance dose.

In an embodiment 16(b), the present invention provides the use of a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating NAFLD in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 25% of the maintenance dose, the second titration dose is about 50% of the maintenance dose and the third titration dose is about 75% of the maintenance dose.

In an embodiment 16(c), the present invention provides the use of a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating NAFLD in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a fourth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

e) administering to said patient a fifth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

f) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 17% of the maintenance dose, the second titration dose is about 33% of the maintenance dose, the third titration dose is about 50% of the maintenance dose, the fourth titration is about 66% of the maintenance dose and the fifth titration dose is about 83% of the maintenance dose.

In an embodiment 17(a), the present invention provides the use of a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating NASH in a patient in need thereof, comprising:

a) administering to said patient a titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and

GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the titration dose is about 50% of the maintenance dose.

In an embodiment 17(b), the present invention provides the use of a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating NASH in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 25% of the maintenance dose, the second titration dose is about 50% of the maintenance dose and the third titration dose is about 75% of the maintenance dose.

In an embodiment 17(c), the present invention provides the use of a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating NASH in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a fourth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

e) administering to said patient a fifth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

f) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 17% of the maintenance dose, the second titration dose is about 33% of the maintenance dose, the third titration dose is about 50% of the maintenance dose, the fourth titration is about 66% of the maintenance dose and the fifth titration dose is about 83% of the maintenance dose.

In an embodiment 18(a), the present invention provides the use of a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inducing remission or regression of diabetes, or preventing diabetes in a patient in need thereof, comprising:

a) administering to said patient a titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the titration dose is about 50% of the maintenance dose.

In an embodiment 18(b), the present invention provides the use of a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inducing remission or regression of diabetes, or preventing diabetes in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and

GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 25% of the maintenance dose, the second titration dose is about 50% of the maintenance dose and the third titration dose is about 75% of the maintenance dose.

In an embodiment 18(c), the present invention provides the use of a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inducing remission or regression of diabetes, or preventing diabetes in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a fourth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

e) administering to said patient a fifth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

f) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 17% of the maintenance dose, the second titration dose is about 33% of the maintenance dose, the third

titration dose is about 50% of the maintenance dose, the fourth titration is about 66% of the maintenance dose and the fifth titration dose is about 83% of the maintenance dose.

In embodiment 19, the titration doses of any of embodiments 12(a)-(c), 13(a)-(c), 14(a)-(c), 15(a)-(c), 16(a)-(c), 17(a)-(c), or 18(a)-(c) are each administered for about four weeks before the administration of the next higher dose begins.

In embodiment 20, the GIP:GLP-1 Peptide of any of embodiments 12(a)-(c), 13(a)-(c), 14(a)-(c), 15(a)-(c), 16(a)-(c), 17(a)-(c), 18(a)-(c), or 19 is a peptideof SEQ ID NO: 3, or a pharmaceutically acceptable salt thereof.

In embodiment 21, the GIP:GLP-1 Peptide of any of embodiments 12(a)-(c), 13(a)-(c), 14(a)-(c), 15(a)-(c), 16(a)-(c), 17(a)-(c), 18(a)-(c), 19 or 20 has a receptor agonist potency ratio that is 2.5:1 to about 5:1 GIP to GLP-1.

In embodiment 22, the GIP:GLP-1 Peptide of any of embodiments 12(a)-(c), 13(a)-(c), 14(a)-(c), 15(a)-(c), 16(a)-(c), 17(a)-(c), 18(a)-(c), 19, or 20 has a receptor agonist potency ratio that is 2.5:1 to about 3.5:1 GIP to GLP-1.

In an embodiment 23(a), the present invention provides a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, for use in treating type 2 diabetes in a patient in need thereof wherein the use comprises:

a) administration of a titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administration of a maintenance dose of that GIP:GLP-1 Peptide;

wherein the titration dose is about 50% of the maintenance dose.

In an embodiment 23(b), the present invention provides a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, for use in treating type 2 diabetes in a patient in need thereof wherein the use comprises:

a) administration of a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administration of a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administration of a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administration of a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 25% of the maintenance dose, the second titration dose is about 50% of the maintenance dose and the third titration dose is about 75% of the maintenance dose.

In an embodiment 23(c), the present invention provides a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, for use in treating type 2 diabetes in a patient in need thereof wherein the use comprises:

a) administration of a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administration of a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administration of a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administration of a fourth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

e) administration of a fifth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

f) administration of a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 17% of the maintenance dose, the second titration dose is about 33% of the maintenance dose, the third titration dose is about 50% of the maintenance dose, the fourth titration is about 66% of the maintenance dose and the fifth titration dose is about 83% of the maintenance dose.

In an embodiment 24(a), the present invention provides a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, for use in improving glycemic control in a patient in need thereof wherein the use comprises:

a) administration of a titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administration of a maintenance dose of that GIP:GLP-1 Peptide;

wherein the titration dose is about 50% of the maintenance dose.

In an embodiment 24(b), the present invention provides a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, for use in improving glycemic control in a patient in need thereof wherein the use comprises:

a) administration of a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administration of a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administration of a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administration of a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 25% of the maintenance dose, the second titration dose is about 50% of the maintenance dose and the third titration dose is about 75% of the maintenance dose.

In an embodiment 24(c), the present invention provides a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, for use in improving glycemic control in a patient in need thereof wherein the use comprises:

a) administration of a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administration of a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administration of a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administration of a fourth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

e) administration of a fifth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

f) administration of a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 17% of the maintenance dose, the second titration dose is about 33% of the maintenance dose, the third titration dose is about 50% of the maintenance dose, the fourth titration is about 66% of the maintenance dose and the fifth titration dose is about 83% of the maintenance dose.

In an embodiment 25(a), the present invention provides a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, for use in improving weight management in a patient in need thereof wherein the use comprises:

a) administration of a titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administration of a maintenance dose of that GIP:GLP-1 Peptide;

wherein the titration dose is about 50% of the maintenance dose.

In an embodiment 25(b), the present invention provides a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, for use in improving weight management in a patient in need thereof wherein the use comprises:

a) administration of a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administration of a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administration of a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administration of a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 25% of the maintenance dose, the second titration dose is about 50% of the maintenance dose and the third titration dose is about 75% of the maintenance dose.

In an embodiment 25(c), the present invention provides a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, for use in improving weight management in a patient in need thereof wherein the use comprises:

a) administration of a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administration of a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administration of a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administration of a fourth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

e) administration of a fifth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

f) administration of a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 17% of the maintenance dose, the second titration dose is about 33% of the maintenance dose, the third titration dose is about 50% of the maintenance dose, the fourth titration is about 66% of the maintenance dose and the fifth titration dose is about 83% of the maintenance dose.

In an embodiment 26(a), the present invention provides a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, for use in treating chronic kidney disease in a patient in need thereof wherein the use comprises:

a) administration of a titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administration of a maintenance dose of that GIP:GLP-1 Peptide ;

wherein the titration dose is about 50% of the maintenance dose.

In an embodiment 26(b), the present invention provides a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, for use in treating chronic kidney disease in a patient in need thereof wherein the use comprises:

a) administration of a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administration of a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administration of a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administration of a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 25% of the maintenance dose, the second titration dose is about 50% of the maintenance dose and the third titration dose is about 75% of the maintenance dose.

In an embodiment 26(c), the present invention provides a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, for use in treating chronic kidney disease in a patient in need thereof wherein the use comprises:

a) administration of a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administration of a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administration of a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administration of a fourth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

e) administration of a fifth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

f) administration of a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 17% of the maintenance dose, the second titration dose is about 33% of the maintenance dose, the third titration dose is about 50% of the maintenance dose, the fourth titration is about 66% of the maintenance dose and the fifth titration dose is about 83% of the maintenance dose.

In an embodiment 27(a), the present invention provides a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, for use in treating NAFLD in a patient in need thereof wherein the use comprises:

a) administration of a titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administration of a maintenance dose of that GIP:GLP-1 Peptide;

wherein the titration dose is about 50% of the maintenance dose.

In an embodiment 27(b), the present invention provides a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, for use in treating NAFLD in a patient in need thereof wherein the use comprises:

a) administration of a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administration of a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administration of a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administration of a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 25% of the maintenance dose, the second titration dose is about 50% of the maintenance dose and the third titration dose is about 75% of the maintenance dose.

In an embodiment 27(c), the present invention provides a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, for use in treating NAFLD in a patient in need thereof wherein the use comprises:

a) administration of a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute

incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administration of a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administration of a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administration of a fourth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

e) administration of a fifth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

f) administration of a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 17% of the maintenance dose, the second titration dose is about 33% of the maintenance dose, the third titration dose is about 50% of the maintenance dose, the fourth titration is about 66% of the maintenance dose and the fifth titration dose is about 83% of the maintenance dose.

In an embodiment 28(a), the present invention provides a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, for use in treating NASH in a patient in need thereof wherein the use comprises:

a) administration of a titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administration of a maintenance dose of that GIP:GLP-1 Peptide;

wherein the titration dose is about 50% of the maintenance dose.

In an embodiment 28(b), the present invention provides a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, for use in treating NASH in a patient in need thereof wherein the use comprises:

a) administration of a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administration of a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administration of a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administration of a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 25% of the maintenance dose, the second titration dose is about 50% of the maintenance dose and the third titration dose is about 75% of the maintenance dose.

In an embodiment 28(c), the present invention provides a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, for use in treating NASH in a patient in need thereof wherein the use comprises:

a) administration of a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administration of a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administration of a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administration of a fourth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

e) administration of a fifth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

f) administration of a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 17% of the maintenance dose, the second titration dose is about 33% of the maintenance dose, the third titration dose is about 50% of the maintenance dose, the fourth titration is about 66% of the maintenance dose and the fifth titration dose is about 83% of the maintenance dose.

In an embodiment 29(a), the present invention provides a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, for use in inducing remission or regression of diabetes, or preventing diabetes in a patient in need thereof wherein the use comprises:

a) administration of a titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administration of a maintenance dose of that GIP:GLP-1 Peptide;

wherein the titration dose is about 50% of the maintenance dose.

In an embodiment 29(b), the present invention provides a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, for use in inducing remission or regression of diabetes, or preventing diabetes in a patient in need thereof wherein the use comprises:

a) administration of a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administration of a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administration of a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administration of a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 25% of the maintenance dose, the second titration dose is about 50% of the maintenance dose and the third titration dose is about 75% of the maintenance dose.

In an embodiment 29(c), the present invention provides a GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, for use in inducing remission or regression of diabetes, or preventing diabetes in a patient in need thereof wherein the use comprises:

a) administration of a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administration of a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administration of a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administration of a fourth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

e) administration of a fifth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

f) administration of a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 17% of the maintenance dose, the second titration dose is about 33% of the maintenance dose, the third titration dose is about 50% of the maintenance dose, the fourth titration is about 66% of the maintenance dose and the fifth titration dose is about 83% of the maintenance dose.

In embodiment 30, the titration doses of any of embodiments 23(a)-(c), 24(a)-(c), 25(a)-(c), 26(a)-(c), 27(a)-(c), 28(a)-(c), or 29(a)-(c) are each administered for about four weeks before the administration of the next higher dose begins.

In embodiment 31, the GIP:GLP-1 Peptide of any of embodiments 23(a)-(c), 24(a)-(c), 25(a)-(c), 26(a)-(c), 27(a)-(c), 28(a)-(c), 29(a)-(c) or 30 is a peptide of SEQ ID NO: 3, or a pharmaceutically acceptable salt thereof.

In embodiment 32, the GIP:GLP-1 Peptide of any of embodiments 23(a)-(c), 24(a)-(c), 25(a)-(c), 26(a)-(c), 27(a)-(c), 28(a)-(c), 29(a)-(c), 30, or 31 has a receptor agonist potency ratio that is 2.5:1 to about 5:1 GIP to GLP-1.

In embodiment 33, the GIP:GLP-1 Peptide of any of embodiments 23(a)-(c), 24(a)-(c), 25(a)-(c), 26(a)-(c), 27(a)-(c), 28(a)-(c), 29(a)-(c), 30, or 31 has a receptor agonist potency ratio that is 2.5:1 to about 3.5:1 GIP to GLP-1.

In embodiment 34, is a composition comprising a GIP-GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1; and a pharmaceutically acceptable excipient.

In embodiment 34 (a) is a composition administered at least two weeks as an escalation dose.

In embodiment 34(a1) is a composition administered at least two weeks as an escalation dose.

In embodiment 34 (b) is a composition administered as a maintenance dose for at least two weeks.

In embodiment 35, is a GIP-GLP-1 Peptide for use to treat diabetes in a patient in need thereof, wherein the GIP:GLP-1 receptor potency ratio of the GIP-GLP-1 Peptide, as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1, is about 2.5:1 to about 10:1.

In embodiment 35(a) is a GIP-GLP-1 Peptide of embodiment 35 wherein the Peptide is administred for a minimum of about 2 weeks.

In embodiment 35(b) is a GIP-GLP-1 Peptide of embodiment 35 or 35(a) wherein the Peptide is administered as at least one escalation dose for a minimum of about 2 weeks.

Also provided herein are methods of using a GIP:GLP-1 Peptide in simultaneous, separate and sequential combinations with one or more agents selected from metformin, a thiazolidinedione, a sulfonylurea, a dipeptidyl peptidase 4 inhibitor, a sodium glucose co-transporter, a SGLT-2 inhibitor, a growth differentiation factor 15 modulator ("GDF15"), a peptide tyrosine tyrosine modulator ("PYY"), a modified insulin, amylin, a dual amylin calcitonin receptor agonist, and oxyntomodulin agonist ("OXM") in the treatment of a condition selected from the group consisting of type 2 diabetes, chronic kidney disease,

atherosclerosis, NALFD and NASH. Further provided herein are methods of using a GIP:GLP-1 Peptide in simultaneous, separate and sequential combinations with one or more agents selected from metformin, a thiazolidinedione, a sulfonylurea, a dipeptidyl peptidase 4 inhibitor, a sodium glucose co-transporter, a SGLT-2 inhibitor, GDF15, PYY, a modified insulin, amylin, a dual amylin calcitonin receptor agonist, and OXM in the improvement of glycemic control and/or weight management. Also provided herein are methods of using a GIP:GLP-1 Peptide in simultaneous, separate and sequential combinations with one or more agents selected from metformin, a thiazolidinedione, a sulfonylurea, a dipeptidyl peptidase 4 inhibitor, a sodium glucose co-transporter, a SGLT-2 inhibitor, GDF15, PYY, a modified insulin, amylin, a dual amylin calcitonin receptor agonist, and OXM to cure diabetes, induce remission or regression of diabetes, or prevent diabetes. In an embodiment, a compound of the present invention is provided in a fixed dose combination with one or more agents selected from metformin, a thiazolidinedione, a sulfonylurea, a dipeptidyl peptidase 4 inhibitor, a sodium glucose co-transporter, a SGLT-2 inhibitor,GDF15, PYY, a modified insulin, amylin, a dual amylin calcitonin receptor agonist, and OXM.

The present invention provides novel dosing regimens that include administering a titration dose about once weekly for a minimum of about two weeks and thereafter administering a maintenance dose wherein the titration dose is about 50% of the maintenance dose. In certain embodiment, the titration dose may be administered for about four weeks. In certain embodiments, the titration dose may be administered for more than about four weeks as determined by the nurse, patient and/or health care provider.

As used herein, the term "treating" or "to treat" includes restraining, slowing, stopping, or reversing the progression or severity of a symptom, condition, or disorder.

As used herein, "normalized against GIP and GLP-1" means that the native peptides, as provided herein as SEQ ID NO:1 and SEQ ID NO:2, are tested in the casein cAMP assay as a control for the test compound, and Raw CPM data for concentration curves of peptides, GLP-1, or GIP are converted to percent inhibition by subtracting nonspecific binding (binding in the presence of excess unlabeled GLP-1, or GIP, respectively) from the individual CPM values and dividing by the total binding signal, also corrected by subtracting nonspecific binding. Data are analyzed using four-

parameter (curve maximum, curve minimum, IC_{50}, Hill slope) nonlinear regression routines (Genedata Screener, version 12.0.4, Genedata AG, Basal, Switzerland).

GIP is a 42 amino acid peptide (SEQ ID NO:1), which, like GLP-1, is also known as an incretin, and plays a physiological role in glucose homeostasis by stimulating insulin secretion from pancreatic beta cells in the presence of glucose. GLP-1 is a 36 amino acid peptide, the major biologically active fragment of which ($GLP\text{-}1_{7\text{-}36}$) is produced as a 30-amino acid, C-terminal amidated peptide (SEQ ID NO:2).

The compounds of SEQ ID NO: 3 provide desired potency at each of the GIP and GLP-1 receptors. In an embodiment, compounds of SEQ ID NO: 3 have desirable GIP and GLP receptor activity wherein the GIP agonist potency is from about 2.5:1 to about 10 times the GLP1 receptor potency as measured by the casein cAMP assay, wherein the potency is normalized against native GIP and GLP on the day the assay is run. In an embodiment, compounds of SEQ ID NO: 3 have desirable GIP and GLP receptor activity wherein the GIP agonist potency is from about 2.5:1 to about 5 times the GLP1 receptor potency as measured by the casein cAMP assay, described herein below, wherein the potency is normalized against native GIP and GLP on the day the assay is run.

As used herein "maintenance dose" means an effective dose to treat the patient with a side-effect profile that supports chronic dosing. The term "effective dose" refers to the amount or dose of a GIP:GLP-1 Peptide, which, upon single or multiple dose administration to the patient, provides the desired effect in the patient under diagnosis or treatment. An effective doe can be determined by a person of skill in the art using the clinical trial descriptions set forth herein together with known techniques and by observing results obtained under analogous circumstances. In determining the effective amount for a subject, a number of factors are considered, including, but not limited to: the species of mammal; its size, age, and general health; the specific disease or disorder involved; the degree of or involvement or the severity of the disease or disorder; the response of the individual patient; the particular compound administered; the mode of administration; the bioavailability characteristics of the preparation administered; the dose regimen selected; the use of concomitant medication; and other relevant circumstances.

As used herein, the term "titration" or "titration dose(s)" also means and can be interchangable with an escalation or escalation dose(s).

As used herein, the term GIP to GLP-1 also means and can be interchangeable with GIP:GLP-1. Thus, when "about 2.5 to about 10:1 GIP to GLP-1" or "about 2.5:1 to about 10:1 GIP to GLP-1" is used, it also means about 2.5 to about 10 GIP activity to 1 GLP-1 activity or about 2.5 to about 10 GIP activity:1 GLP-1 activity.

When used herein in reference to one or more of the GIP or GLP-1 receptors, the terms "activity," "activate[s]" "activat[ing]" and the like refers to the capacity of a compound to bind to and induce a response at the receptor(s), as measured using assays known in the art, such as the in vitro assays described below. Such activity may be measured *in vivo* using serum. The receptor agonist potency ratio of a GIP:GLP-1 Peptide is measured using the casein cAMP assay, as described herein below.

The affinity of a particular GIP:GLP-1 co-agonist compound for each of the GIP and GLP-1 receptors may be measured using techniques known for measuring receptor binding levels in the art, including, for example those described in the examples below, and is commonly expressed as a Ki value; however, the GIP potency ratio that is about 2.5 to about 10 times the receptor potentcy at the GLP-1 receptor determined using the casein cAMP assay, below.

In an embodiment, a pharmaceutical composition of a GIP:GLP-1 Peptide is suitable for administration by a parenteral route (*e.g.*, subcutaneous, intravenous, intraperitoneal, intramuscular, or transdermal). In an embodiment, a pharmaceutical composition of a GIP:GLP-1 Peptide is suitable for oral administration (e.g., tablet, capsule). Such pharmaceutical compositions and processes for preparing same are generally well known in the art. (*See, e.g.*, Remington: The Science and Practice of Pharmacy (D.B. Troy, Editor, 21st Edition, Lippincott, Williams & Wilkins, 2006). In an embodiment of the present invention, the route of administration is subcutaneous. In an embodiment of the present invention, the route of administration is oral.

As used herein "glycemic control" refers to the maintenance or reduction of a patient's HbA1c levels; "improving" glycemic control refers to reductions in HbA1c.

As used herein "weight management" refers to the management of obesity in an individual; "improving" weight management refers to a reduction in body weight.

As used herein "HbA1c" refers to glycated hemoglobin levels, which develop when hemoglobin joins with glucose in the blood. HbA1c levels are a commonly used measure of glycemic control in patients with diabetes, with decreased HbA1c levels

generally indicating improved glycemic control. In the context of the methods of the present invention, the methods of the present invention result in a decrease in HbA1c. In certain embodiments, the decrease in HbA1c is decreased relative to the HbA1c levels resulting from treatment with a lower dose of a GIP:GLP-1 Peptide.

As used herein, the term "administering" means the administration by a nurse, health care provider, patient or any other individual including self-administration as directed by the doctor. This includes not only delivering into the body but also prescribing, dispensing or assisting in any way with delivery.

As used herein, the terms "treatment," "treat," "treating," and the like, mean to include slowing or attenuating the progression of a disease or disorder. The terms mean to alleviate, ameliorate, or reduce one or more symptoms of a disorder or condition, even if the disorder or condition is not eliminated. The term includes preventing the manifestation.

As used herein "diabetes remission" means that a patient, using a GIP:GLP-1 Peptide for the treatment of diabetes reaches their glycemic control treatment goal.

As used herein, the term GIP:GLP-1 Peptide is a compound, or a pharmaceutically acceptable salt thereof, with a GIP:GLP agonist potency ratio of from about 2.5:1 to about 10:1. The GIP:GLP-1 Peptide treatment to cure diabetes can prevent, reduce the severity of, or induce remission of diabetes in such patient. In an embodiment, a patient using a GIP:GLP-1 Peptide for treatment of diabetes, reaches their glycemic control treatment goal, and requires no concomitant diabetes medicine to maintain the glycemic control goal. In an embodiment, a patient using a GIP:GLP-1 Peptide in the treatment of diabetes reaches at least their glycemic control treatment goal, and the treatment goal is maintained with cessation of treatment using a GIP:GLP-1 Peptide and all other diabetes medication. In an embodiment, a patient using a GIP:GLP-1 Peptide in the treatment of diabetes reaches at least their glycemic control treatment goal, and the treatment goal is maintained for at least a about a month with cessation of treatment using a GIP:GLP-1 Peptide and all other diabetes medications. In an embodiment, a patient using a GIP:GLP-1 Peptide in the treatment of diabetes reaches at least their glycemic control treatment goal, and the treatment goal is maintained for at least about six months with cessation of treatment using a GIP:GLP-1 Peptide and all other diabetes medications. In an embodiment the patient is unable to reach their glycemic goals prior to a GIP:GLP-1

Peptide treatment. In an embodiment, the patient has failed to reach their glycemic goal using oral diabetes medication. In an embodiment, the patient has failed to reach their glycemic goal using metformin treatment. In an embodiment, the patient glycemic goal is less than about 5.7%.

As used herein "patient" or "patients" refers to a mammal in need of treatment for a condition or disorder. In an embodiment, the patient is a human with a disease or condition that would benefit from treatment with a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio of from about 2.5:1 to about 10:1.

As used herein "EDTA" means ethylenediaminetetraacetic acid. As used herein "DMSO" means dimethyl sulfoxide. As used herein "CPM" means counts per minute. As used herein "IBMX" means 3-isobutyl-1-methylxanthine. As used herein "LC/MS" means liquid chromatography/mass spectrometry. As used herein "HTRF" means homogeneous time-resolved fluorescence. As used herein "BSA" mean bovine serum albumin.

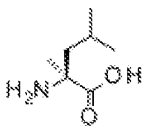
CURE DIABETES, INDUCE REMISSION OR REGRESSION OF DIABETES, OR PREVENT DIABETES

Despite advances in the treatment of diabetes, many patients receiving such treatment are unable to reach their glycemic control goal or HbA1c goal. This invention provides a cure for diabetes wherein a patient receiving treatment for diabetes using a GIP:GLP1 Peptide, is able to reach their HbA1c goal, and wherein such patient maintains their HbA1c goal after cessation of GIP:GLP1 Peptide treatment. In an embodiment, the patient receiving GIP:GLP1 Peptide treatment for diabetes maintains their HbA1c goal after cessation of all medications approved for use in the treatment of glycemic control or diabetes. As used herein, the term "diabetes medication," "diabetes medicine" and the like, means a medication approved by the pertinent regulatory agency for use in the treatment of glycemic control or Type II diabetes. In an embodiment, the HbA1c measurement in the patient treated for diabetes is less than or equal to about 5.9%. In an embodiment, the patient maintains their HbA1c goal level for at least one month without further GIP:GLP1 Peptide administration. In an embodiment, the patient previously treated for diabetes using GIP:GLP1 Peptide maintains their HbA1 goal level for at least one month without administration of further GIP:GLP1 Peptide or any other diabetes medication. In an embodiment, the patient maintains their HbA1c goal level for at least

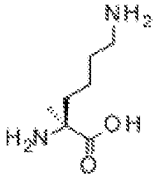
6 months without administration of further GIP:GLP1 Peptide or any other diabetes medication.

As used herein the term "amino acid" means both naturally occurring amino acids and unnatural amino acids. The amino acids are typically depicted using standard one letter codes (e.g., L = leucine), as well as alpha-methyl substituted residues of natural amino acids (e.g., α-methyl leucine, or αMeL and α-methyl lysine, or αMeK) and certain other unnatural amino acids, such as alpha amino isobutyric acid, or "Aib," "4Pal," "Orn," and the like. The structures of these amino acids appear below:

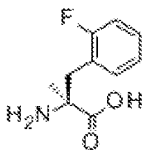
αMeL



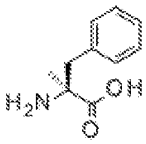
αMeK



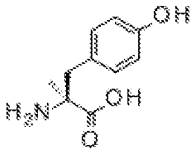
αMeF(2F)



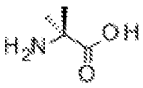
αMeF



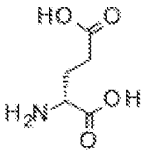
αMeY



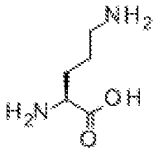
Aib



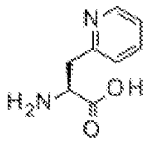
D-Glu



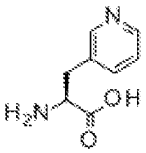
Orn



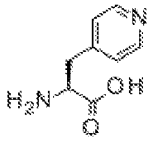
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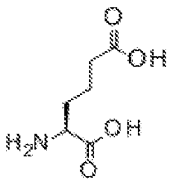
3Pal



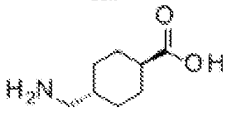
4Pal



Aad



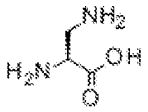
Tm



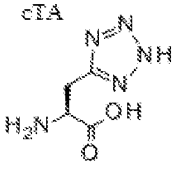
AOC



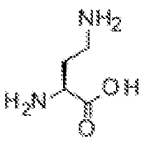
Dap



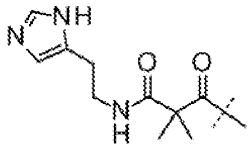
cTA



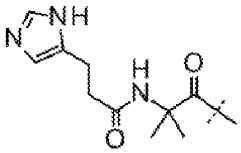
Dab



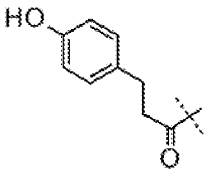
desH-ψ(NHCO)-Aib



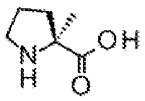
desHis-Aib



desY



αMeP



As used herein "Orn" means ornithine. As used herein "4Pal" means 3-(4-Pyridyl)-L-alanine. As used herein "αMeF(2F)" means alpha-methyl 2-Fl-phenylalanine. As used herein "αMeY," "αMeK," and "αMeL" mean alpha methyl tyrosine, alpha methyl lysine, and alpha methyl leucine, respectively. As used herein, "e" and "D-Glu" mean D-glutamic acid.

When used herein, the term "amino acid conjugated to a C_{16}-C_{22} fatty acid" refers to any natural or unnatural amino acid with a functional group that has been chemically modified to conjugate to a fatty acid by way of a direct bond to the fatty acid or, preferably, by way of a linker. Examples of such functional groups include amino, carboxyl, chloro, bromo, iodo, azido, alkynyl, alkenyl, and thiol groups. Examples of natural amino acids which include such functional groups include K (amino), C (thiol), E (carboxyl) and D (carboxyl). In an embodiment the conjugated amino acid is K.

The term "C_{16}-C_{22} fatty acid" as used herein means a carboxylic acid with between 16 and 22 carbon atoms. In an embodiment, the C_{16}-C_{22} fatty acid suitable for use herein can be a saturated diacid. In an embodiment, the fatty acid is C_{20}-C_{22}. In an embodiment q is selected from the group consisting of 14, 16, 18, and 20. In an embodiment q is selected from 18 and 20. In an embodiment q is 18. In an embodiment q is 20.

In an embodiment, specific saturated C_{16}-C_{22} fatty acids that are suitable for the compounds and uses thereof disclosed herein include, but are not limited to, hexadecanedioic acid (C_{16} diacid), heptadecanedioic acid (C_{17} diacid), octadecanedioic acid (C_{18} diacid), nonadecanedioic acid (C_{19} diacid), eicosanedioic acid (C_{20} diacid), heneicosanedioic acid (C_{21} diacid), docosanedioic acid (C_{22} diacid), including branched and substituted derivatives thereof.

In an embodiment, the C_{16}-C_{22} fatty acid is selected from the group consisting of a saturated C_{18} diacid, a saturated C_{19} diacid, a saturated C_{20} diacid, and branched and substituted derivatives thereof. In an embodiment, the C_{16}-C_{22} fatty acid is selected from the group consisting of stearic acid, arachadic acid and eicosanedioic acid. In an embodiment, the C_{16}-C_{22} fatty acid is arachadic acid.

As used herein "time-extension technology" means a peptide time-extension technology for example, recombinant human serum albumin ("rHSA"), peptide conjugation to a pharmaceutically acceptable polymer, such as polymeric sequence of amino acids ("XTEN"), unsulfated heparin-like carbohydrate polymer ("HEP"), hydroxyl ethyl starch ("HES"), llama heavy-chain antibody fragments ("VHH"), pegylation, Fc conjugation, bovine serum albumin ("BSA") (Sleep, D. *Epert Opin Drug Del* (2015) 12, 793-812; Podust VN *et.al.* J Control. Release, 2015; ePUB; Hey, T. et. al. in: R. Kontermann (Ed.), Therapeutic Proteins: Strategies to Modulate their Plasma Half-Lives, Wiley-VCH Verlag Gmbh & Co. KGaA, Weinheim, Germany, 2012, pp117-140; DeAngelis, PL, *Drug Dev Delivery* (2013) January, 12/31/2012. In an embodiment time-extension technology is applied using a linker group. In an embodiment, the time-extension technology is applied using 0, 1, 2, or 3 amino acid as linker.

A compound having a GIP potency ratio that is about 2.5 to about 10 times the receptor potency at the GLP-1 receptor may be further modified using a peptide time-extension technology for example, recombinant human serum albumin ("rHSA"), peptide conjugation to a pharmaceutically acceptable polymer, such as polymeric sequence of amino acids ("XTEN"), unsulfated heparin-like carbohydrate polymer ("HEP"), and hydroxyl ethyl starch ("HES").

In an embodiment is a GIP:GLP-1 Peptide of the formula:

$R_1X_1X_2X_3GTX_6TSDX_{10}X_{11}X_{12}X_{13}X_{14}DX_{16}X_{17}AX_{19}X_{20}X_{21}X_{22}X_{23}X_{24}X_{25}X_{26}X_{27}$ $X_{28}X_{29}X_{30}X_{31}$ (SEQ ID NO: 3)

wherein:

R_1 is a modification of the N-terminal amino group wherein the modification is selected from the group consisting of Ac and absent;

X_1 is selected from the group consisting of Y, H, D-Tyr, F, desH, and desY,

X_2 is selected from the group consisting of Aib, αMeP, A, P, and D-Ala;

or X_1 and X_2 combine to form desH-ψ[NHCO]-Aib;

X_3 is selected from the group consisting of E, N, Aad, and cTA;

X_6 is selected from the group consisting of F, αMeF, and αMeF(2F);

X_{10} is selected from the group consisting of A, L, H, 3Pal, 4Pal, V, Y, E, αMeF, αMeF(2F), I, αMeY, Q, D-His, D-Tyr, cTA, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)qCO_2H$;

X_{11} is selected from the group consisting of S, αMeS, and D-Ser;

X_{12} is selected from the group consisting of I, S, D-Ile, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)qCO_2H$;

X_{13} is selected from the group consisting of Nle, Aib, L, αMeL, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)qCO_2H$;

X_{14} is selected from the group consisting of L and K, wherein K is conjugated to a C_{16}-C_{22} fatty acid wherein said fatty acid is optionally conjugated to said K via a linker;

X_{16} is selected from the group consisting of K, E, Orn, Dab, Dap, S, T, H, Aib, αMeK, R, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)qCO_2H$;

X_{17} is selected from the group consisting of K, Q, I, and an amino acid conjugated to a C_{16}-C_{22} fatty acid wherein said fatty acid is optionally conjugated to said amino acid via a linker;

X_{19} is selected from the group consisting of Q, A, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)qCO_2H$;

X_{20} is selected from the group consisting of Aib, Q, H, R, K, αMeK, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)qCO_2H$;

X_{21} is selected from the group consisting of H, Aad, D, Aib, T, A, E, I, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)qCO_2H$;

X_{22} is selected from the group consisting of F and αMeF;

X_{23} is selected from the group consisting of I, L, A, G, F, H, E, V, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)qCO_2H$;

X_{24} is selected from the group consisting of S, Aad, D-Glu, E, Aib, H, V, A, Q, D, P, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)qCO_2H$;

X_{25} is selected from the group consisting of Y and αMeY;

X_{26} is selected from the group consisting of L, αMeL, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)qCO_2H$;

X_{27} is selected from the group consisting of L, I, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)qCO_2H$;

X_{28} is selected from the group consisting of E, A, S, D-Glu, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)qCO_2H$;

X_{29} is selected from the group consisting of Aib, G, A, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)qCO_2H$;

X_{30} is selected from the group consisting of C, G, G-R_2 and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO_2H;

X_{31} is absent or is selected from the group consisting of $PX_{32}X_{33}X_{34}$-R_2 (SEQ ID NO:4), $PX_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}$-$R_2$ (SEQ ID NO:5), $PX_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}$-$R_2$ (SEQ ID NO:6), K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO_2H] $X_{32}X_{33}X_{34}$-R_2 (SEQ ID NO:7), K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO_2H] $X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}$-$R_2$ (SEQ ID NO:8), and K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO_2H] $X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}$-$R_2$ (SEQ ID NO:9);

wherein:

X_{32} is S or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO_2H];

X_{33} is S or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO_2H];

X_{34} is selected from the group consisting of G, C, and K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO_2H];

X_{35} is A or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO_2H];

X_{36} is P or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO_2H];

X_{37} is P or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO_2H];

X_{38} is P or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO_2H];

X_{39} is selected from the group consisting of C, S, and K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO_2H];

X_{40} is selected from the group consisting of C and K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO_2H];

q is selected from the group consisting of 14, 15, 16, 17, 18, 19, and 20; and

R_2 is a modification of the C-terminal group, wherein the modification is NH_2 or absent;

or a pharmaceutically acceptable salt thereof;

wherein if X_{30} is G-R_2, then X_{31} is absent;

wherein no more than one of X_{10}, X_{12}, X_{13}, X_{14}, X_{16}, X_{17}, X_{19}, X_{20}, X_{21}, X_{23}, X_{24}, X_{26}, X_{27}, X_{28}, X_{29}, X_{30}, X_{31}, X_{32}, X_{33}, X_{34}, X_{35}, X_{36}, X_{37}, X_{38}, X_{39}, and X_{40} may be a substituent that contains a fatty acid; and

wherein no more than one of X_{30}, X_{34}, X_{39}, and X_{40} may be C; and

wherein if one of X_{30}, X_{34}, X_{39}, and X_{40} is C, then none of X_{10}, X_{12}, X_{13}, X_{14}, X_{16}, X_{17}, X_{19}, X_{20}, X_{21}, X_{23}, X_{24}, X_{26}, X_{27}, X_{28}, X_{29}, X_{30}, X_{31}, X_{32}, X_{33}, X_{34}, X_{35}, X_{36}, X_{37}, X_{38}, X_{39}, and X_{40} is a substituent that contains a fatty acid;

wherein the GIP:GLP-1 Peptide has a receptor agonist potency ratio that is about 2.5:1 to about 10:1.

A further embodiment provides a novel GIP:GLP-1 Peptide of SEQ ID NO:3, wherein the GIP:GLP-1 Peptide has a GIP:GLP-1 receptor agonist potency ratio that is

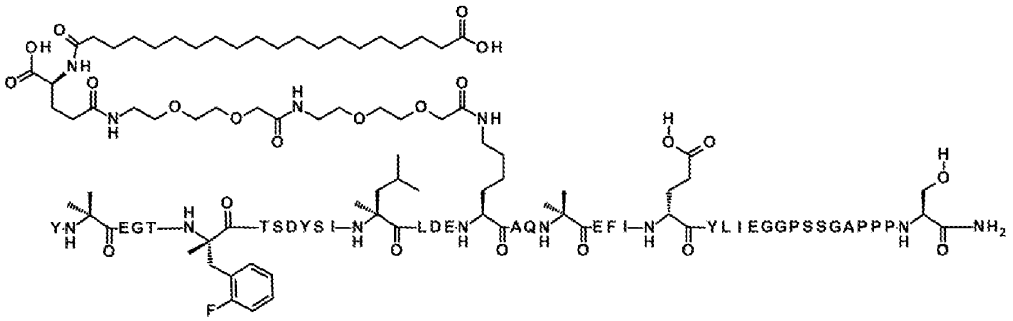
about 2.5:1 to about 5:1. A further embodiment of the present invention is a novel GIP:GLP-1 Peptide of SEQ ID NO:3, wherein the GIP:GLP-1 Peptide has a GIP:GLP-1 receptor agonist potency ratio that is about 2.5:1 to about 3.5:1.

The invention is further illustrated by the following compounds demonstrating the desired GIP potency ratio that is about 2.5:1 to about 10 times greater than the receptor potentcy at the GLP-1 receptor using the cAMP casein assay, however, these example peptides are not to be construed as limiting.

PEPTIDE SYNTHESIS – Peptide 1

Y-Aib-EGT-αMeF(2F)-TSDYSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-EFI-(D-Glu)-YLIEGGPSSGAPPPS-NH$_2$ (SEQ ID NO:10).

The structure of SEQ ID NO:10 is depicted below using the standard single letter amino acid codes with the exception of residues Aib2, αMeF(2F)6, αMeL13, K17, Aib20, D-Glu24, and Ser39 where the structures of these amino acid residues have been expanded:



The peptide backbone of Peptide 1 is synthesized using Fluorenylmethyloxycarbonyl (Fmoc)/tert-Butyl (t-Bu) chemistry on a Symphony X peptide synthesizer (Gyros Protein Technologies. Tucson, AZ).

The resin consists of 1% DVB cross-linked polystyrene (Fmoc-Rink-MBHA Low Loading resin, 100-200 mesh, EMD Millipore) at a substitution of 0.3-0.4 meq/g. Standard side-chain protecting groups were used. Fmoc-Lys(Mtt)-OH is used for the lysine at position 17 and Boc-Tyr(tBu)-OH) was used for the tyrosine at position 1. Fmoc groups are removed prior to each coupling step (2 x 7 minutes) using 20% piperidine in

DMF. All standard amino acid couplings are performed for 1 hour to a primary amine and 3 hour to a secondary amine, using an equal molar ratio of Fmoc amino acid (0.3 mM), diisopropylcarbodiimide (0.9 mM) and Oxyma (0.9 mM), at a 9-fold molar excess over the theoretical peptide loading. Exceptions are couplings to Cα-methylated amino acids, which are coupled for 3 hours. After completion of the synthesis of the peptide backbone, the resin is thoroughly washed with DCM for 6 times to remove residual DMF. The Mtt protecting group on the lysine at position 17 is selectively removed from the peptide resin using two treatments of 30% hexafluoroisopropanol (Oakwood Chemicals) in DCM (2 x 40-minute treatment).

Subsequent attachment of the fatty acid-linker moiety is accomplished by coupling of 2-[2-(2-Fmoc-amino-ethoxy)-ethoxy]-acetic acid (Fmoc-AEEA-OH, ChemPep, Inc.), Fmoc-glutamic acid α-t-butyl ester (Fmoc-Glu-OtBu, Ark Pharm, Inc.), eicosanedioic acid (WuXi AppTec, Shanghai, China). 3-Fold excess of reagents (AA: PyAOP: DIPEA=1: 1 :1 mol/mol) are used for each coupling that is 1-hour long.

After the synthesis is complete, the peptide resin is washed with DCM, and then thoroughly air-dried. The dry resin is treated with 10 mL of cleavage cocktail (trifluoroacetic acid: water: triisopropylsilane, 95:2.5:2.5 v/v) for 2 hours at room temperature. The resin is filtered off, washed twice each with 2 mL of neat TFA, and the combined filtrates are treated with 5-fold excess volume of cold diethyl ether (-20°C) to precipitate the crude peptide. The peptide/ether suspension is then centrifuged at 3500 rpm for 2 min to form a solid pellet, the supernatant is decanted, and the solid pellet is triturated with ether two additional times and dried in vacuo. The crude peptide is solubilized in 20% acetonitrile/20%Acetic acid/60%water and purified by RP- HPLC on a Luna 5 μm Phenyl-Hexyl preparative column (21 x 250 mm, Phenomenex) with linear gradients of 100% acetonitrile and 0.1% TFA/water buffer system (30-50% acetonitrile in 60 min). The purity of peptide is assessed using analytical RP-HPLC and pooling criteria is >95%. The main pool purity of compound 1 is found to be 98.0%. Subsequent lyophilization of the final main product pool yielded the lyophilized peptide TFA salt. The molecular weight is determined by LC- MS (obsd: M+3 =1657.2; Calc M+3 =1657.0).

Peptides 2 through Peptide 265

The compounds according to Peptide 2 (SEQ ID NO:11) through Peptide 265 (SEQ ID NO:145), shown in Table 1 below, are prepared substantially as described by the procedures of Peptide 1.

Binding Assays

Glucagon (referred to as Gcg) is a Reference Standard prepared at Eli Lilly and Company. GLP-1, 7-36-NH_2 (referred to as GLP-1) is obtained from CPC Scientific (Sunnyvale, CA, 97.2% purity, 100 µM aliquots in 100% DMSO). GIP 1-42 (referred to as GIP) is prepared at Lilly Research Laboratories using peptide synthesis and HPLC chromatography as described above (>80% purity, 100 µM aliquots in 100% DMSO). [^{125}I]-radiolabeled Gcg, GLP-1, or GIP is prepared using [^{125}I]-lactoperoxidase and obtained from Perkin Elmer (Boston, MA).

Stably transfected cell lines are prepared by subcloning receptor cDNA into a pcDNA3 expression plasmid and transfected into human embryonic kidney (HEK) 293 (hGcgR and hGLP-1R) or Chinese Hamster Ovary (CHO) (hGIPR) cells followed by selection with Geneticin (hGLP-1R and hGIPR) or hygromycin B (hGcgR).

Two methods are used for the preparation of crude cell membranes.

Method 1: Frozen cell pellets are lysed on ice in hypotonic buffer containing 50 mM Tris HCl, pH 7.5, and Roche Complete™ Protease Inhibitors with EDTA. The cell suspension is disrupted using a glass Potter-Elvehjem homogenizer fitted with a Teflon® pestle for 25 strokes. The homogenate is centrifuged at 4°C at 1100 x g for 10 minutes. The supernatant is collected and stored on ice while the pellets are resuspended in homogenization buffer and rehomogenized as described above. The homogenate is centrifuged at 1100 x g for 10 minutes. The second supernatant is combined with the first supernatant and centrifuged at 35000 x g for 1 hour at 4°C. The resulting membrane pellet is resuspended in homogenization buffer containing protease inhibitors at approximately 1 to 3 mg/mL, quick frozen in liquid nitrogen and stored as aliquots in a -80°C freezer until use.

Method 2: Frozen cell pellets are lysed on ice in hypotonic buffer containing 50 mM Tris HCl, pH 7.5, 1 mM $MgCl_2$, Roche Complete™ EDTA-free Protease Inhibitors and 25 units/ml DNAse I (Invitrogen). The cell suspension is disrupted using a glass

Potter-Elvehjem homogenizer fitted with a Teflon® pestle for 20 to 25 strokes. The homogenate is centrifuged at 4°C at 1800 x g for 15 minutes. The supernatant is collected and stored on ice while the pellets are resuspended in homogenization buffer (without DNAse I) and rehomogenized as described above. The homogenate is centrifuged at 1800 x g for 15 minutes. The second supernatant is combined with the first supernatant and centrifuged an additional time at 1800 x g for 15 minutes. The overall supernatant is then centrifuged at 25000 x g for 30 minutes at 4°C. The resulting membrane pellet is resuspended in homogenization buffer (without DNAse I) containing protease inhibitors at approximately 1 to 3 mg/mL and stored as aliquots in a -80°C freezer until use.

Binding Determination Methods

The equilibrium binding dissociation constants (K_d) for the various receptor/radioligand interactions are determined from homologous competition binding analysis instead of saturation binding due to high propanol content in the [^{125}I] stock material. The K_d values determined for the receptor preparations were as follows: hGcgR (3.9 nM), hGLP-1R (1.2 nM) and hGIPR (0.14 nM).

[^{125}I]-Glucagon Binding

The human Gcg receptor binding assays are performed using a Scintillation Proximity Assay (SPA) format with wheat germ agglutinin (WGA) beads (Perkin Elmer). The binding buffer contains 25 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES), pH 7.4, 2.5 mM $CaCl_2$, 1 mM $MgCl_2$, 0.1% (w/v) bacitracin (Research Products), 0.003% (w/v) Polyoxyethylenesorbitan monolaurate (TWEEN®-20), and Roche Complete™ Protease Inhibitors without EDTA. Peptides and Gcg are thawed and 3-fold serially diluted in 100% DMSO (10 point concentration response curves). Next, 5 µL serially diluted compound or DMSO is transferred into Corning® 3632 clear bottom assay plates containing 45 µL assay binding buffer or unlabeled Gcg control (non-specific binding or NSB, at 1 µM final). Then, 50 µL [^{125}I]-Gcg (0.15 nM final), 50 µL human GcgR membranes (1.5 µg/well) and 50 µL of WGA SPA beads (80 to 150 µg/well) are added with a Biotek Multiflo dispenser. Plates are sealed and mixed on a plate shaker (setting 6) for 1 minute and read with a PerkinElmer Trilux MicroBeta® scintillation counter after 12 hours of incubation/settling time at room temperature. Final assay concentration ranges for peptides tested in response curves is typically 1150 nM to 0.058 nM and for the control Gcg from 1000 nM to 0.05 nM.

[^{125}I]-GLP-1 Binding

The human GLP-1 receptor binding assay is performed using an SPA format with WGA beads. The binding buffer contains 25 mM HEPES, pH 7.4, 2.5 mM $CaCl_2$, 1 mM $MgCl_2$, 0.1% (w/v) bacitracin, 0.003% (w/v) TWEEN®-20, and Roche Complete™ Protease Inhibitors without EDTA. Peptides and GLP-1 are thawed and 3-fold serially diluted in 100% DMSO (10 point concentration response curves). Next, 5 µL serially diluted compound or DMSO is transferred into Corning® 3632 clear bottom assay plates containing 45 µL assay binding buffer or unlabeled GLP-1 control (non-specific binding or NSB, at 0.25 µM final). Then, 50 µL [^{125}I]-GLP-1 (0.15 nM final), 50 µL human GLP-1R membranes (0.5 µg/well and 50 µL of WGA SPA beads (100 to 150 µg/well) are added with a Biotek Multiflo dispenser. Plates are sealed and mixed on a plate shaker (setting 6) for 1 minute and read with a PerkinElmer Trilux MicroBeta® scintillation counter after 5 to 12 hours of incubation/settling time at room temperature. Final assay concentration ranges for peptides tested in response curves are typically 1150 nM to 0.058 nM and for the control GLP-1, 250 nM to 0.013 nM.

[125I]-GIP Binding

The human GIP receptor binding assay is performed using an SPA format with WGA beads. The binding buffer contains 25 mM HEPES, pH 7.4, 2.5 mM $CaCl_2$, 1 mM $MgCl_2$, 0.1% (w/v) bacitracin, 0.003% (w/v) TWEEN®-20, and Roche Complete™ Protease Inhibitors without EDTA. Peptides and GIP are thawed and 3 fold serially diluted in 100% DMSO (10 point concentration response curves). Next, 5 µL serially diluted compound or DMSO is transferred into Corning® 3632 clear bottom assay plates containing 45 µL assay binding buffer or unlabeled GIP control (non-specific binding or NSB, at 0.25 µM final). Then, 50 µL [^{125}I]-GIP (0.075-0.15 nM final), 50 µL human GIPR membranes (3 µg/well) and 50 µL of WGA SPA beads (100 to 150 µg/well) are added with a Biotek Multiflo dispenser. Plates are sealed and mixed on a plate shaker (setting 6) for 1 minute and read with a PerkinElmer Trilux MicroBeta® scintillation counter after 2.5 to 12 hours of incubation/settling time at room temperature. Final assay concentration ranges for peptides tested in response curves is typically 1150 to 0.058 nM or 115 nM to 0.0058 nM and for the control GIP, 250 nM to 0.013 nM.

Binding Assay Data Normalization

Raw CPM data for concentration curves of peptides, Gcg, GLP-1, or GIP are converted to percent inhibition by subtracting nonspecific binding (binding in the presence of excess unlabeled Gcg, GLP-1, or GIP, respectively) from the individual CPM values and dividing by the total binding signal, also corrected by subtracting nonspecific binding. Data are analyzed using four-parameter (curve maximum, curve minimum, IC_{50}, Hill slope) nonlinear regression routines (Genedata Screener, version 12.0.4, Genedata AG, Basal, Switzerland). The affinity constant (K_i) is calculated from the absolute IC_{50} value based upon the equation $K_i = IC_{50}/(1 + D/K_d)$ where D = the concentration of radioligand used in the experiment, IC_{50} is the concentration causing 50% inhibition of binding and K_d is the equilibrium binding dissociation constant of the radioligand (described above). Values for K_i are reported as the geometric mean, with error expressed as the standard error of the mean (SEM) and n is equal to the number of independent replicates (determined in assays performed on different days). Geometric Means are calculated as follows:

$$\text{Geometric Mean} = 10^{(\text{Arithmetic Mean of Log Ki Values})}$$

The Ki Ratio (Ki for native control peptide/Ki for test compound) at each receptor and each species is calculated. The Ki Ratio is a rapid indication of the apparent affinity of a peptide compared to the native control peptide. A Ki Ratio < 1 indicates that the test peptide has a lower affinity (higher Ki value) for the receptor than the native peptide, whereas a Ki Ratio >1 indicates that the test peptide has a higher affinity (lower Ki value) for the receptor than the native peptide.

Example 1

cAMP Pharmacological Functional Assay in presence of casein

An additional set of cAMP assays are conducted in HEK293 cells expressing the human GLP-1 receptor (GLP-1R), gastric inhibitory peptide receptor (GIPR), Glucagon receptor (GcgR). Pharmacological activity of the hGLP1R/GIPR peptides are determined in HEK293 cells stably expressing the human GLP-1 receptor (GLP-1R), gastric inhibitory peptide receptor (GIPR), or GLP-2 receptor (GLP-2R). Each receptor over-expressing cell line (20 µl) is treated with the test peptide in DMEM (Gibco Cat# 31053)

supplemented with 0.1% Casein (Sigma Cat# C4765), 250 µM IBMX, 1X GlutaMAXTM (Gibco Cat# 35050), and 20 mM HEPES (HyClone Cat# SH30237.01) in a 20 µl assay volume. After 60 minute incubation at room temperature, the resulting increase in intracellular cAMP is quantitatively determined using the CisBio cAMP Dynamic 2 HTRF Assay Kit (62AM4PEJ). The Lysis buffer containing cAMP-d2 conjugate (20 µl) and the antibody anti-cAMP-Eu3+-Cryptate (20 µl) are then added to determine the cAMP level. After 1hour-incubation at room temperature, HTRF signal is detected with an Envision 2104 plate reader (PerkinElmer). Each of the two incubation steps (60 minutes and 1hour) may be conducted at about room temperature or about 37C, so long as both the 60 minute and 1hour incubations are completed at about the same temperature for each run of the assay. Fluorescent emission at 620 nm and at 665 nm is measured and the ratio between 620 nm and at 665 nm is calculated and then are converted to nM cAMP per well using a cAMP standard curve. Dose response curves of compounds are plotted as the percentage of stimulation normalized to minimum (buffer only) and maximum (maximum concentration of each control ligand) values and analyzed using a four parameter non-liner regression fit with a variable slope (Genedata Screener 13). EC50 is the concentration of compound causing half-maximal simulation in a dose response curve. A relative EC_{50} value is derived by non-linear regression analysis using the percent maximal response vs. the concentration of peptide added, fitted to a four-parameter logistic equation.

Using Homogeneous Time Resolved Fluorescence methods, assays are conducted to determine the intrinsic potency of Example and comparator molecules performed in the presence of casein (instead of serum albumin) as a nonspecific blocker, which does not interact with the fatty acid moieties of the analyzed molecules.

Intracellular cAMP levels are determined by extrapolation using a standard curve. Dose response curves of compounds are plotted as the percentage of stimulation normalized to minimum (buffer only) and maximum (maximum concentration of each control ligand) values and analyzed using a four parameter non-linear regression fit with a variable slope (Genedata Screener 13). EC_{50} is the concentration of compound causing half-maximal simulation in a dose response curve. Each relative EC50 value for the Geometric mean calculation is determined from a curve fitting.

Concentration response curves of compounds are plotted as the percentage of stimulation normalized to minimum (buffer only) and maximum (maximum concentration of each control ligand) values and analyzed using a four parameter non-liner regression fit with a variable slope (Genedata Screener 13). EC50 is the concentration of compound causing half-maximal simulation in a dose response curve. The EC_{50} summary statistics are computed as follows:

Geometric mean:

GM = 10^(arithmetic mean of $\log_{10}$ transformed EC_{50} values).

The standard error of the mean is reported:

SEM = geometric mean x (standard deviation of $\log_{10}$ transformed EC_{50} values / square root of the # of runs) x $\log_e$ of 10.

The log transform accounts for the EC_{50} values falling on a multiplicative, rather than an arithmetic scale.

Each day the assay is run, the test peptides are run plus the native ligands GIP and GLP-1 and buffer only as baseline (minimum), and the highest concentration of the respective GIP and GLP-1 standard that day is used as a maximum for the calculation.

Table 1. Functional activation of hGLP-1R and hGIPR in the presence of 0.1% Casein.

Peptide Number	**Compound Name**	**SEQ ID NO**	**hGIPR cAMP EC_{50} ratio**	**hGLP1R cAMP EC_{50} ratio**	**[hGIPR/ hGLP1R] EC_{50} Ratio**
1	Y-Aib-EGT-αMeF(2F)-TSDYSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH_2)$_{18}$-CO_2H)AQ-Aib-EFI-(D-Glu)-YLIEGGPSSGAPPPS-NH_2	10	4.65	1.12	4.15
2	Y-Aib-EGT-αMeF(2F)-TSDYSI-αMeL-LD-Orn-K((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH_2)$_{16}$-CO_2H)AQ-Aib-EFI-(D-Glu)-YLIEGGPSSGAPPPS-NH_2	11	5.89	0.888	6.63

3	Y-Aib-EGT-αMeF(2F)-TSDYSI-αMeL-LD-Orn-K((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-EFI-(D-Glu)-YLIEGGPSSGAPPPS-NH$_2$	12	4.51	1.25	3.61
4	Y-Aib-EGT-αMeF(2F)-TSD-4Pal-SI-αMeL-LD-Orn-K((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{16}$-CO$_2$H)AQ-Aib-EFI-(D-Glu)-αMeY-LIEGGPSSGAPPPS-NH$_2$	13	5.95	1.41	4.22
8	Y-Aib-EGTFTSDYSILLDKK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-AFIEYLIEGGPSSGAPPPS-NH$_2$	14	1.97	0.419	4.70
9	Y-Aib-EGTFTSDYSILLDSK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-AFIEYLIEGGPSSGAPPPS-NH$_2$	15	0.768	0.314	2.45
20	Y-Aib-EGTFTSDYSI-αMeL-LDKK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-AFIEYLIEGGPSSGAPPPS-NH$_2$	16	2.81	0.577	4.87
21	Y-Aib-EGTFTSDYSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-αMeK-AFIEYLLEGGPSSGAPPPS-NH$_2$	17	1.95	0.402	4.85
22	Y-Aib-EGTFTSDYSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-αMeK-AFIEYLLE-Aib-GPSSGAPPPS-NH$_2$	18	1.86	0.29	6.41
25	Y-Aib-EGTFTSDYSK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)LLDKIAQ-Aib-AFIEYLIEGGPSSGAPPPS-NH$_2$	19	0.636	0.197	3.23
26	Y-Aib-EGTFTSDYSIK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)LDKIAQ-Aib-AFIEYLIEGGPSSGAPPPS-NH$_2$	20	0.585	0.238	2.46
29	Y-Aib-EGTFTSDYSILLDK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)IAQ-Aib-AFIEYLIEGGPSSGAPPPS-NH$_2$	21	0.536	0.0671	7.99
31	Y-Aib-EGTFTSDYSILLDKIAK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)-Aib-AFIEYLIEGGPSSGAPPPS-NH$_2$	22	0.456	0.0708	6.44

32	Y-Aib-EGTFTSDYSILLDKIAQ-Aib-K((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)FIEYLIEGGPSSGAPPPS-NH$_2$	23	0.84	0.136	6.18
33	Y-Aib-EGTFTSDYSILLDKIAQ-Aib-AFK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)EYLIEGGPSSGAPPPS-NH$_2$	24	0.00222	0.000256	8.67
34	Y-Aib-EGTFTSDYSILLDKIAQ-Aib-AFIK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)YLIEGGPSSGAPPPS-NH$_2$	25	0.393	0.0392	10.03
37	Y-Aib-EGTFTSDYSILLDKIAQ-Aib-AFIEYLIK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)GGPSSGAPPPS-NH$_2$	26	0.532	0.0533	9.98
41	Y-Aib-EGTFTSDYSILLDKIAQ-Aib-AFIEYLIEGGPK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)SGAPPPS-NH$_2$	27	0.637	0.0637	10.00
46	Y-Aib-EGTFTSDYSILLDKIAQ-Aib-AFIEYLIEGGPSSGAPK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)PS-NH$_2$	28	0.828	0.0969	8.54
47	Y-Aib-EGTFTSDYSILLDKIAQ-Aib-AFIEYLIEGGPSSGAPPK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)S-NH$_2$	29	0.654	0.089	7.35
48	Y-Aib-EGTFTSDYSILLDKIAQ-Aib-AFIEYLIEGGPSSGAPPPK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)-NH$_2$	30	0.863	0.0966	8.93
50	Y-Aib-EGTFTSDYSILLDKK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-AFIEYLIEGGPSSG-NH$_2$	31	1.96	0.675	2.90
51	Y-Aib-EGTFTSDYSILLDKK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-AFIEYLIEGG-NH$_2$	32	1.69	0.426	3.97
52	Y-Aib-EGTFTSDYSI-αMeL-LDSK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-AFIEYLIEGGPSSGAPPPS-NH$_2$	33	1.4	0.514	2.72
60	Y-Aib-EGTFTSDYSI-αMeL-LD-Aib-K((2-[2-(2-Amino-ethoxy)-ethoxy]-	34	1.06	0.237	4.47

	acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-AFIEYLIEGGPSSGAPPPS-NH$_2$				
62	Y-Aib-EGTFTSDYSI-αMeL-LDKK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-AFIEYLIEGG-NH$_2$	35	2.33	0.463	5.03
63	Y-Aib-EGTFTSDYSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-AFIEYLIEGG-NH$_2$	36	1.58	0.386	4.09
64	Y-Aib-EGTFTSDYSI-αMeL-LDSK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-AFIEYLIEGG-NH$_2$	37	1.57	0.429	3.66
65	Y-Aib-EGTFTSDYSI-αMeL-LDTK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-AFIEYLIEGG-NH$_2$	38	1.04	0.233	4.46
66	Y-Aib-EGTFTSDYSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-AFIEYLLEGGPSSGAPPPS-NH$_2$	39	1.89	0.255	7.41
68	Y-Aib-EGTFTSDY-αMeS-ILLDKK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-AFIEYLIEGGPSSGAPPPS-NH$_2$	40	1.67	0.354	4.72
69	Y-Aib-EGT-αMeF-TSDYSI-αMeL-LDKK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-AFIEYLIEGGPSSGAPPPS-NH$_2$	41	2.73	0.85	3.21
73	Y-Aib-EGTFTSDYSILLDKIAQ-Aib-AFIEYLIK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)GG-NH$_2$	42	0.174	0.0225	7.73
80	Y-(D-Ala)-EGTFTSDYSILLDKK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-AFIEYLIEGGPSSGAPPPS-NH$_2$	43	1.09	0.227	4.80
81	Y-Aib-EGTFTSDY-(D-Ser)-ILLDKK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-AFIEYLIEGGPSSGAPPPS-NH$_2$	44	0.373	0.063	5.92
83	Y-Aib-EGTFTSDYSILLDKK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-	45	0.804	0.166	4.84

	CO-$(CH_2)_{18}$-CO_2H)AQ-Aib-AFIEYLI-(D-Glu)-GGPSSGAPPPS-NH_2				
84	Y-Aib-EGTFTSDYSILLDKK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-$(CH_2)_{18}$-CO_2H)AQ-Aib-AFI-(D-Glu)-YLIEGGPSSGAPPPS-NH_2	46	1.59	0.173	9.19
88	Y-Pro-EGTFTSDYSILLDKK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-$(CH_2)_{18}$-CO_2H)AQ-Aib-AFIEYLIEGGPSSGAPPPS-NH_2	47	0.392	0.0918	4.27
89	Y-Aib-Aad-GTFTSDYSILLDKK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-$(CH_2)_{18}$-CO_2H)AQ-Aib-AFIEYLIEGGPSSGAPPPS-NH_2	48	1.57	0.175	8.97
95	Y-Aib-EGT-αMeF-TSDYSILLDKIAQ-Aib-AFIEYLIK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-$(CH_2)_{18}$-CO_2H)GG-NH_2	49	0.145	0.0576	2.52
97	Y-Aib-EGTFTSDYSI-αMeL-LDKIAQ-Aib-AFIEYLIK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-$(CH_2)_{18}$-CO_2H)GG-NH_2	50	0.0953	0.0268	3.56
98	Y-Aib-EGT-αMeF-TSDYSILLDKK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-$(CH_2)_{18}$-CO_2H)AQ-Aib-AFIEYLIEGGPSSG-NH_2	51	2.43	0.384	6.33
99	Y-Aib-EGT-αMeF-TSDYSI-αMeL-LDSK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-$(CH_2)_{18}$-CO_2H)AQ-Aib-AFIEYLIEGGPSSG-NH_2	52	2.27	0.629	3.61
103	Y-Aib-EGT-αMeF(2F)-TSDYSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-$(CH_2)_{18}$-CO_2H)AQ-Aib-EFIEYLIEGG-NH_2	53	2.01	0.655	3.07
104	Y-Aib-EGT-αMeF(2F)-TSDYSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-$(CH_2)_{16}$-CO_2H)AQ-Aib-EFIEYLIEGG-NH_2	54	4.93	1.85	2.66
108	Y-Aib-EGTFTSDYSILLDKK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)-AOC-(γGlu)-CO-$(CH_2)_{18}$-CO_2H)AQ-Aib-AFIEYLIEGGPSSGAPPPS-NH_2	55	2.19	0.218	10.05
109	Y-Aib-EGTFTSDYSILLDKK(AOC-(2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)-(γGlu)-CO-$(CH_2)_{18}$-CO_2H)AQ-Aib-AFIEYLIEGGPSSGAPPPS-NH2	56	1.83	0.182	10.05

110	Y-Aib-EGTFTSDYSILLDKK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)-(γGlu)-(Trx)-CO-$(CH_2)_{18}$-CO_2H)AQ-Aib-AFIEYLIEGGPSSGAPPPS-NH_2	57	0.929	0.358	2.59
111	Y-Aib-EGTFTSDYSILLDKK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)-(Trx)-(γGlu)-CO-$(CH_2)_{18}$-CO_2H)AQ-Aib-AFIEYLIEGGPSSGAPPPS-NH_2	58	1.1	0.209	5.26
112	Y-Aib-EGTFTSDYSILLDKK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)-(εK)-(γGlu)-CO-$(CH_2)_{18}$-CO_2H)AQ-Aib-AFIEYLIEGGPSSGAPPPS-NH_2	59	1.53	0.402	3.81
113	Y-Aib-EGTFTSDYSILLDKK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(εK)-CO-$(CH_2)_{18}$-CO_2H)AQ-Aib-AFIEYLIEGGPSSGAPPPS-NH_2	60	1.39	0.275	5.05
114	Y-Aib-EGTFTSDYSILLDKK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)-(εK)-(εK)-CO-$(CH_2)_{18}$-CO_2H)AQ-Aib-AFIEYLIEGGPSSGAPPPS-NH_2	61	1.65	0.234	7.05
115	Y-Aib-EGT-αMeF-TSDYSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-$(CH_2)_{18}$-CO_2H)AQ-Aib-AFIEYLIEGGPSSGAPPPS-NH_2	62	1.85	0.743	2.49
118	Y-Aib-EGT-αMeF(2F)-TSDYSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-$(CH_2)_{18}$-CO_2H)AQ-Aib-EFIEYLIEGGPSSGAPPPS-NH_2	63	3.42	1.13	3.03
120	Y-Aib-cTA-GT-αMeF-TSDYSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-$(CH_2)_{18}$-CO_2H)AQ-Aib-AFIEYLIEGGPSSGAPPPS-NH_2	64	1.67	0.319	5.24
123	Y-Aib-EGT-αMeF-TSDYSI-αMeL-LDKK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-$(CH_2)_{18}$-CO_2H)AQ-Aib-EFIEYLIEGGPSSG-NH_2	65	4.04	1.58	2.56
125	Y-Aib-EGT-αMeF-TSDYSI-αMeL-LDKK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)$_2$-CO-$(CH_2)_{18}$-CO_2H)AQ-Aib-AFIEYLIEGGPSSGAPPPS-NH_2	66	3.79	1.31	2.89
126	Y-Aib-EGT-αMeF-TSDYSI-αMeL-LDKK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-$(CH_2)_{18}$-CO_2H)AQ-Aib-AFIEYLIEAGPSSGAPPPS-NH_2	67	2.53	0.869	2.91
128	Y-Aib-EGT-αMeF-TSDHSILLDKK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-	68	2.46	0.7	3.51

	(γGlu)-CO-(CH_2)$_{18}$-CO_2H)AQ-Aib-AFIEYLIEGGPSSGAPPPS-NH_2				
129	Y-Aib-EGT-αMeF-TSDLSILLDKK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH_2)$_{18}$-CO_2H)AQ-Aib-AFIEYLIEGGPSSGAPPPS-NH_2	69	1.88	0.543	3.46
137	Y-Aib-EGT-αMeF-TSDYSI-αMeL-LDKK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH_2)$_{18}$-CO_2H)AQ-Aib-Aad-FIEYLIEGGPSSGAPPPS-NH_2	70	4.47	1.25	3.58
139	Y-Aib-EGT-αMeF-TSDYSI-αMeL-LDKK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH_2)$_{18}$-CO_2H)AQ-Aib-TFIEYLIEGGPSSGAPPPS-NH_2	71	3.61	1.13	3.19
140	Y-Aib-EGT-αMeF-TSDYSI-αMeL-LDKK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH_2)$_{18}$-CO_2H)AQ-Aib-DFIEYLIEGGPSSGAPPPS-NH_2	72	3.76	1.16	3.24
143	Y-Aib-EGT-αMeF-TSDYSI-αMeL-LDKK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH_2)$_{18}$-CO_2H)AQ-Aib-Aib-FIEYLIEGGPSSGAPPPS-NH_2	73	2.78	0.714	3.89
144	Y-Aib-EGT-αMeF-TSDYSI-αMeL-LDKK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH_2)$_{18}$-CO_2H)AQH-Aib-FIEYLIEGGPSSGAPPPS-NH_2	74	3.6	0.851	4.23
147	Y-Aib-EGT-αMeF(2F)-TSDYSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH_2)$_{18}$-CO_2H)AQ-Aib-EFI-Aad-YLIEGGPSSGAPPPS-NH_2	75	4.14	1.13	3.66
148	Y-Aib-EGT-αMeF(2F)-TSDYSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH_2)$_{18}$-CO_2H)AQ-Aib-EFIAYLIEGGPSSGAPPPS-NH_2	76	2.7	0.859	3.14
149	Y-Aib-EGT-αMeF(2F)-TSDYSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH_2)$_{18}$-CO_2H)AQ-Aib-EFIVYLIEGGPSSGAPPPS-NH_2	77	1.82	0.484	3.76
150	Y-Aib-EGT-αMeF(2F)-TSDYSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH_2)$_{18}$-CO_2H)AQ-Aib-EFISYLIEGGPSSGAPPPS-NH_2	78	2.64	0.79	3.34
151	Y-Aib-EGT-αMeF(2F)-TSDYSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-	79	0.262	0.0278	9.42

	acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-EFIPYLIEGGPSSGAPPPS-NH$_2$				
152	Y-Aib-EGT-αMeF(2F)-TSDYSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-EFI-Aib-YLIEGGPSSGAPPPS-NH$_2$	80	2.57	0.484	5.31
153	Y-Aib-EGT-αMeF(2F)-TSDYSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-EFIHYLIEGGPSSGAPPPS-NH$_2$	81	1.7	0.501	3.39
154	Y-Aib-EGT-αMeF(2F)-TSDHSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-EFIEYLIEGGPSSGAPPPS-NH$_2$	82	5.9	1.23	4.80
155	Y-Aib-EGT-αMeF(2F)-TSD-cTA-SI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-EFIEYLIEGGPSSGAPPPS-NH$_2$	83	0.584	0.0978	5.97
157	Y-Aib-EGT-αMeF(2F)-TSD-3Pal-SI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-EFIEYLIEGGPSSGAPPPS-NH$_2$	84	3.15	1.25	2.52
167	Y-Aib-EGT-αMeF(2F)-TSDHSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-TFI-(D-Glu)-YLIEGGPSSG-NH$_2$	85	0.291	0.0487	5.98
168	Y-Aib-EGT-αMeF(2F)-TSDHSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-TFI-(D-Glu)-YLIEGGPSSGAPPPS-NH$_2$	86	0.313	0.0323	9.69
169	Y-Aib-EGT-αMeF(2F)-TSDHSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{16}$-CO$_2$H)AQ-Aib-TFI-(D-Glu)-YLIEGGPSSGAPPPS-NH$_2$	87	0.122	0.0136	8.97
171	Y-Aib-EGT-αMeF(2F)-TSDHSI-αMeL-LD-Orn-K((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-TFI-(D-Glu)-YLIEGGPSSGAPPPS-NH$_2$	88	0.471	0.0609	7.73
172	Y-Aib-EGT-αMeF(2F)-TSDHSI-αMeL-LD-Dab-K((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-	89	0.1	0.038	2.63

	CO_2H)AQ-Aib-TFI-(D-Glu)-YLIEGGPSSGAPPPS-NH_2				
173	Y-Aib-EGT-αMeF(2F)-TSDHSI-αMeL-LD-Dap-K((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH_2)$_{18}$-CO_2H)AQ-Aib-TFI-(D-Glu)-YLIEGGPSSGAPPPS-NH_2	90	0.179	0.0373	4.80
174	Y-Aib-EGT-αMeF(2F)-TSDHSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-CO-(CH_2)$_{18}$-CO_2H)AQ-Aib-TFI-(D-Glu)-YLIEGGPSSGAPPPS-NH_2	91	0.483	0.0968	4.99
176	Y-Aib-EGT-αMeF(2F)-TSDHSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(εK)-CO-(CH_2)$_{16}$-CO_2H)AQ-Aib-TFI-(D-Glu)-YLIEGGPSSGAPPPS-NH_2	92	0.201	0.0427	4.71
178	Y-Aib-EGT-αMeF(2F)-TSDHSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH_2)$_{14}$-CO_2H)AQ-Aib-HFI-(D-Glu)-YLIEGGPSSGAPPPS-NH_2	93	0.0341	0.00349	9.77
179	Y-Aib-EGT-αMeF(2F)-TSDHSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH_2)$_{16}$-CO_2H)AQ-Aib-HFI-(D-Glu)-YLIEGGPSSG-NH_2	94	0.0575	0.0169	3.40
180	Y-Aib-EGT-αMeF(2F)-TSDHSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH_2)$_{16}$-CO_2H)AQ-Aib-HFI-(D-Glu)-YLIEGG-NH_2	95	0.133	0.0212	6.27
181	Y-Aib-EGT-αMeF(2F)-TSD-3Pal-SI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH_2)$_{18}$-CO_2H)AQ-Aib-EFI-(D-Glu)-YLIEGGPSSGAPPPS-NH_2	96	4.1	0.718	5.71
182	Y-Aib-EGT-αMeF(2F)-TSD-4Pal-SI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH_2)$_{18}$-CO_2H)AQ-Aib-EFI-(D-Glu)-YLIEGGPSSGAPPPS-NH_2	97	4.37	0.873	5.01
183	Y-Aib-EGT-αMeF(2F)-TSDLSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH_2)$_{18}$-CO_2H)AQ-Aib-EFI-(D-Glu)-YLIEGGPSSGAPPPS-NH_2	98	3.1	0.843	3.68
187	Y-Aib-EGT-αMeF(2F)-TSDQSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-	99	4.61	0.702	6.57

	acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-EFI-(D-Glu)-YLIEGGPSSGAPPPS-NH$_2$				
189	Y-Aib-EGT-αMeF(2F)-TSD-4Pal-SI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-EFI-Aib-YLIEGGPSSGAPPPS-NH$_2$	100	2.41	0.668	3.61
197	Y-αMePro-EGTFTSDYSILLDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{16}$-CO$_2$H)AQQAFIEYLIEGGPSSG-NH$_2$	101	0.855	0.189	4.52
202	Y-Aib-EGT-αMeF(2F)-TSD-4Pal-SI-αMeL-LDKK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)-(γGlu)-(2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-EFI-(D-Glu)-YLIEGGPSSGAPPPS-NH$_2$	102	4.79	0.712	6.73
203	Y-Aib-EGT-αMeF(2F)-TSD-4Pal-SI-αMeL-LDKK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-EFI-(D-Glu)-YLIEGGPSSGAPPPS-NH$_2$	103	4.95	0.671	7.38
204	Y-Aib-EGT-αMeF(2F)-TSD-4Pal-SI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{16}$-CO$_2$H)AQ-Aib-EFI-(D-Glu)-YLIEGGPSSGAPPPS-NH$_2$	104	4.58	0.689	6.65
205	Y-Aib-EGT-αMeF(2F)-TSD-4Pal-SI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-CO-(CH$_2$)$_{16}$-CO$_2$H)AQ-Aib-EFI-(D-Glu)-YLIEGGPSSGAPPPS-NH$_2$	105	5.71	1.46	3.91
206	Y-Aib-EGT-αMeF(2F)-TSD-4Pal-SI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-EFI-(D-Glu)-YLIEGGPSSGAPPPS-NH$_2$	106	4.75	1.42	3.35
207	Y-Aib-EGT-αMeF(2F)-TSD-4Pal-SI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(εK)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-EFI-(D-Glu)-YLIEGGPSSGAPPPS-NH$_2$	107	4.76	1.23	3.87
208	Y-Aib-EGT-αMeF(2F)-TSDYSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{14}$-CO$_2$H)AQ-	108	5.33	0.587	9.08

	Aib-EFI-(D-Glu)-YLIEGGPSSGAPPPS-NH_2				
209	Y-Aib-EGT-αMeF(2F)-TSDYSI-αMeL-LD-Dab-K((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-$(CH_2)_{16}$-CO_2H)AQ-Aib-EFI-(D-Glu)-YLIEGGPSSGAPPPS-NH_2	109	5.73	1.12	5.12
210	Y-Aib-EGT-αMeF(2F)-TSDYSI-αMeL-LD-Dap-K((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-$(CH_2)_{16}$-CO_2H)AQ-Aib-EFI-(D-Glu)-YLIEGGPSSGAPPPS-NH_2	110	5.4	1.03	5.24
211	Y-Aib-EGT-αMeF(2F)-TSDYSI-αMeL-LDKK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)-(γGlu)-(2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)-CO-$(CH_2)_{18}$-CO_2H)AQ-Aib-EFI-(D-Glu)-YLIEGGPSSGAPPPS-NH_2	111	4.59	1.28	3.59
212	Y-Aib-EGT-αMeF(2F)-TSDYSI-αMeL-LDKK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-$(CH_2)_{18}$-CO_2H)AQ-Aib-EFI-(D-Glu)-YLIEGGPSSGAPPPS-NH_2	112	4.17	0.771	5.41
213	Y-Aib-EGT-αMeF-TSDYSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-$(CH_2)_{16}$-CO_2H)AQ-Aib-EFI-(D-Glu)-YLIEGGPSSGAPPPS-NH_2	113	3.87	0.694	5.58
214	Y-Aib-EGT-αMeF(2F)-TSDYSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-CO-$(CH_2)_{16}$-CO_2H)AQ-Aib-EFI-(D-Glu)-YLIEGGPSSGAPPPS-NH_2	114	6.92	1.74	3.98
215	Y-Aib-EGT-αMeF(2F)-TSDYSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-CO-$(CH_2)_{18}$-CO_2H)AQ-Aib-EFI-(D-Glu)-YLIEGGPSSGAPPPS-NH_2	115	3.53	0.813	4.34
216	Y-Aib-EGT-αMeF(2F)-TSDYSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(εK)-CO-$(CH_2)_{18}$-CO_2H)AQ-Aib-EFI-(D-Glu)-YLIEGGPSSGAPPPS-NH_2	116	4.91	1.31	3.75
217	Y-Aib-EGT-αMeF(2F)-TSDYSI-αMeL-LD-Dab-K((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-$(CH_2)_{18}$-	117	3.41	1.14	2.99

	CO_2H)AQ-Aib-EFI-(D-Glu)-YLIEGGPSSGAPPPS-NH_2				
218	Y-Aib-EGT-αMeF(2F)-TSDYSI-αMeL-LD-Dap-K((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-$(CH_2)_{18}$-CO_2H)AQ-Aib-EFI-(D-Glu)-YLIEGGPSSGAPPPS-NH_2	118	4.43	1.02	4.34
219	Y-Aib-EGT-αMeF(2F)-TSDYSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-$(CH_2)_{16}$-CO_2H)AQ-Aib-EFI-(D-Glu)-YLIEGGPSSG-NH_2	119	5.86	1.03	5.69
220	Y-Aib-EGT-αMeF(2F)-TSDYSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-$(CH_2)_{16}$-CO_2H)AQ-Aib-EFI-(D-Glu)-YLIEGG-NH_2	120	6.3	1.36	4.63
221	Y-Aib-EGT-αMeF(2F)-TSDYSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-$(CH_2)_{16}$-CO_2H)AQ-Aib-EFI-(D-Glu)-YLIEGGPSSGAPPPS-NH_2	121	4.5	0.795	5.66
222	Y-Aib-EGT-αMeF(2F)-TSDYSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-$(CH_2)_{18}$-CO_2H)AQ-Aib-EFI-(D-Glu)--αMeY-LIEGGPSSGAPPPS-NH_2	122	5.84	1.55	3.77
223	Y-Aib-EGT-αMeF(2F)-TSDYSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-$(CH_2)_{18}$-CO_2H)AQ-Aib-EFIE-αMeY-LIEGGPSSGAPPPS-NH_2	123	2.93	0.962	3.05
224	Y-Aib-EGT-αMeF(2F)-TSDYSI-Aib-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-$(CH_2)_{18}$-CO_2H)AQ-Aib-EFI-(D-Glu)-YLIEGGPSSGAPPPS-NH_2	124	3.52	1.06	3.32
225	Y-Aib-EGT-αMeF-TSDYSI-Aib-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-$(CH_2)_{18}$-CO_2H)AQ-Aib-EFI-(D-Glu)-YLIEGGPSSGAPPPS-NH_2	125	1.99	0.523	3.80
226	Y-Aib-EGT-αMeF(2F)-TSDYSILLDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-$(CH_2)_{18}$-CO_2H)AQ-Aib-EFI-(D-Glu)-YLIEGGPSSGAPPPS-NH_2	126	4.27	1.25	3.42

227	Y-Aib-EGT-αMeF-TSDYSI-αMeL-LDEK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-EFI-(D-Glu)-YLIEGGPSSGAPPPS-NH$_2$	127	4.73	1.07	4.42
228	Y-Aib-EGT-αMeF-TSDYSI-αMeL-LDKK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-EFI-(D-Glu)-YLIEGGPSSG-NH$_2$	128	3.86	1.1	3.51
230	Y-Aib-EGT-αMeF(2F)-TSDYSI-αMeL-LDHK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-EFI-(D-Glu)-YLIEGGPSSGAPPPS-NH$_2$	129	3.31	0.599	5.53
233	Y-Aib-EGT-αMeF(2F)-TSD-4Pal-SI-αMeL-LD-Dab-K((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{16}$-CO$_2$H)AQ-Aib-EFI-(D-Glu)-YLIEGGPSSGAPPPS-NH$_2$	130	4.95	0.535	9.25
236	Y-Aib-EGT-αMeF(2F)-TSDYSI-αMeL-LD-Orn-K((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{16}$-CO$_2$H)AQ-Aib-EFI (D-Glu)-αMeY-LIEGGPSSGAPPPS-NH$_2$	131	6.76	1.65	4.10
238	Y-Aib-EGT-αMeF(2F)-TSDLSI-αMeL-LD-Orn-K((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{16}$-CO$_2$H)AQ-Aib-EFI-(D-Glu)-αMeY-LIEGGPSSGAPPPS-NH$_2$	132	7.33	1.15	6.37
239	Y-Aib-EGT-αMeF(2F)-TSD-4Pal-SI-αMeL-LD-Orn-K((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{16}$-CO$_2$H)AQ-Aib-TFI-(D-Glu)-αMeY-LIEGGPSSGAPPPS-NH$_2$	133	5.27	0.987	5.34
241	Y-Aib-EGT-αMeF(2F)-TSDVSI-αMeL-LD-Orn-K((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{16}$-CO$_2$H)AQ-Aib-TFI-(D-Glu)-αMeY-LIEGGPSSGAPPPS-NH$_2$	134	7.12	1.89	3.77
242	Y-Aib-EGT-αMeF(2F)-TSDVSI-αMeL-LD-Orn-K((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{16}$-CO$_2$H)AQ-Aib-AFI-(D-Glu)-αMeY-LIEGGPSSGAPPPS-NH$_2$	135	5.58	1.96	2.85
243	Y-Aib-EGT-αMeF(2F)-TSDLSI-αMeL-LD-Orn-K((2-[2-(2-Amino-ethoxy)-	136	8.69	1.22	7.12

	ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{16}$-CO$_2$H)AQ-Aib-TFI-(D-Glu)-αMeY-LIEGGPSSGAPPPS-NH$_2$				
244	Y-Aib-EGT-αMeF(2F)-TSDLSI-αMeL-LD-Orn-K((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{16}$-CO$_2$H)AQ-Aib-AFI-(D-Glu)-αMeY-LIEGGPSSGAPPPS-NH$_2$	137	8.27	1.29	6.41
246	Y-Aib-EGT-αMeF(2F)-TSDASI-αMeL-LD-Orn-K((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{16}$-CO$_2$H)AQ-Aib-AFI-(D-Glu)-αMeY-LIEGGPSSGAPPPS-NH$_2$	138	6.36	2.56	2.48
247	Y-Aib-EGT-αMeF(2F)-TSDYSI-Aib-LD-Orn-K((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{16}$-CO$_2$H)AQ-Aib-EFI-(D-Glu)-YLIEGGPSSGAPPPS-NH$_2$	139	2.58	0.614	4.20
248	Y-Aib-EGT-αMeF(2F)-TSDYSILLD-Orn-K((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{16}$-CO$_2$H)AQ-Aib-EFI-(D-Glu)-YLIEGGPSSGAPPPS-NH$_2$	140	5.08	0.8	6.35
249	Y-Aib-EGT-αMeF(2F)-TSDYSI-Nle-LD-Orn-K((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{16}$-CO$_2$H)AQ-Aib-EFI-(D-Glu)-YLIEGGPSSGAPPPS-NH$_2$	141	3.84	0.778	4.94
250	Y-Aib-EGT-αMeF(2F)-TSDYSI-Aib-LD-Orn-K((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-EFI-(D-Glu)-YLIEGGPSSGAPPPS-NH$_2$	142	4.27	0.985	4.34
251	Y-Aib-EGT-αMeF(2F)-TSD-4Pal-SI-αMeL-LD-Orn-K((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(εK)-CO-(CH$_2$)$_{18}$-CO$_2$H)AQ-Aib-AFI-(D-Glu)-αMeY-LIEGGPSSGAPPPS-NH$_2$	143	5.12	1.37	3.74
264	Y-Aib-EGT-αMeF(2F)-TSD-4Pal-SI-αMeL-LD-Orn-K((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH$_2$)$_{16}$-CO$_2$H)AQ-Aib-EFI-(D-Glu)-αMeY-LIEGGPSSG-NH$_2$	144	8.4	3.19	2.63
265	Y-Aib-EGT-αMeF(2F)-TSD-4Pal-SI-αMeL-LD-Orn-K((2-[2-(2-Amino-	145	9.77	3.27	2.99

	ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)-CO-(CH_2)$_{16}$-CO_2H)AQ-Aib-EFI-(D-Glu)-αMeY-LIEGG-NH_2				

As demonstrated by data in Table 1, the peptides, normalized to baseline and native peptides, stimulate cAMP from human GLP-1R and GIPR in the presence of 0.1% casein with a GIP potency ratio that is about 2.5 to about 10 times the GLP-1 receptor potency.

In an embodiment, is a GIP:GLP-1 coagonist compound wherein the peptide is a potent GIPR/GLP-1R dual agonist that is a partial agonist on the GLP-1R as shown by Cell Membrane Guanosine 5'-(gamma-thio) Triphosphate-[^{35}S] (GTPγS) Binding Assay, and a partial agonist on the GLP-1R as shown by the β-arrestin-2 recruitment assay. An embodiment, is a GIP:GLP-1 co-agonist compound, or pharmaceutically acceptable salt thereof, wherein the compound stimulates GLP-1R induced activation of $G\alpha_s$ in the GLP-1R HEK293 Cell Membrane Guanosine 5'-(gamma-thio) Triphosphate-[^{35}S] (GTPγS) Binding Assay. In an embodiment, is a compound showing partial agonism of 75% or less in the GLP-1R HEK293 Cell Membrane Guanosine 5'-(gamma-thio) Triphosphate-[^{35}S] (GTPγS) Binding Assay, and 35% or less in the GLP-CHO Cell β-Arrestin.Recruitment Assay.

In an embodiment is a method for treating diabetes comprising administering an effective amount of a compound showing partial agonism of 75% or less in the GLP-1R HEK293 Cell Membrane Guanosine 5'-(gamma-thio) Triphosphate-[^{35}S] (GTPγS) Binding Assay, and an effective amount of a compound that is a GIP agonist. In an embodiment, the compound showing partial agonism in the GLP-1R HEK293 Cell Membrane Guanosine 5'-(gamma-thio) Triphosphate-[^{35}S] (GTPγS) Binding Assay is co-administered with a compound having GIP agonist activity. In an embodiment, the compound showing partial agonism in the GLP-1R HEK293 Cell Membrane Guanosine 5'-(gamma-thio) Triphosphate-[^{35}S] (GTPγS) Binding Assay is administered as an active agent within one week before or after a compound having GIP agonist activity. In an embodiment, a method for treating diabetes comprises administering an effective amount of a compound showing 35% or less in the GLP-CHO Cell β-Arrestin.Recruitment Assay and administering an effective amount of a compound showing partial agonism of 75% or less in the GLP-1R HEK293 Cell Membrane Guanosine 5'-(gamma-thio) Triphosphate-[^{35}S] (GTPγS) Binding Assay.

GLP-1R HEK293 Cell Membrane [^{35}S]GTPγS Binding Assay

The GLP-1 receptor is a G-protein coupled receptor that increases GTP-bound $G\alpha_s$ upon ligand induced receptor activation. The potency of peptides to stimulate- GLP-1R induced activation of $G\alpha_s$ is determined using preparations of purified membranes from HEK293 cells expressing the human GLP-1R. The assay is performed similarly to that as previously described (Bueno *et al.*, J. Biol. Chem., (2016) 291, 10700 and Willard *et al.*, Mol. Pharmacol. (2012) 82,1066). The test peptides are solubilized in DMSO and diluted in reaction buffer containing 5 μg of membrane in 20 mM HEPES pH 7.4, 50 mM NaCl, 5 mM $MgCl_2$, 40 μg/ml saponin, 0.1% BSA, and 500 pM ^{35}S-labeled GTPγS for 30 minutes at room temperature. Reactions are terminated by addition of 0.2% Nonidet P-40 detergent containing rabbit anti-$G\alpha_s$ polyclonal antibody and 0.5 mg of anti-rabbit polyvinyltoluene beads. Mixtures are developed for 30 minutes, centrifuged at 80 × *g* for 10 minutes, and counted for 1 minute/well using a MicroBeta TriLux instrument. Peptide concentration-response curves are fit to a four-parameter logistic model to calculate potency as an EC_{50}. Data normalization to % stimulation is performed using DMSO and GLP-1(7-36) as minimum and maximum controls for the receptor (Campbell *et al*, Assay Guidance Manual 2017). The potency of a sample peptide to stimulate GIPR induced activation of $G\alpha_s$ is determined. Assay results identify a petpide that is a partial agonist on the GLP-1R with respect to GLP-1R induced activation of $G\alpha_s$.

GLP-1R CHO Cell β-Arrestin Recruitment Assay

Activated G-protein coupled receptors can interact with the β-arrestin family of signalling proteins. The potency of peptides for GLP-1R induced arrestin recruitment is determined using the PathHunter Enzyme Fragment Complementation approach substantially as described (von Degenfeld *et al.*, FASEB J., 2007 (14):3819-26 and Hamdouchi *et al.*, J. Med Chem., 2016 59(24):10891-10916). CHO-K1 cells expressing Pro-Link-tagged Human GLP-1R and enzyme-acceptor-tagged β-arrestin-2 may be obtained from DiscoveRx and prepared as assay-ready frozen cells. Test peptides are solubilized in DMSO and serial dilutions are perfomed using the Echo acoustic dispenser (LabCyte). Assay media is the PathHunter Cell Assay Buffer (DiscoveRx) containing

0.1% w/v hydrolyzed Casein (Sigma). 100 nl of peptide is dispensed into 10 µl of assay media in a 384 well plate and then 10 µl of cells in assay media are added to give 5000 cells per well. Plates are incubated for 90 minutes in a 37'C/5% C02 incubator and 10 µl of PathHunter detection reagent is added (DiscoveRx) and plates are incubated at room temperature for 60 minutes. Luminescence signal is measured. Peptide concentration-response curves fit to a four-parameter logistic model to calculate potency as an EC_{50}. Data normalization to % stimulation is performed using DMSO and GLP-1(7-36) as minimum and maximum controls (Campbell *et al*, Assay Guidance Manual 2017). The potency of a sample peptide to stimulate GLP-1R induced β-arrestin recruitment is determined. Assay results identify a peptide that is a partial agonist on the GLP-1R with respect to β-arrestin-2 recruitment.

Clinical Study to Determine GIP:GLP-1 Peptide Maintenance Dose

A 6-month (26-week) Phase 2 double-blind clinical study is designed to evaluate the safety, efficacy, and PK/PD of 4 dose levels (1mg, 5mg, 10mg and 15mg respectively) of a GIP:GLP-1 Peptide administered once weekly by subcutaneous injection compared with dulaglutide 1.5 mg administered once weekly (QW) and placebo QW in patients with T2DM who have inadequate glycemic control with diet and exercise with or without a stable dose of metformin. The GIP:GLP Peptide dose was up-titrated to the maintenance dose using the following weekly dose increments:

GIP:GLP-1 Peptide dose:	Weekly GIP:GLP-1 Peptide Dose Increments:
1 mg	Week 0-26: 1mg QW
5 mg	Week 0-26: 5 mg QW
10 mg	Week 0: 5 mg Week 1: 5 mg Week 2-26: 10 mg
15 mg	Week 0: 5 mg Week 1: 5 mg Week 2: 10 mg Week 3: 10 mg

	Week 4: 10 mg Week 5: 10 mg Week 6-26: 15 mg

The study also has a 4-week follow up period. In addition to safety and efficacy for treating T2DM, efficacy endpoints include the effect of the GIP:GLP-1 Peptide on HbA1c, FBG, body weight, lipids, and waist circumference compared with placebo and with dulaglutide 1.5 mg. The study also evaluates the effect of the GIP:GLP-1 Peptide on GI tolerability, hypoglycemia, hypersensitivity reactions, and pancreatic safety, as well as the development of treatment-emergent anti-drug antibodies. Model-based dose response analyses are performed to predict potential for significant HbA1c lowering and weight loss in longer studies.

Statistical Analyses:

Efficacy: The primary efficacy outcome of HbA1c change from baseline to the 26-week endpoint is analyzed using a Bayesian dose–response model. Analyses are performed on the intention to treat population (mITT) analysis set. Supportive analysis of the primary efficacy outcome for the mITT dataset are the model for post-baseline measures (MMRM) with body mass index (BMI) (<30 kg/m^2, ≥ 30 kg/m^2), metformin use, treatment, visit, and treatment-by-visit interaction as fixed effects, baseline HbA1c as a covariate, and patient as a random effect.

The mean weight change from baseline at 12 and 26 weeks, along with the mean change from baseline of HbA1c at 12 weeks, is analyzed using similar dose-response models as the primary analyses. The percentages of patients with $\geq 5\%$ or $\geq 10\%$ body weight loss, reaching the HbA1c target of $\leq 6.5\%$ or $\leq 7.0\%$ at 26 weeks, or requiring rescue therapy are analyzed using logistic regression with fixed effects of treatment and strata, and baseline as a covariate. The changes from baseline in FBG (fasting blood glucose), SMBG (self-monitored blood glucose) levels, waist circumference, and mean percentage change in lipids from baseline to 12 and 26 weeks are analyzed using a similar MMRM to the one used for the primary analyses.

Clinical Study to Determine GIP:GLP-1 Peptide Titration Schedule

This is a 12-week treatment with a 1 week screening (Visit 1) followed by a 1 week lead-in (Visit 2), then 12 weeks of treatment (Visits 3-10, including telephone visits), then followed by 4-week safety follow-up. It is a Phase 2 study designed to examine the efficacy and tolerability of subcutaneously once-weekly administration of a GIP:GLP-1 Peptide compared with placebo in patients with type 2 diabetes who have inadequate glycemic control with diet and exercise alone or with a stable dose of metformin. The study was designed per below and conducted to refine the titration scheme.

GIP:GLP-1 Peptide Dose:	Weekly GIP:GLP-1 Peptide Dose Increments:
Placebo	Week 1-12
Group 1	Weeks 1-2: 2.5 mg Weeks 3-4: 5 mg Weeks 5-8: 10 mg Weeks 9-12: 15 mg
Group 2	Weeks 1-4: 2.5 mg Weeks 5-8: 7.5 mg Weeks 9-12: 15 mg
Group 3	Weeks 1-4: 4 mg Weeks: 5-8: 8 mg Weeks 9-12: 12 mg

Amino Acid Sequences

SEQ ID NO:1

GIP (Human)

YAEGTFISDYSIAMDKIHQQDFVNWLLAQKGKKNDWKHNITQ

SEQ ID NO:2

GLP-1 (7-36) (Human)

HAEGTFTSDVSSYLEGQAAKEFIAWLVKGR-NH_2

SEQ ID NO:3

R_1X_1 X_2 X_3GT X_6TSD X_{10} X_{11} X_{12} X_{13} X_{14}D $X_{16}X_{17}$AX_{19} X_{20} X_{21} $X_{22}X_{23}$ X_{24} X_{25} X_{26} X_{27} X_{28} X_{29} $X_{30}X_{31}$

SEQ ID NO:4

PX_{32} X_{33} X_{34}-R_2

SEQ ID NO:5

PX_{32} X_{33} X_{34} $X_{35}X_{36}$ X_{37} X_{38} X_{39}-R_2

SEQ ID NO:6

PX_{32} X_{33} X_{34} $X_{35}X_{36}$ X_{37} X_{38} X_{39} X_{40}-R_2

SEQ ID NO:7

K[(2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-γGlu-CO-$(CH_2)_q$-CO_2H] X_{32} X_{33} X_{34}-R_2

SEQ ID NO:8

K[(2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-γGlu-CO-$(CH_2)_q$-CO_2H] X_{32} X_{33} X_{34} $X_{35}X_{36}$ X_{37} X_{38} X_{39}-R_2

SEQ ID NO:9

K[(2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-γGlu-CO-$(CH_2)_q$-CO_2H] X_{32} X_{33} X_{34} $X_{35}X_{36}$ X_{37} X_{38} X_{39} X_{40}-R_2

WE CLAIM:

1. A method of treating type 2 diabetes in a patient in need thereof, comprising:
   a) administering to said patient a titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter
   b) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;
   wherein the titration dose is about 50% of the maintenance dose.
2. A method of treating type 2 diabetes in a patient in need thereof, comprising:
   a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter
   b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter
   c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter
   d) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;
   wherein the first titration dose is about 25% of the maintenance dose, the second titration dose is about 50% of the maintenance dose and the third titration dose is about 75% of the maintenance dose.
3. A method of treating type 2 diabetes in a patient in need thereof, comprising:
   a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay

normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a fourth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

e) administering to said patient a fifth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

f) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 17% of the maintenance dose, the second titration dose is about 33% of the maintenance dose, the third titration dose is about 50% of the maintenance dose, the fourth titration is about 66% of the maintenance dose and the fifth titration dose is about 83% of the maintenance dose.

4. A method of improving glycemic control in a patient in need thereof, comprising:

a) administering to said patient a titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the titration dose is about 50% of the maintenance dose.

5. A method of improving glycemic control in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 25% of the maintenance dose, the second titration dose is about 50% of the maintenance dose and the third titration dose is about 75% of the maintenance dose.

6. A method of improving glycemic control in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a fourth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

e) administering to said patient a fifth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

f) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 17% of the maintenance dose, the second titration dose is about 33% of the maintenance dose, the third titration dose is about 50% of the maintenance dose, the fourth titration is about 66% of the maintenance dose and the fifth titration dose is about 83% of the maintenance dose.

7. A method of improving weight management in a patient in need thereof, comprising:

a) administering to said patient a titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the titration dose is about 50% of the maintenance dose.

8. A method of improving weight management in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 25% of the maintenance dose, the second titration dose is about 50% of the maintenance dose and the third titration dose is about 75% of the maintenance dose.

9. A method of improving weight management in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a fourth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

e) administering to said patient a fifth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

f) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 17% of the maintenance dose, the second titration dose is about 33% of the maintenance dose, the third titration dose is about 50% of the maintenance dose, the fourth titration is about 66% of the maintenance dose and the fifth titration dose is about 83% of the maintenance dose.

10. A method of treating chronic kidney disease in a patient in need thereof, comprising:

a) administering to said patient a titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the titration dose is about 50% of the maintenance dose.

11. A method of treating chronic kidney disease in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 25% of the maintenance dose, the second titration dose is about 50% of the maintenance dose and the third titration dose is about 75% of the maintenance dose.

12. A method of treating chronic kidney disease in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a fourth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

e) administering to said patient a fifth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

f) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 17% of the maintenance dose, the second titration dose is about 33% of the maintenance dose, the third titration dose is about 50% of the maintenance dose, the fourth titration is about 66% of the maintenance dose and the fifth titration dose is about 83% of the maintenance dose.

13. A method of treating NAFLD in a patient in need thereof, comprising:

a) administering to said patient a titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the titration dose is about 50% of the maintenance dose.

14. A method of treating NAFLD in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 25% of the maintenance dose, the second titration dose is about 50% of the maintenance dose and the third titration dose is about 75% of the maintenance dose.

15. A method of treating NAFLD in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a fourth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

e) administering to said patient a fifth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

f) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 17% of the maintenance dose, the second titration dose is about 33% of the maintenance dose, the third titration dose is about 50% of the maintenance dose, the fourth titration is about 66% of the maintenance dose and the fifth titration dose is about 83% of the maintenance dose.

16. A method of treating NASH in a patient in need thereof, comprising:

a) administering to said patient a titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the titration dose is about 50% of the maintenance dose.

17. A method of treating NASH in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 25% of the maintenance dose, the second titration dose is about 50% of the maintenance dose and the third titration dose is about 75% of the maintenance dose.

18. A method of treating NASH in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a fourth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

e) administering to said patient a fifth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

f) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 17% of the maintenance dose, the second titration dose is about 33% of the maintenance dose, the third titration dose is about 50% of the maintenance dose, the fourth titration is about 66% of the maintenance dose and the fifth titration dose is about 83% of the maintenance dose.

19. A method of curing diabetes, inducing remission or regression of diabetes, or preventing diabetes in a patient in need thereof, comprising:

a) administering to said patient a titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the titration dose is about 50% of the maintenance dose.

20. A method of curing diabetes, inducing remission or regression of diabetes, or preventing diabetes in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 25% of the maintenance dose, the second titration dose is about 50% of the maintenance dose and the third titration dose is about 75% of the maintenance dose.

21. A method of curing diabetes, inducing remission or regression of diabetes, or preventing diabetes in a patient in need thereof, comprising:

a) administering to said patient a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administering to said patient a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administering to said patient a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administering to said patient a fourth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

e) administering to said patient a fifth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

f) administering to said patient a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 17% of the maintenance dose, the second titration dose is about 33% of the maintenance dose, the third titration dose is about 50% of the maintenance dose, the fourth titration is about 66% of the maintenance dose and the fifth titration dose is about 83% of the maintenance dose.

22. The method of any one of Claims 1-21, wherein the titration doses are each administered for about four weeks before the administration of the next higher dose begins.

23. The method of any one of Claims 1-22, wherein the GIP:GLP-1 Peptide is a compound of SEQ ID NO: 3, or a pharmaceutically acceptable salt thereof.

24. The method of any one of Claims 1-23, wherein the GIP:GLP-1 Peptide has a receptor agonist potency ratio that is 2.5:1 to about 5:1 GIP to GLP-1.

25. The method of any one of Claims 1-23, wherein the GIP:GLP-1 Peptide has a receptor agonist potency ratio that is 2.5:1 to about 3.5:1 GIP to GLP-1.

26. A GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, for use in treating type 2 diabetes in a patient in need thereof wherein the use comprises:

a) administration of a titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administration of a maintenance dose of that GIP:GLP-1 Peptide;

wherein the titration dose is about 50% of the maintenance dose.

27. A GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, for use in treating type 2 diabetes in a patient in need thereof wherein the use comprises:

a) administration of a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administration of a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administration of a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administration of a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 25% of the maintenance dose, the second titration dose is about 50% of the maintenance dose and the third titration dose is about 75% of the maintenance dose.

28. A GIP:GLP-1 Peptide, or a pharmaceutically acceptable salt thereof, for use in treating type 2 diabetes in a patient in need thereof wherein the use comprises:

a) administration of a first titration dose of a GIP:GLP-1 Peptide having a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1 for a minimum of about two weeks; and thereafter

b) administration of a second titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

c) administration of a third titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

d) administration of a fourth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

e) administration of a fifth titration dose of that GIP:GLP-1 Peptide for a minimum of about two weeks; and thereafter

f) administration of a maintenance dose of that GIP:GLP-1 Peptide;

wherein the first titration dose is about 17% of the maintenance dose, the second titration dose is about 33% of the maintenance dose, the third titration dose is about 50% of the maintenance dose, the fourth titration is about 66% of the maintenance dose and the fifth titration dose is about 83% of the maintenance dose.

28. A composition comprising a GIP:GLP-1 Peptide having GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using casein cAMP assay normalized against GIP and GLP-1 that is about 2.5:1 to about 10:1; and a pharmaceutically acceptable excipient.

29. A composition as claimed by Claim 28 wherein the composition is administered at least two weeks as an escalation dose.

30. A composition as claimed by Claim 28 or 29 wherein the composition is administered at least four weeks as an escalation dose.

31. A composition as claimed by any one of Claims 28 to 30 wherein the composition is administered as a maintenance dose for at least two weeks.

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