

Clinical outcomes of inhaled Technosphere insulin in adults with type 1 diabetes: A systematic review and meta-analysis

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Abstract

Technosphere insulin (TI) is an ultra-rapid acting inhaled insulin used as an alternative to subcutaneous prandial insulin in adults with type 1 diabetes mellitus (T1DM), though its glycaemic efficacy and pulmonary safety remain debated.

We conducted a systematic review and meta-analysis, in accordance with PRISMA 2020, to evaluate the efficacy and safety of TI in randomised controlled trials comparing TI with subcutaneous prandial insulin in adults with T1DM. PubMed/MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and Scopus were searched from inception to July 2026. Risk of bias was assessed using the Cochrane RoB 2 tool. Six RCTs (one with two intervention arms) yielded seven comparisons and 1,270 participants. Basal insulin was maintained with long-acting analogues or pump therapy. The primary outcome was change in HbA1c; secondary outcomes included body weight, time in range (TIR 70–180 mg/dL), FEV₁, cough, serious adverse events (SAEs), and other adverse events, analysed using random-effects models (RevMan 5.4).

TI showed a mean HbA1c difference of 0.12% (95% CI -0.00 to 0.23; p=0.05) versus subcutaneous insulin, with the upper CI below the 0.40% non-inferiority margin. TI significantly reduced body weight (MD -1.55 kg; 95% CI -2.11 to -0.99; p<0.00001). No significant differences emerged in TIR, FEV₁, or SAEs. Cough was significantly more frequent with TI (RR 7.38; 95% CI 3.50–15.58; p<0.00001); other adverse events were comparable.

TI demonstrated non-inferior glycaemic control and reduced body weight versus subcutaneous insulin in T1DM, though corrective dosing may have influenced HbA1c equivalence. Despite increased cough, pulmonary function and SAEs were unaffected. Larger, longer-term studies are needed to confirm long-term efficacy and pulmonary safety.

Registration

PROSPERO CRD420261472995.

INTRODUCTION

Despite considerable advances in insulin formulations and delivery systems, achieving physiological prandial insulin replacement remains an unmet goal in the management of type 1 diabetes mellitus (T1DM). Rapid acting insulin analogues (RAAs) are recommended as the preferred prandial insulins because of their faster absorption compared with regular human insulin, yet their pharmacokinetic profile still differs substantially from endogenous insulin secretion. Following subcutaneous administration, peak plasma insulin concentrations are generally attained after 30–60 minutes, while glucose lowering activity may continue for 3–5 hours^[1, 2], so insulin action often lags the rapid post meal glucose rise and persists after nutrient absorption has ended, contributing to early postprandial hyperglycaemia and delayed hypoglycaemia.

In addition to pharmacokinetic limitations, the requirement for lifelong subcutaneous insulin injections remains a significant treatment burden for many individuals with T1DM, contributing to injection related discomfort, treatment fatigue, and reduced adherence. These unmet needs have driven the development of alternative insulin delivery systems designed to improve both the physiological profile of prandial insulin replacement and treatment acceptability.

Technosphere insulin (TI; Afrezza®, MannKind Corporation) was developed to minimise this physiological mismatch. Administered by oral inhalation and absorbed through the alveolar capillary network, TI achieves peak insulin concentrations approximately 12–15 minutes after administration, declining to near baseline within 90–120 minutes^[3], more closely resembling the early first phase insulin response and offering potential to improve postprandial control while reducing prolonged peripheral hyperinsulinaemia and late hypoglycaemia^[4].

TI received FDA approval in 2014 for adults with type 1 and type 2 diabetes^[5], but clinical uptake has been modest, constrained by pulmonary safety considerations including a boxed warning for acute bronchospasm, mandatory spirometric monitoring, and contraindication in current or recent smokers^[5, 6].

Evidence from randomised trials suggests TI achieves overall glycaemic control comparable to subcutaneous RAAs. However, most studies evaluated efficacy primarily using HbA1c, whereas CGM derived metrics such as TIR, TBR, and TAR provide a more comprehensive assessment of glycaemic control^[7]. This review synthesises the available evidence to evaluate the effects of TI on glycaemic control, hypoglycaemia, weight, and pulmonary safety in adults with T1DM.

METHODS

Study registration

This systematic review and meta-analysis was conducted and reported in accordance with PRISMA 2020 guidelines.^[8] The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD420261472995). The registered protocol is publicly accessible through the PROSPERO registry under registration number CRD420261472995. No amendments were made to the registered protocol.

Databases and search strategy

PubMed/MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and Scopus were searched from inception to July 2026 to identify randomized controlled trials evaluating Technosphere insulin (Afrezza) in adults with type 1 diabetes mellitus. Search strategies were adapted to the specific syntax of each database and included terms related to type 1 diabetes mellitus and Technosphere/inhaled insulin, with randomized or clinical trial filters applied where appropriate. The reference lists of included studies and relevant articles were also screened to identify additional eligible studies. The complete search strategies for all databases are provided in Supplementary Table S1.

Study selection

Randomized controlled trials comparing Technosphere insulin (TI) with a comparator insulin regimen—subcutaneous prandial insulin analogues, continuous subcutaneous insulin infusion, or usual care including automated insulin delivery systems—in adults (≥ 18 years) with T1DM were eligible.

Two authors independently screened titles and abstracts of retrieved records against the predefined eligibility criteria. Full-text reports of potentially eligible studies were subsequently assessed independently by the same reviewers. Disagreements at either stage were resolved through discussion with the third author and consensus. No automation tools were used for study screening or selection.

Intervention

The experimental group received Technosphere insulin (TI; Afrezza®, MannKind Corporation) as prandial replacement, with basal insulin maintained via long-acting analogues or pump therapy. The control group received subcutaneous prandial insulin analogues, continuous subcutaneous insulin infusion, or usual care (including automated insulin delivery). Six RCTs (one with two intervention arms) yielded seven pooled comparisons across 1,270 participants.

Outcome measures

The primary outcome was change in HbA1c. Secondary outcomes included body weight, time in range (TIR 70–180 mg/dL), FEV₁, cough, serious adverse events (SAEs), and other treatment-emergent adverse events.

For each eligible study, data were sought for the prespecified outcomes at the reported end-of-treatment or study endpoint. Extracted study-level variables included study design, duration, sample size, participant characteristics, intervention and comparator regimens, basal insulin regimen, corrective dosing protocols, and reported outcome measures. Where outcome data were unavailable or unclear, the information was recorded as not reported; no assumptions or imputation of missing outcome data were made.

Data extraction

Two authors independently extracted study characteristics, participant demographics, and outcome data from the included studies, with discrepancies resolved through discussion and consensus. For trials reporting standard error (SE) rather than standard deviation (SD), SD was derived as $SD = SE \times \sqrt{n}$.

Risk of bias and quality appraisal

Risk of bias was assessed independently by two authors using the Cochrane RoB 2 tool [9,17]. Disagreements were resolved through discussion and consensus.

Statistical analysis

Meta-analyses were performed in Review Manager (RevMan) 5.4 using random-effects (DerSimonian–Laird) models throughout, given the anticipated clinical and methodological heterogeneity across trials. Studies were included in each synthesis according to the prespecified outcome definitions and the availability of sufficiently comparable outcome data. Continuous outcomes were pooled as mean differences (MD), and dichotomous outcomes were pooled as risk ratios (RR) using the Mantel–Haenszel method, both with 95% confidence intervals. Individual study characteristics were summarised in tabular form, and pooled estimates were presented using forest plots. Heterogeneity was assessed using the I^2 statistic and Cochran's Q test. Leave-one-out sensitivity analyses were performed for all outcomes with ≥ 3 contributing studies to assess the robustness of the pooled estimates. Subgroup analyses and meta-regression were not performed because of the limited number of contributing studies. Publication bias was explored visually using funnel plots for outcomes with ≥ 4 studies. A formal certainty-of-evidence assessment was not performed.

RESULTS

Study Selection and Characteristics

A total of 930 records were identified through database searching. Following removal of duplicates, the remaining records were screened, and 47 full-text reports were assessed for eligibility; 41 were excluded. Six RCTs (seven pooled comparisons) met eligibility criteria, encompassing 1,270 randomised participants (Table 1, Fig. 1).

Table 1
Characteristics of included randomised controlled trials.

Variable	MKC-TI-009 (2009) ^[10]	MKC-TI-117 (2021) ^[11]	Affinity-1 (2015) ^[12]	STAT (2018) ^[13]	ABC Arm A (2024) ^[14]	ABC Arm B (2024) ^[14]	INHALE-3 (2025) ^[15]
Country	Multinational	USA, Brazil	USA, Russia, Ukraine, Brazil	USA	USA	USA	USA
Design	RCT, OL, Parallel	RCT, OL, Parallel	RCT, OL, Parallel	RCT, OL, Parallel, Pilot	RCT, OL, 3-arm Pilot	RCT, OL, 3-arm Pilot	RCT, OL, Parallel
Duration	52 wk	16 wk	24 wk	4 wk	90 days	90 days	17 wk
N	589	130	345	60	13	10	123
Population	Adults with T1DM; HbA1c $\approx$ 8.0%	Adults with T1DM	Adults with T1DM; HbA1c 7.5–10.0%	Adults with T1DM HbA1c 6.5–10%	Adults with T1DM, AID/CSII	Adults with T1DM, AID/CSII	Adults with T1DM; HbA1c 5.4–10.5%
Age (years)*	NR	38.3 $\pm$ 12.0 / 39.4 $\pm$ 11.5	NR	41 $\pm$ 16 / 42 $\pm$ 14	NR	NR	46 $\pm$ 14 / 45 $\pm$ 16
Male (%)*	NR	63.9 / 50.8	NR	NR	NR	NR	45.2 / 47.5
BMI (kg/m ²)*	NR	25.2 $\pm$ 3.7 / 25.6 $\pm$ 3.1	NR	26.4 $\pm$ 3.0 / 25.3 $\pm$ 2.8	NR	NR	27.6 $\pm$ 4.6 / 28.2 $\pm$ 5.5
Baseline HbA1c (%)*	$\sim$ 8.0 / $\sim$ 8.0	7.8 $\pm$ 0.56 / 7.6 $\pm$ 0.61	7.94 / 7.92	7.7 $\pm$ 0.9 / 8.0 $\pm$ 1.0	NR	NR	7.6 $\pm$ 1.0 / 7.6 $\pm$ 0.8
DM Duration (years)*	NR	16.3 $\pm$ 11.3 / 17.6 $\pm$ 10.4	NR	21 $\pm$ 12 / 19 $\pm$ 13	NR	NR	25 $\pm$ 16 / 22 $\pm$ 13
TI Arm	MedTone TI + glargine	MedTone TI + glargine	Gen2 TI + basal insulin	TI + degludec/glargine	TI meal bolus + AID pump	TI meal bolus + TI correction + degludec	TI + degludec (CGM-guided)
Comparator	Insulin aspart + glargine	Insulin lispro + glargine	Insulin aspart + basal insulin	Insulin aspart + degludec/glargine	Pump-only (CSII)	Pump-only (CSII)	Usual care (AID or MDI)
Corrective dosing: protocol type	Single-point, SMBG	Not reported	Single-point, SMBG	Two-timepoint, CGM	AID algorithm (subcutaneous)	TI bolus + correction + degludec	CGM-guided, multi-correction
Corrective dosing: threshold	10 U TI at 90 min if SMBG $\geq$ 180 mg/dL;	—	10 U TI at 90 min if SMBG $\geq$ 180 mg/dL;	+ 4 U at 1 h if BG 151–200 mg/dL; +8 U if BG $\geq$ 201 mg/dL; additional + 4 U at 2 h if BG $\geq$ 201 mg/dL with < 50 mg/dL decline (CGM-guided)	No inhaled TI corrective dosing; corrections delivered by AID algorithm (subcutaneous insulin)	TI used for both mealtime bolus and corrective doses	TI corrective dose recommended if CGM glucose > 140 mg/dL at 60–90 min after meals; mean 2–3 corrective doses/day

Variable	MKC-TI-009 (2009) ^[10]	MKC-TI-117 (2021) ^[11]	Affinity-1 (2015) ^[12]	STAT (2018) ^[13]	ABC Arm A (2024) ^[14]	ABC Arm B (2024) ^[14]	INHALE-3 (2025) ^[15]
Corrective dosing: timing	90 min post-meal	—	90 min post-meal	1h & 2h post-meal	Continuous	As needed	60–90 min; also overnight
Corrective dosing: usage rate	~ 60% pts ≥ 1 dose	—	~ 60% pts ≥ 1 dose	68% compliant (≥ 90% doses)	100%	Not reported	Avg 2–3 corrections/day
TIR effect of corrective dosing	Not measured	—	Not measured	ITT: NS (p = 0.10); compliant subgroup + 8.7% (p = 0.009)	TIR Δ + 4.69% (n = 9)	TIR Δ – 3.89%	Daytime TIR + 2% (NS); MDI subgroup + 7%
Hypoglycaemia effect	↓ any hypoglycaemia (86.0% vs 92.65%; p = 0.012)	—	Event rate ↓↓ (9.8 vs 14.0/pt-mo; p < 0.0001)	Compliant subgroup: less hypoglycaemia (p < 0.05)	12 L1 events; 0 severe	20 L1 events (> Arm A)	TBR non-inferiority met (p < 0.001)

*Values presented as TI arm / Comparator arm (mean ± SD) unless otherwise noted, as reported in the primary source. ITT=Intention to treat, NR = Not reported; NI = Non-inferiority; NS = Not significant; L1 = Level 1 hypoglycaemia (< 70 mg/dL); TI = Technosphere insulin; OL = Open-label; MDI = Multiple daily injections; AID = Automated insulin delivery; CSII = Continuous subcutaneous insulin infusion; CGM = Continuous glucose monitoring; SMBG = Self-monitored blood glucose; BG = Blood glucose; TIR = Time in range.

Risk of Bias

Risk of bias was assessed using the Cochrane RoB 2 tool (Fig. 2). All studies were rated “some concerns” for the deviations domain owing to the inherent impossibility of blinding inhaled versus subcutaneous insulin administration. MKC-TI-117 was rated “high” overall due to early termination and consequent under-powering. Sponsor involvement (MannKind Corporation) was noted across all studies as a potential source of bias.

Primary Outcome: HbA1c Change

Seven comparisons (601 participants receiving TI; 593 receiving comparator) contributed to the HbA1c meta-analysis (Fig. 3). The pooled mean difference (MD) was 0.12% (95% CI – 0.00 to 0.23; p = 0.05), numerically favouring the comparator but showing no statistically significant difference. Heterogeneity was moderate ($I^2 = 40\%$; $\tau^2 = 0.01$; p = 0.12). The upper limit of the 95% confidence interval (0.23%) remained below the pre-specified non-inferiority margin of 0.40% adopted in the pivotal Technosphere insulin trials, indicating that the pooled findings are consistent with non-inferiority ^[10, 12, 15].

Secondary Outcomes:

Four comparisons (444 participants receiving TI; 471 receiving comparator) reported body weight change (Fig. 4a). TI was associated with a statistically significant reduction in body weight compared with the comparator (MD – 1.55 kg, 95% CI – 2.11 to – 0.99; p < 0.00001), with no evidence of heterogeneity ($I^2 = 0\%$).

Two comparisons (231 TI; 229 comparator) reported FEV₁ data (Fig. 4b). The pooled MD was – 0.03 L (95% CI – 0.09 to 0.03; p = 0.32; $I^2 = 0\%$), indicating no significant pulmonary function decline with TI relative to comparators.

CGM-based glycaemic metrics were available from the STAT Study and INHALE-3 (Fig. 4c). Pooled analysis showed a non-significant improvement in time-in-range (TIR 70–180 mg/dL) with TI (MD 3.38%, 95% CI – 0.97 to 7.74; p = 0.13; $I^2 = 0\%$). No significant differences were observed for time above range (TAR; MD – 2.31%, 95% CI – 6.82 to 2.21; p = 0.32) or time below range (TBR; MD – 0.78%, 95% CI – 2.28 to 0.73; p = 0.31). This pooled TBR estimate reflects a difference-based comparison and is conceptually distinct from the non-inferiority test reported in the original INHALE-3 trial (Table 1), which used a pre-specified non-inferiority margin rather than testing for a between-group difference.

Safety Outcomes

All-cause adverse events were pooled across six comparisons (643 TI; 613 comparator; Fig. 5a). The pooled RR was 1.20 (95% CI 0.97–1.49; $p = 0.09$), indicating a non-significant numerical excess of adverse events in TI arms, with substantial heterogeneity ($I^2 = 71\%$).

Six comparisons contributed to the analysis of serious adverse events (Fig. 5b). The pooled RR was 0.97 (95% CI 0.70–1.35; $p = 0.84$; $I^2 = 0\%$), indicating no significant difference in serious adverse event rates between TI and comparators. This finding, combined with the absence of heterogeneity, provides reassurance that inhaled insulin does not confer excess serious risk in the T1DM population studied.

Vomiting events were analysable in five comparisons (Fig. 5c). The pooled RR was 0.71 (95% CI 0.24–2.07; $p = 0.53$; $I^2 = 0\%$), with no significant difference between groups.

Six comparisons (643 participants receiving TI and 613 receiving comparator therapy, comprising subcutaneous prandial insulin or insulin pump-based therapy) contributed to the analysis of cough (Fig. 5d). Cough was the most commonly reported adverse event associated with TI, occurring significantly more frequently than with comparator therapy (RR 7.38, 95% CI 3.50–15.58; $p < 0.00001$; $I^2 = 42\%$). Across the included trials, cough was consistently described as dry, mild, and transient, with symptoms typically occurring shortly after inhalation and diminishing over time. Importantly, treatment discontinuation due to cough was uncommon. In the INHALE-3 trial, cough was reported in 22.6% of participants receiving TI, but only 2 of 62 participants permanently discontinued treatment because of this adverse event.¹⁵ Similarly, cough-related discontinuation occurred in approximately 5.7% of participants using the Gen2 inhaler in the Affinity-1 trial.¹² Although the relative risk was markedly increased, the absolute clinical impact was limited because cough was rare among participants receiving comparator therapy and infrequently resulted in treatment discontinuation.

UTI (four comparisons; RR 1.25, 95% CI 0.20–7.68; $p = 0.81$), URTI (five comparisons; RR 1.06, 95% CI 0.79–1.44; $p = 0.69$), and bronchitis (four comparisons; RR 1.22, 95% CI 0.41–3.60; $p = 0.72$) did not differ significantly between groups (Fig. 6a–c).

Publication Bias and Sensitivity Analyses

Funnel plots for HbA1c and serious adverse events showed broadly symmetrical distribution of studies, suggesting no obvious publication bias for these outcomes, though the small number of included studies limits reliability of this assessment. Funnel plots for body weight and all-cause adverse events showed visible asymmetry, which may reflect small-study effects, between-study heterogeneity, or genuine publication bias. Leave-one-out sensitivity analyses did not materially alter the direction or magnitude of pooled estimates for any outcome, indicating that results were not driven by any single study.

DISCUSSION

This systematic review and meta-analysis of six RCTs (seven comparisons; 1,270 participants) found that Technosphere insulin (TI) achieves glycaemic control comparable to that of subcutaneous rapid-acting insulin analogues in adults with T1DM, with a pooled HbA1c difference of 0.12% (95% CI – 0.00 to 0.23) that remained within the pre-specified 0.4% non-inferiority margin adopted in the largest included trials. TI was also associated with a statistically significant reduction in body weight (– 1.55 kg) without significant deterioration in pulmonary function as measured by FEV₁.

The finding of HbA1c non-inferiority is consistent with the individual non-inferiority trials and the current product label.^[5] Although moderate heterogeneity was observed ($I^2 = 40\%$), this likely reflects differences in study design, glucose monitoring methods, and corrective dosing strategies rather than fundamental differences in glycaemic efficacy. Collectively, the available evidence supports TI as an effective alternative to subcutaneous prandial insulin in appropriately selected adults with T1DM.

Our findings are broadly consistent with earlier narrative and systematic reviews of inhaled insulin, which similarly concluded that Technosphere insulin achieves glycaemic outcomes comparable to subcutaneous rapid-acting analogues while offering a favourable weight profile^[18, 19, 20]. However, those earlier syntheses predate the CGM-era trials (STAT and INHALE-3) included here, and this review is therefore the first to incorporate contemporary time-in-range and time-below-range outcomes alongside the original efficacy and pulmonary safety evidence base.

Corrective dosing emerged as an important determinant of glycaemic outcomes with TI. Owing to its ultra-rapid onset and short duration of action, TI frequently requires supplemental postprandial doses to maintain glucose control beyond the early postprandial period. This was reflected across the included trials, where more structured correction protocols generally produced more favourable glycaemic outcomes. In the STAT study, participants adhering to $\geq 90\%$ of prescribed corrective doses achieved significantly greater time in range and lower time above range without an increase in hypoglycaemia, while the CGM-guided correction strategy employed in INHALE-3 was

associated with improved daytime glycaemic control.^[13, 15] Similarly, the ABC pilot study suggested that combining TI with automated insulin delivery for correction dosing yielded better glycaemic outcomes than using TI alone for both prandial and correction dosing, underscoring the importance of adequate basal insulin support.^[14] Nevertheless, the structured correction algorithms and high levels of adherence achieved in clinical trials may not be readily reproduced in routine clinical practice. Frequent glucose monitoring and multiple corrective inhalations may increase treatment burden, potentially reduce adherence and attenuating the glycaemic benefits observed under trial conditions. Future studies should therefore focus on pragmatic correction strategies that balance efficacy with long-term patient acceptability.

Cough was the predominant safety signal, with a nearly seven-fold higher risk than comparator therapy. Although the relative increase appears substantial, it should be interpreted in the context of the very low incidence of cough in comparator groups, which magnifies the relative effect. More importantly, permanent discontinuation attributable to cough was uncommon across the included trials, indicating that while cough is frequent, it is generally mild, transient, and rarely treatment-limiting.^[12, 15] Pulmonary safety monitoring, including baseline and periodic spirometry, nevertheless remains an essential component of TI therapy in accordance with current prescribing recommendations.^[5, 16]

The reduction in body weight observed with TI was consistent across all four contributing comparisons. Although modest, this finding may reflect the unique pharmacokinetic profile of TI, which produces a shorter duration of insulin exposure than subcutaneous rapid-acting insulin analogues and may therefore reduce prolonged peripheral hyperinsulinaemia and its associated anabolic effects. Reduced late postprandial insulin exposure and a lower requirement for corrective carbohydrate intake related to delayed hypoglycaemia may also contribute, although these mechanisms remain speculative and were not directly evaluated in the included studies.

This review has several limitations. All included trials were open label because blinding inhaled and subcutaneous insulin administration was impractical, introducing potential performance and detection bias. Differences in corrective dosing protocols and glucose monitoring strategies may also have contributed to between-study heterogeneity. Sample sizes for several outcomes, particularly FEV₁ and CGM-derived metrics, were small, and the ABC pilot arms provided limited statistical power.

In addition, most of the included trials were sponsored by MannKind Corporation, the manufacturer of Technosphere insulin, which may introduce the potential for funding bias despite the randomized study designs. Finally, the limited number of eligible studies precluded robust subgroup analyses and formal statistical assessment of publication bias.

CONCLUSION

In adults with T1DM, Technosphere insulin demonstrates glycaemic efficacy comparable to subcutaneous rapid acting insulin analogues and is associated with a statistically significant reduction in body weight. No significant decline in pulmonary function was observed. Cough remains the principal tolerability concern, although it is rarely treatment limiting. Given the heterogeneity of the available studies and patient populations, further evaluation in broader and more diverse cohorts is warranted. Larger, contemporary, CGM integrated trials with longer follow up are needed to further establish the clinical role of Technosphere insulin and characterise its long-term pulmonary safety.

Declarations

AUTHOR CONTRIBUTIONS

Dr. G. Rachitha: Conceptualization, Methodology, Investigation, Data Curation, Writing Original Draft, Writing Review and Editing.

Dr. Sahana Shetty: Supervision, Methodology, Project Administration, Writing Review and Editing.

Dr. Renuka Suvarna: Formal Analysis, Statistical Analysis, Data Curation, Data Interpretation.

DECLARATIONS

Funding: No specific funding was received for this study.

Conflict of Interest: The authors declare no competing interests.

Ethical Approval: Ethical approval was not required for this study as it involved analysis of data from previously published studies and publicly available sources.

Data Availability Statement: All data used in this study were obtained from previously published studies and publicly available sources. The data supporting the findings of this study are available from the corresponding published sources and references cited in the manuscript. No separate analytic code or additional dataset was generated for this study.

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Figures

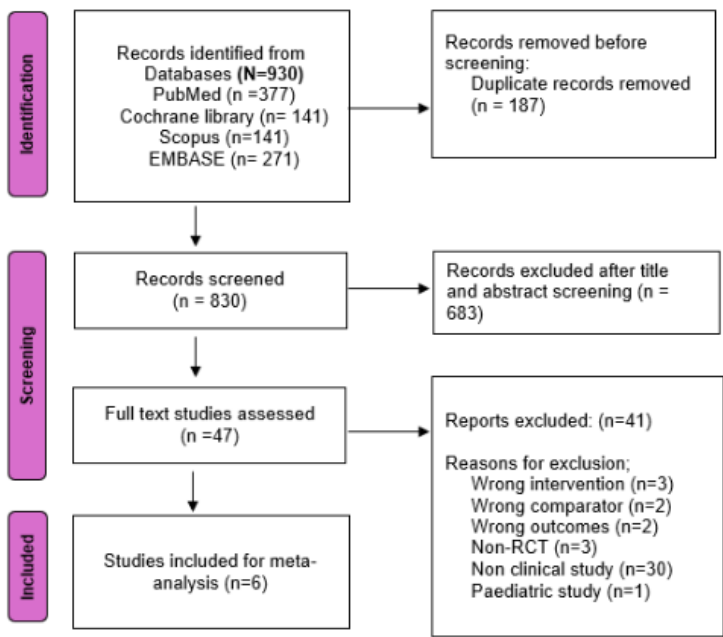


Figure 1
PRISMA flow diagram of study identification and selection.

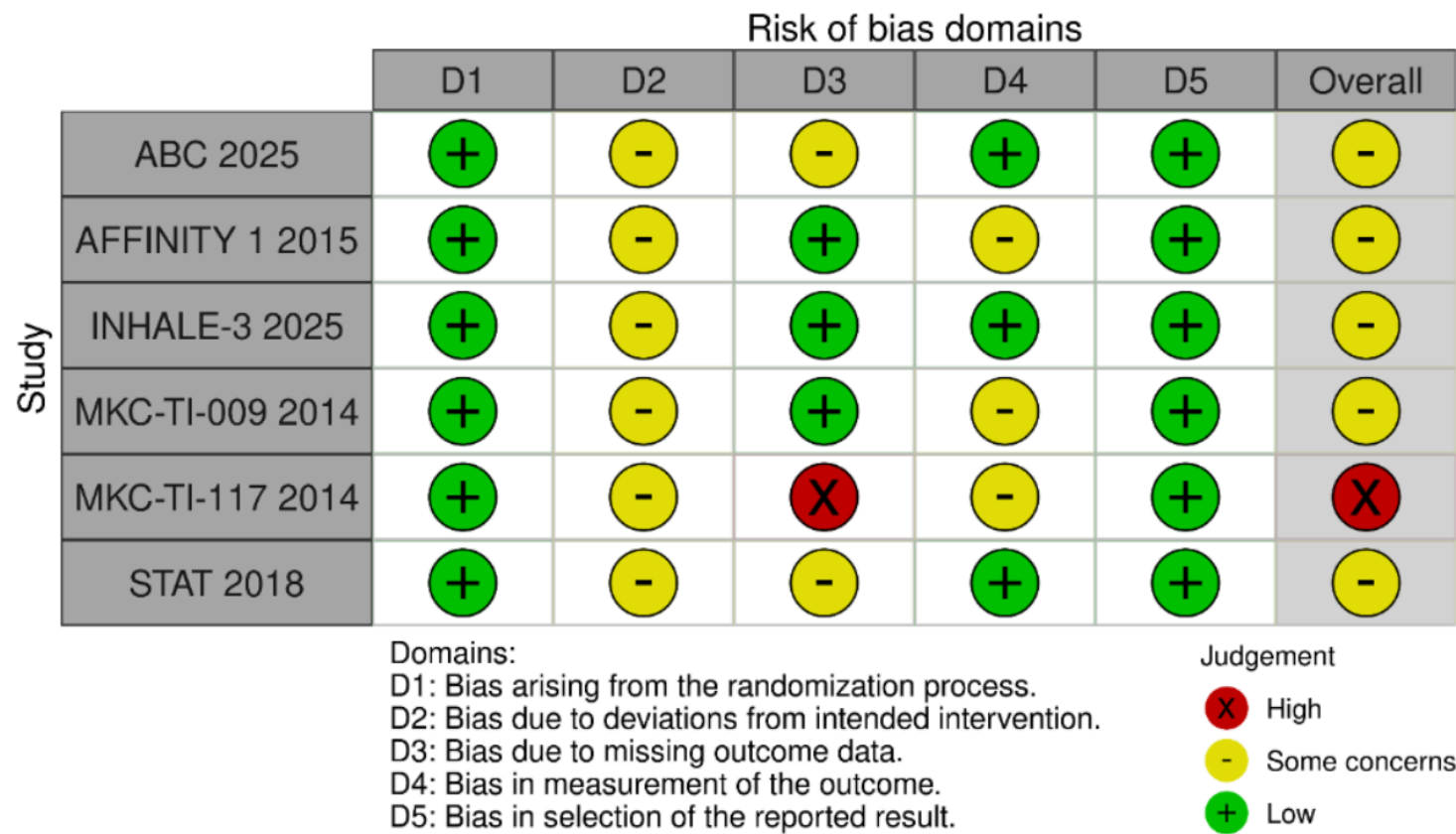


Figure 2

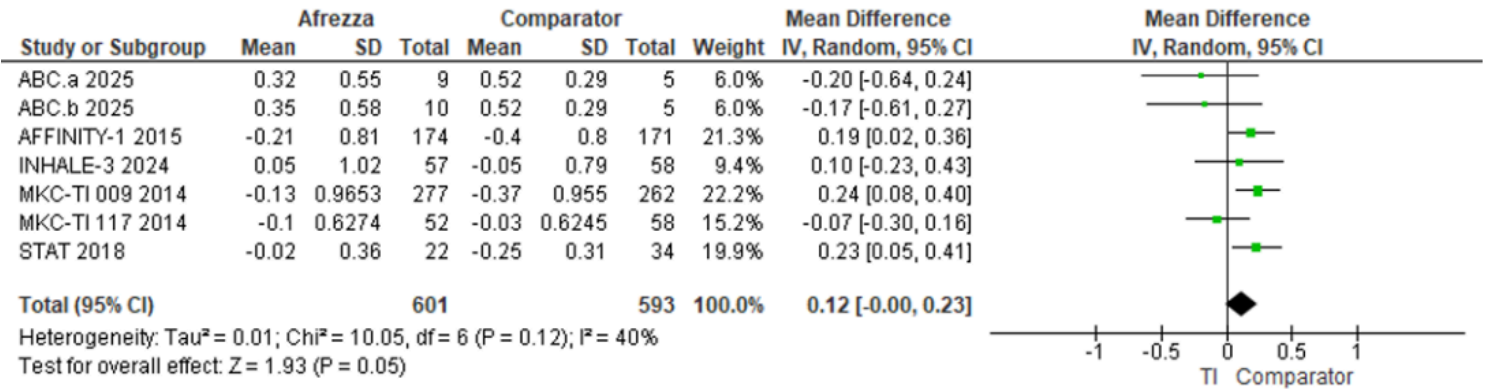


Figure 3

Forest plot of the primary outcome: HbA1c change from baseline (%). Random-effects model (inverse-variance). Positive MD favours comparator.

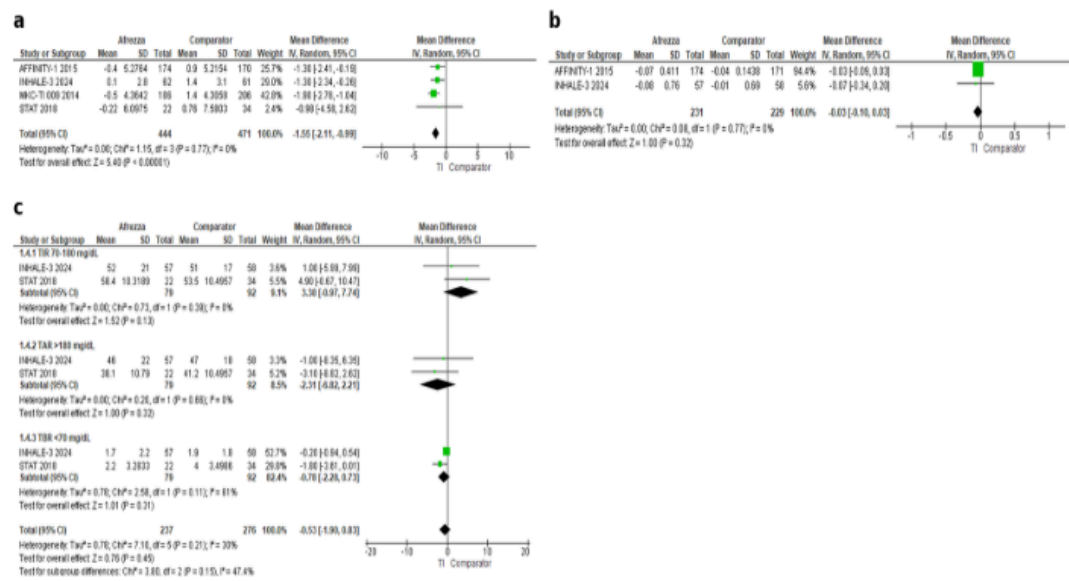


Figure 4

Forest plots of secondary efficacy outcomes. (a) Body weight change (kg); (b) FEV₁ change (L); (c) CGM outcomes – TIR 70–180 mg/dL, TAR >180 mg/dL, TBR <70 mg/dL. Random-effects model. Negative weight MD favours TI.

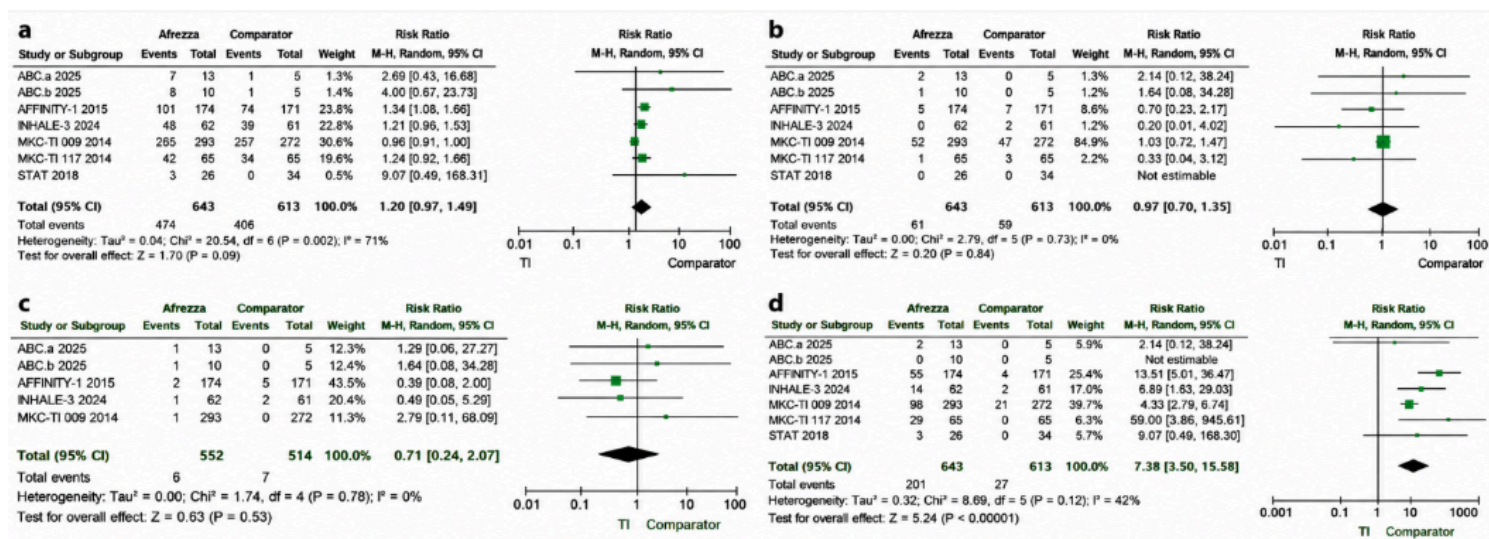


Figure 5

Forest plots of safety outcomes. (a) All-cause adverse events; (b) serious adverse events; (c) vomiting; (d) cough. Risk ratio, Mantel-Haenszel random-effects model.

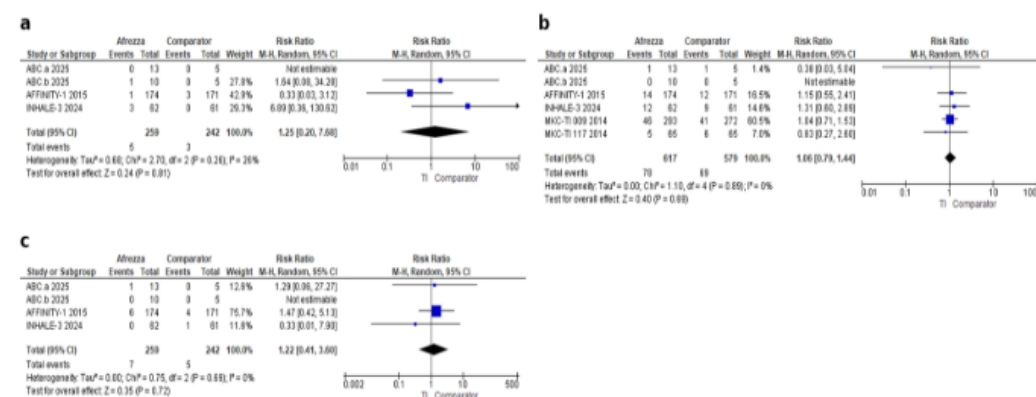


Figure 6

Forest plots of infection-related adverse events. (a) Urinary tract infection; (b) upper respiratory tract infection; (c) bronchitis. Risk ratio, Mantel-Haenszel random-effects model.

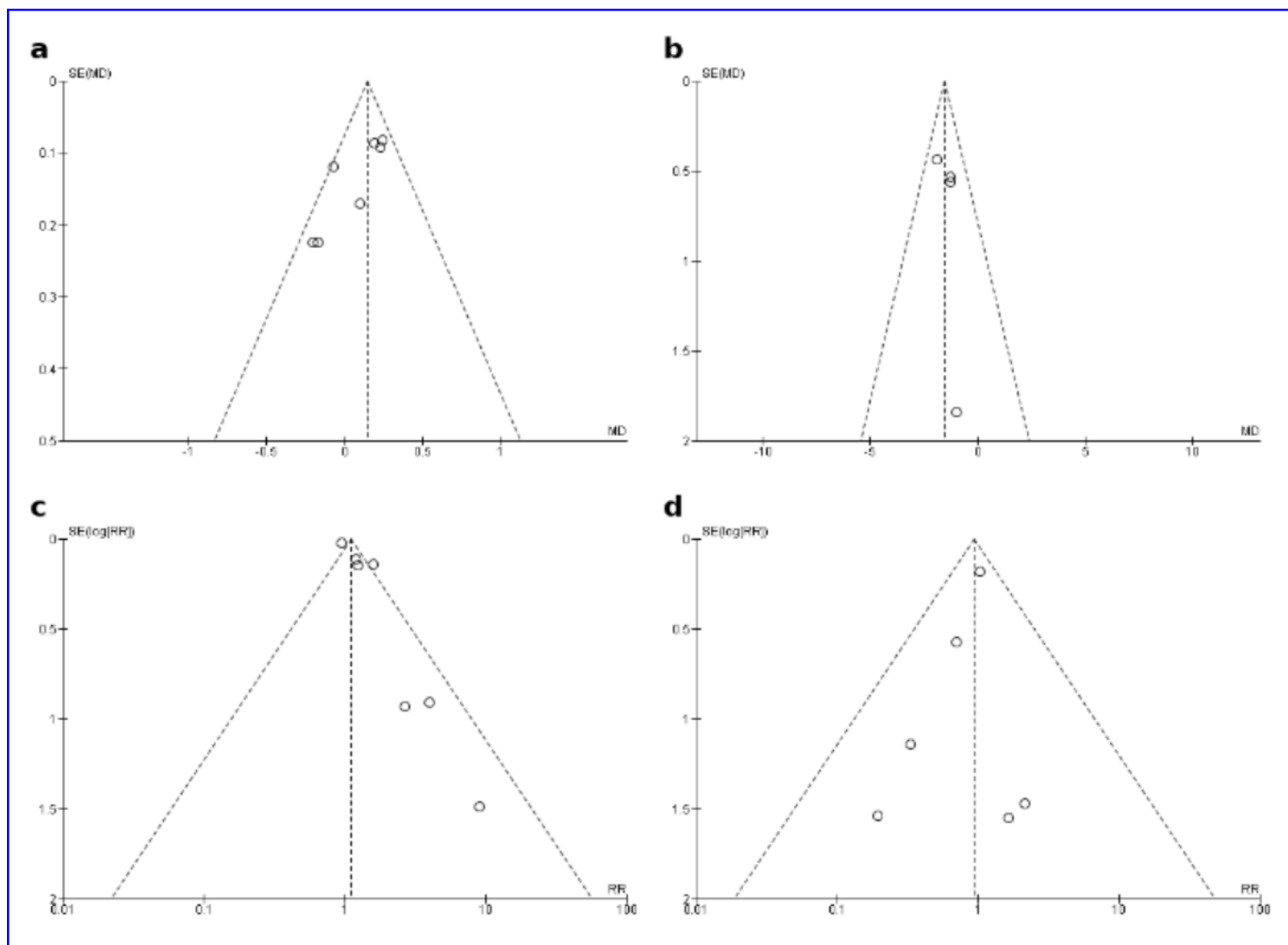


Figure 7

Funnel plots assessing potential publication bias/small-study effects for (a) HbA1c change, (b) body weight change, (c) all-cause adverse events, (d) serious adverse events.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementarytables.docx](#)