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Efficacy and Safety of Once-Weekly Basal Insulins versus Once-Daily Basal Insulin Analogues in Adults with Type 2 Diabetes: A Systematic Review and Meta-Analysis of the ONWARDS and QWINT Phase 3 Clinical Trial Programs

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ADMINISTRATIVE INFORMATION**Support** - Universidad del cauca.**Review Stage at time of this submission** - Completed but not published.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY2026100114**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 26 October 2026 and was last updated on 26 October 2026.**INTRODUCTION**

Review question / Objective Two once-weekly basal insulin analogues, insulin icodec and insulin efsitora alfa, have each completed a parallel phase 3 clinical development program in adults with type 2 diabetes (T2D).

Objective. To systematically review and quantitatively synthesize the efficacy and safety of once-weekly insulin icodec and once-weekly insulin efsitora alfa, each compared with once-daily basal insulin analogues, in adults with T2D.

Rationale Basal insulin therapy remains a cornerstone of glycemic management in type 2 diabetes (T2D) when oral and non-insulin injectable agents fail to achieve glycemic targets, yet its daily administration burden, treatment inertia among prescribers and patients, and the small but persistent risk of hypoglycemia continue to limit its timely initiation and optimal titration.

Once-weekly basal insulin formulations have been developed to reduce this burden while preserving

the glucose-lowering efficacy and safety profile of conventional once-daily analogues. Two such molecules have independently completed large, multinational phase 3 clinical development programs in T2D: insulin icodec, evaluated in the ONWARDS program, and insulin efsitora alfa, evaluated in the QWINT program.

Several meta-analyses of the individual ONWARDS and QWINT programs, and at least one network meta-analysis comparing icodec and efsitora alfa indirectly, have already been published. However, to our knowledge no prior synthesis has (a) restricted pooling strictly to the phase 3, T2D-indicated trials of each program (excluding the type 1 diabetes trials ONWARDS 6 and QWINT-5 and the phase 2 studies), (b) applied an identical, pre-specified, independently re-implemented random-effects statistical method with small-sample adjustment to both programs in parallel, and (c) documented, trial by trial, whether each extracted value originated from the trial's own primary publication or was cross-validated against a secondary source.

We undertook this systematic review and meta-analysis to address this gap and to provide clinicians with directly comparable, program-specific pooled estimates of efficacy and safety for both once-weekly insulins.

Condition being studied Adults (≥ 18 years) with Type 2 Diabetes.

METHODS

Search strategy This review was conducted and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement, adapted to a focused, programmatic evidence-identification strategy appropriate to a trial landscape defined by two complete, named, sponsor-registered phase 3 programs rather than a heterogeneous, dispersed literature.

In this study, the PICOS strategy was used as follows: Population: adults (≥ 18 years) with T2D. Trials conducted exclusively in type 1 diabetes, were excluded a priori. Intervention: once-weekly insulin icodec or once-weekly insulin efsitora alfa, at any fixed or titrated dose evaluated in a registered phase 3 trial. Comparator: once-daily basal insulin analogue (glargine U100 or degludec). Outcomes: (a) mean change in A1c from baseline to the primary efficacy time point; (b) mean change in body weight; (c) proportion of participants achieving A1c $< 7\%$ (53 mmol/mol); (d) clinically significant (level 2) or combined level 2/3 hypoglycemia. Study design: randomized, phase 3, treat-to-target or non-inferiority trials with a parallel once-daily basal insulin comparator arm. Phase 2 dose-finding studies were catalogued for descriptive purposes only and were excluded from all pooled estimates, because they tested non-definitive dose regimens and were not designed as registration trials.

A written protocol specifying the eligibility criteria, outcomes, and statistical analysis plan was developed a priori by the authors.

Participant or population Adults (≥ 18 years) with Type 2 Diabetes.

Intervention Once-weekly insulin icodec or once-weekly insulin efsitora alfa, at any fixed or titrated dose evaluated in a registered phase 3 trial.

Comparator Once-daily basal insulin analogue (glargine U100 or degludec).

Study designs to be included Randomized, phase 3, treat-to-target or non-inferiority trials with a parallel once-daily basal insulin comparator arm.

Eligibility criteria Adults (≥ 18 years) with Type 2 Diabetes.

Information sources Because both eligible bodies of evidence are fully enumerable, closed, sponsor-registered phase 3 programs rather than a diffuse literature requiring exhaustive database searching, evidence identification combined three defined, auditable sources rather than a de novo multi-database search: (a) the published trial-program rationale papers, which prospectively enumerate every phase 3 trial conducted under each program; (b) the primary clinical trial publications; and (c) independently published, peer-reviewed systematic reviews and meta-analyses of each program, used as a secondary extraction source for trials whose primary publication could not be directly obtained.

Main outcome(s) Five ONWARDS trials and four QWINT trials met the eligibility criteria. Icodec reduced A1c significantly more than once-daily basal insulin, whereas efsitora alfa showed a smaller, non-significant difference. Both agents were associated with modestly greater weight gain than their comparators. Neither agent significantly altered the risk of clinically significant hypoglycemia relative to once-daily comparators.

Additional outcome(s) Five ONWARDS trials and four QWINT trials met the eligibility criteria. Icodec reduced A1c significantly more than once-daily basal insulin, whereas efsitora alfa showed a smaller, non-significant difference. Both agents were associated with modestly greater weight gain than their comparators. Neither agent significantly altered the risk of clinically significant hypoglycemia relative to once-daily comparators.

Data management All phase 3 T2D trials of each program were eligible by design (a closed, enumerable set), so no inter-rater study-selection screening was required beyond confirming trial identity against each program's own rationale and registration publication.

For each eligible trial, the following were extracted for the intervention and comparator arms: mean, standard deviation or standard error, and sample size for each continuous outcome; and event counts over total randomized or safety-analysis-set participants for each binary outcome. Every extracted value is traceable to a specific page, table, or figure of a named source document in a line-item extraction log maintained throughout the review.

Data extraction proceeded in two stages. In the first stage, the primary publication of each trial was

sought; when it could not be directly obtained, values were extracted from the digitized forest plots of independently published, peer-reviewed meta-analyses of the same program. In the second stage, every one of the nine included trials was re-extracted directly from its own primary publication and each provisionally extracted value was cross-checked against that source; agreement was exact or within trivial rounding for the great majority of values.

Quality assessment / Risk of bias analysis Risk of bias was assessed at the trial level using the Cochrane RoB 2 tool domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. All nine included phase 3 trials were open-label (no treatment masking of insulin dose or injection schedule, a structural feature of comparing a weekly versus a daily injectable), which confers an inherent "some concerns" rating for the deviations-from-intended-interventions domain in every trial, consistent with the judgment reached by prior independent meta-analyses of these same programs.

All trials used adequate, computer-generated randomization with allocation concealment and pre-specified, centrally analyzed efficacy and safety endpoints under intention-to-treat or full-analysis-set principles, supporting low risk of bias for the remaining four domains in all nine trials. The overall RoB 2 judgment for every included trial was therefore "some concerns", driven uniformly by the open-label design rather than by any differential flaw across trials.

Strategy of data synthesis All phase 3 T2D trials of each program were eligible by design (a closed, enumerable set), so no inter-rater study-selection screening was required beyond confirming trial identity against each program's own rationale and registration publication.

For each eligible trial, the following were extracted for the intervention and comparator arms: mean, standard deviation or standard error, and sample size for each continuous outcome; and event counts over total randomized or safety-analysis-set participants for each binary outcome. Every extracted value is traceable to a specific page, table, or figure of a named source document in a line-item extraction log maintained throughout the review.

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Subgroup analysis No subgroup, meta-regression, or publication-bias analysis was performed given the small k, a limitation stated explicitly rather than omitted.

Sensitivity analysis No subgroup, meta-regression, or publication-bias analysis was performed.

Language restriction English.

Country(ies) involved Colombia.

Other relevant information None

Keywords basal insulin; icodec; efsitora alfa; type 2 diabetes mellitus; ONWARDS; QWINT.

Dissemination plans journals of high impact.

Contributions of each author

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