Efficacy and safety of the SGLT2 inhibitor empagliflozin versus placebo and the DPP-4 inhibitor linagliptin versus placebo in young people with type 2 diabetes (DINAMO): a multicentre, randomised, double-blind, parallel group, phase 3 trial

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Summary

Background The incidence of type 2 diabetes in young people is increasing, but treatments remain limited. We aimed to assess the efficacy and safety of an empagliflozin dosing regimen versus placebo and linagliptin versus placebo on glycaemic control in young people with type 2 diabetes.

Methods In this double-blind, placebo-controlled trial done in 108 centres in 15 countries, participants with type 2 diabetes (aged 10–17 years; HbA_{1c} 6·5–10·5% [48–91 mmol/mol]) who had been previously treated with metformin or insulin were randomly assigned (1:1:1) to oral empagliflozin 10 mg, oral linagliptin 5 mg, or placebo. Participants in the empagliflozin group who did not have HbA_{1c} below 7·0% (<53 mmol/mol) by week 12 underwent a second double-blinded randomisation (1:1) at week 14, either remaining on 10 mg or increasing to 25 mg. Participants in the placebo group were randomly reassigned (1:1:1) in a double-blinded manner at week 26 to linagliptin 5 mg or one of the empagliflozin doses (10 mg or 25 mg). Investigators were masked throughout the trial and received assignments of blinded medication kits through interactive response technology for all participants at the initial randomisation and for the re-randomisations at weeks 14 and 26. The primary outcome was change from baseline in HbA_{1c} at 26 weeks. For empagliflozin, results were based on a pooled analysis for all participants on empagliflozin. Safety was assessed until week 52. This trial is registered with ClinicalTrials.gov, NCT03429543.

Findings Between April 26, 2018, and May 26, 2022, of 262 screened participants, 158 (60%) were randomly assigned to treatment (53 [34%] to placebo, 52 [33%] to empagliflozin 10 mg, and 53 [34%] to linagliptin). For the primary outcome, the adjusted mean HbA_{1c} change from baseline at week 26 was –0·84% [–9·2 mmol/mol] in the empagliflozin pooled group versus placebo (95% CI –1·50 to –0·19 [–16·4 to –2·1]; p=0·012); the corresponding change from baseline for linagliptin versus placebo was –0·34% [–3·8 mmol/mol; 95% CI –0·99 to 0·30 [–10·8 to 3·3]; p=0·29). Adverse events occurred in 34 (64%) participants in the placebo group, 40 (77%) in the empagliflozin pooled group, and 37 (71%) in the linagliptin group, up to week 26. Of these, severe adverse events were reported in two (4%) participants in the placebo group, one (2%) in the empagliflozin pooled group, and one (2%) in the linagliptin group. Hypoglycaemia was the most frequently reported adverse event with higher rates for those on active drug treatment compared with placebo. No severe hypoglycaemia cases were reported.

Interpretation Empagliflozin provided clinically relevant placebo-corrected reductions in HbA_{1c}, whereas linagliptin did not, and might offer a new treatment option for young people with type 2 diabetes.

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See Online for appendix

Introduction

There has been a global upsurge in childhood overweight and obesity,[1,2] leading to an increased occurrence of type 2 diabetes in children and adolescents.[3–5] Further, youth-onset type 2 diabetes carries extraordinary risk of complications during early adulthood,[6,7] placing a substantial burden on the individual, their family, and society.[1–3]

In youth-onset type 2 diabetes, pathological processes such as early development of insulin resistance and more rapid deterioration in β-cell function than in individuals diagnosed in adulthood lead to worse glycaemic control and an increased risk of premature diabetes-related complications.[4,6,8]

Over the past few decades, many new therapeutic agents, across different drug classes, have been approved for use in adults with type 2 diabetes.[9] By contrast, there is a paucity of treatments for type 2 diabetes in young people. Until 2019, metformin and insulin were the only approved

Research in context

Evidence before this study

Over the past few decades, there has been a substantial increase in the occurrence of type 2 diabetes in young people, probably due to the epidemic of childhood overweight and obesity. Until the past few years, there were few treatment options for the management of these children and adolescents because only oral metformin and injectable insulin had received regulatory approval for use in people with type 2 diabetes younger than 18 years. In 2019, the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved liraglutide as the first daily injectable GLP-1 receptor agonist for use in children aged 10 years and older with type 2 diabetes. The weekly injectable GLP-1 receptor agonists exenatide and dulaglutide have subsequently been studied in placebo-controlled clinical trials in children and adolescents with type 2 diabetes, leading to FDA regulatory approval of both long-acting agents and EMA regulatory approval of exenatide as well as an expectation of approval of dulaglutide. Nonetheless, despite the availability of multiple oral agents targeting various pathways for the treatment of type 2 diabetes in adults, only one agent, the SGLT2 inhibitor dapagliflozin, has received regulatory approval from the EMA for the treatment of type 2 diabetes from age 10 years, on the basis of a placebo-controlled trial of 72 people aged 10–24 years, of whom only 53 [74%] were aged 10–17 years. We searched PubMed from inception to Oct 25, 2022, with the terms: "type 2 diabetes", "paediatrics", "therapies", and "clinical trials" to identify studies of pharmacological treatment of type 2 diabetes in children and adolescents. We also assessed screening recommendations for type 2 diabetes in young people and assessed relevant studies in paediatric type 2 diabetes from the TODAY study group and the Rise consortium. Given the challenges of maintaining durable glycaemic control and the aggressive development of diabetes complications in youth-onset type 2 diabetes, the diabetes community recognised the need to study the efficacy and safety of additional therapeutic agents in children and adolescents with type 2 diabetes.

Added value of the study

To the best of our knowledge, the DINAMO study is the first successfully completed phase 3 clinical trial using a single placebo group in separate comparisons with two different classes of oral agents for the treatment of type 2 diabetes in young people aged 10–17 years. These two drug classes include the DPP-4 inhibitor linagliptin and the SGLT2 inhibitor empagliflozin, both well studied agents with shown efficacy and safety in adults with type 2 diabetes. The DINAMO study reports that oral treatment with empagliflozin provided clinically meaningful and statistically significant reductions in HbA_{1c} in young people aged 10–17 years with type 2 diabetes, whereas linagliptin did not provide statistically significant improvements in glycaemic control. Furthermore, empagliflozin's safety profile was similar to that seen in studies of adults with type 2 diabetes.

Implications of all the available evidence

The results of this trial support the management of type 2 diabetes in young people with the SGLT2 inhibitor empagliflozin for safe and effective lowering of HbA_{1c} early in the course of the disease. Given the recognised challenges of treating type 2 diabetes in young people, and the likely need for combination pharmacotherapy to achieve target glycaemic control aimed at preventing complications and preserving health, oral administration of empagliflozin along with injectable insulin or GLP-1 analogues might offer a promising approach to care.

and established treatments in children and adolescents.[10,11] In the USA, agents from one new drug class, GLP-1 receptor agonists, are now gaining approvals for use in young people with type 2 diabetes, following placebo-controlled studies showing notable reductions in HbA_{1c} in participants treated with either once-daily liraglutide 1·80 mg, once-weekly exenatide 2·00 mg, or once-weekly dulaglutide 0·75 mg or 1·50 mg.[12–14] Metformin, the longest established treatment for type 2 diabetes in young people other than insulin,[15] is the only globally used oral agent, as the approved GLP-1 receptor agonists and insulin both require injection, which might affect treatment adherence. Thus, there remains an unmet need for additional oral therapies for young people with type 2 diabetes, especially for agents targeting diverse mechanisms of action, to effectively address this condition. Two such agents include DPP-4 inhibitors and SGLT2 inhibitors.

Efficacy and safety of the DPP-4 inhibitor sitagliptin as initial[16] or add-on therapy[17] in young people with type 2 diabetes did not yield durable glycaemic control, despite initial reductions in HbA_{1c}.[16,17] A study investigated the efficacy and safety of the SGLT2 inhibitor dapagliflozin against placebo in young people aged 10–24 years with type 2 diabetes and found a significant difference in HbA_{1c} at 24 weeks favouring dapagliflozin, which was evident in the per protocol but not the intention-to-treat analysis.[18]

The SGLT2 inhibitor empagliflozin and DPP-4 inhibitor linagliptin are both well-established treatments for adults with type 2 diabetes. Further, empagliflozin has shown improved cardiovascular and renal outcomes in adults with type 2 diabetes and established cardiovascular disease, in patients with heart failure, and in patients with chronic kidney disease.[19–23]

Empagliflozin and linagliptin have both been investigated in dose-finding paediatric studies,[24,25] supporting investigation of their efficacy and safety in placebo-controlled trials in young people with type 2 diabetes.[24,25] However, given the recognised challenges with recruitment in such paediatric studies,[26] as well as the dearth of evidence regarding the benefits of screening and early treatment for type 2 diabetes in young people,[27–29]

new paediatric studies, including those with novel approaches to study design, are needed.

Most individual studies to date report findings in fewer than 200 participants, highlighting recruitment challenges.[12–16,18] The DIabetes study of liNAgliptin and eMpagliflozin in children and adOlescents (DINAMO) trial was designed to overcome such recruitment difficulties and, as such, included a novel design. The main objective of DINAMO was to assess the efficacy and safety of a daily dosing regimen with empagliflozin and a single dose of linagliptin, both compared with a shared placebo group, in children and adolescents with type 2 diabetes. Given the proven efficacy of SGLT2 inhibitors and DDP-4 inhibitors in adults, we hypothesised that these agents compared with placebo would show improved glycaemic control in children and adolescents (aged 10–17 years) with type 2 diabetes receiving background treatment with metformin or insulin along with standard lifestyle efforts directed at diet and exercise management.

Methods

Study design and participants

DINAMO was a global, multicentre, randomised, double-blind, placebo-controlled, parallel group trial in 108 centres and 13 countries.

Eligible participants were aged 10–17 years at the time of randomisation and had type 2 diabetes for at least 8 weeks before screening, with HbA_{1c} 6·5% to 10·5% or lower (48–91 mmol/mol) at screening and a BMI of at least the 85th percentile at entry into run-in. Inclusion criteria included a negative test for both insulinoma-associated antigen-2 and glutamic acid decarboxylase autoantibodies as measured by the central laboratory at first visit. Exclusion criteria included any antidiabetic medication (except metformin or insulin background therapy, which were continued during the study) within 8 weeks before the first visit. Notably, because of the dynamic nature of HbA_{1c} in young people with type 2 diabetes,[30] potential participants with modifiable exclusion criteria on initial screening (eg, HbA_{1c} <6·5% [<48 mmol/mol]) could rescreen up to five times (appendix pp 8–9).

There were eight versions of the clinical trial protocol, of which two versions (version 1, dated May 29, 2017, and version 6, dated July 14, 2021) were only submitted to the US Food and Drug Administration and never implemented because of the requested changes. Six global amendments were issued (dated Oct 3, 2019; Sept 28, 2020; Dec 14 2020; July 14, 2021; Sept 28, 2021; and May 23, 2022), all of which required independent ethics committees or institutional review boards' approval before implementation. Main changes were related to requests from regulators to revise the statistical analysis plan, modifications because of the COVID-19 pandemic, and the addition of an ancillary study (DINAMO MONO, NCT03429543, currently ongoing) that is not the subject of this manuscript (appendix p 4). The final version of the protocol (May 23, 2022) is included in the appendix (pp 50–346). A steering committee of academic paediatric endocrinologists and diabetologists designed the study and provided trial oversight (appendix p 5).

The trial was done in accordance with principles of the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines and was approved by local authorities. Independent ethics committees or institutional review boards approved the protocol at participating centres. Participants provided written informed assent (children and adolescents) and consent (parents or guardians) before study entry.

Randomisation and masking

Participants were randomly assigned (1:1:1) to receive oral doses of linagliptin 5 mg, empagliflozin 10 mg, or placebo once daily for 26 weeks as double-blind, double-dummy medication kits, followed by a double-blind active treatment safety extension period to 52 weeks (appendix p 17). Randomisation was stratified by age (<15 years or ≥15 to <18 years) with a limit to ensure at least 30% and no more than 70% of the randomly assigned participants were younger than 15 years. A limit for sex ensured that 30–70% of randomly assigned participants were female.

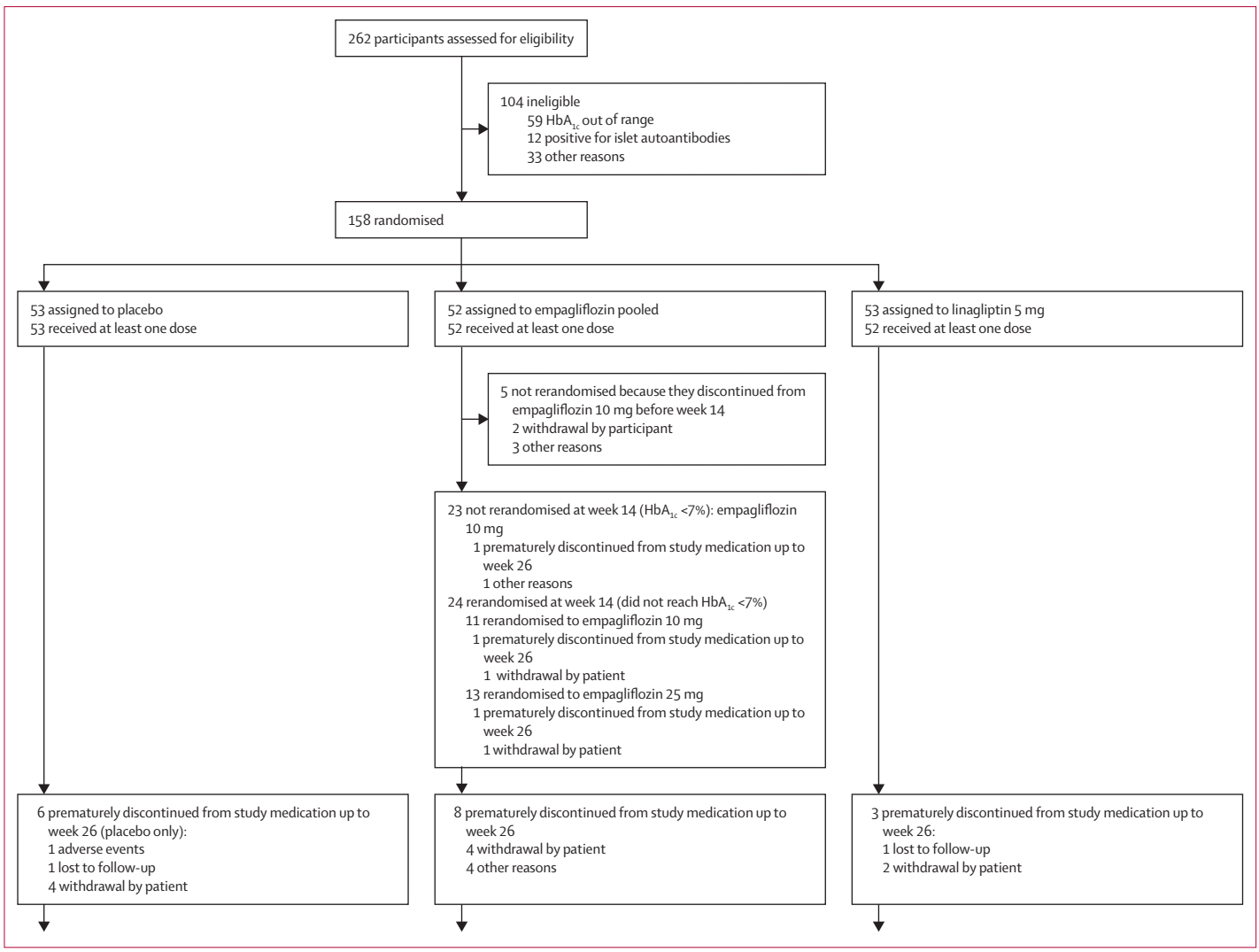
Participants in the empagliflozin group who did not have HbA_{1c} less than 7·0% (<53 mmol/mol) by week 12 underwent a second double-blinded randomisation (1:1) at week 14, either remaining on the empagliflozin 10 mg dose or increasing to the 25 mg dose. Participants on placebo were re-randomised (1:1:1) in a double-blinded manner at week 26 to linagliptin 5 mg or one of the empagliflozin doses (10 mg or 25 mg). Investigators were masked throughout the trial and received assignments of blinded medication kits through interactive response technology for all participants at the initial randomisation and for the re-randomisations at weeks 14 and 26.

The randomisation scheme was generated by an independent group of the sponsor who kept the randomisation confidential up to the database lock of DINAMO. Medication kits were provided by the sponsor to the interactive response technology provider, who also managed the re-supply to the investigational sites.

Procedures

Because of the COVID-19 pandemic, screening was suspended between March and July, 2020, extending the enrolment timeline from January to May, 2021 (appendix p 18). Participants who were already on treatment or in follow-up completed primary and secondary endpoint visits onsite if possible. For all other visits, alternative approaches to study performance, such as telephone visits, local laboratory testing, and delivery of study medication via courier, were used if onsite visits were not possible (appendix p 14).

A separate ongoing ancillary and exploratory study, DINAMO MONO (operationally under the same protocol



(Figure 1 continues on next page)

NCT03429543) is investigating the same treatment regimens but in young people who are treatment naive or not on active treatment after metformin withdrawal. The DINAMO MONO ancillary study was added during the conduct of the DINAMO study on the basis of a request from regulators and is not the subject of this report.

Insulin was the rescue medication, with protocol guidance for initiation. Insulin or increased dose of insulin could be initiated from the first day of treatment until week 52 in case of acute metabolic decompensation or repeatedly increased blood ketone concentrations. If new insulin treatment or insulin treatment at increased dose (ie, a dose increase of basal insulin of more than 0·1 IU/kg above the baseline prescribed dose) continued for more than 21 consecutive days, including the weaning phase, then the participant was classified as requiring rescue therapy (further details are in the protocol; appendix pp 50–346).

Outcomes

The primary efficacy endpoint was the change in HbA_{1c} from baseline to 26 weeks. For empagliflozin, results were based on a pooled analysis for all participants on empagliflozin. Secondary endpoints were the changes from baseline to 26 weeks in fasting plasma glucose (FPG), bodyweight, and systolic and diastolic blood pressure, and proportions of patients with HbA1c below 6·5% and below 7·0% at week 26. Safety was assessed on the basis of adverse events that occurred throughout the 52-week treatment period and were coded using the Medical Dictionary for Regulatory Activities (MedDRA; version 25.0).

Statistical analysis

The primary hypotheses were the two pairwise comparisons of the treatment effect of empagliflozin pooled doses versus placebo and linagliptin versus placebo,

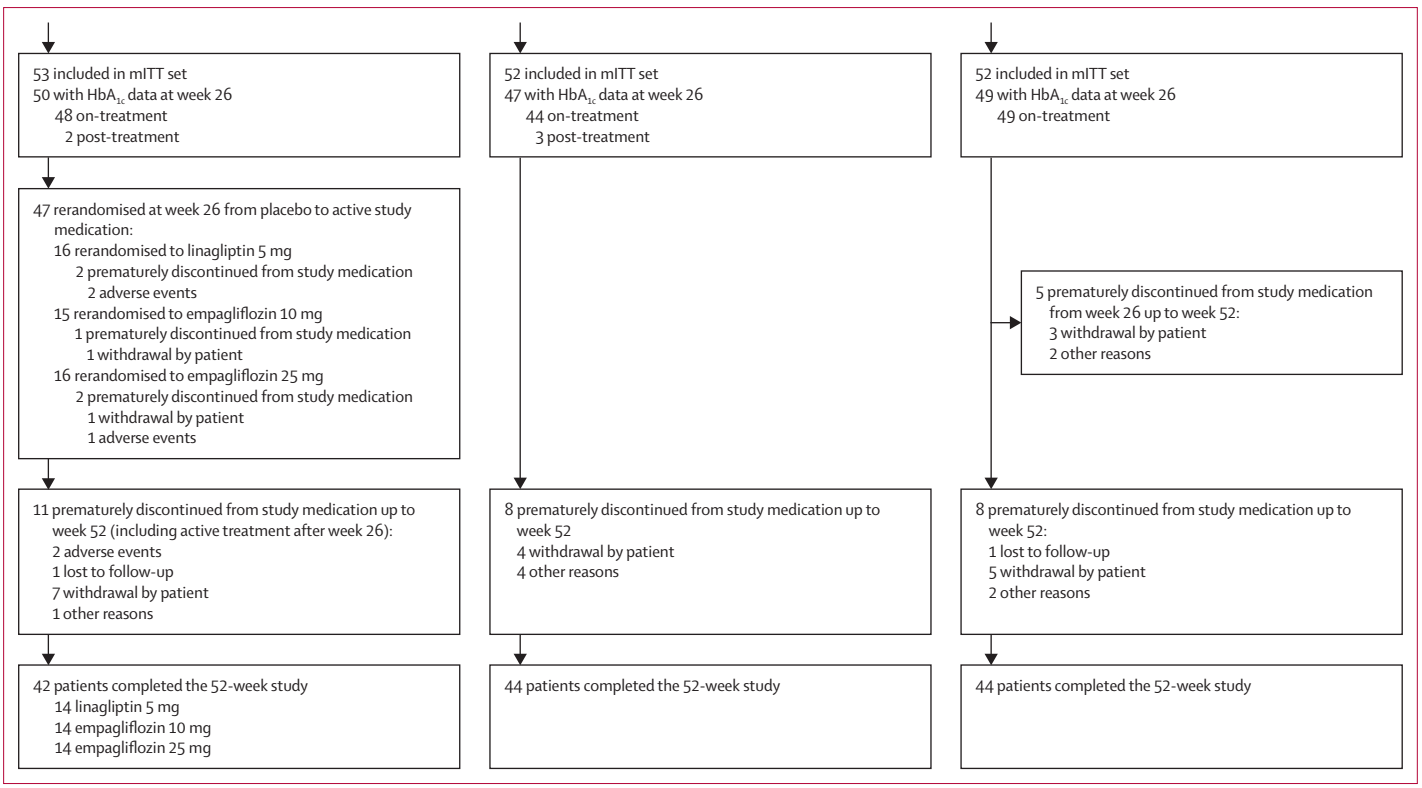


Figure 1: **Trial profile**
Among those discontinuing treatment before week 26, on-treatment HbA_{1c} values were available for one participant. Reasons for discontinuation of empagliflozin treatment described as other reasons were (1) insulinoma-associated antigen 2 auto-antibody result was received more than 2 weeks after randomisation, and was positive; therefore, the participant was discontinued per sponsor; (2) principal investigator decision to discontinue because of non-compliance; (3) participant decided to stop taking study medication and, following the study protocol, participant was willing to attend visit 8 only; (4) lost to follow-up. mITT=modified intention to treat.

followed by the secondary hypotheses comparing the effect of each empagliflozin dosing regimen with placebo. In the primary hypotheses, the Hochberg procedure accounted for multiple testing of two active treatments, empagliflozin and linagliptin, each versus placebo. Statistical significance could be concluded for one treatment if the p value was below 0·025, or for both treatments if both p values were below 0·05. If both primary null hypotheses were rejected, the secondary hypotheses comparing two empagliflozin dosing regimens versus placebo could be tested in a hierarchical manner (appendix p 19): (1) a regimen with a dose increase to 25 mg for participants not reaching HbA_{1c} less than 7·0% (53 mmol/mol) at week 12, and (2) a regimen of staying on empagliflozin 10 mg throughout the trial.

The modified intention-to-treat set was the basis for primary analyses and included all randomly assigned participants who were treated with at least one dose of study medication and who had a baseline HbA_{1c} measurement. All available on-treatment and off-treatment HbA_{1c} data at week 26 were included in the primary analysis and missing data were replaced by multiple imputation, imputing missing off-treatment values in active treatment groups on the basis of the primary endpoint distribution in the placebo group. This conservative wash-out approach in the active treatment groups considered missing off-treatment data being not at random. Missing on-treatment data or data missing in the placebo group were considered missing at random and multiply imputed following the distribution in the respective treatment group. 500 complete trial imputations were generated, assessed with an ANCOVA model, and the model estimates were combined using Rubin's rules to calculate the p values for the hypothesis tests.

The primary endpoint was tested by an ANCOVA model with baseline HbA_{1c} as a continuous covariate and with categorical covariates for treatment and age groups (<15 years or ≥15 to <18 years). A weighted ANCOVA combined the empagliflozin subgroups either having HbA_{1c} less than 7·0% (53 mmol/mol) at week 12 (weight=1) or randomly assigned to the empagliflozin regimen of interest at week 14 (weight=2) to test the individual hypotheses in the secondary group of hypotheses. Participants who were not randomly assigned to the empagliflozin regimen of interest at week 14 were assigned a weight of 0. This inverse probability weighting[31] accounted for the treatment re-assignment of 50% of the randomly reassigned empagliflozin participants at week 14 (appendix pp 20–21). For example, to compare the dosing regimen of empagliflozin non-responders who were randomly reassigned to the 25-mg dose with the placebo

	Placebo (n=53)	Empagliflozin pooled (n=52)	Linagliptin 5 mg (n=52)
Sex			
Male	19 (36%)	19 (37%)	22 (42%)
Female	34 (64%)	33 (63%)	30 (58%)
Region			
North America	34 (64%)	36 (69%)	37 (71%)
South America	11 (21%)	9 (17%)	7 (13%)
Europe	7 (13%)	6 (12%)	5 (10%)
Asia	1 (2%)	1 (2%)	3 (6%)
Race			
American Indian or Alaska Native	1 (2%)	4 (8%)	3 (6%)
Asian	3 (6%)	2 (4%)	4 (8%)
Black or African American	17 (32%)	19 (37%)	13 (25%)
Native Hawaiian or Other Pacific Islander	1 (2%)	0	2 (4%)
White	29 (55%)	23 (44%)	26 (50%)
All other	2 (4%)	4 (8%)	4 (8%)
Ethnicity			
Non-Hispanic or non-Latino	32 (60%)	35 (67%)	30 (58%)
Hispanic or Latino	21 (40%)	17 (33%)	22 (42%)
Age, years			
Mean (SD)	14·6 (1·8)	14·4 (1·9)	14·6 (1·9)
Median (IQR)	14·0 (14·0–16·0)	15·0 (13·0–16·0)	14·5 (13·0–16·0)
Time since diagnosis of diabetes			
<1 year	18 (34%)	17 (33%)	16 (31%)
1–3 years	24 (45%)	21 (40%)	21 (40%)
>3 years	11 (21%)	14 (27%)	15 (29%)
BMI, kg/m²			
Mean (SD)	36·07 (10·07)	35·54 (7·17)	36·50 (7·55)
Median (IQR)	34·62 (29·81–41·31)	34·48 (30·41–40·95)	34·83 (31·63–40·77)
BMI Z score			
>2 to ≤3 (class 1 obesity)	17 (32%)	21 (40%)	20 (38%)
>3 (class 2 to 3 obesity)	27 (51%)	26 (50%)	28 (54%)
Bodyweight, kg			
Mean (SD)	98·38 (29·55)	98·66 (24·35)	102·76 (26·40)
Median (IQR)	94·00 (78·50–116·60)	93·95 (85·10–110·65)	97·55 (87·95–115·20)
Blood pressure, mean (SD)*			
Systolic blood pressure	118·13 (11·85)	120·23 (9·97)	122·31 (10·97)
Diastolic blood pressure	72·22 (9·27)	72·03 (8·38)	73·78 (8·08)
Fasting C-peptide, nmol/L			
Mean (SD)	0·8967 (0·4311)	0·9598 (0·5302)	1·1245 (0·6269)
Median (IQR)	0·8432 (0·5710–1·2112)	0·8449 (0·7096–1·1914)	0·9934 (0·6733–1·4257)
eGFR, mL/min/1·73 m²			
Mean (SD)	124·28 (22·96)	130·09 (26·78)	135·11 (36·42)
Median (IQR)	123·39 (106·04–141·14)	124·62 (107·87–146·42)	122·59 (110·75–148·23)
Tanner staging scoring score			
1	0	0	0
2–4	21 (40%)	24 (46%)	19 (37%)
5	32 (60%)	28 (54%)	33 (63%)
HbA_{1c}, %			
Mean (SD)	8·05 (1·23)	8·00 (1·29)	8·05 (1·11)
<8·5%	37 (70%)	36 (69%)	31 (60%)
≥8·5%	16 (30%)	16 (31%)	21 (40%)

(Table 1 continues on next page)

	Placebo (n=53)	Empagliflozin pooled (n=52)	Linagliptin 5 mg (n=52)
(Continued from previous page)			
Fasting plasma glucose, mg/dL			
Mean (SD)	158·6 (53·8)	154·4 (57·8)	162·8 (56·0)
Median (IQR)	151·6 (122·5–174·0)	143·0 (112·1–191·1)	157·1 (114·1–193·0)

Data are n (%), unless otherwise indicated. To convert the values for HbA_{1c} percentage to mmol/mol, subtract 2·15 and multiply the result by 10·929. To convert the values for plasma glucose to mmol/L, multiply by 0·05551. eGFR=estimated glomerular filtration rate. *Data quoted from descriptive analyses over time by treatment, which did not include study totals.

Table 1: **Baseline characteristics of the participants in the modified intention-to-treat set**

group, those in the empagliflozin non-responder group who were randomly reassigned to 10 mg were excluded (weight=0), and the contribution of those who were randomly reassigned to 25 mg was doubled (weight=2), along with a weighting of 1 for the placebo group and for the empagliflozin responders who were not randomly reassigned at 14 weeks.

Mixed models for repeated measurements (MMRMs) provided sensitivity analyses of the primary endpoint by either including all available HbA_{1c} values regardless of start of rescue medication and premature treatment discontinuation or by including only on-treatment HbA_{1c} values before the start of rescue medication and premature drug discontinuation. A multiple-imputation-based per protocol analysis explored the effect of important protocol deviations on the primary results.

Pre-planned subgroup analyses of the primary endpoint explored the consistency of the treatment effects across subgroups, using the imputation strategy of the primary analysis. Sensitivity and subgroup analyses are reported in the appendix (pp 23–25). Secondary and further efficacy endpoints and safety endpoints were only analysed descriptively.

The sample size of 50 randomly assigned participants per group resulted from a balance of clinical, regulatory, feasibility, and statistical considerations. On the basis of previous studies of empagliflozin or linagliptin in adults with type 2 diabetes receiving background medication of metformin or insulin, we estimated the mean differences in the HbA_{1c} change from baseline to week 26 in the treatment groups compared with those in the placebo group. Dropouts from active treatment groups in the adult studies were taken into account and the mean differences were corrected by assigning these dropouts with the same mean HbA_{1c} change as was observed in the placebo group. The dropout-corrected target mean difference to placebo was estimated as –0·55% for the HbA_{1c} change from baseline to week 26, with an SD of 0·9% and a resulting standardised effect size of –0·61%. Because the target treatment difference was already corrected for dropouts, no allowance for dropout was added to the DINAMO sample size. With 50 participants per treatment group, a treatment difference of –0·55% could be detected with 85% power at a two-sided α level of 5%.

	Participants analysed, n	Baseline, mean (SD)	Change from baseline, adjusted mean (95% CI)	Comparison *vs* placebo, adjusted mean (95% CI)
Primary hypotheses (empagliflozin pooled *vs* placebo and linagliptin *vs* placebo)				
Placebo	53	8·05 (1·23)	0·68 (0·23 to 1·13)	..
Empagliflozin pooled	52	8·00 (1·29)	–0·17 (–0·64 to 0·31)	–0·84 (–1·50 to –0·19)*
Linagliptin 5 mg	52	8·05 (1·11)	0·33 (–0·13 to 0·79)	–0·34 (–0·99 to 0·30)†
Secondary hypothesis (empagliflozin responders on 10 mg plus empagliflozin non-responders randomly reassigned to empagliflozin 25 mg *vs* placebo)				
Placebo	53	8·05 (1·23)	0·66 (0·12 to 1·21)	..
Empagliflozin 10/25 mg	41	7·80 (1·26)	0·14 (–0·42 to 0·71)	–0·52 (–1·31 to 0·27)‡
Secondary hypothesis (empagliflozin responders on 10 mg plus empagliflozin non-responders randomly reassigned to empagliflozin 10 mg *vs* placebo)				
Placebo	53	8·05 (1·23)	0·68 (0·19 to 1·17)	..
Empagliflozin 10/10 mg	39	7·92 (1·36)	–0·49 (–1·03 to 0·04)	–1·18 (–1·90 to –0·45)§

Primary endpoint was HbA_{1c} percentage change from baseline at week 26 in the modified intention-to-treat set. Analyses included all available HbA_{1c} data on treatment, after start of rescue medication, and after premature treatment discontinuation. Missing data were multiply imputed with wash-out approach, using ANCOVA with baseline HbA_{1c} as a linear covariate, treatment and age as categorical covariates, and applying Rubin's rules to combine multiple imputations. Mean change from baseline was adjusted for baseline HbA_{1c} and age category for all hypotheses and additionally weighted for secondary hypotheses. Baseline means were not weighted. To convert the values for HbA1c percentage to mmol/mol, subtract 2·15 and multiply the result by 10·929. *p=0·012. †p=0·29. ‡p=0·19. §p=0·0015.

Table 2: **Primary outcomes**

Alternative scenarios were considered in the protocol (appendix p 19), and the effect on power was explored for higher and lower SDs and for a two-sided α level of 2·5% to account for the stricter of the multiplicity-adjusted significance thresholds according to the Hochberg procedure. An independent data monitoring committee (DMC) reviewed unblinded safety data during the trial (appendix p 5). During the conduct of the study, the DMC met ten times (at least every 6 months as defined in the charter) to assess the progress of the clinical trial, including an unblinded safety review, and to recommend to the sponsor whether to continue, modify, or stop the trial. No formal analysis of efficacy data was done by the DMC.

All analyses were pre-planned, apart from the analysis of adverse events in the placebo-treated participants following re-randomisation at week 26, which was post hoc. We used SAS (version 9.4) for statistical analysis. This study is registered with ClinicalTrials.gov, NCT03429543.

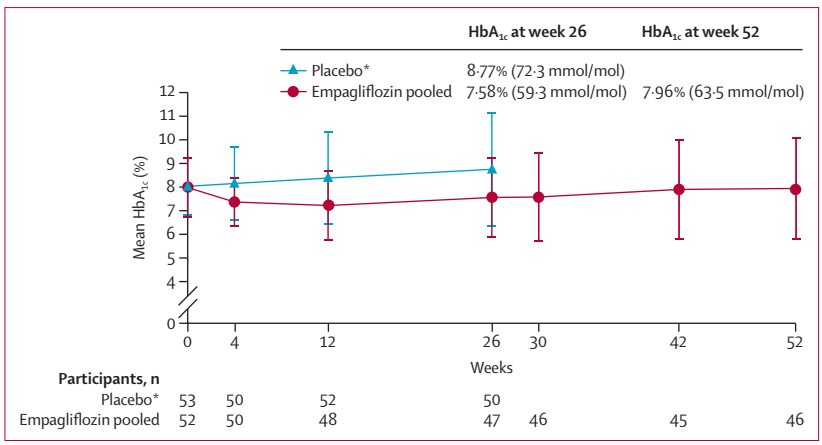


Figure 2: **Change in HbA_{1c} from baseline to week 26**
Descriptive data reflecting mean HbA_{1c} over time from baseline to week 52 for empagliflozin versus placebo in the modified intention-to-treat population. Error bars denote SDs. *Placebo treatment stopped at week 26.

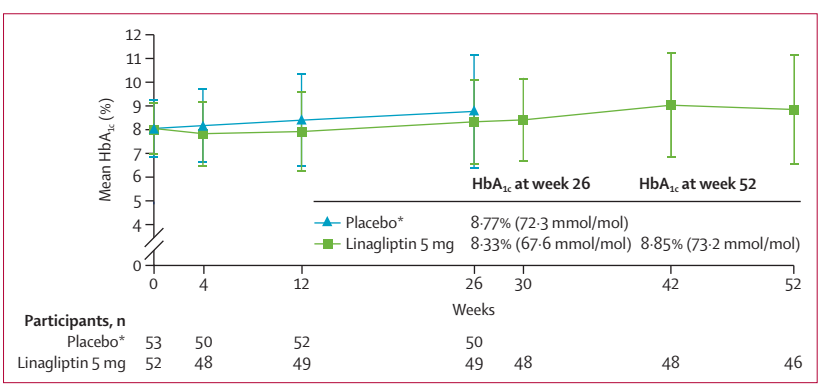


Figure 3: **Change in HbA_{1c} from baseline to week 52**
Descriptive data reflecting mean HbA_{1c} over time from baseline to week 52 for linagliptin versus placebo in the modified intention-to-treat population. Error bars denote SDs. *Placebo treatment stopped at week 26.

Results

Between April 26, 2018, and May 26, 2022, we screened 262 children and adolescents aged 10–17 years. 158 (60%) were randomly assigned to a treatment group (53 to placebo, 52 to empagliflozin 10 mg, and 53 to linagliptin) and 157 (60%) received treatment (figure 1). 24 participants were rescreened, 11 of whom were randomly assigned (7% of all randomised participants) after the initial modifiable screen failure reason resolved. Among the 11 participants rescreened and randomly assigned, seven (64%) initially were excluded because of HbA_{1c} being out of range. Baseline characteristics were balanced among treatment group (table 1) and also balanced across empagliflozin responders and non-responders, other than for glycaemic metrics, which were lowest in the empagliflozin 10 mg responder group (appendix p 34). 107 (68%) participants were from North America, with the remainder from South America (n=27 [17%]), Europe (n=18 [11%]), and Asia (n=5 [3%]). By week 26, 17 (10·8%) participants had discontinued study medication prematurely and by week 52, 27 (17·2%) had discontinued study medication prematurely. Upon enrolment, 143 (91%) were treated with metformin or metformin with insulin, five (3%) were treated with insulin only, and nine (6%) received no antidiabetic therapy other than diet and exercise because of metformin intolerance. The proportion of participants receiving these various background therapies was similar across groups (appendix p 37). Treatment adherence by pill count at week 26 was similar across groups, with adherence at 89% in placebo, 90% in empagliflozin pooled, and 92% in linagliptin groups (appendix p 22). At week 26, no on-treatment data were missing. HbA_{1c} data at week 26 were missing for 11 (65%) of 17 participants after treatment discontinuation (missing for 11 [7%] of treated participants): placebo (n=3), empagliflozin (n=5), and linagliptin (n=3). The main reason for missing data was complete withdrawal of the participant from the trial.

At 26 weeks, the mean change in HbA_{1c} was –0·17% (95% CI –0·64 to 0·31) for the empagliflozin pooled doses, 0·33% (95% CI –0·13 to 0·79) for linagliptin, and 0·68% (0·23 to 1·13) for the placebo groups (table 2). For the primary outcome, the adjusted mean change from baseline in HbA_{1c} at week 26 was –0·84% [–9·2 mmol/mol] in the empagliflozin group versus placebo (95% CI –1·50 to –0·19 [–16·4 to –2·1]; p=0·012); the corresponding change from baseline for linagliptin versus placebo was –0·34% [–3·8 mmol/mol] (–0·99 to 0·30 [–10·8 to 3·3]; p=0·29; table 2). In the empagliflozin group, HbA_{1c} decreased by week 4 and remained below the placebo group until week 26, followed by a gradual increase at week 52, albeit below the week-26 value in the placebo group (figure 2). In the linagliptin group, we found an initial decrease in HbA_{1c} at week 4, followed by an increase towards baseline values at week 26 (figure 3).

We did sensitivity analyses (including MMRM and a per protocol analysis) to assess the influence of premature treatment discontinuation, important protocol deviations, and the effect of missing data and its handling on the primary study results. These sensitivity analyses showed treatment differences versus placebo that were generally consistent with the primary analysis for the linagliptin group (appendix p 23). For empagliflozin, the sensitivity analyses showed slightly greater reductions in HbA_{1c} versus placebo (appendix p 23). The MMRM (observed case) on-treatment analysis, excluding HbA_{1c} values after treatment discontinuation and after rescue medication, resulted in adjusted mean changes of 0·62% (SE 0·22) for placebo and –0·37% (0·23) for the pooled empagliflozin group, with an adjusted mean difference versus placebo of –0·99%.

Additionally, subgroup analyses, including sex, age, race, time since diagnosis, and BMI, revealed treatment effects for empagliflozin and linagliptin consistent with the primary endpoint (appendix pp 24–25). For empagliflozin, we found numerically greater efficacy in participants with higher HbA_{1c} (>9·0%; adjusted mean –1·93 [95% CI

	Participants analysed, n	Baseline, mean (SD)	Change from baseline, adjusted mean (95% CI)	Comparison *vs* placebo, adjusted mean (95% CI)
Fasting plasma glucose, mg/dL				
Placebo	52	158·62 (53·80)	15·70 (−0·53 to 31·93)	..
Empagliflozin pooled	48	154·43 (57·78)	−19·48 (−36·39 to −2·57)	−35·18 (−58·61 to −11·74)
Linagliptin 5 mg	51	162·81 (56·01)	10·29 (−6·12 to 26·69)	−5·41 (−28·49 to 17·67)
Bodyweight, kg				
Placebo	52	98·87 (29·62)	−0·04 (−1·40 to 1·32)	..
Empagliflozin pooled	52	98·66 (24·35)	−0·79 (−2·17 to 0·59)	−0·75 (−2·68 to 1·19)
Linagliptin 5 mg	50	102·73 (26·81)	1·42 (0·04 to 2·81)	1·46 (−0·48 to 3·41)
Systolic blood pressure, mm Hg				
Placebo	52	118·34 (11·87)	1·30 (−1·01 to 3·61)	..
Empagliflozin pooled	52	120·23 (9·97)	−0·12 (−2·47 to 2·24	−1·42 (−4·72 to 1·88)
Linagliptin 5 mg	50	122·39 (11·13)	2·21 (−0·14 to 4·56)	0·91 (−2·40 to 4·22)
Diastolic blood pressure, mm Hg				
Placebo	52	72·60 (8·94)	0·76 (−1·01 to 2·53)	..
Empagliflozin pooled	52	72·03 (8·38)	0·78 (−1·04 to 2·60)	0·02 (−2·52 to 2·56)
Linagliptin 5 mg	50	74·01 (8·13)	2·26 (0·46 to 4·05)	1·50 (−1·03 to 4·02)

Analyses included all available data on treatment, after start of rescue medication, and after premature treatment discontinuation. Mean change from baseline was adjusted for baseline value and age category. Fasting plasma glucose was analysed using ANCOVA with baseline value as linear covariate, treatment and age as categorical covariates, and baseline carried forward for missing fasting plasma glucose at week 26. All other endpoints analysed by mixed models for repeated measurements including additional visit as fixed, categorical covariate, and interactions of treatment and baseline with visit and participant as random effect with unstructured covariance structure.

Table 3: **Secondary endpoints analysed as the change from baseline at week 26 in the modified intention-to-treat set**

−3·35 to −0·05]) and higher FPG (≥200 mg/dL; −1·79 [−3·13 to −0·45]) at baseline (appendix p 24).

By week 26, insulin rescue therapy was initiated in six (11%) participants in the placebo group, five (10%) in the empagliflozin pooled group, and four (8%) in the linagliptin group. For the secondary outcomes, the adjusted mean change in FPG was −35·2 mg/dL (−2·0 mmol/L; 95% CI −58·61 to −11·74 [−3·25 to −0·65]) for empagliflozin pooled doses versus placebo and −5·4 mg/dL (−0·3 mmol/L; −28·49 to 17·67 [−1·58 to 0·98]) for linagliptin versus placebo (table 3). The adjusted mean change in bodyweight from baseline to week 26 was −0·75 kg (−2·68 to 1·19) in the empagliflozin versus placebo group; the corresponding change for linagliptin was 1·46 kg (−0·48 to 3·41; table 3). The adjusted mean change in systolic blood pressure with empagliflozin versus placebo was −1·42 mm Hg (−4·72 to 1·88), and with linagliptin versus placebo was 0·91 mm Hg (−2·40 to 4·22; table 3). No decreases in diastolic blood pressure from baseline were observed with either agent (table 3).

At week 26, greater proportions of participants in the empagliflozin pooled group versus placebo group had HbA_{1c} less than 6·5% (48 mmol/mol; difference *vs* placebo 11·7% [−2·4 to 26·3]) and less than 7·0% (53 mmol/mol; difference *vs* placebo 10·1% [−7·7 to 28·1]; appendix p 26). For empagliflozin, this effect was sustained up to week 52 (appendix p 28).

In a prespecified, descriptive analysis comparing participants receiving empagliflozin 10 mg and 25 mg doses, the re-randomisation of placebo participants at week 26 (n=47) offered a direct comparison of the two doses in SGLT2-inhibitor-naive participants. Mean HbA_{1c} values decreased from weeks 26 to 30 in both the 10 mg (n=15 [32%] of 47) and 25 mg (n=16 [34%]) empagliflozin groups of randomly reassigned placebo participants; from weeks 30 to 52, HbA_{1c} values were lower in participants randomly reassigned to empagliflozin 25 mg versus 10 mg (appendix p 29). The mean HbA_{1c} from weeks 26 to 52 in those randomly reassigned to linagliptin at week 26 decreased from weeks 26 to 30, followed by a gradual increase between weeks 30 to 52 (appendix p 33).

For participants who did not have a target HbA_{1c} less than 7·0% at week 12, the mean HbA_{1c} values from week 14 to 52 were lower in participants randomly reassigned to empagliflozin 10 mg versus 25 mg (appendix p 30). The weighted adjusted mean change in HbA_{1c} values at week 26 in the dosing regimen up-titrating non-responders to empagliflozin 25 mg was −0·52% [−5·7 mmol/mol] versus the placebo group (95% C, −1·31 to 0·27 [−14·3 to 2·9]; p=0·19) (appendix p 31); the corresponding change from baseline in those who remained on 10 mg was −1·18% [−12·9 mmol/mol; 95% CI −1·90 to −0·45 [−20·8 to −4·9]; p=0·0015; appendix p 32).

The safety of active study drug treatment groups was compared with that of the placebo group up to week 26. At week 26, adverse events were reported in 34 (64%) participants in the placebo group, 40 (77%) in the empagliflozin pooled group, and 37 (71%) participants in the linagliptin group. Of these, severe adverse events were reported in two (4%) participants in the placebo group, one (2%) in the empagliflozin pooled group, and one (2%) in the linagliptin group (table 4).

	Placebo (n=53)	Empagliflozin pooled (n=52)	Linagliptin 5 mg (n=52)
Any adverse event	34 (64%)	40 (77%)	37 (71%)
Severe adverse event	2 (4%)	1 (2%)	1 (2%)
Drug-related adverse event (investigator-defined)	6 (11%)	9 (17%)	9 (17%)
Adverse event leading to discontinuation	2 (4%)	0	0
Serious adverse event	2 (4%)	2 (4%)	2 (4%)
Fatal	0	0	0
Life threatening*	1 (2%)	1 (2%)	0
Persistent or significant disability or incapacity	0	0	0
Requiring or prolonging hospitalisation*	2 (4%)	2 (4%)	0
Congenital anomaly or birth defect	0	0	0
Other*	0	1 (2%)	2 (4%)
Other significant adverse events (according to ICH E3)	1 (2%)	0	0
Adverse events of special interest and specific adverse events			
Hypersensitivity reactions	1 (2%)	4 (8%)	2 (4%)
Skin lesions	0	0	0
Pemphigoid in bullous conditions	0	0	0
Pancreatitis	1 (2%)	0	0
Pancreatic cancer	0	0	0
Hepatic injury	1 (2%)	2 (4%)	2 (4%)
Decreased renal function	1 (2%)	0	0
Diabetic ketoacidosis	1 (2%)	0	0
Increased ketone reported as adverse event	2 (4%)	2 (4%)	4 (8%)
Adverse events leading to lower limb amputation	0	0	0
Hypoglycaemia adverse events	5 (9%)	12 (23%)	10 (19%)
PG <54 mg/dL	4 (8%)	10 (19%)	8 (15%)
Severe hypoglycaemia requiring assistance	0	0	0
Urinary tract infection	1 (2%)	3 (6%)	1 (2%)
Genital infection	1 (2%)	1 (2%)	2 (4%)
Acute pyelonephritis or urosepsis	0	0	0
Bone fracture	0	0	0
Arthralgia	1 (2%)	1 (2%)	2 (4%)
Volume depletion	1 (2%)	0	0
Other adverse events in >5% of participants			
Infections and infestations	13 (25%)	18 (35%)	23 (44%)
Nasopharyngitis	3 (6%)	3 (6%)	3 (6%)
Influenza	0	0	3 (6%)
Metabolism and nutrition disorders	12 (23%)	16 (31%)	16 (31%)
Vitamin D deficiency	5 (9%)	5 (10%)	3 (6%)
Hyperglycaemia	3 (6%)	1 (2%)	0
Gastrointestinal disorders	10 (19%)	12 (23%)	12 (23%)
Abdominal pain	4 (8%)	3 (6%)	4 (8%)
Diarrhoea	5 (9%)	2 (4%)	3 (6%)
Vomiting	2 (4%)	3 (6%)	5 (10%)
Nausea	3 (6%)	3 (6%)	3 (6%)
Nervous system disorders	11 (21%)	11 (21%)	10 (19%)
Headache	7 (13%)	8 (15%)	9 (17%)
Dizziness	3 (6%)	2 (4%)	1 (2%)
Respiratory, thoracic, and mediastinal disorders	8 (15%)	2 (4%)	11 (21%)
Cough	4 (8%)	0	3 (6%)
Epistaxis	0	0	3 (6%)
Renal and urinary disorders	3 (6%)	1 (2%)	6 (12%)

(Table 4 continues on next page)

Hypoglycaemia was the most frequently reported adverse event, with higher rates for those on active study drug treatment compared with placebo up to week 26 (table 4). In the comparison of four groups (placebo, empagliflozin 10 mg responder group, randomly reassigned empagliflozin 10 mg group, and randomly reassigned empagliflozin 25 mg group) during weeks 15–26, hypoglycaemic events were low and balanced (appendix p 38). No severe hypoglycaemia cases requiring assistance were reported. Up to week 26, we found a few drug-related adverse events in all groups (table 4), with rates across treatment groups generally similar, with hypoglycaemia as the most frequent MedDRA preferred term. Serious adverse events were reported by two (4%) participants in each treatment group; none was fatal (table 4). The occurrence of urinary tract infections was slightly higher in the empagliflozin group than in the placebo and linagliptin treatment groups (table 4). No episodes of diabetic ketoacidosis or necrotising fasciitis were reported with empagliflozin treatment, and no cases of pancreatitis reported with linagliptin treatment (table 4). Overall, from weeks 15 to 26, the rates of adverse events in non-responders who were randomly reassigned to empagliflozin 10 mg and 25 mg were low and similar to rates in the placebo group (appendix p 38).

Safety was further assessed up to week 52 without a placebo comparison group because of re-randomisation at week 26. Rates of adverse events in the empagliflozin 10 mg and 25 mg and linagliptin groups following re-randomisation at week 26, as well as adverse events in the empagliflozin 10 mg and 25 mg groups following re-randomisation at week 14 were balanced (appendix pp 42–43). Rates of adverse events for empagliflozin pooled doses and linagliptin up to week 52 were also well balanced (appendix p 44).

Adverse events of special interest as well as specific adverse events were prespecified in the clinical trial protocol. Adverse events of special interest were hypersensitivity reactions such as angioedema, angioedema-like events, and anaphylaxis (an identified risk with DPP-4 inhibitors), skin lesions (a potential risk with DPP-4 inhibitors), pancreatitis (identified risk with DPP-4 inhibitors), pancreatic cancer (a potential risk with DPP-4 inhibitors), hepatic injury (of potential interest for both investigational drugs), decreased renal function (of potential interest for both investigational drugs), diabetic ketoacidosis (an identified risk with SGLT2 inhibitors), and events involving lower limb amputation (a potential risk with SGLT2 inhibitors). The analysis of specific adverse events comprised hypoglycaemia, urinary tract infections, genital infections, acute pyelonephritis or urosepsis, bone fracture, arthralgia, pemphigoid in bullous conditions, volume depletion, and ketone measurements reported as an adverse event. Up to weeks 26 and 52, few participants had adverse events of special interest, and we found no imbalances in rates among the treatment groups (table 4; appendix p 44).

Discussion

The DINAMO study is one of the largest studies in young people with type 2 diabetes to date. The study used a unique design that included investigation of two oral treatments—the SGLT2 inhibitor empagliflozin and the DPP-4 inhibitor linagliptin—separately against a single placebo group. The somewhat complex nature of this study design answered the call from regulators and experts for multi-arm efficacy and safety studies in paediatric patients, given the challenges of recruitment in this population,[26] and allowed for successful trial completion within 4 years, despite interruption by the COVID-19 pandemic. All modifications to the study based on the COVID-19 pandemic were assessed on the basis of the CONSERVE 2021 Statement[32] and were considered minor changes with no meaningful effect on the study's objectives or research question, ethical acceptability, internal validity and generalisability, feasibility, or analytical methods and statistical power. Notably, for the primary endpoint analysis, no HbA_{1c} data were missing at week 26 as a result of the COVID-19 pandemic.

In this study, empagliflozin showed a clinically relevant and statistically significant reduction of HbA_{1c} versus placebo at week 26. As per previous paediatric type 2 diabetes studies, a placebo-corrected HbA_{1c} reduction of at least 0·5% is considered as clinically relevant, whereas reductions of around 0·3% are considered as borderline, with uncertainties regarding the clinical relevance.[12–18] Similarly, we found a clinically relevant reduction in adjusted mean FPG by about 35 mg/dL (about 2 mmol/L) at week 26 in the empagliflozin group versus in the placebo group. During the safety follow-up period, weeks 26–52, HbA_{1c} in the empagliflozin pooled group was lower than HbA_{1c} in the placebo group at week 26; although, HbA_{1c} had gradually increased, similar to that observed in other paediatric studies,[13,18,33] probably reflecting the progressive β-cell failure seen in paediatric patients with type 2 diabetes.[34]

In studies investigating the efficacy and safety of the GLP-1 receptor agonists dulaglutide (AWARD-PEDS study),[12] liraglutide (Ellipse study),[13] and exenatide[14] in paediatric patients with type 2 diabetes, the placebo-corrected HbA_{1c} reductions were –1·4% for the pooled dulaglutide groups, –1·06% with liraglutide, and –0·85% with exenatide. In a study with the SGLT2 inhibitor dapagliflozin,[18] the placebo-corrected HbA_{1c} change was –0·75%. Because of differences in trial samples, (eg, less use of metformin plus insulin in AWARD-PEDS and in the Ellipse study than in this study and participants aged up to <24 years in the dapagliflozin study), it is difficult to directly compare the efficacy of these different studies. Of note, almost half of participants in DINAMO were on insulin therapy, which has been associated with inadequate durable glycaemic control and viewed as a marker of more rapid deterioration of β-cell function.[35]

In our trial, the linagliptin group did not meet the primary endpoint at week 26. The placebo-corrected HbA_{1c} was lower by about 0·3% with a modest adjusted mean difference in FPG of about –5 mg/dL (–0·3 mmol/L) at week 26 with linagliptin. Furthermore, HbA_{1c} in the linagliptin group gradually increased between weeks 26 and 52, in line with previous paediatric studies of DPP-4 inhibitors, suggesting that these agents do not provide durable improvements in glycaemic control[17] in children and adolescents when added to metformin or insulin therapy. These agents have shown efficacy in adults with type 2 diabetes, further showing that responses to antidiabetic medications in young people with type 2 diabetes differ from those in adults, which might reflect pathophysiologic differences in disease progression.[16,34,36] The TODAY[33] and RISE[34] studies show the challenges of glycaemic control in youth-onset type 2 diabetes. The challenges appear to arise from a combination of the early development of insulin resistance and more rapid deterioration of β-cell function in children and adolescents compared with adults with type 2 diabetes. Further, there is the added physiological insulin resistance of puberty present in adolescents and not adults. Last, BMI in youth-onset type 2 diabetes (10–17 years) is often higher than that observed in adults with type 2 diabetes.[33] These factors might affect the responsiveness to DPP-4 inhibitors in young people with type 2 diabetes.

Other secondary outcomes related to bodyweight and blood pressure, although numerically favourable for empagliflozin, did not achieve statistical significance, a finding consistent with other paediatric studies of GLP-1 receptor agonists[12,13] and dapagliflozin[18] but different from studies in adults with type 2 diabetes.[37] It is unclear why reductions in bodyweight and blood pressure are not generally seen in paediatric studies.

Randomly reassigning participants in the empagliflozin group from 10 mg to either 10 mg or 25 mg at 14 weeks yielded unanticipated results by contrast with the week-52 results among the placebo-treated participants

	Placebo (n=53)	Empagliflozin pooled (n=52)	Linagliptin 5 mg (n=52)
(Continued from previous page)			
Microalbuminuria	1 (2%)	0	3 (6%)
Skin and subcutaneous tissue disorders	1 (2%)	5 (10%)	4 (8%)
Rash	0	3 (6%)	1 (2%)
Immune system disorders	0	4 (8%)	0
Seasonal allergy	0	4 (8%)	0

Data are n (%). Serious adverse events were death, life-threatening event (participant at risk of death, not an event that might cause death if more severe), hospitalisation, prolongation of hospitalisation, significant disability, congenital anomaly or birth defect, and medical or surgical intervention. *For serious adverse events defined as life threatening, requiring or prolonging hospitalisation, or other, the following were reported: in the placebo group one participant had life-threatening events requiring hospitalisation (splenic vein thrombosis, abdominal pain, pancreatitis acute, systemic inflammatory response syndrome, diabetic ketoacidosis, acute kidney injury, acute respiratory failure, and hypovolaemic shock) and one participant required hospitalisation (hyperglycaemia); in the empagliflozin group one participant had life-threatening events requiring hospitalisation (suicidal ideation) and other events (road traffic accident) and one participant required hospitalisation (skin candida); and in the linagliptin group one participant had other events (breast abscess) and one participant had other events (pneumomediastinum).

Table 4: **Overall summary of adverse events to week 26**

who were randomly reassigned to 10 mg or 25 mg at week 26. Participants who were randomly reassigned at week 26 showed the expected dose response, with a larger reduction in HbA_{1c} with 25 mg versus 10 mg, whereas participants who were randomly reassigned at week 14 did not. Although reasons for these contrary observations are unclear, the small numbers in each subgroup make meaningful interpretation challenging and can yield results susceptible to outliers. Nonetheless, safety profiles of empagliflozin 10 mg and 25 mg were similar and both empagliflozin and linagliptin treatment showed similar safety profiles with those established in adults with type 2 diabetes.

There were limitations to the study. Although the novel design of DINAMO helped to overcome the recruitment difficulties seen with previous trials of young people with type 2 diabetes, we had a somewhat small number of study participants, limiting detailed subgroup analyses. Thus, future observational studies or clinical trials might help to further assess clinical responsiveness in various subgroups, such as those on insulin only and at risk of hypoglycaemia. Additionally, much of the clinical trial was conducted during the COVID-19 pandemic, which might have affected the ability of participants to attend in-person clinic visits, limiting personal interactions between study staff and families. Further, the pandemic and its associated travel restrictions might have reduced lifestyle efforts on the part of participants, but probably affected all treatment groups similarly. Another potential limitation relates to the geographic distribution of the study participants. Although the study was done in multiple geographic regions (North America, South America, Europe, and Asia), most participants were enrolled in the Americas, which limits generalisability to the broader worldwide population of children and adolescents with type 2 diabetes.

Our findings show that an empagliflozin dosing regimen provides a clinically relevant and statistically significant reduction in HbA_{1c} in young people aged 10–17 years with type 2 diabetes, whereas linagliptin did not provide statistically significant improvements in glycaemic control. Furthermore, the safety profile of empagliflozin was similar to that seen in studies in adults, with no episodes of diabetic ketoacidosis or necrotising fasciitis reported in these paediatric participants. The results of this trial support the management of type 2 diabetes in young people with orally administered SGLT2 inhibitors for safe and effective lowering of HbA_{1c}.

Contributors

All authors contributed to the acquisition, analysis, or interpretation of data and revision of the manuscript. All authors had full access to all the data in the study, had final responsibility for the decision to submit for publication, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors were involved in the study design. LML, JM, and DN accessed and verified the data. DN was responsible for statistical analysis. The manuscript was drafted by LML, JM, and DN, and revised by all authors.

Declaration of interests

LML has received consulting fees from Provention, Dompe, Medtronic, Roche, Janssen, Eli Lilly, Dexcom, Novo Nordisk, and Vertex. TD has received speaker, advisory panel, or research support from AstraZeneca, Bayer, Boehringer Ingelheim, Dexcom, Eli Lilly, Insulet, Lifescan, Medtronic, Novo Nordisk, Roche, and Sanofi; and is a shareholder of DreaMed Diabetes. WVT has received consulting fees from AstraZeneca, Boehringer Ingelheim, Novo Nordisk, and Medtronic Diabetes. SW has served on a data safety monitoring board for the National Institute of Diabetes and Digestive and Kidney Diseases/US National Institutes of Health; and served on an advisory panel or board for Roche Diagnostics and Medtronic MiniMed. PZ has consulted for Boehringer Ingelheim, Merck, Eli Lilly, Janssen, I-ACT, and Novo Nordisk. DN and JM are employees of Boehringer Ingelheim. GJK declares no competing interests.

Data sharing

To ensure independent interpretation of clinical study results and enable authors to fulfil their role and obligations under the ICMJE criteria, Boehringer Ingelheim grants all external authors access to clinical study data pertinent to the development of the publication. In adherence with the Boehringer Ingelheim policy on transparency and publication of clinical study data, scientific and medical researchers can request access to clinical study data when it becomes available at https://vivli.org/, 2 years after publication of the primary manuscript in a peer-reviewed journal. Please visit https://www.mystudywindow.com/msw/datasharing for further information.

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