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SUMMARY OF RESEARCH

Summary of Research: 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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ABSTRACT

The increasing occurrence of childhood overweight and obesity has been followed by a substantial increase in youth-onset type 2 diabetes (T2D). Pharmacological treatment options for youth-onset T2D remain limited, with a clear unmet need for additional oral agents. This summary of research reports on the efficacy and safety of empagliflozin and linagliptin on glycaemic control in children and adolescents aged 10–17 years with T2D in the randomised, double-blind, parallel group, phase 3 DINAMO trial. Empagliflozin provided a clinically relevant, statistically significant, and durable improvement in glycaemic control; however, linagliptin did not. The safety profile of both empagliflozin and linagliptin was comparable to those observed in studies in adults. These results suggest that empagliflozin could be a new oral therapy option for youth-onset T2D.

Keywords: Adolescent; Child; Dipeptidyl peptidase-4 inhibitor; Empagliflozin; Linagliptin; Sodium-glucose co-transporter-2 inhibitor; Type 2 diabetes

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This article provides a summary of a previously published paper describing the efficacy and safety of empagliflozin versus placebo and linagliptin versus placebo on glycaemic control in young people with type 2 diabetes (T2D) in the DINAMO trial [1].

INTRODUCTION

- The incidence of T2D in young people has increased over the last few decades in line with the childhood overweight and obesity epidemic.
- Achieving durable glycaemic control is particularly important in youth-onset T2D because this population experiences substantial insulin resistance, deterioration in β-cell function, and premature diabetes-related complications at a more aggressive rate than adults with T2D.
- Up to 2019, metformin (oral) and insulin (injectable) were the only treatment options for T2D in young people under 18 years, which is in stark contrast to the wide range of drug therapies from different classes available for adults with T2D.
- Oral treatment options for youth-onset T2D remain limited, with the sodium-glucose co-transporter-2 (SGLT2) inhibitor dapagliflozin the only additional oral agent to receive regulatory approval in Europe in children aged 10 years and above.

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- The SGLT2 inhibitor empagliflozin and the dipeptidyl peptidase-4 inhibitor linagliptin are two oral agents with demonstrated efficacy and safety in adults with T2D. They have also been successfully investigated in dose-finding paediatric studies. As such, these two agents may fill the unmet need for new oral treatment options for youth-onset T2D.

Study Objective

The phase 3, randomised, double-blind, parallel group DINAMO trial (NCT03429543) assessed the efficacy and safety of empagliflozin and linagliptin versus a shared placebo group on glycaemic control in children and adolescents with T2D aged 10–17 years.

METHODS

Study Design

- The DINAMO phase 3 trial used a novel multi-arm design in an attempt to overcome the known difficulties in recruiting young people for paediatric trials (Fig. 1).
- Participants were randomised (1:1:1) to receive empagliflozin 10 mg, linagliptin 5 mg, or placebo once daily.
- At week 14, participants in the empagliflozin group who did not attain glycated haemoglobin (HbA1c) < 7.0% at week 12 (non-responders) were re-randomised (1:1) to empagliflozin 10 mg or 25 mg.
- At week 26, the placebo group was re-randomised (1:1:1) to linagliptin 5 mg, empagliflozin 10 mg, or empagliflozin 25 mg.
- Empagliflozin and linagliptin were analysed separately against a single placebo group, with the empagliflozin results for 10 mg and 25 mg pooled for all participants treated with empagliflozin.

Participant Eligibility

- Participants eligible for the trial were aged 10–17 years with T2D for ≥ 8 weeks prior to screening, HbA1c ≥ 6.5% and ≤ 10.5%, and a body mass index ≥ 85th percentile.
- The only background antidiabetic medication allowed was metformin or insulin, which were continued during the study.

Study Outcomes

- The primary endpoint was change from baseline in HbA1c at week 26.
- Secondary outcomes included the change from baseline at week 26 in fasting plasma glucose (FPG), bodyweight, systolic (SBP) and diastolic blood pressure (DBP).

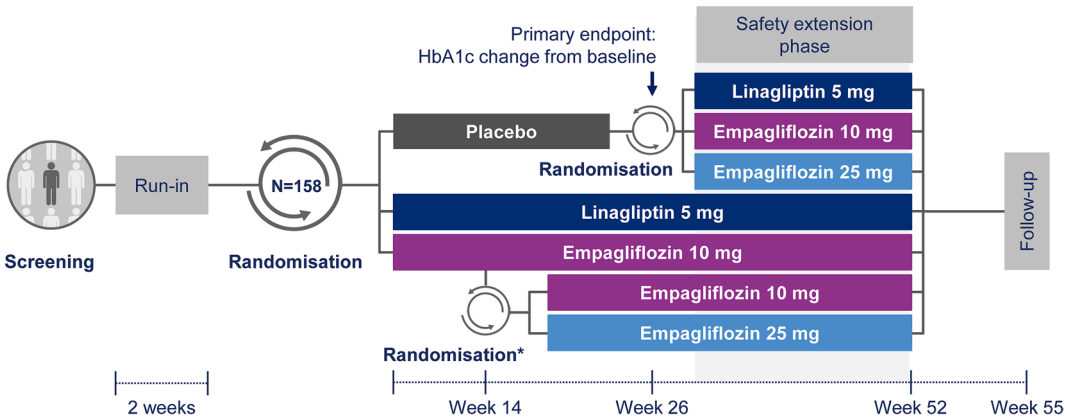

Fig. 1 Study design of the DINAMO trial. *HbA1c*, glycated haemoglobin. *Re-randomisation at week 14 for participants not achieving HbA1c < 7.0% at week 12. Reprinted from [1], copyright (2023), with permission from Elsevier

- Safety was assessed for the 52-week period and was based on reported adverse events (AEs).

RESULTS

Participants

- Of 158 randomised participants [placebo, $n=53$; empagliflozin pooled, $n=52$; linagliptin 5 mg, $n=53$], 157 received treatment.
- Baseline characteristics were generally balanced across treatment groups.

Efficacy

Empagliflozin Pooled Group

- There was a significant adjusted mean change from baseline in HbA1c of –0.84% (95% CI -1.50 to -0.19; p=0.012) for the empagliflozin pooled group versus placebo at week 26.
- HbA1c levels in the empagliflozin pooled group slowly increased from weeks 26 to 52, but remained below that of placebo at week 26 (Fig. 2a).
- Participants in the empagliflozin pooled group had a reduction from baseline to week 26 in FPG (–35.18 mg/dL), bodyweight (–0.75 kg), and SBP (–1.42 mmHg); the reductions in bodyweight and SBP were not. There was a negligible change in DBP (0.02 mmHg).

Linagliptin Group

- At week 26, there was a non-significant adjusted mean change from baseline in HbA1c of –0.34% (95% CI –0.99 to 0.30; p=0.29) for the linagliptin group.
- Levels of HbA1c in the linagliptin group gradually increased from weeks 26 to 42, decreasing to around the level of the week 26 placebo group at week 52 (Fig. 2b).
- The linagliptin group had a mean reduction of –5.41 mg/dL for FPG versus placebo; however, bodyweight (1.46 kg), SBP (0.91 mmHg) and DBP (1.50 mmHg) increased.

Safety

- AE reports at week 26 were similar for empagliflozin pooled (77%), linagliptin (71%), and placebo (64%).
- The predominant AE was hypoglycaemia, with higher rates in the empagliflozin pooled (23%) and linagliptin (19%) groups versus placebo (9%), and no reports of severe hypoglycaemia.
- There was no diabetic ketoacidosis or necrotizing fasciitis in the empagliflozin pooled group and no pancreatitis in the linagliptin group.

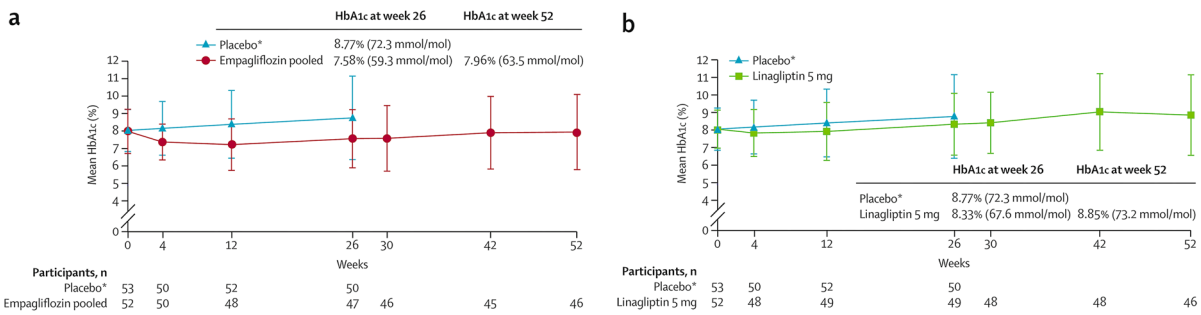

Fig. 2 Mean HbA1c change from baseline to week 52 in **a** the empagliflozin pooled and **b** linagliptin treatment groups. Error bars indicate SDs. *HbA1c* glycated haemoglobin, *SD* standard deviation. *Placebo treatment stopped at week 26 Reprinted from [1], copyright (2023), with permission from Elsevier

Strengths and Weaknesses

- DINAMO is one of the largest trials in youth-onset T2D to date and used a novel multi-arm study design investigating two oral agents against a shared placebo group.
- The somewhat small number of participants enrolled in the study limited meaningful subgroup analyses and made the results susceptible to outliers.
- The geographic spread of participants was focused mainly on the Americas, narrowing the applicability of the results to the global population of young people with T2D.

Study Conclusion

Empagliflozin demonstrated a statistically significant and clinically relevant reduction in the primary outcome of HbA1c in participants aged 10–17 years living with T2DM relative to placebo. With a safety profile similar to that reported in adults, these results support the use of empagliflozin as a new oral treatment option in young people with T2D.

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Data Availability. The datasets generated and analysed during the current study are available in the Vivli repository (https://vivli.org/).

Declarations

Conflict of Interest. Please see original article for full author disclosures for Lori M. Laffel.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. Please see the referenced article for ethics relating to the original study.

REFERENCE

1. Laffel LM, Danne T, Klingensmith GJ, et al. 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. Lancet Diabetes Endocrinol. 2023;11(3):169–81. https://doi.org/10.1016/S2213-8587(22)00387-4.