SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Foundayo 2.5 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains orforglipron calcium equivalent to 2.5 mg orforglipron.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Light yellow, round tablet (approximately 6 mm in diameter) debossed with ‘G2’ on one side and ‘L’ on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Weight management

Foundayo is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management, including weight loss and weight maintenance, in adults with an initial Body Mass Index (BMI) of

- ≥30 kg/m2 (obesity), or
- ≥27 kg/m2 to < 30 kg/m2 (overweight) in the presence of at least one weight-related comorbidity e.g. prediabetes or type 2 diabetes mellitus, hypertension, dyslipidaemia, obstructive sleep apnoea, or cardiovascular disease.

Type 2 diabetes mellitus

Foundayo is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus to improve glycaemic control as an adjunct to diet and exercise:

- as monotherapy, or
- in combination with other medicinal products for the treatment of diabetes.

For study results with respect to combinations, effects on glycaemic control, and the populations studied, see section 4.4, 4.5 and 5.1.

4.2 Posology and method of administration

Posology

The starting dose for orforglipron film-coated tablet is 0.8 mg once daily. After at least 30 days, the dose should be increased to 2.5 mg once daily. After at least 30 days on the current dose, the dose can be increased to the next dose 5.5 mg once daily. The dose may be increased to the next dose level (9 mg, 14.5 mg, or 17.2 mg once daily) after at least 30 days on the current dose, based on treatment response and tolerability.

The maximum daily dose is 17.2 mg once daily. More than one film-coated tablet a day should not be taken to achieve the effect of a higher dose.

Dose adjustments

Strong CYP3A4 inhibitors

The maximum orforglipron dose should be the 9.0 mg film-coated tablet once daily when co-administered with a strong CYP3A4 inhibitor (see section 4.5).

Strong CYP3A4 inducers

Avoid concomitant use of strong CYP3A4 inducers when taking orforglipron (see section 4.5).

OATP1B inhibitors

The maximum orforglipron dose should be the 9.0 mg film-coated tablet once daily when used concomitantly with a clinical OATP1B inhibitor (see section 4.5).

Concomitant use of insulin secretagogues or insulin

When orforglipron is added to existing therapy of a sulphonylurea and/or insulin, a reduction in

the dose of sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia.

Blood glucose self-monitoring is necessary to adjust the dose of sulphonylurea and/or insulin. A

stepwise approach to insulin reduction is recommended (see sections 4.4 and 4.8).

Missed dose

If a dose is missed, dosing should be resumed as soon as possible. More than one film-coated tablet should not be taken per day.

Special populations

Elderly, gender, race, ethnicity, body weight, renal impairment or hepatic impairment
No dose adjustment is required based on age, gender, race/ethnicity, body weight, renal function including end-stage renal disease (see section 5.2), or mild or moderate hepatic impairment (see section 5.2). Only very limited data are available from patients aged 85 years and older.

Severe hepatic impairment

Orforglipron is not recommended for use in patients with severe hepatic impairment (see section 5.2).

Paediatric population

The safety and efficacy of orforglipron in children aged less than 18 years have not yet been established. No data are available.

Method of administration

For oral use.

This medicinal product should be taken once-daily at any time of day, without food or water restriction.

Film-coated tablets should be swallowed whole and should not be broken, crushed, or chewed.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Acute pancreatitis

Orforglipron has not been studied in patients with a history of pancreatitis and should be used with

caution in these patients. Acute pancreatitis has been reported in patients treated with orforglipron. Necrotizing pancreatitis and pancreatitis with a fatal outcome have also been reported in patients treated with GLP-1 receptor agonists. Patients should be informed of the symptoms of acute pancreatitis including persistent, severe abdominal pain. Patients should be advised to seek immediate medical attention if they occur. If pancreatitis is suspected, orforglipron should be discontinued. If the diagnosis of pancreatitis is confirmed, orforglipron should not be restarted. In the absence of other signs and symptoms of pancreatitis, elevations in pancreatic enzymes alone are not predictive of pancreatitis (see section 4.8).

Hypoglycaemia with concomitant use of insulin secretagogues or insulin

Patients receiving orforglipron in combination with an insulin secretagogue (for example, a sulfonylurea) or insulin may have an increased risk of hypoglycaemia (see section 4.8). The risk of hypoglycaemia may be lowered by a reduction in the dose of the insulin secretagogue and/or insulin (see section 4.2).

Severe gastrointestinal adverse reactions

Use of orforglipron has been associated with gastrointestinal adverse reactions, sometimes severe. (see section 4.8).

Orforglipron has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and should be used with caution in these patients. Events related to impaired gastric emptying, including severe gastroparesis, have

been reported with the use of GLP-1 receptor agonists. Patients should be monitored for gastrointestinal adverse events while on treatment, Dose modification or discontinuation should be considered for patients who develop severe gastrointestinal symptoms.

Acute kidney injury due to volume depletion

Orforglipron has been associated with gastrointestinal adverse reactions, which include nausea, vomiting, and diarrhoea (see section 4.8). These reactions may lead to dehydration and volume depletion, which could cause a deterioration in renal function, including acute kidney injury. Patients treated with orforglipron should be advised of the potential risk of dehydration, due to the gastrointestinal adverse reactions and take precautions to avoid fluid depletion.

Hypotension

Orforglipron may lead to a decrease in blood pressure. Adverse reactions related to hypotension have been reported in patients treated with orforglipron. Hypotension occurred more frequently in patients receiving concomitant antihypertensive therapy. (see section 4.8).

Acute gallbladder disease

Acute gallbladder disease has been reported in patients receiving GLP-1 receptor agonists, including orforglipron. Acute gallbladder events were associated with weight reduction. If cholecystitis is suspected, gallbladder diagnostic studies and appropriate clinical follow-up are indicated.

Diabetic retinopathy complications

Orforglipron has not been studied in patients currently receiving or planning to receive treatment for diabetic retinopathy and/or macular oedema and should be used with caution in these patients. Experience with orforglipron in patients with severe non-proliferative or proliferative diabetic retinopathy is limited. Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy.

Pulmonary aspiration during general anesthesia or deep sedation

GLP-1 receptor agonists, including orforglipron delay gastric emptying. Pulmonary aspiration has been reported in patients receiving long acting GLP-1 receptor agonists undergoing general anesthesia or deep sedation. This should be considered prior to such procedures.

General

There is no experience in patients with congestive heart failure NYHA class IV and orforglipron is therefore not recommended in these patients.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on the pharmacokinetics of orforglipron

Orforglipron is a substrate of CYP3A4 and CYP2J2 as well as P-gp, OATP1B1 and OATP1B3.

Interaction studies were conducted with a hard capsule pharmaceutical form (see section 5.1 for dose equivalence of film-coated tablets and hard capsules).

For a summary of the impact on orforglipron dosing, please see section 4.2

Strong CYP3A4/OATP1B inhibitors

Strong CYP3A4 inhibitors that also inhibit OATP1B (e.g., ritonavir, telaprevir) should be avoided when taking orforglipron.

Strong CYP3A4 inhibitors

Coadministration of the strong CYP3A4 inhibitor clarithromycin (500 mg twice daily) with orforglipron increased orforglipron AUC(0-∞) and C_{max} by 3.5-fold and 1.9-fold, respectively. The maximum orforglipron dose should be the 9 mg film-coated tablet dose when coadministered with a strong CYP3A4 inhibitor (e.g. ketoconazole, clarithromycin, itraconazole) (see section 4.2).

Moderate and Strong CYP3A4 inducers

Coadministration of the strong CYP3A4 inducer carbamazepine (300 mg twice daily) with orforglipron decreased orforglipron AUC(0-∞) and C_{max} by 82% and 55%, respectively.

Coadministration of a moderate CYP3A4 inducer (e.g. bosentan, efavirenz) or strong CYP3A4 inducer (e.g. rifampicin, phenytoin, St John's wort [hypericum perforatum])

may reduce the effectiveness of orforglipron. Avoid concomitant use of strong CYP3A4 inducers when taking orforglipron. Monitor orforglipron effectiveness and adjust dose as needed when used concomitantly with moderate CYP3A4 inducers.

OATP1B inhibitors

Coadministration of cyclosporine, a clinical OATP1B inhibitor and weak CYP3A4 inhibitor, (200 mg twice daily) with orforglipron increased orforglipron AUC(0-∞) and C_{max} by 2.6-fold and 1.3-fold, respectively.

The maximum dosage of orforglipron film-coated tablets is 9 mg once daily when used concomitantly with a clinical OATP1B inhibitor, unless they are also strong inhibitors of CYP3A4 (e.g. ritonavir, telaprevir) (see *Strong CYP3A4/OATP1B inhibitors*).

Effects of orforglipron on the pharmacokinetics of other medicinal products

BCRP Substrates

Coadministration of rosuvastatin, a clinical BCRP substrate, with daily dosing of 36 mg orforglipron hard capsules (equivalent to 17.2 mg film-coated tablet) increased rosuvastatin AUC(0-∞) and C_{max} by 1.7-fold and 1.3-fold, respectively. No dose adjustment of BCRP substrates is necessary with orforglipron administration, except for rosuvastatin where caution is advised when the rosuvastatin dose exceeds 20 mg, and oral topotecan, where patients should be carefully monitored for adverse reactions when oral topotecan is administered with orforglipron.

Simvastatin

Coadministration of simvastatin with daily dosing of 24 mg or 36 mg orforglipron hard capsules (equivalent to 14.5 mg or 17.2 mg film-coated tablet) had no clinically meaningful effect on simvastatin (lactone) pharmacokinetics. Exposure of the active metabolite simvastatin acid was increased up to 2.5-fold when simvastatin was coadministered with orforglipron or administered 2 hours after orforglipron. The dose of simvastatin should be halved when administered with orforglipron.

Potential medicinal product interactions due to gastric emptying delay

Orforglipron delays gastric emptying and has the potential to affect the rate of absorption of other orally administered medicinal products. When paracetamol and orforglipron were co-administered, paracetamol C_{max} decreased by 28%. The gastric emptying delay effect is largest after the first 1 mg dose hard capsules (equivalent to 0.8 mg film-coated tablet) and diminishes over time.

No clinically relevant effect of orforglipron-mediated gastric emptying on the pharmacokinetics of commonly administered concomitant medicinal products is expected, based on PBPK modeling, following either a single 1 mg hard capsule (equivalent to 0.8 mg film-coated tablet) dose or with daily dosing up to 36 mg hard capsules (equivalent to 17.2 mg film-coated tablet).

Antidiabetic medicinal products

When orforglipron is added to existing metformin and/or sodium-glucose co-transporter 2 inhibitor (SGLT2i) therapy, the current dose of metformin and/or SGLT2i can be continued.

Oral contraceptives

Use of orforglipron may reduce the efficacy of oral hormonal contraceptives. Patients using oral hormonal contraceptives should be advised to switch to a non-oral contraceptive method or add a barrier method of contraception for 30 days after initiation with orforglipron and for 30 days after each dose escalation.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use effective contraception during treatment with orforglipron.

Pregnancy

There are no adequate and well-controlled studies of orforglipron in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3).

Orforglipron should not be used during pregnancy. If a patient wishes to become pregnant, or pregnancy occurs, orforglipron should be discontinued. Orforglipron should be discontinued for at least 3 weeks before a planned pregnancy due to the half-life of orforglipron.

Breast-feeding

It is unknown whether orforglipron is excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of orforglipron in milk (see section 5.3). A risk to the newborn/infant cannot be excluded.

Orforglipron should not be used during breast-feeding.

Fertility

The effect of orforglipron on fertility in humans is unknown.

Animal studies with orforglipron did not indicate direct harmful effects with respect to fertility.

For other GLP-1 receptor agonists, an increase in oestrous length and a small reduction in number of ovulations were observed at doses associated with maternal body weight loss (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies have been conducted to determine the effects of orforglipron on the ability to drive and use machines. When orforglipron is coadministered with a sulfonylurea or insulin, patients must be advised to take precautions to avoid hypoglycaemia while driving and using machines. (see sections 4.4 and 4.8).

4.8 Undesirable effects

Clinical studies were conducted with a hard capsule pharmaceutical form (see Table 2 in section 5.1 for dose equivalence of film-coated tablets and hard capsules).

Summary of the safety profile

In the placebo-controlled phase 3 studies, 4158 patients were exposed to orforglipron alone or in combination with other glucose lowering medicinal products. The most frequently reported adverse reactions were gastrointestinal disorders and these were mostly mild or moderate in severity. The incidence of nausea, vomiting, and diarrhoea was higher during the dose escalation period and decreased over time (see sections 4.2 and 4.4).

Tabulated list of adverse reactions

The following related adverse reactions from clinical studies are listed below by system organ class and in order of decreasing frequency (very common: ≥ 1/10; common: ≥ 1/100 to < 1/10; uncommon: ≥ 1/1 000 to < 1/100; rare: ≥ 1/10 000 to < 1/1 000; very rare: < 1/10 000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1. Adverse reactions

System organ class	Very common	Common	Uncommon
Metabolism and nutrition disorders	Hypoglycaemia when used with basal insulin, with or without metformin and/or SGLT2i[a]	Hypoglycaemia when used with sulfonylurea[a,b]	Hypoglycaemia when used without concomitant insulin or sulfonylurea[a,b]
Nervous system disorders		Dizziness, Headache	Dysgeusia Dysaesthesia,
Cardiac disorders		Tachycardia	
Vascular disorders		Hypotension	
Gastrointestinal disorders	Nausea, Constipation, Diarrhoea, Vomiting, Dyspepsia, Abdominal pain	Abdominal distention, Eructation, Gastroesophageal reflux disease, Flatulence	Acute pancreatitis
Hepatobiliary disorders		Cholelithiasis	
Skin and subcutaneous tissue disorders		Hair loss	
General disorders and administration site conditions		Fatigue	
Investigations		Amylase increased, Lipase increased	

[a] Clinically significant hypoglycaemia (blood glucose <3.0 mmol/L (<54 mg/dL)) or severe hypoglycaemia in patients with type 2 diabetes. SGLT2i = sodium-glucose co-transporter 2 inhibitor.

[b] With Sulfonylurea alone or Sulfonylurea in combination with up to 2 additional oral antihyperglycaemic medicinal products.

Description of selected adverse reactions

Gastrointestinal adverse reactions

Gastrointestinal adverse reactions were mostly mild or moderate in severity. The incidence of nausea, vomiting, and diarrhoea was higher during the dose escalation period and decreased over time (see section 4.4).

Weight management studies

In the placebo-controlled weight management phase 3 studies, gastrointestinal disorders occurred more frequently in patients receiving orforglipron 6 mg hard capsules (60.1 %), 12 mg hard capsules (67.4 %) and 36 mg hard capsules (68.7 %) compared to patients receiving placebo (36.3 %). More patients receiving orforglipron 6 mg hard capsules (3.7 %), 12 mg hard capsules (6.3 %) and 36 mg hard capsules (6.8 %) discontinued treatment due to gastrointestinal adverse reactions compared to patients receiving placebo (0.6 %).

Gastrointestinal adverse reactions were mostly mild (61.8 %) or moderate (34.3 %) in severity, with 3.9% reporting severe events.

Type 2 diabetes studies

In the placebo-controlled type 2 diabetes phase 3 studies, gastrointestinal disorders occurred more frequently in patients receiving orforglipron 3 mg hard capsules (43.2 %), 12 mg hard capsules (57.6 %) and 36 mg hard capsules (59.1 %) compared to patients receiving placebo (25.9 %). More patients receiving orforglipron 3 mg hard capsules (2.1 %), 12 mg hard capsules (4.1 %) and 36 mg hard capsules (6.2 %) discontinued treatment due to gastrointestinal adverse reactions compared to patients receiving placebo (0.4 %).

Gastrointestinal adverse reactions were mostly mild (64.7%) or moderate (33.5%) in severity, with 1.8% reporting severe events.

Pancreatic enzymes

The clinical significance of elevations in amylase or lipase with orforglipron is unknown in the absence of other signs and symptoms of pancreatitis.

Weight management studies

In the placebo-controlled weight management phase 3 studies, mean percentage increases from baseline in serum pancreatic amylase was observed in 18.9% of orforglipron treated participants and 2.9% in the placebo group. Mean percentage increases from baseline in lipase was 28.8% in orforglipron treated participant and 3.8% in the placebo group.

Type 2 diabetes mellitus studies

In the placebo-controlled type 2 diabetes phase 3 studies, mean percentage increases from baseline in serum pancreatic amylase was observed in 24.9% of orforglipron treated participants and 4.3% in the placebo group. Mean percentage increases from baseline in lipase was 26.9% in orforglipron treated participant and -1.1% in the placebo group.

Hypoglycaemia

Weight management studies

In the placebo-controlled phase 3 study in patients with type 2 diabetes and obesity or overweight taking up to 3 oral antihyperglycaemic medicinal products, clinically significant hypoglycaemia was reported in 2% (0.02 to 0.03 events/patient year) of orforglipron-treated patients versus 0.2% (0.01 events/patient year) of placebo-treated patients. One (0.3%) patient receiving orforglipron 6 mg hard capsules reported an episode of severe hypoglycaemia and no cases were observed in the placebo group. Severe hypoglycaemia with orforglipron cannot be excluded. In the subset of 388 patients taking sulfonylurea in this trial, 6.7% (0.08 to 0.09 events/patient year) of patients taking orforglipron reported hypoglycaemia compared with 0.5% (0.00 to 0.01 events/patient year) of patients not taking a sulfonylurea. No patients reported severe hypoglycaemia in combination with sulfonylurea.

Type 2 diabetes studies

In the placebo-controlled type 2 diabetes phase 3 study when used as monotherapy, clinically significant hypoglycaemia was reported in 0.7% (36 mg hard capsules group) to 1.4 % (3 mg hard capsules group) (0.01 to 0.02 events/patient year) of orforglipron-treated patients compared with 0.7 % (0.02 events/patient year) of placebo-treated patients. No patients reported severe hypoglycaemia when used as monotherapy.

In the placebo-controlled type 2 diabetes phase 3 study when used on a background of insulin glargine, hypoglycaemia was reported in 12.9 to 19.0 % (0.38 to 0.68 events/patient year) of orforglipron-treated patients compared with 20.7 % (1.02 events/patient year) of placebo-treated patients. Three patients receiving orforglipron reported severe hypoglycaemia.

Cholelithiasis

Weight management studies

In placebo-controlled weight management phase 3 studies, cholelithiasis was reported in 1.3% of patients receiving orforglipron and 0.6% receiving placebo.

Type 2 diabetes studies

In placebo-controlled type 2 diabetes phase 3 studies, cholelithiasis was reported in 0.6% of patients receiving orforglipron and 0 receiving placebo.

Tachycardia

Treatment across orforglipron doses resulted in a mean increase in heart rate.

Mean pulse rate increased from baseline with orforglipron, generally peaking during dose escalation in both weight management (6.7 to 8.6 bpm) and type 2 diabetes (4.7 to 7.6 bpm) studies. Mean pulse rate then gradually decreased throughout the study intervention period wherein the mean change from baseline was 3.9 to 5.2 bpm across orforglipron groups at week 72 in weight management studies and 2.8 to 5.7 bpm at

week 52 in type 2 diabetes studies. Results for ECG-measured heart rate were consistent with pulse rate from vital signs.

Mean increases in PR interval were observed with orforglipron when compared to placebo (mean increase of 1.0 to 4.0 msec and mean decrease of 0.8 msec respectively). More participants in the orforglipron groups compared to placebo had arrythmia and cardiac conduction disorder treatment emergent events: orforglipron 3 mg hard capsules (2.9%), 12 mg hard capsules (4.1%), 36 mg hard capsules (6.9%) and placebo (2.2%).

Weight management studies

In placebo-controlled weight management phase 3 studies, tachycardia (tachycardia, heart rate increased, and sinus tachycardia) was reported in 2.7% of patients receiving orforglipron and 0.8% of patients receiving placebo.

Type 2 diabetes studies

In placebo-controlled type 2 diabetes phase 3 studies, tachycardia (tachycardia, heart rate increased, and sinus tachycardia) was reported in 1.7% of patients receiving orforglipron and 0.4% of patients receiving placebo.

Hair loss

Hair loss adverse reactions in orforglipron-treated patients were transient and associated with weight reduction.

Weight management studies

In placebo-controlled weight management phase 3 studies, hair loss was reported in 3.7 % of patients receiving orforglipron and 1.8 % of patients receiving placebo.

Type 2 diabetes studies

In placebo-controlled type 2 diabetes phase 3 studies, hair loss was reported in 0.5 % of patients receiving orforglipron and 0.4 % of patients receiving placebo.

Post-marketing and relevant product information

The following events have been reported with relevant medicinal products with similar structure, activity, target engagement or have been reported during post-approval use of orforglipron. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or to establish a causal relationship to drug exposure.

Eye disorders

Events of non-arteritic anterior ischemic optic neuropathy (NAION), a rare condition associated with the potential for decreased vision, including permanent loss of vision, have been reported in patients treated with products with GLP-1 receptor agonist activity.

Gastrointestinal disorders

Acute pancreatitis, haemorrhagic and necrotising pancreatitis sometimes resulting in death; ileus, intestinal obstruction, severe constipation including faecal impaction.

Hypersensitivity

Anaphylaxis, angioedema

Pulmonary aspiration

Pulmonary aspiration has occurred in patients receiving GLP-1 RAs undergoing elective surgeries or procedures requiring general anaesthesia or deep sedation

Renal and urinary disorders

Acute renal failure or worsening of chronic renal failure, sometimes requiring haemodialysis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme, website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In the event of overdose, begin appropriate supportive treatment according to the patient's clinical signs and symptoms. Patients may experience gastrointestinal adverse reactions including nausea and vomiting. There is no specific antidote for overdose of orforglipron.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, Glucagon-like peptide-1 (GLP-1) analogues, ATC code: Not yet assigned

Mechanism of action

Orforglipron is an oral high-affinity nonpeptide GLP-1 receptor agonist that binds to and activates the human GLP-1 receptor.

GLP-1 receptors exist in brain regions that regulate appetite. In animal studies, orforglipron distributed to and activated neurons in brain regions that regulate appetite and decreased food intake.

GLP-1 agonism mediates glucose-stimulated insulin secretion. In animal studies, orforglipron increased insulin secretion in a glucose-dependent manner.

Pharmacodynamic effects

Decreased body weight

Orforglipron reduces body weight, with greater fat mass loss than lean mass loss. Orforglipron reduces visceral adipose tissue. These effects may lead to increased insulin sensitivity and improved lipid profiles. Orforglipron decreases food intake. This effect is likely mediated by decreased appetite.

Glycaemic improvement

Orforglipron improves glycaemic measures by lowering fasting, pre- and postprandial glucose concentration through several mechanisms including increased glucose dependent insulin secretion, decreased fasting glucagon, and increased insulin sensitivity.

Delay in gastric Emptying

Orforglipron delays gastric emptying. The delay is largest after the first dose, and this effect diminishes over time.

Blood pressure

In the pooled placebo-controlled Phase 3 studies, treatment across orforglipron doses resulted in a mean decrease in systolic and diastolic blood pressure.

Clinical efficacy and safety

Two pharmaceutical forms have been developed for orforglipron:

- 0.8 mg, 2.5mg, 5.5 mg, 9 mg, 14.5 mg, 17.2 mg film-coated tablets
- 1 mg, 3 mg, 6 mg, 12 mg, 24 mg, 36 mg hard capsules

Clinical studies were conducted with the hard capsule pharmaceutical form. Film-coated tablets and hard capsules are not substitutable on a mg-per-mg basis (Table 2). Similar efficacy and safety can be expected for both film-coated tablets and hard capsules with the same identifier imprint. Equivalent doses of the two formulations are outlined in the table below.

Table 2. Equal effect of orforglipron film-coated tablets and hard capsules

Orforglipron film-coated tablet or hard capsule identifier imprint	**Orforglipron film-coated tablet**		**Orforglipron hard capsule**
G1	0.8 mg	Equal effect to	1 mg
G2	2.5 mg		3 mg
G3	5.5 mg		6 mg
G4	9.0 mg		12 mg
G5	14.5 mg		24 mg
G6	17.2 mg		36 mg

Weight management

The effectiveness of orforglipron for weight management, in combination with a healthy diet and physical activity, in patients with obesity, or overweight and at least one weight-related comorbidity was evaluated in 2 randomised, double-blinded, placebo-controlled phase 3 studies (ATTAIN-1 and ATTAIN-2). The primary endpoint was mean percent change in body weight. The secondary endpoints included percentage of patients achieving weight reduction targets, mean change in waist circumference, mean change in systolic blood pressure and mean percent change in triglycerides and non-HDL-cholesterol. A total of 4 740 adult patients (3 161 randomised to orforglipron) were included in these studies. All patients treated with orforglipron started with 1 mg for 4 weeks. Then the dose of orforglipron was increased to the next level every 4 weeks until they reached their assigned dose.

Treatment with orforglipron 6 mg, 12 mg or 36 mg demonstrated clinically meaningful and sustained weight reduction compared with placebo. Furthermore, a higher percentage of patients achieved ≥ 5 %, ≥ 10 %, ≥ 15 % and ≥ 20 % weight reduction with orforglipron compared with placebo. Results from the phase 3 studies are presented below based on all participants who were randomly assigned a study intervention.

ATTAIN -1

In a 72 week double-blind placebo-controlled study, 3,127 adult patients with obesity (BMI ≥ 30 kg/m^2) or with overweight (BMI ≥ 27 kg/m^2 to < 30 kg/m^2) and at least one weight-related comorbid condition (dyslipidaemia, hypertension, obstructive

sleep apnoea, or cardiovascular disease) and without type 2 diabetes, were randomised to orforglipron 6 mg, 12 mg or 36 mg once daily or placebo. All patients were counselled on a healthy diet and physical activity throughout the trial. At baseline, patients had a mean age of 45 years, 64 % were women and 36 % of patients had prediabetes. Mean BMI at baseline was 37.0 kg/m^2

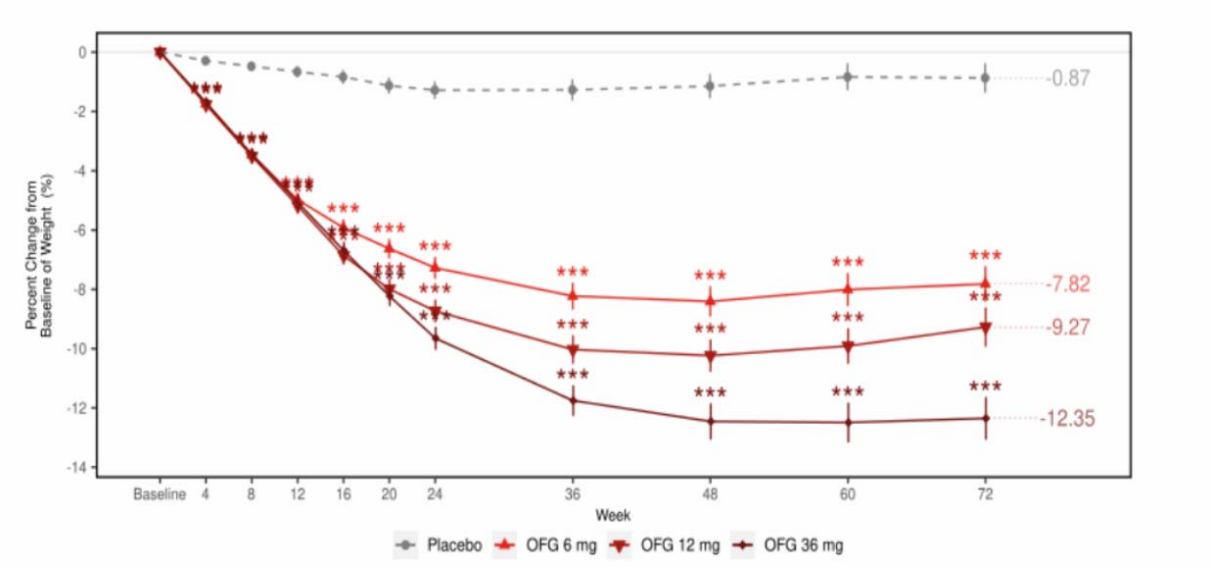
Table 3. ATTAIN -1: Results at week 72

Intent-to-Treat (ITT) population (n)	Orforglipron 6 mg n=723	Orforglipron 12 mg n=725	Orforglipron 36 mg n=730	Placebo n = 949
Body weight				
Baseline mean (kg)	103.2	102.2	103.1	103.9
Change (%) from baseline	-7.8†††	-9.3†††	-12.4†††	-0.9†††
Difference (%) from placebo [95 % CI]	-6.9*** (-7.7, -6.2)	-8.4*** (-9.2, -7.6)	-11.5*** (-12.3, -10.6)	-
Change (kg) from baseline	-8.0†††	-9.4†††	-12.4†††	-1.0†††
Difference (kg) from placebo [95 % CI]	-7.0### (-7.9, -6.2)	-8.4### (-9.2, -7.5)	-11.4### (-12.3, -10.4)	-
Patients (%) achieving body weight reduction				
≥ 5 %	63.8***	69.3***	77.1***	22.1
≥ 10 %	35.9***	45.1***	59.6***	8.6
≥ 15 %	16.5***	24.0***	39.6***	3.6
≥ 20 %	7.2###	11.4***	20.1***	1.6
Waist circumference (cm)				
Baseline mean	112.2	112.0	112.4	112.8
Change from baseline	-7.5†††	-9.0†††	-11.1†††	-2.1†††
Difference from placebo [95 % CI]	-5.4*** (-6.2, -4.7)	-6.9*** (-7.7, -6.1)	-9.0*** (-9.8, -8.2)	-
Triglycerides (mg/dL)				
Baseline geometric mean	121.3	119.2	125.6	125.4
% change from baseline	-12.1†††	-15.2†††	-21.6†††	-4.8†††
Relative difference from placebo [95% CI]	-7.7### (-11.2, -4.0)	-10.9### (-14.4, -7.2)	-17.6### (-20.7, -14.5)	-
LDL Cholesterol (mg/dL)				
Baseline geometric mean	114.9	113.3	114.6	114.3
% change from baseline	-4.6†††	-6.7†††	-5.3†††	-0.5
Relative difference from placebo [95% CI]	-4.2### (-6.6, -1.7)	-6.2### (-8.6, -3.9)	-4.9### (-7.2, -2.5)	-
HDL Cholesterol (mg/dL)				
Baseline geometric mean	48.1	48.7	47.0	47.7
% change from baseline	2.3†††	3.7†††	5.2†††	0.1
Relative difference from placebo [95% CI]	2.3# (0.5, 4.1)	3.6### (1.8, 5.5)	5.2### (3.4, 7.0)	-
hsCRP (mg/L)				
Baseline geometric mean	3.2	3.3	3.2	3.3
% change from baseline	-36.8†††	-41.1†††	-47.7†††	-12.7†††
Relative difference from placebo [95% CI]	-27.7### (-33.6, -21.3)	-32.6### (-38.2, -26.5)	-40.1### (-45.3, -34.4)	-

*p< 0.05, **p<0.01, ***p<0.001 (unadjusted 2-sided) compared to placebo for superiority; controlled for multiplicity.

[#]p< 0.05, [##]p<0.01, [###]p<0.001 (unadjusted 2-sided) compared to placebo; not controlled for multiplicity

[†]p<0.05, [††]p<0.01, [†††]p<0.001 (unadjusted 2-sided) compared to baseline.



Abbreviations: OFG= orforglipron

Figure 1. ATTAIN-1 Mean change in body weight (%) from baseline to week 72

In ATTAIN-1, pooled doses of orforglipron 6 mg, 12 mg, and 36 mg led to a significant improvement compared to placebo in systolic blood pressure (-6.14 mmHg vs. -0.78 mmHg) and non-HDL cholesterol (-7.57 % vs. -1.41 %). Orforglipron 6 mg, 12 mg, and 36 mg all achieved statistically significant improvements in percent change in fasting insulin from baseline to week 72 of -20.64%, -23.87% and -32.78% respectively, compared to -7.30% with placebo.

Among the patients in ATTAIN -1 with prediabetes at baseline (N = 1128), patients treated with orforglipron 6 mg, 12 mg, and 36 mg all had a significantly higher proportion of patients, 89.1%, 87.7% and 91.3% respectively, revert to normoglycaemia at week 72, as compared with 42.4% of patients in the placebo group.

ATTAIN -2

In a 72 week double-blind placebo-controlled study, 1,613 adult patients with obesity (BMI ≥ 30 kg/m^2) or overweight (BMI ≥ 27 kg/m^2) and type 2 diabetes, were randomised to orforglipron 6 mg, 12 mg or 36 mg once daily or placebo. Patients included in the trial had HbA1c ≥7- ≤10 % and were treated with either diet and exercise alone, or with one or more oral anti-hyperglycaemic agent. All patients were counselled on a healthy diet and increased physical activity throughout the trial.

Patients had a mean age of 57 years and 47 % were women. Mean BMI at baseline was 35.6 kg/m^2.

Table 4. ATTAIN -2: Results at week 72

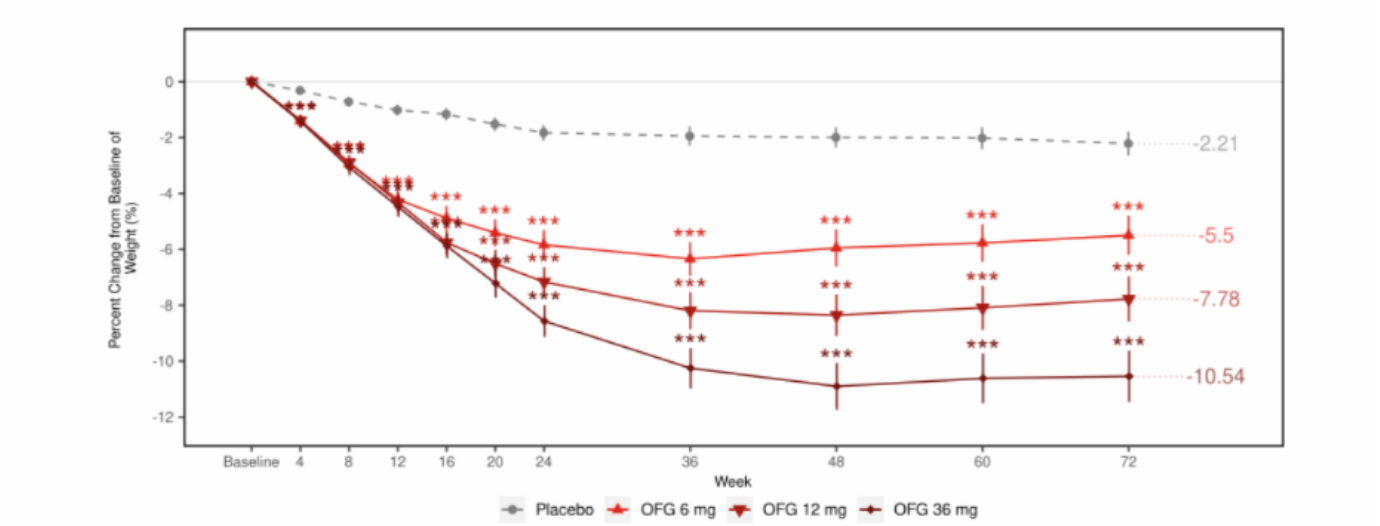
ITT population (n)	Orforglipron 6 mg n=329	Orforglipron 12 mg n=332	Orforglipron 36 mg n=322	Placebo N=630
Body weight				
Baseline mean (kg)	102.3	102.7	99.8	101.2
Change (%) from baseline	-5.5†††	-7.8†††	-10.5†††	-2.2†††
Difference (%) from placebo [95 % CI]	-3.3*** (-4.1, -2.5)	-5.6*** (-6.5, -4.6)	-8.3*** (-9.3, -7.3)	-
Change (kg) from baseline	-5.5†††	-7.9†††	-10.4†††	-2.3†††
Difference (kg) from placebo [95 % CI]	-3.3$^{\#\#\#}$ (-4.1, -2.4)	-5.6$^{\#\#\#}$ (-6.6, -4.7)	-8.1$^{\#\#\#}$ (-9.2, -7.0)	-
Patients (%) achieving body weight reduction				
≥ 5 %	49.8***	60.2***	72.8***	24.4
≥ 10 %	23.9***	35.5***	50.1***	7.0
≥ 15 %	7.3$^{\#\#\#}$	17.7***	28.4***	1.9
≥ 20 %	3.9$^{\#\#}$	6.2$^{\#\#\#}$	12.0$^{\#\#\#}$	0.2
Waist circumference (cm)				
Baseline mean	116.8	116.2	114.7	115.0
Change from baseline	-5.6†††	-7.2†††	-9.2†††	-2.7†††
Difference from placebo [95 % CI]	-3.0$^{\#\#\#}$ (-3.9, -2.1)	-4.5$^{\#\#\#}$ (-5.4, -3.5)	-6.5*** (-7.5, -5.5)	-
HbA_{1c} (mmol/mol)				
Baseline mean	64.3	64.8	64.5	64.3
Change from baseline	-14.1†††	-17.5†††	-19.6†††	-1.5†
Difference from placebo [95 % CI]	-12.6*** (-14.6, -10.7)	-16.0*** (-17.8, -14.2)	-18.1*** (-19.9, -16.2)	-
HbA_{1c} (%)				
Baseline mean	8.0	8.1	8.1	8.0
Change from baseline	-1.3†††	-1.6†††	-1.8†††	-0.1†
Difference from placebo [95 % CI]	-1.2*** (-1.3, -1.0)	-1.5*** (-1.6, -1.3)	-1.7*** (-1.8, -1.5)	-
Patients (%) achieving HbA1c				
< 7 %	70.0***	78.0***	85.1***	23.0
≤ 6.5 %	56.2***	67.5***	75.0***	10.6
< 5.7 %	7.8$^{\#\#\#}$	17.9$^{\#\#\#}$	28.1$^{\#\#\#}$	0.7
FSG (mmol/L)				
Baseline mean	8.5	8.6	8.6	8.4
Change from baseline	-1.8†††	-2.3†††	-2.5†††	0.1
Difference from placebo [95 % CI]	-1.9*** (-2.2, -1.6)	-2.3*** (-2.6, -2.1)	-2.6*** (-2.9, -2.3)	-
FSG (mg/dL)				
Baseline mean	152.9	155.1	154.7	151.5
Change from baseline	-33.0†††	-41.1†††	-45.8†††	1.2
Difference from placebo [95 % CI]	-34.2*** (-39.8, -28.6)	-42.3*** (-47.3, -37.3)	-47.0*** (-52.1, -41.9)	-
Triglycerides (mg/dL)				
Baseline geometric mean	157.4	164.4	157.2	162.8
% change from baseline	-15.3†††	-16.0†††	-21.3†††	-4.7††

Relative difference from placebo [95% CI]	-11.2$^{###}$ (-16.1, -5.9)	-11.9$^{###}$ (-16.8, -6.7)	-17.4$^{###}$ (-22.0, -12.6)	-
LDL Cholesterol (mg/dL)				
Baseline geometric mean	84.3	83.8	85.5	84.6
% change from baseline	0.7	-2.4	-3.0	-2.6
Relative difference from placebo [95% CI]	3.4 (-1.7, 8.8)	0.3 (-4.2, 5.0)	-0.4 (-5.1, 4.5)	-
HDL Cholesterol (mg/dL)				
Baseline geometric mean	43.5	42.8	43.1	42.0
% change from baseline	4.9 †††	4.9 †††	8.9 †††	2.0††
Relative difference from placebo [95% CI]	2.8$^{#}$ (0.5, 5.1)	2.8$^{#}$ (0.4, 5.2)	6.7 $^{###}$ (4.3, 9.3)	-
hsCRP (mg/L)				
Baseline geometric mean	2.7	2.8	2.4	3.0
% change from baseline	-38.3†††	-44.5†††	-50.6†††	-9.0††
Relative difference from placebo [95% CI]	-32.2$^{###}$ (-40.5, -22.8)	-39.1$^{###}$ (-46.2, -31.0)	-45.8$^{###}$ (-52.3, -38.3)	-

*p< 0.05, **p<0.01, ***p<0.001 (unadjusted 2-sided) compared to placebo for superiority; controlled for multiplicity.

$^{#}$p< 0.05, $^{##}$p<0.01, $^{###}$p<0.001 (unadjusted 2-sided) compared to placebo; not controlled for multiplicity

†p<0.05, ††p<0.01, †††p<0.001 (unadjusted 2-sided) compared to baseline.



Abbreviations: OFG= orforglipron

Figure 2. ATTAIN-2 Mean change in body weight (%) from baseline to week 72

In ATTAIN-2, pooled doses of orforglipron 6 mg, 12 mg and 36 mg led to a significant improvement compared to placebo in systolic blood pressure (-4.90 mmHg vs. -1.48 mmHg), and non-HDL cholesterol (6.4 % vs. 3.0 %).

Effect on body composition

Changes in body composition were evaluated in a sub-study in ATTAIN-1 (n = 171) using dual energy X-ray absorptiometry (DEXA). The results of the DEXA

assessment showed that treatment with orforglipron achieved statistically significant percent reduction in total body fat mass compared to placebo after 72 weeks. Furthermore, this reduction in total body fat mass was accompanied by a statistically significant percent reduction in total body lean mass and statistically significant percent reduction in visceral fat mass. These results suggest that body weight reduction was primarily due to a reduction in total fat mass, including visceral fat.

Improvement in physical functioning

Patients with obesity or overweight without diabetes who received orforglipron showed small improvements in health-related quality of life, including physical functioning. The improvements were greater in the orforglipron-treated patients than in those who received placebo. Health-related quality of life was assessed using the generic questionnaire Short Form-36v2 Health Survey Acute, Version (SF-36v2).

Type 2 diabetes mellitus

Improvement of glycaemic control, reduction of cardiovascular morbidity and mortality and weight loss are integral parts of the treatment of type 2 diabetes.

The effectiveness of orforglipron for type 2 diabetes was evaluated in four global randomised, controlled, phase 3 studies (ACHIEVE-1, -2, -3 and -5) assessing change from baseline HbA1c as the primary objective. The studies involved 3765 treated adult patients with type 2 diabetes (2395 treated with orforglipron). The secondary endpoints included percentage of patients reaching target HbA1c, fasting serum glucose (FSG), change in body weight and percentage of patients achieving weight reduction targets. All patients treated with orforglipron started with 1 mg for 4 weeks. Then the dose of orforglipron was increased to the next level every 4 weeks until they reached their assigned dose.

Across the ACHIEVE studies, treatment with orforglipron demonstrated sustained, statistically significant and clinically meaningful reductions from baseline in HbA1c compared to either placebo or active control treatment (dapagliflozin and oral semaglutide) for up to 1 year. Statistically significant and clinically meaningful reductions from baseline in body weight were also demonstrated. The effectiveness of orforglipron was not impacted by age, gender, race, ethnicity, region or by baseline BMI, HbA1c, diabetes duration or renal function. Results from the phase 3 studies are presented below based on all participants who were randomly assigned a study intervention and who took at least 1 dose of study intervention.

ACHIEVE-1 – Monotherapy

In a 40 week double-blind placebo-controlled study, 559 patients with type 2 diabetes and inadequate glycaemic control with diet and exercise alone, were randomised to orforglipron 3 mg, 12 mg or 36 mg once daily or placebo. At baseline the patients had a mean duration of diabetes of 4.4 years, a mean BMI of 33.0 kg/m^2, a mean age of 53.4 years and 51.9 % were men.

Table 5. ACHIEVE-1: Results at week 40

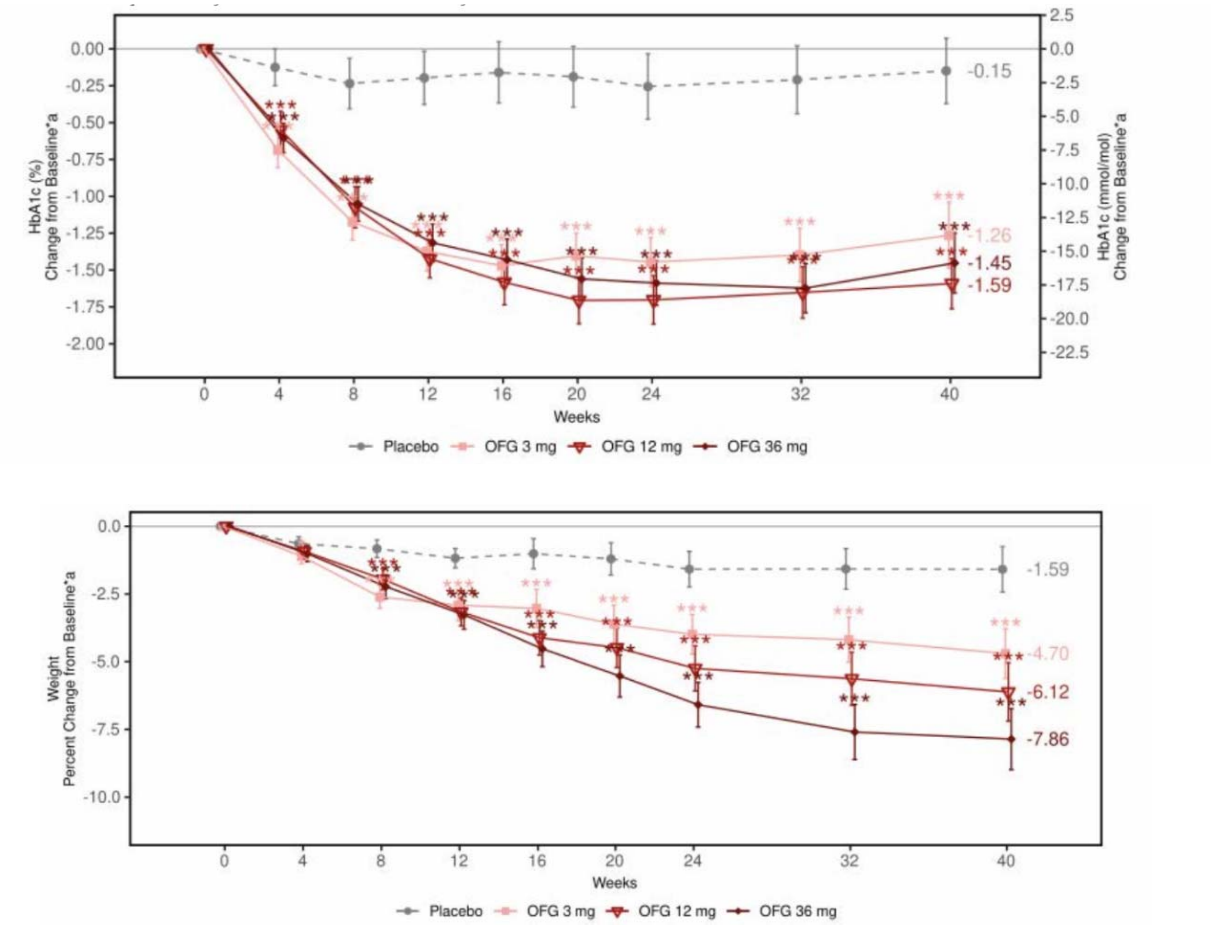
ITT population (n)	Orforglipron 3 mg n=143	Orforglipron 12 mg n=137	Orforglipron 36 mg n=141	Placebo n=138
HbA_{1c} (%)				
Baseline (mean)	7.9	8.0	8.1	8.0
Change from baseline	-1.3†††	-1.6†††	-1.5†††	-0.1
Difference from placebo [95% CI]	-1.1*** (-1.4, -0.8)	-1.4*** (-1.7, -1.2)	-1.3*** (-1.6, -1.0)	
HbA1c (mmol/mol)				
Baseline (mean)	63.2	63.8	64.7	63.6
Change from baseline	-13.8†††	-17.4†††	-15.9†††	-1.6
Difference from placebo [95% CI]	-12.2*** (-15.6, -8.7)	-15.8*** (-18.8, -12.7)	-14.2*** (-17.6, -10.9)	-
Patients (%) achieving HbA_{1c}				
<7%	72.9***	76.2***	74.9***	28.0
≤6.5%	61.5***	62.3***	66.0***	13.5
<5.7%	17.7$^{\#\#\#}$	25.8$^{\#\#\#}$	23.9$^{\#\#\#}$	3.8
FSG (mmol/L)				
Baseline (mean)	7.9	8.6	8.3	8.0
Change from baseline	-1.7†††	-2.1†††	-2.1 †††	-0.1
Difference from placebo [95% CI]	-1.6*** (-2.2, -1.0)	-2.0*** (-2.6, -1.5)	-2.0*** (-2.6, -1.5)	-
FSG (mg/dL)				
Baseline (mean)	142.9	155.3	148.8	143.3
Change from baseline	-30.6	-37.4	-37.8	-1.1
Difference from placebo [95% CI]	-29.4*** (-40.1, -18.7)	-36.3*** (-46.4, -26.3)	-36.7*** (-46.6, -26.8)	-
Body weight (%)				
Baseline (mean) (kg)	90.3	90.6	90.1	90.0
Change from baseline	-4.7	-6.1	-7.9	-1.6
Difference from placebo [95 % CI]	-3.1*** (-4.4-1.8)	-4.5*** (-5.9, -3.1)	-6.3*** (-7.7, -4.8)	-
Body weight (kg)				
Baseline (mean)	90.3	90.6	90.1	90.0
Change from baseline	-4.4†††	-5.5†††	-7.3†††	-1.3†††
Difference from placebo [95% CI]	-3.1$^{\#\#\#}$ (-4.2, -2.0)	-4.2*** (-5.5, -3.0)	-6.0*** (-7.3, -4.6)	-
Patients (%) achieving weight loss				
≥5%	44.7$^{\#\#\#}$	56.6$^{\#\#\#}$	64.2$^{\#\#\#}$	19.4
≥10%	16.8$^{\#}$	29.8$^{\#\#\#}$	31.7$^{\#\#\#}$	7.6
≥15%	5.3	8.3$^{\#}$	10.9$^{\#\#}$	2.2
Triglycerides (mmol/L)				
Baseline (mean)	1.7	1.7	1.9	1.6
Change from baseline (%)	-9.1†	-16.5†††	-14.0†††	0.0
Relative difference from placebo [95% CI]	-9.2 (-18.3, 0.9)	-16.5*** (-24.5, -7.7)	-14.0** (-22.0, -5.3)	-
Non-HDL Cholesterol (mmol/L)				
Baseline (mean)	3.5	3.5	3.5	3.5
Change from baseline (%)	-1.8	-4.8†	-7.9†††	3.2
Relative difference from placebo [95% CI]	-4.8 (-10.3, 1.0)	-7.7* (-13.3, -1.9)	-10.8*** (-15.5, -5.7)	-
Systolic Blood Pressure (mmHg)				
Baseline (mean)	126.5	127.5	128.3	128.4
Change from baseline	-3.2	-6.1	-6.0	-0.5
Difference from	-2.7$^{\#}$	-5.6$^{\#\#\#}$	-5.5$^{\#\#\#}$	-

ITT population (n)	Orforglipron 3 mg n=143	Orforglipron 12 mg n=137	Orforglipron 36 mg n=141	Placebo n=138
placebo (95% CI)	(-5.2,-0.2)	(-8.2,-3.0)	(-8.0,-3.0)	

*p< 0.05, **p<0.01, ***p<0.001 (unadjusted 2-sided) compared to placebo for superiority; controlled for multiplicity.

#p< 0.05, ##p<0.01, ###p<0.001 (unadjusted 2-sided) compared to placebo; not controlled for multiplicity

†p<0.05, ††p<0.01, †††p<0.001 (unadjusted 2-sided) compared to baseline.



Abbreviations: OFG= orforglipron

Figure 3. ACHIEVE-1 Mean HbA_{1c} (%) and mean body weight (%) from baseline to week 40

ACHIEVE-2 – Combination therapy with metformin compared to dapagliflozin

In a 40 week active-controlled open-label study, (double-blind with respect to orforglipron dose assignment) 962 patients were randomised to once daily orforglipron 3 mg, 12 mg or 36 mg, or dapagliflozin 10 mg, all in combination with

metformin. At baseline the patients had a mean duration of diabetes of 8.0 years, a mean BMI of 32.6 kg/m^2, a mean age of 56.1 years and 50.7 % were men.

Table 6. ACHIEVE-2: Results at week 40

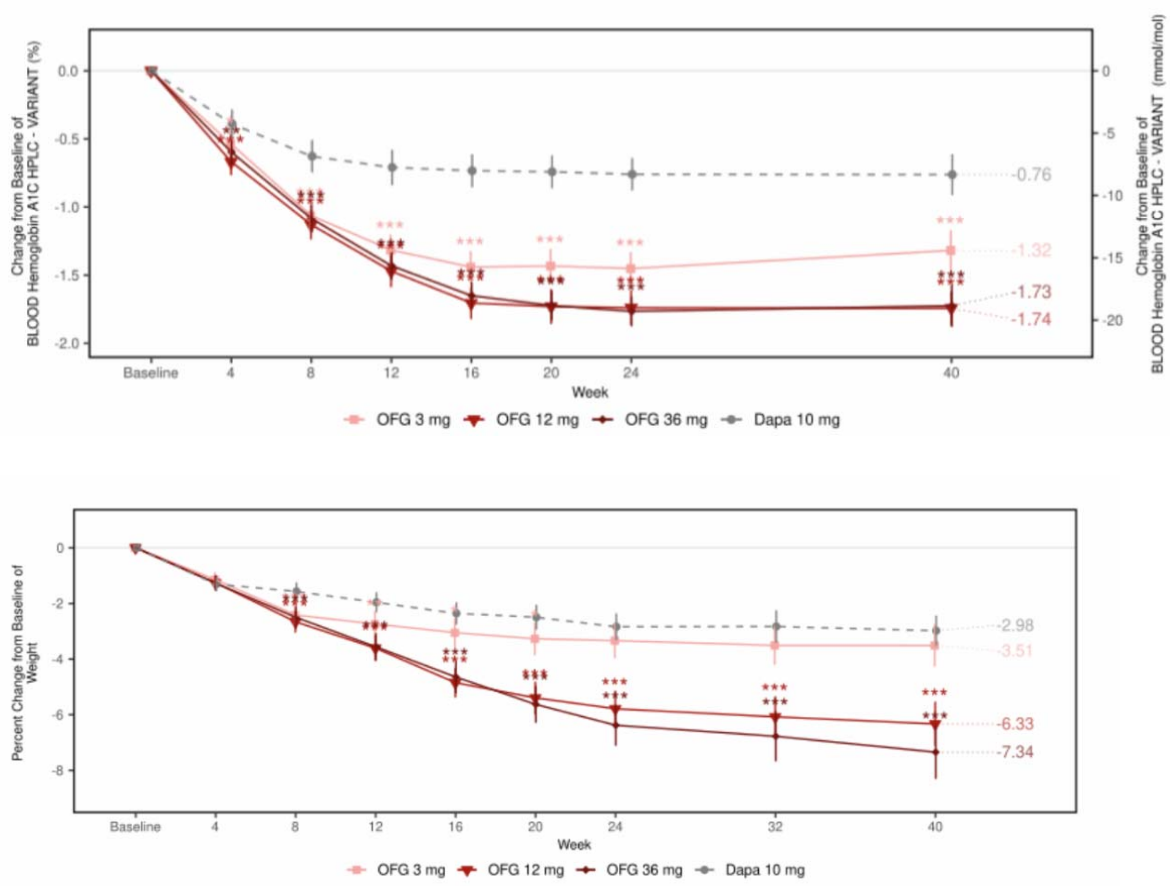
ITT population (n)	Orforglipron 3 mg n=240	Orforglipron 12 mg n=241	Orforglipron 36 mg n=241	Dapagliflozin 10 mg n=240
HbA_{1c} (%)				
Baseline (mean)	8.2	8.1	8.2	8.1
Change from baseline	-1.3†††	-1.7†††	-1.7†††	-0.8†††
Difference from Dapagliflozin [95% CI]	-0.6*** (-0.8, -0.3)	-1.0*** (-1.2, -0.8)	-1.0*** (-1.2, -0.7)	
HbA_{1c} (mmol/mol)				
Baseline (mean)	65.8	65.2	65.9	65.0
Change from baseline	-14.4†††	-19.1†††	-18.9†††	-8.3†††
Difference from Dapagliflozin [95% CI]	-6.1*** (-8.4, -3.8)	-10.7*** (-12.8, -8.6)	-10.5*** (-12.9, -8.2)	-
Patients (%) achieving HbA_{1c}				
<7%	63.2***	80.1***	77.9***	37.0
≤6.5%	54.6***	66.7***	68.6***	21.6
<5.7%	9.7$^{\#}$	15.3$^{\#\#\#}$	23.7$^{\#\#\#}$	4.4
FSG (mmol/L)				
Baseline (mean)	8.8	8.9	8.7	8.5
Change from baseline	-1.8†††	-2.4†††	-2.4†††	-1.2†††
Difference from Dapagliflozin [95% CI]	-0.5$^{\#}$ (-1.0, -0.1)	-1.1$^{\#\#\#}$ (-1.6, -0.7)	-1.2$^{\#\#\#}$ (-1.6, -0.8)	-
FSG (mg/dL)				
Baseline (mean)	159.4	160.1	157.0	152.3
Change from baseline	-32.3	-43.1	-43.9	-22.5
Difference from Dapagliflozin [95% CI]	-9.9$^{\#}$ (-17.5, -2.3)	-20.7$^{\#\#\#}$ (-28.1, -13.3)	-21.4$^{\#\#\#}$ (-28.9, -14.0)	-
Body weight (%)				
Baseline (mean) (kg)	90.1	92.0	88.1	89.4
Change from baseline	-3.5	-6.3	-7.3	-3.0
Difference from Dapagliflozin[95 % CI]	-0.5 (-1.4, 0.4)	-3.4*** (-4.3, -2.4)	-4.4*** (-5.5, -3.3)	-
Body weight (kg)				
Baseline (mean)	90.1	92.0	88.1	89.4
Change from baseline	-3.2†††	-5.8†††	-6.8†††	-2.7†††
Difference from Dapagliflozin [95% CI]	-0.5 (-1.3, 0.4)	-3.1*** (-4.0, -2.2)	-4.0*** (-5.1, -3.0)	-
Patients (%) achieving weight loss				
≥5%	38.6$^{\#}$	55.9$^{\#\#\#}$	61.3$^{\#\#\#}$	27.9
≥10%	14.2$^{\#\#}$	29.7$^{\#\#\#}$	33.6$^{\#\#\#}$	5.7
≥15%	3.2	8.9$^{\#\#\#}$	17.5$^{\#\#\#}$	1.1
Triglycerides (mmol/L)				
Baseline geometric mean	1.7	1.7	1.7	1.7
% change from baseline	-9.9†††	-12.7†††	-14.8†††	-4.0
Relative difference from dapagliflozin [95% CI]	-6.1 (-13.0, 1.3)	-9.1$^{\#}$ (-16.2, -1.5)	-11.2** (-17.8, -4.1)	-
Non-HDL Cholesterol (mmol/L)				
Baseline (mean)	3.1	3.2	32	3.1
Change from baseline	-2.8	-8.2†††	-5.0††	-0.1
Relative difference from Dapagliflozin [95%	-2.9	-8.2$^{\#\#\#}$	-5.0*	-

ITT population (n)	Orforglipron 3 mg n=240	Orforglipron 12 mg n=241	Orforglipron 36 mg n=241	Dapagliflozin 10 mg n=240
CI]	(-7.4, 1.9)	(-12.6, -3.7)	(-9.7, -0.1)	
Systolic Blood Pressure (mmHg)				
Baseline (mean)	127.6	128.1	127.7	128.3
Change from baseline	-2.8 (0.7)	-5.1 (0.7)	-5.8 (0.7)	-3.8 (0.6)
difference from Dapagliflozin [95% CI]	1.1 (-0.7, 2.8)	-1.3 (-3.1, 0.5)	-2.0* (-3.8, -0.2)	-

*p< 0.05, **p<0.01, ***p<0.001 (unadjusted 2-sided) compared to placebo for superiority; controlled for multiplicity.

#p< 0.05, ##p<0.01, ###p<0.001 (unadjusted 2-sided) compared to placebo; not controlled for multiplicity

†p<0.05, ††p<0.01, †††p<0.001 (unadjusted 2-sided) compared to baseline.



Abbreviations: Dapa = dapagliflozin, OFG= orforglipron

Figure 4. ACHIEVE-2 Mean HbA_{1c} (%) and mean body weight (%) from baseline to week 40

ACHIEVE-3 – Combination therapy with metformin compared to oral semaglutide

In a 52 week active-controlled open-label study, 1698 patients were randomised to orforglipron 12 mg or 36 mg once daily or oral semaglutide 7 mg or 14 mg, all in

combination with metformin. At baseline the patients had a mean duration of diabetes of 8.7 years, a mean BMI of 35.1kg/m^2 .

A mean age of 53.9 years and 51.4% were men.

Table 7. ACHIEVE-3: Results at week 52

ITT population (n)	Orforglipron 12 mg n=424	Orforglipron 36 mg n=423	Semaglutide[+] 7 mg n=426	Semaglutide[+] 14 mg n=425
HbA_{1c} (mmol/mol)				
Baseline (mean)	66.8	67.0	67.3	67.2
Change from baseline	-20.8[†††]	-23.6[†††]	-12.2[†††]	-15.8[†††]
Difference from semaglutide 7 mg [95 % CI]	-8.7[***] (-10.5, -6.8)	-11.4[***] (-13.1, -9.6)	-	-
Difference from oral semaglutide 14 mg [95 % CI]	-5.0[***] (-6.8, -3.2)	-7.7[***] (-9.5, -6.0)	-	-
HbA_{1c} (%)				
Baseline (mean)	8.3	8.3	8.3	8.3
Change from baseline	-1.9[†††]	-2.2[†††]	-1.1[†††]	-1.4[†††]
Difference from oral semaglutide 7 mg [95 % CI]	-0.8[***] (-1.0, -0.6)	-1.0[***] (-1.2, -0.9)		
Difference from oral semaglutide 14 mg [95 % CI]	-0.5[***] (-0.6, -0.3)	-0.7[***] (-0.9, -0.5)		
Patients (%) achieving HbA_{1c}				
< 7 %	80.0[***a, ***b]	85.4[***a, ***b]	54.6	66.1
≤ 6.5 %	71.8[***a, ***b]	76.8[***a, ***b]	40.9	50.9
< 5.7 %	25.4[###a, ###b]	37.1[###a, ###b]	7.8	12.5
FSG (mmol/L)				
Baseline (mean)	9.4	9.3	9.4	9.6
Change from baseline	-3.1[†††]	-3.3[†††]	-1.6[†††]	-2.2[†††]
Difference from oral semaglutide 7 mg [95 % CI]	-1.5[###] (-1.8, -1.1)	-1.7[###] (-2.1, -1.4)	-	-
Difference from oral semaglutide 14 mg [95 % CI]	-0.8[###] (-1.2, -0.5)	-1.1[###] (-1.4, -0.8)	-	-
FSG (mg/dL)				
Baseline (mean)	168.5	167.1	169.9	172.4
Change from baseline	-55.2[†††]	-60.1[†††]	-28.9[†††]	-40.2[†††]
Difference from oral semaglutide 7 mg [95 % CI]	-26.2[###] (-32.3, -20.2)	-31.2[###] (-37.0, -25.4)	-	-
Difference from oral semaglutide 14 mg [95 % CI]	-15.0[###] (-20.7, -9.2)	-19.9[###] (-25.4, -14.4)	-	-
Body weight (%)				
Baseline (mean) (kg)	96.1	96.5	97.1	98.4
Change from baseline	-6.7[†††]	-9.2[†††]	-3.7[†††]	-5.3[†††]
Difference from oral semaglutide 7 mg [95 % CI]	-2.9[***] (-3.8, -2.1)	-5.5[***] (-6.4, -4.5)	-	-
Difference from oral semaglutide 14 mg [95 % CI]	-1.4[##] (-2.3, -0.5)	-4.0[***] (-4.9, -3.0)	-	-
Body weight (kg)				
Baseline (mean)	96.1	96.5	97.1	98.4
Change from baseline	-6.6[†††]	-8.9[†††]	-3.6[†††]	-5.0[†††]
Difference from oral semaglutide 7 mg [95 % CI]	-3.1[***] (-3.9, -2.2)	-5.4[***] (-6.3, -4.4)	-	-
Difference from oral semaglutide 14 mg [95 % CI]	-1.6[###] (-2.5, -0.8)	-3.9[***] (-4.9, -3.0)	-	-
Patients (%) achieving body weight reduction				
≥ 5 %	59.2[###a, ##b]	69.5[###a, ###b]	36.9	49.4
≥ 10 %	28.2[###a, #b]	43.5[###a, ###b]	13.2	21.0
≥ 15 %	12.0[###a, ##b]	23.2[###a, ###b]	5.0	6.5
Triglycerides (mmol/L)				
Baseline geometric mean	1.8	1.8	1.9	1.8
% change from baseline	-16.9[†††]	-16.0[†††]	-5.0[††]	-13.4[†††]
Relative difference from oral semaglutide	-12.5[###]	-11.6[###]	-	-

7 mg [95% CI]	(-17.8, -7.0)	(-16.8, -6.0)		
Relative difference from oral semaglutide 14 mg [95 % CI]	-4.0 (-9.2, 1.5)	-2.9 (-8.1, 2.6)	-	-
Non-HDL Cholesterol (mmol/L)				
Baseline geometric mean	3.2	3.3	3.2	3.3
% change from baseline	-7.7†††	-5.5†††	-2.1	-1.9
Relative difference from oral semaglutide 7 mg [95% CI]	-5.7$^{\#\#}$ (-9.3, -2.0)	-3.4$^{\#}$ (-7.1, 0.4)	-	-
Relative difference from oral semaglutide 14 mg [95 % CI]	-5.9$^{\#\#\#}$ (-9.2, -2.4)	-3.6$^{\#}$ (-7.0, -0.1)	-	-
Systolic blood pressure (mmHg)				
Baseline (mean)	129.6	129.1	129.5	128.8
Change from baseline	-4.5†††	-5.4†††	-2.0†††	-2.7†††
Difference from oral semaglutide 7 mg [95 % CI]	-2.5$^{\#\#}$ (-4.0, -0.9)	-3.4$^{\#\#\#}$ (-5.1, -1.7)	-	-
Difference from oral semaglutide 14 mg [95 % CI]	-1.8$^{\#}$ (-3.4, -0.2)	-2.7$^{\#\#}$ (-4.5, -1.0)	-	-

$^{+}$oral semaglutide once daily

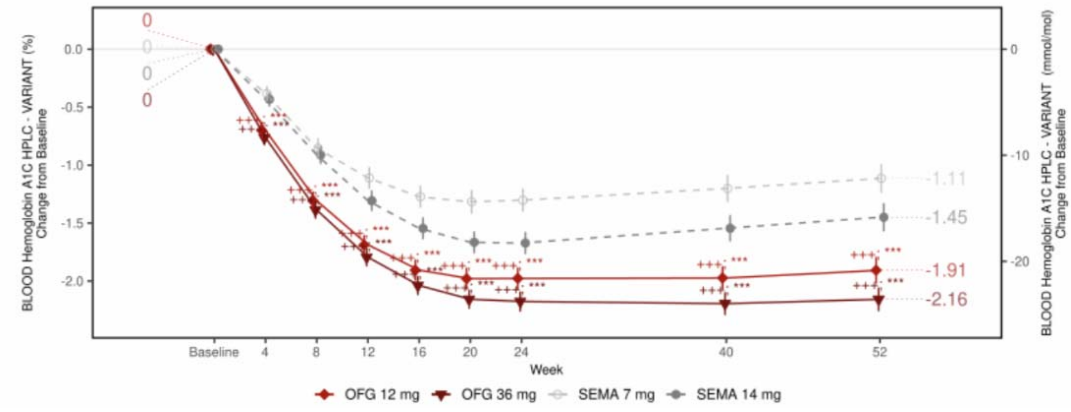
*p< 0.05, **p<0.01, ***p<0.001 (unadjusted 2-sided) compared to oral semaglutide for superiority; controlled for multiplicity.

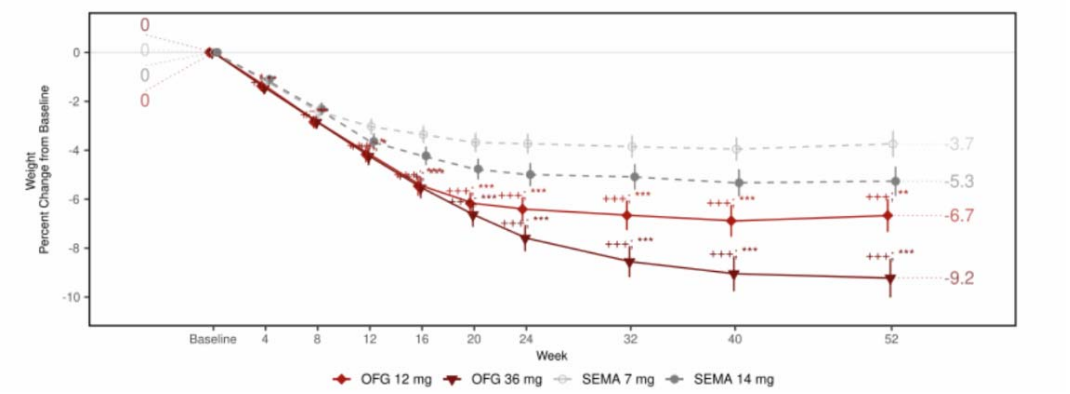
$^{\#}$p< 0.05, $^{\#\#}$p<0.01, $^{\#\#\#}$p<0.001 (unadjusted 2-sided) compared to oral semaglutide; not controlled for multiplicity

†p<0.05, ††p<0.01, †††p<0.001 (unadjusted 2-sided) compared to baseline.

[a] p-value compared to oral semaglutide 7 mg

[b] p-value compared to oral semaglutide 14 mg





Abbreviations: SEMA= semaglutide, OFG= orforglipron

Figure 5. ACHIEVE-3 Mean HbA_{1c} (%) and mean body weight (%) from baseline to week 52

ACHIEVE-5 – Combination therapy with titrated basal insulin, with or without metformin and/or SGLT-2 Inhibitor

In a 40 week double-blind placebo-controlled study, 546 patients with inadequate glycaemic control using insulin glargine with or without metformin and/or SGLT2i were randomised to orforglipron 3 mg, 12 mg or 36 mg once daily or placebo. Insulin glargine doses were adjusted using an algorithm with a fasting blood glucose target of < 5.5 mmol/L. At baseline the patients had a mean duration of diabetes of 15.0 years, a mean BMI of 30.8 kg/m^2, a mean age of 60.2 years and 52.9 % were men. The overall estimated mean dose of insulin glargine at baseline was 36.3 units/day. The mean dose of insulin glargine at week 40 was 44.9, 47.8, 45.5 and 57.3 units/day for orforglipron 3 mg, 12 mg, 36 mg and placebo respectively.

Table 8. ACHIEVE-5: Results at week 40

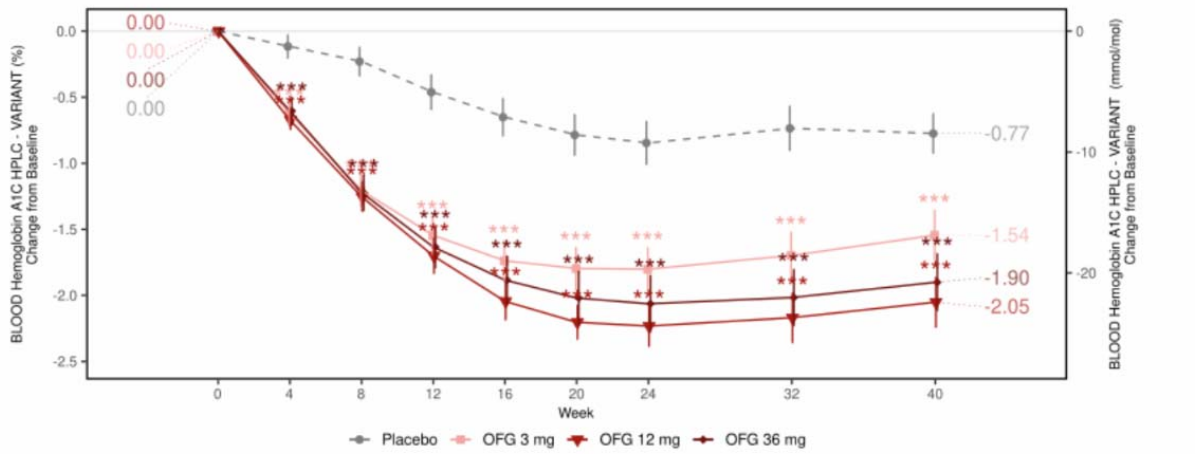
ITT population (n)	**Orforglipron 3 mg n=137**	**Orforglipron 12 mg n=132**	**Orforglipron 36 mg n=136**	**Placebo n=141**
HbA_{1c} (mmol/mol)				
Baseline (mean)	70.0	70.2	68.9	68.6
Change from baseline	-16.9†††	-22.4†††	-20.8†††	-8.5†††
Difference from placebo [95 % CI]	-8.4*** (-11.1, -5.7)	-14.0*** (-16.7, -11.3)***	-12.3*** (-15.2, -9.4)	-
HbA_{1c} (%)				
Baseline (mean)	8.6	8.6	8.5	8.4
Change from baseline	-1.5†††	-2.1†††	-1.9†††	-0.8†††
Difference from placebo [95 % CI]	-0.8*** (-1.0, -0.5)	-1.3*** (-1.5, -1.0)	-1.1*** (-1.4, -0.9)	-
Patients (%) achieving HbA_{1c}				
< 7 %	60.7***	80.8***	69.2***	23.7
≤ 6.5 %	45.9***	69.1***	60.1***	11.1
< 5.7 %	8.9$^{\#\#}$	17.4$^{\#\#\#}$	20.7$^{\#\#\#}$	1.2
FSG (mmol/L)				
Baseline (mean)	8.3	8.3	8.0	8.0
Change from baseline	-2.2†††	-2.7†††	-2.5†††	-2.0†††
Difference from placebo [95 % CI]	-0.3 (-0.7, 0.1)	-0.7$^{\#\#\#}$ (-1.1, -0.3)	-0.5$^{\#}$ (-0.9, -0.1)	-
FSG (mg/dL)				
Baseline (mean)	148.9	148.8	143.7	143.7
Change from baseline	-40.5†††	-48.0†††	-44.5†††	-35.3†††
Difference from placebo [95 % CI]	-5.2 (-12.4, 2.1)	-12.6$^{\#\#\#}$ (-19.7, -5.5)	-9.2$^{\#}$ (-16.2, -2.2)	-

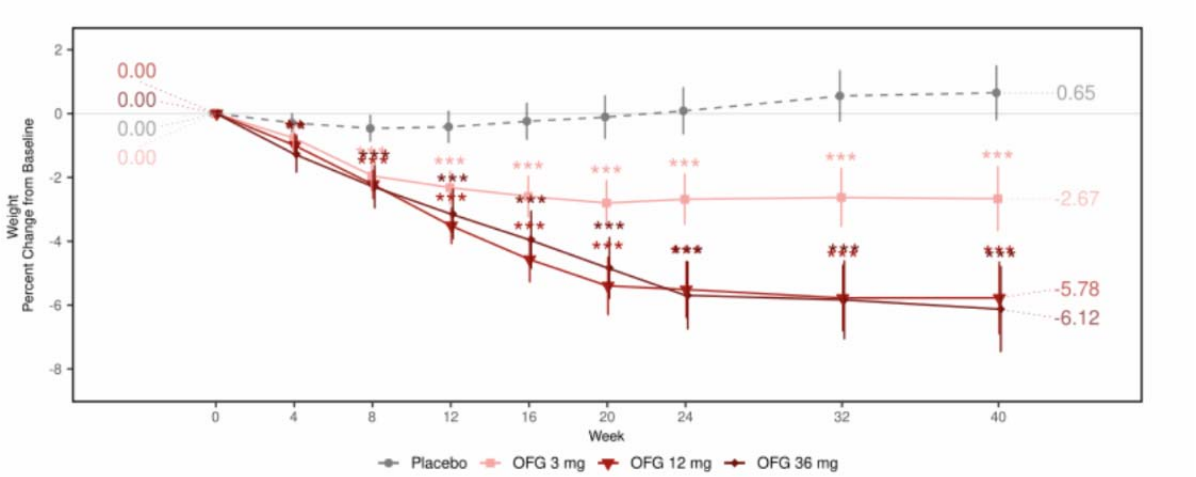
Body weight (%)				
Baseline (mean) (kg)	86.1	86.2	82.9	85.7
Change from baseline	-2.7†††	-5.8†††	-6.1†††	0.6
Difference from placebo [95 % CI]	-3.3*** (-4.6, -2.0)	-6.4*** (-7.8, -5.0)	-6.8*** (-8.4, -5.2)	-
Body weight (kg)				
Baseline (mean)	86.1	86.2	82.9	85.7
Change from baseline	-2.2†††	-5.0†††	-5.2†††	0.5
Difference from placebo [95 % CI]	-2.6*** (-3.8, -1.4)	-5.5*** (-6.7, -4.3)	-5.6*** (-7.1, -4.2)	-
Patients (%) achieving body weight reduction				
≥ 5 %	35.4$^{\#\#\#}$	52.6$^{\#\#\#}$	50.6$^{\#\#\#}$	16.1
≥ 10 %	15.7$^{\#\#}$	23.3$^{\#\#\#}$	27.4$^{\#\#\#}$	4.2
≥ 15 %	6.2	9.9$^{\#}$	14.1$^{\#\#}$	2.5
Triglycerides (mmol/L)				
Baseline geometric mean	1.6	1.7	1.6	1.6
% change from baseline	-4.8	-17.4†††	-14.7†††	-4.7
Relative difference from placebo [95 % CI]	-0.1 (-9.2, 9.9)	-13.4$^{\#\#}$ (-21.6, -4.2)	-10.5$^{\#}$ (-19.1, 1.0)	-
Non-HDL Cholesterol (mmol/L)				
Baseline geometric mean	3.2	3.0	3.2	3.2
% change from baseline	-3.9	-7.6††	-7.8††	-1.1
Relative difference from placebo [95 % CI]	-2.8 (-9.5, 4.4)	-6.6 (-13.5, 0.8)	-6.8 (-13.4, 0.5)	-
Systolic blood pressure (mmHg)				
Baseline (mean)	130.8	131.6	130.1	130.3
Change from baseline	-1.9†	-3.2††	-2.2	0.0
Difference from placebo [95 % CI]	-1.9 (-4.6, 0.9)	-3.2$^{\#}$ (-6.2, -0.2)	-2.2 (-5.4, 1.0)	-

*p< 0.05, **p<0.01, ***p<0.001 (unadjusted 2-sided) compared to placebo for superiority; controlled for multiplicity.

$^{\#}$p< 0.05, $^{\#\#}$p<0.01, $^{\#\#\#}$p<0.001 (unadjusted 2-sided) compared to placebo; not controlled for multiplicity

†p<0.05, ††p<0.01, †††p<0.001 (unadjusted 2-sided) compared to baseline.





Abbreviations: OFG= orforglipron

Figure 6. ACHIEVE-5 Mean HbA_{1c} (%) and mean body weight (%) from baseline to week 40

Cardiovascular evaluation

Maximal mean reductions in systolic blood pressure from baseline showed dose dependency in both the placebo-controlled weight management and type 2 diabetes studies. The maximum reduction was more pronounced in weight management (-6.9 to -7.8 mmHg) than in type 2 diabetes (-4.8 to -6.5 mmHg) studies. Orforglipron reduced diastolic blood pressure in weight management studies (-2.3 to -2.7 mmHg) but had no clinically relevant effect on diastolic blood pressure in type 2 diabetes studies

A greater proportion of participants in the orforglipron groups compared with placebo had treatment-emergent pulse rate elevations to >100 bpm for ≥2 consecutive visits in both weight management (orforglipron 2.68%; placebo, 1.23%) and type 2 diabetes (orforglipron 3.53%; placebo, 0.73%) studies.

Major adverse cardiovascular events (MACE) were adjudicated by an external independent group of experts. Across the placebo-controlled phase 3 studies a total of 59 participants (0.97%) had an adjudication-confirmed MACE, with an incidence of 0.94% in the orforglipron group compared with 1.04% in the placebo group. These results do not suggest an increase in CV risk with orforglipron.

Other information

Fasting serum glucose

Across ACHIEVE-1, -2, -3 and -5 studies, treatment with orforglipron resulted in significant reductions from baseline in FSG (changes from baseline to primary endpoint visit were -1.70 mmol/L (-30.69 mg/dL) to -3.44 mmol/L (-60.1 mg/dL)). Significant reductions from baseline in FSG were observed as early as 4 weeks.

Further improvement in FSG was seen through to 40 weeks then was sustained through the longest study duration of 52 weeks.

Postprandial glucose

In ACHIEVE-1, -2, -3 and -5 studies all doses of orforglipron showed statistically significant decreases compared with placebo or active comparators in the change from baseline in self-monitoring of blood glucose (SMBG) overall daily mean, premeal daily mean, and post meal daily mean. In ACHIEVE-1, -2, -3 and -5, for participants assigned to the orforglipron 12 and 36 mg groups, all 7-point SMBG mean postprandial values remained below 7.8 mmol/L (140 mg/dL), except for the evening 2-hour post meal value in ACHIEVE-5.

Proportion of patients reaching HbA1c < 7 % (< 53 mmol/mol) and ≤ 6.5 % (≤ 39 mmol/mol) without clinically significant hypoglycaemia

In the 3 type 2 diabetes studies without basal insulin or sulfonylurea (ACHIEVE-1, -2 and -3), 98 % to 100 % of patients who achieved an HbA1c < 7 % or ≤ 6.5 % at the primary endpoint visit with orforglipron treatment did so without clinically significant hypoglycaemia.

In ACHIEVE-5 where orforglipron was combined with titrated basal insulin, 85 % of patients who achieved an HbA1c < 7% and 81 % of patients who achieved an HbA1c ≤ 6.5 % at the primary endpoint visit with orforglipron treatment did so without clinically significant hypoglycaemia.

Paediatric population

The Medicines and Healthcare products Regulatory Agency has deferred the obligation to submit the results of studies with Foundayo in one or more subsets of the paediatric population for the treatment of weight management and for type 2 diabetes mellitus (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Pharmacokinetic information summarised below is based on the orforglipron hard capsule formulation unless otherwise specified. An equivalent exposure was shown between 0.8 mg film-coated tablet versus 1 mg hard capsule, 2.5 mg film-coated tablet versus 3 mg hard capsule, 5.5 mg film-coated tablet versus 6 mg hard capsule, 9 mg film-coated tablet versus 12 mg hard capsule, 14.5 mg film-coated tablet versus 24 mg hard capsule and 17.2 mg film-coated tablet versus 36 mg hard capsule The pharmacokinetics of orforglipron is similar among healthy participants and patients with overweight or obesity and patients with type 2 diabetes.

Absorption

Maximum concentration of orforglipron is reached 4 to 8 hours post dose. For film-coated tablet dosing, orforglipron exposure increases in a dose-proportional manner. The geometric mean absolute bioavailability of orforglipron was 77% after a 1 mg oral capsule dose and decreased with increasing capsule dose.

Effect of food

No clinically relevant food effect on orforglipron exposure was observed. Orforglipron can be taken with or without food.

Administration of orforglipron film-coated tablet with a high-fat meal decreased $AUC_{(0\text{-}24h)}$ by 4% to 19%, and C_{max} by 11% to 26%.

Distribution

Orforglipron is highly bound (99.9%) in human plasma and highly binds human serum albumin and human α1-acid glycoprotein. The mean steady-state volume of distribution of orforglipron is approximately 285 L, following intravenous dosing in healthy participants.

In vitro transporter studies show that orforglipron does not inhibit OATP1B1, OATP1B3, OATP2B1, OAT1, OAT3, OCT 1, OCT2, MATE1, or MATE2K at clinically relevant systemic concentrations. Orforglipron is a substrate of P-gp, OATP1B1, OATP1B3, and is not a substrate of BCRP, or OCT1.

Metabolism

Based on *in vitro* data, orforglipron is metabolized by CYP3A4 and CYP2J2.

Based on clinical investigation, orforglipron is metabolised primarily via hepatic CYP3A4 to several oxidative metabolites. These oxidative metabolites undergo further reduction in the intestinal lumen. Orforglipron represents approximately 93% of total orforglipron-related material in plasma. Two minor circulating oxidative metabolites account for approximately 5% of total orforglipron-related material in plasma.

In *vitro* studies show that orforglipron does not inhibit or induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 at clinically relevant concentrations. Orforglipron is a substrate of CYP3A4 and CYP2J2, and is not a substrate of CYP1A2, CYP2B6, CYP2C8, CYP2C19, CYP2D6, and CYP3A5.

Elimination

The mean systemic clearance of orforglipron is 7.15 L/hour with an elimination half-life of approximately 29 to 49 hours, enabling daily administration. Steady state exposure is achieved after approximately 1 week of once daily administration. Accumulation ratios for AUC(0-24) and Cmax after multiple dose administration was approximately 1.6- and 1.5-fold, respectively.

Orforglipron is eliminated by metabolism. The primary excretion route of orforglipron metabolites is faeces. Less than 1% of an orforglipron oral dose is excreted into urine. Intact orforglipron is not observed in faeces following oral administration.

Effects of other medicinal products on the pharmacokinetics of orforglipron

For a summary of the impact on orforglipron dosing, please see section 4.2 and 4.5

OATP1B inhibitors

Coadministration of cyclosporine, a clinical OATP1B inhibitor and weak CYP3A4 inhibitor, (200 mg twice daily) with orforglipron increased orforglipron AUC(0-∞) and C_{max} by 2.6-fold and 1.3-fold, respectively. No dose adjustment of orforglipron is required when coadministered with OATP1B inhibitors unless they are also strong inhibitors of CYP3A4 (e.g. ritonavir, telaprevir).

P-gp inhibitors

Coadministration of the P-gp inhibitor quinidine (200 mg twice daily) decreased orforglipron AUC(0-∞) and C_{max} by 12% and 26%, respectively. No dose adjustment of orforglipron is required when coadministered with P-gp inhibitors unless they are also strong inhibitors of CYP3A4 (see section 4.2 and section 4.5 *Strong CYP3A4 inhibitors* above).

Acid-reducing agents

Coadministration of the proton pump inhibitor esomeprazole had no clinically meaningful effect on orforglipron pharmacokinetics. Coadministration of acid-reducing agents are not expected to have a clinically meaningful effect on orforglipron pharmacokinetics.

Effects of orforglipron on the pharmacokinetics of other medicinal products

CYP3A substrates

Coadministration of the sensitive CYP3A substrate midazolam with daily dosing of 36 mg orforglipron hard capsules increased midazolam AUC(0-∞) by 1.1-fold with no effect on midazolam C_{max}. Therefore, orforglipron has no clinically meaningful effect on CYP3A activity.

P-gp substrates

Coadministration of the P-gp substrate digoxin with daily dosing of 36 mg orforglipron hard capsules increased digoxin AUC(0-∞) and C_{max} by 1.2-fold and 1.2-fold, respectively indicating orforglipron has no clinically meaningful effect on P-gp activity.

OATP1B substrates

Plasma concentrations of endogenous OATP1B biomarker coproporphyrin-1 were not significantly affected following administration of orforglipron at hard capsules at doses up to 24 mg daily, indicating orforglipron does not affect OATP1B activity.

Other *In vitro* Inhibition and Induction Results

CYP enzymes

Orforglipron does not inhibit or induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 at clinically relevant concentrations. Orforglipron is a substrate of CYP3A4 and CYP2J2, and is not a substrate of CYP1A2, CYP2B6, CYP2C8, CYP2C19, CYP2D6, and CYP3A5.

Transporter systems

Orforglipron does not inhibit OATP1B1, OATP1B3, OATP2B1, OAT1, OAT3, OCT 1, OCT2, MATE1, or MATE2K at clinically relevant systemic concentrations. Orforglipron is a substrate of P-gp, OATP1B1, OATP1B3, and is not a substrate of BCRP, or OCT1

Special populations

Renal impairment

Renal impairment does not have a clinically meaningful impact on orforglipron PK. A dedicated renal impairment study was conducted to study orforglipron PK following single 1-mg oral hard capsule dose of orforglipron in participants with normal renal function and in participants with severe renal impairment or end stage renal disease.

Hepatic impairment

Mild to moderate hepatic impairment does not have a clinically meaningful impact on orforglipron PK.

Orforglipron is not recommended for use in patients with severe hepatic impairment. Orforglipron AUC(0∞) increased by 4.63-fold following single 1 mg oral capsule dose in participants with severe hepatic impairment compared to participants with normal hepatic function. C_{max} in participants with severe hepatic impairment (defined as Child-Pugh C) was similar to C_{max} in participants with normal hepatic function.

Elderly, gender, race, ethnicity or body weight

The intrinsic factors of age, gender, race, ethnicity or body weight do not have a clinically relevant effect on the pharmacokinetics of orforglipron.

Paediatric population

Orforglipron has not been studied in paediatric patients.

5.3 Preclinical safety data

Nonclinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity.

Carcinogenicity

Orforglipron is not pharmacologically active in rats or mice. In a 2-year carcinogenicity study in rats, orforglipron was non-carcinogenic at oral daily doses of 5, 30 and 200 mg/kg (AUC-based exposures 3-, 9-, and 24-fold those in humans at the maximum recommended human dose (MRHD). In a 26-week study in transgenic mice, orforglipron was non-carcinogenic at oral daily doses of 5, 30 and 200 mg/kg (AUC-based exposures ~3-, 14-, and 49-fold those in humans at the MRHD). For other GLP-1 receptor agonists that are pharmacologically active in rodents, thyroid C-cell hyperplasia and neoplasia have been observed in rats and mice at clinically relevant exposures and are considered an on-target class effect. The effects are caused by a non-genotoxic, specific GLP-1 receptor-mediated mechanism to which rodents are particularly sensitive. The relevance for humans is considered to be low but cannot be completely excluded.

Ames and in vitro micronucleus tests were negative. In vivo micronucleus genotoxicity testing during the rat 28-day general toxicity test did not demonstrate genotoxic effects.

Reproduction toxicity

There were no effects on male and female fertility in rats orally administered orforglipron up to 200 mg/kg/day (18 times and 33 times the MRHD, respectively, based on AUC). No changes in menstrual cycle lengths or numbers of cycles were noted in female monkeys and no effects on testicular volume, sperm motility, concentration, or count were noted in males monkeys at systemic exposures approximating the MRHD. For other GLP-1 receptor agonists, an increase in oestrous length and a small reduction in number of ovulations were observed in rats at doses associated with maternal body weight loss.

In animal reproduction studies in pregnant cynomolgus monkeys receiving orforglipron, with dosing interruptions in some animals, no embryofoetal development toxicity was observed below clinically relevant exposures. Continuous dosing, higher dose levels and exposure cannot be achieved in monkeys due to body weight effects.

Orforglipron is not pharmacologically active in rabbits. In a rabbit pilot dose-range finding study, slight decreases in foetal and placental weights with external malformations in 2 foetuses from 2 dams were observed at an exposure that was 13-fold higher than the MRHD. No embryofoetal effects were observed in the definitive rabbit study conducted at exposures up to 6-fold higher than the MRHD. For other GLP-1 receptor agonists, reduced foetal growth, major foetal abnormalities, and increased pregnancy loss were observed in animals at or below clinically relevant exposures.

Orforglipron is not pharmacologically active in rats. In a pre- and post-natal study in rats, orforglipron was administered orally once daily from implantation through lactation at doses of 5, 30, and 200 mg/kg/day, which resulted in exposures that were approximately 3, 4 and 12 times the clinical exposure at the MRHD, respectively, based on AUC. No effects were noted at any dose level in the F0 maternal rats or the F1 pups in the pre- and post-natal development study in rats. For other GLP-1 receptor agonists that are pharmacologically active in rats, reduced offspring body weight at birth and during the postnatal period have been observed at exposures associated with maternal toxicity.

In a tissue distribution study, [^{14}C]orforglipron-derived radioactivity was not distributed to foetal tissues in pregnant rats.

[^{14}C]orforglipron-derived radioactivity was excreted into rat breast milk, with concentrations in milk 3-fold higher than in plasma.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Cellulose, microcrystalline

Crospovidone

Copovidone

Sodium carbonate anhydrous

Magnesium stearate

Tablet film coating

Poly(vinyl alcohol)

Titanium dioxide

Macrogol

Talc

Iron oxide red [E172] (0.8 mg, 5.5 mg, 9 mg, 17.2 mg film-coated tablets)

Iron oxide yellow [E172] (0.8 mg, 2.5 mg, 9 mg, 14.5 mg film-coated tablets)

Iron oxide black [E172] (5.5 mg, 17.2 mg film-coated tablets)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original package in order to protect from light. This medicinal product is light sensitive. This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Cold formable aluminium foil (CFAF) blisters sealed with aluminium foil lidding. Pack sizes of 30 and 90 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Orteliuslaan 1000,
3528 BD Utrecht,
The Netherlands

8 MARKETING AUTHORISATION NUMBER(S)

PL 14895/0370

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10/08/2026

10 DATE OF REVISION OF THE TEXT

10/08/2026