

Oral versus Injectable Glucagon-Like Peptide-1 Receptor Agonists for Weight Reduction and Early Type 2 Diabetes: A Systematic Review with Placebo-Anchored Indirect Comparison

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Abstract

Background: Glucagon-like peptide-1 receptor agonists are established therapy for obesity and type 2 diabetes mellitus, but the agents with the strongest evidence are injectable, and injection burden, cold-chain dependence and cost limit their reach. Two oral alternatives now carry phase 3 evidence: high-dose oral semaglutide, a peptide requiring a strict fasting and water-volume routine, and orforglipron, a small molecule with no such restriction. Whether the oral route itself costs efficacy has not been quantified.

Methods: A systematic review was conducted of randomised phase 3 trials of an orally administered glucagon-like peptide-1 receptor agonist reporting change in body weight or glycated haemoglobin, together with the injectable trial needed to anchor a route comparison. 38 records were screened and 8 trials enrolling 18,540 participants were included. Estimated treatment differences against placebo were pooled by random effects with restricted maximum likelihood and the Hartung-Knapp correction. The primary analysis was a placebo-anchored indirect comparison of each oral agent against subcutaneous semaglutide 2.4 mg weekly. Reporting followed PRISMA 2020.

Results: In adults with overweight or obesity without diabetes, oral semaglutide 50 mg reduced body weight by -12.70 (95% CI -14.15 to -11.25) percentage points against placebo and oral semaglutide 25 mg by -11.40 (95% CI -13.85 to -8.95), against -12.40 (95% CI -13.35 to -11.45) for subcutaneous semaglutide 2.4 mg. The indirect comparisons showed no difference attributable to route: -0.30 (95% CI -2.03 to 1.43) percentage points for the 50 mg tablet and 1.00 (95% CI -1.63 to 3.63) for the 25 mg tablet. The oral small molecule orforglipron 36 mg was inferior to the injectable peptide by 3.30 (95% CI 1.87 to 4.73) percentage points ($p < 0.001$). The single within-trial comparison, PIONEER 4, found oral semaglutide 14 mg non-inferior to subcutaneous liraglutide 1.8 mg for glycated haemoglobin and superior for weight by -1.2 kg (-1.9 to -0.6 kg). Oral semaglutide reduced major adverse cardiovascular events in high-risk type 2 diabetes, hazard ratio 0.86 (0.77 to 0.96).

Conclusion: Route of administration does not by itself reduce the efficacy of a glucagon-like peptide-1 receptor agonist. At an adequate dose the oral peptide matches the injectable peptide, while the oral small molecule does not, so the limit is molecular class and dose, not the tablet. Because the oral peptide's absorption depends on a fasting routine many patients cannot reliably follow, the choice between routes should turn on whether that routine is achievable for the individual patient.

Keywords: Oral Semaglutide, Orforglipron, Glucagon-Like Peptide-1 Receptor Agonist, Obesity, Type 2 Diabetes Mellitus, Indirect Comparison.

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Introduction

India carries one of the largest metabolic disease burdens in the world. The Indian Council of Medical Research India Diabetes survey, a door-to-door cross-sectional study across thirty-one states

and union territories, projects 101.3 million adults with diabetes, 136.0 million with prediabetes and 254.2 million with generalised obesity.[1] The prediabetic population is larger than the diabetic

one, which places unusual weight on therapies that act early, before beta-cell reserve is exhausted. Glucagon-like peptide-1 receptor agonists have become the most effective pharmacological option for weight reduction and an increasingly early choice in type 2 diabetes mellitus. The agents carrying the strongest evidence are given by subcutaneous injection, and injection is precisely what limits their reach. Weekly self-injection requires training, disposal and refrigeration, and in a setting where the drug is bought out of pocket the pen is also the most expensive presentation. A tablet removes all of these obstacles at once, which is why the transition from injectable to oral therapy has become a practical question rather than a pharmacological curiosity.

Two oral routes now exist and they are not equivalent. Oral semaglutide is the same peptide given subcutaneously, co-formulated with sodium N-(8-[2-hydroxybenzoyl]amino) caprylate (SNAC), which promotes transcellular absorption across the gastric mucosa. Absolute bioavailability is approximately 0.8 per cent, and absorption depends on the conditions of dosing: bioavailability rises with the post-dose fasting interval to a plateau near 1.4 per cent at 120 minutes and falls when the tablet is swallowed with a large volume of water.[2] Orforglipron is a non-peptide small molecule that requires no fasting interval and no water restriction, and therefore carries none of this fragility.

The available syntheses do not answer the clinician's question. A recent network meta-analysis of 9 trials in 5,766 participants ranked oral agents against one another and against placebo, reporting mean differences of -11.6 per cent for high-dose oral semaglutide and -11.8 per cent for high-dose orforglipron, with certainty judged low to moderate.[3] A narrative review reached the qualitative conclusion that oral agents approach injectable standards.[4] Neither places an oral agent against the injectable form of the same molecule, which is the comparison a physician makes when deciding whether to move a patient from a pen to a tablet. The present review was undertaken to make that comparison explicitly and to separate the contribution of route from the contribution of molecular class and dose.

Material and Methods

Eligible studies were randomised, placebo-controlled or active-controlled phase 3 trials of an orally administered glucagon-like peptide-1 receptor agonist in adults with overweight, obesity or type 2 diabetes mellitus, reporting change in body weight or in glycated haemoglobin at twenty-six weeks or later. One randomised trial of subcutaneous semaglutide 2.4 mg weekly was included to anchor the route comparison. Phase 2

dose-finding reports, single-arm studies, secondary and subgroup analyses of included trials, correspondence and previous evidence syntheses were not eligible for the synthesis; the syntheses were retained as context.

Searches were run on 2026-09-22 across the Europe PubMed Central record interface, the Crossref works interface for single-identifier verification, publisher full texts, and structured searching of trial programme names. Screening, retrieval and extraction were performed by a single reviewer; there was no duplicate independent screening. The review was not prospectively registered. Both departures from systematic review convention are restated under limitations.

Every extracted value was written into a versioned evidence file together with the route by which it was obtained, and every number in this manuscript is read from that file by the analysis script rather than transcribed. Where a trial reported an estimated treatment difference with a confidence interval, that estimate was used directly. Where a trial reported only arm-level estimates with confidence intervals, the treatment difference and its standard error were derived arithmetically and are marked as derived wherever they appear. Reported treatment differences were checked against the difference of the reported arm means and agreed to within one rounding unit in every case.

The effect measure for weight was the estimated treatment difference in percentage points of body weight change and for glycaemia the difference in percentage points of glycated haemoglobin. Where a trial randomised more than one dose, the highest dose evaluated was carried into the analysis, because the question at issue is the maximum effect obtainable by each route rather than the effect of any particular titration step. Estimates were pooled by random effects with the between-study variance estimated by restricted maximum likelihood, the Hartung-Knapp variance correction and a *t* reference distribution; the fixed-effect estimate is reported alongside because that correction is conservative when few trials are pooled. Heterogeneity was quantified by Cochran *Q* and the *I*-squared statistic.

The primary analysis was a Bucher adjusted indirect comparison of each oral agent against subcutaneous semaglutide 2.4 mg weekly through their common placebo comparator, which assumes that the trials are similar in the factors that modify treatment effect. Tolerability endpoints were not pooled because their definitions and observation periods differ. Risk of bias was considered using the revised Cochrane tool.[5] Reporting follows the PRISMA 2020 statement,[6] with the flow of records presented as a table because this journal

publishes no figures. Analyses were performed in Python 3 with a purpose-written meta-analysis module whose output was verified against an independent implementation and against simulation before use; the code accompanies this manuscript.

Result

The search identified 38 records. 18 were excluded at screening, most commonly because they were evidence syntheses rather than primary trials or

secondary analyses of a trial already included. 20 reports were sought in full, of which 7 could not be retrieved because the publisher returned an access error. 8 trials entered the synthesis and 5 further sources were retained as context. Two of the unobtainable reports would have altered the analysis: PIONEER 10 is the only other within-trial comparison of the two routes, and STEP 2 would have supplied an injectable anchor for the diabetic population [Table 1].

Table 1: Search, screening and disposition of records

Stage	Records	Note
Identification		
Records identified by all sources	38	Searched 2026-09-22
Screening		
Excluded on title and record	18	Evidence syntheses, secondary analyses, correspondence, ineligible design
Reports sought in full	20	-
Retrieval		
Not retrievable (publisher access error)	7	Each named in the text and under limitations
Inclusion		
Trials contributing an effect estimate	8	18,540 randomised participants
Sources retained as context only	5	Pharmacokinetics, adherence, prior syntheses, disease burden

Presented as a table rather than as a PRISMA flow diagram because this journal publishes no figures. Counts are computed from an enumerated record list held in the accompanying evidence file. The 8 included trials enrolled 18,540 participants. Three tested oral semaglutide, three tested orforglipron, one tested subcutaneous semaglutide and one

compared oral semaglutide directly against subcutaneous liraglutide. Follow-up ranged from forty weeks to seventy-two weeks, except the cardiovascular outcome trial, which continued for a median of 49.5 months. Four trials enrolled participants without diabetes and four enrolled participants with type 2 diabetes mellitus [Table 2].

Table 2: Characteristics of the eight included trials

Trial	Agent and route	Population	N	Weeks
Overweight or obesity without diabetes				
OASIS 1	Oral semaglutide 50 mg	No diabetes	612	68
OASIS 4	Oral semaglutide 25 mg	No diabetes	307	64
ATTAIN-1	Oral orforglipron 6-36 mg	No diabetes	3,127	72
STEP 1	Subcutaneous semaglutide 2.4 mg weekly	No diabetes	1,961	68
Type 2 diabetes mellitus				
PIONEER 4	Oral semaglutide 14 mg vs subcutaneous liraglutide 1.8 mg	On metformin	711	26
ACHIEVE-1	Oral orforglipron 3-36 mg	Early, diet and exercise alone	559	40
ATTAIN-2	Oral orforglipron 6-36 mg	Obesity with diabetes	1,613	72
SOUL	Oral semaglutide 14 mg	High cardiovascular risk	9,650	median 49.5 months

Weeks are the primary analysis timepoint. For OASIS 1 the denominators are those of the responder endpoint, the only figures retrievable for that trial; total randomised was not obtainable. Against placebo, oral semaglutide 50 mg reduced body weight by -12.70 (95% CI -14.15 to -11.25) percentage points and oral semaglutide 25 mg by -

11.40 (95% CI -13.85 to -8.95) percentage points, while subcutaneous semaglutide 2.4 mg weekly reduced it by -12.40 (95% CI -13.35 to -11.45) percentage points. The oral small molecule orforglipron 36 mg reduced body weight by -9.10 (95% CI -10.16 to -8.04) percentage points in participants without diabetes and by -7.10 (95% CI

-8.15 to -6.05) percentage points in participants with type 2 diabetes mellitus.

Pooling the three oral estimates in participants without diabetes gave -10.99 (95% CI -15.93 to -6.05) percentage points by random effects and -10.47 (95% CI -11.28 to -9.66) by fixed effect,

with substantial heterogeneity (I-squared 87.5 per cent, $Q = 16.02$, $p < 0.001$).

That heterogeneity is structural rather than unexplained: it separates along molecular class, which is why the class-specific comparisons below carry the interpretation [Table 3].

Table 3: Effect on per cent body weight against placebo, by route and molecular class

Trial and agent	Route	Class	Difference vs placebo (percentage points, 95% CI)	Source
Overweight or obesity without diabetes				
OASIS 1, oral semaglutide 50 mg	Oral	Peptide	-12.70 (-14.15 to -11.25)	Reported
OASIS 4, oral semaglutide 25 mg	Oral	Peptide	-11.40 (-13.85 to -8.95)	Reported
ATTAIN-1, orforglipron 36 mg	Oral	Small molecule	-9.10 (-10.16 to -8.04)	Derived
STEP 1, subcutaneous semaglutide 2.4 mg	Subcutaneous	Peptide	-12.40 (-13.35 to -11.45)	Reported
Type 2 diabetes mellitus				
ATTAIN-2, orforglipron 36 mg	Oral	Small molecule	-7.10 (-8.15 to -6.05)	Reported
Pooled oral agents, no diabetes				
Random effects, REML with Hartung-Knapp	Oral	Mixed	-10.99 (-15.93 to -6.05)	Computed
Fixed effect, inverse variance	Oral	Mixed	-10.47 (-11.28 to -9.66)	Computed

Heterogeneity across the three pooled oral estimates was I-squared 87.5 per cent, $Q = 16.02$, $p < 0.001$, and separates along molecular class; the pooled oral figure should therefore not be read as a class effect.

'Derived' means the difference and its standard error were computed arithmetically from the published arm-level confidence intervals. The indirect comparisons against subcutaneous semaglutide 2.4 mg weekly showed no efficacy penalty attributable to the oral route for the peptide. Oral semaglutide 50 mg differed from the injectable by -0.30 (95% CI -2.03 to 1.43)

percentage points ($p = 0.734$) and oral semaglutide 25 mg by 1.00 (95% CI -1.63 to 3.63) percentage points ($p = 0.456$); both intervals include zero. Orforglipron 36 mg was inferior to the injectable peptide by 3.30 (95% CI 1.87 to 4.73) percentage points ($p < 0.001$).

The single within-trial route comparison pointed the same way as the indirect peptide comparisons: in PIONEER 4 oral semaglutide 14 mg was non-inferior to subcutaneous liraglutide 1.8 mg for glycated haemoglobin (-0.1 percentage points, -0.3 to 0.0) and superior for weight (-1.2 kg, -1.9 to -0.6 kg, $p = 0.0003$) [Table 4].

Table 4: Comparison of the oral route against the injectable route

Comparison	Difference (95% CI)	p value	Basis
Indirect, anchored on placebo, against subcutaneous semaglutide 2.4 mg			
Oral semaglutide 50 mg	-0.30 (-2.03 to 1.43) pp	0.734	Bucher
Oral semaglutide 25 mg	1.00 (-1.63 to 3.63) pp	0.456	Bucher
Orforglipron 36 mg	3.30 (1.87 to 4.73) pp	< 0.001	Bucher
Pooled oral agents	1.41 (-1.04 to 3.85) pp	0.259	Bucher
Direct, within trial (PIONEER 4), against subcutaneous liraglutide 1.8 mg			
Oral semaglutide 14 mg, glycated haemoglobin	-0.1 (-0.3 to 0.0) pp	non-inferiority met	Randomised
Oral semaglutide 14 mg, body weight	-1.2 (-1.9 to -0.6) kg	0.0003	Randomised

A negative value favours the oral agent. Indirect comparisons assume the oral and injectable trials are similar in effect-modifying characteristics. pp denotes percentage points.

In early type 2 diabetes mellitus inadequately controlled by diet and exercise, orforglipron 36 mg lowered glycated haemoglobin from a baseline of 8.0 per cent by -1.07 percentage points (-1.33 to -

0.81) against placebo, and 73 per cent of participants reached a glycated haemoglobin below seven per cent against 33 per cent on placebo. Oral semaglutide at 14 mg reduced major adverse cardiovascular events in 9,650 patients with type 2 diabetes mellitus at high cardiovascular risk, hazard ratio 0.86 (0.77 to 0.96, $p = 0.006$), with non-fatal myocardial infarction reduced to a hazard ratio of 0.74 (0.61 to 0.89). Discontinuation for adverse events was higher on active treatment in every trial, but the endpoints are not comparable and were

therefore not pooled. Where event counts were reported, the excess over placebo was 3.9 percentage points (2.6 to 5.3) for any-cause discontinuation over a median of 49.5 months on oral semaglutide, and 3.8 percentage points (2.4 to 5.1) for gastrointestinal discontinuation over sixty-eight weeks on subcutaneous semaglutide. Among trials reporting percentages alone, the excess ranged from 1.0 percentage points for oral semaglutide 25 mg to 7.6 percentage points for orforglipron 36 mg [Table 5].

Table 5: Discontinuation for adverse events, by trial

Trial and agent	Active (%)	Placebo (%)	Excess over placebo (percentage points)	Endpoint
Event counts reported, interval computable				
SOUL, oral semaglutide 14 mg	15.5	11.6	3.9 (2.6 to 5.3)	Any cause, median 49.5 months
STEP 1, subcutaneous semaglutide 2.4 mg	4.5	0.8	3.8 (2.4 to 5.1)	Gastrointestinal, 68 weeks
Percentages only, no interval computable				
OASIS 4, oral semaglutide 25 mg	6.9	5.9	1.0	Any cause, 64 weeks
ACHIEVE-1, orforglipron 36 mg	7.8	1.4	6.4	Any cause, 40 weeks
ATTAIN-1, orforglipron 36 mg	10.3	2.7	7.6	Any cause, 72 weeks
ATTAIN-2, orforglipron across doses	6.1 to 9.9	4.1	not computable	Any cause, 72 weeks

These endpoints are not pooled. The definitions and observation periods differ, so a combined figure would have no referent.

Discussion

The central result of this review is that the oral route does not, by itself, cost efficacy. When the same peptide is compared with itself across routes through a common placebo comparator, the difference is -0.30 (95% CI -2.03 to 1.43) percentage points at the 50 mg oral dose and 1.00 (95% CI -1.63 to 3.63) percentage points at the 25 mg oral dose. Both intervals are centred close to zero and both include it. The long-standing impression that oral glucagon-like peptide-1 therapy is the weaker option arose when the only oral doses available were 3, 7 and 14 mg, chosen for glycaemic control rather than for weight reduction. It is a dose artefact of approximately one per cent bioavailability, not a property of the tablet.

The second result qualifies the first and is equally important. Orforglipron 36 mg, the oral small molecule, was inferior to subcutaneous semaglutide 2.4 mg by 3.30 (95% CI 1.87 to 4.73) percentage points, and this difference is statistically unambiguous. The heterogeneity observed when the three oral estimates were pooled (I-squared 87.5 per cent) is explained by exactly this split, which is why a single pooled oral estimate should not be quoted as though it described a class. What separates the agents is molecular class and dose,

not administration route. The oral estimates reported by Knop et al,[7] Wharton et al[8] and Wharton et al[9] are internally consistent with this reading when set against the injectable anchor reported by Wilding et al,[10] and the smaller effect observed for the same small molecule in patients with diabetes by Horn et al[11] points the same way. The network meta-analysis reported by Kamrul-Hasan et al[3] reached comparable magnitudes for the two oral agents without framing the contrast in terms of route. The only within-trial evidence agrees. Pratley et al [12] found oral semaglutide 14 mg non-inferior to subcutaneous liraglutide 1.8 mg for glycated haemoglobin and superior for weight reduction, at a dose far below those now used for obesity. A randomised comparison is worth more than any indirect estimate, and the fact that the two approaches agree strengthens the transitivity assumption on which the indirect comparisons rest. The loss of PIONEER 10, the only other trial of this kind and one that used a different injectable comparator, is the most consequential gap in this review.

For early type 2 diabetes mellitus the oral small molecule performs differently than it does for weight. Rosenstock et al[13] reported a reduction in glycated haemoglobin of -1.07 percentage points from a baseline of 8.0 per cent, with 73 per cent reaching target. A drug that is clearly second-best for weight may be entirely adequate for glycaemia in a patient whose weight is not the dominant

problem, and the two decisions should be made separately rather than by ranking agents on a single axis.

Evidence that the oral route preserves hard outcomes is now available and is not a minor consideration. McGuire et al[14] showed that oral semaglutide reduced major adverse cardiovascular events in high-risk type 2 diabetes mellitus, hazard ratio 0.86 (0.77 to 0.96), with a reduction in non-fatal myocardial infarction of similar direction and larger magnitude. Before that trial it was reasonable to treat cardiovascular protection as demonstrated only for the injectable presentations. It no longer is.

Against these efficacy findings sits a counterweight that favours the tablet. Wang et al[15] analysed 78,297 insured patients and found that 65.1 per cent of those on oral semaglutide reached a proportion of days covered of at least eighty per cent at twelve months, against 38.8 per cent on injectable semaglutide and 44.5 per cent on liraglutide. If that difference is real and not an artefact of who is offered which formulation, an oral agent of equal efficacy under trial conditions will outperform an injectable one in practice, because a drug taken is worth more than a drug prescribed.

The tablet carries its own fragility, and it is one that trial conditions conceal. Oral semaglutide must be swallowed with no more than 120 mL of water after an overnight fast and at least thirty minutes before food, other liquids or other oral medication. Overgaard et al[2] showed that bioavailability rises with the post-dose fasting interval to a plateau near 1.4 per cent at 120 minutes and falls when the tablet is taken with a large volume of water, although a single deviation produces only a transient change in steady-state exposure. In a trial population that routine is supported by study visits and diaries. In everyday practice in eastern India it collides with morning tea taken on waking, with early household meals, with shared living arrangements, and with religious and seasonal fasting. Orforglipron has no such requirement, and for a patient who cannot hold the fasting window a molecule that is three percentage points weaker under ideal conditions may be the stronger choice in practice. This review cannot quantify that trade-off, because no included trial measured administration fidelity; it identifies the measurement as the missing one.

Several limitations qualify these conclusions. Seven of twenty reports sought could not be retrieved because of publisher access restrictions, so the search was constrained by access rather than by design, and the omissions are named rather than absorbed. Screening was performed by a single reviewer and the review was not prospectively registered, so it is a systematic review in method but not yet in registration. The primary comparison

is indirect and assumes that the oral and injectable trials are similar in effect-modifying characteristics; they differ in size, in duration by four weeks, and in placebo response. Two treatment differences were derived from arm-level confidence intervals rather than reported. The injectable anchor exists only for participants without diabetes, so no indirect route comparison could be made in the diabetic population. Tolerability endpoints were deliberately not pooled, so the review describes them and does not summarise them. Finally, no included trial was conducted in India, and neither cost nor administration fidelity, the two variables most likely to govern the choice of route in this setting, has been measured in any of them.

Conclusion

Route of administration is not the determinant of efficacy for glucagon-like peptide-1 receptor agonists. At an adequate dose, oral semaglutide matches subcutaneous semaglutide for weight reduction and preserves cardiovascular benefit; the oral small molecule orforglipron is a genuinely weaker option for weight while remaining an effective one for glycaemia in early type 2 diabetes mellitus. For practice, this means a patient declining or unable to sustain injections should be offered an oral agent rather than a lesser drug class, and the choice between the two oral agents should be made on whether the patient can reliably keep the fasting and water restriction that the oral peptide requires. Where that routine is not achievable, the unrestricted small molecule is the more realistic prescription.

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