

Oral Orforglipron 17.2 mg Versus Oral Semaglutide 25 mg in Adults With Type 2 Diabetes and BMI ≥ 25 kg/m²: An Indirect Treatment Comparison

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PRESENTER DISCLOSURE

Alice Cheng

Advisory panel/Consulting: Abbott, AbbVie, Aspen, AstraZeneca, Bausch Health, Bayer, Biomea Fusion, BioSynt, Boehringer Ingelheim, Caliway Biopharmaceuticals, Dexcom, Eisai, Eli Lilly and Company, Gan & Lee Pharmaceuticals, HLS Therapeutics, Insulet, Medtronic, Merck, MSD, Novo Nordisk, Sandoz and Sanofi

Speaker: Abbott, Amgen, Astellas Pharma, AstraZeneca, Bausch Health, Bayer, Biomea Fusion, Boehringer Ingelheim, Dexcom, Eisai, Eli Lilly and Company, GSK, HLS Therapeutics, Medtronic, Novo Nordisk, Pfizer and Sanofi

Clinical trial: Applied Therapeutics, Novo Nordisk and Sanofi

Employee/Stocks/Shareholder: Not applicable

BACKGROUND, OBJECTIVE AND METHODS

Background

- Orforglipron (OFG) is a small-molecule, non-peptide glucagon-like peptide-1 (GLP-1) receptor agonist administered orally without food or water restrictions¹
- Semaglutide (SEMA) is a peptide-based GLP-1 receptor agonist¹
- **ACHIEVE-3:** 9 mg and 17.2 mg orforglipron^a demonstrated superior glycated haemoglobin (HbA1c) and body weight (BW) reductions from baseline at Week (W)52 vs. 7 mg and 14 mg oral semaglutide¹
- **PIONEER-PLUS:** Oral semaglutide (25 mg and 50 mg) showed greater HbA1c and BW reductions from baseline at W52 vs. the approved 14-mg dose²

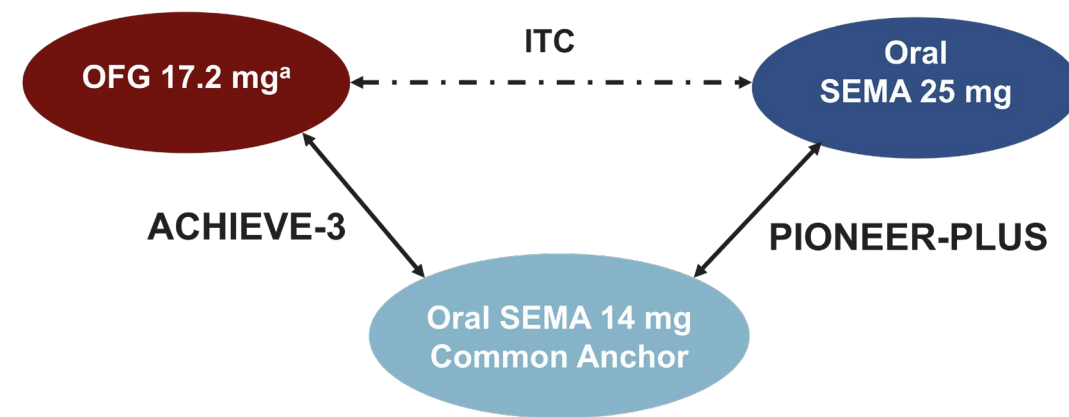
Objective

- To conduct an indirect comparison using ACHIEVE-3 and PIONEER-PLUS data to compare change in HbA1c, BW, waist circumference and systolic blood pressure (BP) achieved with orforglipron 17.2 mg vs. oral semaglutide 25 mg in type 2 diabetes (T2D) and overweight or obesity with elevated glycaemic levels

^aThis publication presents data from the investigational OFG capsule formulation of 12 mg and 36 mg. The doses have been shown as the equivalent tablet doses of 9 mg and 17.2 mg,³ which are approved in some regions.

Methods

Anchored ITC of OFG 17.2 mg vs. Oral SEMA 25 mg in T2D at W52



- Simulated treatment comparison (STC) via G-computation was used for indirect treatment comparison (ITC); sex, age, baseline weight and baseline HbA1c were identified as treatment effect modifiers
- Bucher, matching-adjusted indirect comparison (MAIC) and restricted MAIC (screening HbA1c ≥8%) were used as sensitivity analyses

Baseline Demographics and Clinical Characteristics

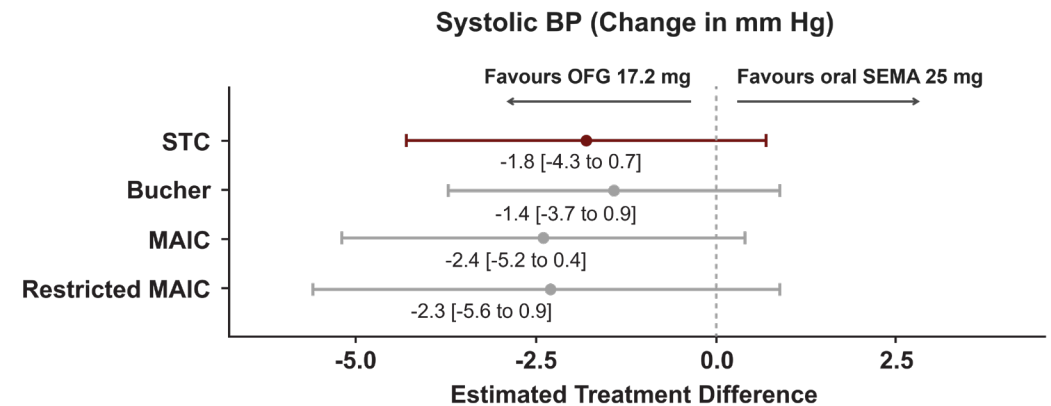
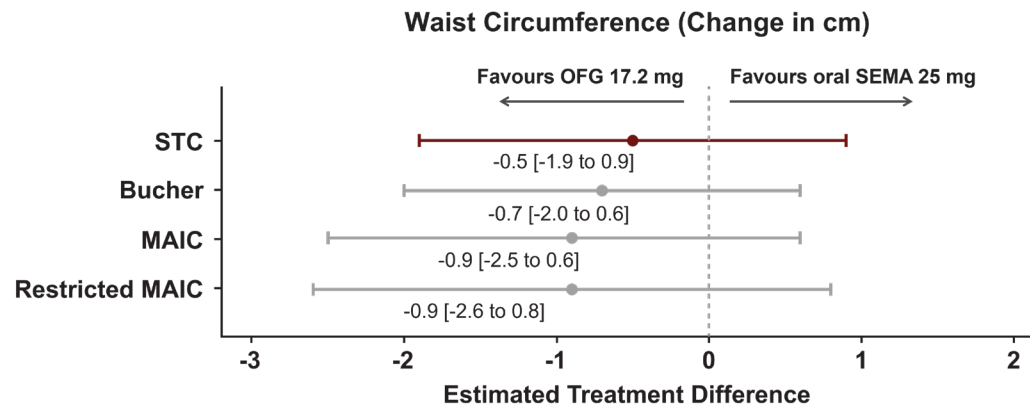
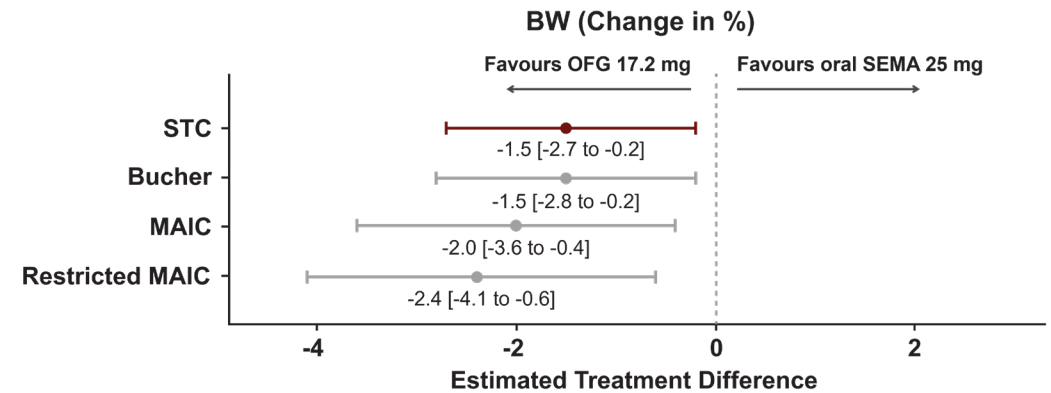
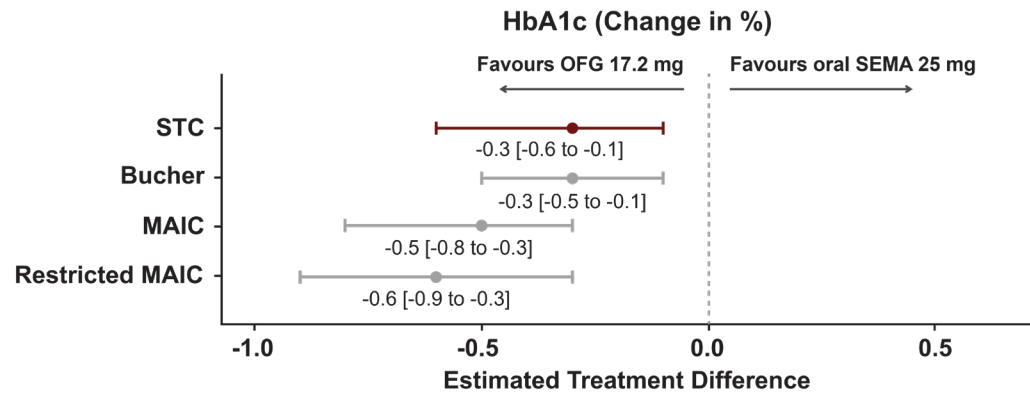
Characteristic	ACHIEVE-3		PIONEER-PLUS	
	OFG 17.2 mg (N=423)	Oral SEMA 14 mg (N=425)	Oral SEMA 14 mg (N=536)	Oral SEMA 25 mg (N=535)
Age, years	53.4 (11.4)	53.4 (10.5)	58.4 (10.4)	58.8 (10.7)
Female, n (%)	218 (51.5)	206 (48.5)	211 (39)	231 (43)
Duration of T2D, years	8.2 (5.8)	8.6 (6.9)	9.4 (5.9)	9.7 (6.7)
HbA1c, mmol/mol	67.0 (12.1)	67.2 (12.3)	74.2 (8.5)	74.6 (8.2)
HbA1c, %	8.3 (1.1)	8.3 (1.1)	8.9 (0.8)	9.0 (0.8)
Fasting glucose, mmol/L	9.3 (2.9)	9.6 (2.9)	10.8 (2.9)	11.0 (3.1)
Weight, kg	96.5 (21.9)	98.4 (22.6)	96.4 (20.8)	96.6 (21.2)
BMI, kg/m ²	35.3 (7.2)	35.5 (7.1)	33.7 (6.1)	34.1 (6.5)
Waist circumference, cm	112.3 (15.2)	113.4 (15.4)	112 (14)	113 (14)
Systolic blood pressure, mm Hg	129.1 (13.1)	128.8 (13.7)	132 (14)	133 (14)

Notes: Data are shown as mean (SD) unless stated otherwise. Data from all randomised participants with non-missing data.

BMI=body mass index; HbA1c=glycated haemoglobin; OFG=orforglipron; SD=standard deviation; SEMA=semaglutide; T2D=type 2 diabetes.

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Orforglipron 17.2 mg Treatment Was Associated With Significantly Greater Reductions in HbA1c and BW vs. Oral Semaglutide 25 mg



- Primary STC analyses were supported by sensitivity analyses including Bucher,¹ MAIC and restricted MAIC,^{2,3} demonstrating consistency across methods

Note: Restricted MAIC=HbA1c ≥ 8 at screening.

1. Bucher HC, et al. *J Clin Epidemiol.* 1997;6:683-691. 2. Signorovitch JE, et al. *Pharmacoeconomics.* 2010;28:935-945. 3. Petto H, et al. *Value Health.* 2019;22:85-91.

BP=blood pressure; BW=body weight; HbA1c=glycated haemoglobin; MAIC=matching-adjusted indirect comparison; OFG=orforglipron; SEMA=semaglutide;

STC=simulated treatment comparison.

CONCLUSIONS

- Using ITC based on ACHIEVE-3 and PIONEER-PLUS, oral orforglipron 17.2 mg was associated with significantly greater reduction in HbA1c and BW, and numerically greater reductions in waist circumference and systolic BP vs. oral semaglutide 25 mg at W52 in adults with inadequately controlled T2D and obesity or overweight
- These findings suggest that the highest dose of orforglipron could be more effective in reducing HbA1c and BW vs. oral semaglutide 25 mg in adults with T2D and overweight or obesity without food or water restrictions
- Direct comparative studies are needed to confirm the treatment differences between orforglipron 17.2 mg and oral semaglutide 25 mg, and clinical meaningfulness needs to be further explored through long-term health outcomes

Limitations

- ITCs may not be able to fully account for residual confounders despite population-adjusted approaches; findings should be confirmed by head-to-head randomised clinical trials
- Between-trial protocol differences may affect comparability
- Participants included in the trials may not be representative of the real-world population

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Sponsored by Eli Lilly and Company

OBJECTIVE

- To conduct an indirect comparison using ACHIEVE-3 and PIONEER-PLUS data to compare change in glycated haemoglobin (HbA1c), body weight (BW), waist circumference and systolic blood pressure (BP) achieved with orforglipron 17.2 mg vs. oral semaglutide 25 mg in adults with type 2 diabetes (T2D) and overweight or obesity with elevated glycaemic levels

CONCLUSION

- Using indirect treatment comparison (ITC) based on ACHIEVE-3 and PIONEER-PLUS, oral orforglipron 17.2 mg was associated with significantly greater reduction in HbA1c and BW, and numerically greater reductions in waist circumference and systolic BP vs. oral semaglutide 25 mg at Week (W)52 in adults with inadequately controlled T2D and obesity or overweight
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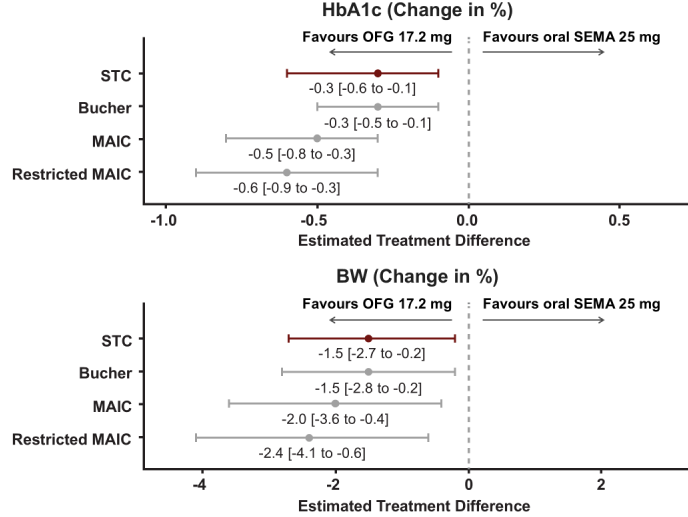
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- Semaglutide is a peptide-based GLP-1 receptor agonist¹
- ACHIEVE-3:** 9 mg and 17.2 mg orforglipron^a demonstrated superior HbA1c and BW reductions from baseline at W52 vs. 7 mg and 14 mg oral semaglutide¹
- PIONEER-PLUS:** Oral semaglutide (25 mg and 50 mg) showed greater HbA1c and BW reductions from baseline at W52 vs. the approved 14-mg dose²

^aData from investigational orforglipron capsule formulation of 12 mg and 36 mg. Doses have been shown as equivalent tablet doses of 9 mg and 17.2 mg.³ which are approved in some regions.

KEY RESULTS

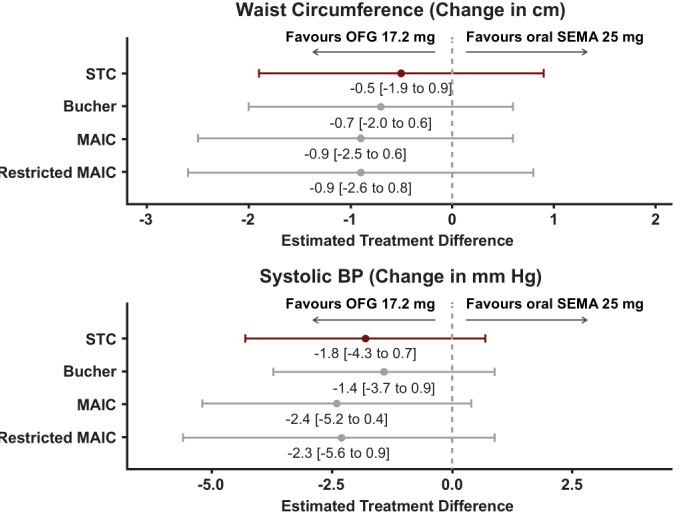
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- Primary STC analyses were supported by sensitivity analyses including Bucher,⁸ MAIC and restricted MAIC,^{9,10} demonstrating consistency across methods

Notes: Negative value favours OFG 17.2 mg. Restricted MAIC=HbA1c ≥8 at screening. Results are under efficacy estimand: Treatment effect among randomised participants, assuming they continued to receive the assigned treatment without initiating additional anti-hyperglycaemic medications for the entire planned treatment duration. Investigational OFG capsule formulation (36 mg) shown as equivalent dose of once-daily OFG tablet (17.2 mg).³ which is approved in some regions.

Orforglipron 17.2 mg Treatment Was Associated With Numerically Greater Reductions in Waist Circumference and Systolic BP vs. Oral Semaglutide 25 mg



Methods

Anchored ITC

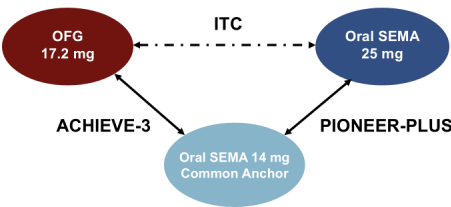
ACHIEVE-3¹

- A 52-week randomised, open-label, active-controlled, multinational Phase 3 study
- Adults ≥18 years with T2D inadequately controlled on metformin (≥1500 mg/day), HbA1c 7.0-10.5% and BMI ≥25 kg/m²
- Randomised 1:1:1:1 to once-daily oral orforglipron (9.0 mg or 17.2 mg) or oral semaglutide (7 mg or 14 mg)

PIONEER-PLUS²

- A 68-week (W52 as primary endpoint) randomised, double-blind, active-controlled, multinational Phase 3b study
- Adults ≥18 years with T2D inadequately controlled on 1-3 oral glucose-lowering therapies, HbA1c 8.0-10.5% and BMI ≥25 kg/m²
- Randomised 1:1:1 to once-daily oral semaglutide (14 mg, 25 mg or 50 mg)

Anchored ITC of OFG 17.2 mg vs. Oral SEMA 25 mg in T2D at W52



- Simulated treatment comparison (STC) via G-computation⁴⁻⁷ was used for ITC; sex, age, baseline weight and baseline HbA1c were identified as treatment effect modifiers
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Results

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References: 1. Rosenstock J, et al. *Lancet*. 2026;407:1147-1160. 2. Aroda V, et al. *Lancet*. 2023;402:693-704. 3. Ma X, et al. *Diabetes Obes Metab*. 2026;28:5803-5809. 4. Philippo DM, et al. *NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE*; 2016. 5. Ishak KJ, et al. *Pharmacoeconomics*. 2015;33:537-549. 6. Remiro-Azocar A, et al. *Res Synth Methods*. 2022;13:716-727. 7. Philippo DM, et al. *Stat Med*. 2020;39:4885-4911. 8. Bucher HC, et al. *J Clin Epidemiol*. 1997;6:583-591. 9. Signorovich JE, et al. *Pharmacoeconomics*. 2010;28:935-945. 10. Peto H, et al. *Value Health*. 2019;22:85-91.

Abbreviations: BMI=body mass index; BP=blood pressure; BW=body weight; GLP-1=glucagon-like peptide-1; HbA1c=glycated haemoglobin; ITC=indirect treatment comparison; MAIC=matching-adjusted indirect comparison; OFG=orforglipron; SD=standard deviation; SEMA=semaglutide; STC=simulated treatment comparison; T2D=type 2 diabetes; W=Week.

A. Cheng has served as advisor and consultant to: Abbott, AbbVie, Aspen, AstraZeneca, Bausch Health, Bayer, Biomea Fusion, BioSyst, Boehringer Ingelheim, Calway Biopharmaceuticals, Dexcom, Eisai, Eli Lilly and Company, Gan & Lee Pharmaceuticals, HLS Therapeutics, Insulet, Medtronic, Merck, MSD, Novo Nordisk, Sandoz and Sanofi, has served as a speaker for: Abbott, Amgen, Astellas Pharma, AstraZeneca, Bausch Health, Bayer, Biomea Fusion, Boehringer Ingelheim, Dexcom, Eisai, Eli Lilly and Company, GSK, HLS Therapeutics, Medtronic, Novo Nordisk, Pfizer and Sanofi; and has been involved in clinical trials for: Applied Therapeutics, Novo Nordisk and Sanofi.

D. Jacobi is affiliated with: CHU de Nantes, CNRS, Inserm, L'institut du Thorax and Nantes Université; and has received consulting fees, honoraria and travel support from: Eli Lilly and Company and Novo Nordisk.

D. Mojdami, **Jinhong Li**, **Jianghao Li**, **Y. Zhao**, **K. Terrell** and **H. Liu-Seifert** are employees and shareholders of: Eli Lilly and Company.

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