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Dasiglucagon, a next-generation ready-to-use glucagon analog, for treatment of severe hypoglycemia in children and adolescents with type 1 diabetes: Results of a phase 3, randomized controlled trial

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Abstract

Background: Dasiglucagon, a next-generation, ready-to-use aqueous glucagon analog formulation, has been developed to treat severe hypoglycemia in individuals with diabetes.

Objective: The aim of this trial was to evaluate the safety and efficacy of dasiglucagon in pediatric individuals with type 1 diabetes (T1DM). Participants were children and adolescents (6–17 years) with T1DM.

Methods: In this randomized double-blind trial, 42 participants were randomly allocated (2:1:1) to a single subcutaneous (SC) injection of dasiglucagon (0.6 mg), placebo, or reconstituted glucagon (GlucaGen; dosed per label) during insulin-induced hypoglycemia. The primary endpoint was time to plasma glucose (PG) recovery (first PG increase ≥20 mg/dL after treatment initiation without rescue intravenous glucose). The primary comparison was dasiglucagon vs. placebo; glucagon acted as a reference.

Results: The median time (95% confidence interval) to PG recovery following SC injection was 10 min (8–12) for dasiglucagon vs. 30 min (20 to –) for placebo (P < .001); the median time for glucagon was 10 min (8–12), which did not include the time taken to reconstitute the lyophilized powder. PG recovery was achieved in all participants in the dasiglucagon and glucagon groups within 20 min of dosing compared to 2 out of 11 patients (18%) with placebo. The most frequent adverse events were nausea and vomiting, as expected with glucagon treatment.

Conclusions: Consistent with adult phase 3 trials, dasiglucagon rapidly and effectively restored PG levels following insulin-induced hypoglycemia in children and adolescents with T1DM, with an overall safety profile similar to glucagon.

KEYWORDS
double-blind trial, glucagon, hypoglycemia, hypoglycemic agent, type 1 diabetes

1 | INTRODUCTION

Insulin therapy is central to the treatment of type 1 diabetes (T1DM); as pancreatic β-cell function declines, insulin treatment is also required to achieve glycemic control in many people with type 2 diabetes. Hypoglycemia is a common side effect of insulin treatment, with severe hypoglycemia often requiring prompt medical intervention to prevent potentially life-threatening complications (seizure, loss of consciousness, and/or coma).[1]

The incidence of severe hypoglycemia in pediatric patients has fallen in recent years with improved hypoglycemia education and the increased use of insulin analogs, insulin pump therapy, and continuous glucose monitoring,[1] but clinically significant hypoglycemia remains a challenge. It has been suggested that multiple hypoglycemic episodes may have negative cognitive effects in pediatric patients, particularly during early development.[2] Therefore, it is of paramount importance, in terms of both acute and potentially more long-term complications, that treatment options are available that can rapidly reverse episodes of severe hypoglycemia.

Glucagon is a well-established and long-standing first-line treatment for severe hypoglycemia in people with diabetes. American Diabetes Association (ADA) treatment guidelines recommend that glucagon is prescribed for all individuals at increased risk for clinically significant hypoglycemia so that it is available in emergencies.[3] Caregivers, school personnel, and family members of patients are furthermore advised that they should know where glucagon treatment is stored and be trained in when and how to administer it.[3]

The majority of glucagon for prescription use is provided in glucagon emergency kits,[4,5] where the need to reconstitute the lyophilized drug product via multiple steps immediately prior to injection represents a significant barrier to timely and accurate administration and has led to underutilization of glucagon for the treatment of hypoglycemia.[6,7]

To overcome these limitations, glucagon products have recently been developed that do not require reconstitution for the treatment of severe hypoglycemia, with human glucagon delivered nasally as a powder[8] or via the subcutaneous (SC) injection of a liquid formulation using dimethyl sulfoxide as diluent.[9] An alternative treatment option is dasiglucagon, a next-generation glucagon analog.[10] Like human glucagon, dasiglucagon comprises 29 amino acids, with seven amino acid substitutions introduced to improve its physical and chemical stability in aqueous media.[10] In addition to enabling continuous infusion via SC pump delivery for glycemic control in diabetes and for other unique indications currently being pursued, the improved stability in aqueous media has enabled dasiglucagon development and approval (US trade name Zegalogue) as a ready-to-use, aqueous product for treatment of severe hypoglycemia via SC injection in pediatric and adult patients with diabetes aged 6 years and older. Zegalogue is stored in the refrigerator and can be kept at room temperature between 20 °C and 25 °C for a single period of up to 12 months.

Two recent phase 3 trials in adults with T1DM have shown dasiglucagon to be a rapid and effective treatment for severe hypoglycemia when administered as a single SC dose of 0.6 mg, with a median time to plasma glucose (PG) recovery (defined as the time to first observed increase in PG of ≥20 mg/dL [1.1 mmol/L] after SC injection) of 10 min in both trials.[11,12]

We report the results of a phase 3 trial that evaluated the efficacy and safety of dasiglucagon relative to placebo and glucagon for treatment of severe hypoglycemia in children and adolescents (age range: 6–17 years) with T1DM.

2 | METHODS

2.1 | Study design

This multicenter, randomized, placebo-controlled, double-blind, parallel-group phase 3 trial in children and adolescents with T1DM was conducted at five sites in three countries (Germany, Slovenia, and the US) between September 28, 2018, and June 28, 2019. Participants were randomly allocated (2:1:1) to receive a single SC injection of dasiglucagon 0.6 mg, placebo, or reconstituted glucagon (GlucaGen [glucagon for injection], Novo Nordisk A/S). A dasiglucagon dose of 0.6 mg (same dose used in adults) was selected based on pharmacokinetics (PK)/pharmacodynamics (PD) modeling and simulation, which showed that the higher total exposure and PD response at lower weight is partially compensated by a higher clearance, lower bioavailability, and practically saturated PD response, all contributing to a safe and effective drug response. Glucagon was dosed according to label (1.0 mg for body weight > 25 kg; 0.5 mg for body weight < 25 kg).

The trial protocol, consent form, and other information provided to participants and parents/legal representatives were approved by independent ethics committees or institutional review boards at participating sites and by competent authorities. The trial was conducted according to the Declaration of Helsinki and Good Clinical Practice with written informed consent obtained from parents/caregivers and assent from participants (as required) before trial enrollment. The trial is registered at www.clinicaltrials.gov (NCT03667053).

2.2 | Participants

Eligible participants were aged between 6 and 17 years (both inclusive) and had diagnosed T1DM per ADA criteria for at least 1 year prior to trial participation, were receiving daily insulin, and were ≥ 20 kg in body weight.

Children and adolescents with a presence or history of pheochromocytoma or insulinoma were excluded from participation, as were those who had hypoglycemic events associated with seizures or hypoglycemia unawareness (as assessed at the investigators' discretion) in the prior year or severe hypoglycemia in the prior month. Trial exclusion criteria also included regular use of beta blockers, indomethacin, warfarin, or anticholinergic drugs in the 28 days prior to screening or use of prescription or nonprescription medications known to cause QT prolongation (see Supplementary Table 1 and Supplementary Table 2 for a list of all inclusion and exclusion criteria).

2.3 | Randomization and blinding

Randomization was stratified by age group (6–11 years; 12–17 years) and injection site (abdomen; thigh) using a central, dynamic variance minimization randomization method via an interactive web response system. Both investigators and participants were blinded to the investigational therapy. However, due to differences in the appearance of dasiglucagon (aqueous formulation) and glucagon (lyophilized powder for reconstitution), the preparation and administration of trial medication were performed by unblinded trial personnel who were not involved in any other trial procedures or assessments. Treatment assignment was also blinded for trial personnel involved in medical and safety monitoring, data cleaning, and defining analysis sets until the database was released for statistical analysis.

2.4 | Procedures

Participants attended an on-site dosing visit where they were randomized to receive a single SC dose of dasiglucagon 0.6 mg, placebo, or glucagon in an insulin-induced hypoglycemic state. The on-site dosing visit included an overnight stay prior to dosing (participants fasted overnight from 10 PM).

The participants' regular insulin therapy was stopped in advance of dosing according to predefined timelines (see Supplementary Table 3). Hypoglycemia was induced by intravenous (IV) infusion of insulin glulisine (Apidra, 100 U/mL), using a dose and infusion rate chosen by the investigator to facilitate a controlled decline in PG concentration to a target of 80 mg/dL (4.4 mmol/L). This PG threshold for stopping insulin infusion was deliberately set conservatively to ensure safety. PG was monitored using glucose analyzers (YSI 2300, Yellow Springs Instruments, or the Super GL analyzer, Dr. Müller Gerätebau GmbH). After the start of the insulin infusion, PG was monitored approximately every 10 min while PG was >110 mg/dL and approximately every 5 min once PG was ≤110 mg/dL. The insulin infusion was stopped once the PG concentration was <80 mg/dL (4.4 mmol/L). After 5 min, if PG was ≥54 mg/dL and < 80 mg/dL (3.0–4.4 mmol/L), the study drug was administered by SC injection. If the PG concentration was outside this range, sufficient IV glucose or insulin was administered to bring the PG concentration within the target range. The needle length of the prefilled syringe used for administering the study drug was 0.5 inch (12.7 mm). The trial protocol instructed that dosing be done subcutaneously but did not otherwise actively discriminate between intramuscular and SC injections, as the risk of an inadvertent intramuscular injection was considered low. Blood samples for PG measurement at a central laboratory (efficacy assessments) were taken within 2 min prior to dosing and at predefined intervals at 4, 6, 8, 10, 12, 15, 17, 20, 30, and 45 min (as well as 60 min if the patient's body weight was ≥21 kg) postdose. Blood samples for PK measurements (dasiglucagon and glucagon) were taken prior to dosing and at predefined intervals up to 300 min postdose, after which the participant was discharged from the trial facility. Safety assessments including recording of adverse events

(AEs) were done at screening, at the dosing visit, and at a safety follow-up visit 28 days after dosing.

2.5 | Statistical analyses

The primary endpoint was time from dosing to PG recovery, defined as time to first observed increase in PG of ≥20 mg/dL (1.1 mmol/L) from time of administration (baseline) without IV glucose rescue treatment. PG was considered "not recovered" if IV glucose was administered prior to recovery or if recovery was not achieved by 45 min. Sample size was determined based on the primary objective of confirming superiority of dasiglucagon to placebo with respect to the primary endpoint. Phase 2 results in adults were used to determine sample size.[10] These results showed that the median time to an increase in PG of 20 mg/dL was approximately 10 min for dasiglucagon 0.6 mg compared to an assumed median time of 50 min for placebo. Assuming an exponential distribution with median times of 10 and 50 min, this difference can be detected with 90% power at a 5% significance level using a two-sided log-rank test in 20 participants randomized to dasiglucagon and 10 participants randomized to placebo with a follow-up time of 45 min. Glucagon was included as a reference to compare the responses and AE profile of dasiglucagon with those of a marketed product; no formal statistical comparison between dasiglucagon and glucagon was conducted, and a glucagon group of 10 participants was considered sufficient for this comparison.

The primary endpoint was summarized by treatment group using survival analysis methods (median time to event). Participants who received rescue IV glucose before 45 min (as well as those without PG recovery within 45 min of dosing) were censored at 45 min. The treatment difference for dasiglucagon versus placebo was evaluated inferentially using a two-sided log-rank test stratified by age group and injection site. Plots show the estimated probability of having recovered ("inverted" Kaplan–Meier curves) for each treatment group, with results for the primary endpoint expressed as Kaplan–Meier estimates of the median time to PG recovery. Kaplan–Meier plots are also presented by age group and injection site. Two sensitivity analyses were performed, whereby the primary analysis was repeated without censoring for participants receiving rescue IV glucose within 45 min and with censoring at the time of rescue for participants receiving rescue IV glucose within 45 min.

In addition to determining the observed time from dosing to PG recovery, a prespecified supportive analysis was performed to calculate the true time from dosing to PG recovery for each participant using linear interpolation between the two time points before and after PG recovery had occurred (i.e., to determine the predicted time of an exact 20-mg/dL increase in PG). As for the primary endpoint, results were summarized by treatment group using survival analysis methods (median time to event).

Confirmatory secondary endpoints were achievement of PG recovery within 30, 20, 15, and 10 min of dosing and change in PG from baseline at these time points. As for the primary endpoint, formal statistical comparisons were made between dasiglucagon and placebo. The 30-, 20-, 15-, and 10-min recovery rates were compared at each time

point using a Cochran–Mantel–Haenszel test stratified by age group and injection site. Change from baseline in PG was compared at each time point using an analysis of covariance model with treatment group, age group, and injection site as fixed effects and baseline PG as a covariate. For participants who required rescue IV glucose treatment, the PG value at the time of rescue was carried forward.

For the primary and secondary confirmatory endpoints, the overall type 1 error was controlled via a prespecified hierarchical (fixed sequence) inferential testing procedure (Supplementary Figure 1).

3 | RESULTS

3.1 | Participant disposition and characteristics

Of the 59 children and adolescents screened for the trial, 42 eligible participants were randomly assigned in a 2:1:1 ratio to dasiglucagon (n = 21), placebo (n = 11), and glucagon (n = 10). One participant (dasiglucagon group) withdrew for logistical reasons prior to receiving the investigational product. In total, 41 participants received investigational product (dasiglucagon: n = 20; placebo: n = 11; glucagon: n = 10), all of whom completed the trial (see Supplementary Figure 2 for further details).

Overall, baseline characteristics at randomization were well matched among treatment groups (Table 1), with the exception of a higher proportion of male participants in the glucagon group. Most of the participants were White (95.1%), and 80.5% of participants were non-Hispanic/Latino. PG at baseline following the hypoglycemic clamp procedure was similar across treatment groups, with median values in the range of 72–73 mg/dL across groups (Table 1).
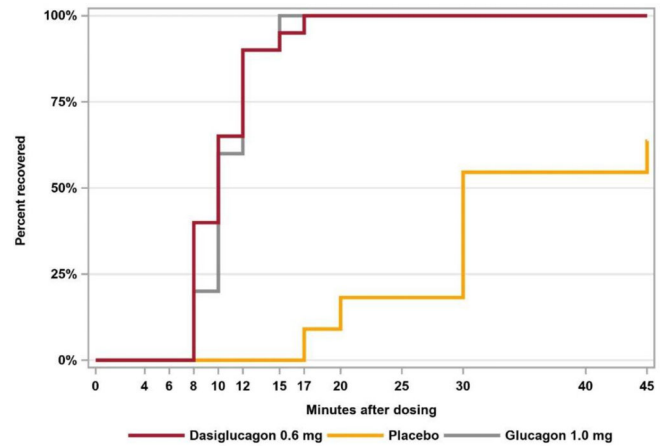
FIGURE 1 Kaplan–Meier plot of observed time to plasma glucose recovery. Data are for the full analysis set. Percent of participants with plasma glucose recovery with type 1 diabetes over time after a single dose of dasiglucagon 0.6 mg, placebo, or glucagon 1.0 mg. Plasma glucose recovery was defined as an increase from baseline of at least 20 mg/dL without administration of rescue intravenous glucose

TABLE 1 Participant baseline characteristics

	Dasiglucagon	Placebo	Glucagon
Full analysis set, No.	20	11	10
Female/male, No.	10/10	6/5	2/8
Age (years)	12.5 (7–17)	15.0 (7–17)	12.0 (7–17)
Age groups, No.			
6–11 years	8	4	4
12–17 years	12	7	6
Weight (kg)	53.00 (21.2–117.0)	53.30 (23.0–91.7)	53.70 (25.0–67.1)
BMI (kg/m^2)	19.55 (13.8–35.3)	19.90 (13.3–28.2)	19.05 (15.0–24.0)
Duration of diabetes (years)	5.59 (1.8–12.9)	5.21 (1.1–14.1)	4.64 (1.1–16.3)
HbA$_{1c}$ (%)	7.55 (6.0–11.2)	7.80 (5.3–9.9)	7.50 (5.3–11.2)
Race, No.			
White	19	10	10
Multiple race	1	0	0
Missing	0	1[a]	0
Ethnicity, No.			
Not Hispanic or Latino	16	8	9
Hispanic or Latino	4	2	1
Missing	0	1[a]	0
Plasma glucose (mg/dl)	72.61 (57.1–81.1)	73.15 (59.1–82.2)	72.16 (56.0–77.1)

Note: Values are medians (min–max) unless otherwise specified.
Abbreviations: BMI, body mass index; HbA$_{1c}$, hemoglobin A$_{1c}$.
[a]Missing data.

3.2 | Time to PG recovery

Dasiglucagon was superior to placebo with respect to the primary endpoint of observed time from dosing to PG recovery, with an estimated median of 10 min (95% confidence interval [CI], 8–12) for dasiglucagon versus 30 min (95% CI, 20; upper limit not estimable) for placebo (P < .001; Figure 1). In the glucagon group, the median time to PG recovery was 10 min (95% CI, 8–12), that is, similar to the results obtained for dasiglucagon.

Both sensitivity analyses confirmed the results of the primary analysis. Results for the first sensitivity analysis (without censoring) were identical to those for the primary analysis and almost identical for the second sensitivity analysis (with censoring), since only one participant required IV glucose rescue treatment within 45 min (placebo group, rescued at 12 min).

No clinically relevant differences in time to PG recovery were seen with respect to age group (Supplementary Figure 3) or injection site (Supplementary Figure 4).
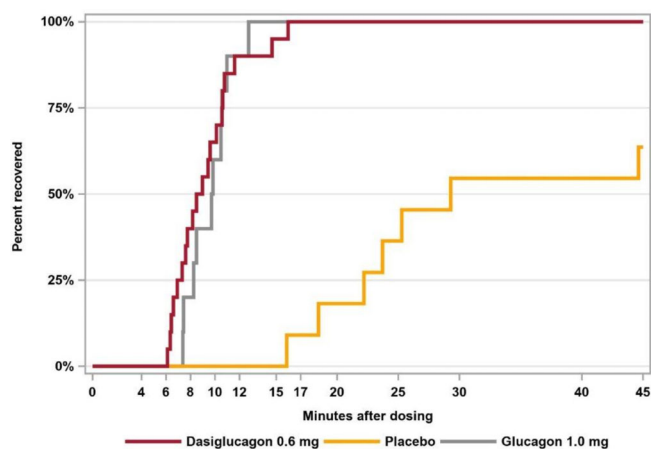
FIGURE 2 Kaplan–Meier plot of estimated true time to plasma glucose recovery (linear interpolation). Data are for the full analysis set. Percent of participants with plasma glucose recovery with type 1 diabetes over time after a single dose of dasiglucagon 0.6 mg, placebo, or glucagon 1.0 mg. Plasma glucose recovery was defined as an increase from baseline of at least 20 mg/dL without administration of rescue intravenous glucose

Using linear interpolation to estimate the true time from dosing to PG recovery, the median time to recovery was 8.7 min (95% CI, 6.9–10.6) for dasiglucagon, 29.3 min (95% CI, 18.5; upper limit not estimable) for placebo, and 9.8 min (95% CI, 7.4–10.6) for glucagon (Figure 2).

3.3 | Proportion of participants in whom PG recovery was achieved

All but one participant in the dasiglucagon group experienced PG recovery within 15 min (19 [95%] participants), and all had PG recovery by 20 min (Table 2). In contrast, no participants had PG recovery in the placebo group within 15 min of dosing, two participants had PG recovery by 20 min, and four participants had PG recovery after more than 45 min. IV glucose rescue was required for one participant in the placebo group (12 min after dosing) but none in the dasiglucagon or glucagon groups. The proportion of participants in whom glucose recovery was achieved within 10, 15, 20, and 30 min of dosing was significantly greater for dasiglucagon than placebo (P < .01 at each time point; Table 2).

3.4 | PG change from baseline

Mean PG increase from baseline over time is shown in Figure 3. After 30 min, mean PG had increased from baseline by 98.2 mg/mL with dasiglucagon compared to 17.3 mg/mL with placebo; for glucagon the mean increase was 84.4 mg/mL. The increase in mean PG from baseline was significantly greater for dasiglucagon versus placebo at 10, 15, 20, and 30 min postdose (P < .001 at each time point).

3.5 | Safety

No serious or severe AEs were reported. Nausea and vomiting were the most frequently reported AEs for dasiglucagon and the active comparator, with a higher proportion of participants experiencing these transient events with dasiglucagon than with glucagon (Table 3). This was attributed to nausea and vomiting being more frequently reported for dasiglucagon in the 12-to-17-year age group; no treatment-related

TABLE 2 Plasma glucose recovery within 30, 20, 15, and 10 min of dosing

Plasma glucose recovery[a]	Dasiglucagon No. (%)	Placebo No. (%)	Glucagon No. (%)	Dasiglucagon vs. placebo[b]
Full analysis set	20	11	10	
Within 10 min	13 (65)	0 (0)	6 (60)	<.001
Within 15 min	19 (95)	0 (0)	10 (100)	<.001
Within 20 min	20 (100)	2 (18)	10 (100)	<.001
Within 30 min	20 (100)	6 (55)	10 (100)	.007

[a]Defined as first increase in plasma glucose of ≥20 mg/dL (1.1 mmol/L) from baseline within 45 min during the hypoglycemic clamp procedure without administration of rescue intravenous glucose.
[b]P values calculated using a Cochran–Mantel–Haenszel test stratified by age group and injection site.

imbalance was apparent in the 6-to-11-year age group (Table 4). There was no apparent correlation between dasiglucagon exposure (area under the curve or C_{max}) and nausea and/or vomiting by either age (Supplementary Figure 5) or body weight (Supplementary Figure 6).

For both dasiglucagon and glucagon, most AEs of nausea had an onset within 1.5–3 h of dosing, with the majority of events lasting less than 2 h. Vomiting tended to occur later than nausea. The majority of events occurred between 2 and 3 h of dosing and had a duration of less than 5 min. There was no apparent difference between age groups (6–11 years; 12–17 years) in the time to onset or duration of nausea or vomiting.

Three injection site erythema events were reported; all were mild and transient events following glucagon treatment (Table 3). Hypoglycemia AEs did not appear temporally related to the clamp procedure or investigational product dosing. One hypoglycemia AE (in the placebo group) was recorded as having an onset at 5 min after dosing; the remainder had an onset between approximately 5 and 33 days of investigational product administration.

There were no clinically significant changes in laboratory evaluations, vital signs, electrocardiogram measurements, or physical examinations. One participant in the dasiglucagon group had positive test results for anti-drug antibodies at the end-of-trial follow-up visit and after completion of the trial. The antibodies had a low titer and did

FIGURE 3 Mean increase in plasma glucose over time. Data are for the full analysis set. Mean increase in plasma glucose (mg/dL) is shown as change from baseline with 95% CIs in participants with type 1 diabetes after a single dose of dasiglucagon 0.6 mg, placebo, or glucagon 1.0 mg. The horizontal line represents the definition of plasma glucose recovery used for the primary endpoint (an increase from baseline of at least 20 mg/dL without administration of rescue intravenous glucose)

TABLE 4 Nausea and vomiting adverse events by age group

	Dasiglucagon No. (%), E	Placebo No. (%), E	Glucagon No. (%), E
6–11 years			
Safety analysis set	n = 8	n = 4	n = 4
All AEs[a]	3 (37.5), 5	1 (25.0), 1	4 (100.0), 8
Nausea	2 (25.0), 2	0 (0.0), 0	2 (50.0), 2
Vomiting	2 (25.0), 2	0 (0.0), 0	1 (25.0), 1
12–17 years			
Safety analysis set	n = 12	n = 7	n = 6
All AEs[a]	12 (100.0), 31	6 (85.7), 22	5 (83.3), 7
Nausea	11 (91.7), 12	0 (0.0), 0	1 (16.7), 1
Vomiting	8 (66.7), 11	0 (0.0), 0	0 (0.0), 0

Note: No. indicates number of patients experiencing at least one event; %, percentage of patients experiencing at least one event; E, number of events.
[a]Treatment-emergent adverse events (AEs) defined as AEs with onset at or after initiation of the investigational product until the end of the observation period.

TABLE 3 Summary of common adverse events

	Dasiglucagon No. (%), E	Placebo No. (%), E	Glucagon No. (%), E
Safety analysis set	n = 20	n = 11	n = 10
All AEs[b]	15 (75.0), 36	7 (63.6), 23	9 (90.0), 15
Most common AEs[a,b]			
Nausea	13 (65.0), 14	0 (0.0), 0	3 (30.0), 3
Vomiting	10 (50.0), 13	0 (0.0), 0	1 (10.0), 1
Upper respiratory tract infection	2 (10.0), 3	0 (0.0), 0	0 (0.0), 0
Hypoglycemia	2 (10.0), 2	4 (36.4), 16	2 (20.0), 2
Injection site erythema	0 (0.0), 0	0 (0.0), 0	3 (30.0), 3
Headache	2 (10.0), 2	1 (9.1), 1	1 (10.0), 1

Note: No. indicates number of patients experiencing at least one event; %, percentage of patients experiencing at least one event; E, number of events.
[a]Occurring in >1 patient in any treatment group.
[b]Treatment-emergent adverse events (AEs) defined as AEs with onset at or after initiation of the investigational product until the end of the observation period.

not cross-react with glucagon. Thus, the ADA specificity was to dasiglucagon-specific epitopes. No neutralizing activity was detected.

4 | DISCUSSION

This phase 3 trial in children and adolescents with T1DM (6–17 years) investigated the efficacy and safety of a single SC dose of 0.6 mg dasiglucagon, the first glucagon analog in a ready-to-use aqueous formulation, as a rescue treatment for severe hypoglycemia.

The PG target prior to dosing with dasiglucagon, placebo, or glucagon was 54–80 mg/dL (3.0–4.4 mmol/L), which was induced through an insulin-induced hypoglycemic clamp procedure. Insulin infusion was stopped once PG was <80 mg/dL. To further ensure the safety of trial participants, use of IV rescue glucose was allowed throughout the procedure. Based on PK/PD modeling and simulation, the same dasiglucagon dose as used for adults (0.6 mg) was considered appropriate for pediatric participants of 6–17 years of age. As previously done for the two pivotal phase three trials of dasiglucagon in adult patients with T1DM,[11,12] we chose time from injection to PG recovery as the primary endpoint, reflecting the critical importance of fast reversal of hypoglycemia in an emergency situation.

Consistent with the results for the two pivotal adult trials,[11,12] superiority was confirmed for dasiglucagon relative to placebo with regard to the primary endpoint and all confirmatory secondary endpoints. The median time from injection to PG recovery was 10 min for dasiglucagon versus 30 min for placebo and 10 min for glucagon, with no clinically relevant differences seen for dasiglucagon with respect to age group (6–11 years; 12–17 years) or injection site (abdomen; thigh). It is noteworthy that the median time to PG recovery was similar for dasiglucagon in pediatric and adult participants (approximately 10 min). Furthermore, dasiglucagon increased PG levels by a similar magnitude from baseline in pediatric and adult participants.[11,12]

Using data interpolation to obtain a more precise estimate of recovery times, the median true time from dosing to PG recovery was 8.7 min for dasiglucagon versus 29.3 min for placebo. The corresponding median true time to PG recovery for glucagon was 9.8 min. It should be noted, however, that this does not include the time taken to reconstitute the lyophilized glucagon reference product and, hence, the real-life time to response for glucagon would be longer.

Overall, dasiglucagon was well tolerated. The safety profile of dasiglucagon was consistent with the known side effects of glucagon treatment, with nausea and vomiting the most commonly reported AEs with active treatment. A higher proportion of participants experienced these transient events with dasiglucagon than with glucagon, due to nausea and vomiting being more frequently reported for dasiglucagon in the 12-to-17-year age group. There was no apparent relationship between dasiglucagon exposure and nausea and/or vomiting by either age or body weight, suggesting that the higher proportion of 12- to17-year-old patients with these events in the dasiglucagon group may be a coincidental finding in this relatively small trial with 42 participants. This is further supported by the results from a larger phase 3 trial in adult patients testing dasiglucagon in a similar trial setting, which showed no difference between dasiglucagon and glucagon with respect to incidences of nausea and vomiting.[11]

Pediatric guidelines recommend that glucagon should be readily accessible to all parents and caregivers.[1] Currently available treatments for severe hypoglycemia, when a child or adolescent is unable to safely swallow oral carbohydrates, are limited to IV dextrose and glucagon. Patients reported various administration issues (unsuccessful injection, delays in injection) in using injectable glucagon emergency kits that need complex, time-consuming procedures for reconstitution.[13-15] Nasal glucagon was recently approved for children in a fixed-dose drug-device combination for children older than 4 years but may cause side effects such as headache, upper airway discomfort, lacrimation, or nasal congestion in addition to the known side effects of glucagon.[16] Thus, an aqueous, ready-to-use glucagon analog formulation may be a welcome addition to the options for the treatment of severe hypoglycemia in childhood.

The strengths of this trial include its randomized, placebo-controlled, multicenter design as well as the blinding of the investigator and participants to study treatment to reduce potential bias. However, it is acknowledged that the trial was conducted in a highly controlled investigational inpatient setting that may not fully reflect conditions in the real world where, for example, the PG level at which dasiglucagon is used in clinical practice may be lower than that used in the trial (where a PG target of 80 mg/dL [4.4 mmol/L] was set for the hypoglycemic clamp).

In conclusion, dasiglucagon is rapid, effective, and reliable in restoring PG levels following insulin-induced hypoglycemia in children and adolescents with T1DM. The overall safety profile of dasiglucagon appears similar to that of reconstituted lyophilized glucagon. These findings are in line with results for dasiglucagon trials in adults, supporting the use of a common SC dose of dasiglucagon (0.6 mg) to treat severe hypoglycemia in pediatric (6–17 years) and adult individuals with diabetes.

AUTHOR CONTRIBUTIONS

Zealand Pharma A/S sponsored the study and was involved in the design (Ramin Tehranchi and Thomas Danne designed the trial) and conduct of the study and analysis and interpretation of the data, including collection, management, and statistical analysis of the data.

Ramin Tehranchi and Anita Melgaard are employees of Zealand Pharma A/S. The authors had full access to the clinical trial report and associated documents. Tadej Battelino, Timothy Bailey, Klemen Dovc, Jenine Y. Stone, Stephanie Woerner, Thekla von dem Berge, Linda A. DiMeglio, and Thomas Danne were trial investigators and helped obtain data. Ramin Tehranchi was the medical project director responsible for the trial, and Anita Melgaard was responsible for the statistical considerations and analyses. All authors were involved in drafting the manuscript or revising it critically for important intellectual content, approved the final version to be published, and take full responsibility for the accuracy and integrity of the content.

CONFLICT OF INTEREST

Tadej Battelino has served on advisory panels for Medtronic and Sanofi; consulted for Indigo Diabetes; received research support from Medtronic, Novo Nordisk A/S, and Zealand Pharma A/S; received speaker's honoraria from Abbott, AstraZeneca, Dexcom, Lilly Diabetes, and Medtronic; and holds stock in DreaMed Diabetes. Timothy Bailey has received research support from Abbott Diabetes, Abbott Rapid Diagnostics, Biolinq, Capillary Biomedical , Dexcom, Eli Lilly, Kowa, Lexicon, Livongo, Medtronic, Medtrum, Novo Nordisk, REMD, Sanofi, Sanvita, Viacyte, vTv Therapeutics, and Zealand Pharma; consulting honoraria from Abbott, Lifescan, Medtronic, Novo, and Sanofi; and speaking honoraria from BD, Medtronic, and Sanofi. Thomas Danne has served on advisory panels for AstraZeneca, Boehringer Ingelheim International GmbH, Eli Lilly and Company, Medtronic, Novo Nordisk A/S, and Sanofi. Thekla von dem Berge has received speaker honoraria from Medtronic, Sanofi, and Ypsomed. Klemen Dovc received spearker honoraria from Pfizer, Novo Nordisk and Eli Lilly. Stephanie Woerner, Linda DiMeglio, and Jenine Y. Stone declare no duality of interest.

DATA AVAILABILITY STATEMENT

The individual patient data are not made available for sharing with third parties.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.