# Durable Improvement in HbA1c in Youth-Onset T2D: A *Post Hoc* Analysis of the DINAMO Trial of Empagliflozin and Linagliptin versus Placebo

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## BACKGROUND

- The worldwide increase in overweight and obesity in children and adolescents[1] has led to an upsurge in type 2 diabetes (T2D) in young people.[2]
- The clinical course of youth-onset T2D is more aggressive than in adults, with early development of insulin resistance and faster deterioration in beta-cell function. This leads to suboptimal glycemic control and an increased risk of the premature onset of complications.[3]
- There is a dearth of treatment options for youth-onset T2D, especially compared with adults with T2D, with metformin as the only globally approved oral agent,[4] and all other treatment options requiring injection. Thus, there is an unmet need for additional oral therapies.
- The DINAMO trial compared the efficacy and safety of 2 oral diabetes agents, the sodium-glucose co-transporter-2 (SGLT2) inhibitor empagliflozin versus placebo, and the dipeptidyl peptidase-4 inhibitor linagliptin versus placebo, in children and adolescents with T2D.[5]

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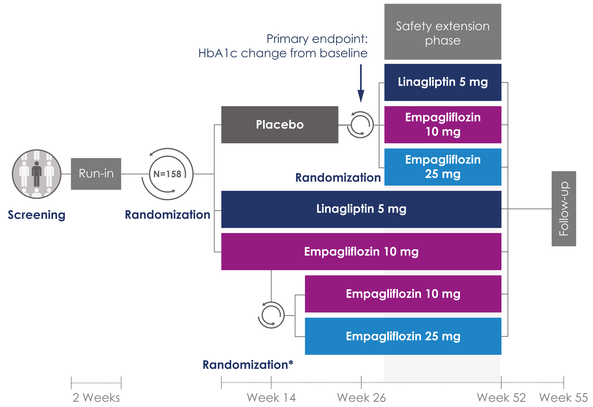
## OBJECTIVE

- The aim of this *post hoc* analysis of the DINAMO trial was to analyze glycemic control in the participants at 26 weeks and determine its durability at 52 weeks.

## METHODS

- DINAMO was a global, multicenter, randomized, double-blind, placebo-controlled, parallel group trial across 13 countries.
- Eligible participants were aged 10–17 years with T2D for ≥8 weeks prior to screening, glycated hemoglobin (HbA1c) ≥6.5% and ≤10.5%, and a body mass index ≥85th percentile.
- Participants were treated with diet and exercise plus either metformin at a stable dose or stable basal or multiple daily injection insulin therapy. In those unable to tolerate metformin, diet and exercise and/or insulin therapy were continued.
- Participants were randomized (1:1:1) to receive linagliptin 5 mg, empagliflozin 10 mg, or placebo once daily over 26 weeks (**Figure 1**).
- Those in the empagliflozin 10 mg group not achieving HbA1c <7.0% at Week 12 were re-randomized (1:1) to empagliflozin 10 mg or 25 mg at Week 14.
- The placebo group participants were re-randomized (1:1:1) at Week 26 to either linagliptin 5 mg or one of the empagliflozin doses (10 mg or 25 mg).
- There was a double-blind active treatment safety extension period up to 52 weeks.
- The primary endpoint was the change in HbA1c from baseline to Week 26.
- Responders were defined *post hoc* as having no rescue medication and a reduction in HbA1c from baseline ≥0.5% or attained HbA1c <7.0% at Week 26 and Week 52.

**Figure 1. Study design**




*Re-randomization at Week 14 for patients not achieving HbA1c <7.0% at Week 12.
HbA1c, glycated hemoglobin.

## RESULTS

### Participants

- Of 158 randomized participants, 157 received treatment (placebo: 53, linagliptin: 52, pooled empagliflozin: 52).
- Baseline characteristics were generally balanced across the 3 treatment groups (placebo, linagliptin, and empagliflozin) (**Table 1**).
- Compared with non-responders, responders had a higher frequency of metformin-only background therapy and a lower rate of background metformin and insulin use.
- Of the responders, the empagliflozin group had the highest mean baseline HbA1c and fasting plasma glucose (FPG) levels.

### Glycemic control

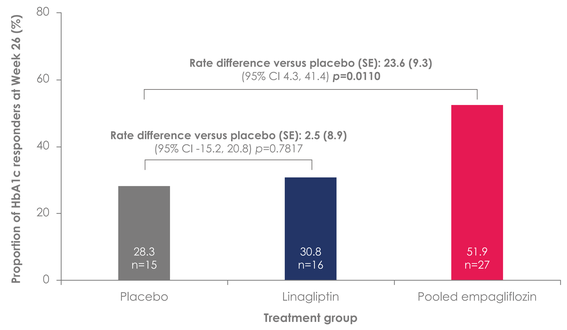
- Significantly more participants responded to empagliflozin versus placebo, but not to linagliptin versus placebo (**Figure 2**).
- The improvement in HbA1c levels in the empagliflozin group was maintained to Week 52 in 40% of the participants (**Table 2**).

**Table 1. Demographics, baseline efficacy variables and background diabetes therapy at baseline by HbA1c responder category* at Week 26**

| | | Responders n=58 | Non-responders n=99 |
|---|---|---|---|
| **Age, years, mean ± SD** | | | |
| Placebo | | 14.7 ± 1.4 | 14.6 ± 1.9 |
| Linagliptin | | 15.0 ± 1.8 | 14.4 ± 2.0 |
| Pooled empagliflozin | | 14.6 ± 2.0 | 14.2 ± 1.9 |
| **BMI, kg/m², mean ± SD** | | | |
| Placebo | | 37.1 ± 13.1 | 35.7 ± 8.8 |
| Linagliptin | | 37.9 ± 8.8 | 35.9 ± 7.0 |
| Pooled empagliflozin | | 34.6 ± 6.6 | 36.6 ± 7.7 |
| **Weight, kg, mean ± SD** | | | |
| Placebo | | 100.3 ± 37.0 | 97.6 ± 26.6 |
| Linagliptin | | 111.1 ± 30.3 | 99.1 ± 24.0 |
| Pooled empagliflozin | | 99.3 ± 23.3 | 97.9 ± 25.9 |
| **Female, n (% within responder category and treatment group)** | | | |
| Placebo | | 11 (73.3) | 23 (60.5) |
| Linagliptin | | 8 (50.0) | 22 (61.1) |
| Pooled empagliflozin | | 15 (55.6) | 18 (72.0) |
| **Background diabetes therapy, n (% within responder category and treatment group)†** | | | |
| Placebo | Metformin only | 10 (66.7) | 18 (47.4) |
| | Metformin and insulin | 4 (26.7) | 15 (39.5) |
| Linagliptin | Metformin only | 12 (75.0) | 14 (38.9) |
| | Metformin and insulin | 3 (18.8) | 19 (52.8) |
| Pooled empagliflozin | Metformin only | 17 (63.0) | 9 (36.0) |
| | Metformin and insulin | 9 (33.3) | 13 (52.0) |
| **Time since diagnosis of T2D, n (% within responder category and treatment group)** | | | |
| Placebo | <1 year | 7 (46.7) | 11 (28.9) |
| | 1–3 years | 4 (26.7) | 20 (52.6) |
| | >3 years | 4 (26.7) | 7 (18.4) |
| Linagliptin | <1 year | 3 (18.8) | 13 (36.1) |
| | 1–3 years | 8 (50.0) | 13 (36.1) |
| | >3 years | 5 (31.3) | 10 (27.8) |
| Pooled empagliflozin | <1 year | 7 (25.9) | 10 (40.0) |
| | 1–3 years | 13 (48.1) | 8 (32.0) |
| | >3 years | 7 (25.9) | 7 (28.0) |
| **HbA1c, %, mean ± SD** | | | |
| Placebo | | 7.27 ± 0.90 | 8.36 ± 1.21 |
| Linagliptin | | 7.12 ± 0.75 | 8.46 ± 0.98 |
| Pooled empagliflozin | | 7.87 ± 1.41 | 8.14 ± 1.17 |
| **FPG, mg/dl, mean ± SD** | | | |
| Placebo | | 129.5 ± 26.4 | 169.3 ± 57.5 |
| Linagliptin | | 123.2 ± 32.0 | 180.9 ± 55.6 |
| Pooled empagliflozin | | 145.8 ± 49.8 | 164.6 ± 65.7 |

*Responders were defined as having no rescue medication and a reduction in HbA1c from baseline ≥0.5% or attained HbA1c <7.0%.
†Results for 'no background diabetes therapy' and 'insulin only' were omitted from the table due to small subgroup sizes.
BMI, body mass index; FPG, fasting plasma glucose, HbA1c, glycated hemoglobin; SD, standard deviation; T2D, type 2 diabetes.

**Figure 2. Proportion of HbA1c responders* at Week 26 in each treatment group**




*Responders were defined as having no rescue medication and a reduction in HbA1c from baseline ≥0.5% or attained HbA1c <7.0% at Week 26.
CI, confidence interval; HbA1c, glycated hemoglobin; SE, standard error.

**Table 2. Proportion of HbA1c responders* at Week 52 in each treatment group**

| Treatment group | n/N (%) | 95% CI |
|---|---|---|
| Linagliptin | 11/52 (21.2) | 11.1, 34.7 |
| Pooled empagliflozin | 21/52 (40.4) | 27.0, 54.9 |

*Responders were defined as having no rescue medication and a reduction in HbA1c from baseline ≥0.5% or attained HbA1c <7.0% at Week 52.
CI, confidence interval; HbA1c, glycated hemoglobin.

## CONCLUSIONS

- More than half of the empagliflozin group demonstrated a substantial glycemic response with an HbA1c improvement of ≥0.5% or attained HbA1c <7.0% at Week 26 while less than one third of participants in the linagliptin and placebo groups did; this glycemic response in the empagliflozin group was evident despite that group having the highest mean baseline HbA1c and FPG levels.
- Empagliflozin provided clinically relevant, durable, and statistically significant reductions in HbA1c whereas linagliptin did not.
- These results support the use of SGLT2 inhibitors as an oral add-on treatment option for the management of T2D in young people.

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