Predicting true time to recovery from insulin-induced hypoglycemia with dasiglucagon

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ABSTRACT

Background: The efficacy of dasiglucagon 0.6 mg has been investigated in multiple trials in individuals with type 1 diabetes mellitus. The primary endpoint was time to plasma glucose (PG) recovery from insulin-induced hypoglycemia, defined as first PG increase ≥20 mg/dL after treatment initiation without the need for rescue intravenous glucose. Different sampling schemes were used in phase 2 (5-min intervals) vs phase 3 trials (more frequent sampling) to quantify PG increase. Using linear interpolation to estimate the actual time to PG recovery for individuals receiving dasiglucagon enables better comparison between trials compared to observed time to PG recovery only.
Objective: The objective of this study was to use linear interpolation to estimate the true but unmeasured time to individual PG recovery following dasiglucagon treatment in phase 2 and phase 3 trials.
Methods: The true time was calculated using linear interpolation between the time points before and after PG recovery occurred, assuming a linear PG increase in the limited time interval between 2 consecutive sampling time points.
Results: In the trials included in this study, linear interpolation estimated a 20-mg/dL PG increase to occur earlier than the observed time to PG recovery. Using interpolated values, the median estimated true time to recovery for dasiglucagon was 8.7 minutes in the phase 2 trial and ranged from 9.0 to 9.3 minutes in phase 3 trials.
Conclusions: These data provide further insight into the true but unmeasured time to PG recovery and confirm the consistent efficacy of dasiglucagon in the treatment of hypoglycemia.

OBJECTIVES

- Dasiglucagon has undergone an extensive clinical development program and is approved by the US Food and Drug Administration (FDA) for use in severe hypoglycemia (SH) in both children and adults with diabetes aged ≥6 years old[1]
- The objective of this study was to use linear interpolation to estimate the true but unmeasured time to individual plasma glucose (PG) recovery following dasiglucagon treatment in phase 2 and phase 3 trials

CONCLUSIONS

- **Using interpolated values, median estimated true times to PG recovery ranged from 8.7–9.3 minutes in phase 2 and phase 3 trials**
- **These results confirm the consistent efficacy of dasiglucagon for the treatment of hypoglycemia**
- **Estimating true time to recovery enables better comparison between trials versus observed time to PG recovery only**

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INTRODUCTION

- Dasiglucagon is a novel, ready-to-use glucagon analog approved by the FDA for use in SH that has been investigated in a comprehensive clinical development program including one phase 2 trial and three phase 3 registration trials
- Primary and secondary end points in phase 2 and phase 3 trials included time to PG recovery from insulin-induced hypoglycemia, defined as first PG increase ≥20 mg/dL after treatment initiation without the need for intravenous glucose[2–4]
- Different PG sampling schemes were used in phase 2 (5-minute intervals) vs phase 3 trials (more frequent intervals)
- Therefore, linear interpolation enables a more accurate measure of actual time to PG recovery in patients receiving dasiglucagon across the comprehensive clinical development program

METHOD

- Linear interpolation between the two time points before and after PG recovery occurred was calculated
- This interpolation assumed PG increased linearly in the limited time interval between 2 consecutive time points

RESULTS

- In a representative patient, a PG sample taken at 10 minutes was the first sample showing an increase of at least 20 mg/dL from the pre-dose level (Figure 1)
- The observed time to PG recovery for this patient was 10 minutes
- Linear interpolation estimated that the increase of 20 mg/dL occurred at 9 minutes
- Linear interpolation estimates that PG recovery occurs earlier than the predetermined time point in patients treated with dasiglucagon
- Observed time to PG recovery is a discrete measure dependent on the PG sampling scheme (Figure 2)
- Linear interpolation of PG recovery estimates the true time to recovery on a continuous time scale (Figure 3)
- Median estimated true time to recovery with dasiglucagon ranges from 8.7 to 9.3 minutes across trials (Table 1)

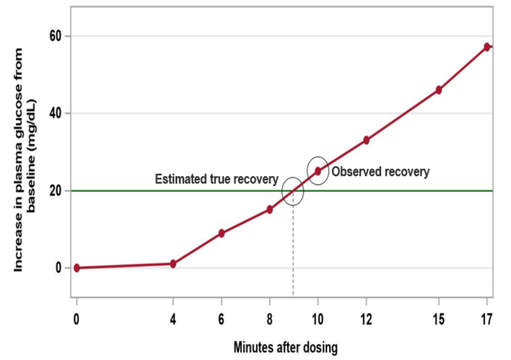

Figure 1: Estimated true time to PG recovery in a representative patient treated with dasiglucagon during insulin-induced hypoglycemia

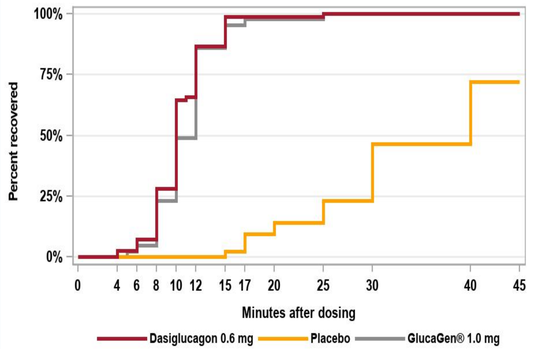

Figure 2: Observed time to PG recovery, one minus Kaplan–Meier plot, first adult phase 3 trial

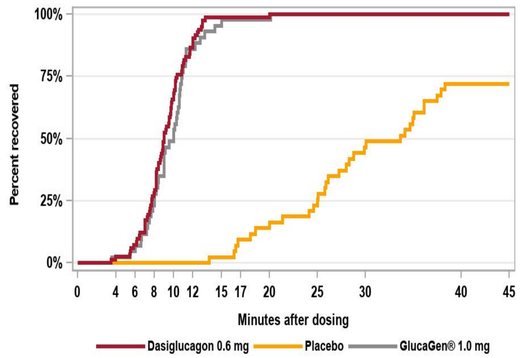

Figure 3: Estimated true time to PG recovery, one minus Kaplan–Meier plot, first adult phase 3 trial

Interpolated true time to recovery (minutes), median (95% CI)	Dasiglucagon 0.6 mg	GlucaGen® 1.0 mg	Placebo
Phase 2 trial	8.7 (8.0–10.3)	9.0 (8.5–10.0)	-
First adult phase 3 trial	9.0 (8.4–9.7)	10.0 (9.0–10.6)	33.7 (26.1–36.1)
Second adult phase 3 trial	9.3 (7.8–10.4)	–	32.0 (19.2–NE)
Pediatric phase 3 trial	8.7 (6.9–10.6)	9.8 (7.4–10.6)	29.3 (18.5–NE)

NE, not estimable.

Table 1: Estimated true time to PG recovery across phase 2 and phase 3 trials

REFERENCES
1. Dasiglucagon. Prescribing information. Zealand Pharma A/S; 2021.
2. Hovelmann U, et al. *Diabetes Care*. 2018;41:531–7.
3. Pieber T, et al. *Diabetes Care*. 2021;44:1361–7.
4. Battelino T, et al. *Pediatr Diabetes*. 2021;22:734–41.

DISCLOSURES
Tadej Battelino: Advisory Panel/Consultant: Medtronic, Eli Lilly, Novo Nordisk, Sanofi, Abbott, Indigo, GluSense; Speakers Panel: Medtronic, Eli Lilly, Novo Nordisk, Sanofi, Abbott, AstraZeneca; Research Support: NIH-NIDDK, EU-Commission, Slovenian Research Agency, Novo Nordisk, Sanofi, Novartis, Medtronic, Eli Lilly, Abbott, Zealand Pharma A/S; Stock/Shareholder: DreaMed Diabetes

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