Health Technology Briefing
October 2024

Orforglipron for treating type 2 diabetes

Company/Developer	Eli Lilly and Company Ltd
☒ New Active Substance	☐ Significant Licence Extension (SLE)

NIHRIO ID: 34120	NICE ID: Not available	UKPS ID: 674530

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Orforglipron is currently in phase III clinical development for the treatment of type 2 diabetes. Type 2 diabetes is a lifelong condition that develops when the body becomes resistant to or does not produce enough insulin – a hormone produced in the pancreas that enables sugar to enter body cells. Signs and symptoms of type 2 diabetes often develop slowly. Signs and symptoms may include increased thirst, frequent urination, increased hunger, and unintended weight loss. Current oral treatment options for type 2 diabetes, including glucagon-like peptide-1 receptor (GLP-1R) agonists, are peptide based and need to be taken at least thirty minutes before the first food, beverage, or other oral medications of the day with no more than 120 mL of plain water only. There remains a need for oral once-daily non-peptide GLP-1R agonists without such restrictions.

Orforglipron is a new medication that helps manage blood sugar levels by activating a specific receptor in the body. It is taken by mouth once a day, with or without food. Orforglipron stays active in the body for a long time—between 29 and 49 hours—which helps it work effectively as a partial activator of this receptor. If licensed, orforglipron would be an additional treatment option for adult patients with type 2 diabetes.

Proposed Indication

Orforglipron is indicated for the treatment of adults with type 2 diabetes.

Technology

Description

Orforglipron (LY3502970) is a newly developed non-peptide glucagon-like peptide-1 receptor (GLP-1R) agonist that is taken orally once a day. GLP-1R agonists work by increasing the levels of incretins – hormones – which help the body produce more insulin when needed, increase insulin sensitivity and lower blood sure level.[1,2] Orforglipron stands out due to its prolonged half-life of 29–49 hours, which makes it a powerful partial agonist of the GLP-1R. It is expected to have a stronger effect on cyclic AMP signalling than on β-arrestin recruitment, resulting in a lower risk of receptor desensitisation than other GLP-1R agonists.[3] This oral non-peptide, GLP-1R agonist taken with or without food, with comparable efficacy and tolerability to injectable agents could enhance medication uptake in this important therapeutic class.[4]

Orforglipron is currently in phase III clinical trial development (NCT05803421, NCT05971940, NCT06045221, NCT06109311, NCT06192108, NCT06010004) for the treatment of type 2 diabetes.[5-10] Patients will receive orforglipron administrated orally once a day.[7]

Key Innovation

GLP-1R agonists are efficacious antidiabetic medications that work by enhancing glucose-dependent insulin secretion and improving energy balance. Currently approved GLP-1R agonists are peptide based, and it has proven difficult to obtain small-molecule activators possessing optimal pharmaceutical properties.[11] The peptide-based GLP-1R requires an absorption enhancer for gastric delivery and needs to be taken at least 30 minutes before the first food, beverage, or other oral medications of the day with no more than 120 mL of plain water only. An oral once-daily non-peptide GLP-1R agonist without such restrictions could improve the utilisation and accessibility of incretin therapies to patients and remains an unmet need despite the increased number of agents under development.[12] If licensed, orforglipron would be an additional treatment option for adult patients with type 2 diabetes.

Regulatory & Development Status

Orforglipron does not currently have marketing authorisation in the EU/UK for any indication.

Orforglipron is also in phase III clinical development for the treatment of obesity and overweight.[13]

Patient Group

Disease Area and Clinical Need

Type 2 diabetes is a lifelong condition that develops when the body becomes resistant to or does not produce enough insulin (a hormone produced in the pancreas).[14] In type 2 diabetes, the body builds up resistance to insulin and more insulin is needed to bring down blood glucose levels. As a result, the pancreas needs to produce more insulin than it would normally need to. If the pancreas can no longer produce enough insulin to bring down sugar levels, the symptoms of diabetes will begin to appear. Type 2 diabetes comes on gradually and it can take up to years for symptoms to appear.[15] Signs and symptoms of type 2 diabetes often develop slowly. When signs and symptoms are present, they may include increased thirst, frequent urination, increased hunger, unintended weight loss, fatigue, blurred vision, slow-healing sores, frequent infections, numbness or tingling in the hands or feet, areas of darkened skin,

usually in the armpits and neck.[16] Type 2 diabetes is caused by several factors, including being overweight and having obesity, not being physically active, insulin resistance and genes.[17] Comorbidities that tend to coexist with type 2 diabetes include: obesity, hypertension, dyslipidaemia, depression and arthritis.[18]

Type 2 diabetes can occur in all age groups and is increasingly being diagnosed in adolescents and young adults.[19] In the UK, more than 5.6 million people are living with diabetes with over 3.2 million people are at an increased risk of type 2 diabetes.[20] Using the estimation that 90% of individuals with diabetes have type 2 diabetes, almost 4 million people would be eligible for this treatment in England. In 2023-24, in England, there were 56,673 finished consultant episodes (FCE) for type 2 diabetes (ICD code E11), 32,095 admissions and 261,242 FCE bed days and 4,093 day cases.[21]

Recommended Treatment Options

National institute for Health and Care Excellence (NICE) recommended the following treatment options for type 2 diabetes:[19]

- Metformin
- SGLT-2 inhibitors
- DPP-4 inhibitors
- Pioglitazone
- Sulfonylureas
- GLP-1R agonists
- Insulin (glargine, detemir, neutral protamine Hagedorn)

Clinical Trial Information

Trial	**ACHIEVE-4**, NCT05803421, 2022-502833-25-00 ; A Phase 3, Open-Label Study of Once Daily LY3502970 Compared With Insulin Glargine in Adult Participants With Type 2 Diabetes and Obesity or Overweight at Increased Cardiovascular Risk **Phase III**- Active, not recruiting **Location(s):** Eight EU countries, USA and other countries **Primary completion date:** April 2025
Trial Design	Randomised, parallel assignment, open label
Population	N=2,620 (estimated); adults aged 18 years or older; participants with type 2 diabetes and obesity or overweight at increased cardiovascular risk
Intervention(s)	Participants will receive escalated doses of orforglipron orally
Comparator(s)	Participants will receive insulin glargine subcutaneously (SC). Doses will be individualized and titrated according to a treat-to-target algorithm.
Outcome(s)	Primary outcome measure: • Time to first occurrence of any major adverse cardiovascular event (MACE-4) [Myocardial Infarction (MI), Stroke, Hospitalisation for Unstable Angina, or Cardiovascular (CV) Death] [Time frame: baseline to end of the study (approximate maximum 104 weeks]

	See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**ACHIEVE-1,** NCT05971940; A Phase 3, Randomized, Double-Blind Study to Investigate the Efficacy and Safety of Once Daily Oral LY3502970 Compared With Placebo in Adult Participants With Type 2 Diabetes and Inadequate Glycemic Control With Diet and Exercise Alone **Phase III**- Active, not recruiting **Location(s):** Japan, USA and other countries **Primary completion date:** April 2025
Trial Design	Randomised, parallel assignment, double-masked
Population	N=520 (estimated); adults aged 18 years and over with type 2 diabetes and inadequate glycaemic control with diet and exercise alone
Intervention(s)	Participants will receive orforglipron orally
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome measure: • Change in Haemoglobin A1c: (HbA1c) [time frame from baseline to week 40] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**ACHIEVE-5,** NCT06109311; A Phase 3, Randomized, Double-Blind Study to Investigate the Efficacy and Safety of Once Daily Oral Orforglipron Compared With Placebo in Adult Participants With Type 2 Diabetes and Inadequate Glycemic Control With Insulin Glargine, With or Without Metformin and/or SGLT-2 Inhibitor **Phase III**-Recruiting **Location(s):** One EU country, Japan, USA and other countries **Primary completion date:** June 2025
Trial Design	Randomised, parallel assignment, double masked
Population	N=520 (estimated); adults aged 18 years and older with type 2 diabetes and inadequate glycaemic control with insulin glargine, with or without metformin and/or sglt-2 inhibitor
Intervention(s)	Participants will receive orforglipron orally

Comparator(s)	Matched placebo
Outcome(s)	Primary outcome measure: • Orforglipron Dose 1, 2: Change in Haemoglobin A1c: (HbA1c) [Time frame from baseline to week 40] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**ACHIEVE-J,** NCT06010004; A Phase 3, Long-term Safety Study of LY3502970 in Adult Participants With Type 2 Diabetes and Inadequate Glycemic Control With Diet and Exercise Alone or in Combination With Oral Antihyperglycemic Medications **Phase III**-Active, not recruiting **Location(s):** Japan **Primary completion date:** June 2025
Trial Design	Randomised, parallel assignment, open label
Population	N=399 (estimated); adults aged 18 years and older, with type 2 diabetes and inadequate glycaemic control with diet and exercise alone or in combination with oral antihyperglycemic medications
Intervention(s)	Participants will receive orforglipron administered orally
Comparator(s)	-
Outcome(s)	Primary outcome measure: • Number of participants with treatment emergent adverse events [time frame from baseline to week 52] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**ACHIEVE-3,** NCT06045221; A Phase 3, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Once Daily Oral LY3502970 Compared With Oral Semaglutide in Adult Participants With Type 2 Diabetes and Inadequate Glycemic Control With Metformin **Phase III**-Active, not recruiting **Location(s):** USA, Japan, and other countries **Primary completion date:** July 2025
Trial Design	Randomised, parallel assignment, open label

Population	N= 1,576 (estimated); adults aged 18 years and older, with type 2 diabetes and inadequate glycaemic control with metformin
Intervention(s)	Participants will receive orforglipron orally
Comparator(s)	Participants will receive semaglutide orally
Outcome(s)	Primary outcome measures: • Change in Haemoglobin A1c: (HbA1c) [Time frame from baseline to week 52] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**ACHIEVE-2,** NCT06192108, 2023-507206-13-00; **;** A Phase 3, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Once Daily Oral Orforglipron Compared With Dapagliflozin in Adult Participants With Type 2 Diabetes and Inadequate Glycemic Control With Metformin (ACHIEVE-2) **Phase III**- Recruiting **Location(s):** Two EU countries, USA, and other countries **Primary completion date:** November 2025
Trial Design	Randomised, parallel assignment, open label
Population	N=888 (estimated), participants, aged 18 years and older, with type 2 diabetes and inadequate glycaemic control with metformin
Intervention(s)	Participants will receive orforglipron orally
Comparator(s)	Participants will receive dapagliflozin orally
Outcome(s)	Primary outcome measure: • Change in Haemoglobin A1c: (HbA1c) [time frame from baseline to week 40] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	NCT05048719; 2021-002806-29**;** A Phase 2 Study of Once-Daily LY3502970 Compared With Placebo and Once-Weekly Dulaglutide in Participants With Type 2 Diabetes Mellitus **Phase II-Completed** **Location(s):** Three EU countries, USA and other countries **Completion date:** September 2022

Trial Design	Randomised, parallel assignment, double-masked
Population	N=383 (actual); adults aged 18 to 75 years; participants with type 2 diabetes who failed to achieve adequate glycaemic control on diet and exercise alone or on a stable dose of metformin
Intervention(s)	Participants received maintenance dose of 3 mg, 12mg, 24mg, 36mg, 45mg orforglipron with dose escalation starting from 2 mg LY3502970 administered orally once daily
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome measure: • Change from baseline in HbA1c in LY3502970 as Compared to Placebo [Time frame: baseline, week 26] See trial record for full list of other outcomes
Results (efficacy)	At week 26, mean change in HbA_{1c} with orforglipron (45 mg maintenance dose) was up to -2.10% (-1.67% placebo adjusted), versus -0.43% with placebo and -1.10% with dulaglutide. HbA_{1c} reduction was statistically superior with orforglipron versus placebo (estimated treatment difference -0.8% to -1.7%). Change in mean bodyweight at week 26 was up to -10.1 kg (95% CI -11.5 to -8.7; 7.9 kg placebo adjusted [-9.9 to -5.9]) with orforglipron (45 mg maintenance dose) versus -2.2 kg (-3.6 to -0.7) for placebo and -3.9 kg (-5.3 to -2.4) for dulaglutide.[4] See trial record for full list of efficacy results per dose.
Results (safety)	The safety profile of orforglipron was consistent with that established for the GLP-1 RA class. The incidence of treatment-emergent adverse events ranged from 61.8% to 88.9% in orforglipron-treated participants, compared with 61.8% with placebo and 56·0% with dulaglutide. The majority were gastrointestinal events (44.1% to 70.4% with orforglipron, 18.2% with placebo, and 34.0% with dulaglutide) of mild to moderate severity. Three participants receiving orforglipron and one participant receiving dulaglutide had clinically significant (<54 mg/dL [<3 mmol/L]) hypoglycaemia and no participants had severe hypoglycaemia. One death occurred in the placebo group and was not related to study treatment.[4] See trial record for full list of safety results per dose.

Estimated Cost

The cost of orforglipron is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Sotagliflozin for treating type 2 diabetes [ID1657]. Expected date of issue to be confirmed.
- NICE technology appraisal in development. Semaglutide for treating type 2 diabetes [ID1450]. Expected date of issue to be confirmed.
- NICE technology appraisal in development. Insulin icodec for treating type 2 diabetes [ID6175]. Expected publication date: 21 May 2025.
- NICE technology appraisal. Tirzepatide for treating type 2 diabetes (TA924). October 2023.
- NICE technology appraisal. Ertugliflozin with metformin and a dipeptidyl peptidase-4 inhibitor for treating type 2 diabetes. (TA583). June 2019.
- NICE technology appraisal. Ertugliflozin as monotherapy or with metformin for treating type 2 diabetes (TA572). March 2019.
- NICE technology appraisal. Dapagliflozin in combination therapy for treating type 2 diabetes (TA288). November 2016.
- NICE technology appraisal. Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes. (TA390). May 2016.
- NICE technology appraisal. Dapagliflozin in triple therapy for treating type 2 diabetes (TA418). November 2016.
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- NIC clinical guideline in development. Type 2 diabetes in adults: management (medicines update). [GID-NG10336]. Expected publication date: 19 June 2025.
- NICE clinical guideline. Type 2 diabetes in adults: management (NG28). June 2022.
- NICE quality standard. Type 2 diabetes in adults [QS209]. March 2023.

NHS England (Policy/Commissioning) Guidance

- NHS England. Action for Diabetes. January 2014.
- NHS England. 2013/14 NHS Standard Contract for specialised endocrinology services (Adult) A03/S/a.

Other Guidance

- Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of glycaemic control in people with type 2 diabetes. 2017.[22]
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Additional Information

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