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Oral Orforglipron vs Oral Semaglutide 25 mg (ATTAIN-1 vs OASIS 4) in Adults with Obesity or Overweight Without Type 2 Diabetes: An Indirect Treatment Comparison

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OBJECTIVE

- Orforglipron QD[1] and semaglutide 25 mg QD[2] are the only two oral GLP-1 RAs approved by the FDA for weight management in adults.
- This ITC compared their efficacy and safety for treatment of obesity or overweight in adults without T2D, using the pivotal trials ATTAIN-1[3] and OASIS 4.[4]

CONCLUSION

- Compared to semaglutide 25 mg:
  - Orforglipron 36 mg had comparable improvements in % weight, absolute weight, BMI and waist circumference
  - All orforglipron doses had similar estimated odds of achieving most weight-reduction thresholds
  - All orforglipron doses had comparable profiles for most safety and discontinuation outcomes

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BACKGROUND

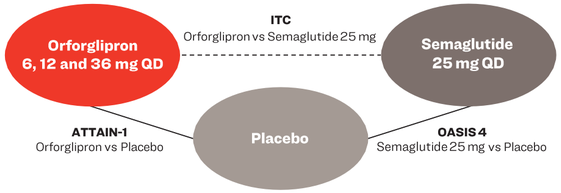
Obesity management medications

- Most patients with obesity do not reach obesity management goals with lifestyle interventions alone.[5] Therefore, OMMs may be required to help patients achieve their health goals.
- While injectable formulations of GLP-1 RAs have been available for a number of years, in the past year oral formulations have been approved.[1,2]

Comparative evidence

- There are no published direct (head-to-head) comparisons between oral orforglipron and oral semaglutide 25 mg.
- This ITC compared their efficacy, safety and discontinuation in adults with obesity or overweight and without T2D.

Figure 1. ITCs compared orforglipron 6, 12 and 36 mg QD with oral semaglutide 25 mg QD connected via placebo

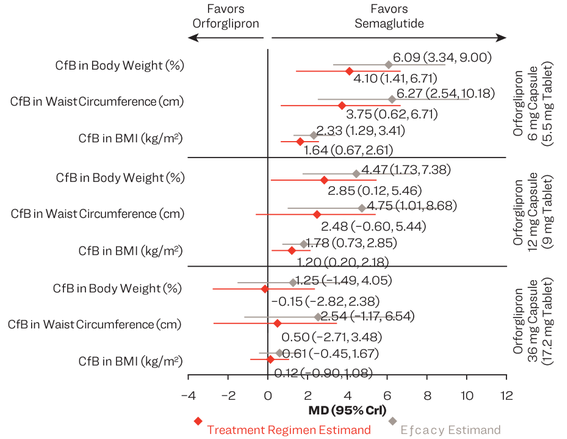


METHODS

- Data are presented from the investigational orforglipron capsule doses of 6, 12 and 36 mg, shown to be equivalent to the FDA approved tablet doses of 5.5, 9 and 17.2 mg.[6]
- Comparisons were based on data at the primary endpoint of ATTAIN-1 (Week 72) and OASIS 4 (Week 64). For both studies, this was at least 52 weeks after dose escalation had been completed in all treatment arms.
- A feasibility assessment was conducted to identify TEMs, and assess any heterogeneity in TEMs which may violate the assumption of similarity required for ITCs. Most TEMs were similar between trials, but substantial imbalances were identified in sex (percentage female: ATTAIN-1, 64.2%; OASIS 4, 78.8%) and ethnicity (percentage Hispanic/Latino: ATTAIN-1, 37.6%; OASIS 4, 7.8%).
- To ensure a robust comparison, population-adjusted ML-NMR[7] was conducted for the weight reduction outcomes and HbA1c to control for the observed heterogeneity in sex and ethnicity between the two trials, separately for the efficacy (treatment adherence with no rescue therapy) and treatment regimen (regardless of adherence or rescue therapy) estimands.
- Bucher ITCs[8] without population-adjustment were conducted to assess safety and discontinuation outcomes in the safety population as these were not anticipated to vary by sex and ethnicity.

KEY RESULTS

Figure 2. Orforglipron was associated with comparable or smaller improvements in weight reduction outcomes to semaglutide 25 mg



Footnotes: Diamonds represent MDs and error bars represent 95% CrIs. Points below 0 indicate where orforglipron had a greater reduction from baseline than semaglutide 25 mg QD. Points above 0 indicate where orforglipron had a smaller reduction from baseline than semaglutide 25 mg QD. Statistical significance is indicated where the error bars do not cross 0.

RESULTS

Weight reduction outcomes (ML-NMR)

- Orforglipron 36 mg was associated with similar estimates for reductions in % weight, absolute weight, BMI and waist circumference vs. semaglutide 25 mg for both estimands.
- All orforglipron doses were associated with similar estimates for odds of participants achieving most weight-reduction targets vs. semaglutide 25 mg for both estimands.

HbA1c (ML-NMR)

- All orforglipron doses were associated with statistically significant greater reductions in HbA1c % vs. semaglutide 25 mg for the treatment regimen estimand, but comparable reductions for the efficacy estimand. Although improvements in HbA1c % were observed, differences may be of limited clinical relevance.

Safety and discontinuation (Bucher ITC)

- Safety profiles had similar estimates for all orforglipron doses and semaglutide 25 mg for both GI AEs and nausea.
- Orforglipron 36 mg was associated with a statistically significant higher odds of treatment discontinuation due to AEs vs. semaglutide 25 mg.

Table 1. Orforglipron was associated with comparable or smaller improvements in most outcomes to semaglutide 25 mg

Outcome	Measure	ML-NMR (Treatment Regimen Estimand)		
		Orforglipron 6 mg Capsule (5.5 mg Tablet)	Orforglipron 12 mg Capsule (9 mg Tablet)	Orforglipron 36 mg Capsule (17.2 mg Tablet)
CfB in body weight (%)	MD	4.10 (1.41, 6.71)	2.85 (0.12, 5.46)	−0.15 (−2.82, 2.38)
CfB in body weight (kg)	MD	4.44 (1.72, 7.15)	3.24 (0.48, 6.07)	0.31 (−2.39, 3.16)
CfB in waist circumference (cm)	MD	3.75 (0.62, 6.71)	2.48 (−0.60, 5.44)	0.50 (−2.71, 3.48)
CfB in BMI (kg/m²)	MD	1.64 (0.67, 2.61)	1.20 (0.20, 2.18)	0.12 (−0.90, 1.08)
≥5% weight reduction (%)	OR	0.76 (0.40, 1.42)	0.91 (0.48, 1.76)	1.45 (0.75, 2.73)
≥10% weight reduction (%)	OR	0.56 (0.25, 1.16)	0.82 (0.36, 1.66)	1.59 (0.71, 3.23)
≥15% weight reduction (%)	OR	0.37 (0.11, 1.14)	0.59 (0.17, 1.80)	1.40 (0.40, 4.24)
≥20% weight reduction (%)	OR	0.43 (0.08, 1.83)	0.70 (0.14, 3.04)	1.64 (0.33, 7.05)
CfB in HbA1c (%)	MD	−0.08 (−0.14, −0.02)	−0.07 (−0.13, −0.01)	−0.14 (−0.20, −0.07)
Treatment discontinuation due to AEs	OR	1.67 (0.55, 5.07)	2.57 (0.86, 7.69)	
Patients with GI AEs	OR	0.67 (0.39, 1.14)	0.97 (0.57, 1.68)	0.97 (0.56, 1.67)
Patients with nausea	OR	0.92 (0.49, 1.71)	1.26 (0.68, 2.36)	1.14 (0.61, 2.14)

Footnotes: Results are presented as estimated MD or OR, with their associated 95% CrIs for ML-NMR results and CIs for Bucher ITCs. Green indicates where orforglipron was associated with a statistically significant improvement vs. semaglutide 25 mg; red indicates where semaglutide 25 mg was associated with a statistically significant improvement vs. orforglipron; white indicates no statistically significant difference. Efficacy estimand results are not presented in the table as they were similar to treatment regimen estimand results, and the treatment regimen estimand results are most reflective of clinical practice as they incorporate treatment discontinuation and rescue therapy but any differences between estimands are explained in the text. For the ML-NMR, complete cases of covariates and outcomes of ATTAIN-1 IPD were used.

STRENGTHS AND LIMITATIONS

- These results are based on a comprehensive feasibility assessment leading to an ITC based on high-quality studies, alongside the use of appropriate statistical population-adjustment methods to account for heterogeneity in sex and ethnicity.
- However, as comparisons were not direct, as only two trials were available and as adjustment used aggregate trial-level modifiers, the impact of residual cross-trial confounding cannot be excluded.
- Additionally, the comparisons were limited by the small number of participants in OASIS 4 (102–205 per arm) compared to ATTAIN-1 (723–949 per arm).

Abbreviations: AE, adverse event; BMI, body mass index; CfB, change from baseline; CI, confidence interval; CrI, credible interval; FDA, US Food and Drug Administration; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; IPD, individual participant data; ITC, indirect treatment comparison; MD, mean difference; ML-NMR, multi-level network meta-regression; OMM, obesity management medication; OR, odds ratio; QD, once daily; RA, receptor agonist.

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Disclosures: DJ: Personal fees from Eli Lilly and Company, participation in Eli Lilly and Company advisory boards, travel/accommodation support, and service as a principal/local investigator and/or national lead in several Eli Lilly and Company-sponsored phase 3 randomized clinical trials; received grants and honoraria from various pharmaceutical companies, including companies with an interest in the subject matter of this paper; **SVM**, **KV**, **TP**, **SS**, **SZR:** Employee and shareholder of Eli Lilly and Company; **MR**, **LJC:** Employee of Costello Medical, which received payment from Eli Lilly and Company for analytical services for this study; **MJP:** Received grants and honoraria from various pharmaceutical companies, inclusive those interested in the subject matter of this paper, advises Eli Lilly and Company on pharmacoeconomic aspects of weight-loss treatments, shareholder of Pharmacoeconomics Advice Groningen (Groningen, Netherlands) and Health-Ecore (Zeist/Groningen, Netherlands) and advisor to ASC Academics (Groningen, Netherlands).

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