NIHR | Innovation Observatory

Newcastle University

# Health Technology Briefing
# August 2024

## Orforglipron as an adjunct treatment for obesity or overweight with co-morbidities

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

| NIHRIO ID: 34209 | NICE ID: Not Available | UKPS ID: 674625 |
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## Licensing and Market Availability Plans

Currently in phase III clinical trials.

## Summary

Orforglipron is in clinical development for the treatment of adults living with obesity or overweight with weight-related comorbidities. Overweight and obesity are typically defined by a body mass index (BMI) over 25 and 30, respectively. This is commonly caused by excessive calorie intake, particularly from high-fat and high-sugar foods, along with genetic and environmental factors. In the UK, about 1 in 4 adults are obese, leading to serious health conditions and a life expectancy reduced by three to ten years. For some people, lifestyle and behavioural changes alone may not help. Existing medicines may be taken orally, or via an injection. There is a particular need for other effective oral treatments that would increase uptake and acceptability amongst those people living with obesity.

Orforglipron is a 'GLP-1 receptor agonist'. It acts in the same way as GLP-1 (a hormone produced in the gut) by increasing the amount of insulin that the pancreas releases in response to food. This helps with the control of blood glucose levels. Other GLP-1 receptor agonist medicines are usually administered as an injection, and some have food and water restrictions. If licenced, orforglipron taken orally would offer an additional treatment option for people with obesity, or those overweight who have weigh-related comorbidities.

## Proposed Indication

Adults with obesity or overweight with weight-related comorbidities. [1,2]

## Technology

### Description

Orforglipron (LY3502970) is a non-peptide oral glucagon-like peptide-1 (GLP-1) receptor agonist being studied for chronic weight management in participants with obesity or overweight.[3,4] When orforglipron binds to the upper helical bundle of the GLP-1 receptors, it induces cyclic adenosine monophosphate accumulation with little effect on GLP-1R-mediated β-arrestin recruitment.[5] This design feature may be therapeutically beneficial for orforglipron, since β-arrestin proteins are associated with receptor internalisation, intracellular trafficking and desensitisation.[4,6] This profile is reported to enhance the efficacy of GLP-1R agonism and stimulate insulin release from the pancreas when it is needed. It also slows down how fast-food travels through your digestive tract. This can help you feel fuller for longer, reduce how much you eat and lead to weight loss.[4,7]

Orforglipron is in clinical development for the treatment of adult patients with obesity or overweight with weight-related comorbidities. In the phase III clinical trials ATTAIN-1 (NCT05869903) and ATTAIN-2 (NCT05872620), orforglipron is given to participants once daily orally, for a period of 72 and 77 weeks respectively.[1,2]

### Key Innovation

Orforglipron is a chemically synthesised oral GLP-1 receptor agonist.[4] Only two other GLP-1 receptor agonists have been approved for weight management, both of which are peptides in injectable formulations. Although these treatments have demonstrated efficacy, the injection has been associated with barriers to uptake and acceptability.[4,8,9] These drugs are peptide-based and are administered by subcutaneous injection or by a complex oral dosing regimen involving significant food and water restrictions.[4] There is a need for oral treatment options that are easy to use and have weight-reduction efficacy similar to that of the approved injectable GLP-1 receptor agonists.[10]

As a non-peptide agonist, orforglipron has no dietary restrictions regarding oral delivery.[3,4] Furthermore, the pharmacokinetic profile of orforglipron, with a half-life of 29 to 49 hours, supports once-daily oral administration.[10,11] If licensed, orforglipron will offer an additional treatment option for adult patients living with obesity or that are overweight with co-morbidities.

### Regulatory & Development Status

Orforglipron does not currently have Marketing Authorisation in the EU/UK for any indication.

Orforglipron is not in late-stage clinical trials for any other indication.

## Patient Group

### Disease Area and Clinical Need

Overweight and obesity are defined as abnormal or excessive fat accumulation that presents a risk to health. For most adults a body mass index (BMI) over 25 is considered overweight, and over 30 is obese although for those with Asian, Chinese, Middle Eastern, Black African or African-Caribbean family background a lower BMI score is used (23-27.4 is considered overweight and 27.5 or above is considered obese).[12,13] Obesity and overweight are caused when extra calories, particularly those from foods high in fat and sugar, are stored in the body as fat. Obesity is an increasingly common problem because the environment we live in makes it difficult for many people to eat healthily and do enough physical activity. Genetics can also be a cause of obesity for some people. Genes can affect how the body uses food and stores fat.[13] Living with obesity can cause a number of further problems, including difficulties with daily activities and health conditions including tiredness, joint and back pain and low confidence as well as more serious health conditions such as type 2 diabetes, gallstones and several types of cancer.[13]

In the UK it's estimated that around 1 in every 4 adults are living with obesity, and the disease can reduce life expectancy by an average of 3 to 10 years, depending on how severe it is.[13] In England (2022-23), there were 10,042 finished consultant episodes (FCE) and 8,903 admissions for obesity (ICD-10 code E66) which resulted in 24,726 FCE bed days and 2,349 day cases.[14]

## Recommended Treatment Options

NICE recommends prevention and lifestyle weight management services for adults who are becoming overweight or obese.[15] Drug treatment should only be considered once dietary and physical activity interventions have been started and evaluated, or as part of an integrated approach to weight management.[16]

NICE recommends the following treatment options for managing a person who is overweight or obese:[17]

- Orlistat
- Liraglutide
- Semaglutide

## Clinical Trial Information

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| Trial | **ATTAIN-1**, NCT05869903; 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 Obesity or Overweight With Weight-Related Comorbidities (ATTAIN-1)<br>**Phase III** – Active, not recruiting.<br>**Locations:** Two EU countries, USA and other countries<br>**Primary completion date:** September 2025 |
| Trial Design | Randomised, parallel assignment, double blind |
| Population | N=3,000 (estimated); participants with obesity or overweight with weight-related comorbidities, defined as having a BMI ≥30.0 kg/m²; ≥27.0 kg/m² and presence of at least one of the following weight-related comorbidities (treated or untreated) at screening: hypertension, dyslipidemia, obstructive sleep apnoea, cardiovascular disease (for example, ischemic cardiovascular disease, New York Heart Association Functional Class I-III heart failure); adults aged 18 years and over. |
| Intervention(s) | Orforglipron administered orally |

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| Comparator(s) | Oral placebo |
| Outcome(s) | Primary outcome measure: mean percent change from baseline in body weight from baseline to week 72.<br><br>See trial record for full list of other outcomes. |
| Results (efficacy) | - |
| Results (safety) | - |

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| Trial | **ATTAIN-2,** NCT05872620; 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 Obesity or Overweight and Type 2 Diabetes (ATTAIN-2)<br>**Phase III** – Active, not recruiting.<br>**Locations:** Three EU countries, USA and other countries<br>**Primary completion date:** June 2025 |
| Trial Design | Randomised, parallel assignment, double blind |
| Population | N=1,500 (estimated); patients with obesity or overweight, defined as having a BMI ≥27.0 kg/m² with a history of at least one self-reported unsuccessful dietary effort to lose body weight and type 2 diabetes; adults aged 18 years and over. |
| Intervention(s) | Oral orforglipron |
| Comparator(s) | Oral placebo |
| Outcome(s) | Primary outcome measure: mean percent change from baseline in body weight from baseline to week 72.<br><br>See trial record for full list of other outcomes. |
| Results (efficacy) | - |
| Results (safety) | - |

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| Trial | NCT05051579, 2021-002805-88; A Phase 2 Study of Once-Daily LY3502970 Compared With Placebo in Participants Who Have Obesity or Are Overweight With Weight-Related Comorbidities<br>**Phase II** – Completed<br>**Locations:** One EU country, USA, Canada and Puerto Rico<br>**Primary completion date:** August 2022 |
| Trial Design | Randomised, parallel assignment, double blind |
| Population | N=272 (actual); who have obesity or are overweight defined as having a BMI of ≥30 kg/m²; or a BMI ≥27 kg/m² and <30 kg/m² with at least one of the following weight-related comorbidities: hypertension, or dyslipidemia, cardiovascular disease; adults aged 18 to 75 years. |

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| Intervention(s) | Once-daily LY3502970 orally, at doses of 12 mg, 24 mg, 36 mg or 45 mg. |
| Comparator(s) | Oral placebo |
| Outcome(s) | The primary outcome measure: percent change from baseline in body weight from baseline to week 26.<br><br>See trial record for full list of other outcomes. |
| Results (efficacy) | The use of orforglipron resulted in a dose-dependent, continuous absolute decrease in body weight. Across dose cohorts, the placebo-corrected absolute change from baseline in body weight ranged from −6.9 kg to −11.2 kg at week 26 and ranged from −7.4 kg to −13.0 kg at week 36. Weight reductions of at least 5%, at least 10%, and at least 15% were more likely to occur with orforglipron than with placebo.[10] |
| Results (safety) | The safety of orforglipron was similar to that of injectable GLP-1 receptor agonists that have been approved for weight management.[10] |

## Estimated Cost

The cost of orforglipron is not yet known.

## Relevant Guidance

### NICE Guidance

- NICE technology appraisal in development. Oral semaglutide for managing overweight and obesity (ID6188). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Tirzepatide for managing overweight and obesity (ID6179). Expected October 2024.
- NICE technology appraisal. Semaglutide for managing overweight and obesity (TA875). March 2023.
- NICE technology appraisal, Liraglutide for managing overweight and obesity (TA664). December 2020.
- NICE clinical guideline in development. Obesity and overweight management (GID-NG10182). Expected date of issue to be confirmed.
- NICE clinical guideline. Obesity prevention (CG43). March 2015.
- NICE clinical guideline. Obesity: identification, assessment and management (CG189). November 2014.
- NICE guideline. Preventing excess weight gain (NG7). March 2015
- NICE quality standard in development. Obesity: prevention and lifestyle management (GID-QS10184). Expected date of issue to be confirmed.
- NICE quality standard in development. Obesity: clinical assessment and management (GID-QS10183). Expected date of issue to be confirmed.
- NICE quality standard. Obesity: clinical assessment and management (QS127). August 2016.
- NICE quality standard. Obesity in adults: prevention and lifestyle weight management programmes (QS111). January 2016.
- NICE interventional procedures guidance. Endoscopic sleeve gastroplasty for obesity (IPG783). February 2024.
- NICE interventional procedures guidance. Implantation of a duodenal–jejunal bypass sleeve for managing obesity (IPG471). November 2013.

- NICE public health guidance. Weight management: lifestyle services for overweight or obese adults (PH53). May 2014.

NHS England (Policy/Commissioning) Guidance

- NHS England. Enhanced service specification: Weight management 2024/25. March 2024.
- NHS England. NHS Standard Contract for Severe and Complex Obesity – All Ages (A05/S/a). October 2013.
- NHS England. Clinical Commissioning Policy: Complex and Specialised Obesity Surgery. NHSCB/A05/P/a. April 2013.

Other Guidance

- UK Department of Health and Social Care. Tackling obesity: empowering adults and children to live healthier lives. July 2020.[10]
- Yumuk V, Tsigos C, Fried M, Schindler K, Busetto L, Micic D et al. European Guidelines for Obesity Management in Adults. December 2015.[18]
- Scottish Intercollegiate Guidelines Network. Management of Obesity – A national clinical guideline. 2010.[19]

## Additional Information

## References

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