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ORIGINAL ARTICLE

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Integrated safety and efficacy analysis of dasiglucagon for the treatment of severe hypoglycaemia in individuals with type 1 diabetes

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Abstract

Aims: To perform an integrated analysis of the safety and efficacy of dasiglucagon, a glucagon analogue available in a ready-to-use aqueous formulation, to treat severe hypoglycaemia (SH) in type 1 diabetes (T1D).

Materials and Methods: An integrated analysis of dasiglucagon safety was conducted on data from two placebo-controlled trials (placebo-controlled pool) and two placebo-controlled and four non-placebo-controlled trials (broad pool) in adults with T1D. An integrated analysis of dasiglucagon efficacy was conducted of pooled data and within demographic subgroups from the two placebo-controlled and two non-placebo-controlled trials in adults with T1D.

Results: Dasiglucagon had a similar safety and tolerability profile to that of reconstituted glucagon. In the placebo-controlled datasets, no serious adverse events (AEs), AEs leading to withdrawal from the trial, or deaths were reported. The most common causally related AEs were nausea (56.5%) and vomiting (24.6%). The broad pool safety analysis showed similar results. Dasiglucagon efficacy in time to plasma glucose recovery from insulin-induced SH was similar to that of reconstituted glucagon (median 10.0 and 12.0 minutes, respectively) and superior to placebo (median 40.0 minutes; $P < 0.0001$). The median recovery time was consistent across all placebo-controlled trial subgroups.

Conclusions: Dasiglucagon was well tolerated and effective as a rapid rescue agent for insulin-induced SH in people with T1D.

KEYWORDS
glucagon, glycaemic control, hypoglycaemia, type 1 diabetes

1 | INTRODUCTION

Severe hypoglycaemia (SH), also called level 3 hypoglycaemia, is a common and serious side effect of treatment with insulin in people with diabetes.[1-3] SH is characterized by altered mental and/or physical status, requiring assistance from other people to recover.[4] It affects people with type 1 diabetes (T1D; approximately 1%-29%)[5] and people with type 2 diabetes (T2D; 4%–17%).[6] The exact prevalence and incidence of SH are challenging to establish owing to differences between the rates of SH suggested by hospitalizations for hypoglycaemia versus the rates reported by people experiencing SH and by their care partners.[5,6] Many people with diabetes often do not recognize mild hypoglycaemic events or, in the case of SH, they are often reluctant to discuss these episodes with their healthcare providers for a number of reasons (including work issues, driving certification, and others).[7,8] In people with T1D or T2D, SH episodes are associated with several adverse health outcomes, including cardiac dysfunction and sudden death,[9] as well as non-cardiac conditions, such as impaired cognitive function and seizures.[10]

Glucagon is a first-line emergency treatment for SH. The American Diabetes Association recommends that glucagon be prescribed to all people who are at risk of level 2 and level 3 hypoglycaemia to ensure that treatment is available in case of an emergency.[4] These recommendations aim to improve accessibility to, and use of, emergency treatment for SH to help prevent a delay in recovery from SH and ultimately reduce the need for hospitalization following SH.[11]

Despite its established efficacy in improving recovery from SH, glucagon remains underprescribed and underused as an emergency treatment for SH.[11-14] In a recent study, 85% (n = 225/264) of adults with T1D reported having been prescribed a glucagon emergency kit (GEK), but only 29% of those who had a GEK (n = 45/154) always carried it with them.[13] Moreover, only 52% (n = 90/172) of adults who experienced SH were treated with glucagon, with most (82% [n = 74/90]) experiencing issues when receiving it.[13] The range of issues was broad and included problems with glucagon dose preparation and administration, as well as the procedure being too complex.[13] This low uptake of glucagon and the problems with its use likely reflect several underlying factors, including the lack of frequent practical training of caregivers on how to use glucagon in an emergency,[12,15] caregivers' reluctance to use glucagon in an emergency for fear of harming the individual with SH,[11,12] and the complexity of glucagon preparation and administration in GEKs.[12,13,15] GEKs such as the GlucaGen HypoKit (Novo Nordisk) and Glucagon for Injection (Lilly) require reconstitution of the lyophilized glucagon powder with a diluent before its subcutaneous (SC) or intramuscular injection.[11,15] Both the reconstitution and injection techniques require appropriate training and are challenging for caregivers to execute quickly and accurately, particularly when responding under the stress of an SH episode.[8,13,15,16] In addition to the need for training on the emergency use of glucagon, its cost, its short shelf-life, the poor knowledge of its importance and the lack of people who could administer glucagon collectively contribute to the low levels of glucagon prescriptions and uptake in people with T1D.[13,17] The availability of affordable, easy-to-use glucagon products has the potential to increase glucagon uptake and prescription and to improve the health outcomes of people with T1D.

Ready-to-use glucagon products, including injectable liquid glucagon (Gvoke; Xeris Pharmaceuticals)[18] and nasal dry powder glucagon (Baqsimi; Lilly),[19] offer easier administration and have similar safety and efficacy profiles to those of pre-existing GEKs.[8] Dasiglucagon (Zegalogue; Zealand Pharma) is the first glucagon analogue available in a ready-to-use aqueous formulation. Its altered chemical structure improves its physical and chemical stability, providing improved long-term stability in aqueous solution and allowing dasiglucagon to be stored in a prefilled syringe and autoinjector.[20] Based on a comparison of the prescribing information for dasiglucagon, injectable liquid glucagon (Gvoke) and nasal dry powder glucagon (Baqsimi), dasiglucagon provides a slightly quicker recovery from hypoglycaemia and reduces the occurrence of injection-site reactions linked to the use of nonaqueous solvents (Gvoke).[21] Dasiglucagon is approved in the United States as a rescue therapy for SH for adult and paediatric individuals with diabetes aged 6 years and older.[22] Approval was based on data from three randomized, double-blind, placebo-controlled, multicentre trials in adults (NCT03378635,[20] NCT03688711[23]) and paediatric participants with T1D (NCT03667053[24]). This study presents a cross-programme integrated analysis of dasiglucagon safety in placebo-controlled and broad pools, and of dasiglucagon efficacy across subgroups, in adults with T1D. It summarizes the currently available data and identifies any subgroups that warrant further research based on any new safety or efficacy findings.

2 | MATERIALS AND METHODS

2.1 | Study design

Integrated analyses of dasiglucagon safety and efficacy were performed on participant populations from six randomized, double-blind clinical trials, summarized in Figure 1 and Table S1. The integrated safety analysis was performed on placebo-controlled (Figure 1A) and broad pool datasets (Table S1). The placebo-controlled pool included data from two Phase 3 pivotal placebo-controlled trials in adults with T1D (NCT03378635 and NCT03688711; Figure 1A).[20,23] The aim of this analysis was to compare the safety of dasiglucagon with that of placebo. The broad pool safety analysis included the two adult placebo-controlled trials and four adult non-placebo-controlled trials (NCT02660008,[25] NCT03895697,[26] NCT03216226[27] and NCT02367053[28]; Table S1). The aim of the broad pool safety analysis was to detect any potential trends in less frequent adverse events (AEs).

The integrated analysis of efficacy across different demographic and other subgroups (see Statistics section) was performed on four trials of adults with T1D. This included two Phase 3 pivotal placebo-controlled trials (NCT03378635[20] and NCT03688711[23]), as well as the non-placebo-controlled dose-finding (NCT02660008)[25] and bridging trials (NCT03895697)[26] (Figure 1B). The inclusion of non-placebo-controlled trials ensured enough data for an analysis of efficacy by

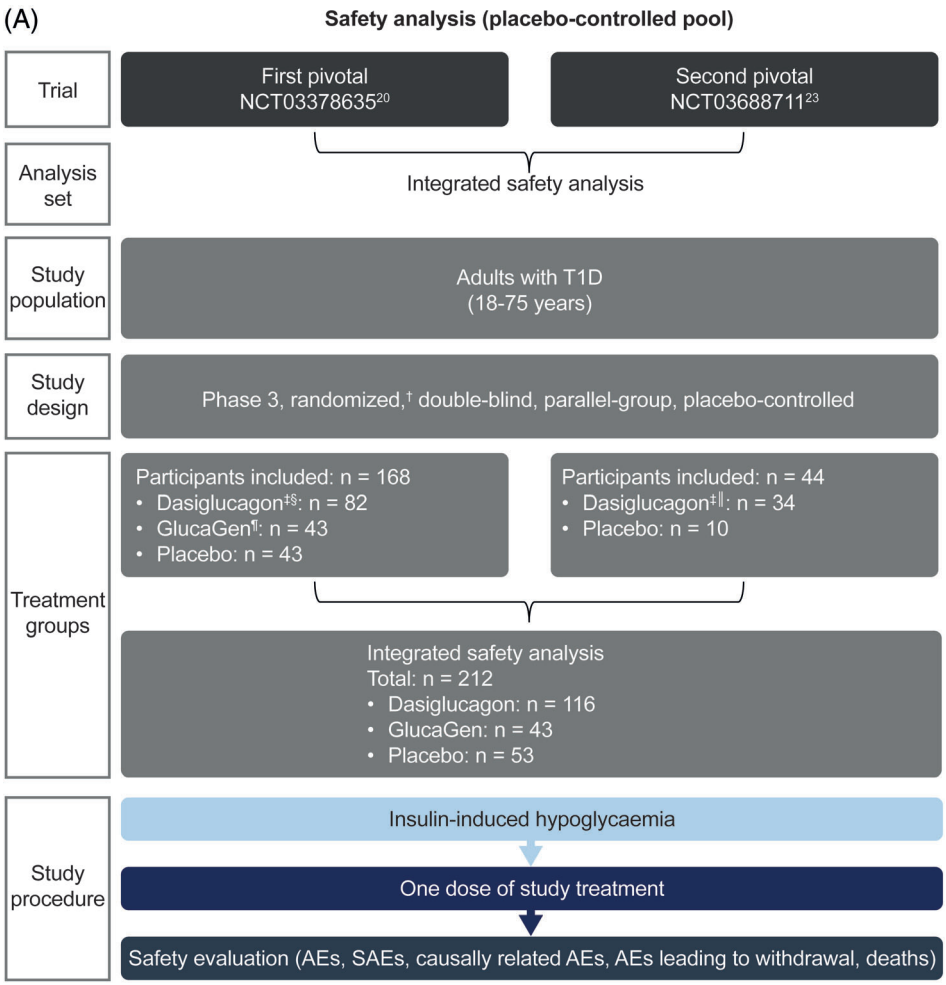

FIGURE 1 Summary of clinical trials included in safety (placebo-controlled pool) (A) and efficacy (B) analyses. (A) An integrated analysis of dasiglucagon safety versus placebo was conducted on data from two placebo-controlled trials in adults with type 1 diabetes (T1D; NCT03378635[20] and NCT03688711[23]). (B) An integrated efficacy analysis of dasiglucagon was conducted on pooled data and within demographic subgroups from two placebo-controlled (NCT03378635[20] and NCT03688711[23]) and two non-placebo-controlled trials (NCT02660008[25] and NCT03895697[26]) in adults with T1D. †Randomization ratios were: first pivotal trial – 2:1:1 to dasiglucagon, GlucaGen and placebo; second pivotal trial – 3:1 to dasiglucagon and placebo; dose-finding trial – 3:1 to 0.1 mg dasiglucagon or 1.0 mg GlucaGen (subsequently randomized participants were allocated to one of three treatment groups in which they were randomized to one of two treatment sequences in a crossover design. The treatments studied in these three groups were different single doses of dasiglucagon versus different single doses of GlucaGen); bridging trial – 1:1 to different sequences of the two batches of dasiglucagon in a crossover design; ‡0.6 mg dasiglucagon was determined as the optimal dose based on data from the dose-finding trial; §administered via a prefilled syringe; ¶administered using the injection kit provided; ‖administered via an autoinjector with a mounted prefilled syringe. AE, adverse event; SAE, serious adverse event

demographic and other subgroups. The inclusion of the non-placebo-controlled trials was supported by the consistency of the primary efficacy outcomes across all four trials (Table S2) as well as by their similar trial designs (Figure 1B) and participant characteristics (Table S2).[20,23,25,26] Participants in the placebo-controlled trials were unevenly randomized to receive dasiglucagon, placebo or a reference product, reconstituted glucagon (GlucaGen HypoKit; Novo Nordisk), hereafter called GlucaGen (Figure 1). This was done to ensure adequate exposure to dasiglucagon for the safety analysis. The protocols of trials included in the integrated analysis were reviewed and approved by the local health authorities and independent ethics committees, as previously reported.[20,23,25-28] The trials were registered at ClinicalTrials.gov (NCT03378635, NCT03688711, NCT02660008, NCT03895697, NCT03216226, NCT02367053) and conducted in accordance with the Declaration of Helsinki and International Council for Harmonisation Good Clinical Practice. All participants were recruited based on the databases of the study sites and gave written informed consent before any study-related activities were initiated.[20,23,25-28]

2.2 | Participants

The trials included participants aged 18 to 75 years at study enrolment (trial-specific age ranges are summarized in Figure 1 and

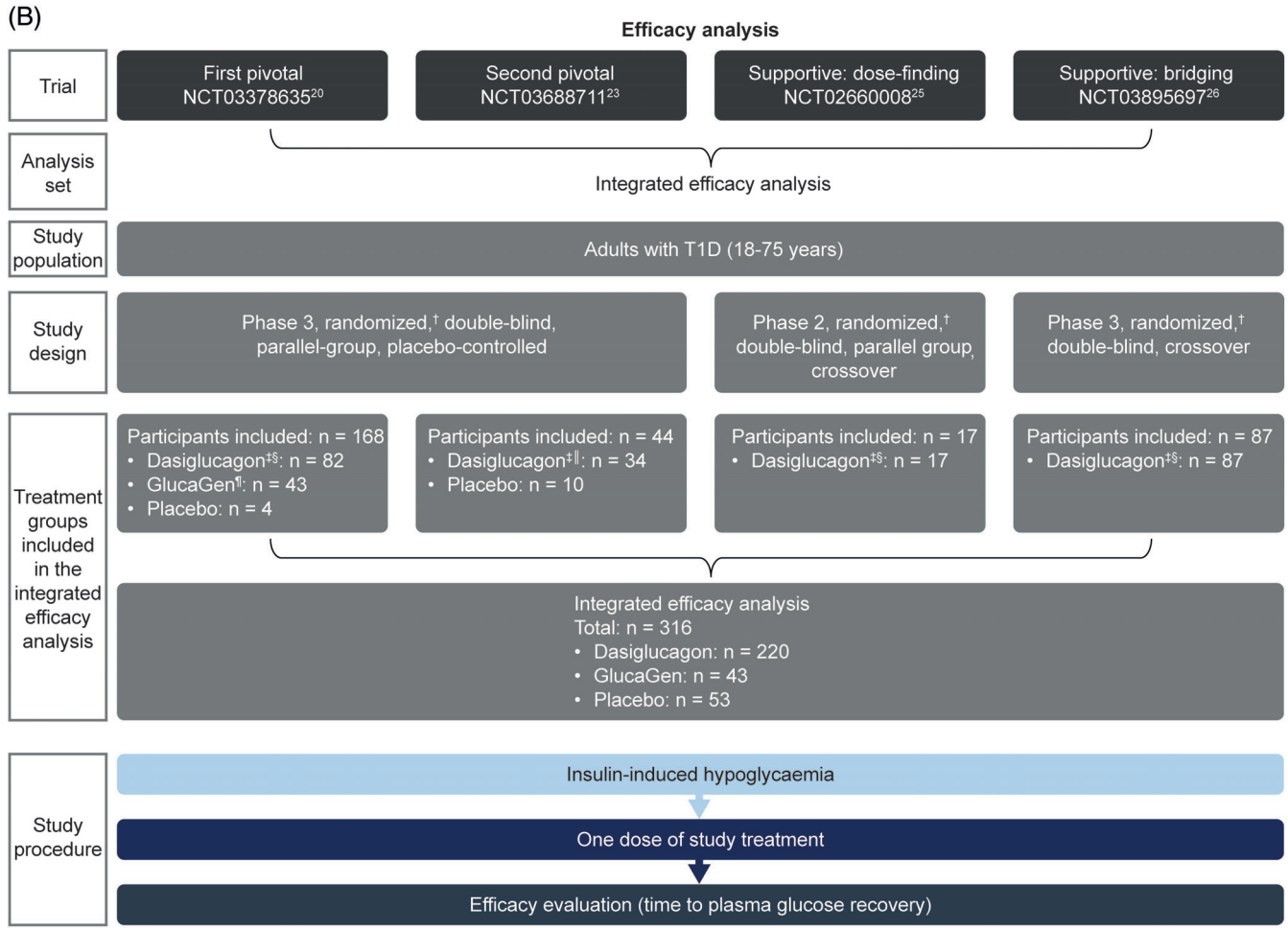

FIGURE 1 (Continued)

Table S1). The participants had T1D, received a stable insulin treatment for T1D (or other antidiabetic treatment in the immunogenicity trial)[27] for at least 1 month before joining the study (at least 1 year for participants in the placebo-controlled and dose-finding trials)[20,23,25] and had glycated haemoglobin levels <10%[20,23,26,27] (<8.5% for participants in the dose-finding[25] and first-in-human trials[28]). Participants were excluded from the placebo-controlled trials if they used daily systemic beta-blocker drugs, indomethacin, warfarin or anticholinergic drugs at screening, or if they had experienced hypoglycaemia (plasma glucose [PG] <2.8 mmol/L) in the previous 24 hours, or induction of hypoglycaemia.[20,23]

2.3 | Study procedures and endpoints

Dasiglucagon, GlucaGen and placebo were administered as SC injections. Participants in the two placebo-controlled[20,23] and first-in-human[28] trials received a single SC injection of their study treatment after a controlled induction of hypoglycaemia using an intravenous (IV) infusion of insulin. Participants in the dose-finding trial received a single dasiglucagon injection,[25] whereas those in the immunogenicity trial received up to three repeated single doses of dasiglucagon[27]; those in the bridging trial received a single dasiglucagon injection that was stored under similar conditions to dasiglucagon in other trials, followed by a single dasiglucagon injection stored under different conditions 28 days later or vice versa (only data obtained from similar storage conditions are included in this analysis).[26] The inclusion of crossover trials was supported by the consistency of the primary efficacy results and by the similar study design and participant characteristics (Figure 1B and Table S2). Importantly, only one observation per participant from crossover trials was included. GlucaGen was included as a reference treatment in some trials and was not included in the statistical comparison of safety or efficacy.

The safety evaluation included causally related AEs, as well as AEs, serious AEs (SAEs), AEs leading to withdrawal from the trial, and deaths. In the placebo-controlled safety analysis set, AEs and causally related AEs that occurred within 12 hours of dosing were analysed. This time frame was chosen because dasiglucagon is a fast-acting, single-dose hypoglycaemia rescue treatment, with a short half-life (30 minutes),[25] and no causally related AEs are expected to occur outside this time. However, not all trials in the broad pool safety analysis included data at 12 hours after dosing, so the entire observation period was analysed instead. The entire observation period was defined as the time from a treatment dose and either the next dose (crossover trials), end of trial follow-up or withdrawal from the trial,

whichever was first. It ranged between 28 and 105 days.[20,23,25-28] The percentage of participants with AEs and causally related AEs was adjusted using the Cochran–Mantel–Haenszel method to account for potential bias due to differences between trials, including different randomization ratios. The efficacy endpoint was time to PG recovery, defined as the first increase in PG of ≥1.1 mmol/L after treatment administration (excluding time for reconstitution) without the need for rescue IV glucose following insulin-induced hypoglycaemia. A participant was considered to have "not recovered" if IV glucose was administered before recovery or if recovery was not achieved within 45 minutes. Insulin-induced hypoglycaemia was defined as PG ≥2.5 and < 3.3 mmol/L.[20,23,25,26] Hyperglycaemic events were monitored as a safety aspect (Table S3). The integrated efficacy analysis included a subgroup analysis of the effect of participant demographics and other characteristics on time to PG recovery.

2.4 | Statistics

The safety analysis set included participants who received at least one dose of study treatment. Data were included from participants from the placebo-controlled and broad pools. Descriptive statistics were used to present the safety data, and no comparative statistical analysis was performed.

The efficacy analysis set included all participants randomized to a study treatment who received at least one dose. Participants who received rescue IV glucose before recovery, or who did not recover in the 45 minutes after dosing, were censored and considered "not recovered". Data were included from all participants from the four trials who received 0.6 mg dasiglucagon stored under the same conditions. Subgroup analysis was performed in subgroups for which n ≥ 10. Subgroups included sex (female, male) and region (US, non-US) of participants, as well as different durations of diabetes since diagnosis (<20 years, ≥20 years), treatment injection sites (abdomen, buttock, deltoid, thigh) and baseline PG (<3.0 mmol/L, ≥3.0 mmol/L). Time to PG recovery was presented using a Kaplan-Meier plot stratified by treatment, inverted and displayed as cumulative events of time to PG recovery. The null hypothesis between dasiglucagon and placebo for time to PG recovery was evaluated using two-sided log-rank testing on a 5% significance level for the overall efficacy dataset. The median (95% confidence interval [CI]) time to PG recovery was similarly estimated per subgroup, and data for the dasiglucagon treatment group were presented as a forest plot. A log-rank test of equality across categories within a subgroup was included. The forest plot included all subgroups of more than one category with at least 10 observations in the dasiglucagon treatment group.

3 | RESULTS

3.1 | Participant disposition and baseline characteristics

The integrated placebo-controlled safety analysis included data from 212 participants from two placebo-controlled trials, including 116 who received 0.6 mg dasiglucagon, 43 who received 1.0 mg GlucaGen, and 53 who received placebo. The integrated broad pool safety analysis included data from participants from two placebo-controlled and four non-placebo-controlled trials, which included 316 participants who received ≥0.6 mg dasiglucagon, 151 who received 1.0 mg GlucaGen, and 53 who received placebo. The integrated efficacy analysis included data from 316 participants from two placebo-controlled trials and two non-placebo-controlled trials. Of these, 220 received dasiglucagon, 43 received GlucaGen and 53 received placebo. The participant characteristics of both the placebo-controlled safety and efficacy datasets are summarized in Table 1 (see Table S4 for broad pool safety dataset).

3.2 | Safety

The most common AEs were nausea and vomiting (Table S5). There were no SAEs, AEs leading to withdrawal from the trial or deaths reported in the placebo-controlled analysis set. In the broad pool analysis set, SAEs and AEs leading to withdrawal from the trial were reported for 0.4% (n = 1/316) and 1.9% (n = 5/316), respectively, of participants in the dasiglucagon group. Table 2 summarizes causally related AEs that occurred in the 12 hours after dose administration in the placebo-controlled pool. The most common causally related AEs in the placebo-controlled analysis set were nausea and vomiting (Table 2). The results of the broad pool analysis dataset were predominantly consistent with those of the placebo-controlled safety dataset, with only slightly lower rates of causally related nausea and vomiting reported with GlucaGen (Table S6). Nausea mainly occurred 1 to 3 hours after dosing in both the dasiglucagon and GlucaGen groups, whereas vomiting mainly occurred 2 to 3 hours after dosing (Figure 2A).

3.3 | Time to PG recovery

The median time to PG recovery after treatment administration was 10.0 minutes for participants who received dasiglucagon (95% CI 10.0-10.0; n = 220), 12.0 minutes for those who received GlucaGen (95% CI 10.0-12.0; n = 43) and 40.0 minutes for those who received placebo (95% CI 30.0-40.0; n = 53 Figure 3A). The time to PG recovery was significantly faster in the dasiglucagon group than the placebo group ($P < 0.0001$, log-rank test) and was consistent across all trials included in the analysis.[20,23,25] The median time to PG recovery was consistent across all demographic and other subgroups analysed in this study, including sex, duration of diabetes, baseline PG concentrations, dasiglucagon injection-site and study-site region ($P > 0.05$, log-rank test Figure 3B).

4 | DISCUSSION

The aim of this integrated analysis was to assess the currently available data from clinical trials on the safety and efficacy of dasiglucagon

TABLE 1 Summary of participant characteristics for safety (A) and efficacy (B) analysis sets.

(A) Safety analysis placebo-controlled set participant characteristics			
	Dasiglucagon (n = 116)	**GlucaGen (n = 43)**	**Placebo (n = 53)**
Age, years, median (range)	38.0 (18-71)	38.0 (23-66)	35.0 (18-65)
Sex, n (%)			
Female	50 (43.1)	15 (34.9)	17 (32.1)
Male	66 (56.9)	28 (65.1)	36 (67.9)
Race, n (%)			
White	110 (94.8)	39 (90.7)	46 (86.8)
Black or African American	1 (0.9)	2 (4.7)	2 (3.8)
Asian	3 (2.6)	0	2 (3.8)
Native Hawaiian or other Pacific islander	0	1 (2.3)	1 (1.9)
Other	1 (0.9)	0	1 (1.9)
Multiple	1 (0.9)	1 (2.3)	1 (1.9)
Ethnicity, n (%)			
Non-Hispanic or Latino	110 (94.8)	40 (93.0)	48 (90.6)
Hispanic or Latino	6 (5.2)	3 (7.0)	5 (9.4)
BMI, kg/m^2, mean (SD)	26.8 (4.77)	25.9 (3.42)	26.5 (3.50)
Duration of diabetes, years, median (range)	20.2 (1-55)	17.2 (2-56)	17.3 (2-50)
HbA1c, mmol/mol, mean (%, mean [SD])	57 (7.4 ([.94])	57 (7.4 [0.97])	54 (7.1 [0.76])
(B) Efficacy analysis set participant characteristics			
	Dasiglucagon (n = 220)	**GlucaGen (n = 43)**	**Placebo (n = 53)**
Age, years, median (range)	36.0 (18-71)	38.0 (23-66)	35.0 (18-65)
Sex, n (%)			
Female	91 (41.4)	15 (34.9)	17 (32.1)
Male	129 (58.6)	28 (65.1)	36 (67.9)
Race, n (%)			
White	212 (96.4)	39 (90.7)	46 (86.8)
Black or African American	1 (0.5)	2 (4.7)	2 (3.8)
Asian	3 (1.4)	0	2 (3.8)
Native Hawaiian or other Pacific islander	0	1 (2.3)	1 (1.9)
Other	3 (1.4)	0	1 (1.9)
Multiple	1 (0.5)	1 (2.3)	1 (1.9)
Ethnicity, n (%)			
Non-Hispanic or Latino	196 (89.1)	40 (93.0)	48 (90.6)
Hispanic or Latino	7 (3.2)	3 (7.0)	5 (9.4)
Not available	17 (7.7)	0	0
BMI, kg/m^2, mean (SD)	26.5 (4.22)	25.9 (3.42)	26.5 (3.50)
Duration of diabetes, years, median (range)	19.4 (1-55)	17.2 (2-56)	17.3 (2-50)
HbA1c, mmol/mol, mean (%, mean [SD])	57 (7.34 [0.821])	57 (7.41 [0.969])	55 (7.17 [0.760])

Abbreviations: BMI, body mass index; HbA1c, glycated haemoglobin; n, number of participants; SD, standard deviation.

in adults with T1D to determine whether any demographic or other subgroups warrant further research based on any newly identified safety or efficacy concerns. The integrated analysis of safety found that dasiglucagon has a safety and tolerability profile similar to that of GlucaGen. Across all placebo-controlled trials and age groups, no SAEs, AEs leading to withdrawal from the trial, or deaths were reported. The safety profile of dasiglucagon in participants from the placebo-controlled pool appears to be similar to the safety profile seen in the broad pool participants as well as that reported for children and adolescents with T1D.[24] Furthermore, it appears to be

TABLE 2 Summary of causally related adverse events reported in ≥5% participants of the placebo-controlled pool within 12 hours after dose administration

	Dasiglucagon	GlucaGen	Placebo
	Most common causally related AEs,[a] n (%)		
Placebo-controlled pool safety analysis set, N	116	43	53
All events[b]	73 (63.0)	27 (62.8)	4 (7.7)
Nausea	66 (56.5)	23 (53.5)	2 (4.1)
Vomiting	29 (24.6)	9 (20.9)	1 (1.8)
Headache	11 (9.5)	4 (9.3)	1 (1.8)

Note: N, number of participants in the safety analysis set; n, number of participants experiencing at least one event; %, percentage of participants experiencing at least one event (adjusted using Cochran–Mantel–Haenszel method for data from adult participants to account for potential bias due to differences between trials including different randomization ratios).

Abbreviation: AE, adverse event.

[a]Most common causally related AEs include those that occurred in ≥5% participants in the dasiglucagon group in the 12 hours after dose administration.

[b]"All events" represent the total number of participants in a treatment group who had at least one causally related AE, whether or not this event was common.

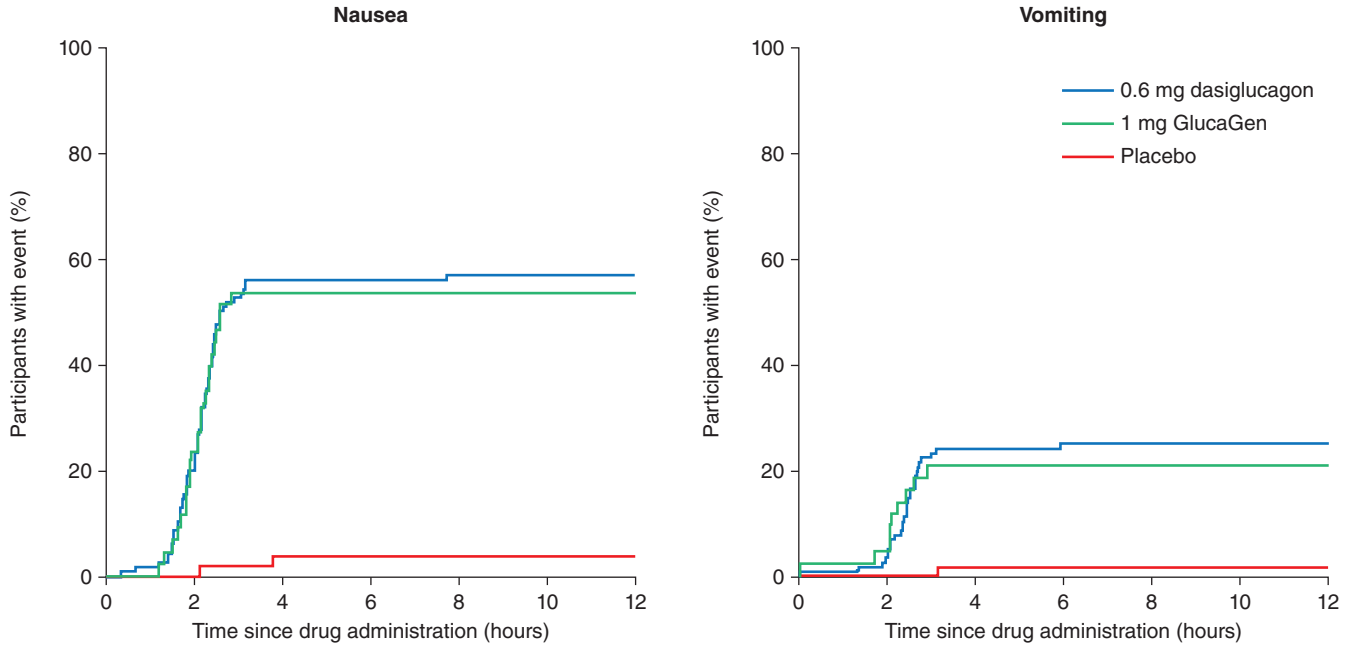

FIGURE 2 Time to nausea and vomiting in the 12 hours after dose administration for participants receiving dasiglucagon, GlucaGen or placebo (safety analysis set). One minus the Kaplan-Meier survival probability plotted for the time to the first occurrence of nausea and vomiting (in minutes). One participant had a vomiting event with onset on the same day as dosing with missing onset time; for this event, the onset time was imputed as the dosing time

consistent with that of other glucagon products,[29-31] with the most common causally related AEs being nausea and vomiting.

Causally related AEs were reported for a similar proportion of participants in the dasiglucagon and GlucaGen groups (63.0% vs. 62.8% in the placebo-controlled pool Table 2). Data from the broad adult safety pool were broadly similar but with a slightly lower incidence of causally related AEs in the GlucaGen group (55.3% vs. 63.8% in the dasiglucagon group).

An integrated efficacy analysis found that dasiglucagon significantly decreases the time to PG recovery compared with placebo ($P < 0.0001$), with a time to PG recovery from insulin-induced hypoglycaemia after treatment administration consistent with that of GlucaGen (Figure 3A) and SC glucagon.[32] Additionally, the time to PG recovery in the dasiglucagon group was consistent across both placebo-controlled trials[20,23] and with the previously published efficacy results from a pivotal paediatric trial.[24] Finally, the median time to recovery in the dasiglucagon group was consistent across all demographic and other subgroups included (Figure 3B). These results show that dasiglucagon is on par with reconstituted glucagon and statistically superior to placebo in recovering a PG level of ≥1.1 mmol/L after treatment administration.

Although this study provides useful information about the safety and efficacy of dasiglucagon in adults with T1D, it has several limitations. First, most of the participants included in this integrated analysis

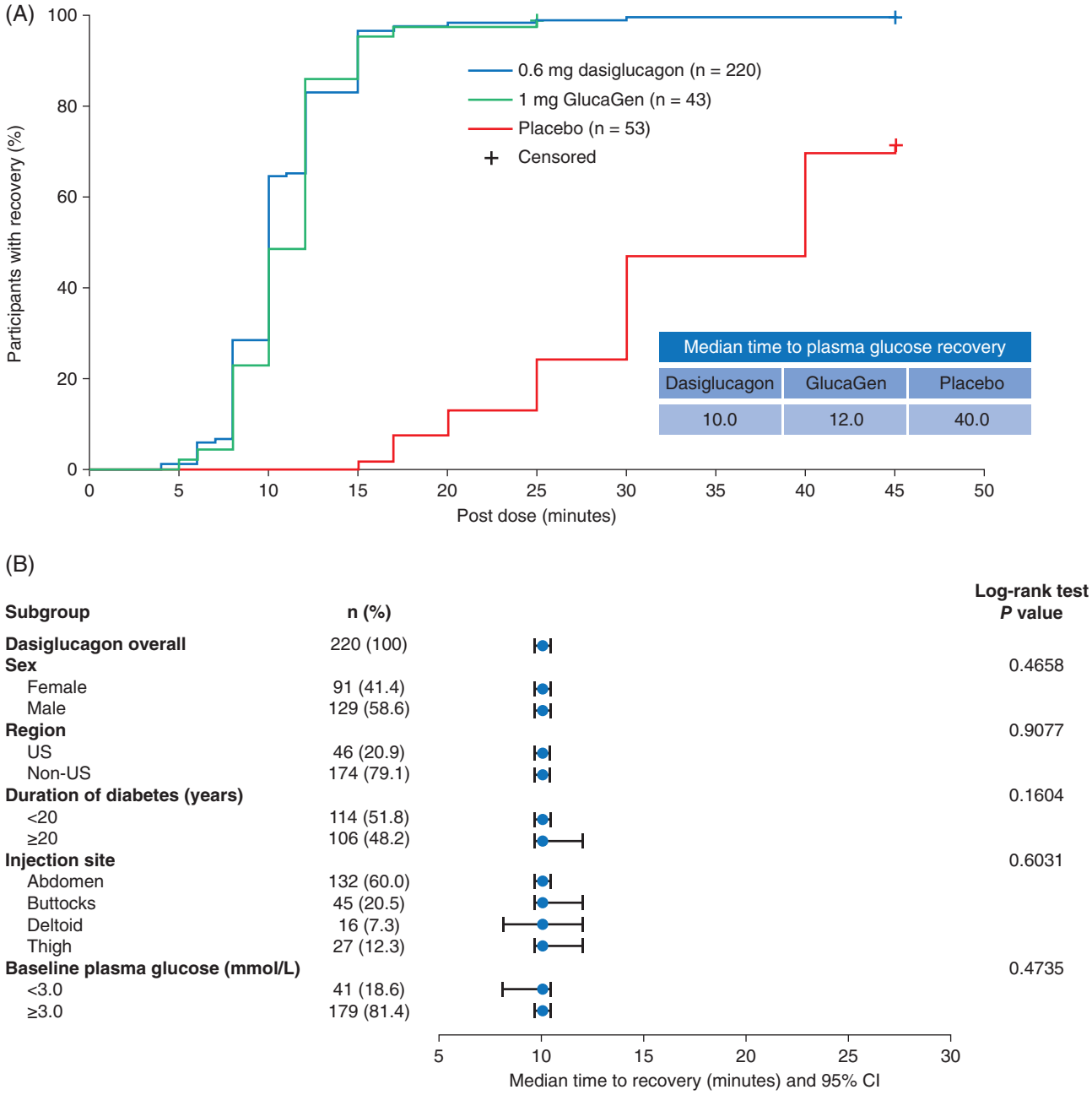

FIGURE 3 Time to plasma glucose (PG) recovery by treatment (A) and different demographic and other subgroups (B) (efficacy analysis set). (A) Kaplan-Meier plot and a summary of time to PG recovery (in minutes) from treatment administration by treatment arm (inset; dasiglucagon n = 220, GlucaGen n = 43, placebo n = 53). (B) Forest plot of median time to PG recovery from treatment administration by subgroup (sex, region, diabetes duration, injection site and baseline glucose). Data were analysed using a two-sided log-rank test, and confidence limits were calculated using a nonparametric method. Subgroup categories containing <10 patients were excluded. CI, confidence interval

of safety and efficacy were White (Table 1 and Table S4). It remains to be determined whether race affects dasiglucagon safety or efficacy. Future studies should ensure a more diverse racial representation of participants to address this important consideration. Second, it should be noted that experimentally induced hypoglycaemia does not accurately reflect clinical episodes of hypoglycaemia. Thus, it does not take into account factors such as physical exercise that may affect the induction of, and recovery from, hypoglycaemia.[33] Similarly, the experimental design of the trials included in this study does not capture the complexity of dose administration by non-trained caregivers or preparation stability. It remains to be determined how the total time to PG recovery (ie, including the time for preparation and administration of the rescue product) differs between dasiglucagon and GlucaGen. A recent study has shown that a dasiglucagon autoinjector was administered faster than Glucagon for Injection (Lilly) by both trained caregivers and untrained bystanders (caregivers = 75 seconds,

bystanders = 137 seconds) than for those using a GEK (caregivers = 126 seconds, bystanders = 227 seconds), suggesting that a dasiglucagon autoinjector has the potential to improve the speed of SH treatment.[34] Therefore, the real-world effectiveness of dasiglucagon in recovery from hypoglycaemia still needs to be assessed. Third, GlucaGen was used as a reference product rather than a true comparator. Although the comparison of efficacy between dasiglucagon and GlucaGen showed a numerical difference, a formal analysis was not conducted because the trials were not powered for statistical analysis. Finally, it should be noted that all trials included in the integrated analyses of safety and efficacy of dasiglucagon were funded by Zealand Pharma A/S.

In conclusion, this cross-programme integrated safety and efficacy analysis illustrated that, overall, dasiglucagon was well tolerated and effective, and had a rapid onset of action as a rescue agent for insulin-induced hypoglycaemia in individuals with T1D. Currently available first-generation injectable GEKs are difficult and time-consuming to prepare and administer under pressure in simulated emergency hypoglycaemic situations,[34] highlighting the need for stable glucagon formulations that can be easily administered by caregivers or bystanders. A study comparing the rate of administration of dasiglucagon and injectable GEK found that the mean time to successful completion of administration was significantly faster using the dasiglucagon autoinjector for both trained caregivers and untrained bystanders, with most participants finding the dasiglucagon autoinjector easier to use than a GEK (90%, 47/52).[34] It is hoped that the ease of use of dasiglucagon, along with its efficacy and a safety and tolerability profile similar to that of reconstituted glucagon, may help to increase the uptake and utilization of the currently underprescribed and underused glucagon rescue therapies for people with T1D, along with other ready-to-use glucagon rescue agents.[34]

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the interpretation of data for the manuscript, and drafted and critically revised the manuscript. All authors contributed to the design, analysis and writing of the manuscript (including the first draft). All authors are responsible for the integrity of the work as a whole.

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CONFLICT OF INTEREST STATEMENT

Zealand Pharma sponsored the trials included in this study. It 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. Simon Heller has served on speaker panels for Eli Lilly, Novo Nordisk, and AstraZeneca, for which he has received remuneration. He has served on advisory panels or as a consultant for Zealand, Novo Nordisk, Eli Lilly, Zucara Therapeutics, and Vertex, for which his institution has received remuneration. He has received research support from Dexcom. Tadej Battelino has served on advisory panels for Medtronic, Novo Nordisk, 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; holds stock in DreaMed Diabetes; and was supported in part by the Slovenian Research Agency grant # P3-0343. Timothy S. Bailey received research support from Abbott Diabetes, Abbott Rapid Diagnostics, Biolinq, Capillary Biomedical, Dexcom, Eli Lilly, Kowa, LifePlus, Livongo, Mannkind, Medtronic, Novo Nordisk, PKVitality, REMD, Sanofi, Sanvita, Senseonics, Viacyte, vTv Therapeutics, and Zealand Pharma. He received consulting honoraria from Abbott, CeQur, Lifescan, Mannkind, Medtronic, Novo, and Sanofi, as well as speaking honoraria from Medtronic and Sanofi. Thomas R. Pieber has received research funding (paid to university) from Zealand Pharma A/S, AstraZeneca, Novo Nordisk, and Sanofi and consulting fees from Adocia, Arecor, AstraZeneca, Eli Lilly, Novo Nordisk, Sanofi, and The Longevity Lab. Ulrike Hövelmann has no conflict of interest. Leona Plum-Mörschel has received travel grants and speaker fees from Eli Lilly, Gan & Lee Pharmaceuticals, and Novo Nordisk. Anita E. Melgaard is an employee at Zealand Pharma A/S. Ronnie Aronson 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. Linda A. DiMeglio is a consultant for Vertex and Abata Therapeutics, and has received research support paid to Indiana University from Eli Lilly, Mannkind, Medtronic, and Provention. Thue Johansen is an employee in Zealand Pharma A/S and a shareholder of Zealand Pharma shares. Thomas Danne has served on advisory panels for AstraZeneca, Boehringer Ingelheim International GmbH, Eli Lilly and Company, Medtronic, Novo Nordisk A/S, and Sanofi.

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DATA AVAILABILITY STATEMENT

Research data are not shared.

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REFERENCES

1. UK Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. *Diabetologia*. 2007;50:1140-1147.

2. Khunti K, Alsifri S, Aronson R, et al. Rates and predictors of hypoglycaemia in 27 585 people from 24 countries with insulin-treated type 1 and type 2 diabetes: the global HAT study. *Diabetes Obes Metab*. 2016;18:907-915.
3. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care*. 2013;36:1384-1395.
4. American Diabetes Association Professional Practice Committee, Draznin B, Aroda VR, et al. 6. Glycemic targets: standards of medical care in diabetes—2022. *Diabetes Care*. 2022;45:S83-S96.
5. Pedersen-Bjergaard U, Thorsteinsson B. Reporting severe hypoglycemia in type 1 diabetes: facts and pitfalls. *Curr Diab Rep*. 2017;17:131.
6. Silbert R, Salcido-Montenegro A, Rodriguez-Gutierrez R, Katabi A, McCoy RG. Hypoglycemia among patients with type 2 diabetes: epidemiology, risk factors, and prevention strategies. *Curr Diab Rep*. 2018;18:53.
7. Pedersen-Bjergaard U, Faerch L, Allingbjerg ML, et al. The influence of new European Union driver's license legislation on reporting of severe hypoglycemia by patients with type 1 diabetes. *Diabetes Care*. 2015;38:29-33.
8. Porcellati F, Di Mauro S, Mazzieri A, et al. Glucagon as a therapeutic approach to severe hypoglycemia: after 100 years, is it still the antidote of insulin? *Biomolecules*. 2021;11:1281.
9. International Hypoglycaemia Study Group. Hypoglycaemia, cardiovascular disease, and mortality in diabetes: epidemiology, pathogenesis, and management. *Lancet Diabetes Endocrinol*. 2019;7:385-396.
10. Frier BM. Hypoglycaemia in diabetes mellitus: epidemiology and clinical implications. *Nat Rev Endocrinol*. 2014;10:711-722.
11. Kedia N. Treatment of severe diabetic hypoglycemia with glucagon: an underutilized therapeutic approach. *Diabetes Metab Syndr Obes*. 2011;4:337-346.
12. Harris G, Diment A, Sulway M, et al. Glucagon administration – underevaluated and undertaught. *Pract Diab Int*. 2001;18:22-25.
13. Haymond MW, Liu J, Bispham J, Hickey A, McAuliffe-Fogarty AH. Use of glucagon in patients with type 1 diabetes. *Clin Diabetes*. 2019;37:162-166.
14. Pearson T. Glucagon as a treatment of severe hypoglycemia: safe and efficacious but underutilized. *Diabetes Educ*. 2008;34:128-134.
15. Valentine V, Newswanger B, Prestrelski S, Andre AD, Garibaldi M. Human factors usability and validation studies of a glucagon autoinjector in a simulated severe hypoglycemia rescue situation. *Diabetes Technol Ther*. 2019;21:522-530.
16. Yale JF, Dulude H, Egeth M, et al. Faster use and fewer failures with needle-free nasal glucagon versus injectable glucagon in severe hypoglycemia rescue: a simulation study. *Diabetes Technol Ther*. 2017;19:423-432.
17. Novo Nordisk Limited. GlucaGen Hypokit 1 mg (glucagon) – summary of product characteristics 2021. 2021; https://www.medicines.org.uk/emc/product/1289/smpc#gref Accessed 10 November, 2022.
18. Wilson LM, Castle JR. Stable liquid glucagon: beyond emergency hypoglycemia rescue. *J Diabetes Sci Technol*. 2018;12:847-853.
19. Settles JA, Gerety GF, Spaepen E, Suico JG, Child CJ. Nasal glucagon delivery is more successful than injectable delivery: a simulated severe hypoglycemia rescue. *Endocr Pract*. 2020;26:407-415.
20. Pieber TR, Aronson R, Hovelmann U, et al. Dasiglucagon—a next-generation glucagon analog for rapid and effective treatment of severe hypoglycemia: results of phase 3 randomized double-blind clinical trial. *Diabetes Care*. 2021;44:1361-1367.
21. Syed YY. Dasiglucagon in severe hypoglycemia: a profile of its use. *Drugs Ther Perspect*. 2022;38:105-111.
22. Blair HA. Dasiglucagon: First approval. *Drugs*. 2021;81:1115-1120.
23. Bailey TS, Willard J, Klaff LJ, Yager Stone J, Melgaard A, Tehranchi R. Dasiglucagon, a next-generation glucagon analogue, for treatment of severe hypoglycaemia via an autoinjector device: results of a phase 3, randomized, double-blind trial. *Diabetes Obes Metab*. 2021;23:2329-2335.
24. Battelino T, Tehranchi R, Bailey T, et al. 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. *Pediatr Diabetes*. 2021;22:734-741.
25. Hövelmann U, Bysted BV, Mouritzen U, et al. Pharmacokinetic and pharmacodynamic characteristics of dasiglucagon, a novel soluble and stable glucagon analog. *Diabetes Care*. 2018;41:531-537.
26. Maarbjerg SJ. A trial to compare the efficacy and safety of 2 different batches of subcutaneous dasiglucagon in patients with T1DM. ClinicalTrials.gov identifier: NCT03895697 2019; https://clinicaltrials.gov/ct2/show/NCT03895697. Accessed 10 November, 2022.
27. Pieber TR, Ajala O, Steen O, et al. Immunogenicity of the novel glucagon analogue dasiglucagon: results of a dedicated imunogenicity trial in type 1 diabetes. *Diabetes Technol Ther*. 2021;23:773-776.
28. Jax T. Single ascending doses of ZP4207 administered in HV and in T1D to evaluate safety, tolerability PKs and PDs of ZP4207 compared to a comparator. ClinicalTrials.gov identifier: NCT02367053. 2015; https://clinicaltrials.gov/ct2/show/NCT02367053. Accessed 10 November, 2022.
29. Abraham MB, Jones TW, Naranjo D, et al. ISPAD clinical practice consensus guidelines 2018: assessment and management of hypoglycemia in children and adolescents with diabetes. *Pediatr Diabetes*. 2018;19(Suppl 27):178-192.
30. Sherr JL, Ruedy KJ, Foster NC, et al. Glucagon nasal powder: a promising alternative to intramuscular glucagon in youth with type 1 diabetes. *Diabetes Care*. 2016;39:555-562.
31. Thieu VT, Mitchell BD, Varnado OJ, Frier BM. Treatment and prevention of severe hypoglycaemia in people with diabetes: current and new formulations of glucagon. *Diabetes Obes Metab*. 2020;22:469-479.
32. La Sala L, Pontiroli AE. New fast acting glucagon for recovery from hypoglycemia, a life-threatening situation: nasal powder and injected stable solutions. *Int J Mol Sci*. 2021;22:10643.
33. Lu X, Zhao C. Exercise and type 1 diabetes. *Adv Exp Med Biol*. 2020;1228:107-121.
34. Bailey NC, Dimsits J, Hammer M, Kendall DM, Bailey TS. A comparative study of dasiglucagon ready-to-use autoinjector and glucagon emergency kit during rescue from simulated severe hypoglycemia. *Diabetes Technol Ther*. 2022;24:231-240.

SUPPORTING INFORMATION

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

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