Dasiglucagon—A Next-Generation Glucagon Analog for Rapid and Effective Treatment of Severe Hypoglycemia: Results of Phase 3 Randomized Double-Blind Clinical Trial

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Diabetes Care 2021;44:1361–1367 | https://doi.org/10.2337/dc20-2995

OBJECTIVE

To evaluate the efficacy and safety of dasiglucagon, a ready-to-use, next-generation glucagon analog in aqueous formulation for subcutaneous dosing, for treatment of severe hypoglycemia in adults with type 1 diabetes.

RESEARCH DESIGN AND METHODS

This randomized, double-blind trial included 170 adult participants with type 1 diabetes, each randomly assigned to receive a single subcutaneous dose of 0.6 mg dasiglucagon, placebo, or 1 mg reconstituted glucagon (2:1:1 randomization) during controlled insulin-induced hypoglycemia. The primary end point was time to plasma glucose recovery, defined as an increase of ≥20 mg/dL from baseline without rescue intravenous glucose. The primary comparison was dasiglucagon versus placebo; reconstituted lyophilized glucagon was included as reference.

RESULTS

Median (95% CI) time to recovery was 10 (10, 10) minutes for dasiglucagon compared with 40 (30, 40) minutes for placebo ($P < 0.001$); the corresponding result for reconstituted glucagon was 12 (10, 12) minutes. In the dasiglucagon group, plasma glucose recovery was achieved within 15 min in all but one participant (99%), superior to placebo (2%; $P < 0.001$) and similar to glucagon (95%). Similar outcomes were observed for the other investigated time points at 10, 20, and 30 min after dosing. The most frequent adverse effects were nausea and vomiting, as expected with glucagon treatment.

CONCLUSIONS

Dasiglucagon provided rapid and effective reversal of hypoglycemia in adults with type 1 diabetes, with safety and tolerability similar to those reported for reconstituted glucagon injection. The ready-to-use, aqueous formulation of dasiglucagon offers the potential to provide rapid and reliable treatment of severe hypoglycemia.

Glucagon is well established as a first-line pharmaceutical emergency treatment for severe (level 3) hypoglycemia in people with diabetes. Rescue glucagon can be

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Received 9 December 2020 and Accepted 11 March 2021

Clinical trial reg. no. NCT03378635, clinicaltrials.gov

This article contains supplementary material online at https://doi.org/10.2337/figshare.14207960.

carried by patients or caregivers, providing them with a valuable safety measure. As the only prescription treatment for severe hypoglycemia that is not limited to dosing by health care professionals, glucagon has been recommended in the most recent American Diabetes Association treatment guidelines (1) to be prescribed for all individuals at increased risk of level 2 hypoglycemia, defined as blood glucose <54 mg/dL (<3.0 mmol/L), so it is available if needed. Caregivers, school personnel, or family members of these individuals are advised that they should know where glucagon treatment is stored and when and how to administer it.

Despite these recommendations, glucagon is underused for the treatment of severe hypoglycemia in individuals with diabetes, even when available to well-informed patients and caregivers (2–4). This underuse may be at least partly attributable to the fact that the majority of glucagon for prescription use is provided in glucagon emergency kits (Glucagon for Injection, Eli Lilly and Company; GlucaGen HypoKit, Novo Nordisk) that require multistep reconstitution before subcutaneous or intramuscular injection. The complexity of the multistep reconstitution process is a known barrier to timely, accurate, and effective administration of glucagon, often resulting in both delays and inaccurate dosing and the potential for total failure in dose administration (3,5,6). More recently, ready-to-use glucagon products for subcutaneous injection (Gvoke; formulation in the organic solvent DMSO) and intranasal dry powder administration (Baqsimi) have become available. These newer products have unique benefit-risk profiles because of the characteristics of drug formulation and/or mode of administration (7,8).

The next-generation glucagon analog dasiglucagon is the first glucagon product to be provided in a ready-to-use, aqueous formulation. Like endogenous glucagon, dasiglucagon is composed of 29 amino acids, but with seven amino acid substitutions compared with endogenous glucagon to increase the physical and chemical stability in aqueous media. Aqueous formulation is thereby enabled, eliminating the need for reconstitution before injection. Dasiglucagon maintains specificity for the glucagon receptor and has potency comparable to that of native glucagon. In adults with type 1 diabetes, dasiglucagon rapidly and effectively restored euglycemia after insulin-induced hypoglycemia at doses from 0.1 to 1.0 mg (9). The present phase 3 trial was conducted to demonstrate the efficacy and safety of a single subcutaneous dose of 0.6 mg dasiglucagon as a treatment for severe hypoglycemia in those with type 1 diabetes.

RESEARCH DESIGN AND METHODS

Trial Design

This trial used a multicenter, randomized, placebo-controlled, double-blind, parallel-group design in a clinical research inpatient setting. The trial was conducted in two centers in Germany and one in each of the following: Austria, the U.S., and Canada. It included three parallel treatment arms, with participants randomly assigned 2:1:1 to receive a single subcutaneous dose of 0.6 mg dasiglucagon, placebo, or 1.0 mg reconstituted lyophilized glucagon (GlucaGen; 1 mg/mL glucagon for injection). The primary objective of the trial was to demonstrate superiority of dasiglucagon over placebo; reconstituted glucagon was included as a reference. Randomization was performed using a fixed-block randomization scheme, which was generated before the trial began by an independent statistician/programmer who was not a member of the trial team; the investigators were unaware of the block size of the randomization scheme. Randomization was stratified by injection site (abdomen, buttocks, or thigh) via an interactive web response system. Dasiglucagon and placebo were provided in ready-to-use aqueous formulations, and glucagon was provided as a lyophilized powder requiring reconstitution. Because the medications were different in appearance, the preparation and administration of trial medication were performed by unblinded trial personnel who were not involved in any other trial procedures or assessments. The tested aqueous formulation of dasiglucagon contained 1 mg dasiglucagon per mL, and hence, the injected volume was 0.6 mL (similar for placebo).

Dasiglucagon is developed for commercialization in two presentations: a prefilled syringe and an autoinjector. Trial product was for this trial was administered via prefilled syringe.

The trial was performed in accordance with the Declaration of Helsinki, International Conference on Harmonisation guidelines, and Good Clinical Practice. An institutional review board or independent ethics committee approved the trial at each center, and all participants provided written informed consent before undergoing any trial procedures or assessments.

Participants

The trial included adults (aged 18–75 years, inclusive) with type 1 diabetes receiving stable insulin therapy and with HbA_{1c} <10% (85.8 mmol/mol). Participants were excluded if they had previously received dasiglucagon, had an allergy to any trial product, or had experienced hypoglycemia with seizure during the preceding year or severe hypoglycemia during the preceding month. Participants were also excluded if they had used β-blockers, indomethacin, warfarin, or anticholinergic drugs daily during the 28 days before screening.

Procedures

Participants were screened between 30 and 3 days before dosing. Eligible participants attended a single dosing visit and a safety follow-up visit 28 days after dosing. The dosing visit required an overnight stay in the center before dosing. Participants fasted from 2200 h but were allowed to have small amounts of carbohydrates (up to 20 g total) to prevent hypoglycemia. Participants' insulin therapy was stopped in advance according to predefined timelines: insulin degludec and insulin glargine U300 48 h before dosing, other long-acting insulins 24 h before dosing, and insulin NPH and short-acting insulins (except insulin glulisine) 16 h before dosing. Insulin pumps were stopped on the morning of the dosing day (insulin glulisine) or at least 6 h before dosing (other insulins).

Intravenous insulin glulisine was administered at 150% of the participant's usual basal rate, with adjustments to achieve a controlled decline in plasma glucose, targeting a plasma glucose level of 55 mg/dL (3.1 mmol/L). Plasma glucose concentrations were measured using glucose analyzers (YSI 2300; Yellow Springs Instruments, Yellow Springs, OH; or Super GL

analyzer; Dr. Müller Gerätebau GmbH, Freital, Germany). After the start of the insulin infusion, plasma glucose was measured approximately every 10 min while plasma glucose was >110 mg/dL (6.1 mmol/L) and approximately every 5 min once plasma glucose was ≤110 mg/dL.

The insulin infusion was stopped once the glucose concentration was <60 mg/dL (3.3 mmol/L). After 5 min and if plasma glucose was ≥45 mg/dL and <60 mg/dL (2.5–3.3 mmol/L), the trial drug was administered by subcutaneous injection, with location assigned to the abdomen, buttock, or thigh. Serial blood samples for central laboratory plasma glucose assessments were taken predose and at predefined intervals at 4, 6, 8, 10, 12, 15, 17, 20, 25, 30, 40, 50, 60, 75, and 90 min after dosing. Blood samples for pharmacokinetic measurements (data not shown) and safety assessment were taken predose and at predefined intervals up to 120 and 300 min after dosing, respectively.

Antidrug antibody (ADA) samples were analyzed using a multitiered testing approach. In tier 1, screening for antidasiglucagon antibodies was conducted based on an ELISA. The same assay with inclusion of excess dasiglucagon was used as confirmatory analysis in tier 2. Confirmed positive samples were analyzed for in vitro neutralizing activity in a cell-based assay (tier 3). Finally, ADA-positive samples were titrated using the tier 1 assay. A similar set of assays were used to analyze ADA-positive samples for antibodies cross-reacting with glucagon.

Statistical Analysis

The sample size was set to 78 participants treated with dasiglucagon, with a total of 156 participants completing the dosing visit. In a phase 2 trial, median time to plasma glucose recovery (glucose increase of 20 mg/dL) was approximately 10 min with dasiglucagon. With a 2:1:1 randomization for dasiglucagon to placebo to glucagon in this trial, and assuming an exponential time-to-recovery distribution with median times of 10 min for dasiglucagon and at least 20 min for placebo, a two-sided log-rank test was expected to detect a difference between dasiglucagon and placebo with 90% power at a 5% significance level, given a follow-up time of 45 min. Median time to recovery for placebo was expected to be >20 min, which would result in a power >90%.

The primary end point was time from dosing to plasma glucose recovery, defined as time to first increase in plasma glucose of ≥20 mg/dL (1.1 mmol/L) from baseline (time of injection) without rescue intravenous glucose. Individuals were considered not to have recovered if rescue intravenous glucose was administered or if recovery was not achieved within 45 min. In addition to the observed time to recovery, a supportive analysis using linear interpolation between observed time points before and after plasma glucose recovery occurred was prespecified to find an individual's true time to plasma glucose recovery (i.e., the predicted time of an exact 20 mg/dL increase in plasma glucose). The primary end point was summarized by treatment group using survival analysis methods (median time to event and mean time to event when no censoring occurred). The treatment group difference between dasiglucagon and placebo was evaluated inferentially using a two-sided log-rank test stratified by injection site. Time to recovery is displayed as cumulative recovery (i.e., as one minus Kaplan-Meier estimate). The influence of injection site was evaluated in a proportional hazards model, including treatment group and injection site as categorical effects and baseline plasma glucose as a continuous covariate.

The key secondary end points of achievement of plasma glucose recovery within 30, 20, 15, and 10 min were compared between treatment groups using Fisher's exact test. The key secondary end points of plasma glucose change from baseline at 30, 20, 15, and 10 min were analyzed using an ANCOVA model. The treatment group differences between dasiglucagon and placebo for the primary and key secondary end points were tested in a prespecified order (as listed above) using a hierarchical testing approach to control for multiplicity.

RESULTS

Participant Disposition and Characteristics

Between December 2017 and May 2018, 170 participants were randomly assigned, of whom 168 received a single dose of trial drug (dasiglucagon, *n* = 82; placebo, *n* = 43; and glucagon, *n* = 43); details are provided in Supplementary Fig. 1. A majority of participants were male (63%), White (92%), and non-Hispanic (96%). Mean age was 39.1 years (range, 18–71 years), mean BMI was 26.1 kg/m^2, mean HbA_{1c} was 7.4% (57 mmol/mol), and mean duration of diabetes was 20.0 years. Demographic data and baseline diabetes characteristics were similar across the three treatment groups (Table 1).

Efficacy

Results for plasma glucose recovery are shown in Table 2. Median (95% CI) time from dosing to plasma glucose recovery was 10 min for dasiglucagon (10, 10) compared with 40 min for placebo (30, 40) ($P < 0.001$). Median time to plasma glucose recovery for the reference glucagon product was 12 min (10, 12). A one minus Kaplan-Meier plot is shown in Fig. 1*A*.

Using linear interpolation to estimate the true time to plasma glucose recovery, median (95% CI) time to recovery was 9.0 min for dasiglucagon (8.4, 9.7), 33.7 min for placebo (26.1, 36.1), and 10.0 min for glucagon (9.0, 10.6).

A high proportion of dasiglucagon-treated participants achieved plasma glucose recovery within predefined time points; 65%, 99%, and 99% of participants recovered within 10, 15, and 20 min after dose administration, respectively. The single dasiglucagon-treated participant who did not recover within 20 min closely approached the recovery threshold, with a plasma glucose increase from baseline to 20 min of 19.98 mg/mL (1.1 mmol/L). In contrast, only one (2%) participant in the placebo group recovered within 15 min, with 47% of participants achieving recovery within 30 min after injection (Table 2). Pairwise comparisons of the proportion of participants achieving glucose recovery were significantly in favor of dasiglucagon versus placebo at 10, 15, 20, and 30 min ($P < 0.001$ for each time point). In the reference glucagon group, recovery rates were 49%, 95%, and 98% after 10, 15, and 20 min, respectively. Intravenous glucose rescue was not required by participants in the dasiglucagon or glucagon groups but was required by seven (16%) participants in the placebo group.

Plasma glucose increase from baseline is shown for the three treatment

Table 1—Demographic data and baseline diabetes characteristics

	Dasiglucagon (n = 82)	Placebo (n = 43)	Glucagon (n = 43)
Sex, n (%)			
Male	50 (61)	27 (63)	28 (65)
Female	32 (39)	16 (37)	15 (35)
Race, n (%)			
White	76 (93)	39 (91)	39 (91)
Other	6 (7)	4 (9)	4 (9)
Age, years, median (range)	37.0 (18–71)	36.0 (18–65)	38.0 (23–66)
Weight, kg	78.3 (13.5)	79.5 (12.9)	80.7 (15.1)
BMI, kg/m^2	26.1 (4.13)	26.1 (3.34)	25.9 (3.42)
HbA_{1c}, %	7.52 (0.95)	7.17 (0.74)	7.41 (0.97)
Diabetes duration, years	21.5 (12.32)	18.3 (11.02)	18.7 (11.17)
Plasma glucose, mg/dL	58.9 (5.59)	58.8 (4.44)	58.5 (5.11)

Data are mean (SD) unless otherwise indicated.

groups in Fig. 2. After 30 min, mean plasma glucose increase from baseline was 90.9 mg/mL for dasiglucagon compared with 19.1 mg/mL for placebo; the corresponding mean increase for the reference glucagon product was 88.5 mg/mL. Plasma glucose change from baseline was significantly greater for dasiglucagon than placebo at 10, 15, 20, and 30 min ($P < 0.001$ for each time point).

Injection site (abdomen, buttock, or thigh) did not influence time to plasma glucose recovery across the three treatment groups ($P = 0.152$).

Safety

The safety profiles of both dasiglucagon and glucagon were consistent with the known adverse effects of glucagon treatment, with the most common drug-related adverse events of nausea, vomiting, and headache comparable between treatment groups (Table 3). In both active treatment groups and in this trial setting, nausea generally occurred ~1 to 3 h after dosing and lasted <3 h in most cases. Vomiting tended to occur later than nausea, with most events occurring between 2 and 3 h after injection and lasting <3 h. No serious or fatal adverse events occurred.

Local tolerability assessments showed few events: two events in two (2%) participants in the dasiglucagon group, two events in two (5%) participants in the placebo group, and three events in three (7%) participants in the glucagon group. All injection site reactions were mild and transient (e.g., redness, edema, and pain on palpation).

One participant in the dasiglucagon group tested positive for ADAs at the 28-day follow-up visit. The antibodies had a low titer, were nonneutralizing in vitro, and did not cross-react with glucagon. These nonneutralizing antibodies were no longer evident 17 months after dosing.

CONCLUSIONS

In this phase 3 trial, a single subcutaneous dose of 0.6 mg dasiglucagon resulted in rapid and sustained reversal of insulin-induced hypoglycemia in adults with type 1 diabetes. Dasiglucagon treatment resulted in significant treatment benefits relative to placebo across all key end points comprising time to plasma glucose recovery, proportion of participants achieving recovery, and change in plasma glucose from baseline. Median time from injection to plasma glucose recovery (defined as first increase in plasma glucose of ≥20 mg/dL [1.1 mmol/L]) was 10 min for dasiglucagon and 12 min for glucagon, with corresponding values of 9.0 vs. 10.0 min when applying linear interpolation to estimate the true time to plasma glucose recovery. A numerically greater proportion of participants achieved plasma glucose recovery within 10, 15, and 20 min after dasiglucagon administration (65%, 99%, and 99%, respectively) compared with those receiving reference glucagon treatment (49%, 95%, and 98%, respectively). By comparison, in a similar clinical trial comparing intranasal and intramuscular glucagon (where success was defined as an increase in plasma glucose to ≥70 or ≥20 mg/dL from the glucose nadir), the respective proportions of participants achieving recovery within 10, 15, and 20 min of dosing were 21%, 71%, and 90% with intranasal glucagon and 48%, 86%, and 100% with intramuscular glucagon (10).

Table 2—Plasma glucose recovery

	Dasiglucagon (n = 82)	Placebo (n = 43)	Glucagon (n = 43)
Time to recovery,* minutes (primary end point)	10 (10, 10) $P < 0.001$†	40 (30, 40)	12 (10, 12)
True time to recovery* estimated using linear interpolation, minutes	9.0 (8.4, 9.7) $P < 0.001$†	33.7 (26.1, 36.1)	10.0 (9.0, 10.6)
Proportion of patients achieving plasma glucose recovery* within, %			
30 min	100	47	100
20 min	99	14	98
15 min	99	2	95
10 min	65	0	49
		$P < 0.001$ for all tests†	

Data are median (95% CI) unless otherwise indicated. *Defined as first increase in plasma glucose of ≥20 mg/dL from baseline without administration of rescue intravenous glucose (censoring at 45 min). †Test relative to placebo.

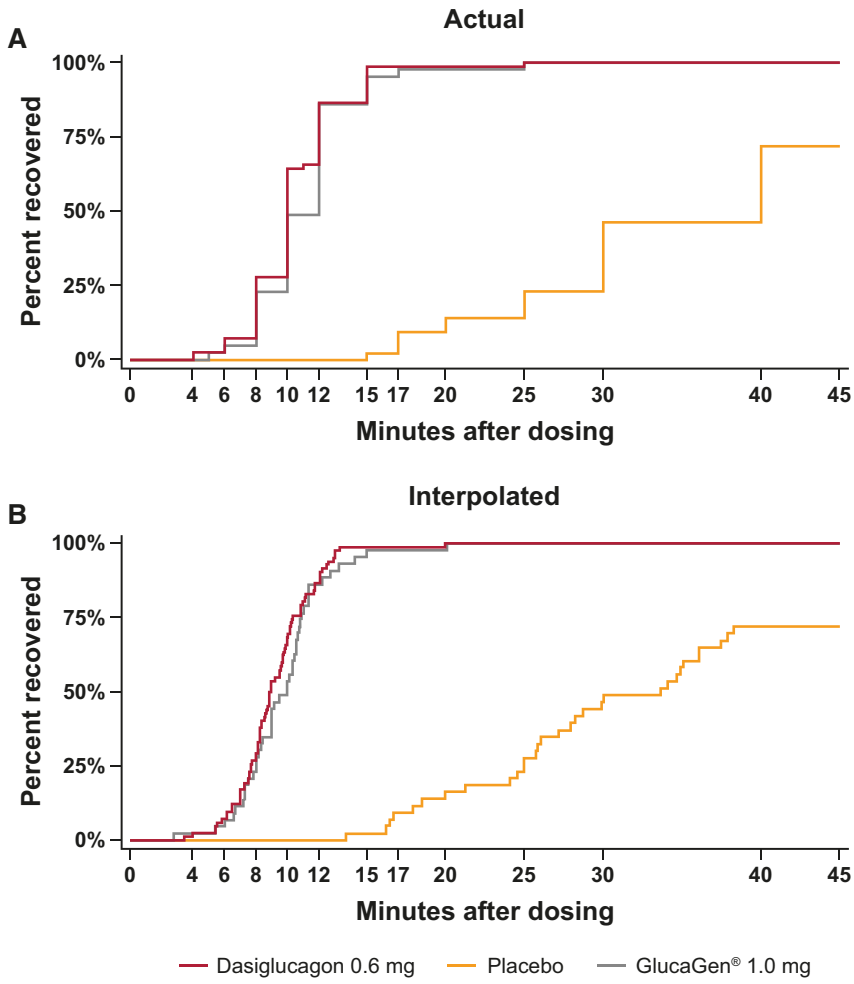

Figure 1—One minus Kaplan-Meier plots of time to plasma glucose recovery. Plasma glucose recovery was defined as an increase from baseline of at least 20 mg/dL without rescue intravenous glucose. *A*: Time to plasma glucose recovery. *B*: Estimated true time to plasma glucose recovery (linear interpolation).

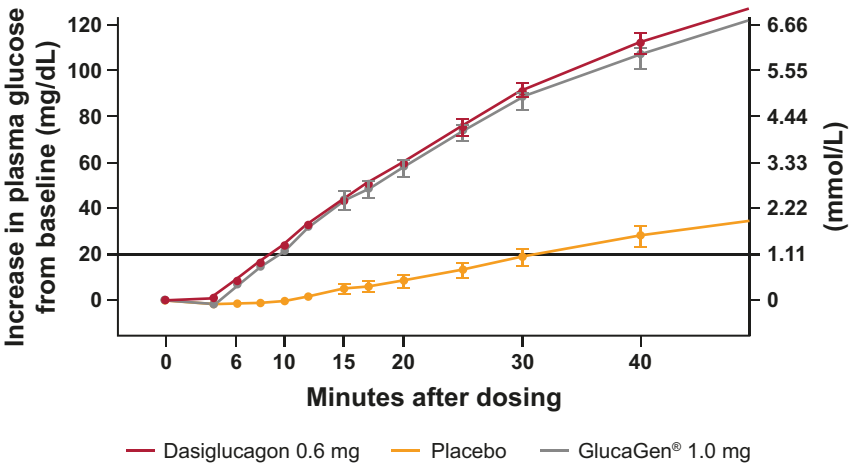

Figure 2—Mean increase in plasma glucose (mg/dL) shown as change from baseline with 95% CIs after a single dose of 0.6 mg dasiglucagon (red), placebo (orange), or 1.0 mg glucagon (gray). The horizontal line represents the definition of plasma glucose recovery used for the primary end point (an increase from baseline of at least 20 mg/dL).

In the current trial, the speed and efficacy of dasiglucagon in achieving plasma glucose recovery were fully on par with those of reconstituted glucagon. Importantly, time to response in this trial was measured from the time of injection and as such did not capture the benefit of being able to administer the ready-to-use dasiglucagon preparation directly as opposed to having to reconstitute glucagon before injection, which is associated with high rates of unsuccessful injection and delayed dosing (5,6). A similar benefit of avoiding the reconstitution step is obtained with the currently marketed ready-to-use glucagon products for subcutaneous injection (Gvoke) or intranasal dry powder administration (Baqsimi). Although they represent an improvement relative to the hypo kit products, these newer products have unique benefit-risk profiles because of the characteristics of drug formulation and/or mode of administration, with injection site edema and pain being more prevalent for Gvoke and nasal and ocular adverse events being more prevalent for Baqsimi, both relative to reconstituted glucagon (7,8). Within the referenced summaries, both of these newer products are characterized by a prolonged time from product administration to achievement of plasma glucose target when compared with reconstituted glucagon (prolonged by 3–4 min for Gvoke (7) and by 1–4 min for Baqsimi (8)). No head-to-head trials comparing these products versus dasiglucagon have been conducted; however, in this trial, dasiglucagon showed no delay in time elapsed from product administration to plasma glucose target achievement compared with reconstituted glucagon. With the combination of the ready-to-use formulation and the rapid and effective reversal of hypoglycemia, dasiglucagon may provide significant benefit to patients for the most clinically relevant parameter of time elapsed from initiating product handling to achieving recovery from severe hypoglycemia.

Glucagon is widely known to be underused as a treatment for severe hypoglycemia (4,11), with only a small proportion of insulin-treated patients being prescribed glucagon rescue medication from the start of insulin therapy (2). Prescribers may be more confident in prescribing a ready-to-

Table 3—Adverse events

	Dasiglucagon (*n* = 82)	Placebo (*n* = 43)	Glucagon (*n* = 43)
All adverse events	66 (80)	14 (33)	32 (74)
Drug-related* adverse events	52 (63)	3 (7)	27 (63)
Most commonly reported† drug-related* adverse events			
Nausea	45 (55)	1 (2)	23 (53)
Vomiting	19 (23)	1 (2)	9 (21)
Headache	8 (10)	1 (2)	4 (9)
Injection site erythema	1 (1)	2 (5)	2 (5)

Data are *n* (%). *Possibly or probably drug-related adverse events, as reported by the investigator. †Occurring in ≥5% of participants in any treatment group.

use glucagon analog such as dasiglucagon. A ready-to-use product is likely to increase the probability of successfully administering the drug, especially for nonmedical caregivers, who often find the complexity of reconstitution highly stressful in an emergency situation (3,4). The simplicity of dosing and short time to hypoglycemia recovery achieved with dasiglucagon may also result in fewer cases of severe and persistent hypoglycemia that require additional medical intervention, which would be expected to reduce the overall cost burden of treatment. The cost of treating a severe hypoglycemic event in an emergency medical or hospital setting is substantial, including direct costs (e.g., hospital treatment, ambulance, primary health care professional contacts, and treatment at home) that may exceed $1,100 and indirect costs (e.g., expected productivity loss) as high as $580 per event (12). In contrast, for severe hypoglycemic episodes that require only nonmedical assistance (e.g., by a relative or caregiver), the cost of treatment has been estimated at <$250 (12). A model of the potential downstream health care savings of successful nonhospital glucagon use (13) has shown a potential cost savings of >$1,000 per episode.

The safety profile of dasiglucagon was comparable to that of reconstituted lyophilized (reference) glucagon. Nausea and vomiting were the most frequently reported adverse events, consistent with these gastrointestinal events being well-known adverse effects of glucagon treatment.

The strengths of this trial include the multicenter design and the rigorous elimination of residual injected insulin predosing. A stable confirmed period of hypoglycemia before dosing, as well as blinding of investigators and participants, also reduced any potential bias. Adverse event review throughout a prolonged follow-up period and systematic review of injection sites were helpful in determining the full adverse effect profile. However, the therapy was assessed in a highly controlled investigational inpatient setting, which may not fully reflect real-world settings. Additional investigations should explore the efficacy and safety of dasiglucagon in real-life situations.

In conclusion, this randomized, controlled clinical trial demonstrated that dasiglucagon provided rapid and effective reversal of hypoglycemia in adults with type 1 diabetes. The ready-to-use, aqueous formulation of dasiglucagon offers the potential to provide rapid and reliable treatment of severe hypoglycemia.

Acknowledgments. The authors acknowledge patients who participated in the trial and contributed to the outcome of the trial, as well as Fiona Swain of Mediwrite Ltd. for providing medical writing support (funded by Zealand Pharma).

Duality of Interest. This trial was sponsored by Zealand Pharma. T.R.P. has received research funding (paid to university) from Zealand Pharma, AstraZeneca, Novo Nordisk, and Sanofi and consulting fees from Adocia, Arecor, AstraZeneca, Eli Lilly, Novo Nordisk, Sanofi, and The Longevity Lab. R.A. has received research support from Novo Nordisk, Becton Dickinson Technologies, Eli Lilly, Zealand Pharma, Xeris, Insulet, Dexcom, and Tandem Diabetes and consulting fees from Sanofi, Novo Nordisk, Boehringer Ingelheim, Eli Lilly, and Gilead. U.H., J.W., and L.P.-M. have received research support from Zealand Pharma. K.M.K., B.B., and R.T. are employees of Zealand Pharma. No other potential conflicts of interest relevant to this article were reported.

Zealand Pharma sponsored this trial and was involved in the design and conduct of the trial and analysis and interpretation of the data, including collection, management, and statistical analysis of the data.

Author Contributions. T.R.P., R.A., U.H., J.W., and L.P.-M. were involved in conducting the trial. T.R.P. and R.T. wrote the manuscript. All authors reviewed, edited, and approved the manuscript for submission. T.R.P. and K.M.K. are guarantors of this work and, as such, had full access to all data in the trial and take responsibility for the integrity of the data and the accuracy of the data analyses.

T.R.P., R.A., U.H., J.W., and L.P.-M. are the principal investigators from the five participating sites.

Prior Presentation. Parts of this trial were presented in abstract form at the 79th Scientific Sessions of the American Diabetes Association, San Francisco, CA, 7–11 June 2019, and at the 13th International Conference on Advanced Technologies & Treatments for Diabetes, Madrid, Spain, 19–22 February 2020.

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