CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

GLUCAGON NASAL POWDER (BAQSIMI)

(Eli Lilly Canada Inc)

Indication: For the treatment of severe hypoglycemic reactions which may occur in the management of insulin treated patients with diabetes mellitus, when impaired consciousness precludes oral carbohydrates.

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Abbreviations

AE	adverse event
AP	acquaintance participant
CP	caregiver participant
EAP	efficacy analysis population
IM	intramuscular
IN	intranasal
IQR	interquartile range
MSAP	main safety analysis population
PWD	person with diabetes
RCT	randomized controlled trial
SAE	serious adverse event
SH	severe hypoglycemia
SSAP	sensitivity safety analysis population
T1D	type 1 diabetes
T2D	type 2 diabetes

Drug	Glucagon nasal powder (Baqsimi)
Indication	For the treatment of severe hypoglycemic reactions which may occur in the management of insulin-treated patients with diabetes mellitus, when impaired consciousness precludes oral carbohydrates
Reimbursement request	As per indication
Dosage form and route of administration and strength	Single use nasal dosing device containing 3 mg of glucagon powder
NOC date	September 25, 2019
Manufacturer	Eli Lilly Canada Inc.

Executive Summary

Introduction

Hypoglycemia is defined by: one, the development of neurogenic (autonomic) or neuroglycopenic symptoms; two, a low plasma glucose level (< 4.0 mmol/L for people with diabetes treated with insulin or an insulin secretagogue); and three, symptoms responding to the administration of carbohydrate.[1] Neurogenic (autonomic) symptoms include trembling, palpitations, sweating, anxiety, hunger, nausea, and tingling. Neuroglycopenic symptoms include difficulty concentrating, confusion, weakness, drowsiness, vision changes, difficulty speaking, headache, and dizziness.[1]

The severity of hypoglycemia is defined by clinical manifestations. Severe hypoglycemia is defined in recent Diabetes Canada Guidelines as hypoglycemia requiring the assistance of another person.[1] Unconsciousness may occur in severe hypoglycemia and plasma glucose is typically less than 2.8 mmol/L. Hypoglycemia is more frequent in people with type 1 diabetes (T1D) compared to people with type 2 diabetes (T2D) managed with insulin.[1,2]

Dangerous situations may arise when a person is experiencing hypoglycemia (e.g., while driving or operating machinery). Prolonged coma is sometimes associated with transient neurological symptoms, such as paresis, convulsions, and encephalopathy. Long-term complications of severe hypoglycemia include mild intellectual impairment and hemiparesis. There are some data suggesting that there is an association between severe hypoglycemia and cognitive disorders, though causality remains uncertain.[1-3]

Glucagon increases plasma glucose concentration by activating hepatic glucagon receptors, thereby stimulating glycogen breakdown and release of glucose from the liver. Baqsimi (glucagon intranasal powder) is indicated for the treatment of severe hypoglycemic reactions which may occur in the management of insulin-treated patients with diabetes mellitus, when impaired consciousness precludes oral carbohydrates. It is supplied as a powder in a single use nasal delivery device. Inhalation is not required by the patient. It is administered as a single 3 mg dose in both adults and children.[4]

The objective of this review was to perform a systematic review of the beneficial and harmful effects of glucagon nasal powder (Baqsimi) for the treatment of severe hypoglycemic reactions which may occur in the management of insulin-treated patients with diabetes mellitus, when impaired consciousness precludes oral carbohydrates.

Stakeholder Engagement

Patient Input

Two submissions were received from the Type 1 Together patient group and Diabetes Canada. Type 1 Together performed an online survey to which 543 responses were received from respondents across Canada. Diabetes Canada gathered information through an online survey to which 272 responses were received — 120 people living with T1D and 152 people caring for someone living with T1D.

Patients who responded to the surveys described some of the negative impacts of hypoglycemia on their lives including increased anxiety, fear of nocturnal hypoglycemia, complications of timing insulin dosing and self-blood glucose monitoring, and fear of being alone with no one to assist if needed. Caregivers and parents also expressed significant stresses experienced in the course of their responsibilities for caring for someone with diabetes.

Many respondents were familiar with injectable glucagon and some had experience using an injectable glucagon kit, with approximately one in five patients reporting that they were unsatisfied with the experience. Patients and caregivers cited limitations in affordability, usability, and portability of injectable glucagon. Some caregivers said that preparing the injectable glucagon in an urgent situation is stressful and there are significant feelings of uncertainty regarding preparing and properly administering the product. Anxiety was reported as high for parents whose young children have experienced severe hypoglycemia. Respondents said that they would like to see an alternative product to intramuscular glucagon that is easy and quick to administer, has a small chance of error, and would result in a fast recovery from hypoglycemia.

Clinician Input[a]

Severe hypoglycemia is defined in recent Diabetes Canada Guidelines as hypoglycemia requiring the assistance of another person. Unconsciousness may occur in severe hypoglycemia and plasma glucose is typically less than 2.8 mmol/L.[1] Glucagon is indicated for severe hypoglycemia in patients using insulin where oral administration of carbohydrates is not possible or safe. Glucagon is currently available as a subcutaneous or intramuscular injection. Glucagon is effective when used correctly but often it is not available in the setting of unexpected severe hypoglycemia. The need for it to be mixed and injected may make first responders to a severe hypoglycemia episode uncomfortable or uncertain on how to use it. Glucagon administration in children is weight based, which can also be difficult for caregivers to calculate in stressful situations, such as when their child is seizing or unconscious due to a severe hypoglycemic episode.

An ideal treatment will raise the blood glucose levels of the person with severe hypoglycemia quickly and safely with minimal adverse effects. Current available forms of glucagon need to be reconstituted and administered by injection, and in a stressful situation a family member or caregiver may struggle to do this. Glucagon should be available, and people close to the person with diabetes (PWD) should be knowledgeable in how to administer it, but ideally oral carbohydrates will always be sufficient to correct

[a] This information is based on information provided by the clinical expert consulted by the CADTH Common Drug Review reviewers for the purpose of this review.

hypoglycemia. The decision to use the already available intramuscular glucagon versus the drug under review would be personal and would depend on the living situation of the PWD.

All patients who use insulin are at risk of hypoglycemia and will exhibit a response to glucagon during a hypoglycemic episode when it is administered correctly. Severe hypoglycemia is more common in patients with T1D of long duration who have experienced frequent hypoglycemia and lack hypoglycemia awareness. Patients without good hypoglycemia awareness no longer experience the early signs and symptoms of hypoglycemia (including trembling, sweating, and hunger) that usually prompt patients to check their blood glucose and administer oral carbohydrates before hypoglycemia becomes more severe, leading to confusion, somnolence, and eventually seizure or coma. Patients least suitable for the drug under review would be those without any risk factors for hypoglycemia, including patients with T2D who are taking basal insulin only. Diabetes care team members should identify patients suitable for a glucagon prescription at diagnosis and also conduct an annual review of severe hypoglycemia at which glucagon should be prescribed and administration of glucagon should be reviewed with the patient.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

Four open label, randomized studies met the inclusion criteria for the systematic review, including two pivotal studies. Studies IGBC (pivotal study, N = 77, T1D), IGBI (N = 70, T1D), IGBJ (N = 72, type 1 and 2 diabetes) were all performed in adults. Study IGBB (pivotal study, N = 48) was performed in children aged 4 to 17 years. Hypoglycemia (not severe hypoglycemia) was induced as part of the study procedures in the three adult studies and the single pediatric study. In all studies, patients received a single 3 mg intranasal glucagon dose, and this was compared to a single dose of 1 mg intramuscular glucagon in crossover fashion.

Adult Studies

The primary outcome of all three of the adult studies was treatment success or response. In all adult studies, response was defined as an increase in plasma glucose to greater than 3.9 mmol/L or an increase of greater than 1.1 mmol/L from nadir within 30 minutes of the glucagon dose, with no additional actions. A noninferiority margin of 10% was selected for the absolute difference of response rates between intranasal and intramuscular glucagon for all three adult studies. The secondary outcomes of the adult studies included were similar across the three adult studies and included time to response (IGBC, IGBI, IGBJ); serial glucose measurements after receiving glucagon (IGBC, IGBI, IGBJ); serial insulin level measurements (IGBC, IGBJ); serial glucagon level measurements (IGBC, IGBJ); hypoglycemia symptoms as measured by the Edinburgh Hypoglycemia Scale (IGBC, IGBI, IGBJ); and nasal or non-nasal adverse symptom scores (IGBC, IGBI, IGBJ). The Edinburgh Hypoglycemia Scale was used to assess severity of hypoglycemic symptoms at the time of receipt of glucagon and for up to 60 minutes after the glucagon dose was administered. The maximum total score is 91, and a higher score indicated greater severity of symptoms.

Pediatric Study

The pediatric study (pivotal study, IGBB) did not have a predefined primary outcome. Glucose levels were monitored at regular intervals for at least 90 minutes after glucagon

was administered. Treatment success in Study IGBB (pediatric study) was established post hoc as an increase in plasma glucose of at least 1.4 mmol/L within 20 minutes following induction of hypoglycemia (not severe hypoglycemia).

Efficacy Results

Response Rates

As shown in Table 1, in study IGBC, response criteria in Study IGBC were met in 74 out of 75 patients (99%) after receiving intranasal glucagon and in 75 out of 75 patients (100%) after receiving intramuscular glucagon with a mean adjusted difference of 0.015 (one-sided 97.5% confidence interval [CI], 0.043). In Study IGBI, response criteria were met in 66 out of 66 patients (100%) after receiving intranasal glucagon and in 66 out of 66 patients (100%) after receiving intramuscular glucagon with a mean difference of 0.0 (95% CI, –1.52 to 1.52). In Study IGBJ, response criteria were met in 68 out of 68 patients (100%) after receiving intranasal glucagon and in 68 out of 68 patients (100%) after receiving intramuscular glucagon with a mean difference of 0.0 (95% CI, –1.47 to 1.47). The results of the primary outcome in all adult studies met the pre-specified criteria for noninferiority since the upper boundary of the CIs did not exceed 10% in any of the adult studies.

In the pediatric Study (IGBB), response criteria were met in 12 out of 12 (100%) patients after receiving intranasal glucagon and in six out of six patients (100%) after receiving intramuscular glucagon (no statistical testing results reported).

Other Outcomes

Time-to-event analyses were performed on the response data in all studies. In Study IGBC, the mean time-to-treatment response was 16.2 minutes after intranasal glucagon and the mean time-to-treatment response after intramuscular glucagon was 12.2 minutes (difference of four minutes, $P < 0.001$ for comparison, variance not reported). In Study IGBI, the median time-to-treatment response was 10 minutes (range = 5 to 25 minutes) after intranasal glucagon and the median time-to-treatment response was 10 minutes (range 10 to 20 minutes) after intramuscular glucagon (log rank $P = 0.069$). In the pediatric study (IGBB), the median time to response was not reported but the sponsor reported a statistical comparison of the time to response data in the children (hazard ratio = 0; 95% CI, 0 to 0).

In Study IGBC, the Edinburgh Hypoglycemia Scale scores were numerically higher (worse) for the intranasal glucagon treatment at all time points (15, 30, 45, and 60 minutes) after glucagon was administered than those of the intramuscular glucagon treatment (Table 9). [5] In Study IGBI, the Edinburgh Hypoglycemia Scale scores were similar between intranasal glucagon and intramuscular glucagon at 15, 30, 45, and 60 minutes.[6] In Study IGBJ, the score was higher (worse) for the intranasal glucagon treatment than that of the intramuscular glucagon treatment 15 minutes after the glucagon dose was administered.[7] The Edinburgh Hypoglycemia Scale was not used in the IGBB (pediatric) study.

Harms Results

Intranasal glucagon has a harms profile that is similar to intramuscular glucagon, with the exception of events that are related to the route of administration. The most frequently reported adverse events (AEs) reported after intranasal glucagon use (range across trials) included nausea (7% to 31%), vomiting (3% to 16%), headache (1% to 20%), nasal discomfort (0% to 10%), nasal congestion (0% to 8%), increased lacrimation (0% to 8%), fatigue (0% to 8%), nasopharyngitis (0% to 6%), and upper respiratory tract irritation (4% to 19%). Compared to intramuscular glucagon, oropharyngeal and eye symptoms occurred

more frequently in patients after receiving intranasal glucagon in Study IGBC.[5] These symptoms included: nasal discomfort (intranasal 10% versus intramuscular); nasal congestion (intranasal 8% versus intramuscular 1%), increased lacrimation (intranasal 8% versus intramuscular 1%), and upper respiratory tract irritation (intranasal 19% versus intramuscular 1%).[5] In Study IGBI, nasal itching (49%) and sneezing (24%) occurred more frequently after treatment with intranasal glucagon compared to intramuscular glucagon (0%).[6] Intranasal administration of glucagon avoids adverse effects related to intramuscular administration such as injection site pain and irritation. There was one serious adverse event (SAE) of positional vertigo after a patient received intranasal glucagon and intramuscular glucagon, and one SAE of hypoglycemia that occurred in a child during hypoglycemia induction. There were no deaths in the studies.

Other Relevant Studies

Four studies that used intranasal glucagon were identified and summarized as additional evidence. These studies reported information that may help to understand the application of intranasal glucagon under conditions that were designed to mimic real-world administration. Two studies enrolled patients with T1D (B001, B002) and two studies were performed using mannequins instead of patients (IGBM, AMG111).

In the B001 and B002 studies, moderate hypoglycemic events in adults and children with diabetes (defined as the presence of neuroglycopenic signs and/or symptoms and low blood glucose) and severe hypoglycemic events in adults were treated using intranasal glucagon under real-world conditions These two studies reported a high rate of administration success: 100% of moderate hypoglycemic events in the pediatric patients and 96.2% of hypoglycemic events (including all severe hypoglycemic events) in adult patients were successfully resolved within 30 minutes of administration. Limitations of these studies include the small sample size of events (particularly for severe hypoglycemic events), the lack of a comparison with intramuscular glucagon, and the possibility that caregivers and adult patients were more recently trained and therefore better prepared to treat hypoglycemia in the studies than they would be under real-world conditions.

Studies IGBM and AMG111 compared the usage of intranasal glucagon and intramuscular glucagon in mannequins and focused on the caregiver experience. These studies reported higher rates of successful administration with intranasal glucagon versus intramuscular glucagon and found that most people administering the glucagon products expressed a preference for the intranasal over the injectable form. Investigators also reported a shorter mean time to successful administration of intranasal glucagon compared to intramuscular glucagon, with times ranging between 30 seconds and 2 minutes faster. These estimates were subject to major limitations, in particular the small sample sizes and uncertainty in the generalizability of the simulated events to real-life hypoglycemic events.

Table 1: Summary of Key Efficacy Results From Pivotal and Protocol Selected Studies

Outcome[a]	Intranasal glucagon 3 mg	Intramuscular glucagon 1 mg	Comparison
IGBC (adults) treatment success, n/N (%)	74/75 (99)	75/75 (100)	Difference 0.015 (one-sided 97.5% CI, 0.043)[b]
Mean time-to-treatment success (SD), minutes	16.2 (NR)	12.2 (NR)	Difference 4 minutes (SD NR) P < 0.001[c]
IGBI (adults) treatment success, n/N (%)	66/66 (100)	66/66 (100)	Difference 0.0 (95% CI, –1.52 to 1.52)[d]

Outcome[a]	Intranasal glucagon 3 mg	Intramuscular glucagon 1 mg	Comparison
Mean time-to-treatment success (SD), minutes	11.44 (3.01)	9.85 (3.03)	Difference 1.6 minutes (SD NR) Log rank P = 0.002
IGBJ (adults) treatment success, n/N (%)	68/68(100)	68/68 (100)	0.0 (95% CI, –1.47 to 1.47)[d]
Mean time-to-treatment success (SD), minutes	10.0 (5.0 to 25.0) N = 68	10.0 (5.0 to 20.0) N = 68	Log rank P = 0.069
IGBB (children) treatment success n/N (%) 4 to ≤ 8 years old 8 to < 12 years old 12 to < 17 years old	 12/12 (100) 12/12 (100) 12/12 (100)	 6/6 (100) 6/6 (100) 12/12 (100)	 NR NR NR
Median time-to-treatment success 4 to ≤ 8 years old 8 to < 12 years old 12 to < 17 years old	 NR NR NR	 NR NR NR	 HR = 0 (95% CI, 0 to 0) HR = 3.6 (95% CI, 0.5 to 23.9) HR = 0.4 (95% CI, 0.2 to 1.1)

CI = confidence interval; HR = hazard ratio; NR = not reported; PG = plasma glucose; SD = standard deviation.

[a] Treatment success in adult studies: PG increase to ≥ 3.9 mmol/L or increase of ≥ 1.1 mmol/L from nadir 30 min after glucagon (primary outcome). Treatment success in pediatric study: PG ≥ 1.4mmol/L increase after 20 minutes.

[b] Difference in proportions adjusted for treatment period and blood glucose value immediately before administration of glucagon.

[c] Cox proportional hazards model.

[d] Wald's method with continuity correction.

Source: Clinical Study Reports for IGBC,[5] Rickels et al,[8] IGBI,[6] IGBJ,[7] IGBB,[9] Sherr et al.[10]

Table 2: Summary of Key Harms From Pivotal and Protocol Selected Studies

	IGBC (adults, T1D and T2D)		IGBI (adults T1D)		IGBJ (adults)	
	Intranasal glucagon N = 83	Intramuscular glucagon N = 82	Intranasal glucagon N = 70	Intramuscular glucagon N = 69	Intranasal glucagon N = 71	Intramuscular glucagon N = 70
Notable Harms: Patients reporting worsening of nasal and non-nasal symptoms post dose to 90 minutes, n (%)						
Nasal symptoms						
Runny nose	27 (32)	NR	26 (37)	0	5 (7)	1 (1)
Nasal congestion	38 (46)	NR	27 (39)	3 (4)	8 (11)	2 (3)
Nasal itching	26 (31)	NR	34 (49)	0	3 (4)	0
Sneezing	13 (16)	NR	17 (24)	0	0	0
Non-nasal symptoms		NR				
Watery eyes	46 (55)	NR	44 (63)	0	15 (21)	1 (1)
Itchy eyes	19 (23)	NR	14 (20)	1 (1)	1(1)	0
Redness of eyes	23 (28)	NR	15 (21)	0	3 (4)	1 (1)
Itching of ears	3 (4)	NR	2 (3)	0	0	0
Itching of throat	10 (12)	NR	9 (13)	0	0	0

NR = not reported; T1D = type 1 diabetes mellitus; T2D = type 2 diabetes mellitus.

Source: Clinical Study Reports for IGBC,[5] Rickels et al,[8] IGBI,[6] IGBJ,[7] IGBB,[9] Sherr et al.[10]

Critical Appraisal

The primary outcome for Study IGBB (pediatric) does not appear to have been defined a priori. The publication states that the primary outcome was a 1.4 mmol/L or greater rise in plasma glucose within 20 minutes after glucagon administration, but this is not stated in either the sponsor's statistical analysis plan or in the trial registry.[9-11] There was no formal sample size calculation performed for this study. The primary objective of the study was to assess the pharmacokinetics and pharmacodynamics of intranasal glucagon relative to intramuscular glucagon, and there were other inconsistencies in the way the study was reported in the publication compared to the clinical study report, with the publication referring to it as a phase I study and the clinical study report classifying it as a phase III study. The subgroup analyses were predefined in the study protocol, but the numbers of children in the subgroups by age were small and for these reasons the data from this trial cannot be considered conclusive evidence of intranasal glucagon efficacy or of its harms relative to intramuscular glucagon.

Six patients in Study IGBC received oral carbohydrates after receiving intranasal glucagon. This would bias the results of the serial glucose measurements in favour of the intranasal treatment since no patients received oral carbohydrates after receiving intramuscular glucagon in the study. One of these six patients was excluded from efficacy analyses but the other five patients were included in the analyses and it was not clear whether oral carbohydrate consumption was taken into account in any of the post-glucagon glucose assessments.

The primary limitation of the four trials that met the inclusion criteria for the systematic review is that the trials did not attempt to mimic real-world conditions. The study medications were administered under controlled conditions by trained health care professionals. Hypoglycemia was induced and symptom criteria for hypoglycemia were not used in the protocol to induce hypoglycemia. The achievement of hypoglycemia was based on glucose levels alone. Intranasal glucagon is indicated for treatment of severe hypoglycemic reactions, but the controlled trials were not designed to study recovery from severe hypoglycemia. Reviewers acknowledge that real-world studies including the conditions specified in the indication (e.g., impaired consciousness) would be difficult to achieve, however, a major limitation of the studies remains since there were no controlled trials that tested the product under the conditions specified in the indication. Given the uniformity of the pharmacodynamic response to exogenous glucagon, reviewers believe that the extrapolation of the results of the trials to severe hypoglycemia is reasonable, but there remains uncertainty about the time to response relative to intramuscular glucagon since this has not been directly quantified under severe hypoglycemic conditions.

Conclusions

Patients receiving intranasal glucagon for treatment of experimentally induced hypoglycemia (not severe hypoglycemia) have rates of treatment response similar to those of intramuscular glucagon in three studies in adults and one study in children. Intranasal glucagon is indicated for treatment of severe hypoglycemic reactions, but the controlled trials were not designed to study recovery from severe hypoglycemia. The mean time-to-treatment response was between 1.6 and 4 minutes longer for patients receiving intranasal glucagon compared to intramuscular glucagon in two adult trials under controlled experimental conditions. The differences in time-to-treatment response between intranasal glucagon and intramuscular glucagon may be improved under real-world conditions

because of potential reduction in administration time for intranasal glucagon but the degree to which this would be mitigated is not known. Limited evidence from simulated emergency scenarios suggests that successful administration of glucagon is more likely with intranasal delivery compared with intramuscular delivery, though the generalizability to real-world conditions and users remains unclear. The effectiveness of intranasal glucagon relative to intramuscular glucagon in real-world conditions of severe hypoglycemia in which the patient requires external assistance is not known.

Introduction

Disease Background

Hypoglycemia is defined by: one, the development of neurogenic (autonomic) or neuroglycopenic symptoms; two, a low plasma glucose level (< 4.0 mmol/L for people with diabetes treated with insulin or an insulin secretagogue); and three, symptoms responding to the administration of carbohydrate.[1] Neurogenic (autonomic) symptoms include trembling, palpitations, sweating, anxiety, hunger, nausea, and tingling. Neuroglycopenic symptoms include difficulty concentrating, confusion, weakness, drowsiness, vision changes, difficulty speaking, headache, and dizziness.[1]

The severity of hypoglycemia is defined by clinical manifestations. Severe hypoglycemia is defined in recent Diabetes Canada Guidelines as hypoglycemia requiring the assistance of another person.[1] Unconsciousness may occur in severe hypoglycemia and plasma glucose is typically less than 2.8 mmol/L. Hypoglycemia is more frequent in people with T1D compared to people with T2D managed by insulin.[1,2]

Dangerous situations may arise when a person is experiencing hypoglycemia (e.g., while driving or operating machinery). Prolonged coma is sometimes associated with transient neurological symptoms, such as paresis, convulsions, and encephalopathy. Long-term complications of severe hypoglycemia include mild intellectual impairment and hemiparesis. There are some data suggesting that there is an association between severe hypoglycemia and cognitive disorders, though causality remains uncertain.[1-3]

Glucagon increases blood glucose concentration by activating hepatic glucagon receptors, thereby stimulating glycogen breakdown and release of glucose from the liver. Baqsimi (glucagon intranasal powder) is indicated for the treatment of severe hypoglycemic reactions which may occur in the management of insulin-treated patients with diabetes mellitus, when impaired consciousness precludes oral carbohydrates. It is supplied as a powder in a single use nasal delivery device. Inhalation is not required by the patient. It is administered as a single 3 mg dose in both adults and children.[4]

Standards of Therapy

Treating severe hypoglycemia requires the assistance of another person to administer carbohydrate, glucagon, or other resuscitative actions. Patients with IV access can be given 25 g of 50% glucose (dextrose) intravenously.[2] Alternatively, glucagon can be administered intramuscularly, subcutaneously, or intranasally. The clinical expert consulted by CADTH for this review indicated that one dose is usually adequate for patient recovery from severe hypoglycemia. Administration of glucagon usually leads to recovery of consciousness within approximately 15 minutes, and it may be followed by nausea or vomiting.[1,2] Glucagon administration is often followed by glucose administration either by infusion, or orally if level of consciousness permits.[1,2] Glucagon increases blood glucose concentration by activating hepatic glucagon receptors, thereby stimulating glycogen breakdown and the release of glucose from the liver. Hepatic stores of glycogen are necessary for glucagon to produce an antihypoglycemic effect.[4]

Drug

Glucagon powder for intranasal administration (Baqsimi) is approved for the treatment of severe hypoglycemic reactions which may occur in the management of insulin-treated patients with diabetes mellitus, when impaired consciousness precludes oral carbohydrates.[4] It received a Notice of Compliance from Health Canada on September 25, 2019. Intranasal glucagon (Baqsimi) received a Health Canada drug schedule of "ethical" (non-prescription status), which is the same category as many insulin products and epinephrine autoinjectors.[12]

No glucagon product has previously been reviewed through the CADTH Common Drug Review process. The sponsor requested that intranasal glucagon be reimbursed for the same population as stated in the Health Canada indication.

Table 3 summarizes the characteristics of intranasal glucagon and its relevant comparator, glucagon for parenteral administration.

Table 3: Key Characteristics of Glucagon Products

	Glucagon nasal powder (Baqsimi)	Glucagon powder for injection (Glucagen, Glucagen Hypokit)
Mechanism of action	Increases blood glucose concentration by activating hepatic glucagon receptors, thereby stimulating glycogen breakdown and release of glucose from the liver	
Indication[a]	Treatment of severe hypoglycemic reactions which may occur in the management of insulin-treated patients with diabetes mellitus, when impaired consciousness precludes oral carbohydrates	
Route of administration	Intranasal	Intramuscular
Dosage form	Supplied as a powder in a single use nasal delivery device; inhalation not required	Supplied as a powder for injection; requires reconstitution via syringe
Recommended dose	3 mg (for adults and children)	1 mg (0.5 mg for children below 25 kg or younger than 6 to 8 years)
Other	Helpful in treating hypoglycemia only if sufficient liver glycogen is present	

[a] Health Canada approved indication.

Source: Baqsimi product monograph,[13] Glucagen product monograph.[14]

Stakeholder Engagement

Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

Two submissions were received for this review from the Type 1 Together patient group and Diabetes Canada. The goal of Type 1 Together is to connect Canadian patients living with T1D, supporting social connection, information sharing, and advocacy. Type 1 Together primarily communicates with members through social media and articles shared on Facebook pages and groups. Diabetes Canada aims to help those affected by diabetes live healthy lives, prevent the onset and consequences of diabetes, and discover a cure.

Type 1 Together shared an online survey with members of the Canadian T1D community through social media and word of mouth. The survey was only available in English and data were collected from August 2 to 13, 2019. During this time, 543 responses were received from respondents across all provinces, Yukon, and Nunavut. Of the 543 respondents, 53.4% were parents who directly managed a child's T1D, 29.8% were patients living with T1D, 12.5% were family members of someone with T1D, and 2.6% were other types of caregivers. The age of respondents ranged from "under 13" to the "70- to 84-year old" age groups, with 91% of respondents between the ages of 26 and 69.

Type 1 Together reported that they sent a request to the sponsor (Eli Lilly) to contact investigators involved in the Canadian clinical trials regarding help with distribution of the survey URL to trial patients, but whether this was successful is unknown. Type 1 Together also reported that they wrote the survey and collected and analyzed survey data independently.

Diabetes Canada gathered information through an online survey in July of 2019 that was advertised through their social media channels. The survey had 272 respondents – 120 living with T1D and 152 caring for someone living with T1D. Of the 129 who answered questions about age and time since diagnosis, approximately half were under 24 years of age, 36% were between 25 and 54 years, and 16% were above 55 years. Also, 24% had been living with T1D for more than 20 years, 20% for 11 to 20 years, 14% from six to 10 years, 20% from three to five years, 12% from one to two years, and 9% for less than one year. Most provinces were represented and there were no respondents from the Territories. Diabetes Canada stated that they received no outside help in completing the submission or in collecting or analyzing data.

2. Condition-Related Information

Type 1 diabetes is a chronic, progressive, autoimmune disease where the body stops producing insulin. The disease is not caused by lifestyle choices and patients must take insulin to avoid death. The amount of insulin that is required is affected by a variety of factors, ranging from the types of food and drink that are consumed and activity levels to hormones, body weight, and inflammation. Altitude, emotions, and pregnancy can also impact insulin requirements. Patients or caregivers must administer insulin by injection or pump and monitor diet and blood glucose, and patients must engage in regular physical activity and manage stress. It is clear that "managing type 1 diabetes well requires extraordinary behavioural commitments and being attentive to it 24 hours a day, every day of your life, even when you're sleeping," as the Type 1 Together submission describes.

Regarding management of blood glucose levels, taking too much insulin may result in hypoglycemia, which may include the following symptoms: shakiness, anxiety, sweating, lethargy, confusion, rapid heartbeat, hunger, nausea, sleepiness, impaired vision, headaches, tongue or nose tingling, anger, crying, or gastrointestinal disturbances. In severe cases, hypoglycemia may result in seizures, loss of consciousness, brain damage, and death. Insufficient insulin, leading to hyperglycemia, can also be problematic and is associated with similar symptoms, in addition to extreme thirst or dehydration, frequent urination, increased appetite, blurred vision, and light-headedness in the short-term. More seriously, hyperglycemia can also cause rapid-onset coma and death. Multiple significant comorbidities, such as cardiovascular disease, lower limb amputations, kidney disease, and blindness, are some of the long-term consequences of not taking enough insulin. Poor glycemic control and the presence of comorbidities can also increase the risk of depression.

Most respondents to the Diabetes Canada survey indicated that diabetes has negatively affected all aspects of their lives and limited their activities and opportunities including those related to travel and career. Respondents described being forced to live in a regimented manner with limited room for spontaneity, as well as feeling anger and frustration associated with the daily challenge of managing the disease. Losses associated with the disease included the ability to drive (loss of licence), loss of employment, and loss of opportunities for normal social activities (such as drinking). Respondents reported significant financial hardship due to diabetes-related medication, devices, and supplies, particularly when opting for certain types of insulin, insulin pumps, and/or continuous glucose monitors.

In 140 of the Diabetes Canada survey respondents, the following symptoms of hypoglycemia had been experienced: low plasma glucose of less than 4.0 mmol/L (87%), trembling, palpitations, sweating, anxiety, nausea, tingling, or hunger (82%), confusion, weakness, drowsiness or vision changes (73%), a need for assistance (55%), difficulty speaking, headaches or dizziness (54%), and loss of consciousness, coma, or seizure (6%). Specific to hypoglycemia, one respondent to the Diabetes Canada survey described its negative impacts on sleep:

> It [diabetes] has increased my stress and anxiety levels and impacted my sleep. I rarely get a good nights sleep due to diabetes. I've awoken before to paramedics standing over me – way more than once. That has a terrible effect on one's mind and body to be scared to go to sleep.

Another respondent also expressed anxiety at the possibility of a severe hypoglycemic event:

> Did I test, did I bolus when I ate, do I have enough insulin for the day, when does my sensor expire, will alarms go off in meetings? The big one – will someone be able to take care of me if I lose consciousness?

Parents of children with diabetes described fear and anxiety over the possibility of low glucose levels. One parent described constant blood glucose monitoring in their child, including monitoring for delayed low glucose for up to 24 hours following sporting activities.

The Type 1 Together submission corroborated some of the results of the Diabetes Canada survey. The submission referred to a study conducted in 2016 that summarized the experiences of Canadians with T1D who had lived with the disease for an average of 21 year. This study stated that 48% of patients registered high levels of "significant emotional distress that interfered with diabetes outcomes." The study also highlighted the impact of T1D on caregivers, many of whom (33% of study participants) experienced high diabetes distress as well. An exercise conducted by Type 1 Together that was designed to elicit

positive and negative emotions related to T1D returned the following themes: helplessness, exhaustion, anger, and fear, as well as optimism and resiliency.

3. Current Therapy-Related Information

According to the patient submissions, glucagon is acknowledged as an effective life-saving drug and patients and caregivers are "happy that it's available." According to the Type 1 Together survey, 25% of survey respondents could confirm they had used glucagon in the past, and 96% reported that it had resolved their hypoglycemia. In the Diabetes Canada survey, 30% of those who completed the section of the survey on hypoglycemia had experience using injectable glucagon for severe hypoglycemia, with 23% being "very satisfied" or "satisfied" with their experience; 58% "neither satisfied nor unsatisfied;" and 19% "unsatisfied" or "very unsatisfied." Side effects of glucagon included nausea (17%), vomiting (13%), skin rash (3%), and difficulty breathing (3%). Respondents to the Diabetes Canada survey indicated benefits of using a smaller dose of glucagon for hypoglycemia when feeling unwell but not unconscious, when feeling nauseous, or when unable to consume food or beverages.

Patients describe affordability, usability, and portability as the predominant issues with the injectable glucagon treatment that is currently available. Although most Type 1 Together survey respondents had a glucagon kit for themselves (70%) or a child they care for (98%), the kits are often left at home. The submission cites that approximately only 2 in 3 children have a glucagon kit at school, and that they are less common at work. Issues surrounding the inconvenient size of the kit and concerns about keeping the kit at a stable temperature were reported. Further, if the kit is available, there is a lack of confidence among patients and caregivers in the administration of glucagon. Caregivers find the prospect of administering a glucagon injection intimidating and in the Type 1 Together survey, 12% of respondents reported the process of preparing glucagon as stressful or confusing. For example, one parent stated:

> "When your child lays helpless and you're in an emergency situation, you can get overwhelmed with the steps it takes to prepare glucagon. The long, large needle is intimidating, and it makes you hesitate to put into such a little leg. Being able to be more confident, and fast acting with glucagon administration will save lives, it will remove the barrier for the general population to help."

Outside of parents, others may be unreceptive to or uncomfortable with being trained in the use of glucagon:

> "When we used expired glucagon to demonstrate how to administer it to our daughter's care providers, they find the whole thing very intimidating, especially the giant needle. The fact that you have to mix the powder with the liquid is also an issue. Everyone is scared they won't remember or know what to do in an actual emergency."

Several situations were described concerning the size of the needle and the difficulty or hesitation with its administration. The occurrence of seizures during hypoglycemic episodes decreases the confidence that patients and caregivers have in delivering the injection of glucagon successfully. In the Type 1 Together survey, 45% of respondents reported confidence in their ability to administer glucagon to a conscious patient, and 19% for a patient having a seizure. Patients may also be resistant to receiving an injection. This resistance was described by the patient group along with an example of three police officers who were unable to hold down a resistant man experiencing severe hypoglycemia to administer glucagon and needed to tase the man to proceed with treatment. A parent also described this situation with their child:

> "My daughter was hysterical and hallucinating as I was trying to offer a juice box, sugar packets and gummy worms. She was screaming at the top of her lungs as if I was a stranger. I decided to pull out the glucagon kit. It was very frustrating having to read the instructions quick and having to draw the powder to be then added to the liquid vial all the while she is screaming at the top of her lungs having a panic attack over the big syringe. There was no calming her down, and she never got the dose as it was too dangerous of a situation as she was becoming a danger to herself."

Type 1 Together reported that school-age children are particularly susceptible to the barriers associated with the use of glucagon as 68% of children attend a school in Canada that does not receive support for glucagon injections from school staff. In many instances staff are forbidden from administering glucagon, and 5% of parents reported that they rely on a single volunteer to administer glucagon when needed. This barrier to the administration of glucagon was further described as preventing children living with T1D from integrating into society. As a result, some children are homeschooled, and others are denied participation in school trips where there is a risk of a delay in receiving emergency services. The Diabetes Canada submission also identified challenges with school personnel being unwilling to administer glucagon to students.

Alternatively, some patients opt to keep their blood glucose level above target to avoid hypoglycemia, which increases the risk of diabetes complications. In the Type I Together survey, 60% of respondents indicated that they used this approach on a daily or weekly basis. In addition, affordability was also highlighted as an issue with glucagon. In the Type I Together survey some mentioned that it becomes a choice between food, shelter, and insulin to keep them alive, or glucagon. "We should not have to pay as this is not a luxury, it is about our child's avoiding a coma, brain damage or death."

4. Expectations About the Drug Being Reviewed

A total of four respondents among the two surveys indicated having experience with nasal glucagon through a clinical trial, although the respondents did not appear to provide information about their experience with nasal glucagon.

The Type 1 Together submission highlighted that ultimately patients, family, and caregivers would prefer a treatment that can cure T1D. If not available, they would like to see treatment regimens that improve health and the management of blood glucose levels with less work, that are as effective or more effective than current treatments. In addition, they reported the desire to consume a "normal" diet, and have treatments available with reduced risk of complications, increased safety, reduced emotional and financial burden, and less pain. Lastly, a desire for quality and choice was mentioned, noting that cost is a predominant factor in the selection of treatments to manage T1D.

According to the submission from Type 1 Together, patients expect that access to nasal glucagon should reduce their reliance on emergency medical technicians to treat severe hypoglycemia, while improving their confidence in the administration of glucagon, ultimately reducing the rates of diabetes complications. According to the Diabetes Canada survey, almost all respondents rated the following criteria as important in a treatment for severe hypoglycemia: quick to administer, small chance of error, and fast recovery. Respondents would like a glucagon treatment that is pre-mixed or in an inhaled form that is easy to administer, so that others, including school personnel, would be more willing to administer the treatment. Patients also noted that the injectable glucagon treatment that is currently available draws a lot of attention when used and adds to the stigma associated with the disease. Therefore, a less conspicuous treatment would also represent an improvement. Respondents also indicated they would like a more compact glucagon kit or glucagon integration into insulin pump systems to improve portability.

5. Additional Information

The free-text response portion of the Type 1 Together survey received comments from many respondents who felt that nasal glucagon kits should be a standard in first aid kits, free, and widely available. Comparisons were made to the availability of other live-saving therapies such as naloxone (Narcan) and defibrillators, which are available under public programs.

The Diabetes Canada submission highlighted the importance, alongside introducing treatment, of educating patients and their support persons about preventing, recognizing, and treating hypoglycemia.

Clinician Input

All CADTH review teams include at least one clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process. For example, these experts provide guidance on the development of the review protocol, assist in the critical appraisal of clinical evidence, interpret the clinical relevance of the results, and provide guidance on the potential place in therapy. The following input was provided by a clinical specialist with expertise in the diagnosis and management of diabetes mellitus.

Description of the Current Treatment Paradigm for the Disease

Severe hypoglycemia is defined in recent Diabetes Canada Guidelines as hypoglycemia requiring the assistance of another person. Loss of consciousness may occur in severe hypoglycemia and plasma glucose is typically less than 2.8 mmol/L.[1] Glucagon is indicated for severe hypoglycemia in patients using insulin where oral administration of carbohydrates is not possible or safe. Glucagon is currently available as a subcutaneous or intramuscular injection. It is stored at room temperature as a powder that needs to be mixed into solution and used immediately. Glucagon is effective when used correctly but often it is not available in the setting of unexpected severe hypoglycemia. The need for it to be mixed and injected may make first responders to a severe hypoglycemia episode uncomfortable or uncertain on how to use it. Glucagon administration in children is weight based, which can also be difficult for caregivers to calculate in stressful situations, such as when their child is seizing or unconscious due to a severe hypoglycemic episode.

Treatment Goals

An ideal treatment will raise the blood glucose levels of the person with severe hypoglycemia quickly and safely with minimal adverse effects. Glucagon is an emergency treatment for life-threatening hypoglycemia and can be lifesaving. Although the injectable glucagon that is currently available is a life-saving treatment, it is not easy to administer and has significant gastrointestinal side effects.

Unmet Needs

The unmet goal is that an emergency treatment needs to be simple to prepare and can be administered in a timely fashion. Currently available forms of glucagon need to be reconstituted and administered by injection, and in a stressful situation a family member or caregiver may struggle to do this.

Place in Therapy

The drug under review offers a novel delivery mechanism for glucagon. It appears to be stable up to 30°C and requires no reconstitution.

Ideally, a stable and well-controlled patient with diabetes will never experience severe hypoglycemia. In this way, there is a parallel between glucagon for severe hypoglycemia and the epinephrine for anaphylaxis delivered via autoinjector. Glucagon should be available and people close to the PWD should know how to administer it, but ideally oral carbohydrates will always be sufficient to correct hypoglycemia. The decision to use the already available intramuscular glucagon versus the drug under review would be personal and would depend on the living situation of the PWD. Intranasal glucagon may be very helpful in young adults living away from home at university where roommates may be much more comfortable using the intranasal formulation than the intramuscular formulation.

Patient Population

All patients who use insulin are at risk of hypoglycemia and will exhibit a response to glucagon during a hypoglycemic episode when it is administered correctly. Severe hypoglycemia is more common in patients with T1D of long duration who have experienced frequent hypoglycemia and lack hypoglycemia awareness. Patients without good hypoglycemia awareness no longer experience the early signs and symptoms of hypoglycemia (including trembling, sweating, and hunger) that usually prompt patients to check their blood glucose and administer oral carbohydrates before hypoglycemia becomes more severe, leading to confusion, somnolence, and eventually seizure or coma. Patients least suitable for the drug under review would be those without any risk factors for hypoglycemia, including patients with T2D who are taking basal insulin only. Diabetes care team members should identify patients suitable for a glucagon prescription at diagnosis and also conduct an annual review of severe hypoglycemia at which glucagon should be prescribed and administration of glucagon should be reviewed with the patient.

Assessing Response to Treatment

A clinically meaningful response to treatment for severe hypoglycemia would be an improvement of blood glucose and symptoms such that the patient with diabetes is able to function normally without assistance.

Prescribing Conditions

A specialist in diabetes may help to identify those most at risk and prescribe the drug under review prophylactically. The need to use glucagon in an episode of severe hypoglycemia should prompt a review of insulin doses with a diabetes care team member.

The decision to administer the drug is made in the moment by family and first responders. Ideally, intranasal glucagon would be administered in the community setting.

Clinical Evidence

The clinical evidence included in the review of glucagon nasal powder is presented in three sections. Section 1, the Systematic Review, includes pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those studies that were selected according to an a priori protocol. Section 2 includes indirect evidence from the sponsor (if submitted) and indirect evidence selected from the literature that met the selection criteria specified in the review. Section 3 includes long-term extension studies submitted by the sponsor and additional relevant studies that were considered to address important gaps in the evidence included in the systematic review.

Systematic Review (Pivotal and Protocol Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of glucagon nasal powder for the treatment of severe hypoglycemic reactions which may occur in the management of insulin-treated patients with diabetes mellitus when impaired consciousness precludes oral carbohydrates.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those meeting the selection criteria presented in Table 4.

Table 4: Inclusion Criteria for the Systematic Review

Patient population	Adult and pediatric patients who receive treatment with insulin and who experience impaired consciousness **Subgroups of interest** • Children and adults • Type 1/2 diabetes mellitus • Patients with higher risk for developing severe hypoglycemia compared to patients with lower risk for developing severe hypoglycemia
Intervention	Glucagon nasal powder using the approved device (3 mg per dose)
Comparators	Glucagon (subcutaneous, intramuscular) Dextrose (IV) Placebo
Outcomes	**Efficacy outcomes** • Resolution of hypoglycemic episodes[a] • Time to dose administration • Validated measures for Quality of Life[a] • Validated measures of caregiver and patient satisfaction[a] **Harms outcomes** SAEs, AEs, WDAEs Notable harms: administration-related AEs, nausea, vomiting
Study design	Prospective studies with a control group

AE = adverse event; RCT = randomized controlled trial; SAE = serious adverse events; WDAE = withdrawal due to adverse events.

[a] These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the PRESS Peer Review of Electronic Search Strategies checklist (https://www.cadth.ca/resources/finding-evidence/press).[15]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were baqsimi (glucagon intranasal spray) and hypoglycemia. Clinical trial registries were searched: the US National Institutes of Health's clinicaltrials.gov and the World Health Organization's International Clinical Trials Registry Platform (ICTRP) search portal.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on August 23, 2019. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on December 11, 2019.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters: a practical tool for searching health-related grey literature checklist (https://www.cadth.ca/grey-matters):

- health technology assessment agencies
- health economics
- clinical practice guidelines
- drug and device regulatory approvals
- advisories and warnings
- drug class reviews
- clinical trials registries
- databases (free).

Google was used to search for additional internet-based materials. These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts. In addition, the sponsor of the drug was contacted for information regarding unpublished studies. See Appendix 2 for more information on the grey literature search strategy.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Findings From the Literature

A total of four studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 5. A list of excluded studies is presented in Appendix 2.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

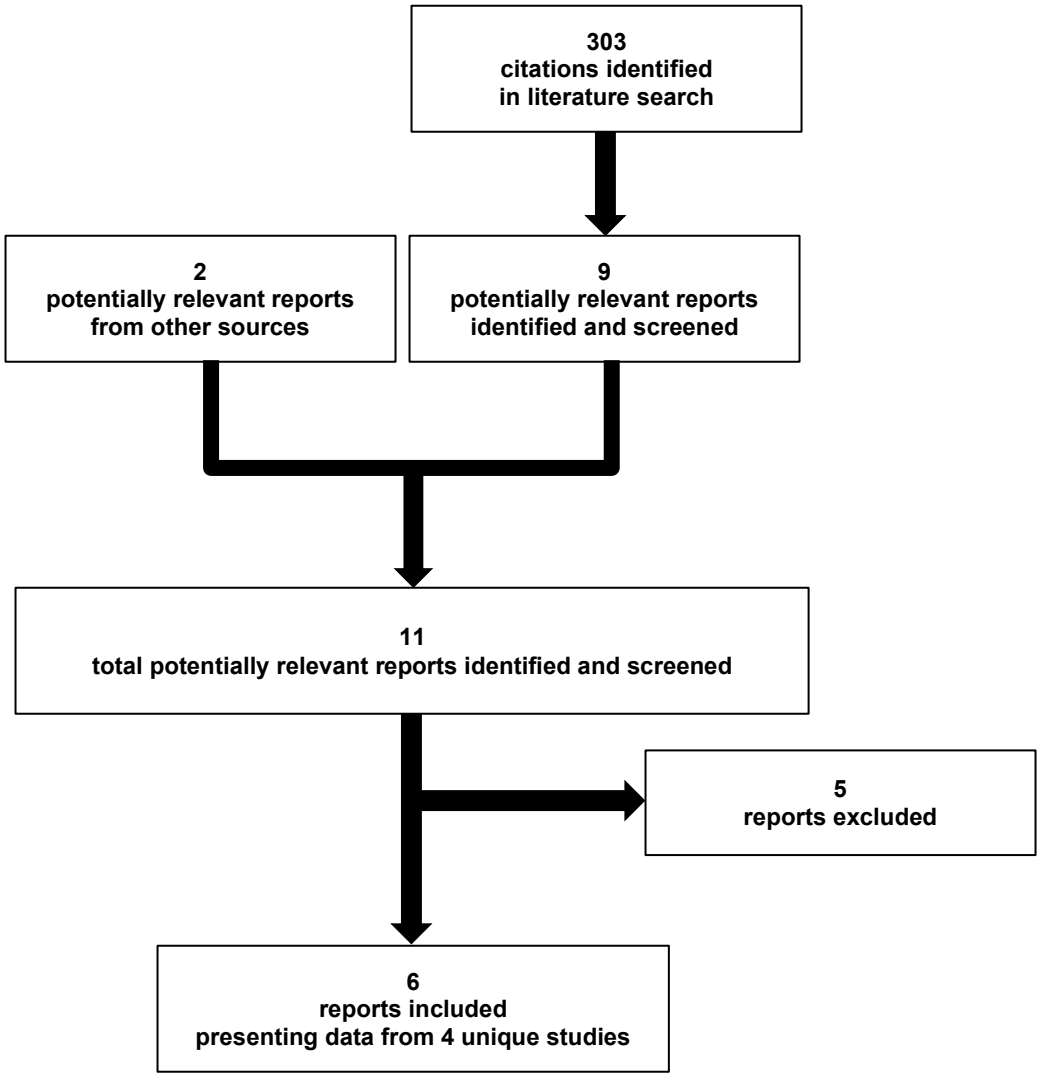


Table 5: Details of Included Studies

		IGBC (adults)	IGBI (adults)	IGBJ (adults)	IGBB (children)
Designs and Populations	**Study design**	OL RCT crossover, noninferiority	OL RCT crossover, noninferiority	OL RCT crossover, noninferiority	RCT, quasi-blinded, quasi-crossover
	Locations	US (8 sites)	Germany (2 sites)	Japan (4 sites)	US (7 sites)
	Randomized (N)	N = 77 with T1D; N = 6 with T2D	N = 70 with T1D	N = 33 with T1D; N = 39 with T2D	N = 48 with T1D (N = 36 aged 4 to 11; N = 12 aged 12 to 16)
	Inclusion criteria	• Age 18 to 65 • Diagnosis of T1D or T2D • Receiving insulin for ≥ 2 years • BMI between 20 to 35 kg/m^2 • Weight ≥ 50 kg	• Age 18 to 64 • Diagnosis of T1D • Receiving insulin for ≥ 2 years • Total daily insulin dose ≥ 1.5 U/kg • Hemoglobin A1C ≤ 10% • BMI between 18.5 to 35 kg/m^2	• T1D • Age 18 to 64 • BMI 18.5 to 30 kg/m^2 • Daily insulin for ≥ 1 year **or** • T2D • Age 20 to 70 • BMI 18.5 to 30 kg/m^2 • Daily insulin for ≥ 1 year **and** • Hemoglobin A1C ≤ 10%	• Age 4 to 16 years • T1D • Receiving insulin for ≥ 12 months
	Exclusion criteria	• Severe hypoglycemia needing assistance during month prior to study start • ≥ 3 alcoholic beverages per day	• Severe hypoglycemia needing assistance during month prior to study start	• Severe hypoglycemia needing assistance during month prior to study start • Loss of consciousness in past 2 years	• Severe hypoglycemia needing assistance during month prior to study start
	Experimentally induced hypoglycemia with insulin?	Yes	Yes	Yes	Yes
Drugs	**Intervention**	Single dose intranasal glucagon 3 mg	Single dose intranasal glucagon 3 mg	Single dose intranasal glucagon 3 mg	**Cohort 4 to 11 years:** single dose intranasal glucagon 2 mg and 3 mg on separate visits **Cohort 12 to 16 years:** single dose intranasal glucagon 3 mg
	Comparator(s)	Single dose intramuscular glucagon 1 mg	Single dose intramuscular glucagon 1 mg	Single dose intramuscular glucagon 1 mg	**All patients:** single dose intramuscular glucagon 1 mg
Duration	**Visits**	Visit 1, followed by washout period of 7 to 28 days, followed by Visit 2	Visit 1, followed by washout period of 1 to 7 days, followed by Visit 2	Visit 1, followed by washout period of 3 to 14 days, followed by Visit 2	**Age 4 to 11 years:** Group 1: single dose intranasal glucagon 2 mg at visit 1; single dose intranasal glucagon 3 mg at visit 2

		IGBC (adults)	IGBI (adults)	IGBJ (adults)	IGBB (children)
		Group 1: intranasal dose, intramuscular dose Group 2: intramuscular dose, intranasal dose	Group 1: intranasal dose, intramuscular dose Group 2: intramuscular dose, intranasal dose	Group 1: intranasal dose, intramuscular dose Group 2: intramuscular dose, intranasal dose	Group 2: single dose intranasal glucagon 3 mg at visit 1; single dose intranasal glucagon 2 mg at visit 2 **Age 12 to 16 years:** Group 1: intranasal dose, intramuscular dose Group 2: intramuscular dose, intranasal dose
Outcomes	**Primary end point**	Response defined as increase in plasma glucose to ≥ 3.9 mmol/L or an increase of ≥ 1.1 mmol/L from nadir within 30 minutes of glucagon dose, with no additional actions; noninferiority margin 10%	Response defined as increase in plasma glucose to ≥ 3.9 mmol/L or an increase of ≥ 1.1 mmol/L from nadir within 30 minutes of glucagon dose, with no additional actions; noninferiority margin 10%	Response defined as increase in plasma glucose to ≥ 3.9 mmol/L or an increase of ≥ 1.1 mmol/L from nadir within 30 minutes of glucagon dose, with no additional actions; noninferiority margin 10%	Glucagon pharmacokinetics and glucose pharmacodynamics (no distinct primary end point was described); response defined as ≥ 1.4 mmol/L increase in plasma glucose within 20 minutes
	Secondary and exploratory end points	• Time to response • Glucose levels • Symptoms of hypoglycemia • Insulin levels • Glucagon levels • Adverse events	• Time to response • Glucose levels • Symptoms of hypoglycemia • AEs	• Time to response • Glucose levels • Symptoms of hypoglycemia • Insulin levels • Glucagon levels • Adverse events	• AEs • Physical examination
Notes	**Publications**	Rickels et al.[8]	No	No	Sherr et al.[10]

AE = adverse events; BMI = body mass index; NR = not reported; OL = open label; RCT = randomized controlled trial; T1D = type 1 diabetes; T2D = type 2 diabetes.

Note: No additional reports were included in the CADTH submission.[16]

Source: Clinical Study Reports for IGBC,[5] Rickels et al,[8] IGBI,[6] IGBJ,[7] IGBB,[9] Sherr et al.[10]

Description of Studies

Four studies met the inclusion criteria for the systematic review. The sponsor classified Studies IGBC, IGBJ, and IGBB as phase III studies.[5,9,17] Study IGBI was classified as a phase I study by the sponsor and Study IGBB was classified as a phase I study by the authors of the study publication.[6,10] All four studies had study design features that would normally be expected in phase III studies (e.g., inclusion of patients) and phase I studies (e.g., serial pharmacokinetic and pharmacodynamic assessments). Three studies were performed in adults and one study was performed in children.

All studies used randomization to assign the order of treatments and all studies used intramuscular glucagon as the comparator drug. In Study IGBC, the order of treatment was assigned by a central computer-generated randomization list that was revealed to clinic

centre staff using a central study website upon enrolment of each participant. The randomization followed a 1:1 allocation ratio of treatment received at first study dosing visit using a block of N = 2 and stratified by clinic site.[5] Allocation of treatment sequence was not described for Study IGBI. In Study IGBJ, the treatment sequence to be administered for each enrolled patient was determined according to a randomization table.[7] In Study IGBB, for patients 4 to 11 years old, the treatment group was sequentially assigned from a computer-generated randomization list revealed to clinic centre staff using a central study website upon enrolment of each participant. The randomization followed a 1:1:1 allocation ratio using blocks of N = 3. The randomization list was stratified by age group (4 to 7 years old and 8 to 11 years old). For patients 12 to 16 years old, the treatment order was sequentially assigned from a computer-generated randomization list revealed to clinic centre staff using a central study website. The randomization followed a 1:1 allocation ratio using blocks of N = 2.[9]

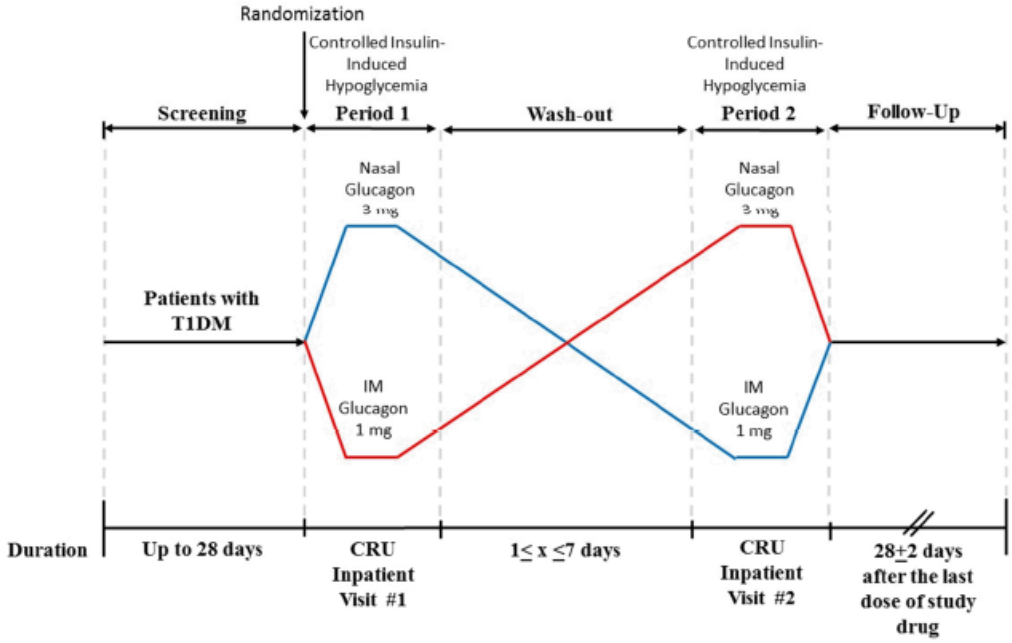
There were 273 patients enrolled across the four studies (225 adults and 48 children aged 4 to 16 years old). No studies had sites in Canada. The objectives of the studies included assessment of the efficacy and safety of 3 mg glucagon administered intranasally in comparison with commercially available intramuscular glucagon in reversing insulin-induced hypoglycemia in patients with T1D or T2D and comparison of the pharmacokinetic and pharmacodynamic parameters of intranasal and intramuscular glucagon.

The adult studies (IGBC, IGBI, and IGBJ) were open label crossover studies that consisted of two treatment visits. Patients were randomized into two groups, with half of the patients receiving intranasal glucagon on one visit followed by intramuscular glucagon on the second visit. The other half of the patients received the treatments in reverse order. Figure 2 depicts the study design of IGBI, with Studies IGBC and IGBJ having similar designs. The treatment visits were separated by a washout period which differed between studies (IGBC = 7 to 28 days old, IGBI = 1 to 7 days old, and IGBJ = 3 to 14 days old). Patients were followed for one month following the second treatment visit.

In the pediatric study, patients 12 to 16 years old had a screening visit and two clinic visits, with random assignment to receive intranasal glucagon 3 mg during one visit and intramuscular glucagon during the other (Figure 3). Patients 4 to 11 years old had a screening visit and were randomized to either one clinic visit to receive intramuscular glucagon or two clinic visits with random blinded assignment to receive intranasal glucagon 2 mg during one visit and intranasal glucagon 3 mg during the other. Data from the 2 mg treatment groups are not included in this report as the dose approved by Health Canada is 3 mg.

Investigators and patients were not blinded to treatment in the adult studies. In Study IGBC the laboratory personnel were blinded to treatment. Study staff and patients were not blinded in the pediatric Study (IGBB) with the exception of staff and children being blinded to the intranasal dose (either 2 mg or 3 mg) in the 4 to 11 year old age group.

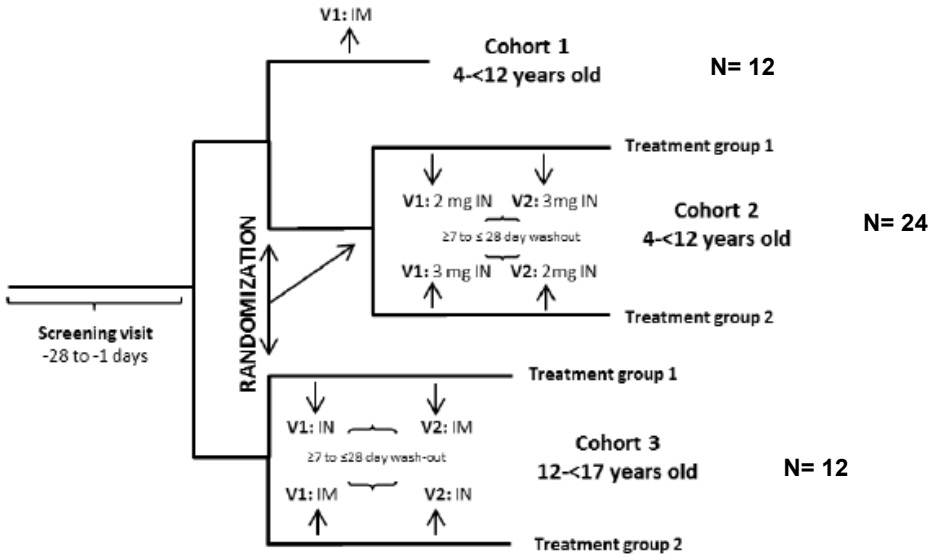
Figure 2: IGBI (Adults) Study Design



CRU = clinical research unit; IM = intramuscular; IN = intranasal; T1DM = type 1 diabetes mellitus.

Source: Clinical Study Report for IGBI.[6]

Figure 3: IGBB (Children) Study Design



IM = intramuscular; IN = intranasal.

Source: Clinical Study Report for IGBB.[9]

Adult Studies: Procedure for Induction of Hypoglycemia

Experimentally induced hypoglycemia was achieved via insulin infusion and monitored via a second catheter for blood sampling. Procedures for induction of hypoglycemia were similar across the adult studies. The procedure in Study IGBC is described here and is depicted in Figure 4 for Study IGBJ. Each glucagon dosing visit was conducted after an overnight fast of at least 8 hours with a starting plasma glucose of greater than or equal to 5.1 mmol/L. If the starting plasma glucose level was greater than 11.1 mmol/L, a priming dose of 2 to 4 units of IV insulin may have been given. Hypoglycemia was induced by an IV infusion of regular insulin diluted in normal saline at a rate of 2 mU/kg/min. Once the plasma glucose level reached less than 5.1 mmol/L, the infusion rate may have been decreased at the investigator's discretion to 1.5 or 1.0 mU/kg/min. The infusion rate may have been adjusted as necessary up to a rate of 3 mU/kg/min to reach the target nadir plasma glucose level of less than 2.7 mmol/L. During the insulin infusion to induce hypoglycemia, plasma glucose levels were measured no more than 10 minutes apart while the plasma glucose level was greater than 5.6 mmol/L and no more than 5 minutes apart when the plasma glucose level was less than 5.6 mmol/L.

A blood sample was collected for glucagon level and glucose level analysis 5 minutes after the insulin infusion was stopped (immediately prior to glucagon administration, T = 0). The insulin level also was also measured. If the plasma glucose level reached less than 60 mg/dL after receiving insulin for at least 3 hours, the assigned glucagon for the visit was administered.

[redacted]

Figure 4: [redacted]

Source: Clinical Study Report for IGBJ.[7]

Pediatric Study: Induction of Hypoglycemia

In the pediatric study (IGBB), the glucose targets were not as aggressive as they were in the adult studies. Each visit for a glucagon dose was conducted after an overnight fast of at least 8 hours. On arrival to the research centre, an IV catheter was inserted into an arm vein for blood sampling. For patients using an insulin pump for diabetes management, the basal insulin infusion rate was increased by 25 to 50% to cause a gradual decline in plasma glucose. Bolus doses of insulin equal to 1 hour of the patient's basal rate and further increases in basal insulin rate were administered, as needed, to achieve the target glucose of less than 4.4 mmol/L. Patients on injection therapy received their usual dose of long-acting insulin analogue in the 24 hours prior to the visit. Insulin was administered at a rate of 1 mU/kg/min intravenously to reach the target glucose of less than 4.4 mmol/L. A priming dose of 2 to 4 units of insulin IV also was given if needed. For patients who arrived at the centre with a plasma glucose of less than 4.4 mmol/L, no additional insulin was administered, the randomized glucagon preparation was given immediately after IV access was obtained, and baseline blood samples were collected.

Populations

Inclusion and Exclusion Criteria

All three adult studies enrolled patients between the ages of 18 to 65 years with T1D. Study IGBC enrolled six patients with T2D but data for these patients were not summarized in this report because inferences from the T2D population would be highly uncertain and the sponsor did not perform analyses on this subgroup for all outcomes. Study IGBI enrolled exclusively patients with T1D. Study IGBJ enrolled approximately equal numbers of patients with T1D and T2D. All studies excluded patients who had experienced severe hypoglycemia during the month prior to the study start.

Baseline Characteristics

The median age of patients in the adult trials ranged from 31 years (interquartile range [IQR] = 21 to 41) in the North American study (IGBC) to 52 years (range = 21 to 70 years) in Study IGBJ. Most patients had longstanding diabetes with median duration since diagnosis of more than 11 years in the three adult studies (age range across adult studies: 1 to 43 years). Most patients in the North American study (IGBC) used an insulin pump as their primary means of administering insulin. More than half of the patients in the North American study had never experienced severe hypoglycemia, despite a median duration of diabetes of 17 years (IQR = 9 to 25 years). Only 7% of patients in this study experienced severe hypoglycemia in the year prior to the study. The proportion of patients with reduced hypoglycemia awareness was low (4% to 16%) across the adult studies.

The age of children in the pediatric study (IGBB) ranged from 4 to 17 years. Most children were between the ages of 6 and 13, with six children with ages between 4 to 5 years and eight children between the ages of 14 and 17. More than half of the children in this study used an insulin pump as the primary means of administering insulin. A majority of children in the study had never experienced severe hypoglycemia.

Table 6: Summary of Baseline Characteristics

	IGBC (adults)		IGBI (adults)		IGBJ (adults)		IGBB (children)					
Characteristics	**N = 77 (T1D)**		**N = 70 (T1D)**		**N = 72 (T1D, T2D)**		**4 to < 8 years N = 18**		**8 to < 12 years N = 18**		**12 to < 17 years N = 12**	
Median age	31 (IQR, 22 to 42)		41 (range 20 to 64)		52 (21 to 70)		6.5 (IQR, 5.7 to 7.5)		11.1 (IQR, 10.5 to 11.8)		14.5 (IQR, 13.2 to 15.8)	
Female, n (%)	45 (58)		27 (39)		22 (31)		3 (17)		8 (44)		5 (42)	
White, non-Hispanic, n (%)	74 (96)		[redacted]		0 (100% Japanese)		18 (100)		16 (89)		10 (83)	
Median BMI (range), kg/m^2	NR		25.4 (19.6 to 34.5)		23.9 (18.5 to 32.0)		NR		NR		NR	
Median duration of diabetes, years	17.6 (IQR, 8.6 to 24.6)		20 (3 to 43)		11.5 (1 to 43)		2.8 (IQR, 2.1 to 3.8)		4.6 (IQR, 3.8 to 6.7)		5.9 (IQR, 3.5 to 8.0)	
Primary insulin modality, n (%) Insulin pump MDI	 57 (74) 20 (26)		NR		NR		 10 (56) 8 (44)		 16 (89) 2 (11)		 9 (75) 3(25)	
Median total daily insulin (IQR), U/kg	0.58 (0.46 to 0.68)		NR		30 U/day (5 to 79)		0.71 (0.55 to 0.95)		0.75 (0.68 to 0.84)		0.88 (0.77 to 0.99)	
Most recent SH event with third party help, n (%)	Never: 46 (60) < 365 days: 6 (8) ≥ 365 days: 25 (32)		NR		NR		Never: 12 (67) < 365 days: 4 (23) ≥ 365 days: 2 (11)		Never: 16 (89) < 365 days: 2 (11) ≥ 365 days: 0		Never: 7 (58) < 365 days:1 (8) ≥ 365 days: 4 (33)	
Mean Hemoglobin A1C (SD), %	8.3 (1.8)		7.3 (0.9)		7.9 (1.0)		8.1 (0.8)		7.9 (0.9)		8.2 (1.5)	
Clarke HUS, n (%) Reduced awareness Intermediate Aware	 10 (13) 10 (13) 57 (74)		[redacted]		[redacted]		NR		NR		NR	
Mean plasma glucose at nadir (SD), mmol/L	IN N = 75 2.4 (0.4)	IM N = 75 2.6 (0.4)	IN[a] N = 68 3.3 (NR)	IM[a] N = 69 3.2 (NR)	IN[a] N = 71 2.9 (NR)	IM[a] N = 70 2.8 (NR)	IN N = 12 3.7 (0.6)	IM N = 6 3.9 (0.4)	IN N =12 3.9 (0.3)	IM N = 6 4.0 (0.7)	IN N = 12 4.1 (0.5)	IM N =12 3.8 (0.6)
Insulin received to induce hypoglycemia (IQR), U/kg	0.09 (0.07 to 0.13)	0.10 (0.08 to 0.14)	NR		NR		NR		NR		NR	

BMI = body mass index; HUS = hypoglycemia awareness; IN = intranasal glucagon; IM = intramuscular glucagon; IQR = interquartile range (25th to 75th percentile); NR = not reported; MDI = multiple daily injections; SD = standard deviation; SH = severe hypoglycemia; T1D = type 1 diabetes.

[a] Glucose at time immediately prior to glucagon administration.

Source: Clinical Study Reports for IGBC,[5] Rickels et al.,[8] IGBI,[6] IGBJ,[7] IGBB,[9] Sherr et al.[10]

Interventions

Intranasal glucagon powder was used in the studies, but it was not clear if the formulation and device used in the studies is the same as the product to be marketed in Canada. The dose was 3 mg in all studies and the total mass of the powder was 30 mg. In the pediatric study there was also a 2 mg intranasal glucagon treatment group. The 2 mg intranasal glucagon data are not summarized in this report because the approved Health Canada dosage is 3 mg. The device used to administer the intranasal glucagon is a single use device. The tip of the device is inserted into the nostril and the dose is delivered by depressing a plunger connected to a piston that discharges the powder into the nostril. No inhalation is required from the patient.

The injectable glucagon product used in the studies was GlucaGen (Novo Nordisk) and is supplied as a dry powder for reconstitution with diluent to a concentration of 1 mg/mL.

Glucagon was delivered with the subject lying in a lateral recumbent position either in the deltoid muscle of the nondominant arm for the intramuscular administration or nare of the same side for the intranasal administration. Both the intranasal and intramuscular glucagon doses were administered to the patient by study staff. Both the intranasal and intramuscular glucagon doses were administered approximately 5 minutes after the insulin infusion was stopped.

Outcomes

Adult Studies

Primary Outcome

The three adult studies had the same primary outcome of treatment success, defined as a plasma glucose increase to greater than or equal to 3.9 mmol/L *or* increase of greater than or equal to 1.1 mmol/L from nadir 30 minutes after glucagon administration.

Other Outcomes

Time to success was also assessed using Kaplan–Meier methods and Cox proportional hazards models. The components of the primary outcome were also assessed individually (e.g., achievement of ≥ 3.9 mmol/L *or* increase of ≥ 1.1 mmol/L).

Serial blood samples for glucose and glucagon were collected at regular intervals. For example, in Study IGBC this was assessed at baseline and 5, 10, 15, 20, 25, 30, 40, 50, 60, and 90 minutes after baseline (and up to 240 minutes in Study IGBJ). Insulin levels were measured during the first hour after baseline. Hypoglycemia symptoms were assessed by the Edinburgh Hypoglycemia Scale at baseline and 15, 30, 45, and 60 minutes after the administration of glucagon. Nasal and non-nasal symptoms were ascertained at baseline and at 15, 30, 60, and 90 minutes after glucagon administration.

Pediatric Study

Primary Outcome

The primary objective of the study was to assess the pharmacokinetics and pharmacodynamics of intranasal glucagon relative to intramuscular glucagon, but there was no predefined primary outcome and there was no formal sample size estimation for this study.

Other Outcomes

Response was assessed applying the definition of achieving a 1.4 mmol/L increase in plasma glucose by 20 minutes following glucagon administration. Other outcomes assessed in the pediatric study included blood glucagon and plasma glucose levels at baseline and 5, 10, 15, 20, 25, 30, 40, 50, 60, and 90 minutes following glucagon dosing. Nasal and non-nasal symptom scores were also assessed at 15, 30, 60, and 90 minutes following glucagon dosing.

Edinburgh Hypoglycemia Scale

Symptoms of hypoglycemia were assessed in the adult studies using the Edinburgh Hypoglycemia Scale. The version of the scale used in the IGBI and IGBJ studies consists of 13 symptoms categorized into three subscales: cognitive dysfunction (inability to concentrate, blurred vision, anxiety, confusion, difficulty speaking, and double vision); neuroglycopenia (drowsiness, tiredness, hunger, and weakness); and autonomic symptoms (sweating, trembling, and warmness).

Each of the 13 symptoms could be scored as follows:

1 = not experiencing this (no symptom as all)

2 = only experiencing a very mild case of this and it is easily tolerated

3 = only experiencing a mild case of this and it is tolerated

4 = experiencing a mild to moderate case of this and it is tolerated

5 = experiencing a moderate case of this and it is tolerated

6 = experiencing a moderate to severe level of this symptom; it is bothersome but tolerable

7 = experiencing a severe level of this symptom; it is hard to tolerate

The maximum total score is 91 and the maximum subscale scores are 42 for the cognitive dysfunction subscale, 28 for the neuroglycopenia subscale, and 21 for the autonomic symptoms subscale. The version of the scale used in Study IGBC was not described in detail in the clinical study report or in the corresponding publication.

The symptoms used in the 13-symptom version have been shown to be specific to hypoglycemia in an analysis of nine previous studies in a mixture of patients with T1D and normal hypoglycemia awareness (N = 92) and persons without diabetes (N = 77).[18] Hypoglycemia was induced by insulin infusion or hyperinsulinemic glucose clamp and a previous version of the Edinburgh Hypoglycemia Scale[19] was used to assess symptoms on similar rating scales.[18] There were 13 symptoms common to all nine studies and their intensities and frequencies were similar regardless of diabetic status or hypoglycemia induction method.[18] Principal components analysis was used to obtain the three subscales and these formed the basis of the 13-symptom scale.[18] Most of the studies assessed cognitive function with mental performance tests, and symptoms in the cognitive dysfunction subscale may have been more prominent (compared with the non-specific neuroglycopenic symptoms) when patients were asked to perform mental tasks.[18] A minimal important difference for the total score or subscale scores of any version of the Edinburgh Hypoglycemia Scale was not found.

Adverse Event Monitoring of Nasal and Non-nasal Symptoms

A scoring system that included nasal (rhinorrhea, nasal stuffiness/congestion, nasal itching, and sneezing) and non-nasal (itching/burning eyes, tearing/watering eyes, redness of eyes, and itching of ears or palate) symptoms were individually graded using a four-point scale approximately 15, 30, 60, and 90 minutes after each glucagon administration. The following scoring system was used during this study in order to quantify nasal symptoms:

0 = I am not experiencing this (no symptoms at all).

1 = I am only experiencing a mild case of this and it is easily tolerated.

2 = I am only experiencing a moderate level of this symptom. It is bothersome but tolerable.

3 = I am experiencing a severe level of this symptom. It is hard to tolerate and interferes with my activities.

Statistical Analysis

Adult Studies

Primary outcome analysis approaches are described for the individual studies below and were similar across the studies. Sample size calculations for Study IGBC to test the noninferiority of intranasal glucagon treatment and intramuscular glucagon treatment among subjects with T1D used the following assumptions: 80% power; a response rate of 95% for both treatments; a noninferiority limit of 10 percentage points (absolute value); a one-sided alpha level of 0.025; and a correlation of zero. Given these assumptions, the sample size required was 75 participants with T1D. An additional seven participants with T2D were also to be enrolled but were only analyzed as exploratory analyses. Sample size calculations for Study IGBI for the same primary outcome included the following assumptions: 90% power; a treatment success rate of 98% for both treatments; a noninferiority margin of 10%; a two-sided alpha level of 0.05; and a within-patient correlation of zero between two treatment visits. Therefore, assuming a 5% dropout rate, the study planned to enroll 70 patients with a target of having at least 66 patients with evaluable data from both treatment visits. Sample size calculations for Study IGBJ for the same primary outcome included the following assumptions: 90% power; a treatment success rate of 98% for both treatments; a noninferiority margin of 10%; a one-sided alpha level of 0.025; and a within-patient correlation of zero between two treatment visits. Therefore, assuming an approximately 10% dropout rate, the study planned to enroll 75 patients with a target of having at least 66 patients with evaluable data from both treatment visits.

Noninferiority of nasal glucagon was declared when the upper limit of the two-sided 95% CI of the mean difference in proportion of patients with the primary outcome of success was less than the noninferiority margin of 10%. The sponsor stated that its selection of a noninferiority margin of 10% for all studies was based upon data from a simulated emergency study in which 10% of the patients (parents of children and adolescents with T1D) failed entirely to administer injectable glucagon.[7,20]

The individual components of the primary outcome were summarized but no formal statistical testing was performed on these data. There was also a subgroup analysis of the time to primary outcome in patients with type 1 and type 2 diabetes, but these subgroups were very small and there was no formal testing done for statistical interaction by diabetes type.

The statistical analysis plans for Studies IGBC, IGBI, and IGBJ indicated that Kaplan–Meier curves would be constructed for the time-to-primary-outcome analyses, using standard censoring techniques. A treatment group comparison of the time from treatment to primary outcome was also completed, using the marginal Cox proportional hazard models for clustered data (to account for the correlation due to the crossover design), adjusted for central lab nadir blood glucose and treatment period. For Study IGBC, the P value of the treatment arm comparison of the time from treatment to outcome was derived using the marginal Cox proportional hazards model for clustered data. The log rank test was used to assess these data in Studies IGBI and IGBJ. There was no statistical testing for carryover effects. All analyses on the primary end point were conducted in the population of patients who completed both treatment visits and who also had evaluable data (i.e., the per-protocol population). Sensitivity analyses were conducted using the population of patients who were randomized (i.e., the intent-to-treat population).

A treatment comparison of the Edinburgh Hypoglycemia Scale score at each time point after glucagon administration was completed using linear mixed models with repeated measures adjusting for the treatment period and score at visit arrival.

Study IGBC: A one-sided 97.5% CI was obtained from the one-sample mean of the paired differences in the primary outcome of success. Noninferiority of intranasal glucagon was declared if the upper limit of the one-sided 97.5% CI constructed on the difference in proportions (intramuscular glucagon:intranasal glucagon), was less than the noninferiority limit of 10%. The difference in the proportion of successes between the treatment arms and the one-sided 97.5% CI was also calculated using a Poisson regression model, incorporating a generalized estimating equation with adjustments for nadir glucose and the treatment period (i.e., first treatment for participant versus second treatment for participant). The primary analysis for IGBC excluded six patients with T2D. For serial measurements of plasma glucose the analysis was completed using a linear mixed model with repeated measures that accounted for the correlation due to the crossover design and the correlation due to multiple measures, adjusting for starting glucose level and time period.

Summary statistics for plasma glucose concentrations at each time point across the dosing visit were calculated with imputation for missing glucose values and glucose values after receipt of intervention treatment using Rubin's multiple imputation method, based on available glucose measurements and treatment arm. A treatment comparison of the blood glucose concentration over the 90 minutes after administration of glucagon was performed using a linear mixed model with repeated measures adjusted for nadir glucose and time period.

Studies IGBI and IGBJ: For the primary outcome, a two-sided 95% CI was obtained from the one-sample mean of the paired differences in the primary outcome (1 = outcome observed; 0 = outcome not observed) across the two treatment visits. For each patient the paired difference of treatment success between intramuscular glucagon and nasal glucagon was calculated and a t-test was used to create the 95% CI of the mean difference.

Descriptive statistics were used to summarize the serial measurements of plasma glucose. A between-treatment comparison of baseline and post-dose plasma glucose values over the 90 minutes of the post-dose period (240 minutes for Study IGBJ) was performed using a linear mixed model with repeated measures. This model accounted for the correlation due to the crossover design and the correlation due to multiple measures. It included baseline and treatment period time points and their interaction as covariates. Least squares means

and two-sided 95% CIs were calculated for the difference in plasma glucose between treatment groups at each time point.

Pediatric Study

Study IGBB

There was no pre-specified primary outcome for Study IGBB and no formal sample size estimation was performed. Separate analyses were conducted for each age cohort (4 to 7, 8 to 11, and 12 to 17 years old). The proportion of participants in each treatment arm achieving at least a 1.4 mmol/L rise in central laboratory glucose above the glucose nadir within 20 minutes after receiving study glucagon, in the absence of additional actions to increase the blood glucose level, was computed post hoc and no statistical testing was reported. A Kaplan–Meier curve for each treatment group were constructed for the time to occurrence of a greater than 1.4 mmol/L rise in blood glucose above basal level, using standard censoring approaches. Point estimates and CIs of the hazard ratio were calculated using the marginal Cox proportional hazards model for clustered data (to account for the correlation due to the crossover design), adjusted for central lab blood glucose at nadir level and treatment period.

Analysis Populations

The main analyses for the primary outcome for the three adult studies was a per-protocol analysis based on the population of patients who completed two treatment visits and who had evaluable data from those visits. Evaluable data meant that these patients received glucagon and had no rescue treatment for severe hypoglycemia prior to or within the first 10 minutes after glucagon administration. The main analyses for Study IGBC excluded the six patients with T2D. In the adult studies, secondary outcome analyses were performed in the population that received at least one dose of study drug.

Safety analysis populations included all data from dosing visits where glucagon was received.

The pharmacokinetic and pharmacodynamic analyses in the pediatric study included patients who provided evaluable data for at least one treatment.

Results

Patient Disposition and Exposure to Study Treatments

The number of patients who completed both dosing visits was between 92 to 99% of all randomized patients, across the four studies (Table 7).

Table 7: Patient Disposition

	Adults			Children
	IGBC[a]	IGBI	IGBJ	IGBB
Screened, N	88	NR	NR	NR
Randomized, N	77	70	75	36
Completed at least one visit, N	77	70	72	36
Completed both visits,	75	69	69	35
Withdrawn from study, N	2	[redacted]	[redacted]	1
Protocol violation	1	[redacted]	[redacted]	0
Withdrawal by patient	1	[redacted]	[redacted]	1
Withdrawal by physician	0	[redacted]	[redacted]	0
Population used for primary outcome analyses (two visits completed with evaluable data)	75	66	68	NA

NA = not applicable.

[a] Type 1 diabetes (T1D) patients. The main analyses of the study were performed in T1D patients; study excludes patients with type 2 diabetes (seven enrolled, five completed).

Source: Clinical Study Reports for IGBC,[5] Rickels et al.,[8] IGBI,[6] IGBJ,[7] IGBB,[9] Sherr et al.[10]

In Study IGBC, of the 77 T1D randomized patients, 75 were included in the primary analysis. [redacted]. Therefore, a total of 75 T1D patients were included in the primary analysis.

In Study IGBI, of the 70 randomized patients, 66 were included in the primary analysis. [redacted].

In Study IGBJ, of the 75 randomized patients, 68 were included in the primary analysis. [redacted]

[redacted] Overall, 35 of the 36 patients randomized to two dosing visits completed the requirements of their study arm, with one patient in the 8 to less than 12 year group requesting study withdrawal prior to dosing visit 2. One patient in the 12 to less than 17 year group had a repeat 3 mg intranasal glucagon dose administered due to a device malfunction during the initial dosing visit. The sponsor stated that the design defect that led to the device malfunction was corrected to prevent future malfunction. In total, there were 36 visits for 3 mg intranasal glucagon doses and 24 for intramuscular glucagon doses.

Rescue Oral Carbohydrates

[redacted]

[redacted]

[redacted]

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported below. See Appendix 3 for detailed efficacy data.

Resolution of Hypoglycemia Episodes

Treatment Success

The primary outcome of the three adult studies was treatment success defined as a plasma glucose increase to greater than or equal to 3.9 mmol/L or an increase of greater than or equal to 1.1 mmol/L from nadir 30 minutes after glucagon administration (Table 8). The rates of treatment success were 100% for both intranasal and intramuscular glucagon in both the IGBI and IGBJ studies. The treatment success rate was also 100% for intramuscular glucagon in the IGBC study but not for intranasal glucagon in Study IGBC, which had a success rate of 99%. The results of the primary outcome in all three adult studies met the pre-specified criteria for noninferiority since the upper boundary of the CIs did not exceed 10% in any of the three adult studies.

In the pediatric trial IGBB, treatment success rates were 100% in all treatment groups.

The two components of the primary outcome were also assessed individually (plasma glucose increase to ≥ 3.9 mmol/L or plasma glucose increase of ≥ 1.1 mmol/L from nadir). For Study IGBC, the success rates of the individual components were similar between the intranasal and intramuscular treatments. The success rates for Studies IGBI and IGBJ were 100% for both intranasal and intramuscular glucagon.

Time-to-Treatment Success

Time-to-event analyses were performed on the primary outcome in all studies. The mean time-to-treatment success in the adult studies ranged from 10 to 16 minutes (Table 8, Figure 5, Figure 6, andFigure 7). The mean time-to-treatment success was longer with intranasal glucagon relative to intramuscular glucagon in Studies IGBC and IGBI. The difference between the treatments was approximately four minutes in Study IGBC and 1.6 minutes in Study IGBI (variance not reported) and the difference was statistically significant in both studies. [redacted]. There was no statistically significant difference in time-to-treatment success in Study IGBJ.

In Study IGBB, post hoc analyses of time-to-treatment success were similar between intranasal and intramuscular glucagon groups.

Table 8: Summary of Treatment Success

Outcome[a]	Intranasal glucagon 3 mg	Intramuscular glucagon 1 mg	Comparison
IGBC (adults) cuccess criteria, n/N (%)			
PG increase to ≥ 3.9mmol/L *or* increase of ≥ 1.1 mmol/L from nadir 30 minutes after glucagon (primary outcome)	74/75 (99)	75/75 (100)	Difference 0.015 (one-sided 97.5% CI, 0.043) [b]
PG increase to ≥ 3.9 mmol/L	72/75 (97)	74/75 (99)	NR
PG increase of ≥ 1.1 mmol/L from nadir	74/75 (100)	75/75 (100)	NR
Both	72/75 (97)	74/75 (99)	NR
Mean time to PG increase to ≥ 3.9mmol/L *or* increase of ≥ 1.1 mmol/L from nadir within 30 minutes of glucagon, minutes (SD)	16.2 (NR)	12.2 (NR)	Difference 4 minutes (SD NR) P < 0.001[c]
IGBI (adults) success criteria, n/N (%)			
PG increase to ≥ 3.9mmol/L *or* increase of ≥ 1.1 mmol/L from nadir 30 minutes after glucagon (primary outcome)	66/66 (100)	66/66 (100)	Difference 0.0 (95% CI, –1.52 to 1.52)[d]
PG increase to ≥ 3.9 mmol/L	66/66 (100)	66/66 (100)	NR
PG increase of ≥ 1.1 mmol/L from nadir	66/66 (100)	66/66 (100)	NR
Both	66/66 (100)	66/66 (100)	NR
Mean time to PG increase to ≥ 3.9mmol/L *or* increase of ≥ 1.1 mmol/L from nadir within 30 minutes of glucagon, minutes (SD)	11.44 (3.01)	9.85 (3.03)	Difference 1.6 minutes (SD NR) Log rank P = 0.002
IGBJ (adults) success criteria, n/N (%)			
PG increase to ≥ 3.9mmol/L *or* increase of ≥ 1.1 mmol/L from nadir 30 minutes after glucagon (primary outcome)	68/68 (100)	68/68 (100)	0.0 (95% CI, –1.47 to 1.47) [d]
PG increase to ≥ 3.9 mmol/L	68/68 (100)	68/68 (100)	NR
PG increase of ≥ 1.1 mmol/L from nadir	68/68 (100)	68/68 (100)	NR
Both	68/68 (100)	68/68 (100)	NR
T1D and T2D patients: Median time to PG increase to ≥ 3.9mmol/L *or* increase of ≥ 1.1 mmol/L from nadir within 30 minutes of glucagon (range), minutes	10.0 (5.0 to 25.0) N = 68	10.0 (5.0 to 20.0) N = 68	Log rank P = 0.069
T1D patients: Median time to PG increase to ≥ 3.9mmol/L *or* increase of ≥ 1.1 mmol/L from nadir within 30 minutes of glucagon (range), minutes	10.0 (10.0 to 25.0) N = 32	10.0 (5.0 to 15.0) N = 32	Log rank P = 0.314
T2D patients: Median time to PG increase to ≥ 3.9mmol/L *or* increase of ≥ 1.1 mmol/L from nadir within 30 min of glucagon (range), minutes	13.5 (5.0 to 15.0) N = 36	10.0 (5.0 to 20.0) N = 36	Log rank P = 0.217
IGBB (children) success criteria, n/N (%)			
PG ≥ 1.4mmol/L increase by 20 minutes [c] 4 to ≤ 8 years old 8 to < 12 years old 12 to < 17 years old	 12/12 (100) 12/12 (100) 12/12 (100)	 6/6 (100) 6/6 (100) 12/12 (100)	 NR NR NR

Outcome[a]	Intranasal glucagon 3 mg	Intramuscular glucagon 1 mg	Comparison
Median time to ≥ 1.4 mmol/L increase above nadir 4 to ≤ 8 years old 8 to < 12 years old 12 to < 17 years old	 NR NR NR	 NR NR NR	 HR = 0 (95% CI, 0 to 0) HR = 3.6 (95% CI, 0.5 to 23.9) HR = 0.4 (95% CI, 0.2 to 1.1)

HR = hazard ratio; NR = not reported; PG = plasma glucose; SD = standard deviation.

[a] Treatment success in adult studies: PG increase to ≥ 3.9mmol/L or increase of ≥ 1.1 mmol/L from nadir 30 minutes after glucagon (primary outcome). Treatment success in pediatric study: PG ≥ 1.4mmol/L increase by 20 minutes.

[b] Difference in proportions adjusted for treatment period and blood glucose value immediately before administration of glucagon. P value of the treatment arm comparison of the time from treatment to outcome using the marginal Cox proportional hazards model for clustered data.

[c] Cox proportional hazards model.

[d] Wald's method with continuity correction.

Source: Clinical Study Reports for IGBC,[5] Rickels et al.,[8] IGBI,[6] IGBJ,[7] IGBB,[9] Sherr et al.[10]

Figure 5: [redacted]

Source: Clinical Study Report for IGBC.[5]

[redacted]

Plasma Glucose Concentrations

Plasma glucose concentrations were measured in all studies at regular intervals up to 90 to 240 minutes after the glucagon dose. See Appendix 3 for detailed outcome data.

Symptoms of Hypoglycemia

The Edinburgh Hypoglycemia Scale was used to assess severity of hypoglycemic symptoms at the time of administration of glucagon and for up to 60 minutes after. The maximum total score is 91 and the maximum subscale scores are: 42 for the cognitive dysfunction subscale; 28 for the neuroglycopenia subscale; and 21 for the autonomic symptoms subscale. A higher score indicated greater severity of symptoms. Arithmetic means were provided for Study IGBC and least squares means were provided for Studies IGBI and IGBJ (Table 9); the reason for this was not provided by the sponsor.

In Study IGBC, the scores were higher (worse) at all time points after glucagon was administered for the intranasal glucagon treatment compared to the intramuscular glucagon treatment, and the differences were statistically significant at 15, 30, 45, and 60 minutes. [redacted].

Table 9: Edinburgh Hypoglycemia Scale Total Score Summary

	IGBC			IGBI			IGBJ		
Time post-glucagon dose	IN glucagon 3 mg N = 77 Mean (SD)	IM glucagon 1 mg N = 76 Mean (SD)	Comparison	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time = 0	4.8 (5.3)[a]	4.3 (3.9)[a]	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15 minutes	8.8 (8.3)	5.3 (5.2)	P < 0.001	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30 minutes	4.9 (4.7)	3.5 (3.9)	P = 0.01	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45 minutes	3.8 (3.1)	3.0 (3.0)	P = 0.02	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60 minutes	3.9 (3.1)	3.1 (2.9)	P = 0.04	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

IM = intramuscular; IN = intranasal; LSM = least squares mean; NR = not reported; PG = plasma glucose; SD = standard deviation; SE = standard error.

Note: A treatment comparison of the Edinburgh Hypoglycemia Scale score at each time point after glucagon administration was completed using linear mixed models with repeated measures adjusting for the treatment period and score at visit arrival.

[a] When PG was < 4.2 mmol/L.

Source: Clinical Study Reports for IGBC,[5] IGBI,[6] IGBJ,[7] and IGBB.[9]

There were no data available for the protocol-specified efficacy outcomes of time to dose administration, quality of life, or measures of caregiver and patient satisfaction (as listed in Table 4).

Harms

Only those harms identified in the review protocol are reported as follows and can also be found in Table 4.

Adverse Events

Across the adult studies the proportion of patients reporting at least one AE ranged from 19% to 57% after receiving either intranasal glucagon or intramuscular glucagon (Table 10). The overall rates of AEs were similar between the two treatments. The most frequently reported AEs included nausea, vomiting, headache, nasal discomfort, nasal congestion, increased lacrimation, fatigue, nasopharyngitis, and upper respiratory tract irritation. Oropharyngeal and eye symptoms occurred more frequently in patients after receiving intranasal glucagon compared to intramuscular glucagon in Study IGBC. This included nasal discomfort (10% with intranasal versus 0% with intramuscular), nasal congestion (8% intranasal versus intramuscular 1%), lacrimation increased (intranasal 8% versus intramuscular 1%), upper respiratory tract irritation (intranasal 19% versus intramuscular 1%). Nasal itching (49%) and sneezing (24%) occurred more frequently in Study IGBI after treatment with intranasal glucagon compared to intramuscular glucagon (0%).

[redacted][4] The proportion of patients reporting at least one AE in the pediatric study ranged from 42% to 100% across the different age subgroups after receiving either intranasal glucagon or intramuscular glucagon. The most commonly reported AEs after receiving intranasal glucagon were nausea (8% to 23%), vomiting (17% to 50%), and headache (8% to 33%).

Serious Adverse Events

[redacted]

In the pediatric study (IGBB), one seven-year-old male child experienced a SAE of hypoglycemia during induction of hypoglycemia with insulin. The patient made a full recovery after receiving oral carbohydrates.

Withdrawals Due to Adverse Events

There were two withdrawals due to the AE of vomiting in the adult studies that occurred in relation to receiving intranasal glucagon.

Mortality

There were no deaths in the studies.

Table 10: Summary of Harms in Adult Studies (Safety Population)

	IGBC (adults, T1D and T2D)		IGBI (adults T1D)		IGBJ (adults)	
	Intranasal glucagon N = 83	Intramuscular glucagon N = 82	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						
Patients with ≥ 1 TEAE	47 (57)	37 (45)	[redacted]	[redacted]	[redacted]	[redacted]
Most common events[a]						
Nausea	18 (22)	22 (27)	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	13 (16)	9 (11)	[redacted]	[redacted]	[redacted]	[redacted]
Headache	18 (22)	7 (9)	[redacted]	[redacted]	[redacted]	[redacted]
Nasal discomfort	8 (10)	0	[redacted]	[redacted]	[redacted]	[redacted]
Nasal congestion	7 (8)	1 (1)	[redacted]	[redacted]	[redacted]	[redacted]
Lacrimation increased	7 (8)	1 (1)	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	7 (8)	7 (8)	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	0	0	[redacted]	[redacted]	[redacted]	[redacted]
URT irritation	16 (19)	1 (1)	[redacted]	[redacted]	[redacted]	[redacted]
Increased blood pressure					[redacted]	[redacted]
SAE, n (%)						
Patients with ≥ 1 SAE	0	0	[redacted]	[redacted]	[redacted]	[redacted]
Deaths	0	0	[redacted]	[redacted]	[redacted]	[redacted]
Patients who discontinued study due to adverse events, n (%)						
Vomiting	1 (1)	0	[redacted]	[redacted]	[redacted]	[redacted]
Notable harms: Patients reporting worsening of nasal and non-nasal symptoms post dose to 90 minutes[b], n (%)						
Nasal symptoms						
Runny nose	27 (32)	NR	[redacted]	[redacted]	[redacted]	[redacted]
Nasal congestion	38 (46)	NR	[redacted]	[redacted]	[redacted]	[redacted]
Nasal itching	26 (31)	NR	[redacted]	[redacted]	[redacted]	[redacted]
Sneezing	13 (16)	NR	[redacted]	[redacted]	[redacted]	[redacted]
Non-nasal symptoms		NR				

	IGBC (adults, T1D and T2D)		IGBI (adults T1D)		IGBJ (adults)	
	Intranasal glucagon N = 83	Intramuscular glucagon N = 82	[redacted]	[redacted]	[redacted]	[redacted]
Watery eyes	46 (55)	NR	[redacted]	[redacted]	[redacted]	[redacted]
Itchy eyes	19 (23)	NR	[redacted]	[redacted]	[redacted]	[redacted]
Redness of eyes	23 (28)	NR	[redacted]	[redacted]	[redacted]	[redacted]
Itching of ears	3 (4)	NR	[redacted]	[redacted]	[redacted]	[redacted]
Itching of throat	10 (12)	NR	[redacted]	[redacted]	[redacted]	[redacted]

SAE = serious adverse event; TEAE = treatment-emergent adverse event; T1D = type 1 diabetes; T2D = type 2 diabetes; irritation = upper respiratory tract irritation (rhinorrhea, nasal discomfort, and nasal congestions in Study IGBC; nasal discomfort, cough, epistaxis, and oropharyngeal pain for study IGBI).

[a] Frequency greater than 5%.

[b] 120 minutes for IGBJURT.

Source: Clinical Study Reports for IGBC,[5] Rickels et al.,[8] IGBI,[6] IGBJ,[7] IGBB,[9] Sherr et al.[10]

Table 11: Summary of Harms in Pediatric Studies

	4 to 7 years		8 to 11 years		12 to 16 years	
	Intranasal glucagon 3 mg N = 12	Intramuscular glucagon 1 mg N = 6	Intranasal glucagon 3 mg N = 12	Intramuscular glucagon N = 6	Intranasal glucagon 3 mg N = 13	Intramuscular glucagon N = 12
Treatment-emergent adverse event, n (%)						
Patients with ≥ 1 TEAE	5 (42)	5 (83)	6 (50)	6 (100)	9 (69)	7 (58)
Abdominal pain	0	1 (17)	1 (8)	0	0	0
Diarrhea	0	0	0	1 (17)	0	0
Nausea	2 (17)	4 (67)	1 (8)	3 (50)	3 (23)	1 (8)
Vomiting	3 (25)	1 (17)	4 (33)	3 (50)	4 (31)	5 (42)
Headache	1 (8)	0	4 (33)	2 (33)	4 (31)	1 (8)
Nasal congestion	0	0	0	0	2 (15)	0
Nasal discomfort	2 (17)	0	0	0	1 (8)	0
Sneezing	0	0	1 (8)	0	0	0
Eye irritation	0	0	0	0	1 (8)	0
Ocular discomfort	0	0	0	0	1 (8)	0
Catheter site pain	0	0	0	1 (17)	0	0
Injection site pain	0	2 (33)	0	3 (50)	0	0
Hypoglycemia	0	1 (17)	0	0	0	0
Dizziness	0	0	0	1 (17)	0	0
SAE, n (%)						
Patients with ≥ 1 SAE	0	1 (17)[a]	0	0	0	0
Deaths	0	0	0	0	0	0
Patients who discontinued study due to AEs, n (%)						
	0	0	0	0	0	0

AE = adverse events; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] Hypoglycemia.

Source: Clinical Study Report for IGBB,[9] Sherr et al.[10]

Critical Appraisal

Internal Validity

It was not possible to assess the balance of some baseline prognostic factors between the randomized groups since baseline characteristics were often reported for the entire patient population and not for the separate groups based upon sequence (e.g., intranasal followed by intramuscular versus intramuscular followed by intranasal).[21] Where these were reported, there appeared to be adequate balance of prognostic factors between the randomized groups. For example, the glucose level at nadir (Table 6) was balanced between the groups.

The investigators suggest that delays in plasma glucose response to intranasal glucagon would be offset by reductions in administration time relative to intramuscular glucagon.[22] Reviewers agree that this this is a rational hypothesis, but it is based on indirect evidence and has not been directly demonstrated in the intranasal glucagon trials performed to date.

The primary outcome for Study IGBB (children) does not appear to have been defined a priori. The publication states that the primary outcome was a greater than 1.4 mmol/L rise in plasma glucose within 20 minutes after glucagon administration, but this is not stated in either the sponsor's statistical analysis plan or in the trial registry.[9-11] There was no formal sample size calculation performed for this study. For this reason, it is not known if intranasal glucagon is noninferior to intramuscular glucagon in the pediatric population. Although this study was designed to assess the pharmacokinetics and pharmacodynamics of intranasal glucagon relative to intramuscular glucagon, there were other inconsistencies about the way the study was reported in the publication compared to the clinical study report. For example, the publication referred to it as a phase I study and the clinical study report classified it as a phase III study. The subgroup analyses were predefined in the study protocol, but the number of children in the subgroups by age were small, and for these reasons the data from this trial cannot be considered conclusive evidence of intranasal glucagon efficacy and its harms relative to intramuscular glucagon.

[redacted]

All studies were open label, and this could have impacted assessment of subjective outcomes such as the AEs and Edinburgh Hypoglycemia Symptoms.

External Validity

The primary limitation of the four trials that met the inclusion criteria for the systematic review is that the trials did not attempt to mimic real-world conditions. The study medications were administered under controlled conditions by trained health professionals, and not by caregivers or bystanders who may not have the same level of training in patient assessment and administration technique. Hypoglycemia was induced and symptom criteria for hypoglycemia were not used in the protocol to induce hypoglycemia. Achieving hypoglycemia was based on glucose levels alone. Intranasal glucagon is indicated for

treatment of severe hypoglycemic reactions, but the controlled trials were not designed to study recovery from severe hypoglycemia. Reviewers acknowledge that real-world studies including the conditions specified in the indication (e.g., impaired consciousness) would be difficult to achieve; however, a major limitation of the studies remains since there were no controlled trials that tested the product under the conditions specified in the indication. Given the uniformity of the pharmacodynamic response to exogenous glucagon, reviewers believe that the extrapolation of the results of the trials to severe hypoglycemia is reasonable, but there remains uncertainty about the time to response relative to intramuscular glucagon since this has not been directly quantified under severe hypoglycemic conditions.

According to the clinical expert consulted for this review, the populations enrolled in the clinical trials are reasonably similar to the Canadian patients who would be prescribed glucagon nasal powder. Most patients were white, non-Hispanic, or Japanese, but there are no known reasons to believe that intranasal glucagon would have variable effects based on ethnicity. For example, the clinical expert confirmed that the rates of hypoglycemia awareness reported in the adult trials were similar to what would be expected in the Canadian population of adults with diabetes. There were some groups under-represented in the trials. Trials lacked older (e.g., > 65 years) populations who would be expected to have a longer duration of disease and a higher proportion of individuals with reduced awareness of hypoglycemia. Trials also enrolled lower numbers of patients with T2D, although it would be expected from the T2D clinical trial data and underlying physiology that the response to glucagon would be similar in this patient population.

The primary outcome of the three adult trials was resolution of low glucose levels within a 30-minute interval. Clinicians and patients would expect a resolution of low glucose levels in less than 30 minutes given the serious sequelae that can result from severe hypoglycemia that is not promptly and successfully treated.

Other Relevant Studies

Four open label studies that were not included in the systematic review are summarized in this section (Table 12). Two studies enrolled patients with T1D (B001 and B002) and two studies were performed using mannequins instead of patients (IGBM and AMG111).

Table 12: Overview of Other Relevant Studies

		B001	B002	IGBM	AMG111
Designs and Populations	**Study design**	OL, prospective, single-arm study	OL, prospective, single-arm study	Simulation study with randomized crossover	Simulation study with randomized crossover
	Locations	3 sites in the US (1 excluded due to GCP non-compliance)	3 sites in the US and 6 sites in Canada (1 excluded due to GCP non-compliance)	1 site in the US	1 site in the US
	Enrolled (N)	26	129	39 CP-PWD dyads and 34 APs	20 CP-PWD dyads and 20 APs
	Treated (N)	22	87	NA	NA
	Analyzed (N)	14	69	32 CP-PWD dyads and 33 APs	16 CP-PWD dyads and 15 APs
	Inclusion criteria	• Age ≥ 4 years and < 18 years • T1D of > 1 year duration • Living with one or more caregivers • In good general health	• Age ≥ 18 years and ≤ 75 years • T1D of > 1 year duration • BMI of ≥ 18.5 kg/m^2 and ≤ 35.0 kg/m^2 • Living with or is in frequent contact with one or more caregivers • In good general health	No experience in administering glucagon or another rescue medication CP: Close friend, relative, or caregiver for a PWD AP: No caregiving responsibilities to a PWD and no training in the use of a rescue device, but would try to help if an acquaintance experienced a severe hypoglycemia event	No training in administering glucagon in the past 6 months CP: Primary caregiver for a PWD AP: No experience with glucagon and diabetes, but would try to help if an acquaintance experienced a severe hypoglycemia event
	Exclusion criteria	• Pheochromocytoma or insulinoma • Use of systemic beta blockers, indomethacin, warfarin, or anticholinergic drugs		None	
	Evaluable events	Moderate or severe hypoglycemic event		Simulated emergency situation in which patients were told a mannequin was in severe hypoglycemia and then had to administer study drug to the mannequin	
Drugs	**Intervention**	• Single 3 mg dose of intranasal glucagon • Each patient was dispensed four doses (additional doses could be dispensed in Study B002)		Intranasal glucagon device	
	Comparator(s)	None		Injectable glucagon emergency kit	
Duration	**Phase**				
	Active period	6 months		NA	NA
	Study visits	2, 4, and 6 months		CP-PWD dyads: 3 sessions, at least 1 week apart	CP-PWD dyads: 3 sessions, 1 to 2 weeks apart APs: 1 session

		B001	B002	IGBM	AMG111
				APs: 2 sessions, at least 1 week apart	
Outcomes	**Primary end point**	Proportion of patients with severe and moderate hypoglycemia awaking or returning to a normal status within 30 minutes following study drug administration	Proportion of patients awaking or returning to a normal status within 30 minutes following study drug administration	Percentage of CPs that perform a successful administration (complete dose delivered and all critical steps completed)	NA
	Secondary and exploratory end points	**Secondary** • Time required to administer the drug • Caregiver degree of satisfaction • Delivery method preference • Tolerability assessed using a nasal score questionnaire (patient-reported in Study B002)		**Secondary** • Percentage of APs that perform a successful administration • Time required to successfully administer the drug (CPs and APs) • Device preference (PWDs) **Exploratory** • Preference questionnaire (CPs and APs)	• Time taken to administer treatment • Percentage of dose administered (success/failure for intranasal glucagon) • Preference questionnaire
Notes	**Publications**	Deeb et al., 2018[23]	Seaquist et al., 2018[24]	None	Yale et al., 2017[25]

AP = acquaintance participant; BMI = body mass index; CP = caregiver participant; GCP = good clinical practice; NA = not applicable; OL = open label; PWD = person with diabetes; T1D = type I diabetes.

Source: Clinical study reports for Studies B001,[26] B002,[27] and IGBM;[28] study report for Study AMG111, Deeb et al. (2018),[23] Seaquist et al. (2018),[24] and Yale et al. (2017).[25]

Non-Randomized Studies of Intranasal Glucagon Use in a Community Setting

The studies included in the systematic review do not provide evidence on symptom resolution following intranasal glucagon administration or use of the intranasal delivery device during real-world hypoglycemia. Two manufacturer-sponsored studies assessing the use of intranasal glucagon 3 mg to treat real-life events of hypoglycemia were conducted, one in pediatric patients (Study B001[23,26]) and one in adult patients (Study B002[24,27]).

Methods

The B001 and B002 studies were multi-centre, single-arm, open label studies. Study B001 was conducted in 2015 at three centres in the US, and Study B002 was conducted from 2014 to 2015 at three centres in the US and six centres in Canada. In both studies, one centre was excluded from efficacy analyses due to non-compliance with good clinical practice (GCP). Study B002 was paused due to an issue with powder aggregation and resulting underdosing in some patients. An evaluation period of approximately six months was expected for both studies to reach the required sample size of evaluable events. Patients continued in the study until one or more hypoglycemic events occurred or the

study was complete, whichever occurred first. Patients (and caregivers in Study B001) attended study visits two and four months following enrolment, as well as at the end of the study.

Populations

Patients in both studies were required to have had T1D for more than one year and be in good general health to be included. Patients in Study B001 were at least four years of age and under 18 years of age and living with at least one caregiver. Patients in Study B002 were adults of 75 years of age or younger, had a body mass index between 18.5 and 35.0 kg/m^2, and were living with or in frequent contact with at least one caregiver. Patients in both studies were excluded if they had pheochromocytoma or insulinoma, or were using systemic beta blockers, indomethacin, warfarin, or anticholinergic drugs.

Patients in the efficacy analysis population (EAP) of Study B001 (see the statistical analysis section below for definitions) had a mean age of 10.2 years and a mean duration of diabetes of 6.3 years (Table 13). Most patients used an insulin pump as their primary insulin modality. In this population, 42.9% of patients had never experienced a severe hypoglycemic event and 21.4% had reduced hypoglycemia awareness according to the Clark Unawareness Score. For those patients who had experienced a severe hypoglycemic event in the past year, all patients had experienced it within the last 90 days.

Patients in the Study B002 safety population (see the statistical analysis section below for definitions) had a mean age of 46.2 years and a mean duration of diabetes of 26.3 years (Table 13). Approximately half used an insulin pump and half used insulin injection as their primary insulin modality. In this population, 9.5% of patients had never experienced a severe hypoglycemic event and 40.6% had reduced hypoglycemia awareness. A severe hypoglycemic event had occurred in the past year in 58.2% of patients.

Table 13: Summary of Baseline Characteristics (B001 and B002 Studies)

	B001 EAP N = 14	B002 MSAP N = 74
Mean age, years (SD)	10.2 (3.58)	46.2 (15.00)
Median age, years (range)	10.5 (5.0 to 17.0)	46.5 (19.0 to 71.0)
Female, n (%)	5 (35.7)	39 (52.7)
Male, n (%)	9 (64.3)	35 (47.3)
Mean weight, kg (SD)	43.1 (25.32)	77.8 (15.37)
Mean body mass index, kg/m^2 (SD)	NR	26.6 (4.39)
Country, n (%)		
Canada	0	55 (74.3)
US	14 (100.0)	19 (25.7)
Mean duration of diabetes, years (SD)	6.3 (3.48)	26.3 (13.56)
Primary insulin modality, n (%)		
Pump	10 (71.4)	39 (52.7)
Injection	4 (28.6)	35 (47.3)
Mean total daily insulin dose, units (SD)	42.3 (31.16)	49.5 (21.68)
Time since most recent severe hypoglycemic event, n (%)		
< 30 days	2 (14.3)	16 (21.6)

	B001 EAP N = 14	B002 MSAP N = 74
31 to 90 days	1 (7.1)	13 (17.6)
91 to 180 days	0	9 (12.2)
181 to 365 days	0	5 (6.8)
> 365 days	5 (35.7)	24 (32.4)
Never	6 (42.9)	7 (9.5)
Hypoglycemia unawareness status (based on Clarke Unawareness Score[a]), n (%)		
Reduced awareness	3 (21.4)	28 (40.6)
Intermediate	1 (7.1)	8 (11.6)
Aware	10 (71.4)	33 (47.8)

EAP = efficacy analysis population; MSAP = main safety analysis population; NR = not reported; SD = standard deviation.

[a] Clarke Unawareness Score was 4 or more for reduced awareness, 3 for intermediate, and 2 or less for aware.

Source: Clinical study reports for Studies B001 and B002.[26,27]

Interventions

In both studies, each patient was dispensed four doses of intranasal glucagon 3 mg and patients and caregivers were trained in its use. Patients and caregivers were also encouraged to keep one dose and one set of questionnaires with them at all times and the other doses and questionnaires in convenient locations. Patients in Study B001 were limited to four doses while patients in Study B002 could be dispensed additional doses.

Evaluable Events

Both moderate and severe hypoglycemic events were to be treated with intranasal glucagon and the definitions of each differed between the two studies. For hypoglycemic events to be considered evaluable, patients had to refrain from ingesting carbohydrates or injecting glucagon before responding or within 30 minutes of intranasal glucagon administration and not require external professional medical assistance. Events from centres with GCP non-compliance or occurring during the study pause in Study B002 were not considered evaluable events.

In Study B001, severe hypoglycemia was defined as the patient having severe neuroglycopenia (described as “usually resulting in coma or seizure”) requiring treatment with parenteral glucagon or IV glucose. In Study B002, severe hypoglycemia was defined as clinical incapacitation of the patient (i.e., unconscious, convulsing, or with severe mental disorientation) to the point where they required third-party assistance to treat the hypoglycemia.

Moderate hypoglycemic events in Study B001 were those in which the patient had signs and/or symptoms of neuroglycopenia and a blood glucose level of 70 mg/dL (equivalent to 3.9 mmol/L) or less at or near the time of treatment. The definition was similar in Study B002, except that the blood glucose level threshold was “approximately” 60 mg/dL (3.3 mmol/L) or less and did not appear to be strictly enforced.

Outcomes

The primary end point in both studies was originally the proportion of patients awaking or returning to a normal status within 30 minutes following study drug administration. The end point was amended to the proportion of hypoglycemic events rather than the proportion of patients.

Secondary end points in both studies included time to administer study drug, caregiver degree of satisfaction, and delivery method preference assessed with a hypoglycemia episode questionnaire completed by the caregiver. A set of pre-specified treatment-emergent AEs was assessed in the hypoglycemia episode questionnaire and could be recorded up to five hours post-administration in Study B002. More targeted AEs were assessed using a nasal score questionnaire, which was completed by caregivers in Study B001 and patients in Study B002. A tertiary end point of change in blood glucose level from time of study drug administration to 15, 30, and 45 minutes following administration was reported.

Statistical Analysis

No statistical tests were performed on the data. Efficacy end points were evaluated in the EAP, defined as enrolled patients who received at least one dose of study drug in an evaluable event and with evaluable information on treatment response. Questionnaire-based outcomes were reported for the EAP in Study B001 and for the main safety analysis population (MSAP) in Study B002, which was defined as enrolled patients who received at least one dose of study drug and experienced at least one hypoglycemic event (patients from GCP non-compliant sites and those underdosed during the pause in Study B002 were excluded). A sensitivity safety analysis population (SSAP) was also defined, which consisted of all enrolled patients who received at least one dose of study drug.

Study B001 was designed to include approximately 20 events of severe or moderate hypoglycemia. Study B002 targeted a sample size of 129 events of severe or moderate hypoglycemia, assuming that 75% of events would involve a successful response. The sample size was selected to yield a 95% CI for the primary end point with a width of 15%.

Patient Disposition

Details on patient disposition in the studies are provided in Table 14. Since patients could have experienced hypoglycemic events prior to discontinuation, early discontinuation did not necessarily exclude patients from efficacy analyses.

Outside of the GCP non-compliant centre, there were no protocol deviations in Study B001 that were considered by the sponsor as likely to have affected the results or conclusions. In Study B002, seven severe hypoglycemic events were excluded from the EAP due to: dose administration before the study pause (n = 1); consumption of oral carbohydrates (n = 2); not fully depressing the device plunger (n = 2); and GCP non-compliance (n = 2). In the total pool of hypoglycemic events, 22 events were excluded from the EAP for the above reasons, including seven events during which the device plunger was not fully depressed. Other reasons for exclusion were primary outcome data missing; patient was found to be ineligible; and device was triggered in the air (n = 1).

Table 14: Patient Disposition (B001 and B002 Studies)

	B001	B002
Screened, N	26	129
Enrolled, N	26	129
Discontinued, N	14	28
Reason for discontinuation, n		
Withdrawal due to reasons related to clinical events	3	1
Withdrawal not due to clinical events	1	2
Death	0	1
Site termination due to GCP non-compliance	10	5
Study placed on hold	0	16
Withdrawal due to safety reasons (investigator's decision)	0	1
Lost to follow-up	0	1
Met exclusion criteria	0	1
Completed, n	12	101
SSAP, n	22	87
MSAP, n	14	74
EAP, n	14	69

EAP = efficacy analysis population; GCP = good clinical practice; MSAP = main safety analysis population; SSAP = sensitivity safety analysis population.

Source: Clinical study reports for Studies B001 and B002.[26,27]

Treatment Exposure

[redacted]

Table 15: Treatment Exposure (B001 and B002 Studies — Safety Population)

	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Source: Clinical study reports for Studies B001 and B002.[26,27]

[redacted]

Efficacy

Response To Study Drug Administration

Results for the primary end point and time to response in evaluable hypoglycemic events are presented in Table 16. In Study B001, there were 33 evaluable events (all of them moderate hypoglycemia) in 14 patients. Blood glucose recorded at the time of glucagon administration ranged from 2.3 to 3.9 mmol/L. In all events, the patient returned to normal status within 30 minutes of study drug administration.

In Study B002, there were 157 evaluable events of moderate or severe hypoglycemia in 69 patients and the patient awoke (in cases of unconsciousness or convulsion) or returned to normal status in 96.2% of the events. In 3.4% of events, the patient returned to normal status after more than 30 minutes had elapsed following study drug administration, and in one event (0.7%) the patient did not return to normal status due to extreme headache. Blood glucose recorded at the time of glucagon administration ranged from 1.2 to 4.1 mmol/L. There were 12 events of severe hypoglycemia in seven patients (with one patient experiencing six of these events) and in all of these events the patients awoke or returned to normal status within 15 minutes of study drug administration, regardless of whether they were conscious at the time of administration.

Table 16: Summary of Hypoglycemic Events and Resolution (B001 and B002 Studies)

	B001 EAP N = 14 patients	B002 EAP N = 69 patients
Total number of hypoglycemic events	33	157
Number of severe hypoglycemic events	0	12[a]
Number of moderate hypoglycemic events	33	145
Events after which patients awoke or returned to normal within 30 minutes of study drug administration, n (%)	N = 33 events **33 (100.0)**	N = 157 events **151 (96.2)**
Patients who awoke or returned to normal within 30 minutes of study drug administration, n (%)	N = 14 patients	N = 69 patients
In at least 1 event	14 (100.0)	66 (95.7)
In all events	14 (100.0)	64 (92.8)
Time to return to normal status from moderate event, n (%)	N = 33 events	N = 145 events
< 5 minutes	7 (21.2)	27 (18.6)
5 to < 10 minutes	11 (33.3)	43 (29.7)
10 to < 15 minutes	4 (12.1)	33 (22.8)
15 to < 20 minutes	5 (15.2)	23 (15.9)
20 to < 25 minutes	5 (15.2)	7 (4.8)
25 to < 30 minutes	1 (3.0)	6 (4.1)
30 to < 45 minutes	0	5 (3.4)
Other	0	1 (0.7)[b]
Time to awaken from severe event where patient was unconscious or had convulsions, n (%)		N = 10
< 5 minutes	NA	1 (10.0)
5 to < 10 minutes	NA	6 (60.0)
10 to < 15 minutes	NA	3 (30.0)

	B001 EAP N = 14 patients	B002 EAP N = 69 patients
Time to return to normal status from severe event where patient was conscious, n (%)		N = 2
5 to < 10 minutes	NA	2 (100.0)
Median blood glucose level at glucagon administration, mmol/L (range)	N = 33 events 2.9 (2.3 to 3.9)	N = 156 events 2.7 (1.2 to 4.1)

EAP = efficacy analysis population; NA = not applicable; NR = not reported; SD = standard deviation.

Note: Primary end point results are denoted with boldface font.

[a] Evaluable events occurred in seven patients. One patient experienced six severe events and the other patients experienced one event each.

[b] Response given was "Extreme headache prevented returning to a normal mental status."

Source: Clinical study reports for Studies B001 and B002.[26,27]

Time To Administer Study Drug

According to the hypoglycemia episode questionnaire in Study B001, the time to administer the study drug (starting from when the device canister was opened) was less than two minutes in all evaluable events, with 60.6% of administration times being less than 30 seconds (Table 17). In Study B002, the time to administer the study drug was less than five minutes in all hypoglycemic events in the MSAP, with 70.4% of events having an administration time of less than 30 seconds.

User Satisfaction and Device Preference

The hypoglycemia episode questionnaire in both studies also collected data from users on their satisfaction with use of the intranasal glucagon device and preference compared with needle-based glucagon delivery (Table 17). After most events, users found their overall experience in administering the study drug to be "very easy" (66.7% in Study B001 and 70.9% in Study B002) or "easy" (24.2% in Study B001 and 22.9% in Study B002). The remaining responses were either "average" or "relatively easy." After most events, users strongly agreed (75.8% in Study B001 and 73.2% in Study B002) or agreed (6.1% in Study B001 and 16.2% in Study B002) that intranasal delivery of glucagon is preferable over needle-based delivery of glucagon for the treatment of severe hypoglycemia.

Table 17: Selected Results From the User-Friendliness Questionnaire (B001 and B002 Studies)

	B001 EAP N = 33 events	B002 MSAP N = 179 events
Time to administer study drug[a], n (%)		
< 30 seconds	20 (60.6)	126 (70.4)
30 to < 60 seconds	9 (27.3)	40 (22.3)
1 to < 2 minutes	4 (12.1)	9 (5.0)
2 to < 5 minutes	0	4 (2.2)
Degree of satisfaction[b]		
4 (average)	2 (6.1)	4 (2.2)
5 (relatively easy)	1 (3.0)	7 (3.9)
6 (easy)	8 (24.2)	41 (22.9)

	B001 EAP N = 33 events	B002 MSAP N = 179 events
7 (very easy)	22 (66.7)	127 (70.9)
Intranasal delivery of glucagon is preferable over needle-based delivery of glucagon – level of agreement[c]		
1 (strongly disagree)	0	2 (1.1)
2 (disagree)	1 (3.0)	0
3 (relatively disagree)	0	1 (0.6)
4 (neutral)	3 (9.1)	8 (4.5)
5 (relatively agree)	1 (3.0)	6 (3.4)
6 (agree)	2 (6.1)	29 (16.2)
7 (strongly agree)	25 (75.8)	131 (73.2)
Missing	1 (3.0)	2 (1.1)

EAP = efficacy analysis population; MSAP = main safety analysis population.

[a] Question wording was: "From the time you began to open the canister with the Dry-Mist Nasal Glucagon, please indicate how long it took to administer the Dry-Mist Nasal Glucagon in the patient's nostril."

[b] Question wording was: "How would you rate your overall experience in administering Dry-Mist Nasal Glucagon?" Possible answers ranged from 1 (very difficult) to 7 (very easy).

[c] Question wording was: "Based on your experience using and administrating Dry-Mist Nasal Glucagon in this study…I believe intranasal delivery of glucagon is preferable over needle-based delivery of glucagon for the treatment of severe hypoglycemia."

Source: Clinical study reports for Studies B001 and B002.[26,27]

Harms

The SSAP consisted of enrolled patients who received at least one dose of study drug, regardless of study site or, in Study B002, whether they were underdosed prior to the study pause. In Study B001, no patients in the SSAP (N = 22) reported a SAE and there were no deaths. In Study B002, one patient in the SSAP (N = 87) discontinued treatment due to an AE and there was one death from *Klebsiella pneumoniae* infection. Spontaneous AEs were not collected in either study.

Caregivers reported at least one AE in the hypoglycemia episode questionnaire for all patients in the EAP in Study B001 and 87.8% of patients in the MSAP in Study B002 (Table 18). The most commonly reported AEs were nasal discomfort/irritation (82.4% to 92.9%), watery eyes (85.7% in Study B001), and headache (54.1% to 71.4%). At least one AE that lasted for more than an hour was reported for half of the patients in Study B002.

All caregivers for patients in the EAP in Study B001 and 72.4% of patients in the MSAP in Study B002 reported at least one AE in the nasal score questionnaire (Table 18). The most commonly reported AEs were runny nose (64.3% to 66.2%), watery eyes (55.4% to 78.6%), nasal congestion (36.5% to 50.0%), sneezing (33.8% to 50.0%), and nasal itching (28.6% to 56.8%).

Table 18: Summary of Questionnaire-Solicited Adverse Events (B001 and B002 Studies)

	B001 EAP N = 14 patients	B002 MSAP N = 74 patients
Patients with ≥ 1 AE in the hypoglycemia episode questionnaire, n (%)	14 (100.0)	65 (87.8)
Nausea	4 (28.6)	17 (23.0)
Vomiting	1 (7.1)	7 (9.5)
Nasal discomfort/irritation	13 (92.9)	61 (82.4)
Watery eyes	12 (85.7)	NR
Headache	10 (71.4)	40 (54.1)
Other	9 (64.3)	31 (41.9)
Patients with AE duration of > 1 hour, n (%)	7 (50.0)	NR
Patients with ≥ 1 AE in the nasal score questionnaire, n (%)	14 (100.0)	63 (72.4)
Runny nose	9 (64.3)	49 (66.2)
Nasal congestion (nostrils plugged)	7 (50.0)	27 (36.5)
Nasal itching	4 (28.6)	42 (56.8)
Sneezing	7 (50.0)	25 (33.8)
Watery eyes	11 (78.6)	41 (55.4)
Itchy eyes	3 (21.4)	22 (29.7)
Redness of eyes	6 (42.9)	16 (21.6)
Itching of ears	0	8 (10.8)
Itching of throat	1 (7.1)	12 (16.2)

AE = adverse event; EAP = efficacy analysis population; MSAP = main safety analysis population; NR = not reported.

Note: Spontaneous adverse events were not collected.

Source: Clinical study reports for Studies B001 and B002.[26,27]

Critical Appraisal

Overall, the B001 and B002 studies provide insight into the efficacy and harms of intranasal glucagon treatment in real-life events of moderate and severe hypoglycemia. The primary end point was assessed during real-life events as opposed to induced events of hypoglycemia. However, the results may overestimate the effectiveness of intranasal glucagon under real-world conditions due to the following factors: reporting of outcomes on a per-event basis rather than a per-patient basis, the more recent training of patients and caregivers in administering glucagon than would be expected in the real world, and the exclusion in Study B002 of events during which a full dose was not administered due to user error.

Internal Validity

All of the results in the studies come from questionnaires filled out by caregivers (and patients in Study B002) and reliability of the reporting is unknown. While the use of caregiver reporting likely did not affect the results for the primary end point (though the reliability of timing of patient recovery remains uncertain), reporting of AEs by caregivers in the questionnaires was likely subjective.

[redacted]

[redacted]

Results were reported on a per-event basis (as opposed to a per-patient or -caregiver basis) for the time for administration, ease of use, and device preference. The outcomes for multiple events within a patient cannot be considered independent of one another. It is possible that caregivers found ease of use to increase with recurring events and time to administer the study drug could have decreased with recurring events. Therefore, results for these outcomes cannot be interpreted as being representative of first-time users and the potential clustering of effects within patients could have led to more favourable results.

The lack of a comparator in these studies means that comparative evidence is not available for real-life hypoglycemic events and that the device preference results should be interpreted with this consideration. Since 42.9% of the pediatric patients and 9.5% of the adult patients had not previously experienced an event of severe hypoglycemia, a significant proportion of caregivers may have had no previous experience with administering injectable glucagon. While caregivers would possess the relevant skills due to experience with administering insulin, the lack of experience with injectable glucagon precludes a fair comparison with intranasal glucagon in terms of preference.

While a validated tool was not used to assess device preference, the clinical expert consulted for this review considered the results for this outcome to be meaningful.

External Validity

The primary end point results should be interpreted as being in the context of successful administration of intranasal glucagon. Time to administer study drug and ease of use may have been more favourable in the studies than they would be in a real-world cohort since evaluable events occurred within six months of all patients and caregivers being instructed in the use of intranasal glucagon. According to the clinical expert consulted for this review, caregivers may go for years without reviewing the technique for administering the currently available injectable glucagon if they do not commonly encounter severe hypoglycemia.

While the sample size and number of centres were limited in Study B001 and only patients with T1D were included, the populations in both studies were generally representative of patients who would be dispensed glucagon in Canadian practice. The patient samples had a wide range in age and duration of diabetes and represented a mixture in the categories of hypoglycemia awareness and history of severe hypoglycemia.

While only 12 severe hypoglycemic events in seven adult patients were evaluable among the two studies, this reflects the rarity of these types of events. Severe hypoglycemic events did not occur in Study B001, though the definition for severe hypoglycemia used in the pediatric population was more restrictive than the one used in the adult population.

Studies Comparing Modes of Glucagon Administration in Simulated Emergency Scenarios (Mannequins)

While ease of use of the intranasal mode of delivery may offer a benefit over currently available comparators for the drug under review, ease of use and device preference were not assessed in the included randomized controlled trials (RCTs). Two published manufacturer-sponsored studies (unpublished Study IGBM[28] and published Study

AMG111[25,29]) comparing administration success, time to administration, and usability between intranasal and injectable glucagon during simulated severe hypoglycemia events using mannequins may address this gap in evidence.

Methods

The IGBM and AMG111 studies were randomized, crossover, single-centre studies conducted in the US. Each study was conducted in two cohorts — caregiver-patient dyads, and acquaintance participants (APs) who were meant to represent non-caregiver bystanders. Details of the studies are provided in Table 12.

Caregiver-patient dyads attended three separate sessions spaced one week (Study AMG111) or at least one week (Study IGBM) apart. In the first session, patients received training on one glucagon device (randomized to injectable or intranasal) in the first session and subsequently trained their caregivers in the use of that device. In the second session, caregivers used the device in a simulated emergency situation, and patients received training in the other device and subsequently trained their caregivers in the use of the second device. In the third session, caregivers used the second device in a simulated emergency severe hypoglycemic event.

In these studies, APs attended either one session (Study AMG111) or two sessions spaced at least one week apart (Study IGBM). They were shown one glucagon device (randomized to injectable or intranasal) and then used it in a simulated emergency severe hypoglycemic event. This was repeated with the second device in the same session or in the second session.

Populations

Each caregiver participant (CP) in Study IGBM was a close friend, relative, or caregiver of the PWD and had not previously administered injectable glucagon or another rescue medication. In Study AMG111, CPs were the primary caregivers for the PWDs and had not previously used injectable glucagon and had not received recent training in the use of glucagon. The median age of CPs was 51 years (range of 18 to 75 years) in Study IGBM and 54 years (range of 20 to 69 years) in Study AMG111 (Table 19).

Most PWDs had T2D and the median duration of diabetes was 16 years in Study IGBM and 15 years in Study AMG111. In Study IGBM, PWDs were permitted to have been previously trained in the use of injectable glucagon, but not in the two years prior to the study. In Study AMG111, none of the PWDs had ever seen or received training on a glucagon device previously and none owned one at the time of the study.

APs were those who stated that they would try to help if an acquaintance experience a severe hypoglycemic event, and had no caregiving responsibilities to a PWD (Study IGBM) or had no experience with glucagon and diabetes (Study AMG111). The median age of APs was younger than those of CPs, being 41 years in Study IGBM and 40 years in Study AMG111.

Table 19: Summary of Baseline Characteristics (Simulation Studies)

	IGBM	AMG111
Caregiver participants	[redacted]	N = 16
Median age, years (range)	[redacted]	54 (20 to 69)
Female, n (%)	[redacted]	10 (62.5)
Male, n (%)	[redacted]	6 (37.5)
Persons with diabetes	[redacted]	N = 16
T1D, n	[redacted]	NR[a]
T2D, n	[redacted]	NR[a]
Relationship to caregiver, n (%)		
Friend	[redacted]	NR
Family member	[redacted]	NR
Domestic partner	[redacted]	NR
Median age, years (range)	[redacted]	57 (26 to 76)
Median duration of diabetes, years (range)	[redacted]	15 (2 to 39)
Acquaintance participants	[redacted]	N = 15
Median age, years (range)	[redacted]	40 (22 to 78)
Female, n (%)	[redacted]	9 (60.0)
Male, n (%)	[redacted]	6 (40.0)

NR = not reported; SD = standard deviation; T1D = type 1 diabetes; T2D = type 2 diabetes.

Note: Demographics are presented for those who participated in at least one simulation session.

[redacted]

Source: Clinical Study Report for Study IGBM,[28] study report for Study AMG111,[29] and Yale et al., 2017.[25]

Glucagon Administration Training

For each glucagon delivery device, PWDs in Study IGBM were trained for a maximum of 30 minutes by study personnel who reviewed the instructions for use and demonstrated the use of the device. PWDs were then given the device to verbalize and demonstrate understanding of the instructions. They also opened a new device and demonstrated the steps for administration, with study personnel correcting errors, reteaching missed steps, and answering questions on use of the device. After an hour-long break that included a distractor task for the PWD, the PWD relayed the device instructions to their caregiver and were allowed to show but not actuate a new glucagon delivery device (the intranasal device had to remain in its shrink-wrapped tube).

For each glucagon delivery device in Study AMG111, study personnel read the instructions for use to the PWDs and demonstrated the administration procedure without actuating the device. PWDs could handle the device but not actuate it. After a 10- to 30- minute break which included distractor tasks, PWDs then discussed how to use the device with their CPs. The intranasal device was not available for demonstration.

In both studies, APs received no training on the glucagon delivery devices. In Study IGBM they were given basic information about severe hypoglycemia, and in both studies APs were shown each device.

Simulated Severe Hypoglycemic Events

In both studies, CPs and APs participated in videotaped simulated severe hypoglycemic events in which they had to find a glucagon device (injectable or intranasal) and administer glucagon to a mannequin representing the person experiencing severe hypoglycemia. Device order for the sessions was randomized in Study IGBM, while device order in Study AMG111 appeared to be assigned according to whether the participant's identification number in the study was odd or even.

In Study IGBM, the medical mannequin was clothed and had simulating breathing, blinking, pulse, heart sounds, and perspiration. Prior to starting the simulation, participants were informed that they would find a mannequin in the room that represented their associated PWD (for CPs) or a fictional co-worker (for APs). Participants were informed that the person had passed out due to hypoglycemia, and the importance of administering rescue medication was emphasized. They were also informed that their performance was being timed and recorded on video, that the glucagon rescue device would in the bedroom drawer (for CPs) or the mannequin's backpack (for APs), and that the ambulance would not arrive for 15 minutes. Alongside the glucagon rescue device were other items, including diabetes supplies. For CP simulations, there was a television playing and a cell phone alarm sound. For AP simulations, there was a computer that was on and a cell phone alarm sound.

In Study AMG111, the mannequin was clothed. Prior to starting the simulation, participants were informed that the mannequin was in severe hypoglycemia and that they needed to find the glucagon rescue device in the mannequin's backpack (which also contained diabetes supplies) and administer glucagon to the mannequin as quickly as possible.

In the first session, participants were told that they were being recorded on video and that the video was being streamed live over the internet and could appear in future educational and promotional material. They were also told that a team of experts was watching and evaluating them from behind a one-way mirror and the importance of administering rescue medication was emphasized. During the scenario, someone knocked loudly on the door and stated that they would make sure the ambulance was on its way once the participant found the glucagon device.

In the second session, participants were reminded of the situation and distractions were more frequent than in the first session. A loud beeping sound at one beep per second played throughout the simulation and increased in speed and intensity while study personnel made statements meant to simulate those of a distressed bystander if they deemed the participant was not engaging in the scenario. There were also distractions when the participants opened the glucagon packaging and at 30 seconds after the glucagon was found.

Outcomes

The primary end point in Study IGBM was the percentage of CPs who successfully administered a complete dose of glucagon, defined as at least 90% of glucagon drug solution for the injectable glucagon kit and the device plunger being fully depressed for the intranasal glucagon device, and completed all critical steps for the administration. The critical steps for the intranasal device were removing the device from packaging (which included shrink-wrap); not testing before use; inserting the device tip into one of the mannequin's nostrils; and pushing the plunger (keeping the tip inside the nostril) until the green line no longer showed. The critical steps for the injectable glucagon kit were removing the device from packaging; injecting the diluent from the syringe into the vial containing drug powder; ensuring the drug powder was dissolved (by shaking and/or

swirling); drawing the dissolved drug into the syringe; and injecting the drug into the mannequin at an appropriate site for intramuscular administration (thigh, buttock, or upper arm). The percentage of APs who successfully administered a complete dose of glucagon was a secondary end point. No primary end point was defined in Study AMG111, though the percentages of CPs and APs successfully administering a full dose of glucagon were reported, as well as the percentages of CPs and APs administering a partial dose of injectable glucagon. Partial dose administration was not possible with intranasal glucagon because the actuation mechanism ensured the entire dose was expelled.

Time to complete administration, starting from when the participant found the glucagon device and ending when the dose was administered, was measured in both studies. In Study IGBM, the simulation timer was stopped when the participant administered a dose of glucagon or after 15 minutes had elapsed.

Device preference was assessed using questionnaires in both studies for CPs, APs, and PWDs. Participants and PWDs in Study IGBM rated strength of preference on a 5-point Likert scale for the respective items. In Study AMG111, PWDs were asked to indicate which device they preferred and CPs and APs were asked to indicate the preferred device, with an option for no preference. Satisfaction was also assessed in Study IGBM.

Statistical Analysis

[redacted]

Sample size considerations were not described for Study IGBM. In Study AMG111, sample sizes were based on the expected numbers of CPs and APs needed for 95% power to detect a within-subject difference of at least 40 seconds (with a standard deviation of 40 seconds) in time to administer study drug (intranasal versus injectable glucagon) at a significance level of 0.05. However, the sample size of 16 for each cohort was not reached due to many of the CPs and APs not completing administration of glucagon for both devices.

Patient and Participant Disposition

[redacted] In Study AMG111, 19 dyads and 20 APs were recruited. Of these, two dyads withdrew for personal reasons, one CP did not attempt the emergency simulations, and five APs either did not show up to sessions or withdrew from the study.

Table 20: Patient and Participant Disposition (Simulation Studies)

	IGBM		AMG111	
	[redacted]	[redacted]	Dyads	APs
Enrolled/recruited, N	[redacted]	[redacted]	19	20
Discontinued, N	[redacted]	[redacted]	3	5
Completed, N	[redacted]	[redacted]	16	15

AP = acquaintance participant.

Source: Clinical Study Report for Study IGBM,[28] study report for Study AMG111,[29] and Yale et al., 2017.[25]

Efficacy

Drug Administration Success

Intranasal glucagon was consistently associated with higher rates of successful administration compared with injectable glucagon in CPs and APs in both studies (Table 21). In Study IGBM, a significantly greater percentage of CPs successfully administered intranasal glucagon versus injectable glucagon (90.3% versus 15.6%; P < 0.0001). In Study AMG111, a full dose was successfully administered by 94% of CPs for intranasal glucagon and 13% of CPs for injectable glucagon, while a partial dose of injectable glucagon was successfully administered by 38% of CPs.

In Study IGBM, 90.9% of APs successfully administered intranasal glucagon and no APs successfully administered a full or partial dose of injectable glucagon (Table 21). In Study AMG111, 93% of APs successfully administered intranasal glucagon, no APs successfully administered a full dose of injectable glucagon, and 20% of acquaintance patients successfully administered a partial dose of injectable glucagon.

In Study AMG111, partial rather than full doses of injectable glucagon were administered by some participants due to failure to draw up all the solution into the syringe and/or failure to entirely depress the plunger.

Time To Administer Study Drug

Time to administer study drug was assessed for all successful administrations of glucagon (including partial or full dose in Study AMG111). In Study IGBM, the median time for CPs to administer glucagon was 30 seconds (range of 10 to 237 seconds; N = 28) for intranasal glucagon and 73 seconds (range of 62 to 105 seconds; N = 5) for injectable glucagon (Table 21). In Study AMG111, the median time for CPs to administer glucagon was 12 seconds (range of 2 to 56 seconds; N = 15) for intranasal glucagon and 108 seconds (range of 78 to 165 seconds; N = 8) for injectable glucagon.

In Study IGBM, the median time for APs to administer intranasal glucagon was 29.5 seconds (range of 10 to 243 seconds; N = 30). In Study AMG111, the median time for APs to administer glucagon was 29 seconds (range of 10 to 47 seconds; N = 15) for intranasal glucagon and 120 seconds (range of 78 to 236 seconds; N = 3) for injectable glucagon.

Table 21: Drug Administration Success and Time to Administer Study Drug (Simulation Studies)

	IGBM		AMG111	
	IN	Injectable	IN	Injectable
Caregiver participants	**N = 31[a]**	**N = 32[a]**	**N = 16**	**N = 16**
Successful administration, n (%)	28 (90.3)	5 (15.6)	NA	NA
P value[b]	**< 0.0001**		NA	
Full dose administration, n (%)	NA	NA	15 (94)	2 (13)
Partial dose administration, n (%)	NA	NA	NA	6 (38)
Time to deliver drug during successful administration[c], seconds	N = 28	N = 5	N = 15	N = 8
Mean (SD)	47.3 (52.0)	81.8 (18.6)	16.2 (NR)	113.4 (NR)
Median (range)	30.0 (10 to 237)	73.0 (62 to 105)	12 (2 to 56)	108 (78 to 165)
Acquaintance participants	**N = 33**	**N = 31**	**N = 15**	**N = 15**
Successful administration, n (%)	30 (90.9)	0	NA	NA
Full dose administration, n (%)	NA	NA	14 (93)	0
Partial dose administration, n (%)	NA	NA	NA	3 (20)
Time to deliver drug during successful administration[c], seconds (SD)	N = 30	N = 0	N = 15	N = 3
Mean (SD)	44.5 (47.8)	NA	26.4 (NR)	144 (NR)
Median (range)	29.5 (10 to 243)	NA	29 (10 to 47)	120 (78 to 236)

IN = intranasal; NA = not applicable; NR = not reported; SD = standard deviation.

[a] Results are presented for patients who found the device during the simulation.

[b] P value is for the McNemar test in the 31 patients who took part in both simulations and found the device in both simulations. There was no control for type I error outside of the primary end point.

[c] Could be partial or full dose in Study AMG111.

Source: Clinical Study Report for Study IGBM,[28] study report for Study AMG111,[29] and Yale et al. (2017).[25]

Device Preference

In both studies, most CPs, PWDs, and APs expressed a preference for the intranasal glucagon device over the injectable glucagon kit (Table 22). In Study IGBM, 80.6% of CPs strongly preferred or preferred intranasal glucagon and 13.0% of CPs strongly preferred or preferred injectable glucagon. In terms of overall satisfaction, 74.2% of CPs strongly preferred or preferred intranasal glucagon and 9.7% preferred injectable glucagon. In Study AMG111, 87% of CPs preferred intranasal delivery of glucagon and 13% of CPs preferred needle-based delivery of glucagon for treating severe hypoglycemia.

In Study IGBM, 90.3% of PWDs strongly preferred or preferred intranasal glucagon in terms of feeling safe during a severe hypoglycemic event and 6.5% strongly preferred injectable glucagon. In Study AMG111, 69% of PWDs preferred intranasal delivery of glucagon and 19% preferred needle-based delivery of glucagon for the treatment of severe hypoglycemia by a third party.

In Study IGBM, 93.5% of APs strongly preferred or preferred intranasal glucagon and 3.2% strongly preferred injectable glucagon. In terms of overall satisfaction, 87.1% of APs strongly preferred or preferred intranasal glucagon and 3.2% strongly preferred injectable glucagon. In Study AMG111, all APs indicated that they would recommend that PWDs carry

intranasal glucagon for the APs to treat them with (as opposed to injectable glucagon or neither device).

Table 22: Selected Results From the Preference Questionnaire (Study IGBM)

	IGBM
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
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[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

Source: Clinical Study Report for Study IGBM.[29]

Critical Appraisal

While the differences in administration success and time to administration were pronounced and consistent between intranasal and intramuscular delivery in both studies, the generalizability of the results to the Canadian population of potential glucagon users is less clear.

Internal Validity

Statistical testing of time to administer study drug in Study AMG111 was not performed because the planned sample size was not reached due to the low proportions of CPs and APs successfully administering glucagon with both devices. Interpretation of the results for time to administer study drug was limited in both studies due to low sample sizes.

In both studies, there were significant proportions of participants who did not complete the study after enrolment, and it is unclear whether there was any bias in the results from this.

There were notable differences between the two studies in time for drug administration which may be partly explained by differences in study design. Training of CPs was more thorough and mannequins were more realistic in Study IGBM. Planned distractions also differed between the studies. The clinical study report for Study IGBM specifically mentioned that intranasal glucagon was supplied in shrink-wrapped packages while there was no such description in the report for Study AMG111. If there was no shrink-wrap for the intranasal device in Study AMG111, this could explain the longer drug administration times in Study IGBM for intranasal glucagon.

External Validity

There are a number of issues that likely affect the generalizability of the success rates and administration times observed in the studies. A major limitation common to both studies is the fact that they were small, single-centre studies and they therefore do not reflect the potentially large amount of variation in caregiver and acquaintance ability to administer glucagon. In Study AMG111, none of the CPs or PWDs indicated during screening that they had owned a glucagon device or seen one. While this may resemble some Canadian patients with diabetes who should have glucagon but do not, it does not reflect the population of patients who receive the injectable glucagon that is currently available. As well, there were no pediatric PWDs in either study and it is likely that primary caregivers of pediatric patients would be more aware of glucagon injection technique and more experienced in administering subcutaneous insulin injections than caregivers of adult patients. Overall, there are likely to be caregivers in the greater population with more awareness of, and possibly experience with, glucagon administration than those included in the two mannequin studies.

It is difficult to predict to what degree the simulated nature of the hypoglycemic events impacted the differences between intranasal glucagon and injectable glucagon in terms of drug administration success rates, drug administration times, and device preference. CPs in the studies had recent training on the device and CPs and APs had advance knowledge of when they would have to respond to a hypoglycemic emergency. Therefore, participants were likely better prepared to administer glucagon in the simulations than caregivers or acquaintances would be in real life. As mentioned previously, caregivers of patients with diabetes who have not experienced severe hypoglycemia may not review the technique for administering injectable glucagon for years. According to the clinical expert consulted for this review, those administering glucagon during actual severe hypoglycemic events may

experience greater stress than during the simulations, leading to more delays and errors in administration of glucagon. As well, glucagon would be much more challenging to administer in a patient having a tonic-clonic seizure or in a resistant patient (as described in one of the patient input submissions), which are situations that could not be replicated in the study mannequins. In the clinical expert's opinion, intranasal glucagon would be easier to administer than intramuscular glucagon during a seizure.

Overall, it would appear that successful administration rates may be lower and administration times may be longer for both intranasal and injectable glucagon in real-life hypoglycemic events compared with the simulations. It is also possible that in at least some real-life events the differences between intranasal and injectable glucagon may be more pronounced than in the simulation studies. However, there is no evidence available comparing intranasal and injectable glucagon administration in real-life versus simulated severe hypoglycemic events.

Discussion

Summary of Available Evidence

Four open label, randomized studies met the inclusion criteria for the systematic review. Hypoglycemia (not severe hypoglycemia) was induced as part of the study procedures in all patients. Three of the studies were performed in adults with T1D or T2D and one study was performed in children aged 4 to 17 with T1D. Patients received a single 3 mg intranasal glucagon dose and this was compared to a single dose of 1 mg intramuscular glucagon in all studies in crossover fashion. The primary objective of the adult studies was to assess the impact of intranasal glucagon on treatment success and time-to-treatment success relative to intramuscular glucagon.

Key limitations of these studies are their open-label design, an imbalance of patients who received oral carbohydrate rescue with intranasal glucagon, and the absence of any study patients experiencing severe hypoglycemia with impaired consciousness (the event for which intranasal glucagon is indicated).

Other Relevant Studies

Four additional studies which were designed to mimic real-world administration conditions did not meet the inclusion criteria for the systematic review but were summarized as additional evidence. Two studies enrolled patients with T1D and two studies were performed using mannequins instead of patients.

Interpretation of Results

Efficacy

Compared to intramuscular glucagon, patients receiving intranasal glucagon for hypoglycemia have similar rates of treatment success but a longer time for recovery to normal glycemia and recovery from symptoms of hypoglycemia. The pharmacodynamic response was measured by observing glucose levels after administration of glucagon and the glucose recovery profiles were similar for intranasal glucagon compared to intramuscular glucagon. However, the blood glucose levels were lower after intranasal glucagon compared to intramuscular glucagon for most time points up to 90 minutes post-glucagon. These results were achieved under the experimental conditions of induced

hypoglycemia. The 10% noninferiority boundary that was used in the adult studies may not be stringent enough for some clinicians to accept, but the limits of the CIs for treatment success rates fell below this threshold and did not exceed 4% in any of the three adult studies.

While there may be merits to using a more stringent noninferiority margin, reviewers and the clinical expert believe that there are more significant limitations to the primary outcome selected in the adult studies. The first limitation is that the outcome did not include resolution of symptoms of severe hypoglycemia. Severe hypoglycemia is defined in the Diabetes Canada Guidelines as "Individual requires assistance of another person. Unconsciousness may occur. Plasma glucose is typically < 2.8 mmol/L." (See Appendix 4 for review of definitions of severe hypoglycemia.) Recovery of consciousness from severe hypoglycemia would be a more relevant outcome since this would reflect the indication of intranasal glucagon and because blood glucose levels are a surrogate end point for what is a life-threatening condition. Reviewers acknowledge that there may be significant ethical and logistical barriers to completing such a study, but it is nevertheless important to highlight that the studies did not reflect the clinical condition for which intranasal glucagon is indicated. The second limitation is that the primary outcome selected a 30-minute time frame for recovery from hypoglycemia. Clinicians and patients desire a resolution of low glucose levels in less than 30 minutes given the serious sequelae that can result from severe hypoglycemia that is not promptly resolved.

The single pediatric study did not use any formal sample size estimation and did not have a predefined primary outcome. Results in children for recovery from hypoglycemia were congruent with the results of the adult studies. The limitations of the pediatric data are similar to the adult data because the pediatric studies did not include any instances of children recovering from severe hypoglycemia. The number of children in the study was low, but was sufficient to warrant an indication in children with the Health Canada reviewers stating that the pediatric data are sufficient given the history of usage of currently available injectable glucagon products.[30]

Other Relevant Studies

Moderate hypoglycemic events in adults and children with diabetes and severe hypoglycemic events in adults were treated using intranasal glucagon under real-world conditions in two studies (B001 and B002). When intranasal glucagon was successfully administered as the sole intervention for hypoglycemia, all moderate hypoglycemic events in the pediatric patients and 96.2% of hypoglycemic events (including all severe events) in adult patients were successfully resolved within 30 minutes of administration. Limitations of these studies include the small sample size of events (particularly for severe hypoglycemic events), the lack of a comparison with intramuscular glucagon, and the possibility that caregivers and adult patients were more recently trained and therefore better prepared to treat hypoglycemia in the studies than they would be under real-world conditions.

In the two mannequin studies, caregivers trained in use of the glucagon devices and untrained non-CPs administered both types of glucagon to mannequins during simulated scenarios of severe hypoglycemia. Most of these participants, in addition to the patient participants who trained the caregivers, expressed a preference for using intranasal glucagon over injectable glucagon. The magnitude of the differences in these outcomes between intranasal and intramuscular glucagon strongly suggest some degree of benefit with intranasal glucagon despite limitations in the ability of simulated scenarios to mimic real-world conditions. Conclusions could not be made regarding glucagon administration

times as the times for intramuscular glucagon administration were based on a few successful injections. According to the clinical expert consulted for this review, low success rates are expected with intramuscular glucagon administration, as it is rare for caregivers to have real-life experience in administering intramuscular glucagon to treat severe hypoglycemia. Notably, all PWDs in the AMG111 study were adults who indicated during screening that they did not own a glucagon device and had never seen one. However, the success rates for administration of a full dose of intramuscular glucagon were lower than expected by the clinical expert. It is unclear how representative the study populations are of the indicated population as many patients would be expected to currently own a glucagon kit and caregivers of pediatric patients may be more prepared to administer intramuscular glucagon than caregivers in the studies.

Patient groups expressed a desire for a product for treatment of severe hypoglycemia that would be easier to administer to patients as this could reduce stress in the context of an emergency situation that is already very stressful for the caregiver and patient. Patients and caregivers expressed that they would like to see a product that is pre-mixed, is fast to administer, has a small chance of error, and results in fast recovery. Patients also expressed a desire for a product that was less conspicuous, thereby lessening the attention to the patient and the stigma associated with the disease. Data from the real-world studies and the mannequin studies suggest that intranasal glucagon possesses some of these characteristics that are considered desirable to patients and caregivers. However, some desirable outcomes, such as the ability of intranasal glucagon to reduce the need for professional emergency medical services, have not been demonstrated from the available evidence.

Harms

The harms profile of intranasal glucagon is similar to intramuscular glucagon with additional AEs observed that were related to the route of administration. AEs that occurred after treatment with intranasal glucagon included nausea, headache, vomiting, nasal discomfort/congestion, increased lacrimation, and upper respiratory tract irritation. The risk of injection site irritation and pain is avoided with the administration of intranasal glucagon.

Other Relevant Studies

The safety profile of intranasal glucagon was similar in the B001 and B002 studies as in the RCTs. No treatment-related SAEs or deaths were reported. While nasal discomfort, watery eyes, headache, and runny nose were reported at higher rates than in the RCTs, these AEs were specifically solicited in questionnaires and reported by caregivers.

Other Studies

[redacted].[31]

Conclusions

Patients receiving intranasal glucagon for treatment of experimentally induced hypoglycemia (not severe hypoglycemia) have similar rates of treatment response compared to treatment responses with intramuscular glucagon in three studies in adults and one study in children. Intranasal glucagon is indicated for treatment of severe hypoglycemic reactions, but the controlled trials were not designed to study recovery from severe hypoglycemia. The mean time-to-treatment response was between 1.6 and 4 minutes longer for patients receiving intranasal glucagon compared to intramuscular glucagon in two adult trials under controlled experimental conditions. The differences in time-to-treatment response between intranasal glucagon and intramuscular glucagon may be improved under real-world conditions because of potential reduction in administration time for intranasal glucagon but the degree to which this would be mitigated is not known. Limited evidence from simulated emergency scenarios suggests that successful administration of glucagon is more likely with intranasal delivery compared with intramuscular delivery, though the generalizability to real-world conditions and users remains unclear. The effectiveness of intranasal glucagon relative to intramuscular glucagon in real-world conditions of severe hypoglycemia in which the patient requires external assistance is not known.

Appendix 1: Literature Search Strategy

Clinical Literature Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946 to present) Embase (1974 to present) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	August 23, 2019
Alerts:	Bi-weekly search updates until project completion
Study Types:	No publication type filters were applied.
Limits:	Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.ot	Original title (MEDLINE)
.dq	Candidate term word (Embase)
.rn	Registry number
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
Line #	**Search Strategy**
1	baqsimi*.ti,ab,kf,ot,hw.
2	glucagon/
3	(glucagon* or HSDB 3337 or HSDB3337 or 76LA80IG2G).ti,ab,kf,ot,hw,rn,nm.
4	2 or 3
5	((Nasal sprays/ or nebulizers.mp.) and vaporizers/) or exp Aerosols/ or administration, intranasal/ or nasal absorption/ or administration, inhalation/ [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy]
6	(intranasal* or intra-nasal* or nasal* or needleless or needle-less or inhal* or aerosol* or nebuliz* or nebulis* or needlefree or needle-free or atomizer* or atomiser* or injection-free or injectionfree or non-inject* or noninject* or spray* or dry or powder* or vapori* or vapouri*).ti,ab,kf,ot,hw.
7	5 or 6
8	exp hypoglycemia/
9	(hypoglycemi* or hypoglycaemi* or hypo glycemi* or hypo glycaemi* or (low adj4 sugar*) or (low adj4 glucose)).ti,ab,kf,ot,hw.

MULTI-DATABASE STRATEGY	
Line #	**Search Strategy**
10	((hypo or low or dropped) adj4 (glucose or BGL)).ti,ab,kf,ot,hw.
11	8 or 9 or 10
12	4 and 7 and 11
13	1 or 12
14	13 use medall
15	Baqsimi*.ti,ab,kw,dq.
16	*glucagon/
17	(glucagon* or HSDB 3337 or HSDB3337).ti,ab,kw,dq.
18	16 or 17
19	Nose spray/ or exp nebulizer/ or exp aerosol/ or intranasal drug administration/ or drug absorption/ or inhalational drug administration/
20	(intranasal* or intra-nasal* or nasal* or needleless or needle-less or inhal* or aerosol* or nebuliz* or nebulis* or needlefree or needle-free or atomizer* or atomiser* or injection-free or injectionfree or non-inject* or noninject* or spray* or dry or powder* or vapori* or vapouri*).ti,ab,kw,dq.
21	19 or 20
22	exp hypoglycemia/
23	(hypoglycemi* or hypoglycaemi* or hypo glycemi* or hypo glycaemi* or (low adj4 sugar*) or (low adj4 glucose)).ti,ab,kw,dq.
24	((hypo or low or dropped) adj4 (glucose or BGL)).ti,ab,kw,dq.
25	22 or 23 or 24
26	18 and 21 and 25
27	15 or 26
28	27 use oemezd
29	(conference abstract or conference review).pt.
30	28 not 29
31	14 or 30
32	remove duplicates from 31

CLINICAL TRIAL REGISTRIES		
ClinicalTrials.gov	Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials. Search terms: (baqsimi OR (glucagon OR HSDB 3337 OR HSDB3337) AND (intranasal OR nasal OR needle-free OR injetction-free)) AND (hypoglycaemia OR hypoglycemia)	
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. Search terms: (baqsimi OR (glucagon OR HSDB 3337 OR HSDB3337) AND (intranasal OR nasal OR needle-free OR injetction-free)) AND (hypoglycaemia OR hypoglycemia)	

OTHER DATABASES		
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	

Grey Literature

Dates for Search:	August 16 to 19, 2019
Keywords:	(baqsimi OR (glucagon OR HSDB 3337 OR HSDB3337) AND (intranasal OR nasal OR needle-free OR injetction-free)) AND (hypoglycaemia OR hypoglycemia)
Limits:	Publication years: all

Relevant websites from the following sections of the CADTH grey literature checklist Grey Matters: a practical tool for searching health-related grey literature (https://www.cadth.ca/grey-matters) were searched:

- health technology assessment agencies
- health economics
- clinical practice guidelines
- drug and device regulatory approvals
- advisories and warnings
- drug class reviews
- clinical trial registries
- databases (free)
- databases (subscription-based)
- internet search.

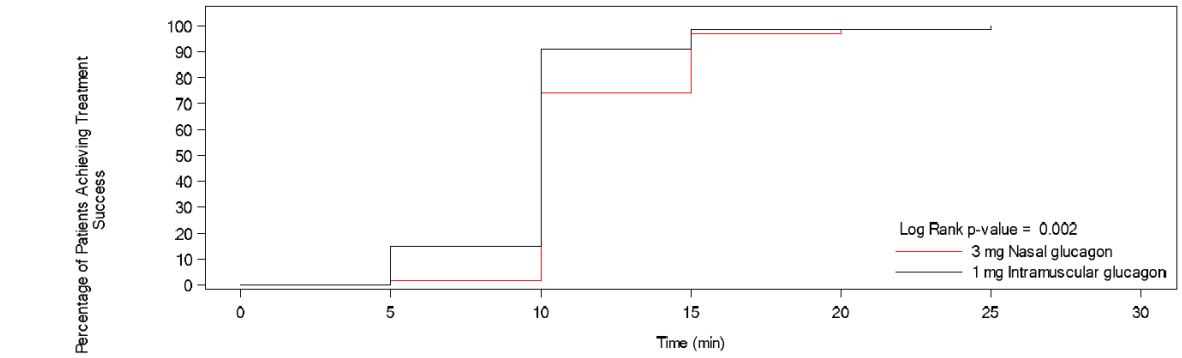
Appendix 2: Excluded Studies

Table 23: Excluded Studies

Reference	Reason for exclusion
Study IGBF[32]	No induction of hypoglycemia
Study IGBG[31]	No induction of hypoglycemia; inappropriate comparator
Study IGBD[16]	Population: healthy volunteers
Study IGBE[16]	Population: healthy volunteers
Study IGBA[16]	Dose finding study; very small sample size for group receiving 3 mg intranasal glucagon

Appendix 3: Detailed Outcome Data

Figure 6: Study IGBI Kaplan–Meier Plot of Treatment Success (PG Increase to ≥ 3.9 mmol/L or Increase of ≥ 1.1 mmol/L From Nadir 30 Minutes After Glucagon; Primary Outcome), T1D patients (N = 66)



Cumulative no. of event:no. of patients at risk

1 mg IM glucagon	0:66	10:56	60:6	65:1	65:1	66:0
3 mg nasal glucagon	0:66	1:65	49:17	64:2	65:1	66:0

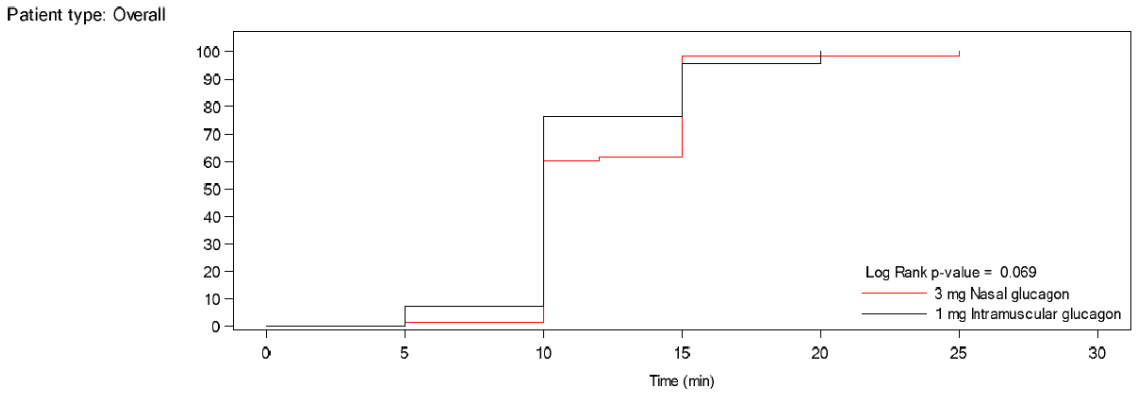
Cox proportional hazard model p-value = <.001

IM = intramuscular

Note: per-protocol population.

Source: Clinical Study Report for IGBI.[6]

Figure 7: Study IGBJ Kaplan–Meier Plot of Treatment Success (PG Increase to ≥ 3.9 mmol/L or Increase of ≥ 1.1 mmol/L From Nadir 30 Minutes After Glucagon; Primary Outcome), T1D and T2D Patients (N = 68)



Cumulative no. of successes:no. of patients at risk

1 mg IM glucagon	0:68	5:63	52:16	65:3	68:0	
3 mg nasal glucagon	0:68	1:67	41:27	67:1	67:1	68:0

Cox proportional hazard model p-value = 0.005

IM = intramuscular.

Note: Per-protocol population.

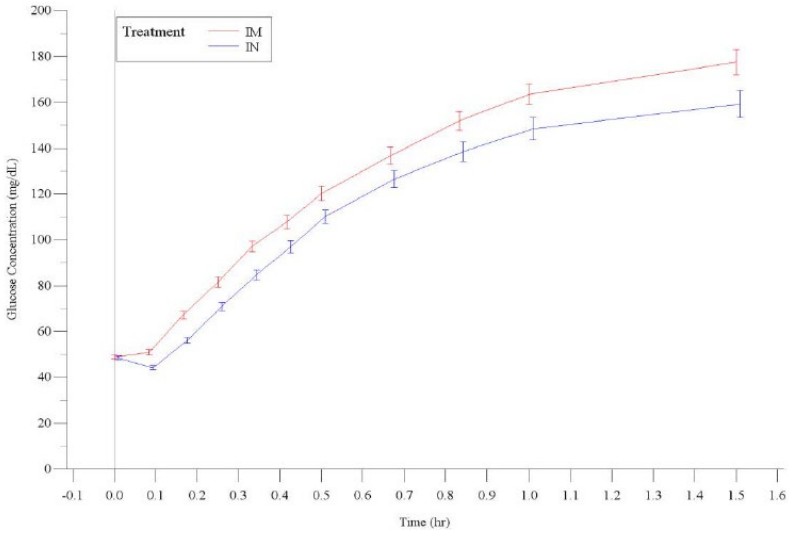
Source: Clinical Study Report for IGBJ.[7]

Figure 8: [redacted]

[redacted]

Source: Clinical Study Report for IGBB.[9]

Figure 9: Study IGBC — Mean Glucose Concentrations Post-Glucagon Dose (mg/dL); Patients With T1D (N = 75)



Note: Error bars represent standard error.

Source: Clinical Study Report for IGBC.[5]

Table 24: Glucose Concentrations Post-Glucagon (mmol/L)

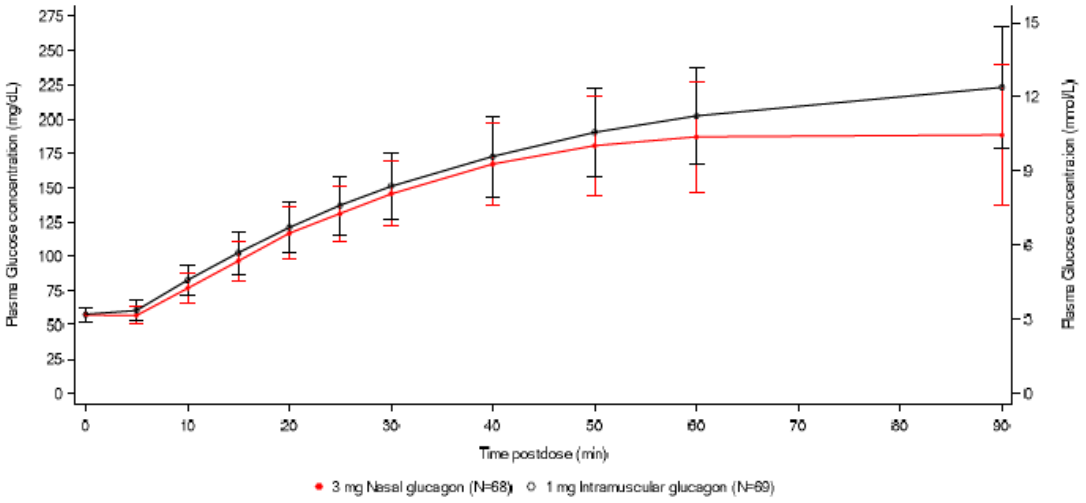
Study		Time post-glucagon (minutes) Plasma glucose, mmol/L												
		0	5	10	15	20	25	30	40	50	60	90	120	240
IGBC T1D	Intranasal N = 75	2.7	2.5	3.1	3.9	4.7	5.4	6.1	6.9	7.7	8.2	8.8	NR	NR
	Intramuscular N = 75	2.7	2.8	3.7	4.5	5.4	6.0	6.7	7.6	8.4	9.1	9.9	NR	NR
IGBI	Intranasal N = 68	3.3	3.3	4.4	5.4	6.6	7.3	8.2	9.3	10.1	10.4	10.6	NR	NR
	Intramuscular N = 69	3.2	3.3	4.6	5.7	6.7	7.6	8.4	9.6	10.5	11.2	12.4	NR	NR
IGBJ	Intranasal N = 71	2.9	2.8	3.9	4.8	5.6	6.3	6.9	7.9	8.5	8.9	8.6	8.0	6.7
	Intramuscular N = 70	2.9	3.1	4.2	5.1	5.8	6.5	7.0	7.9	8.5	9.1	9.6	9.1	6.6

NR = not reported; T1D = type 1 diabetes population.

Note: Statistically significant differences (P < 0.05) between intranasal and intramuscular glucagon. No statistical testing results were reported for IGBC.

Source: Clinical Study Report for IGBC[5] IGBI,[6] IGBJ.[7]

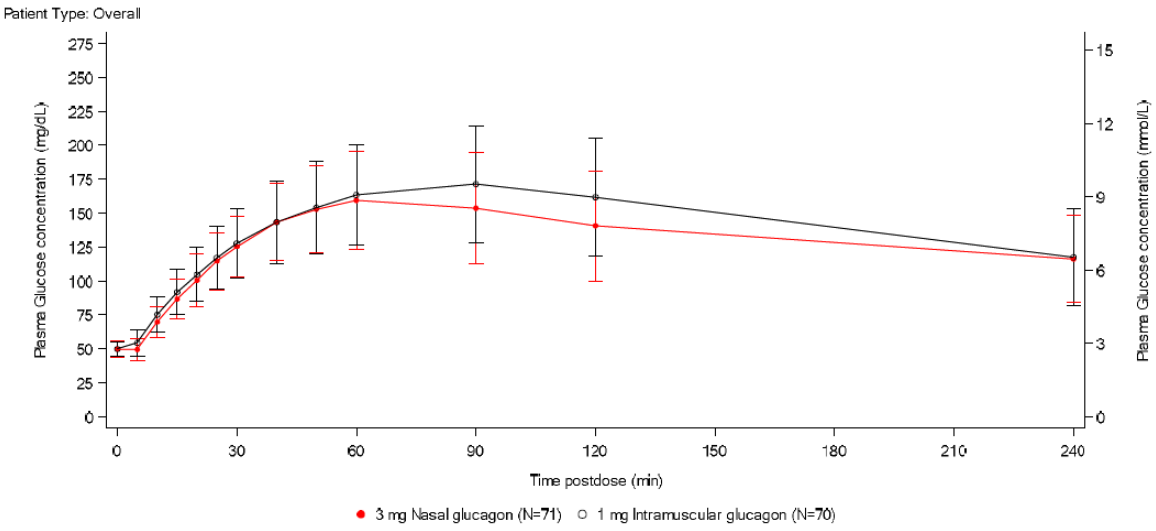
Figure 10: Study IGBI — Mean Glucose Concentrations Post-Glucagon Dose (mmol/L/mg/dL)



Note: Error bars represent standard deviation.

Source: Clinical Study Report for IGBI.[6]

Figure 11: Study IGBJ — Mean Glucose Concentrations Post-Glucagon Dose (mmol/L/mg/dL)



Note: Error bars represent standard deviation.

Source: Clinical Study Report for IGBJ.[7]

Appendix 4: Definitions of Severe Hypoglycemia

Aim

To summarize international clinical consensus on definitions for severe hypoglycemia in PWDs.

Findings

Recent guidelines and statements published by major diabetes clinician associations were reviewed. The Diabetes Canada 2018 Clinical Practice Guidelines define hypoglycemia as the development of autonomic or neuroglycopenic symptoms, a low plasma glucose level (less than 4.0 mmol/L for patients on insulin), and symptoms responding to the administration of carbohydrate.[1] Severe hypoglycemia is defined in the guidelines as follows: "Individual requires assistance of another person. Unconsciousness may occur. PG is typically < 2.8 mmol/L."[1]

The 2013 scientific statement on hypoglycemia and diabetes by the American Diabetes Association (ADA) and The Endocrine Society reconfirmed their previous definitions of hypoglycemia in diabetes.[33] Severe hypoglycemia is defined in the scientific statement as follows:

> Severe hypoglycemia is an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.[33]

The 2013 ADA scientific statement notes that no single threshold value for plasma glucose concentration can be used to define hypoglycemia because recent hypoglycemic events and glycemic control influence the threshold at which patients experience symptoms of hypoglycemia.[33] However, it provides a cut-off value of equal to or less than 3.9 mmol/L for alerting patients and caregivers to the risk for developing hypoglycemia.[33]

The 2017 joint position statement of the ADA and the European Association for the Study of Diabetes, prepared by the International Hypoglycaemia Study Group (IHSG), proposes definitions to guide clinical trial reporting of hypoglycemia.[34] It proposes a glucose level of less than 3.0 mmol/L for identifying clinically important hypoglycemia, due to the increased risk of short-term and long-term harms associated with that threshold.[34] It also considers the 2013 ADA definition of severe hypoglycemia to be appropriate.[34]

The International Society for Pediatric and Adolescent Diabetes (ISPAD) 2018 clinical practice consensus guidelines aimed to harmonize definitions of hypoglycemia with the IHSG.[35] The ISPAD definition of severe hypoglycemia, considered to be in alignment with the IHSG definition in adults, is:

> an event associated with severe cognitive impairment (including coma and convulsions) requiring external assistance by another person to actively administer carbohydrates, glucagon, or take other corrective actions.[35]

The ISPAD notes that defining severe hypoglycemia by the occurrence of coma or convulsions alone would underestimate the frequency of severe hypoglycemia in pediatric patients.[35] The 2018 ISPAD definition requires some judgment on the caregiver and clinician's part to determine whether hypoglycemia-induced cognitive dysfunction is present, as young children also require external assistance for mild hypoglycemia.[35]

Overall, there is international consensus that severe hypoglycemia can be defined by the requirement of third-party assistance to take corrective action. There is also consensus that a blood glucose threshold is not required for defining severe hypoglycemia. In children, severe hypoglycemia can be further distinguished by determining whether or not hypoglycemia-induced cognitive impairment is present.

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