17 October 2019
EMA/CHMP/602404/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

BAQSIMI

International non-proprietary name: glucagon

Procedure No. EMEA/H/C/003848/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ACE	affinity capture elution
ADA	antidrug antibody
AP-HIRS	affinity-purified, hyper-immune rabbit serum
API	active pharmaceutical ingredient
ASMF	active substance master file
AUC(0-∞)	area under the concentration versus time curve from zero to infinity
AUC(0-t_{last})	area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
CAD	collisionally activated dissociation
CQA	critical quality attribute
Cmax	maximum plasma concentration
CL/F	apparent total body clearance of drug calculated after extra-vascular administration
DCP	dodecylphosphocoline
DSC	differential scanning calorimetry
ESI	electrospray ionisation
ESI-MS	electrospray ionisation mass spectrometry
ECL	electrochemiluminescence
ECLU	ECL unit
FDA	Food and Drug Administration
FMCEA	failure mode effect and criticality analysis
GC	gas chromatography
GC-MS	gas chromatography mass spectrometry
HPC	high positive control
HPLC	high performance liquid chromatography
IC	ion chromatography
ICH	international conference on harmonisation of technical requirements for registration of pharmaceuticals for human use
ICP-MS	inductively coupled plasma mass spectrometry
IM	intramuscular
IMG	glucagon administered intramuscularly

Ig	immunoglobulin
KF	Karl Fischer titration
LPC	low positive control
LY900018	nasal glucagon
mAb	monoclonal antibody
MPC	mid positive control
MRD	minimum required dilution
MS	mass spectrometry
NAb	neutralising antibody
NC	negative control
NG	nasal glucagon
NHS	normal human serum
NMT	not more than
OFAT	one factor at the time
PAR	proven acceptable range
PC	positive control
Ph. Eur.	European Pharmacopoeia
PXRD	powder X-ray diffraction
QC	quality control
QTPP	quality target product profile
RH	relative humidity
RLU	relative luminescence unit
RP	reverse phase
RT	room temperature
SA	streptavidin
SD	standard deviation
SPPS	solid phase peptide synthesis
T1D	type 1 diabetes
T2D	type 2 diabetes
$t_{1/2}$	half-life associated with the terminal rate constant in non-compartmental analysis

TAMC	total aerobic microbial count
TE	treatment emergent
tmax	time of maximum observed drug concentration
Tonset	the time when blood glucose exceeds the upper normal limit
TYMC	total combined yeasts/moulds count
UV-CD	ultraviolet circular dichroism
V/F	apparent volume of distribution after extra-vascular administration

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Eli Lilly Nederland B.V. submitted on 19 July 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for BAQSIMI, through the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 February 2018. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of significant technical innovation.

The applicant applied for the following indication: treatment of severe hypoglycaemia in adults, adolescents, and children aged 4 years and over with diabetes mellitus.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0184/2015 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0184/2015 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request for consideration

New active Substance status

The applicant indicated the active substance glucagon contained in the above medicinal product to be considered as a known active substance.

Scientific advice

The applicant did not seek Scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Koenraad Norga Co-Rapporteur: Martina Weise

The application was received by the EMA on	19 July 2018
The procedure started on	16 August 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	5 November 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	5 November 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	19 November 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	13 December 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	22 February 2019
The following GCP inspection was requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
➢ A GCP inspection at two investigator sites in the United States between 04.12.2018 to 07.12.2018 and 15.01.2019 to 18.01.2019, respectively, and one sponsor site in the United States between 21.01.2019 to 25.01.2019. The outcome of the inspection carried out was issued on	22 March 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	29 March 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 April 2019
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	26 April 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	20 June 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	11 July 2019

The CHMP agreed on a 2nd list of outstanding issues to be sent to the applicant on	25 July 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	13 September 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	02 and 11 October 2019
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to BAQSIMI on	17 October 2019

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The claimed indication is:

"Baqsimi is indicated for the treatment of severe hypoglycaemia in adults, adolescents, and children aged 4 years and over with diabetes mellitus."

Severe hypoglycemia is an episode of hypoglycemia that causes neurological impairment and requires the assistance from another person to actively administer carbohydrates, glucagon, or take other corrective actions (IHSG 2015).

Episodes of severe hypoglycemia are characterized by neurological impairment that, if left untreated, can lead to serious consequences, such as loss of consciousness, seizures, coma, adverse cardiovascular outcomes, and even death. Injectable glucagon is a safe and efficacious emergency treatment for severe hypoglycemia and is currently the only treatment option for patients and their caregivers outside of the hospital or emergency medical setting. However, practical considerations, such as the multistep preparation of the solution for administration and injection by untrained users, have limited the use of injectable glucagon and can lead to delays in treatment and increased use of costly emergency medical services.

Peptide hormones are typically administered via a parenteral route such as intravenous, intramuscular, or subcutaneous. Oral administration is not practical since they undergo digestion and inactivation in the gastrointestinal tract and significant first pass metabolism, resulting in significant loss of efficacy. To overcome the usability challenges of injectable therapy and preserve efficacy, intranasal administration of peptide hormones has been studied. Known examples of intranasal peptides include desmopressin, oxytocin, and calcitonin. Nasal delivery of glucagon has previously been shown to increase blood glucose concentration in healthy subjects and patients with T1D. This application describes the clinical development of nasal glucagon (NG) and supports the use of Lilly's NG as an improvement in the delivery of treatment for the serious condition of severe hypoglycemia.

2.1.2. Epidemiology

Severe hypoglycemia is one of the most significant complications of diabetes treatment, occurring more frequently in patients with profound endogenous insulin deficiency—type 1 diabetes mellitus (T1D) and advanced type 2 diabetes mellitus.

2.1.3. Biologic features, Aetiology and pathogenesis

Glucagon increases blood glucose concentration by activating hepatic glucagon receptors, thereby stimulating glycogen breakdown and release of glucose from the liver. Hepatic stores of glycogen are necessary for glucagon to produce an antihypoglycemic effect.

2.1.4. Clinical presentation, diagnosis

Severe hypoglycemia has serious clinical implications for patients with T1D or T2D, including:

- death. Based upon recent reports of mortality rates, it is estimated that 4% to 10% of all deaths in patients with T1D can be attributed to hypoglycemia). NICE-SUGAR Study Investigators (2012) reported an increased risk of death in critically ill patients.
- seizures and loss of consciousness associated with hypoglycemia, which have been reported by approximately 1 in 9 participants in the T1D Exchange registry in the US.
- cognitive impairment (for example, difficulty concentrating, confusion, incoordination), drowsiness, weakness, and behavior changes secondary to neuroglycopenia, which can lead to more serious consequences including seizures, coma, and even death. Cognitive impairment can lead to other adverse outcomes such as falls, fractures, or motor vehicle accidents.
- serious cardiac complications such as arrhythmias.
- impaired hypoglycemic awareness following repeated episodes of hypoglycaemia, which can increase the risk for more severe hypoglycemic episodes.
- prevention of optimal glycemic control, due to fear or avoidance of hypoglycemia.
- decreased quality of life due to interference with employment, personal relationships, and other activities and possible onset or acceleration of dementia or cognitive decline.

2.1.5. Management

Currently available treatments for severe hypoglycemia are limited to intravenous dextrose and injectable glucagon. Intravenous dextrose requires administration by trained personnel within a hospital or emergency medical setting; thus, injectable glucagon is the only treatment option for caregivers outside of these settings. However, injectable glucagon is currently not available in a ready-to-use formulation. Glucagon is unstable in the aqueous state, therefore, the glucagon powder in currently available glucagon emergency kits must be reconstituted using a multiple-step process before the drug can be administered to the patient by either subcutaneous or intramuscular injection. Specifically, the instructions for use state that caregivers must remove the flip-off seal from the vial of glucagon, wipe the rubber stopper with an alcohol swab (Glucagon for Injection only), remove the needle protector from the syringe and inject the entire contents into the vial of glucagon, swirl the vial until the glucagon is completely dissolved, withdraw all of the solution, remove air bubbles from the syringe (GlucaGen HypoKit only), cleanse the injection site (Glucagon for Injection only), insert the needle into the skin to inject glucagon, and then withdraw the needle and press on the injection site. This process may delay or even preclude treatment,

especially in emergencies when caregivers without medical training must treat patients having a severe hypoglycemic event. Adding to this multiple-step process of administration, the caregiver may also need to determine if a weight-based dose adjustment is necessary for pediatric patients (Glucagon for Injection Product Monograph, 2012; GlucaGen HypoKit UK SmPC, 2015; GlucaGen HypoKit USPI, 2015; GlucaGen HypoKit Product Monograph, 2016; Glucagon for Injection USPI, 2017). In addition to these complexities, there are challenges associated with any type of injectable therapy including unfamiliarity with needles and syringes as well as a common fear of needles which could prevent effective administration of injectable glucagon.

Although few clinical studies have been conducted to evaluate usability issues, available evidence suggests that people without medical training find it challenging to administer injectable glucagon in an emergency, more than two-thirds (69%) of the parents of children and adolescents with diabetes had difficulty reconstituting and injecting glucagon with the emergency kit (difficulties included opening the pack, sheath removal, mixing, bent needles), even though the parents were familiar with injection techniques and had been trained to administer injectable glucagon. In some circumstances (10%), these difficulties led to the caregiver aborting the injection or inadvertently not administering any glucagon at all. During episodes of severe hypoglycemia, delays or errors in injectable glucagon administration may have a significant negative impact on patient outcomes.

All of these challenges likely contribute to the underutilization of injectable glucagon. In a study using a questionnaire to assess the coping strategies of 102 patients with T1D, 83% of patients said they had received instructions on how to use the injectable glucagon emergency kit but only 60% of patients actually owned one. Furthermore, of those patients who had experienced an episode of severe hypoglycemia, only 19% used the injectable glucagon emergency kit. More recently, Mitchell et al. (2016) examined the glucagon prescription pattern of patients with T1D or T2D who were newly prescribed insulin and found that the proportion of prescriptions filled was low, but varied with the type of insulin therapy and type of diabetes. Although the reason(s) that patients filled or did not fill the glucagon prescriptions were not known, these data further support that injectable glucagon is underutilized. Additionally, the US emergency medical service has policies restricting the use of injectable medications, including glucagon, by emergency medical technicians in many states.

Nasal glucagon provides easy administration of glucagon via a ready to use needle-free device, could represent an improvement in the evolution of the treatment of severe hypoglycaemia outside of the hospital or emergency medical setting.

About the product

Nasal glucagon (NG; LY900018; formerly known as AMG504-1 [originally developed by A.M.G Medical Inc. and later by Locemia Solutions ULC]) is a drug/device combination product containing a novel, nasally administered glucagon powder intended for the treatment of severe hypoglycemia in adult and pediatric patients with diabetes. A 3 mg dose of ready-to-use NG dry powder, which does not require reconstitution, is administered by inserting the tip of the single use device into the patient's nostril and depressing the plunger to expel the glucagon powder into the nostril where it is passively absorbed in the anterior nasal mucosa. Patients do not need to inhale or breathe deeply after dosing, enabling drug delivery even in unconscious patients.

Glucagon increases blood glucose concentration by activating hepatic glucagon receptors, thereby stimulating glycogen breakdown and release of glucose from the liver. Hepatic stores of glycogen are necessary for glucagon to produce an antihypoglycemic effect. Glucagon has been used clinically in the treatment of severe hypoglycaemia since the 1950s, and glucagon for injection (produced from animal sources) was first approved by the United States Food and Drug Administration (US FDA) in 1960.

Recombinant glucagon was approved for the treatment of severe hypoglycemia in the 1990s. Currently, the injectable Glucagon for Injection emergency kit (Eli Lilly and Company [Lilly]) is approved in the US and Canada, and the injectable GlucaGen HypoKit (Novo Nordisk) is approved in the US, European Union (EU), and Canada for the treatment of severe hypoglycemia.

The primary sequence of glucagon is highly conserved in mammals and is identical in man, cattle, pigs, dogs, and rats. The synthetic glucagon peptide is structurally identical to naturally occurring human glucagon as well as glucagon extracted from beef and pork pancreas. The drug substance in NG is synthetic glucagon which is the same single-chain, 29 amino acid polypeptide as the recombinant glucagon used in currently marketed glucagon emergency kits. The NG commercial drug product contains a dry powder formulation, which consists of synthetic glucagon and uses a novel excipient, the phospholipid dodecylphosphocholine (DPC), as a surfactant and absorption enhancer, and beta-cyclodextrin (β-CD) as a filler/bulking agent and absorption enhancer.

Type of Application and aspects on development

To address the need for an improved method of glucagon delivery, a clinical development was conducted to evaluate the efficacy, effectiveness, and safety of NG, as well as to characterize NG pharmacokinetics (PK) and pharmacodynamics (PD).

In addition, the Sponsor has completed a comprehensive nonclinical program including studies to evaluate the novel route of administration and the novel excipient DPC in accordance with published guidance and previous regulatory advice.

Nasal glucagon was originally developed by A.M.G Medical Inc. (AMG Medical) and later by Locemia Solutions ULC (Locemia) prior to acquisition by Lilly in 2015. The clinical development program for NG was comprehensive and is generally aligned with regulatory guidance. Adult patients with T1D or T2D, pediatric patients with T1D, and their caregivers were included in the development program in order to assess the drug product in the intended patient populations in both randomized controlled trials and real-world settings. The NG development program provides adequate exposure in both adult and pediatric patients using a combination of pivotal, bridging and confirmatory, actual use, and other supportive studies to allow conclusions to be drawn on the efficacy, PK/PD, and safety of NG.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as nasal powder containing 3 mg of glucagon as active substance.

Other ingredients are: betadex (E459) and dodecylphosphocholine.

The product is available in a single-dose container. The single-dose container consists of polyethylene and polypropylene. The single-dose container is stored in a shrink wrapped tube made of polyethylene and polypropylene containing a desiccant as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

Glucagon is a synthetic linear 29-amino acid peptide with a free amino group at the N-terminus and a free carboxylic acid at the C-terminus.

The chemical name of glucagon is
L-Histidyl-L-seryl-L-glutaminyl-glycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-aspartyl-L-tyrosyl-L-seryl-L-lysyl-L-tyrosyl-L-leucyl-L-aspartyl-L-seryl-L-arginyl-L-arginyl-L-alanyl-L-glutaminyl-L-aspartyl-L-phenylalanyl-L-valyl-L-glutaminyl-L-tryptophanyl-L-leucyl-L-methionyl-L-asparaginyl-L-threonine corresponding to the molecular formula $C_{153}H_{225}N_{43}O_{49}S$. It has a monoisotopic mass of 3480.6 g/mol and the following structure:

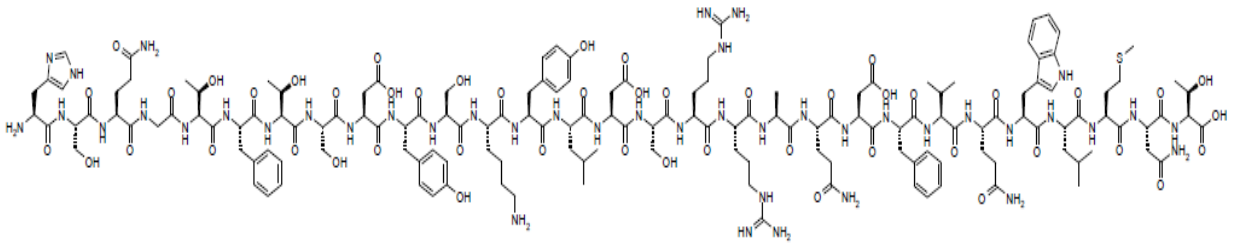


Figure 1: Active substance structure

The chemical structure of glucagon was elucidated by a combination of methods including different mass spectrometric (MS) techniques and circular dichroism (UV CD). The solid state properties of the active substance were measured by different methods, including powder X-ray diffraction (PXRD), raman spectroscopy and differential scanning calorimetry (DSC).

The active substance is a very hygroscopic, amorphous white powder, freely soluble in ammonium hydroxide and very slightly soluble in water.

All optically active amino acids are in L-configuration, glycine residue is achiral. The contents of the D-isomers of amino acids have been determined in three commercial batches of glucagon by a GC-MS technique upon hydrolysis of the active substance with hydrochloric acid.

Polymorphism has not been observed for the active substance.

Manufacture, characterisation and process controls

The active substance is manufactured in one manufacturing site.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.
The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packaged in wide-neck bottles made of amber glass (hydrolytic type III soda-lime-silica glass) which complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for appearance (visual), appearance of solution (visual), identification (HPLC, amino acid analysis, MS), related substances (HPLC), assay (HPLC), water content (KF), acetic acid content (IC), ammonium content (IC), chloride content (potentiometric titration), residual organic solvents (GC), bacterial endotoxins (Ph. Eur.) and microbial limit test (TAMC, TYMC, Ph. Eur.).

The applicant has provided a justification for all the tests and acceptance criteria in the specifications based on the relevant compendial and regulatory requirements. The specification was developed by following the recommendations of the ICH guidelines Q3C, Q6A, M7, the Ph. Eur. general monograph, the Glucagon EP monograph and the Glucagon USP monograph and is considered appropriate.

The analytical methods used have been adequately described and where necessary, appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and identification testing has been presented.

Batch analysis data of 5 commercial batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 60 months under long term conditions (-20 °C and 5 °C) and for up to 6 months under accelerated conditions (25 ºC / 60% RH and 40 °C/75% RH) according to the ICH guidelines were provided.

The following parameters were tested*:* appearance, assay, purity and related substances (total and individual), chloride content, ammonium content and water content.

All tested parameters were within their specified limits after 60 month storage at -20 °C and 5 °C, and during 6 month storage at 25 °C/60% RH. However, a significant degradation of glucagon, a significant increase of related substances and a significant decrease of corrected assay values were observed during storage at the accelerated storage condition of 40 °C/75% RH.

Photostability testing following the ICH guideline Q1B was performed on one batch. It has been shown that the active substance is sensitive towards irradiation with a dose of 1.2 Million lux hours (Mlxh) and is highly sensitive towards irradiation with a dose of 6 Mlxh.

Results on stress conditions to evaluate the influence of temperature and moisture in solid state and hygroscopicity were also provided on one batch.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months when stored in a freezer (< -15 °C) in the original container in order to protect from light.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

Baqsimi 3mg nasal powder is a white to off-white, freeze-dried powder to be administered to the nasal mucosa via a single-use delivery device.

The finished product was designed to meet the needs of patients with hypoglycemia based on the Quality Target Product Profile (QTPP).

The Critical quality attributes (CQAs) for the finished product, which are necessary to ensure that the patient receives the desired outcome from use of the product include identification, description, potency, purity and combination product functionality.

Nasal glucagon, intended for the treatment of severe hypoglycemia in adult and pediatric patients, is a novel drug/device combination product consisting of a single use nasal dosing device that delivers glucagon powder for absorption via the nasal mucosa.

Glucagon is a naturally occurring hormone produced by the pancreas. Glucagon is known to be prone to self-association or aggregation. The process used to manufacture nasal glucagon was developed to minimize the potential for aggregation. The process has been shown to effectively inhibit aggregation while the glucagon is in solution.

The choice of the excipients has been justified. The excipients (except novel excipient: dodecylphosphocholine) are of Ph. Eur. quality. Information on dodecylphosphocholine (DPC) is included below. No compatibility issues between the active substance and the excipients or between the excipients themselves have been observed during development and stability studies. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The novel excipient used in the manufacture of nasal glucagon is DPC. DPC is a structural analogue of lauroyl lysophosphatidylcholine and is more stable to hydrolytic degradation than other excipients. DPC has been shown to improve paracellular permeability of hydrophilic compounds by modulating the tight junctions, which may have implications on its use for oral or nasal drug delivery. DPC is a surfactant and absorption enhancer. DPC is an appropriate choice as the surfactant in this formulation. Detailed information on the manufacturing and control of DPC was requested by the CHMP during the assessment procedure and the provided data was considered satisfactory.

β-cyclodextrin is used to provide bulk or structure to the lyophilized material, and also acts as an absorption enhancer. It can have a positive influence on glucagon solution stability as well as enhance mucosal permeation in the formulation.

The nasal glucagon finished product provides a ready-to-use (no reconstitution) dry powder formulation for absorption via the nasal mucosa as an alternative to injection of a freeze-dried and reconstituted formulation. The formulation used during clinical studies is the same as that intended for marketing.

The selection of the manufacturing process flow and unit operations with their process parameters (target values) is justified and is based on scientific principles, early process development and ability to control finished product properties.

A risk-based approach was used for the development of the manufacturing process. The risk assessment focused on the potential influence of manufacturing unit operations on CQA of the finished product. Individual unit operations were evaluated by Failure Mode Effect and Criticality Analysis (FMECA) risk assessment and the outcome was based on early process development (process characterization data) and prior knowledge. As a result of the initial risk assessment, one factor at the time (OFAT) experiments

were performed to study the impact of process parameters and to mitigate risks. A comprehensive discussion of the results is given which supports the proven acceptable ranges (PAR) for critical and non-critical process variables. Risk of interaction among process parameters is deemed small. Compliance with the CQAs is always fulfilled within the PARs investigated. Based on the experiments and initial risk assessment, a final risk assessment was performed.

The product is packed in a primary container closed on one end with a centerpiece and on the opposite end with a ball. A green stripe is printed onto the button of the device to indicate dose completion. The pre-filled device is stored in a rigid plastic tube with attached hinged cap containing a desiccant in order to protect the device from mechanical damage and the glucagon drug powder from moisture. The tube has a shrink band as indicator that the tube has not been opened.

All packaging components comply with Food Contact EU Regulation No 10/2011. Since the finished product and the delivery device form a single integral product which is not reusable, the delivery device falls under the scope of the Medicinal Products Directive 2001/83/EC and not the Medical Device Directive 93/42/EEC. The delivery device is not assessed by a Notified Body for CE mark. Conformance with the essential requirements of Annex I of Regulation (EU) 2017/745 has been demonstrated. The suitability of the packaging components for protection from light and moisture is supported with ICH (photo) stability studies, spectral transmission and water vapor transmission data. The primary container and delivery device have been evaluated with regard to extractables and leachables and the studies conclude that the observed leachable concentrations are of no toxicological relevance. The suitability of the packaging components for drug delivery has been studied with clinical and commercially representative batches.

Manufacture of the product and process controls

The manufacturing process consists of 10 unit operations. The manufacturing process is a non-standard process.

The manufacturing process has been validated with 3 consecutive production batches for formulation, product processing, combination product filling and combination product assembly. The functional secondary packaging process has been validated with 3 consecutive previously assembled product batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this pharmaceutical form.

Product specification

The finished product release and shelf life specifications include appropriate tests for this kind of dosage form: identity (RP-HPLC, peptide map), assay (RP-HPC), uniformity of dosage units (RP-HPLC), shot weight (mass), delivered dose uniformity (RP-HPLC), acetic acid (RP-HPLC), impurities (RP-HPLC), description (visual), water content (KF), β-Cyclodextrin Content (RP-HPLC), dodecylphosphocholine content (RP-HPLC), particle size distribution (laser diffraction), and aerodynamics particle size (cascade impaction). Only the stability indicating tests have shelf life specifications.

The proposed release and shelf-life acceptance limits for fine particle fraction (FPF) and percent less than eleven (PLE) fraction for aerodynamic particle size, as determined by cascade impaction are established considering the commercially representative APSD results and CI method variability. Due to the limited number of batches available, the CHMP recommended to re-evaluate the finished product release and shelf-life acceptance limits for FPF and PLE after 30 batches have been manufactured using the commercial manufacturing process and 24 months of stability are available for the process validation and three additional commercial batches put into stability in Q1 2020.

An elemental impurities risk assessment as per ICH Q3D (finished product approach) has been performed. The results are found below the control threshold (30% of PDE considering 30mg maximum daily finished product dose) for each elemental impurity of concern for inhalation products.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used has been presented.

Batch analysis results are provided for 3 full commercial scale process validation batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 3 commercial scale batches of finished product stored for up to 24 months under long term conditions (25 ºC / 60% RH, 30 ºC / 65% RH, 30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) in both the upright and inverted orientations according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the functional secondary container proposed for marketing.

In addition, long-term stability data are available for 4 supporting stability batches manufactured with the same unit formula as the representative clinical and development batches, stored for up to 20 months at 30° C/65% RH, up to 24 months at 25° C/60% RH and 30° C/75% RH, and for up to 6 months at accelerated storage conditions (40° C/75% RH).

The analytical procedures used are stability indicating.

The real time stability results meet the established acceptance criteria whatever the storage orientations.

Stress stability studies were performed studying the effect of high temperature and humidity and solution stress. The thermal/humidity stress testing study performed on bulk drug powder showed expected degradation products formed with storage at an elevated temperature and humidity and demonstrated that the packaged combination product provides effective protection for humidity.

In addition, 1 batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The photostability study, performed on representative bulk finished product showed light-induced degradation products as a result of the direct exposure to simulated sunlight conditions. The studies showed that the packaged combination product (combination product in the functional secondary packaging) provides effective protection, and therefore is considered photo stable.

Based on available stability data, the proposed shelf-life of 24 months and do not store above 30 °C as stated in the SmPC (section 6.3) are acceptable. Keep glucagon nasal powder in the shrink wrapped tube until ready to use.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. This product is a novel drug/device combination product consisting of a single use nasal dosing device that delivers glucagon powder for absorption via the nasal mucosa instead of the traditional parenteral administration. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product

At the time of the CHMP opinion, there was a minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product (see 2.2.6 Recommendation).

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- to re-evaluate the finished product release and shelf-life acceptance limits for FPF and PLE after 30 batches have been manufactured using the commercial manufacturing process and 24 months of stability are available for the process validation and three additional commercial batches put into stability in Q1 2020.

2.3. Non-clinical aspects

2.3.1. Introduction

Nasal glucagon is classified as an antihypoglycaemic drug, glucagon receptor agonist. Glucagon is a polypeptide hormone, containing 29 amino acids. The physiologic effect of both endogenous and exogenously administered glucagon is to raise the concentration of blood glucose. Glucagon increases blood glucose concentration by activating hepatic glucagon receptors, thereby stimulating glycogen breakdown and release of glucose from the liver.

Glucagon has additional pharmacological effects. In the GI tract, it inhibits tone and motility of stomach, duodenum and small/large intestines. It increases bile flow, and decreases secretion of digestive enzymes. It also increases blood flow in the abdominal region.

Furthermore, glucagon induces the release of catecholamines (adrenal glands). It has a positive chronotropic and inotropic action. It slightly reduces the calcium serum levels, and induces the release of fatty acids.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Pharmacology studies were conducted to characterize Nasal Glucagon (NG). NG is a novel powder formulation, which contains the drug substance glucagon, and two excipients: dodecylphosphocholine (DPC, a novel excipient), and beta-cyclodextrin (β-CD, an approved excipient). NG is intended to be administered intra-nasally using a single-use nasal dosing device for the treatment of severe hypoglycemia.

The PD effects of glucagon are well known and the primary PD of NG was therefore limited to an in vivo study conducted in dogs and comparing the intranasal (IN)-administered drug to a commercialised subcutaneously (SC) injectable glucagon. This was done in the frame of a combined PK/PD study.

The objective of the study was to determine the effect of different dose levels of an intranasally administered powder glucagon formulation (AMG504-1) and injected glucagon on blood glucose and blood glucagon levels in beagle dogs. Two groups of six dogs were used in this study. At one site (ITR), dogs were dosed with glucagon by SC injection (1 mg) and crossed-over to intranasal treatment with a 0.5 mg dose of AMG504-1. At a second site, dogs were dosed intranasally with AMG504-1 at the 1 mg and 2 mg glucagon dose levels.

Data showed that the lowest dose of glucagon, 0.5 mg IN, only slightly increased the blood glucose level that did not exceed the upper normal range of 6mM. In contrast, 1 mg and 2 mg glucagon IN caused a clear glucose excursion with a peak at around 20 min after injection. The glucose response with 1 mg glucagon IN was somewhat smaller than with 1 mg SC. Though this study suggested comparable efficacy of NG as compared to commercially available sc formulation of glucagon, inconsistent values for Tonset of glucose excursion were reported. However, Tonset was calculated the same way for all these studies. It is explained by the variability of the animal responses observed in the 0.5 mg glucagon IN study. Indeed, in contrast to other studies in which all the animals responded to treatment, in the 0.5 mg glucagon IN study, some animals did not respond (i.e. blood glucose concentration did not cross the threshold which defines onset).

In addition, three animals (1 dog in the 1 mg IN group and 2 dogs in the 2mg IN group) were improperly dosed with the IN route. The device was not used properly in that it was pushed quite tightly against the medial or lateral nasal mucosa instead of being directed into the lumen of the nasal passage. The powder was therefore not freely expelled from the device and much of the dose remained plugged in the external aperture of the device. These dogs clearly did not receive the intended dose. The anatomy of the canine nasal cavity (small vestibule due to the presence of ventral and dorsal atrioturbinates) favours mechanical problems of administration. Considering the anatomical difference in human vs canine nasal cavity, it is unlikely that tight obstruction of the device opening occurs in humans.

Secondary pharmacodynamic studies

In view of the well-known PD profile of glucagon, no dedicated secondary pharmacology studies were performed with NG that is acceptable. Yet, off-target effects were investigated in the 28-day toxicity study in dogs.

Safety pharmacology programme

All the safety pharmacology studies were conducted in compliance with GLP.

The evaluation of the potential effects of nasal glucagon on the cardiovascular system was included in the 28-day repeat-dose toxicity study in dogs. The NOEL for NG on the cardiovascular system in dogs was 4 mg/dog.

In the 28-day repeat-dose toxicity, with the exception of transient salivation and some sneezing in most dogs immediately after intranasal dosing, there were no excipient- or nasal glucagon-related adverse clinical signs in respiratory or central nervous system function.

DPC, the novel excipient, was also assessed for potential adverse effects in the cardiovascular, respiratory and central nervous systems.

IV administration of 5 mg DPC (100x the clinical intended dose, based on body weight) to dogs did not show any adverse finding on the cardiovascular function but effects, albeit small, were noted on several cardiovascular parameters including a shortening of the QTc interval and a prolongation of the PQ interval as well as a mild, transient, and reversible increase in blood pressure that was highly variable and unexpectedly high around the time of administration in all groups. No specific reason for the small but consistent changes in CV parameters in response to the excipient DPC could be provided. Blood pressure increase was also noted in a small number of patients following Baqsimi administration (see clinical AR). It is not known whether this was due to pharmacological action of DPC or due to the administration procedure. The changes were small and transient and therefore are not considered a cause for concern.

Regarding the procedure-related BP increase in dogs, it is acknowledged that any handling can cause vegetative responses in the animals. It is expected that the relevance for humans of these findings is low because the product will not be used chronically.

IN administration of 30 mg DPC (60x the clinical intended dose, based on body weight) to dogs showed a mild increase in respiratory rate and minute volume. Furthermore, dogs showed a transient salivation, sneezing and clear frothy nasal discharge. A NOEL was not identified.

IN administration of 30 mg DPC (60x the clinical intended dose) to dogs did not show any neurological adverse effects. The NOEL was 30 mg/dog.

Pharmacodynamic drug interactions

No non-clinical pharmacodynamics drug interaction studies were conducted with NG. Absence of pharmacodynamic drug interaction studies is acceptable since glucagon is a well-established substance. It is not expected that the known potential interactions, which are systemic, differ between the IM and the intranasal preparation.

2.3.3. Pharmacokinetics

The pharmacokinetics (PK) and toxicokinetics (TK) of NG glucagon were evaluated following single-dose IN administration in dogs and repeat-dose administration in rats and dogs. For all studies, the

concentrations of immunoreactive glucagon were determined by validated radioimmunoassay (RIA) methods. The NG formulation also contains β-CD as a filler/bulking agent/absorption enhancer and DPC as an absorption enhancer/surfactant. The PK profile of the novel excipient DPC was determined in rats and dogs following IV and IN administration of DPC to support the DPC toxicology studies.

Following a single-dose IN administration of NG (from 0.5 to 2 mg) in dogs, Cmax and AUC of glucagon increased more than dose proportionally. Tmax was achieved in 10 minutes. T1/2 ranged from 15 to 57 minutes. The relative bioavailability of 1 mg IN-administered glucagon compared to SC administration was 15%.

Glucagon toxicokinetics was studied following once daily IN administration of NG in rats and dogs for 28 days. Glucagon did not accumulate neither in rats nor in dogs over the 28-day treatment period. No sex difference in glucagon exposure was observed, for both animal species. The NOEL for NG on the cardiovascular system in dogs was 4 mg/dog, which correspond to 1.28x (Day 1) and 2.25x (Day 28) multiple exposure based on C_{max} for a therapeutic dose of 3 mg. The data do not indicate any concern that would be clinically relevant for the intended clinical dose. Also, in the 28-day repeat-dose toxicity studies with NG, the NOAEL for systemic target organ toxicity in the rat and in the dog was considered to be 0.2 mg glucagon/day and 4 mg glucagon/day, respectively, corresponding to an exposure that is 10x and 68x, respectively, the human AUC following the planned 3-mg synthetic glucagon IN dose.

Additional data based upon NG distribution support the conclusions that NG does not enter the lung after IN administration of nasal glucagon.

The PK profile of the novel excipient DPC was studied in rats and dogs following a single IV or IN administration. DPC exposure increased with dose, almost proportionally for IN administration in both animal species. DPC bioavailability following IN administration was indeed found to be 38% in rats, and 59% in dogs. T1/2 was 4 hours in rats, and 19 hours in dogs.

- Nonclinical tissue distribution, metabolism and excretion studies were not conducted with nasal glucagon. Interpretation of distribution studies with radiolabeled biologics are confounded by in vivo metabolism, release of label from the peptide following degradation, and potential reincorporation of radiolabelled amino acids into the endogenous protein pool (ICH S6[R1].
- Glucagon is a peptide and presumed to be degraded into component amino acids by general catabolism pathways. Therefore, nonclinical metabolism studies were not performed (ICH S6[R1]).

Furthermore, no metabolism nor excretion studies have been performed with DPC. DPC is likely hydrolyzed by phospholipase D generating alkyl phosphates and choline, which are then further metabolized by phosphatase to produce the long carbon chain alcohol and inorganic phosphate similar to hexadecylphosphocholine. DPC is likely not excreted via the urine.

2.3.4. Toxicology

Single dose toxicity

Nasal glucagon is a single-use product indicated as rescue treatment for severe hypoglycaemia. The drug product is composed of synthetic glucagon and the excipients β-CD, and DPC. Glucagon has long been recognized for its wide safety margin. The systemic toxicity of glucagon has been well characterized for the marketed injectable glucagon products. Single-dose toxicity tests have not been conducted for NG, β-CD and DPC.

Repeat dose toxicity

The nasal glucagon toxicology program characterized not only the local effects of this glucagon drug product but also the systemic effects following nasal administration after repeated administration.

Since DPC is a novel excipient, a series of safety pharmacology, genetic toxicity, and reproduction studies were also conducted with this compound.

The toxicity of nasal glucagon (NG) was adequately evaluated in rats, dogs, and rabbits in a comprehensive battery of GLP compliant non-clinical studies at sufficient nasal surface area-based dose multiple and body weight-based dose multiple as compared to human. As mentioned in the above PK section, the Applicant is requested to further elaborate on exposure multiple by taking into account the systemic exposure data measured in the animal species as compared to the clinical exposure for the recommended therapeutic dose of NG.

The 28-day repeat-dose toxicity studies with nasal glucagon in rats and dogs were conducted by using the intranasal route of administration. These pivotal studies did not reveal any NG treatment-related adverse clinical signs and there was not systemic target organ toxicity at any dose tested in either species. The most important finding was a minimal to moderate degeneration of the olfactory epithelia (with/without subacute inflammation) in the nasal cavity in both animal species (0.2 mg/rat; 2 and 4 mg/dog) after daily IN dosing for 28 days. However, these lesions were reversible since they were no longer present following 14-day recovery.

This nasal finding was attributable to glucagon as the - Placebo Control consisting of DPC + β-CD did not adversely affect the nasal cavity and appeared cumulative since local nasal changes were limited to minimal inflammation, but no atrophy/degeneration of the olfactory epithelia in dog given a single dose of NG as compared animals treated daily dose for 28 days.

The NOAEL for target organ toxicity in the 28-day rat and dog studies was 0.2 mg/rat/day and 4 mg/dog/day, respectively

Considering the important differences in nasal cavity anatomy between the animal species and humans, together with the mild and reversible local irritation observed in the rat and in the dog, such nasal finding is not considered to a relevant safety issue for the clinic.

DPC given IN to dogs for 5 consecutive days at up to 10 mg/dog/day was well tolerated and did not cause any adverse clinical signs or gross pathological changes at necropsy. Histologically, minimal inflammation and mild accumulation of basophilic material was noted in the nasal cavity, but there was no evidence of atrophy/degeneration of the olfactory epithelia.

The excipients β-CD and DPC were also assessed as part of placebo-control powder in the 28-day IN toxicity studies and were both well tolerated in rats and dogs. Mild irritation was observed in dogs from the 28-day repeat dose study for β-CD. For DPC, no local irritation in the nasal cavity of rats was observed, while mild irritation was noticed in dogs from the 28-day repeat-dose studies.

The following specified individual degradation non-genotoxic impurities were assessed in 14-day toxicology qualification studies in rats: acetylated-glucagon, desamido-glucagons, oxidized methionine-glucagons [met(o)-glucagon], aspartimidyl (Asp 15)-glucagon, and Glucagon Isomer. No test item-related effects were noticed. Rats were exposed to greater cumulative doses of these impurities than patients with T1DM will receive, except for oxidized methionine-glucagon (0.914x).

Genotoxicity

Because nasal glucagon is a peptide, no genotoxicity studies were conducted with NG.

The genotoxic potential of DPC was assessed in the bacterial reverse mutation assay, the in vitro mammalian chromosome aberration assay, and the mammalian erythrocyte micronucleus assay. DPC doses of up to 3 mg/kg/day IV did not affect fertility and early embryonic development in rats (NOAEL: 3 mg/kg/day). In embryo-fetal development studies, no adverse fetal effects were seen with DPC at any dose level tested (up to 2.5 mg/kg/day IV in rats, up to 1 mg/kg/day IV in rabbits). DPC was determined to be not teratogenic in either species.

Carcinogenicity

Nasal glucagon is a single-use product indicated as rescue treatment for severe hypoglycemia. In view of the infrequent use no carcinogenicity studies were conducted in accordance with the ICH S1A guideline.

Reproduction Toxicity

Previous reproduction studies in rats and rabbits with glucagon (Glucagen) did not reveal any evidence of impaired fertility or embryo-fetal development. It was also shown not to cross the human placenta. As for β-CD, previous studies had revealed a transient neonatal growth retardation, but no permanent developmental defects had been found. Furthermore, there was no significant maternal toxicity. In view of the known safety profile of glucagon, no toxicity studies on reproduction were conducted with NG; that is acceptable.

No adverse effects on male or female reproduction or early embryonic development through to the F2 generation was noted in a pre- and post-natal study in rats at doses up to 1 mg/kg/day indicating DPC has no effect on F1 growth, behavior, and reproduction in rats. Compared to control animals, the duration of parturition was prolonged for F0 females at all the doses of DPC tested .The NOAEL for maternal toxicity, F1 growth, behavior, and reproduction was 1 mg/kg/day, which correspond to 3 multiple exposure based on $AUC_{0-\infty}$ of the therapeutic dose from 1 IV dose of DPC, and to 36 multiple exposure from 12 IV doses of DPC. The lack of correlative endpoints (no evidence of increased gestation length, no dystocia, and no decreased live birth index) indicates that the risk for prolongation of parturition due to DPC in pregnant patients with diabetes in the context of the intended clinical use of nasal glucagon is minimal.

Toxicokinetic data

Toxicokinetics of glucagon were evaluated in rats and dogs following daily IN administration of nasal glucagon for 28 days. Rats received at dose levels of 0.1 and 0.2 mg/day of glucagon as a solution into the nostrils of the rats. Dogs received daily doses of NG powder at dose levels of 2 and 4 mg/day of glucagon using the intended clinical single-use nasal dosing device.

There were no sex differences in glucagon exposure. Accumulation of glucagon was not observed following daily IN administrations of nasal glucagon for 28 days.

Local Tolerance

From the data of local tolerance, a single ocular instillation with 30 mg NG was shown to be well tolerated in rabbits. This led to a minimal ocular irritation, which was limited to a slight erythema and a localized edema to the conjunctiva and palpebral membrane.

Also, a single intratracheal insufflation of NG was well tolerated in rats.

In a distributional study of IN administered nasal glucagon together with a dye tracer in dogs, staining was present in the nasal passages, the nasopharynx, the stomach, the esophagus and the tongue, but there was no evidence of dye in the larynx or trachea indicating not distribution to the lung.

2.3.5. Ecotoxicity/environmental risk assessment

Nasal glucagon is a powder form of synthetic glucagon that is identical to the natural peptide. In line with the EMA guideline (EMEA/CHMP/SWP/4447/00 corr 2) the applicant provided the following justification for not submitting ERA studies:

"The synthetic polypeptide nasal glucagon is not expected to be released to the environment because polypeptides are not excreted intact from patients and are subject to extensive degradation in sewage treatment. Nasal glucagon is not expected to be persistent, bioaccumulative or toxic. Therefore, environmental studies were not conducted with nasal glucagon".

Nasal glucagon PEC surfacewater value is below the action limit of 0.01 µg/L. NG is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

Because the pharmacological properties of glucagon are well known, no primary pharmacology studies were conducted with NG in animal model of hypoglycaemia. The nonclinical pharmacology program was limited to the evaluation of glucose elevations after a single NG administration compared to subcutaneous (SC) injection of recombinant human glucagon in fasted beagle dog. In view of the comparable pharmacology it is agreed that no further PD studies are deemed necessary. However, it is to note that some dogs could not be successfully dosed with the nasal device because of mechanical problems; glucagon powder was administered in the nostril but obviously was not absorbed. The applicant explained that probably the powder was inadvertently sprayed directly against a small mucosa patch and did not reach larger mucosal areas the nasal cavity as intended. The anatomy of the canine nasal cavity (small vestibule due to the presence of ventral and dorstal atrioturbinates) favours mechanical problems of administration. Considering the anatomical difference in human vs canine nasal cavity, it is unlikely that tight obstruction of the device opening occurs in humans. Further information may come from post-marketing experience.

No secondary PD studies were conducted with NG; that is also acceptable.

The potential effects of nasal glucagon and its excipients on cardiovascular function were evaluated as part of the 28-day repeat-dose toxicity study in dogs. The potential for DPC to affect cardiovascular, respiratory, and central nervous system functioning was evaluated following a single IV (cardiovascular) and IN doses (CNS & respiratory). None of those studies raised concerns for alterations in cardiovascular, respiratory, or CNS function. At high doses of DPC increased BP, decreased HR, as well as shortening of QTc interval and PQ interval prolongation were noted. Though no specific reason for the small but consistent changes in CV parameters in response to the excipient DPC could be provided, the changes were small and transient and therefore not considered a cause for concern.

The PK and TK of glucagon have been appropriately evaluated after single-dose administration in dogs and repeat-dose administration of nasal glucagon by the IN route in rats and dogs. Concentrations of glucagon were determined by a validated RIA method. The pharmacokinetic PK profile of DPC was also appropriately determined in rats and dogs following IV and IN administration of DPC to support the DPC toxicology studies. The TK data demonstrate that there was rapid absorption and adequate exposure of glucagon observed in rats and dogs following IN administration for the toxicology studies. The DPC PK

data supplements the nasal glucagon toxicology studies indicating animals were systemically exposed to DPC following IV and IN administration of DPC in the Placebo Nasal Powder.

In agreement with regulatory recommendations and ICH M3(R2), the toxicology program for nasal glucagon (i.e., combination of synthetic glucagon, β-CD, and DPC) included 28-day repeated-dose toxicity studies in dog and rat, an intra-tracheal insufflation study in rats and an ocular tolerance study in rats. Intranasal administration of NG to rats and dogs for 28 consecutive days was well tolerated and there was no evidence of systemic target organ toxicity in rats or dogs after daily IN dosing with nasal glucagon for 28 days. The NOAELs were 0.2 mg synthetic glucagon/rat/day and 4 mg synthetic glucagon/dog/day respectively, corresponding to an exposure that is 10x and 68x, respectively, the human AUC following the planned 3-mg synthetic glucagon IN dose. In the repeat-dose toxicity studies only mild to moderate fully reversible histological changes to nasal mucosae was noted in both species. In addition, direct deposition into the lungs of rats did not result in adverse findings. Ocular instillation of NG was well tolerated.

Since β-CD has been used as a GRAS (Generally Recognized As Safe) food additive and pharmaceutical excipient, no stand-alone toxicology studies were conducted with β-CD. However, β-CD was evaluated in the 28-day intranasal (IN) toxicity studies in rats and dogs as part of the Placebo Control Powder along with the third ingredient, the novel excipient DPC.

For DPC that is a novel excipient, a series of safety pharmacology, genetic toxicity, and reproduction studies, was conducted to evaluate the safety profile in accordance with recommendations from various regulatory authorities and FDA's Nonclinical Studies For The Safety Evaluation Of Pharmaceutical Excipients (FDA 2005).

DPC given IN to dogs for 5 consecutive days at up to 10 mg/dog/day was well tolerated and did not cause any adverse effects. Histologically, there were minimal inflammation and mild accumulation of basophilic material but there was no evidence of atrophy/degeneration of the olfactory epithelia.

When administered by the iv route DPC did not adversely affect male or female reproductive performance or early embryonic development of rats, embryo-fetal development of rats and rabbits, maternal (F0) growth and reproduction or offspring (F1) growth, behaviour, and reproduction.

Compared to control animals, the duration of parturition was prolonged for F0 females at all the doses of DPC tested. The NOAEL for maternal toxicity, F1 growth, behaviour, and reproduction was 1 mg/kg/day, which correspond to 3 multiple exposure based on AUC0-∞ of the therapeutic dose from 1 IV dose of DPC, and to 36 multiple exposure from 12 IV doses of DPC. The lack of correlative endpoints (no evidence of increased gestation length, no dystocia, and no decreased live birth index) indicates that the risk for prolongation of parturition due to DPC in pregnant patients with diabetes in the context of the intended clinical use of nasal glucagon is minimal.

In line with the regulatory guidelines, no carcinogenicity or phototoxicity are warranted.

2.3.7. Conclusion on the non-clinical aspects

As glucagon is a well-known substance, an important aspect of the non-clinical programme is characterisation of the new excipient DPC which allows enhanced absorption through the nasal mucosa.

Overall, the safety pharmacology and toxicity studies of the nasal glucagon program did not reveal adverse issues in animals associated with nasal glucagon or DPC. From a non-clinical point of view, the non-clinical package is supportive for the proposed marketing authorisation application of Baqsimi.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study Identifier	Type of Study	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen	Number of Subjects or Patients Enrolled/ Completed	Healthy Subjects or Diagnosis of Patients
IGBD (AMG101)	PK and PD	NG versus marketed injectable glucagon product	Single-centre, randomized, open-label cross-over	NG: 0.5, 1, 2 mg SCG: 1 mg	16/13	Healthy adult subjects
IGBE (AMG104)	PK and PD	Evaluate effects of common cold and nasal decongestant on NG	Single-centre, open-label, parallel	NG: 3 mg NG: 3 mg with ND	36/35	Adult subjects with colds, but without diabetes
IGBA (AMG102)	PK and PD	NG versus marketed injectable glucagon product	Single-centre, randomized, open-label, crossover	NG: 1, 2, 3 mg SCG: 1 mg	18/18	Adult patients with T1D
IGBG (AMG112)	PK and PD	Single versus repeated administration of NG	Single-centre, randomized, repeated single-dose, open-label, crossover	NG: 3, 6 mg (repeated 3-mg dose)	32/25	Adult patients with T1D or T2D
IGBH (AMG110)	PK and PD	Single versus repeated administration of NG	Single-centre, randomized, repeated single-dose, open-label, crossover	NG: 3, 6 mg (repeated 3-mg dose)	12/0[a]	Adult patients with T1D or T2D
IGBC (AMG106)	Efficacy and Safety	NG versus marketed injectable glucagon product	Multicentre, randomized, open-label, crossover	NG: 3 mg IMG: 1 mg	83/82	Adult patients with T1D or T2D
IGBI	Efficacy and Safety	NG versus marketed injectable glucagon product	Multicentre, randomized, open-label, crossover	NG: 3 mg IMG: 1 mg	70/69	Adult patients with T1D
IGBB (AMG103)	PK and PD Efficacy and Safety	NG versus marketed injectable glucagon product	Multicentre, randomized, crossover	NG: 2, 3 mg IMG: 0.5, 1 mg (weight-based)	48/47	Paediatric patients with T1D
IGBF (AMG105)	Safety	NG versus marketed injectable glucagon product (immunogenicity)	Single-centre, randomized, open-label, parallel	NG: 3 mg IMG: 1 mg	75/73	Adult patients with T1D or T2D
B002	Uncontrolled	Effectiveness of NG	Multicentre,	NG: 3 mg	129/101	Adult

(AMG108)	Clinical Study	in real-world setting	open-label, prospective, actual-use			patients with T1D
B001 (AMG109)	Uncontrolled Clinical Study	Effectiveness of NG in real-world setting	Multicentre, open-label, prospective, actual-use	NG: 3 mg	26/12	Paediatric patients with T1D

Abbreviations: IMG = intramuscular glucagon; ND = nasal decongestant; NG = nasal glucagon; PK = pharmacokinetic; PD = pharmacodynamic; SCG = subcutaneous glucagon; T1D = type 1 diabetes mellitus; T2D = type 2 diabetes mellitus.

[a] Study IGBH was terminated early due to potential sub-target dosing and was repeated under a new trial alias, Study IGBG.

2.4.2. Pharmacokinetics

Over the course of the clinical development, samples were analysed for glucagon using 3 different methods: initially an enzyme-linked immunosorbent assay (ELISA) was used to support studies IGBA and IGBD, next a radioimmunoassay (RIA) format for studies IGBG, IGBB, IGBC and IGBE; and finally a liquid chromatography with tandem mass spectrometry (LC-MS/MS) assay for study IGBI. These assays measured both endogenous and exogenous glucagon. Although the commercial RIA kit was not fully validated according to applicable guidance, comparable results for IM glucagon within all PK analyses indicate comparable results in relation to the GLP-compliant analysis.

A routine GCP inspection of paediatric study IGBB was performed in December 2018 and January 2019. According to the integrated inspection report (GCP/2018/027), dated 22/03/2019, several critical findings were detected in relation to source data and sample management, such as missing instruction on the creation of source data and incorrect handling of PK samples . Due to these findings, only the PD data from this paediatric study are considered reliable and acceptable to be used for MAA. The pivotal adult study IGBC was conducted in parallel to the inspected trial. Since data handling was similar, the inspection team recommended to consider only the PD data for MAA from the adult IGBC trial.

The CHMP received on 12 April 2019 a letter from one of the investigator sites inspected as part of the routine GCP inspection (hereinafter referred to as "third party") in which a number of concerns were discussed with regards to the conclusions of the site inspection . This letter was considered during the assessment and had no impact on the outcome of the application.

In addition, a triggered GCP inspection (INS/GCP/2019/008) of study I8R-MC-IGBI was requested (inspection adopted by the CHMP on 28 March 2019) at the two investigator sites in Germany; the conclusion of this inspection was that overall trial I8R-MC-IGBI was conducted in accordance with international accepted standards and GCP requirements and that the reported data are valid and reliable.

Absorption

PK comparison between NG and injectable glucagon in adults

The first two studies in men, **studies IGBD and IGBA**, compared the PK of different doses of NG (0.5, 1, 2 and 3 mg) to 1 mg subcutaneous glucagon (SCG) in a cross-over way. Study IGBD was conducted in 16 healthy subjects and study IGBA in 18 patients with type 1 diabetes (T1D). In study IGBD, no substantial levels of glucagon were detected in all subjects of the 0.5 mg NG dose group. For 7 subjects treated with 1 mg NG and 15 subjects treated with 2 mg NG, serum glucagon concentrations increased from baseline. In study IGBA, no substantial levels of glucagon were detected in 7 out of 12 patients in the 1 mg NG dose group and in 4 out of 18 patients in the 2 mg NG group. After dosing with 3 mg NG (n = 8) or 1 mg SCG

(n = 18) however, all patients had detectable levels of glucagon. It is important to note that the mean serum glucagon levels exclude patients with no detectable levels of glucagon post-dosing. Quantitative comparison of the results for 2 mg and 3 mg NG from study IGBA is hampered by the small number of subjects (3 mg) and the high LLOQ resulting in exclusion of "nonresponders" and a respective bias (2 mg).

Across studies, the Cmax and the AUC0-t for the NG dose groups were lower than the Cmax and AUC_{0-t} observed with 1 mg SCG (see figures), however, Tmax values were similar (15 to 20 minutes). In study IGBA, absorption appears to be delayed with nasal administration.

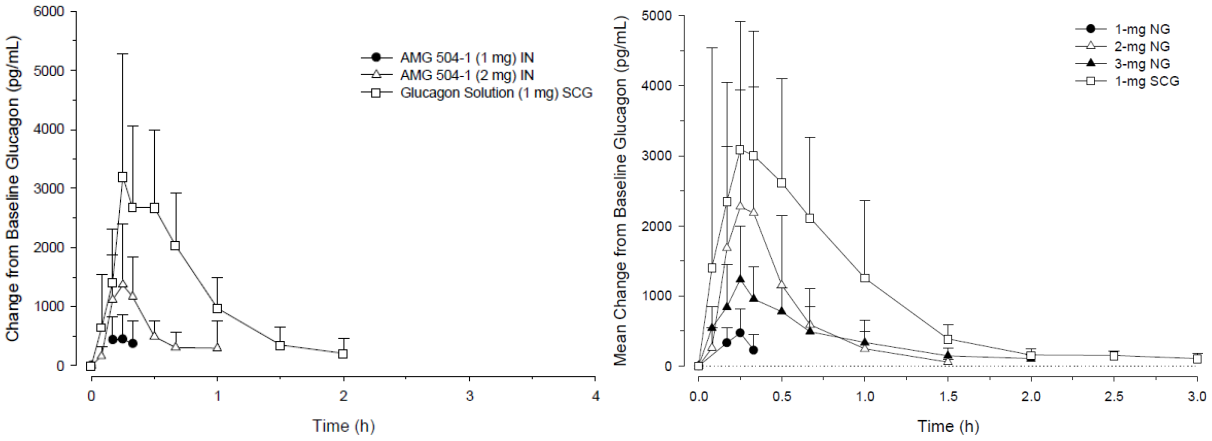
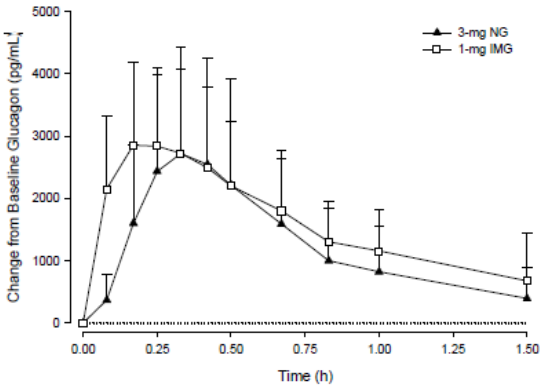


Figure 2. Mean (+SD) glucagon concentration over time (left: IGBD, right: IGBA)

The pivotal adult **study IGBC** was a randomized, 2-way crossover study in 83 adult patients (77 with T1D, 6 with T2D) that assessed the PK and PD after administration of 3 mg NG compared to 1 mg intramuscular glucagon (IMG) for the treatment of insulin-induced hypoglycaemia. A wash-out of at least 7 days was inserted between drug administrations. Similar to studies IGBD and IGBA, Cmax and the AUC0-t were lower in the NG group compared to the injectable glucagon, whereas median Tmax values were comparable (0.33h versus 0.25h). Absorption appears to be delayed with nasal administration . As stated above, PK data obtained in this study cannot be relied upon due to critical GCP findings.It is also to be noted that study IGBC was performed with the clinical trial drug product and, as shown below, different pharmacokinetic behaviour has been observed in comparison with the commercial drug formulation (studies IGBI and IGBJ). However, as only the PD response is relevant for the desired action of Baqsimi, PK data are considered to be supportive to the B/R discussion. The high variability observed for the PK parameters throughout the different studies is considered to be of less relevance as this does not impact the efficacy and safety profile for Baqsimi.

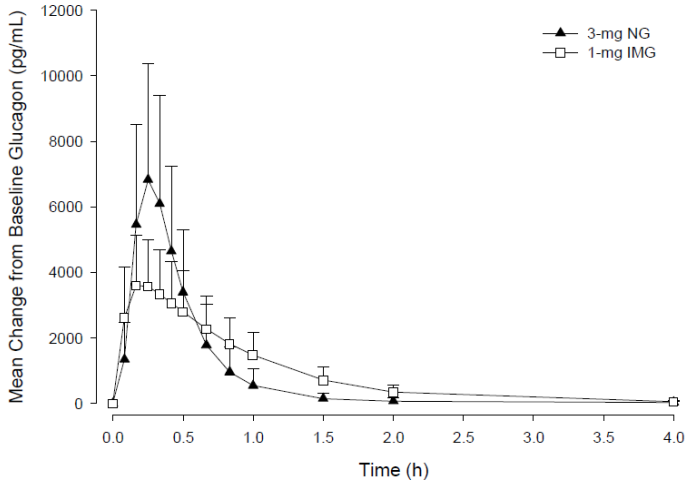


Abbreviations: IMG = intramuscular glucagon (control); NG = nasal glucagon; SD = standard deviation; T1D = type 1 diabetes; T2D = type 2 diabetes.

Figure 3. Mean (+SD) glucagon concentration over time (IGBC)

Study IGBI was designed as a clinical bridging and confirmatory study and assessed the efficacy, safety, PK, and PD of NG 3 mg (commercial drug product) in adult patients with T1DM. This study mimicked the design of study IGBC and aimed to compare indirectly clinical trial and commercial drug product.

In total, 70 adult T1D patients received a single dose of 3 mg NG and 1 mg IMG in a cross-over way. AUC0-t was lower with the nasal route of administration, whereas median Tmax values were the same (0.25h). The Cmax observed in study IGBI (7220 pg/ml) was higher compared to study IGBC (3130 pg/ml). Furthermore, the Cmax in study IGBI was higher relative to 1 mg IMG, which is contradictory to the results of study IGBC.



Abbreviations: IMG = intramuscular glucagon; NG = nasal glucagon; SD = standard deviation.

Figure 4. Mean (+SD) glucagon concentration over time (IGBI)

Study IGBJ is a Phase 3 study in Japanese adult patients, including patients ≥65 years, with type 1 diabetes (T1D) and type 2 diabetes (T2D) and has a similar design as studies IGBC and IGBI. IGBJ was conducted to support registration of NG 3 mg as a treatment for severe hypoglycemia in Japan, and was ongoing at the time of the initial MAA. A total of 69 Japanese patients with T1DM (32 patients) or T2DM (37 patients), received a single dose of both treatments, 3 mg NG and 1 mg IMG, in a cross-over way. Very high Cmax concentrations (mean of 11400 pg/ml) were obtained with 3 mg NG. A separate PK analysis of the 12 patients aged between 65-74 years was performed and gave no evidence for a prominently deviating PK of NG in elderly patients.

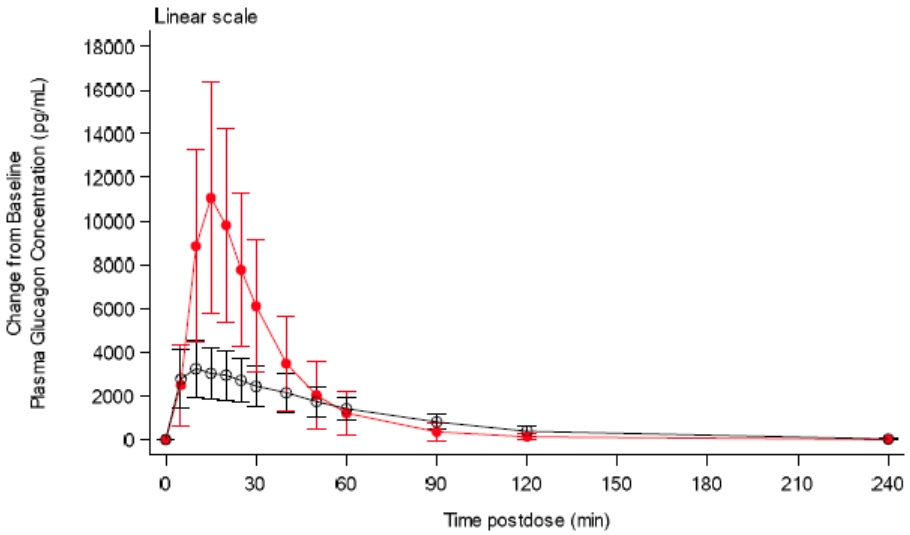


Figure 5. Mean (+SD) glucagon concentration over time (IGBJ)

PK comparison between NG and injectable glucagon in paediatrics

One pivotal study (**IGBB**) was conducted to compare the PK and PD response of NG with IMG in a controlled clinical setting in paediatric patients. The study included 3 cohorts: 4 to <8, 8 to <12, and 12 to <17 years of age. A washout of at least 7 days separated dosing occasions. During each study visit, fasted patients' blood glucose was reduced to <80 mg/dL (<4.4 mmol/L) using insulin. Peak glucagon concentrations were in general higher in the IM-dosing groups, except for the 3 mg NG dosing group in the 8- to <12-year-old.

As stated above, PK data obtained in this study cannot be relied upon due to critical GCP findings. In addition and as already mentioned above, glucagon plasma concentrations were markedly lower in this study (and also in study IGBC) due to differences in drug product. In conclusion, PK data from study IGBB are not relevant for the final Baqsimi preparation. Therefore, there are no reliable NG PK data in the pediatric population at this stage. As shown by adult NG and IV PK data, wide differences in glucagon Cmax and AUC exist, however, the observed glucose response was essentially the same. Therefore, at doses achieving saturation of the glucose response, glucagon PK data per se are less important and should be considered as supportive information.

Repeated administration of NG

In study **IGBG**, two NG doses of 3 mg administered within a 15 minute interval or less than 1 minute apart were less than dose-proportional to a single 3 mg NG dose in terms of AUC and Cmax. Since a single 3 mg NG dose is proposed for the emergency treatment of severe hypoglycaemia in adult and paediatric diabetes patients, a lack of dose-proportionality is not an issue for this application.

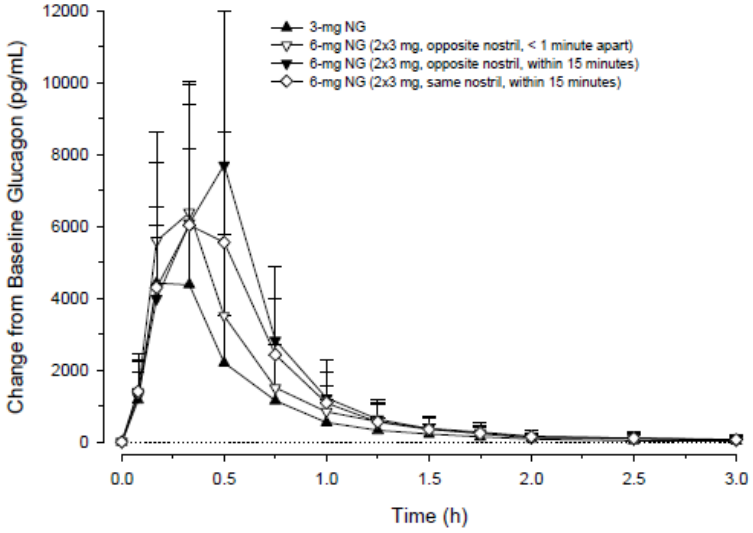


Figure 6. Mean (+SD) glucagon concentration over time (IGBG)

Impact of nasal decongestion

Study **IGBE** was a single-center, open-label, 2-period, parallel study that assessed the impact of nasal decongestant (oxymetazoline) and common cold on 3 mg NG PK and PD in 36 otherwise healthy adults.

Subject Cohorts	Period 1	Period 2
Cohort 1 Subjects #001 to 018	Test / Common cold	Test / No cold symptom
Cohort 2 Subjects #019 to 036	Test + Decongestant / Common cold	

Glucagon exposure of NG 3 mg + Common Cold' was greater than that of the other 2 treatment groups, with numerically higher AUC(0-t) and C_{max}. However, none of these differences reached statistical significance.

Across-study comparison

The essential PK-parameters generated with 1 mg glucagon SC or IM and 3 mg NG are merged in the following tables.

PK results with 1 mg SCG or IMG

	Change from Baseline Glucagon (PK) Parameters		
Study ID (NPK)	C_{max}[a] (pg/mL)	AUC(0-t_{last})[a] (pg.h/mL)	T_{max}[a] (hours)
Pivotal Studies			
I8R-MC-IGBC T1DM (75)	3550 [49]	2520 [39]	0.25 (0.08, 1.00)
T1DM+T2DM (80)	3500 [49]	2510 [40]	0.25 (0.08, 1.00)
I8R-MC-IGBB 4 to <8 y (6; 2 subjects with weight based dose 0.5 mg IMG)	6290 [33]	4080 [51]	0.29 (0.08, 0.50)
8 to <12 y (6)	4740 [65]	3640 [57]	0.29 (0.08, 0.50)
12 to <17 y (12)	4280 [88]	3110 [92]	0.29 (0.08, 0.50)
Clinical Bridging and Confirmatory Study			
I8R-MC-IGBI (65)	4070 [40]	3550 [37]	0.25 (0.08, 0.50)
Supportive Studies			
I8R-MC-IGBD (15)	3720 [54]	2420 [54]	0.33 (0.11, 0.67)
I8R-MC-IGBA (18)	3930 [68]	2390 [57]	0.33 (0.08, 0.67)
Study in Japanese subjects (data received after day120)			
I8R-JE-IGBJ (68)	3510 [38]	3390 [30]	0.17 (0.08, 0.67)

[a] Arithmetic mean [% coefficient of variation] is presented for Cmax and AUC(0-tlast). Median (minimum, maximum) is presented for Tmax. NPK = number of subjects in the PK analysis

Results with 1 mg IMG are consistent and the only deviations (increased PK-values in study IGBB) are easily explained by the study design (children with lower body weight).

PK results with 3 mg NG

	Change from Baseline Glucagon (PK) Parameters		
Study ID (NPK)	C_{max}[a] (pg/mL)	AUC(0-t_{last})[a] (pg.h/mL)	T_{max}[a] (hours)
Pivotal Studies			
I8R-MC-IGBC T1DM (75)	3030 [66]	1880 [65]	0.33 (0.17, 1.50)
T1DM+T2DM (80)	3130 [63]	1940 [65]	0.33 (0.17, 1.50)
I8R-MC-IGBB 4 to <8 y (12)	3960 [62]	2470 [58]	0.29 (0.17, 1.00)
8 to <12 y (11)	5660 [37]	2940 [35]	0.25 (0.17, 0.50)
12 to <17 y (12)	3100 [74]	2000 [66]	0.33 (0.25, 0.50)
Clinical Bridging and Confirmatory Study			
I8R-MC-IGBI (63)	7220 [49]	3200 [50]	0.25 (0.17, 0.50)
Supportive Studies			
I8R-MC-IGBA (8)	1360 [53]	720 [54]	0.29 (0.17, 0.50)
I8R-MC-IGBE Cold (18)	1150 [87]	1040 [98]	0.3 (0.08, 1.50)
Cold+Decongestant (18)	812 [74]	868 [72]	0.3 (0.17, 1.00)
No Cold (17)	746 [74]	632 [63]	0.3 (0.25, 0.67)
I8R-MC-IGBG (27)	4960 [75]	2470 [75]	0.17 (0.17, 0.75)
Study in Japanese subjects (data received after day120)			
I8R-JE-IGBJ (71)	11400 [45]	5600 [41]	0.25 (0.17, 0.67)

[a] Arithmetic mean [% coefficient of variation] is presented for C_{max} and AUC(0-t_{last}). Median (minimum, maximum) is presented for T_{max}. NPK = number of subjects in the PK analysis

PK-results with NG are much more heterogeneous. This might only partly be explained by the small number of subjects (study IGBA) and the higher variability (% CV) observed with NG due to a variable degree of absorption through the nasal mucosa. PK results with 3 mg NG can be grouped in early studies, pivotal studies and studies with the commercial formulation. Lower glucagon exposure mainly appeared in early clinical studies. In the pivotal studies IGBC and IGBB (12 to > 17 years) values for Cmax of ~ 3000 pg / ml and AUC of ~ 2000 pg * h / ml were found. The highest Cmax values were observed with the commercial formulation. In study IGBI, Cmax was doubled compared to study IGBC with Cmax of ~ 7000 pg / ml and AUC moderately increased to ~ 3200 pg * h / ml. Even higher Cmax values (almost 4x Cmax of IGBC) were obtained in study IGBJ.

As a result of the markedly increased Cmax observed with the commercial formulation, administration of this formulation in young children (4 to 12 year old patients), who were tested in the pivotal paediatric study IGBB with the older version of Baqsimi powder only, may lead to extraordinary high plasma concentrations for glucagon. Therefore, it was concluded that the risk associated with these findings renders the B/R of NG 3 mg in patients from 4 to 12 years negative. As requested, the applicant addressed potential safety concerns of high glucagon plasma levels based on results from non-clinical and clinical studies and based on mechanistic considerations. The applicant's view is agreed that none of the analyses performed gave a hint for any unfavourable effect of transiently high plasma levels of glucagon. Existing data indicate that 3 mg nasal glucagon fully occupies the glucagon receptors for a short period of time (see 3.3.2. PD) and that any excess glucagon has no biological effects (maybe except for GLP-1 receptor stimulation; it may cause additional nausea). Therefore, although it is expected that the Cmax in children will exceed the level needed to compensate for variability and needed for rapid onset of action by far, the use of the adult dose in children is not expected to cause any harm and could therefore be accepted. Due to the incorrect sample handling in studies IGBB and IGBC and also taken into account the markedly lower exposure towards glucagon noted in this study in comparison with the results from study IGBI and IGBJ, it is concluded that the PK data from studies IGBB and IGBC should not be taken into account for this MAA. This is acceptable as only the PD response is relevant for the desired action of Baqsimi and, as described above, the high concentrations would not negatively influence the safety of Baqsimi in the pediatric population.

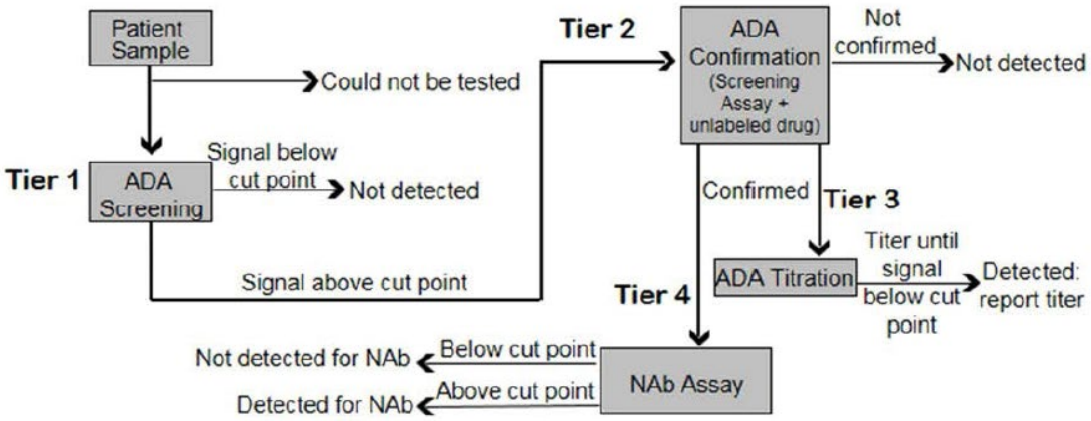
The Applicant was also asked to explore possible explanations for the drift of NG PK-values observed during the drug development program (early/pivotal/confirmatory studies), however, no convincing explanation could be provided. The issue is not further pursued.

Furthermore, a comparison of the delay in administration of IM to the delay in absorption of NG was requested since in most studies a delay in absorption between intranasal and intramuscular glucagon was observed. With the submission of new data from study IGBJ, it seems that a delay in absorption is mainly observed with the older formulation, which is reflected in the time course of the PD response (delay of relevant blood glucose increase of max. 1,5 minutes with the commercial formulation compared to 4 min. with the older formulation, see 3.3.2 PD.)

In conclusion, the issue of incorrect handling of the PK samples is not considered insurmountable as PK data are considered to be only supportive to the B/R discussion , but not critical for the current application.

Determination and characterization of anti-drug antibodies

Patient samples were analysed using a standard 4-tiered approach (see the figure below). All the clinical study samples were assessed in Tier 1 (screening) for possible presence of ADA. Samples testing positive are subsequently confirmed (tier 2) and further titrated (tier 3) and tested for neutralizing capacity (tier 4).



Abbreviations: ADA = antidrug antibody; NAb = neutralizing antibody.

Figure 7: Immunogenicity sample testing paradigm

A treatment-emergent (TE) ADA-positive patient was defined as follows: If baseline result is 'ADA Detected', there should be at least 1 postbaseline titer that is a 4-fold or greater increase in titer from baseline measurement (treatment-boosted). If baseline result is 'ADA Not Detected', there should be at least 1 post-baseline ADA 'Detected' sample with a corresponding titer that is one 2-fold dilution higher than the minimum required dilution (treatment induced). However, for patients with baseline results 'ADA not detected', it is expected that putative ADA positive samples, further confirmed positive and showing a titer equal to the minimum required dilution (MRD) at one or several postbaseline time points are considered in the integrated analysis of the clinical significance of immunogenicity. Further discussion was therefore provided by the Applicant with regard to four patients showing a temporal profile in ADA titer (see end of this section below and discussion on safety).

A validated affinity capture elution (ACE) ligand-binding immunogenicity assay was used to screen, confirm, and titer ADA to NG in patient samples from clinical studies. The neutralizing potential was determined using a less sensitive validated cell based neutralizing ADA (NAb) assay that mimics the *in vivo* mechanism of action of NG.

During sample analysis of the clinical studies IGBF, IGBG, and B002, the three studies investigating the immunogenicity potential of NG, putative positive rates (after Tier 1) were higher than predicted by validation studies in treatment-naïve (baseline) samples (34.7% vs. 18.8%); however, no statistically significant difference was observed between T1D and T2D nor between clinical studies. This difference most likely resulted from a pre-analytical difference between Locemia Solutions ULC (Locemia)-collected and Lilly-derived clinical trial samples. Therefore, it was concluded to establish an in-study cut point for the Tier 1 screening assay. Based on this consistent difference in baseline sample reactivity, it was decided to also re-evaluate the confirmatory (Tier 2), titration (Tier 3), and neutralizing (Tier 4) assay cut points specific for clinical samples collected during Locemia-run trials in a similar fashion. Cut points were updated and applied for sample analysis. The *in silico* sensitivity and *in silico* drug tolerance based on the updated cut points were redetermined. With regard to the antibody assays, further clarifications have been given by the Applicant to support the use of the in-study screening cut point and the performance of the low positive control used for clinical study sample analysis. Missing validation reports and bioanalytical reports were provided. No long-term stability data have been provided by the Applicant. But the results of additional immunogenicity samples without long sample storage from the study IGBJ submitted with the responses to the D120 LoQ and being in line with previous results (i.e. showing a low ADA incidence) as well as the current literature bring further guarantee on the reliability of the previous results. No unresolved issues are remaining regarding the methods used for the detection of ADAs/Nabs.

Distribution

The apparent volume of distribution, based on observed glucagon concentrations (i.e. not baseline-corrected) was determined in study IGBI to be approximately 885 l (geometric mean) following a 3 mg NG administration.

Elimination

After nasal administration and absorption into the circulation, glucagon elimination is expected to be the same as that of injectable glucagon. With the injectable route of administration, studies have shown that glucagon degrades in the liver, kidney, and plasma. Urinary excretion of intact glucagon has not been measured.

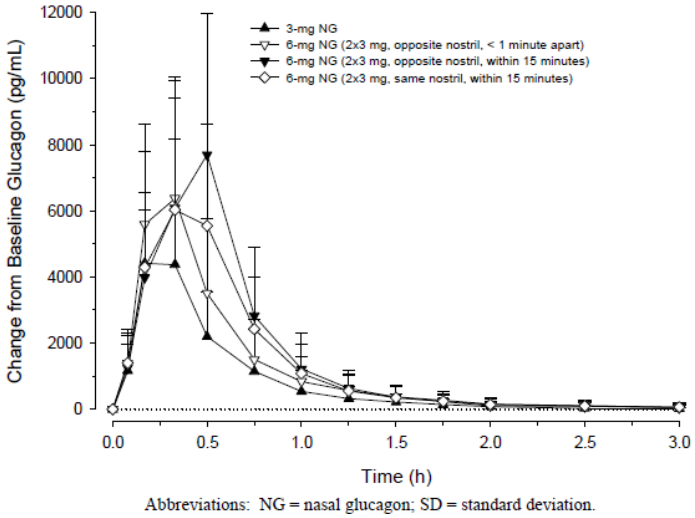
Half-life was short across studies. In study IGBI, the (geometric) mean half-life of glucagon was comparable after nasal and intramuscular administration with values of 0.625 h and 0.634h, respectively.

Dose proportionality and time dependencies

Study IGBG evaluated the effects on the PK and PD of repeating a NG 3 mg dose in adults with T1D or T2D. The study was designed as a single-center, randomized, 4-period, 4-sequence, open-label crossover study.
Thirty-two patients were assigned to a sequence consisting of 4 NG treatments in different order, separated by a wash-out of at least 7 days. After an 8-hour overnight fast and 4 hours after the start of a low-carbohydrate breakfast, the following treatments were administered: 1) a single 3 mg dose; 2) two 3 mg doses, the second of which was administered in the same nostril 15 minutes after the first; 3) two 3 mg doses, the second of which was administered in the other nostril 15 minutes after the first; and 4) two 3 mg doses, the second of which was administered in the other nostril ≤1 minute after the first. Blood samples were collected to measure baseline glucagon and glucose levels at 30, 15, and ≤5 minutes (time 0) before dosing, and further samples were collected 5, 10, 20, 30, 45, 60, 75, 90, 105, 120, 150, and 180 minutes after the first dosing of each treatment.

While NG 6 mg (repeated 3 mg dose) resulted in significantly higher glucagon exposure than a single 3 mg dose, this was not dose-proportional: Cmax of NG 6 mg in all dose configurations (6650 to 8080 pg/mL) was less than 2-fold the Cmax of a single 3 mg dose (4960 pg/mL). Tmax of NG 6 mg doses ranged from 0.33 to 0.50 hours compared with 0.17 hours for NG 3 mg.

Among the double-dose treatment groups, Treatment 3 (two glucagon administrations in the opposite nostril within a 15- minute interval) was associated with slightly higher exposure.



Abbreviations: NG = nasal glucagon; SD = standard deviation.

Figure 8. Mean (+ SD) glucagon over time by treatment group, change from baseline – Study IGBG.

Table 1. Summary of PK parameters – study IGBG

	Change from Baseline Glucagon (PK) Parameters		
Treatment (N_{PK}/N_{PD})	C_{max}[a] (pg/mL)	AUC(0-t_{last})[a] (pg.h/mL)	T_{max}[a] (hours)
3 mg NG (27/27)	4960 [75]	2470 [75]	0.17 (0.17, 0.75)
6 mg NG (2x3 mg same nostril, 15 minutes apart) (28/28)	7140 [46]	4100 [43]	0.33 (0.17, 0.50)
6 mg NG (2x3 mg opposite nostril, 15 minutes apart) (28/25)	8080 [52]	4640 [52]	0.50 (0.17, 0.50)
6 mg NG (2x3 mg opposite nostril, <1 minute later) (29/29)	6650 [55]	3610 [52]	0.33 (0.17, 0.33)

[a] Arithmetic mean [coefficient of variation] is presented for C_{max}, BG_{max}, ΔBG_{max}, and AUC(0-t_{last}). Median (minimum, maximum) is presented for T_{max} and T_{BGmax}.

In summary, two NG doses of 3 mg administered within a 15 minute interval or less than 1 minute apart were less than dose-proportional to a single 3 mg NG dose in terms of AUC and Cmax. A lack of dose-proportionality was also observed in studies IGBD (1 and 2 mg NG) and IGBA (1, 2 and 3 mg NG) with a more than dose-proportional increase in exposure between 1 and 2 mg and a similar exposure for the 2 and 3 mg NG dose levels.

Since a single 3 mg NG dose is proposed for the emergency treatment of severe hypoglycaemia in adult and paediatric diabetes patients, a lack of dose-proportionality is not an issue for this application.

Special populations

No individual studies of special populations (such as patients with renal or hepatic impairment) were conducted during the NG program, given the extensive previous clinical experience with glucagon and because NG is being developed as a rescue treatment for severe hypoglycemia.

However, the NG clinical program evaluated the impact of age (pediatric and adult) on PK of nasal glucagon, and no impact was observed.

Pharmacokinetic interaction studies

Common drug-drug interaction studies were not conducted. This is acceptable in view of the short half-life and the intended occasional use.

2.4.3. Pharmacodynamics

Mechanism of action

Glucagon increases blood glucose concentration by activating hepatic glucagon receptors, thereby stimulating glycogen breakdown and release of glucose from the liver. Hepatic stores of glycogen are necessary for glucagon to produce an anti-hypoglycaemic effect.

Primary and Secondary pharmacology

The clinical pharmacology program for NG consisted of 7 clinical studies providing PK and PD data, including the pivotal adult study I8R-MC-IGBC (IGBC), and the clinical bridging and confirmatory study I8R-MC-IGBI (IGBI) (Table 1). As part of the responses to day 120 questions, the Applicant included the results of a new study in adult Japanese subjects (IGBJ), which was ongoing at the time of the initial MAA.

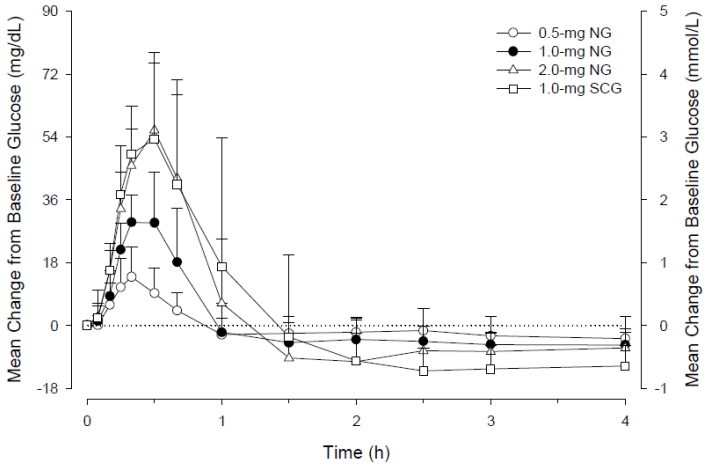
Table 2 Index of Clinical Studies of Nasal Glucagon with PK and PD Results

Brief Description of Study	Trial Alias
Dose Selection Studies	
Single dose (0.5, 1, 2 mg NG; 1 mg SCG) in healthy adult subjects	IGBD
Single dose (1, 2, 3 mg NG; 1 mg SCG) in adult T1D	IGBA
Single (3 mg NG) and double dose (6 mg NG) in adult T1D and T2D	IGBG
Single dose (2, 3 mg NG; 0.5/1 mg IMG) in pediatric T1D	IGBB
Dose Confirmation Studies	
Single dose (3 mg NG; 1 mg IMG) in adult T1D and T2D	IGBC
Single dose (3 mg NG; 1 mg IMG) clinical bridging and confirmatory study in adult T1D	IGBI
Supportive Studies Providing Other PK/PD Information	
Single dose (3 mg NG) in otherwise healthy adult subjects with common cold symptoms	IGBE

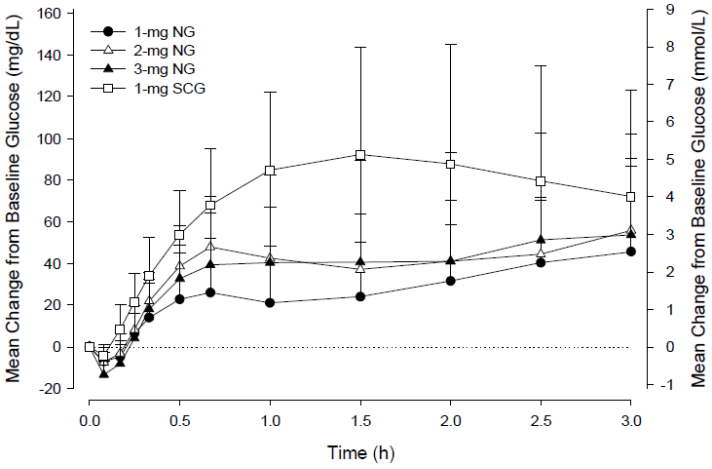
Abbreviations: IMG = intramuscular glucagon; NG = nasal glucagon; PD = pharmacodynamic; PK = pharmacokinetic; SCG = subcutaneous glucagon; T1D = type 1 diabetes; T2D = type 2 diabetes.

Study IGBD (healthy subjects) and study IGBA (T1D patients)

Mean (+SD) concentrations of glucose, change from baseline (n = 14 - 16) (IGBD)



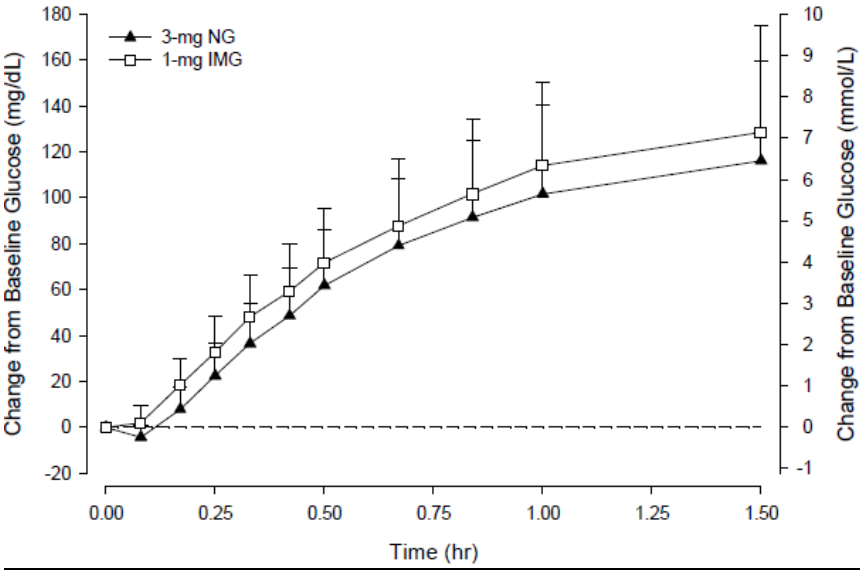
Mean (+SD) concentrations of glucose, change from baseline (IGBA)



Though PK glucagon parameters with 2 mg NG was much smaller compared with SCG, the glucose response was similar in study IGBD. This is in contrast to study IGBA (n=9 for. 1 mg NG, n=8 for. 3 mg NG). Sustained increase of glucose levels seen in study IGBA is expected with T1DM patients.

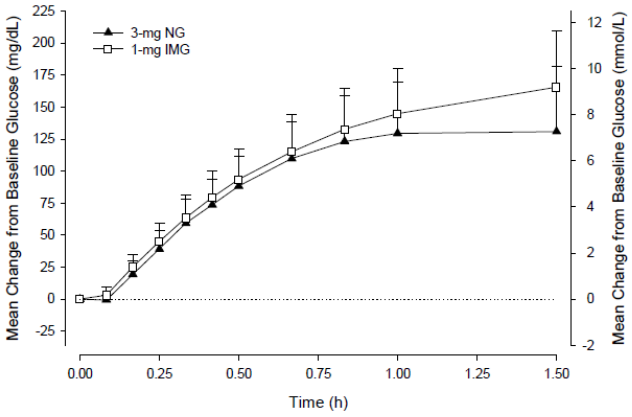
Study IGBC (pivotal study, T1DM and T2DM; n was 75 – 76 and 5 – 6 respectively)

Mean (+SD) change in glucose concentration over time in the combined primary analysis cohort (IGBC)

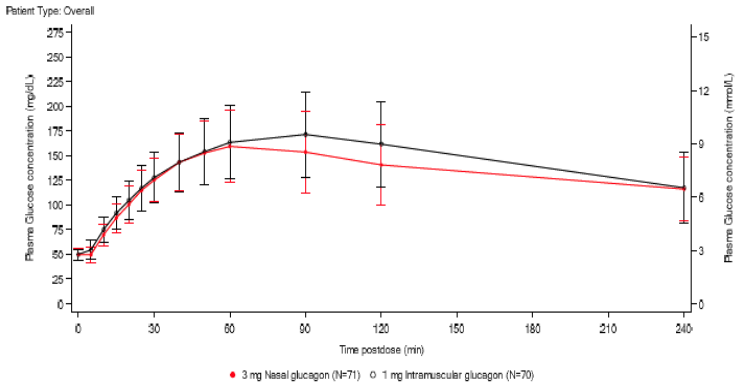


Study IGBI (T1D) and Study IGBJ (T1D and T2D), both commercial formulation

Mean (+SD) change in glucose concentration over time (IGBI)



Mean (+SD) change in glucose concentration over time (IGBJ)



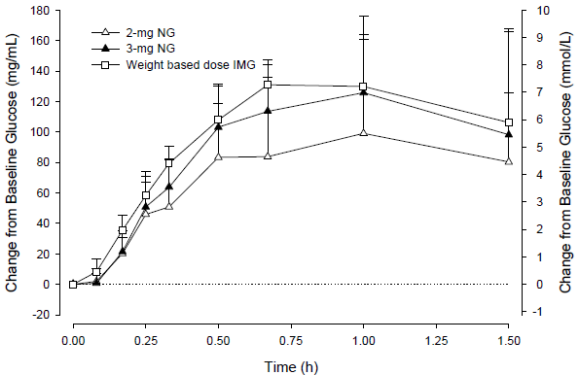
PD data indicate that glucagon receptors are virtually fully occupied after 3 mg NG because the PD response was the same as with injected glucagon despite much lower plasma levels were reached with the latter.

With the commercial product, the time course of blood glucose level is virtually superimposable for injected and nasal glucagon within around the first 40 min. Thereafter, blood glucose decreases somewhat faster with nasal than with injected glucagon, but this is not a concern. In particular, nearly no temporal delay of blood glucose increase (less than 2 min according to the figures) was observed. This is highly desirable but comes at the cost of high Cmax (see 3.3.1 PK). For comparison, lag was around 5 min in the older adult study IGBC and the glucose levels were lower; the same is true for children aged 12 years or above (Study IGBB; for younger children the picture is less clear), see figures below.

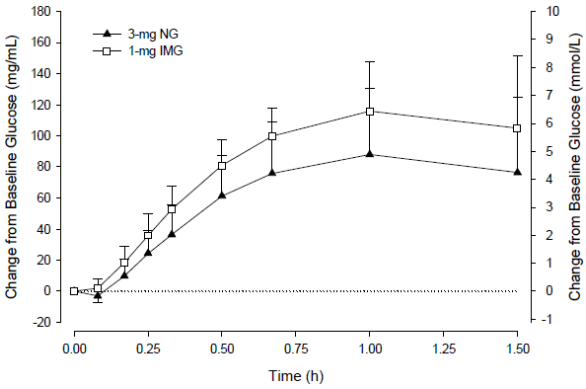
Study IGBB (paediatric patients with T1D)

Mean (+SD) glucose concentration over time, change from baseline

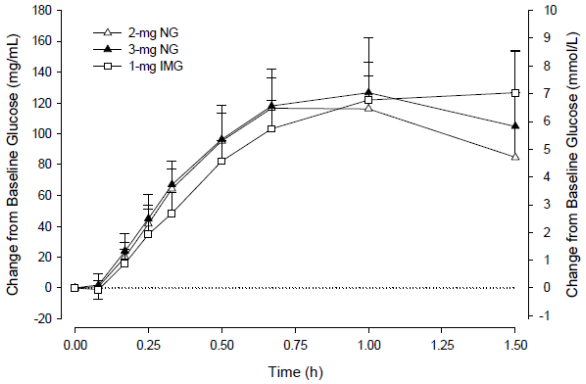
4- to <8-year-old group



12 to <17-year-old group



8- to <12-year-old group



Study IGBG (T1DM and T2DM; n was 17 – 20 and 8 – 9 respectively)

Increase of glucagon plasma concentration by increasing NG dose from 3 mg to 6 mg has almost no consequence for glucose response.

Study IGBE (Common Cold and Concomitant Administration of Nasal Decongestant on the PK and PD of NG in Otherwise Healthy Subjects)

As it was the case for PK common cold and concomitant administration of nasal decongestant has limited impact on plasma glucose. As it was observed in study IGBD with healthy subjects, glucose returns speedily to baseline after T_{max} / TBG_{max}.

2.4.4. Discussion on clinical pharmacology

Glucagon is a single-chain polypeptide containing 29 amino acid residues that increases blood glucose concentration by activating hepatic glucagon receptors, thereby stimulating glycogen breakdown and release of glucose from the liver. The synthetic glucagon peptide used in Baqsimi is structurally identical to naturally occurring human glucagon as well as the recombinant glucagon used in currently marketed glucagon emergency kits. This includes distribution and elimination pathways. No additional data are presented, which is considered appropriate.

Common drug-drug interaction studies were not conducted. Potential risks of drug interactions with beta blockers, indomethacin, and warfarin are proposed for labelling based on precedent set by other marketed glucagon products for the treatment of severe hypoglycaemia. Furthermore, the short half-life of glucagon, in addition to its intended use as an occasional, single-dose treatment, lessens the risk of interaction with other drugs.

PK and PD characterisation was performed in 7 clinical studies, including the pivotal paediatric study IGBB, the pivotal adult study IGBC, and the clinical bridging and confirmatory study IGBI. As part of the responses to day 120 questions, results of a new Japanese study (IGBJ), which was ongoing at the time of the initial MAA, were included. Study IGBI and IGBJ are the only studies in which the final commercial formulation was administered.

PK and PD are closely related in non-diabetic subjects. In T1D patients blood glucose level increase is sustained after T_{max} even though plasma glucagon concentration has returned almost to normal. However, this is expected without counteracting insulin secretion.

A delay in absorption between intranasal and intramuscular glucagon is observed in most studies using the older Baqsimi formulation, which is reflected in a delay in blood glucose increase. However, nearly no temporal delay of blood glucose increase is observed with the commercial formulation in studies IGBI and IGBJ.

PK/PD results with 1 mg SCG or IMG are consistent and the only deviations (increased PK-values in study IGBB and reduced glucose increase in study IGBD) are easily explained by the study design (children with lower body weight and healthy normoglycaemic subjects, respectively).

Contrarily, PK-results with NG are much more heterogeneous and an inexplicable drift of PK-values is observed during the development program. Lower glucagon exposure mainly appeared in early clinical studies (IGBA, IGBE). In contract, Cmax increased markedly with the commercial formulation (IGBI and IGBJ) compared to the older formulation used in the pivotal studies IGBC (adult) and IGBB (paediatric). Based on the important increase in Cmax observed with the commercial formulation, extraordinary high plasma concentrations may appear in young children when receiving the adult dose of the commercial formulation. As requested, the Applicant assessed potential safety concerns of high glucagon plasma levels, but none of the analyses performed gave a hint for any unfavourable effect of transiently high plasma levels of glucagon. This is agreed and therefore the use of the adult dose also for young children is accepted.

It is concluded that, due to considerable PK differences for the commercial vs. the older product in combination with critical GCP findings in study IGBB, PK data from studies IGBB and IGBC are unreliable. However, as at doses achieving saturation of the glucose response, glucagon PK data are not pivotal.

Consistent PD data were demonstrated across adult confirmatory trials using clinical trial drug product and commercially representative drug product, and supported the clinical comparability between them.

Regarding non-GCP-compliant data handling and storage, the applicant pointed out (in their response to the inspection report) that for a rather large fraction of visits the obtained data were recorded independently, i.e. they were not only entered in the non-GCP-compliant eCRFs but were also kept at the individual study sites according to local procedures. This enables re-evaluation of the study results using only patients for which ≥90% of data could be verified. This re-evaluation was performed in response to major objections raised by the CHMP. Assessment of the response concluded that the re-analyses based on source documentation available in Study IGBB demonstrate a benefit/ risk profile consistent with the one determined based on the complete dataset. The MO pertaining to GCP non-compliance of the data recording system is considered addressed through the availability of independent recordings of eCFR data at the individual study sites. The results of the newly performed analysis taking these data detected at the individual study sites into account (including patients for whom >90% of source data were available) are in agreement with the previous analysis including the entire patient population.

Albeit study IGBC has not been inspected, the problem of missing instruction on the creation of source data likewise applies to this study. Unlike for study IGBB, re-evaluation of study IGBC based on patients/ visits with high percentage of verified data was not considered meaningful because only around 25% of visits could be included in this re-analysis.

Hence, evidence of PD in adults has to be derived from study IGBI, which mimicked the design of study IGBC and was conducted with the commercial drug formulation. The latter study has been subject to GCP inspection (INS/GCP/2019/008) and no critical findings were identified in this inspection.

2.4.5. Conclusions on clinical pharmacology

The synthetic glucagon peptide used in Baqsimi is structurally identical to naturally occurring human glucagon as well as the recombinant glucagon used in currently marketed glucagon emergency kits. This allows transfer of many data available from IM glucagon. It has been shown that PK results obtained with the clinical trial drug product were markedly lower than those resulting from the studies with the commercially representative NG drug product. Furthermore, due to critical GCP findings in study IGBB, the reliability of PK data from this study was questioned. However, due to the specific characteristics of glucagon, the PK data are considered only supportive to the B/R discussion.

A re-evaluation of study IGBB was performed, and the conclusion is that the results are in agreement with the previous analysis.

Unlike for study IGBB, re-evaluation of study IGBC based on patients/ visits with high percentage of verified data was not considered meaningful because only around 25% of visits could be included in this re-analysis.

Hence, evidence of PD, efficacy and safety in adults has to be derived from study IGBI, which mimicked the design of study IGBC and was conducted with the commercial drug formulation. This study has been subject to GCP inspection (INS/GCP/2019/008) and no critical findings were identified in this inspection.

Consistent PD data were demonstrated across adult confirmatory trials using clinical trial drug product and commercially representative drug product, and supported the clinical comparability between them.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

Please refer to pharmacodynamic section (above).

2.5.2. Main study(ies)

Study I8R-MC-IGBC (AMG106)

Efficacy and Safety of Intranasal Glucagon for Treatment of Insulin Induced Hypoglycemia in Adults with Diabetes

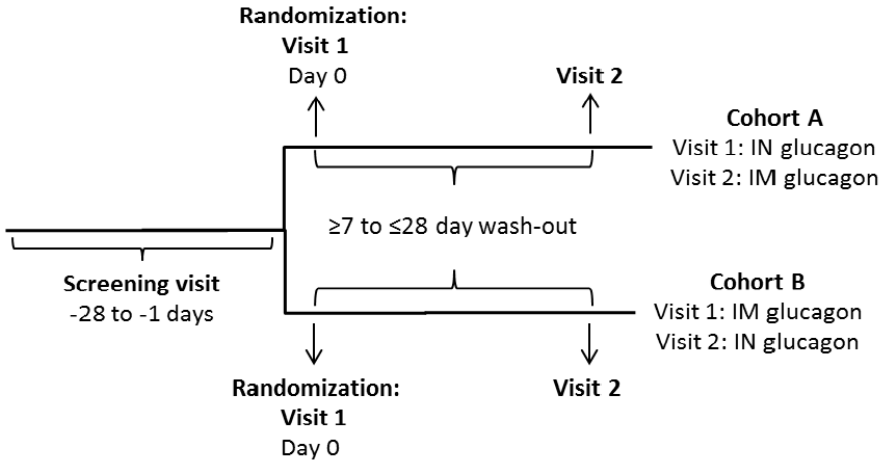


Figure 9 Study design

Methods

Study Participants

Inclusion criteria

To be eligible, the following inclusion criteria must have been met:

1. Clinical diagnosis of either T1D, receiving daily insulin since the time of diagnosis for at least 2 years, or T2D receiving multiple daily insulin doses for at least 2 years.

2. At least 18.0 years of age and less than 65.0 years.

3. Body mass index (BMI) greater than or equal to 20.0 and below or equal to 35.0 kg/m2

4. Weighs at least 50 kg (110 lbs)

5. Females must have met one of the following criteria:

a) Of childbearing potential but agreed to use an accepted contraceptive regimen as described in the study procedure manual throughout the entire duration of the study (from the screening visit until study completion).

or

b) Of non-childbearing potential, defined as a female who had a hysterectomy or tubal ligation, was clinically considered infertile or was in a menopausal state (at least 1 year without menses).

6. In good general health with no conditions that could influence the outcome of the trial, and in the judgment of the Investigator was a good candidate for the study based on review of available medical history, physical examination and clinical laboratory evaluations.

7. Willingness to adhere to the protocol requirements

Exclusion criteria

1. An individual was not eligible if any of the following exclusion criteria were present:Females who were pregnant according to a positive urine pregnancy test, actively attempting to get pregnant, or were lactating.

2. History of hypersensitivity to glucagon or any related products or severe hypersensitivity reactions (such as angioedema) to any drugs.

3. Presence of cardiovascular, gastrointestinal, liver or kidney disease, or any other conditions which in the judgment of the investigator could have interfered with the absorption, distribution, metabolism or excretion of drugs or could have potentiated or predisposed to undesired effects.

4. History of pheochromocytoma (i.e. adrenal gland tumor) or insulinoma.

5. History of an episode of severe hypoglycemia (as defined by an episode that required third party assistance for treatment) in the 1 month prior to enrolling in the study.

6. Used daily systemic beta-blocker, indomethacin, warfarin or anticholinergic drugs.

7. History of epilepsy or seizure disorder.

8. Regularly consumed 3 or more alcoholic beverages per day.

9. Used an Investigational Product in another clinical trial within the past 30 days

10. Donated 225 mL or more of blood in the previous 8 weeks before the first glucagon dosing visit.

Treatments

The study consisted of two outpatient visits each lasting about 6 hours. Induced hypoglycaemia was followed by treatment with either IN or IM glucagon. Prior to dosing on the first visit, the order of treatments for the two visits was randomly assigned. A minimum of 7 days, and a maximum of 28 days was required between Visit 1 and Visit 2.

Patients randomized to Cohort A received the study drugs in the following sequence:

Visit 1: IV insulin followed by IN glucagon (Test product; AMG504-1)

Visit 2: IV insulin followed by IM glucagon (Reference product; GlucaGen®)

Patients randomized to Cohort B received the study drugs in the following sequence:

Visit 1: IV insulin followed by IM glucagon (Reference product; GlucaGen®)

Visit 2: IV insulin followed by IN glucagon (Test product; AMG504-1)

A description of the mode of administration, dose, and dosage schedule of the study medications administered is provided below in Table 8.

Table 3 Study Medication Administration, Dose and Dosage Schedule

	AMG504-1	GlucaGen®	IV insulin
Constituent	Glucagon	glucagon	Commercially available
Dosage form/Route of administration	Powder for intranasal administration	Reconstituted solution for injection	Intravenous infusion *via* an indwelling catheter
Dosage	30 mg AMG504-1 (3 mg dose of glucagon)	1mg/mL glucagon	100 U/mL
Infusion rate	-	-	25 mL/hour / 2 mU/kg/min (range of 1 to 3 mU/kg/min; Section 9.1.3)
Regimen	Administered approximately 5 min after cessation of insulin infusion	Administered approximately 5 min after cessation of insulin infusion	Administered approximately 3 hours prior to glucagon administration to a final blood glucose concentration of < 60 mg/dL
Visit administration schedule	Visit 1 or 2	Visit 1 or 2	Visit 1 and 2

Treatment 1 (reference product): GlucaGen® HypoKit 1 mg, powder and solvent for solution for injection (solution of 1 mg/mL glucagon administered in the deltoid muscle of the patient's non-dominant arm)

Treatment 2 (test product): AMG504-1 30 mg dry-mist nasal glucagon powder (30 mg of AMG504-1 contains 3 mg of glucagon administered in the nostril)

Objectives

The primary objective of AMG106 was to assess the efficacy and safety of 3 mg glucagon administered intranasally in comparison with commercially-available IM glucagon in reversing insulin-induced hypoglycemia in patients with T1D or T2D. In addition, the PK and PD parameters of IN and IM glucagon were evaluated.

Outcomes/endpoints

A responder was defined as a subject who achieved either an increase in blood glucose to ≥ 70 mg/dL (3.9 mmol/L) or an increase of ≥20 mg/dL from nadir within 30 minutes after receiving study glucagon, without receiving additional actions to increase the blood glucose level. Glucose levels were measured from t=0 and, and from glucose "nadir", defined as the minimum glucose measurement at the time of, or within 10 minutes following glucagon administration.

Sample size

The sample size estimate for the study was based on the primary outcome of achieving either an increase in blood glucose to ≥70 mg/dL (3.9 mmol/L) or an increase of ≥20 mg/dL from nadir within 30 minutes after receiving study glucagon without receiving additional interventions to increase the blood glucose level across varying amounts of correlation within participant (to account for the cross-over design).

Table 9 below provides the number of subjects required in the study in order to assess the non-inferiority of intranasal glucagon treatment and intramuscular glucagon treatment among subjects with T1D using the following assumptions:

• 80% power

• A response rate of 95% for both treatments

• A non-inferiority limit of 10 percentage points (absolute value)

• One-sided alpha level of 0.025

• Correlation of zero

Table 4 Sample Size Estimates for Non-Inferiority Limits, Levels of Power, and Amounts of Correlation

Non-Inferiority Limit (upper 97.5% confidence limit on the difference)	Power	Correlation			
		0	0.1	0.2	0.3
10%	80%	75	74	72	68

Given the above assumptions, the sample size required was 75 participants with T1D. An additional 7 participants with T2D were also to be enrolled and an exploratory analysis was performed on the total population (T1D and T2D; N=82).

No adjustment in sample size was made for potential loss to follow-up because participants that were lost to follow-up or drop-out were replaced. The sample size indicated in the cells denotes the number of participants completing the study.

The following considerations were taken into account to justify the choice of the target achievement in the two groups as well as the choice of acceptable non-inferiority limit:

Response Rate

Injection group

The assumed response rate of 95% for glucagon by injection reflects that glucagon is not always effective under real-world use. In Locemia Solution ULC's recently completed phase II study (AMG102), one participant out of 18 (5.6%) treated with glucagon by injection required 30 minutes to achieve a BG increase of 20 mg/dL and in excess of 30 minutes to achieve a BG > 68 mg/dL (3.8 mmol/L).

AMG504-1 group

In the same phase II study, treatment with 2 mg intranasally was 93% effective while 3 mg was 100% effective in causing patients to return to a BG > 68 mg/dL (3.8 mmol/L) by 30 minutes. As AMG504-1 has not been used in the setting of the lower BG levels targeted in this phase III clinical study (i.e., 45-50 mg/dL), a slightly lower percent efficacy of 95% has been projected.

Importantly, even if either treatment failed to meet the narrow definition of the primary endpoint of an increase in glucose level to ≥70 mg/dL within 30 minutes in every patient, the primary clinical outcome of an increase in BG of ≥20 mg/dL was satisfactory from a clinical perspective because sufficient recovery from clinical signs of hypoglycemia occurred at levels below 70 mg/dL which, in turn, permitted the patient to consume carbohydrate and fully recover.

Non-inferiority Margin

The proposed non-inferiority margin of 10 percentage points has been chosen based on the limited data available for glucagon injection (Harris et al. simulated emergency study), the considerable data for an analogous product (EpiPen for treatment of anaphylaxis) and considerations of actual use in an emergency.

Injectable Glucagon

We are not aware of published data documenting patient/caregiver treatment success rates in actual clinical situations wherein the currently injected glucagon must be given to treat an episode of severe hypoglycemia. However, one study has been published in which parents of children and adolescents with T1D used a currently available glucagon kit in a simulated emergency situation. Parents were asked to pretend it was 3:00 am and their child was unconscious. They were then given an unopened emergency glucagon kit (GlucaGen® HypoKit, Novo Nordisk®) and asked to administer the medication into a wrapped piece of meat to simulate a thigh. In this study, 69% of the parents experienced difficulties with the product and 10% completely failed to deliver the medication.

Randomisation

The Investigational Products were to be administered only to patients included in the study following the procedures set out in the clinical study protocol.

Patients were assigned a unique participant identification number upon study enrollment. Each patient retained this number throughout the study. The order of Investigational Product administration was sequentially assigned from a compute-generated randomization list revealed to clinic center staff using a central study website upon enrollment of each participant. The randomization followed a 1:1 allocation ratio of treatment received at first study dosing visit using a blocks of N=2 and stratified by clinic site.

Patients who were discontinued from the study after dosing were to retain their patient number and their randomization number.

Blinding (masking)

This was an open-label, unblinded study.

Statistical methods

The primary analysis was a treatment group comparison of the primary outcome in the T1D cohort (Primary Analysis Cohort).

The proportion of successes in each treatment arm and the difference in proportions was computed. A one-sided 97.5% confidence interval was obtained from the 1-sample mean of the paired differences in outcome (1=outcome observed; 0=outcome not observed) across visits. Non-inferiority of intranasal glucagon was declared if the upper limit of the one-sided 97.5% confidence interval constructed on the difference in proportions (intramuscular glucagon – intranasal glucagon), was less than the non-inferiority limit of 10%. The confidence interval of the difference in proportions was calculated using methods to account for the correlation due to the cross-over design.

The primary efficacy analysis included all participants who complete the two dosing visits with the following exceptions:

• Dosing visits in which a glucose-elevating intervention (e.g., oral carbohydrates or IV glucose) was given either before receipt of study glucagon or within the first 10 minutes after glucagon administration were considered to be aborted dosing visits and not included in the analysis. These visits were either repeated or the participant was replaced with another participant.

• Participants with one or both dosing visits in which the central lab nadir glucose value was ≥70 mg/dL were not included in the efficacy analyses. Information from these visits was used only in the safety analysis.

The primary analysis also was repeated separately in subsets of participants based on the following:

☐ Nadir <60 mg/dL on both Study Visits

☐ Nadir <50 mg/dL on both Study Visits

☐ Nadir within 5 mg/dL on both Study Visits

☐ Complete central lab glucose values preceding and including the 30 minute measurement (i.e. non-missing central lab glucose at time 0, 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, and 30 minutes).

The primary analysis was repeated using the outcome of an increase in blood glucose level to 70 mg/dL or more. For this analysis, a rise in blood glucose level by 20 mg/dL or more that does not reach 70 mg/dL within 30 minutes would not be considered a success.

A Kaplan-Meier curve for each treatment group was constructed for the time to occurrence of central lab blood glucose ≥70 mg/dL or an increase of ≥20 mg/dL from nadir after receiving study glucagon (outcome). A separate Kaplan-Meier curve for each treatment group was constructed for the time to occurrence of an increase in central lab blood glucose of ≥20 mg/dL from nadir after receiving study glucagon.

A treatment group comparison of the time from treatment to outcome was also performed 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. Due to the discrete time data (5, 10, or 30 minute intervals), the exact method was used. This method averages the Cox proportional hazards likelihood over all possible orderings of tied event times.

The proportional hazards assumption was assessed using a Kolmogorov-supremum test. As the proportional hazards assumption held for the adjustment factors (nadir blood glucose, treatment period) and for the treatment group variable, neither the stratified Cox proportional hazards model, nor, the extended Cox proportional hazards model (with time-dependent covariate) was used.

The analysis was repeated in the subgroup of observations with central lab nadir blood glucose value <50 mg/dL.

If a participant received additional intervention treatment to raise blood glucose prior to achieving a blood glucose value that was ≥70 mg/dL or an increase of ≥20 mg/dL from nadir, the remaining time points were considered non-events (i.e. blood glucose was not ≥70 mg/dL and did not increase ≥20 mg/dL from nadir).

A treatment comparison of blood glucose over the 90 minutes following administration of glucagon was completed using a linear mixed model with repeated measures that accounts for the correlation due to the cross-over design and the correlation due to multiple measures, adjusting for starting glucose level and time period. Least-square means were calculated for blood glucose in each treatment group and the difference in blood glucose between treatment groups (IM – IN). Residuals from the model were assessed numerically and graphically to ensure an approximately normal distribution. As the distribution did not appear skewed, and no influential outliers were discovered, a transformation was not attempted.

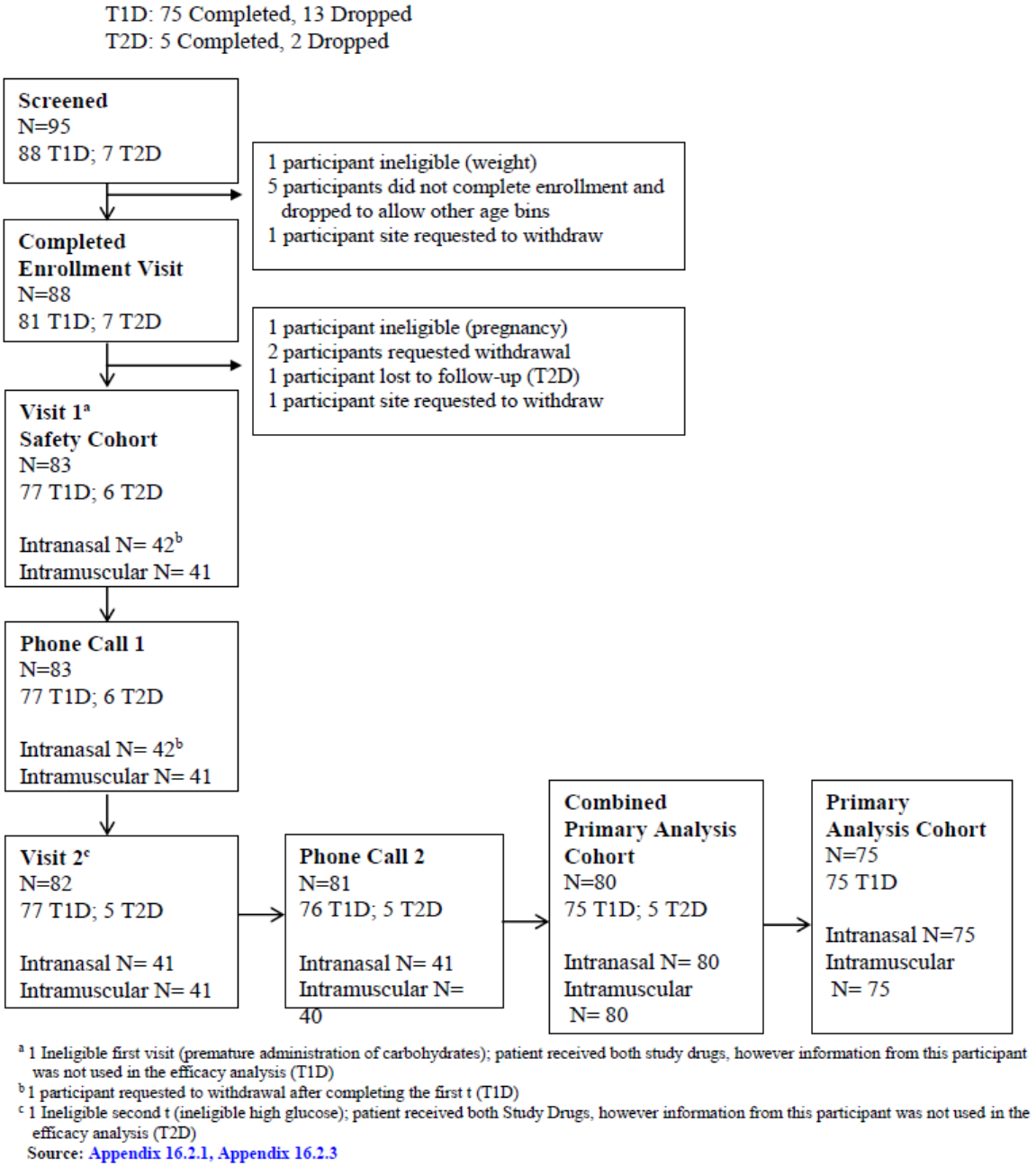
If a participant received additional intervention to raise blood glucose, measurements taken after the time of intervention were excluded from the analysis.

Hypoglycemia symptoms were assessed using the Edinburgh Hypoglycemia Scale. Responses to each symptom on the Edinburgh Hypoglycemia Scale questionnaire were tabulated per instructions on the questionnaire at each time point for both treatment groups. The total score on the questionnaire were computed at each time point for both treatment groups as the sum of the scores for each symptom.

The total score was compared between treatment groups through a linear mixed model with repeated measures accounting for the correlation due to the cross-over design (same participant received both treatments) and the correlation due to multiple measures of the questionnaire (questionnaire administered multiple times during testing). The starting score and treatment period were included as covariates in the model.

Results

Participant flow



[a] 1 Ineligible first visit (premature administration of carbohydrates); patient received both study drugs, however information from this participant was not used in the efficacy analysis (T1D)
[b] 1 participant requested to withdrawal after completing the first t (T1D)
[c] 1 Ineligible second t (ineligible high glucose); patient received both Study Drugs, however information from this participant was not used in the efficacy analysis (T2D)
Source: Appendix 16.2.1, Appendix 16.2.3

Figure 10 Patient Disposition

Recruitment

Study initiation date: 19-Dec-2013 (first patient first visit)

Study completion date: 14-Jan-2015 (last patient last visit)

Conduct of the study

Protocol amendments

Two protocol versions were drafted: AMG106 dated 18-Jul-2013 and v2.0 dated 27-Sep-2013.

No other changes were made to the protocol.

Protocol compliance

A total of 131 protocol violations were reported

All protocol deviations reported in the study were deemed to have no impact on the assessment of the study objectives.

Baseline data

Table 11 presents the demographic and baseline characteristics of the Safety Cohort, by diabetes type. Of the patients included in the Safety Cohort (n=83), the mean (SD) age of participants was lower for T1D patients compared to the T2D patients [32.9 (12.3) years vs. 47.8 (14.7) years]. The majority of patients in both groups were female (58% T1D, 67% T2D), with the mean (SD) age of disease duration comparable between T1D and T2D patients [18.1(11.2) vs. 18.8 (7.8) years, respectively). The majority of patients with T1D reported the use of an insulin pump as their primary modality (n=57, 74.0%), compared to only 17% of T2D patients. T1D patients, also reported lower median total daily insulin (TDI) compared to T2D patients (0.58 units/kg, range: 0.46 to 0.68 units/kg vs.0.81 units/kg, range: 0.57 to1.22 units/kg).

Table 5 Demographic and Baseline Characteristics of the Safety Cohort

	T1D N=77	T2D N=6
Age (years) – *n(%)*		
18 to <25	28 (36%)	1 (17%)
25 to <35	23 (30%)	0
35 to <45	10 (13%)	1 (17%)
45 to <55	11 (14%)	3 (50%)
≥55	5 (6%)	1 (17%)
Median (25th, 75th percentile)	31.0 (21.6, 41.5)	52.8 (41.4, 54.6)
Mean ±SD	32.9 ± 12.3	47.8 ± 14.7
Female – *n(%)*	45 (58%)	4 (67%)
Race/ethnicity – *n(%)*		
White Non-Hispanic	74 (96%)	1 (17%)

	T1D N=77	T2D N=6
Black Non-Hispanic	1 (1%)	2 (33%)
Hispanic or Latino	1 (1%)	1 (17%)
Other Race/Ethnicity	1 (1%)	2 (33%)
Duration of diabetes (years) – *n(%)*		
<10	27 (35%)	0
10 to <20	16 (21%)	4 (67%)
20 to <30	20 (26%)	1 (17%)
≥30	14 (18%)	1 (17%)
Median (25th, 75th percentile)	17.6 (8.6, 24.6)	15.7 (12.7, 26.0)
Mean ±SD	18.1 ± 11.2	18.8 ± 7.8
Primary insulin modality – *n(%)*		
Insulin pump	57 (74%)	1 (17%)
Multiple daily insulin injections	20 (26%)	5 (83%)
Total daily insulin (units/kg) - median (25th, 75th percentile)	0.58 (0.46, 0.68)	0.81 (0.57, 1.22)
Most recent severe hypoglycemic event[a] – *n(%)*		
Never	46 (60%)	4 (67%)
≤30 days	0	0
31 to 90 days	4 (5%)	1 (17%)
91 to 180 days	0	0
181 to 365 days	2 (3%)	0
>365 days	25 (32%)	1 (17%)
HbA1c[b] – *n(%)*		
≤7%	21 (27%)	1 (17%)
7.1 to 8.0%	22 (29%)	2 (33%)
8.1 to 9.0%	15 (19%)	2 (33%)
9.1 to 10.0%	8 (10%)	1 (17%)
>10.0%	11 (14%)	0
Mean ±SD	8.3 ± 1.8	8.0 ± 0.8
Clarke hypoglycemia unawareness score[c] – *n(%)*		
Reduced awareness	10 (13%)	1 (17%)
Intermediate	10 (13%)	2 (33%)
Aware	57 (74%)	3 (50%)

[a]The Safety Cohort consisted of all T1D and T2D patients who were randomized and received at least one dose of the Study Drug
[a]Severe hypoglycemic event defined as an episode that required third party assistance for treatment
[b]HbA1c performed locally
[c]Reduced awareness = 4 or more reduced responses; Intermediate = 3 reduced responses; Aware= 2 or fewer reduced responses
Source: Appendix 16.2.4.1; Appendix 16.2.4.2

Glucose Nadir Values

Glucose nadir values for the 75 patients with T1D are presented in **Table 12.**

Table 6 Glucose Nadir Values in the Primary Analysis Population (Patients with T1D) in Study IGBC

Glucose Nadir (mg/dL)	NG 3 mg N=75	IMG 1 mg N= 75
Mean ± SD	44.2 ± 8.4	48.9 ± 8.4
Median	45.0	49.0
Range (min, max)	20.0, 64.0	28.0, 67.0
Glucose Nadir (mmol/L)		
Mean ± SD	2.5 ± 0.5	2.7 ± 0.5
Median	2.5	2.7
Range (min, max)	1.1, 3.6	1.6, 3.7

Abbreviations: CSR = clinical study report; IMG = intramuscular glucagon; max = maximum; min = minimum; N = number of patients in the analysis population; NG = nasal glucagon; SD = standard deviation; T1D = type 1 diabetes mellitus.

Source: Study IGBC CSR, Table 14.3-8.

Numbers analysed

Of the 88 patients who completed the Enrollment Visit, 83 (77 T1D, 6 T2D) patients received at least one dose of the study drug, and were included in the safety analysis (Safety Cohort). Of these, 3 patients (2 patients with T1D and 1 patient with T2D) were excluded from all further analyses.

The primary analysis, a treatment group comparison of the proportion of patients achieving treatment success, was performed in the T1D patient cohort only (n=75). The primary analysis was repeated to include patients with T2D (Combined Primary Analysis Cohort; n=80). A per protocol analysis was also performed in the T1D population (n=63), which included only inwindow central lab blood glucose values, removed observations where insulin was stopped prior to central lab blood glucose reaching ≤60 mg/dL, and removed observations without an in-window central lab blood glucose value at the 30 minute time point.

Outcomes and estimation

The primary efficacy analysis was a treatment group comparison of the primary outcome in Primary Analysis cohort, composed of all T1D patients having completed both Study/Dosing Visits with eligible glucose and glucagon levels. The primary efficacy outcome, treatment success, was defined as either an increase in blood glucose to ≥70 mg/dL or an increase of ≥20 mg/dL from glucose nadir within 30 minutes after receiving study glucagon, without receiving additional actions to increase the blood glucose level. Due to the residual activity of circulating insulin, glucose nadir was defined as the minimum glucose measurement at the time of, or within 10 minutes following glucagon administration.

Based on these definitions, as shown in

Table 13, the proportion of IN- and IM-dosed patients who achieved treatment success was 0.987 (n=74) and 1.0 (n=75), respectively. Within the population of patients achieving treatment success, and broken down by treatment success parameters, 100% of all patients reported an increase in blood glucose ≥ 20 mg/dL from glucose nadir within 30 minutes of glucagon dosing, and 97% (n=72) of IN-dosed patients and 99% (n=74) of IM-dosed patients reported an increase of ≥70 mg/dL from glucose nadir within 30 minutes of glucagon dosing. The unadjusted and adjusted differences, and their 1-sided upper 97.5% confidence limits, for the proportion of patients achieving treatment success between the IM and IN treatment groups was 0.013 (0.040) and 0.015 (0.043), respectively.

Table 7 Proportion of patients with Increase in Blood Glucose to ≥70 mg/dL or an Increase of ≥20 mg/dL from nadir within 30 Minutes after Administration of Glucagon (without additional glucose-raising treatment) in the Primary Analysis Cohort†

	Intranasal Glucagon N=75	Intramuscular Glucagon N=75
N with success[a]	74	75
Proportion with success[a]	0.987	1.000
Success criterion met[b] – *n(%)*		
≥70 mg/dL	72 (97%)	74 (99%)
Increase by ≥20 mg/dL from nadir	74 (100%)	75 (100%)
Both	72 (97%)	74 (99%)
Difference in proportion with success[c]		
Unadjusted difference (1-sided upper 97.5% confidence limit)[d]	0.013 (0.040)	
Adjusted difference (1-sided upper 97.5% confidence limit)[e]	0.015 (0.043)	

†The Primary Analysis Cohort consisted of all T1D patients who received both doses of the Study Drug with eligible glucose and glucagon concentrations

[a] Success defined as an increase in central lab blood glucose to ≥70 mg/dL or an increase of ≥20 mg/dL from nadir within 30 minutes after glucagon is administered

[b] Proportion based on total number meeting success (N=74 for intranasal and N=75 for intramuscular)

[c] Difference in proportion with success defined as (proportion with success with Intramuscular treatment) – (proportion with success with Intranasal treatment)

[d] 1-sided confidence interval (CI) from a 1-sample mean of the paired differences in occurrence of outcome; non-inferiority margin = 0.1

[e] Difference and 1-sided CI from a Poisson regression model adjusted for treatment period and blood glucose value immediately before administration of glucagon

Source: Appendix 16.2.3; Appendix 16.2.6.3

As indicated in Table 14, the one IN-dosed patient who failed treatment, achieved both glucose threshold levels at 40 minutes post dosing.

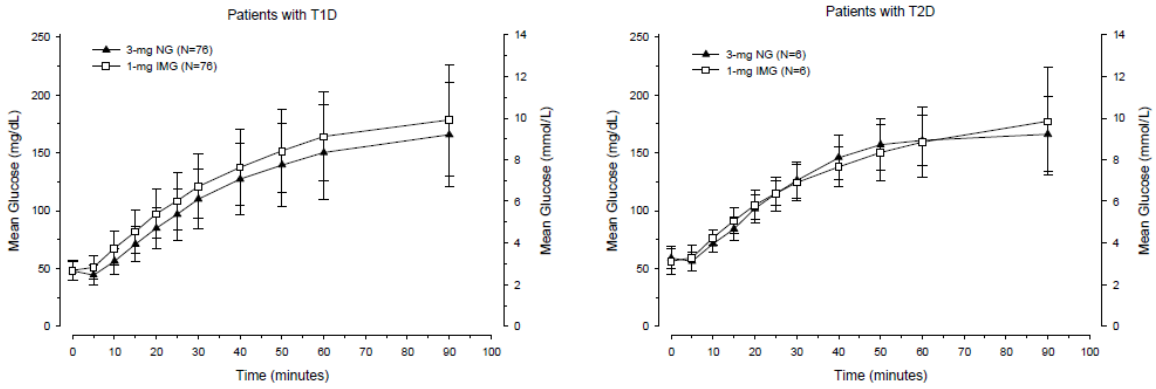
Table 8 Description of lab glucose values (mg/dL) at both visits for 1 patient who failed intranasal treatment in the Primary Analysis Cohort†

		Time Point (minutes)										
Treatment	**Outcome**	**0**	**5**	**10**	**15**	**20**	**25**	**30**	**40**	**50**	**60**	**90**
Intranasal	Failure	50	47	48	53	57	62	65	72	75	79	81
Intramuscular	Success	48	55	60	72	86	98	103	113	142	139	131

†The Primary Analysis Cohort consisted of all T1D patients who received both doses of the Study Drug with eligible glucose and glucagon concentrations

Source: Appendix 16.2.3; Appendix 16.2.6.3

Summary of main efficacy results for study IGBC



Abbreviations: IMG = intramuscular glucagon; N = number of patients; NG = nasal glucagon; T1D = type 1 diabetes mellitus; T2D = type 2 diabetes mellitus: SD = standard deviation.
Note: Figures exclude data after feeding.

Figure 11 Mean (+/-SD) observed glucose concentration over time after glucagon administration by treatment groups in patients with T1D and T2D in Study IGBC.

Study I8R-MC-IGBB (AMG103)

Assessment of Intranasal Glucagon in Children and Adolescents with Type 1 Diabetes

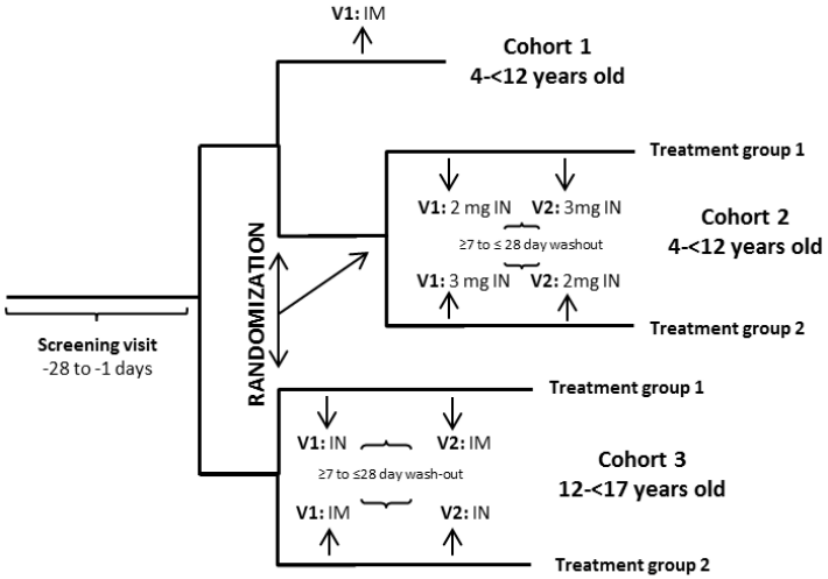


Figure 12 Study design

Methods

Study participants

Inclusion criteria

To be eligible, the following inclusion criteria must have been met:

1. History of type 1 diabetes and receiving daily insulin therapy from the time of diagnosis for at least 12 months.

2. At least 4 years of age and less than 17 years.

3. Females must have met one of the following criteria:

a) Of childbearing potential but agreed to use an accepted contraceptive regimen as described in the study procedure manual throughout the entire duration of the study (from the screening visit until study completion).

or

b) Of non-childbearing potential, defined as a female who had had a hysterectomy or tubal ligation, was clinically considered infertile, or had not yet reached menarche.

4. In good general health with no conditions that could have influenced the outcome of the trial, and in the judgment of the Investigator was a good candidate for the study based on review of available medical history, physical examination and clinical laboratory evaluations.

5. Willingness to adhere to the protocol requirements

Exclusion criteria

An individual was not eligible if any of the following exclusion criteria were present:

1. Females who were pregnant according to a positive urine pregnancy test, were actively attempting to get pregnant, or were lactating.

2. History of hypersensitivity to glucagon or any related products or severe hypersensitivity reactions (such as angioedema) to any drugs.

3. Presence of cardiovascular, gastrointestinal, liver or kidney disease, or any other conditions which in the judgment of the investigator could have interfered with the absorption, distribution, metabolism or excretion of drugs or could have potentiated or predisposed to undesired effects.

4. History of pheochromocytoma (i.e. adrenal gland tumor) or insulinoma.

5. History of an episode of severe hypoglycemia (as defined by an episode that required third party assistance for treatment) in the 1 month prior to enrolling in the study.

6. Use of daily systemic beta-blocker, indomethacin, warfarin or anticholinergic drugs.

7. History of epilepsy or seizure disorder.

8. Use of an Investigational Product in another clinical trial within the past 30 days.

9. Blood donation in 3 months prior to first glucagon Dosing Visit.

Treatments

The study consisted of one or two outpatient visits each lasting about 4 hours. When target glucose of <80 mg/dL was reached, treatment with either IN or IM glucagon followed. Prior to dosing on the first visit, determination of the study visit schedule was randomly assigned: Patients in the 4-<12 year old age group were randomized in a 2:1 ratio to 2 outpatient visits receiving different doses of IN glucagon during each, or to 1 outpatient visit receiving IM glucagon. For 4-<12 year olds randomized to receive two doses of IN glucagon, and for 12- <17 year olds, a minimum of 7, and a maximum of 28 days was required between Visit 1 and Visit 2.

Patients 4-<12 years old randomized to Cohort 1 received the Investigational Product in the following sequence:

Visit 1: Intravenous insulin/ insulin pump, (if needed) followed by IM glucagon (Reference product; GlucaGen® HypoKit (Novo Nordisk®)

Patients 4-<12 years old randomized to Cohort 2, were randomized thereafter to 1 of 2 treatment groups with the following sequence of Investigational Product administration:

Treatment group 1

Visit 1: Intravenous insulin/insulin pump (if needed) followed by 2mg IN glucagon (Test product; AMG504-1)
Visit 2: Intravenous insulin/insulin pump (if needed) followed by 3mg IN glucagon (Test product; AMG504-1)

Treatment group 2

Visit 1: Intravenous insulin/insulin pump (if needed) followed by 3mg IN glucagon (Test product; AMG504-1)
Visit 2: Intravenous insulin/insulin pump (if needed) followed by 2mg IN glucagon (Test product; AMG504-1)

Patients 12-<17 years (Cohort 3) were randomized to 1 of 2 treatment groups with the following sequence of Investigational Product administration:

Treatment Group 1

Visit 1: Intravenous insulin/insulin pump (if needed) followed by 3mg IN glucagon (Test product; AMG504-1)
Visit 2: Intravenous insulin/insulin pump (if needed) followed by 1mg IM glucagon (Reference product; GlucaGen® HypoKit (Novo Nordisk®) (1))

Treatment Group 2

Visit 1: Intravenous insulin/insulin pump (if needed) followed by 1mg IM glucagon (Reference product; GlucaGen® HypoKit (Novo Nordisk®) (1))
Visit 2: Intravenous insulin/insulin pump (if needed) followed by 3mg IN glucagon (Test product; AMG504-1)

Objectives

Primary objective

The primary objective of AMG103 was to assess, in a pediatric population of TID patients, the PK and pharmacodynamics (PD) of glucagon administered intranasally in comparison with commercially-available intramuscular (IM) glucagon.

Secondary objective

The secondary objective of AMG103 was to evaluate the safety and tolerability of IN glucagon in a pediatric population of TID patients.

Outcomes/endpoints

The primary efficacy variables for the study are the PK and PD parameters calculated using both the raw and adjusted concentrations of glucagon and glucose, respectively.

In each study period, blood samples were collected by catheter for the determination of plasma glucagon (4 mL each in K2 EDTA purple top Vacutainers containing 250KIU Aprotinin per mL of blood) and plasma glucose levels (each blood tube were gently inverted 8-10 times immediately after collection to ensure adequate mixing with the anticoagulant. The tubes were then placed on wet/crushed ice for up to 30 minutes without exceeding 30 minutes prior to centrifugation) as follows :

• Glucose: For all participants, plasma glucose levels were measured using a bedside rapid glucose analyzer (Analox, YSI or equivalent). During the insulin infusion, glucose levels were measured no more than 10 minutes apart while the plasma glucose level was >100 mg/dL and no more than 5 minutes apart when the plasma glucose level was <100 mg/dL;

• Glucose and glucagon: Once a plasma glucose level of <80 mg/dL was reached, the basal rate returned to normal for participants using an insulin pump and the insulin infusion stopped for participants using insulin injections, a blood sample was collected for pharmacokinetics (glucagon) and pharmacodynamics (glucose)within 5 minutes before glucagon administration (i.e. 0 hour), and;

• Glucose and glucagon: Plasma glucose levels were measured using a YSI (or equivalent device) for safety and serial blood sampling were performed for pharmacokinetics (glucagon) and pharmacodynamics (glucose) assessments 5, 10, 15, 20, 30, 40, 60 and 90 minutes following glucagon administration.

Sample size

Due to the lack of available data on children, a sample size of 48 participants was selected as a convenience sample based on the FDA guidance for pediatric PK studies which indicates that the standard approach is to administer either single or multiple doses of a drug to a relatively small (e.g., 6-12) group of participants.

A total of 49 participants between the ages of 4 and <12 years (18 participants 4 to <8 years and 18 participants 8 to <12 years) and 13 participants between the ages of 12 and <17 years, were enrolled. One patient in the 12 and <17 years was not randomized due contraindicated concomitant drug use. All participants in the older age group of 12 - <17 years old received the 3.0 mg dose of intranasal glucagon and the IM glucagon, with the order of treatments randomly assigned prior to dosing; participants in the two (2) younger age groups of 4 - <8 and 8 - <12 years of age, were randomized in a 2:1 ratio to either: 1) 2 Study Visits: one to receive the 2.0 mg dose of IN glucagon, and the other to receive the 3.0 mg dose of IN glucagon; 2) 1 Study Visit to receive IM glucagon.

Randomisation

The Investigational Products were to be administered only to patients included in the study following the procedures set out in the clinical study protocol.

Patients were assigned a unique participant identification number upon obtaining consent. Each patient retained this number throughout the study. For patients 4-<12 years old, treatment group (3 mg intranasal at first dosing visit/2 mg intranasal at second dosing visit; 2 mg intranasal at first dosing visit/3 mg intranasal at second dosing visit; intramuscular at first and only dosing visit) was sequentially assigned from a computer-generated randomization list revealed to clinic center staff using a central study website upon enrollment 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-<8 years old and 8-<12 years old).

For patients 12-<17 years old, the treatment order (intramuscular at first dosing visit/3 mg intranasal at second dosing visit vs. 3 mg intranasal at first dosing visit and intramuscular at second dosing visit) was sequentially assigned from a computer-generated randomization list revealed to clinic center staff using a central study website. The randomization followed a 1:1 allocation ratio using blocks of N=2.

Patients who were discontinued from the study after dosing were to retain their patient number and their randomization number.

Blinding (masking)

The randomization code list was not made available to the personnel in charge of the administration of glucagon until the morning of the first Dosing Visit. For those assigned to 2 visits with IN glucagon, the order of the dose of intranasal glucagon (2.0 mg or 3.0 mg) was randomly assigned and blinded throughout the study.

For patients in Cohort 2, patients, investigator staff, persons performing the assessments, and data analysts remained blinded to the identity of the treatment from the time of randomization until database lock, using the following methods: (1) randomization data were kept strictly confidential until the time of unblinding, and were not accessible by anyone else involved in the study (2) the identity of the treatments was concealed by the use of study drugs that were identical in packaging, labeling, schedule of administration, appearance, taste and odor.

Unblinding was only permitted in the case of patient emergencies and at the conclusion of the study.

Statistical methods

Pharmacokinetic (PK) parameters of glucagon were derived NCA based on raw concentrations (AUC0-t, AUC0-∞, CL/F, Cmax, λz, t1/2 and tmax) and baseline-adjusted concentrations (AUC0-t, Cmax and tmax).

Given the blood volume limitations, especially for smaller children, the baseline glucagon concentration was obtained from the sample obtained prior to dosing. Individual concentrations and PK parameters of glucagon were summarized with descriptive statistics by treatment group.

The PD analysis of glucose was performed using SAS 9.4, and PD parameters were calculated by NCA. Key PD parameters were derived to assess the exposure to glucose and duration of exposure above, below and within the normal glucose range. The normal range for glucose was considered to be 70 to 108 mg/dL (3.9 to 6.0 mmol/L). Actual sampling times were used for all calculations, AUECWithin, TAbove, TBelow, TWithin, DurationAbove, DurationBelow and DurationWithin) and baseline-adjusted concentrations (AUEC0-1.5, Cmax, and t max).

Baseline glucose concentrations were calculated as the mean of concentrations from samples obtained when the insulin infusion was stopped and immediately prior to dosing (i.e., times - 0.08 and 0.00 hours).

Exploratory analyses were performed to evaluate exposure-response relationship, a fundamental component for the understanding of drug effect and supporting efficacy endpoints. The relationship between the exposure (concentrations and parameters) of glucagon and glucose was explored using graphical displays and numerically using correlation analysis. More specifically, scatterplots showing the relationship between (i) plasma glucagon and plasma glucose levels, (ii) baseline-adjusted PK parameters and baseline-adjusted PD parameters were generated.

The primary analysis (pharmacokinetic and pharmacodynamics) included all participants who provide evaluable data for at least one of the treatments. Concentration data of the remaining participants is presented separately.

The analysis was be stratified by age cohort (4-<8, 8-<12, and 12-<17 years old), except where otherwise indicated. The analyses for the 4-<8 and 8-<12 years old cohorts may have been pooled if the data suggests homogeneity of effect.

The 2mg and 3mg intranasal glucagon treatment arms may have been pooled if the data suggests homogeneity of effect.

The central lab glucose and glucagon measurements were used for analysis. If a central lab glucose measurement was missing, then the YSI (or equivalent) measurement from that time point was used.

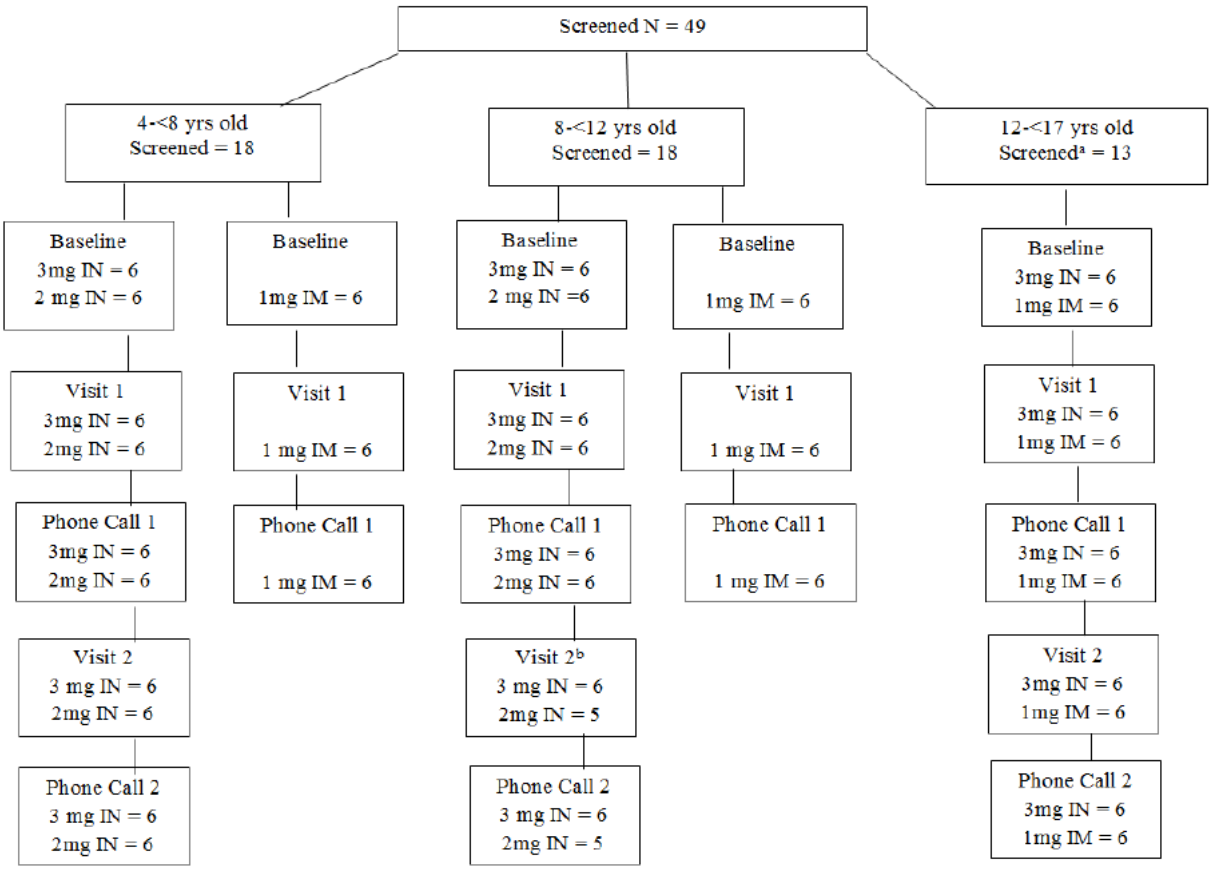
- Nadir glucose was defined as the minimum glucose measurement at the time of or within 10 minutes following glucagon administration.
- Blood draws taken for quality control assessment (QC samples) were not included in the primary or exploratory analysis, apart from the designated quality control analysis
- Missing glucose measurements (i.e. no central lab or site measurement available) were imputed using Rubin's* method based on available lab glucose measurements.
- For exploratory analysis, out-of-window blood draws (blood draws taken before/after the midpoint between consecutive planned measurements) were included. Due to the exploratory nature of the analyses, both 95% and 99% confidence intervals were calculated, except where otherwise indicated.

*Rubin's method for imputation is a statistical technique used to estimate each missing data value based on the lab glucose measurements that are available at other time points. Multiple plausible values are imputed for each missing data value to quantify the increased statistical margin of error due to the missing data.

Results

Participant flow

A total of 49 T1D pediatric patients were screened at the enrollment visit, 18 of which were in the 4-<8 years old age category and 8-<12 years old age category, each, and 13 of which were in the 12-<17 years old age category. Of the 49 patients screened, 1 patient in the 8-<12 years old age category requested withdrawal prior to receiving the second dose of Study Drug (Dosing Visit 1: 3mg IN; Dosing Visit 2: 2mg IN), and 1 patient in the 12-<17 years old age category was excluded from the study due to regular use of a prohibited concomitant medication. A total of 48 patients therefore received one (1) dose of the Study Drug, with 47 of the 48 patients completing the requirements of their Study Arm. In addition, one patient in the 12-<17 year old group had a repeat 3mg IN Dosing Visit due to insufficient administration of glucagon (device malfunction during the initial Dosing Visit - the design defect that led to the device malfunction was corrected to prevent future malfunction). As a result, 11 patients were dosed with 2mg IN glucagon, and 18 patients each, were dosed with 3mg IN glucagon and IM glucagon across a total of 84 Dosing Visits (23 2mg IN Dosing Visits, 37 3mg IN Dosing Visits- 1 patient dosed twice, and 24 IM glucagon Dosing Visits.



[a]1 participant regularly taking Flonase was excluded from the study
[b]1 participant requested to withdraw prior to the second visit
Source: Appendix 16.2.4.4

Figure 13 Patient Disposition

Recruitment

Study initiation date: 18-Dec-2013 (first patient first visit)

Study completion date: 13-Jan-2015 (last patient last visit)

Conduct of the study

Protocol amendments

AMG103 Protocol v1.0 (dated the 23rd of July, 2013) was amended on the 15th of October, 2013 (Protocol Amendment #1). Due to the FDA's request that both doses of AMG504-1 (2mg and 3mg formulations) be evaluated in participants aged 4-<12 years of age, Protocol Amendment #1 dictated that the total number of study participants increase from 40, to 48 participants (12 participants required in the 12-<17 year old age cohort, and 18 participants, each, required in the 4-<8 and 8-<12 year old age cohorts).

AMG103 Protocol v2.0 (dated 15th of October 2013 was amended on the 18th of June, 2014 (Protocol Amendment #2). The minimum weight requirement was removed from the protocol (enacted in v3.0 dated 18-Jun-2014). Clarification was added that the number of blood draws was reduced for participants who did not weigh enough to collect all blood samples for the study. The maximum amount of blood collected remained at 5% of the participant's total blood volume. The rationale for this change was that many participants 4 and 5 years of age did not meet the minimum weight requirement for the study. In order to enroll younger participants, the weight requirement was being removed and the number of blood samples was reduced to accommodate the volume allowed for younger and smaller participants.

Protocol deviations

A total of 107 protocol violations were reported, none of which were deemed to have an impact on the assessment of the primary and secondary objectives.

Baseline data

Table 16 summarizes the demographic and clinical characteristics per age cohort of all 48 patients who were enrolled in the study and received at least one dose of the Study Drug. The mean (SD) age in the 4 –<8 year old cohort was 6.5 (1.2) years old. In the 8-<12 year old cohort, mean (SD) age was 11.1 (0.8) years old and in the 12-<17 year old cohort mean (SD) age was 14.6 (1.6) years old. In all age cohorts, the population was predominantly male (83.3% in the 4-<8 year old cohort; 55.6% in the 8-<12 year old cohort; 58.3% in the 12-<17 year old cohort), and ethnicity was predominantly White Non-Hispanic (100% in the 4-<8 year old cohort; 88.9% in the 8-<12 year old cohort; 83.3% in the 12-<17 year old cohort). As expected, duration of diabetes increased as age cohort increased, with a mean (SD) disease duration of: 2.8 (1.3) years in the 4-<8 year old cohort; 4.9 (1.8) years in the 8-<12 year old cohort; 6.6 (3.9) in the 12-<17 year old cohort. The proportion of patients in the 4-<8 year old age cohort who reported a severe hypoglycaemic event in the last 365 days (23%; n=4) was higher compared to the 8-<12 year old age cohort (11%; n=2) and the 12-<17 year old age cohort (8%; n=1).

Table 9 Demographic and Clinical Characteristics

	4 to <8 years old N=18	8 to <12 years old N=18	12 to <17 years old N=12
Age (years) – *n(%)*			
4 to <6	6 (33)	--	--
6 to <8	12 (67)	--	--
8 to <10	--	1 (6)	--
10 to <12	--	17 (94)	--
12 to <14	--	--	4 (33)
14 to <17	--	--	8 (67)
Median (25^{th}, 75^{th} percentile)	6.8 (5.7, 7.5)	11.1 (10.5, 11.8)	14.5 (13.2, 15.8)
Mean ±SD	6.5 ± 1.2	11.1 ± 0.8	14.6 ± 1.6
Female – *n(%)*	3 (16.7)	8 (44.4)	5 (41.7)
Race/ethnicity – *n(%)*			
White Non-Hispanic	18 (100)	16 (88.9)	10 (83.3)
Black Non-Hispanic	0	1 (6)	1 (8)
Hispanic or Latino	0	0	1 (8)
Other Race/Ethnicity	0	1 (6)	0
Duration of diabetes (years) – *n(%)*			
1 to <2	4 (22)	0	0
2 to <4	11 (61)	6 (33)	4 (33)
4 to <6	3 (17)	6 (33)	2 (17)
6 to <8	0	5 (28)	3 (25)
8 to <10	--	1 (6)	1 (8)

	4 to <8 years old N=18	8 to <12 years old N=18	12 to <17 years old N=12
≥10	--	0	2 (17)
Median (25th, 75th percentile)	2.8 (2.1, 3.8)	4.6 (3.8, 6.7)	5.9 (3.5, 8.0)
Mean ±SD	2.8 ± 1.3	4.9 ± 1.8	6.6 ± 3.9
Primary insulin modality – *n(%)*			
Insulin pump	10 (56)	16 (89)	9 (75)
Multiple daily insulin injections	8 (44)	2 (11)	3 (25)
Total daily insulin (units/kg) - median (25th, 75th percentile)	0.71 (0.55, 0.95)	0.75 (0.68, 0.84)	0.88 (0.77, 0.99)
Most recent severe hypoglycemic event[a] – *n(%)*			
≤30 days	0	0	0
31 to 90 days	2 (11)	0	0
91 to 180 days	1 (6)	2 (11)	0
181 to 365 days	1 (6)	0	1 (8)
>365 days	2 (11)	0	4 (33)
Never	12 (67)	16 (89)	7 (58)
HbA1c[b] – *n(%)*			
≤7%	2 (11)	2 (11)	3 (25)
7.1 to 8.0%	8 (44)	9 (50)	4 (33)
8.1 to 9.0%	5 (28)	4 (22)	2 (17)
9.1 to 10.0%	3 (17)	3 (17)	2 (17)
>10.0%	0	0	1 (8)
Mean ±SD	8.1 ± 0.8	7.9 ± 0.9	8.2 ± 1.5

* Includes only eligible participants with type 1 diabetes who completed the enrollment visit
[a]Severe hypoglycemic event defined as an episode that required third party assistance for treatment
[b]HbA1c performed locally
Source: Appendix 16.2.4.1 and Appendix 16.2.8.4

Numbers analysed

The primary analysis (PK and PD) and exploratory analyses (inferential statistics, PK/PD relationship, time to maximum blood glucose concentrations, and time to achieving an increase in blood glucose of ≥ 20 mg/dL and ≥25 mg/dL) included all participants who provide evaluable data for at least one of the treatments. One (1) patient's 2mg IN glucagon Dosing Visit (patient E057-0006; 4-<8 year old group) was excluded from the primary and exploratory analyses due to the fact that he blew his nose immediately after glucagon administration. In addition, one patient in the 12-<17 year old group (patient E057-0003) had a repeat 3mg IN Dosing Visit due to insufficient administration of glucagon (device malfunction during the initial Dosing Visit - the design defect that led to the device malfunction was corrected to prevent future malfunction) during the first Dosing Visit; this first visit was therefore considered as ineligible and not included in the efficacy and safety analyses. Therefore, all 48 patients who received at least one dose of Study Drug, had all completed Study Visits included in the primary analysis, with the exception of patient E057-0006, whose Dosing Visit was not considered as valid. The secondary analysis (safety and tolerability) included all completed Dosing Visits, regardless of validity.

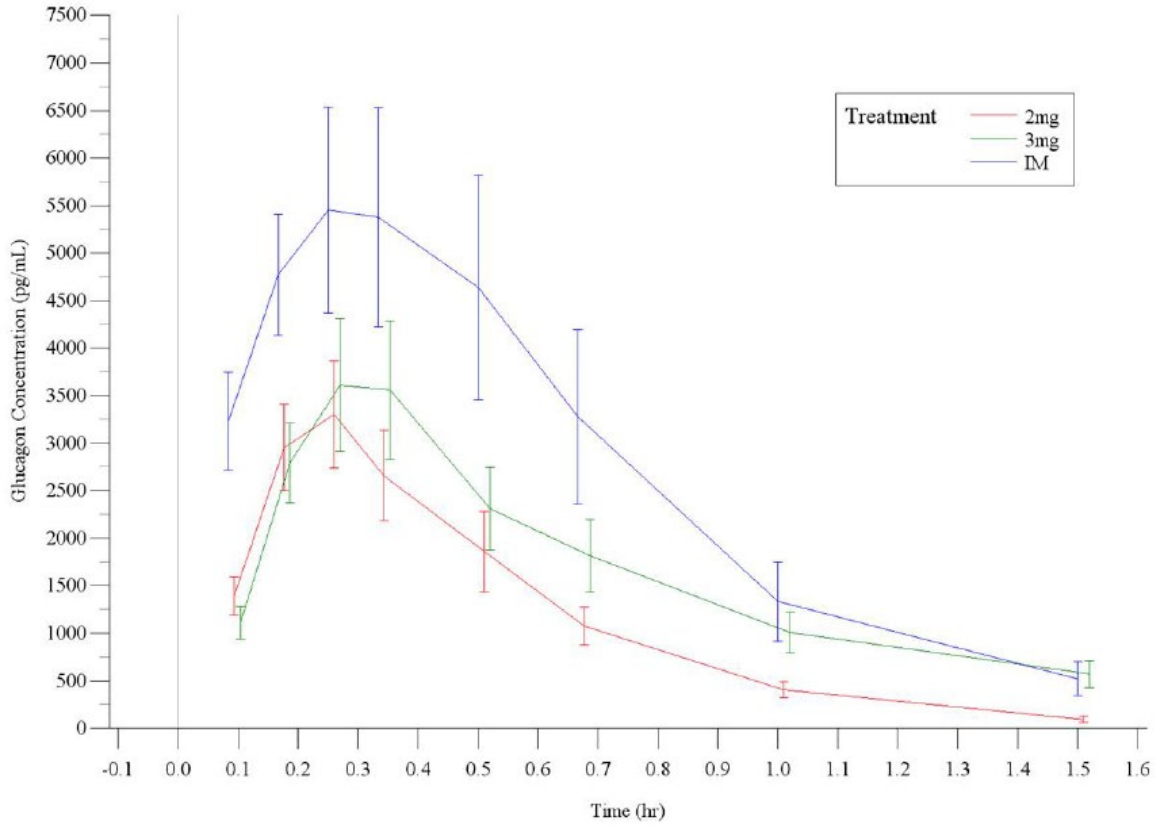
Overall, all 48 patients were included in the Primary, Safety, and Exploratory Analyses, with 84 Dosing Visits included in the Safety Analysis, and 82 Dosing Visits included in the Primary and Exploratory Analyses.

Outcomes and estimation

Table 10 Summary of Pharmacokinetic Parameters of Glucagon

	4 to <8 years old			8 to <12 years old			12 to <17 years old	
PK Parameter	IM Mean (CV%)	2mg† Mean (CV%)	3mg Mean (CV%)	IM Mean (CV%)	2mg†† Mean (CV%)	3mg Mean (CV%)	IM Mean (CV%)	3mg Mean (CV%)
N	6	11	12	6	11	12	12	12
$AUC_{0-1.5}$ (hr.pg/mL)	4158.18 (49.33)	1844.86 (53.78)	2583.90 (55.20)	3747.02 (54.76)	1767.92 (38.65)	3191.44 (35.70)	3267.09 (86.98)	2123.19 (62.12)
$AUC_{0-\infty}$ (hr.pg/mL)[b]	4446.48 (50.46)	1912.57 (54.02)	3177.21 (53.07)	4470.05 (49.46)	2065.96 (49.25)	3554.49 (38.54)	4134.62 (82.95)	2418.67 (58.16)
C_{max} (pg/mL)	6343.33 (31.99)	3530.55 (49.90)	4032.92 (60.38)	4817.17 (64.06)	2951.73 (34.68)	5832.42 (36.11)	4381.83 (86.06)	3185.58 (72.00)
T_{max} (hr)[a]	0.29 (0.08,0.50)	0.25 (0.17,0.33)	0.29 (0.17,1.00)	0.29 (0.08,0.50)	0.25 (0.17,0.33)	0.25 (0.17,0.50)	0.29 (0.08,0.50)	0.33 (0.25,0.50)
λ_z(1/hr)	2.18 (18.29)	2.48 (18.26)	1.60 (43.27)	1.36 (39.32)	1.79 (31.28)	2.00 (29.31)	1.24 (47.76)	1.73 (34.43)
CL(L/hr)[b]	0.0002 (67.76)	0.0020 (152.33)	0.0017 (108.81)	0.0003 (58.81)	0.0011 (35.10)	0.0010 (53.67)	0.0003 (40.08)	0.0019 (76.50)
$t_{1/2}$(hr)[ab]	0.33 (0.24,0.38)	0.27 (0.23,0.47)	0.51 (0.25,1.31)	0.55 (0.33,0.95)	0.36 (0.25,0.86)	0.35 (0.21,0.59)	0.63 (0.23,0.96)	0.40 (0.22,0.70)

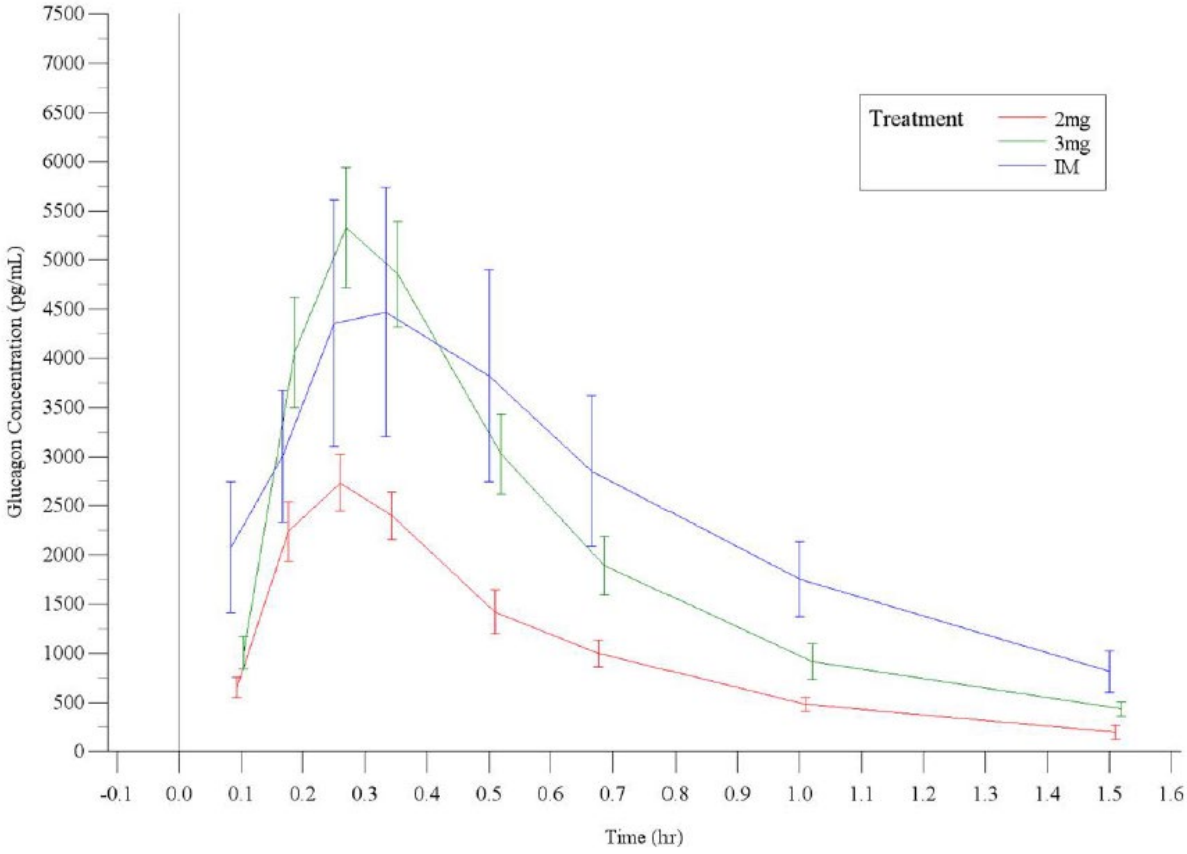
†Participant E057-0006(4-<8 years old) for practical reasons did not receive the full dose and was therefore excluded from the analysis of this period.
††E018-0003 (8-<12 years old) withdrew from study after the 3mg treatment.
[a]Median (Min, Max); [b]Not computable for patient E057-0003 age group 12-<17 at 3mg treatment
Source: Appendix 16.2.6.2



Source: JSS Medical Research

Source: Appendix 16.2.6.1

Figure 14 Average (±SE) Glucagon Concentration over Time by Treatment Group (Baseline-Adjusted): 4-<8 year old group

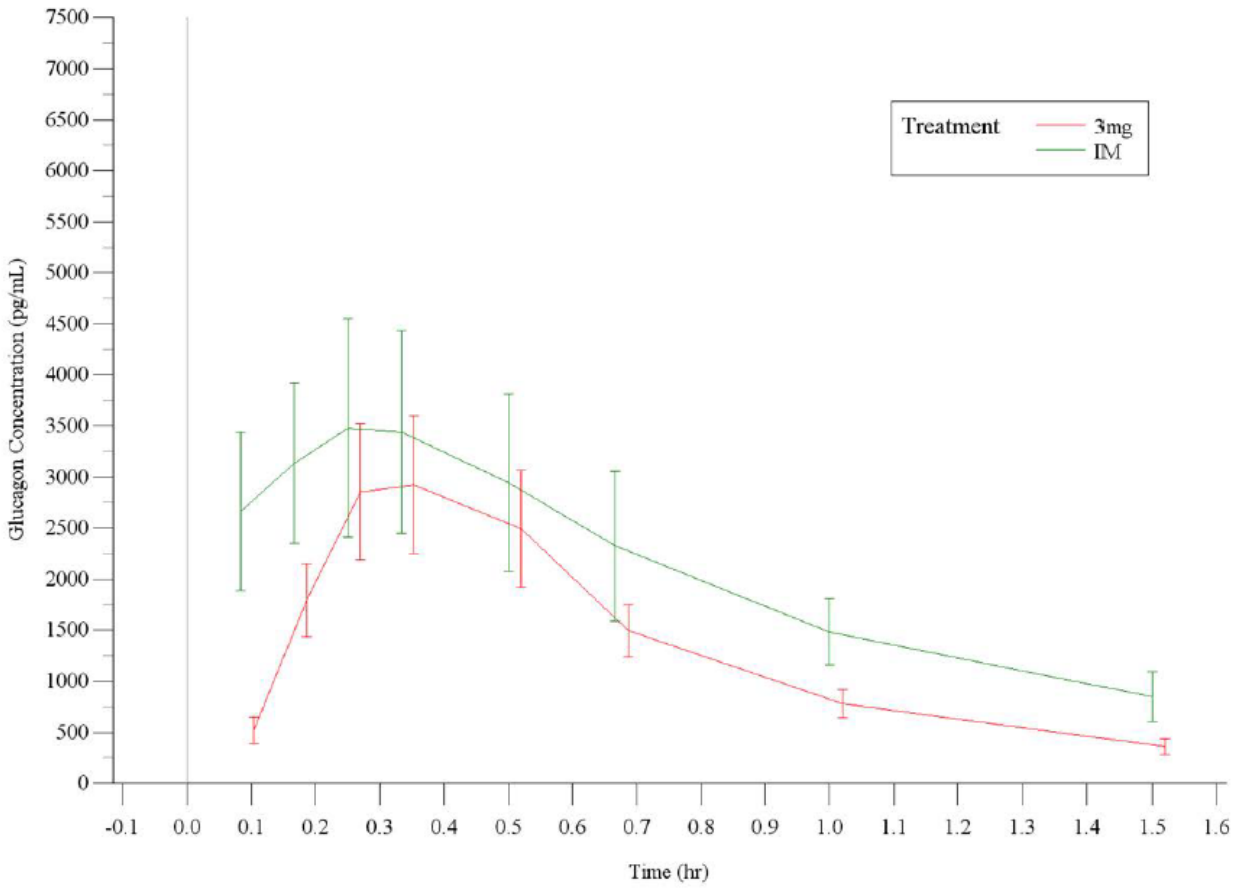


Source: JSS Medical Research

Source: Appendix 16.2.6.1

Figure 15 Average (±SE) Glucagon Concentration over Time by Treatment Group

(Baseline-Adjusted): 8-<12 year old group



Source: JSS Medical Research

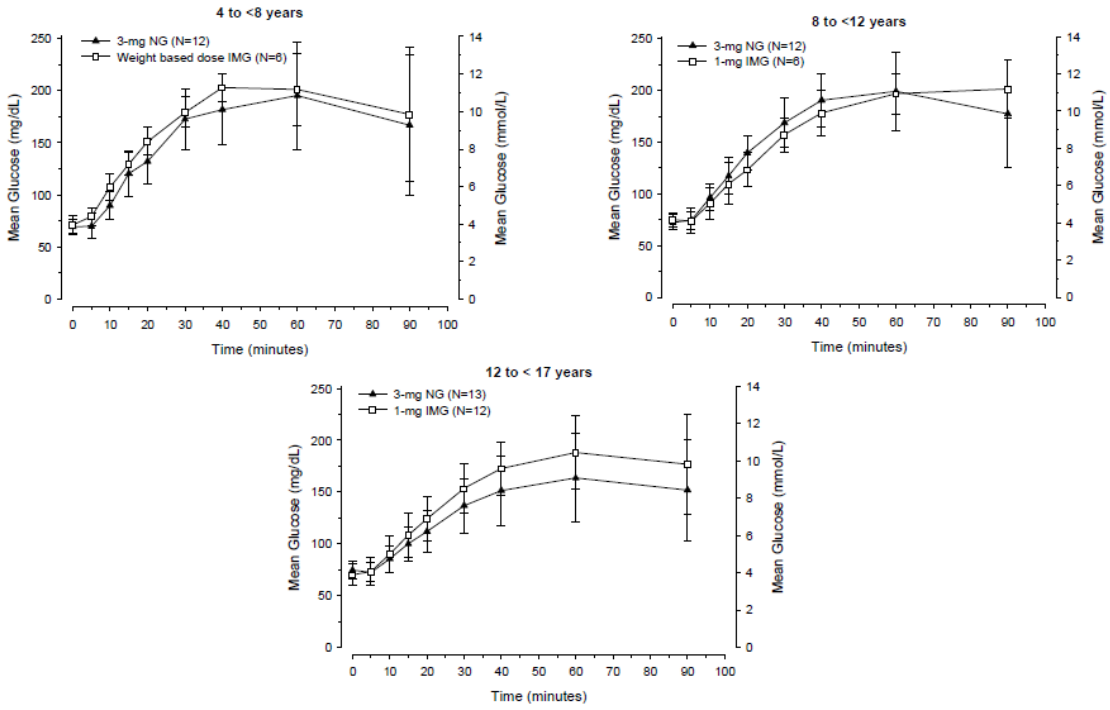
Source: Appendix 16.2.6.1

Table 11 Summary of Pharmacodynamic Parameters of Glucose

	4 to <8 years old			8 to <12 years old			12 to <17 years old	
PD Parameter	IM Mean (CV%)	2mg† Mean (CV%)	3mg Mean (CV%)	IM Mean (CV%)	2mg†† Mean (CV%)	3mg Mean (CV%)	IM Mean (CV%)	3mg Mean (CV%)
N	6	11	12	6	11	12	12	12
$AUEC_{0-1.5}$ (hr.mg/dL)	254.07 (12.89)	223.45 (31.07)	246.51 (22.07)	244.46 (11.25)	243.06 (14.15)	247.50 (15.91)	232.86 (17.02)	215.02 (13.62)
C_{max} (mg/dL)	210.33 (13.35)	188.3 6 (27.37)	207.00 (20.90)	205.33 (11.86)	201.27 (13.88)	205.83 (15.54)	193.83 (17.19)	178.17 (15.30)
T_{max} (hr)[a]	1.00 (0.67,1.50)	0.67 (0.33,1.00)	1.00 (0.50,1.50)	1.50 (1.00,1.50)	1.00 (0.67,1.50)	1.00 (0.50,1.50)	1.00 (0.67,1.50)	1.00 (0.50,1.50)
$AUEC_{Above}$	96.19 (33.90)	74.03 (75.83)	92.24 (54.75)	88.68 (27.79)	86.08 (38.13)	90.92 (42.15)	78.19 (46.17)	59.88 (46.31)
$AUEC_{Below}$	103.91 (2.28)	103.70 (2.66)	104.03 (1.62)	104.59 (0.97)	104.98 (0.05)	104.37 (1.59)	104.59 (0.64)	104.76 (0.77)
$AUEC_{Within}$	52.62 (3.00)	45.69 (32.04)	49.56 (9.87)	51.20 (5.52)	51.98 (3.80)	51.56 (3.61)	50.10 (8.07)	50.40 (4.67)
T_{Above}	0.17 (20.83)	0.20 (30.74)	0.23 (30.32)	0.25 (28.82)	0.21 (23.12)	0.22 (24.90)	0.27 (33.73)	0.28 (24.16)
T_{Below}[b]	NC	NC	NC	NC	NC	NC	NC	NC
T_{Within}	0.02 (180.45)	0.06 (166.20)	0.05 (121.82)	0.04 (244.95)	0.02 (222.62)	0.04 (115.36)	0.06 (113.02)	0.03 (250.06)
$Duration_{Above}$	1.31 (3.80)	1.08 (44.72)	1.19 (17.96)	1.25 (5.90)	1.27 (6.25)	1.27 (4.21)	1.19 (17.62)	1.17 (11.79)
$Duration_{Below}$	0.02 (180.45)	0.14 (188.05)	0.06 (125.45)	0.04 (244.95)	0.02 (222.62)	0.04 (104.74)	0.06 (113.02)	0.02 (272.81)
$Duration_{Within}$	0.17 (27.91)	0.27 (81.52)	0.25 (71.42)	0.22 (21.24)	0.21 (25.87)	0.18 (21.55)	0.25 (68.34)	0.31 (44.78)

†Participant E057-0006 (4-<8 years old) for practical reasons did not receive the full dose and was therefore excluded from the analysis of this period.
††E018-0003 (8-<12 years old) withdrew from study after the 3mg treatment.
[a]Median (Min, Max); [b]Not Computable

Summary of main efficacy results study IGBB



Abbreviations: IMG = intramuscular glucagon; N = number of patients; NG = nasal glucagon; SD = standard deviation.

Figure 16 Mean (+/-SD) observed glucose concentration over time by treatment group for the three age groups in Study IGBB.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the <benefit risk assessment><biosimilarity assessment> (see later sections).

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 12. Summary of main Efficacy for trial I8R-MC-IGBC

Title: Efficacy and Safety of Intranasal Glucagon for Treatment of Insulin Induced Hypoglycaemia in Adults with Diabetes			
Study identifier	**I8R-MC-IGBC**		
Design	Multicentre, randomised, open-label, 2-period crossover non-inferiority study which compared the efficacy and safety of nasal glucagon (NG; LY900018) 3 mg versus commercially-available intramuscular glucagon (IMG) 1 mg in reversing insulin-induced hypoglycaemia (insulin infusion was stopped when glucose was <60 mg/dL [3.3 mmol/L]) in adult patients with type 1 diabetes (T1D) or type 2 diabetes (T2D).		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Two dosing visits ≥7-28 days apart, each with a single dose of glucagon (NG or IMG) Not applicable Not applicable
Hypothesis	Non-inferiority		
Treatments groups (Randomised patients receiving study drug)	A single dose of nasal glucagon (NG) 3mg		83
	A single dose of intramuscular glucagon (IMG) 1mg		82
Endpoints and definitions	Primary endpoint	Percentage of patients achieving treatment success	Percentage of patients who achieved treatment success, defined as either an increase in glucose to ≥70 mg/dL (3.9 mmol/L) or an increase of ≥20 mg/dL (1.1 mmol/L) from nadir[a] within 30 minutes after receiving study glucagon.
	Other endpoint	Increase in glucose to ≥70 mg/dL (3.9 mmol/L)	Percentage of patients who achieved an increase in glucose to ≥70 mg/dL (3.9 mmol/L) from nadir[a] within 30 minutes after receiving study glucagon.
	Other endpoint	Increase of ≥20 mg/dL (1.1 mmol/L)	Percentage of patients who achieved a glucose increase of ≥20 mg/dL (1.1 mmol/L) from nadir[a] within 30 minutes after receiving study glucagon
	Other endpoint	Increase in glucose to ≥70 mg/dL (3.9 mmol/L) and an increase of ≥20 mg/dL (1.1 mmol/L)	Percentage of patients who achieved both an increase in glucose to ≥70 mg/dL (3.9 mmol/L) and an increase of ≥20 mg/dL (1.1 mmol/L) from nadir[a] within 30 minutes after receiving study glucagon

	Other endpoint	Time to achieving treatment success	Time to achieving either an increase in glucose to ≥70 mg/dL (3.9 mmol/L) or an increase of ≥20 mg/dL (1.1 mmol/L) from nadir[a] within 30 minutes after receiving study glucagon
Database lock	June 10, 2015		

Results and Analysis

Analysis Description	**Primary Analysis**			
Analysis population and time point description	Efficacy population: all randomised patients who received both NG and IMG with evaluable primary outcome Timepoint: within 30 minutes after receiving study glucagon			
	T1D		T1D and T2D	
Treatment Group (number of patients)	NG 3mg (N=75)	IMG 1mg (N=75)	NG 3mg (N=80)	IMG 1mg (N=80)
Treatment success n (%)	74 (98.7%)	75 (100%)	79 (98.8%)	80 (100%)
Treatment Difference (2-sided 95 % confidence interval)[b, c]	1.3% (-3.8%, 7.2%)		1.3% (-3.6%, 6.8%)	
Other endpoints				
Increase in glucose to ≥70 mg/dL (3.9 mmol/L)[d] n (%)	72 (97 %)	74 (99 %)	77 (97 %)	79 (99 %)
Increase in glucose of ≥20 mg/dL (1.1 mmol/L) [d] n (%)	74 (100 %)	75 (100 %)	79 (100 %)	80 (100 %)
Increase in glucose to ≥70 mg/dL (3.9 mmol/L) and an increase of ≥20 mg/dL [d] (1.1 mmol/L) n (%)	72 (97 %)	74 (99 %)	77 (97 %)	79 (99 %)
Time to treatment success (minutes)	16.2	12.2	15.9	12.1

a. Nadir is defined as the minimum glucose value at the time of or within 10 minutes following glucagon administration

b Difference calculated as (percentage in IMG) – (percentage in NG).

c 2-sided 95 % confidence interval (CI) using the unconditional profile likelihood method based on 'exact' tail areas; non-inferiority margin = 10 %.

[d] Percentage based on number of patients meeting treatment success.

Table 13. Summary of Efficacy for trial I8R-MC-IGBB

Title: Assessment of Intranasal Glucagon in Children and Adolescents with Type 1 Diabetes			
Study identifier	**I8R-MC-IGBB**		
Design	Multicentre, randomised, crossover study in paediatric patients (ages 4 to <17 years) with T1DM, assessing the PK, PD, efficacy and safety of glucagon administered intranasally (nasal glucagon; LY900018) in comparison with commercially-available intramuscular glucagon; insulin was used if necessary to attain a glucose <80 mg/dL (4.44 mmol/L) before glucagon dosing.		
	Duration of main phase:		1 (single dose of intramuscular glucagon) dosing visit or 2 dosing visits for patients randomised to cross-over treatment (7to 56 days apart, each with a single dose of intramuscular or nasal glucagon)
	Duration of Run-in phase:		Not applicable
	Duration of Extension phase:		Not applicable
Hypothesis	Exploratory: efficacy was assessed based on descriptive summary statistics		
Treatments groups (Randomised patients receiving study drug)	A single dose of nasal glucagon (NG) 3mg		36
	A single dose of intramuscular glucose (IMG): 0.5 mg (children below 25 kg) or 1 mg (children 25 kg or above)		24
Endpoints and definitions	Exploratory Efficacy endpoint	Percentage of treatment success	Percentage of patients who achieved treatment success, defined as an increase in glucose of ≥20 mg/dL (1.1 mmol/L) from nadir[a] within 30 minutes after receiving study glucagon
	Exploratory efficacy endpoint	Time to achieving treatment success	Time (in minutes) to achieving an increase in glucose of ≥20 mg/dL (1.1 mmol/L) from nadir[a] within 30 minutes after receiving study glucagon
Database lock	June 10, 2015		

Results and Analysis						
Analysis description	Exploratory Efficacy Analysis based on descriptive statistics					
Analysis population and time point description	Efficacy population: all randomised patients who received at least a dose of glucagon with evaluable efficacy outcome. Timepoint: within 30 minutes after receiving study glucagon					
Exploratory Endpoints						
	Young Children (4 to < 8 years old)		Children (8 to < 12 years old)		Adolescents (12 to < 17 years old)	
Treatment Group (number of patients)	NG 3mg (N=12)	IMG 0.5/1mg (N=6)	NG 3mg (N=12)	IMG 0.5/1mg (N=6)	NG 3mg (N=12)	IMG 0.5/1mg (N=12)
% of patients achieving an increase in glucose of ≥ 20 mg/dL (≥ 1.1 mmol/L)	100%	100%	100%	100%	100%	100%
Mean time to achieving an increase in glucose of ≥ 20 mg/dL (≥ 1.1 mmol/L), minutes	10.8	10.0	11.3	12.5	14.2	12.5

a. Nadir is defined as the minimum glucose value at the time of or within 10 minutes following glucagon administration

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

Clinical studies in special populations

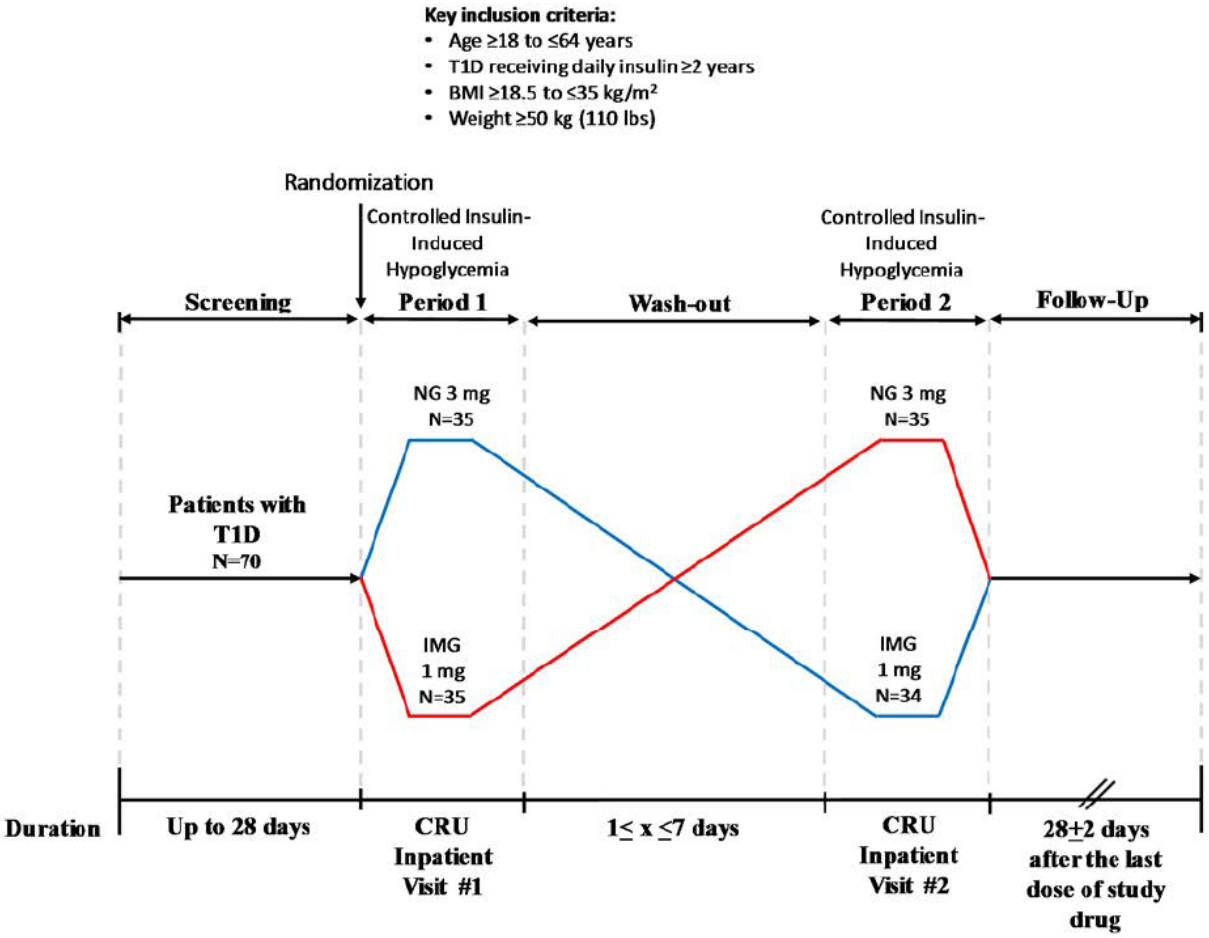
No studies were conducted in the elderly (>65 years) nor in patients with renal or hepatic impairment.

2.5.3. Supportive study(ies)

Study I18R-MC-IGBI

Study IGBI was a multicenter, randomized, open-label, 2-treatment, 2-period, crossover study conducted in adult patients with T1D. The primary objective of the study was to compare NG 3 mg commercial drug product and IMG 1 mg in the percent of adult patients with T1D achieving treatment success during controlled insulin-induced hypoglycemia. Once patient's glucose level was <60 mg/dl (3.3 mmol/L), the insulin infusion was stopped and approximately 5 minutes later NG or IMG was administered.

Figure 19 illustrates the study design for Study IGBI. The primary endpoint was the proportion of patients achieving treatment success.



Abbreviations: BMI = body mass index; CRU = clinical research unit; IMG = intramuscular glucagon; N = number of patients who received treatment; NG = nasal glucagon; T1D = type 1 diabetes mellitus.

Figure 17 Study design for Study IGBI

The primary endpoint in Study IGBI was the proportion of patients with T1D achieving "treatment success" during controlled insulin-induced hypoglycemia. Treatment success was defined as an increase in glucose to ≥ 70 mg/dL (3.9 mmol/L) or an increase of ≥20 mg/dL (1.1 mmol/L) from the glucose nadir within 30 minutes after receiving glucagon.

Seventy patients were randomized and received at least 1 dose of study drug. Sixty-nine patients completed the study. One patient discontinued the study due to an adverse event (AE) of vomiting. Three patients were excluded from the primary efficacy analysis since they had 1 treatment visit in which the nadir glucose concentration was ≥70 mg/dL (3.9 mmol/L), leaving 66 patients with T1D included in the efficacy analysis set. No patients received oral carbohydrates during the assessment period of treatment response.

Of the 70 enrolled patients, the mean (SD) age of participants was 41.7 (12.7) years. The majority of patients were male (N=43, 61.4%). The mean (SD) age of disease duration was 19.8 (10.6) years. All (100%) patients were white. Mean (SD) HbA1c levels at baseline were 7.3% (0.9%).

Glucose Nadir Values

Glucose nadir values for the 66 patients with T1D in the Efficacy Analysis Set are presented in Table 21.

Table 14 Glucose Nadir Values in the Efficacy Analysis Set in Study IGBI

Glucose Nadir (mg/dL)	NG 3 mg N=66	IMG 1 mg N=66
Mean ± SD	54.2 (5.6)	55.7 (5.3)
Median	56.0	56.0
Range (min, max)	(40.0, 65.0)	(41.0, 67.0)
Glucose Nadir (mmol/L)		
Mean ± SD	3.0 (0.3)	3.1 (0.3)
Median	3.1	3.1
Range (min, max)	(2.2, 3.6)	(2.3, 3.7)

Abbreviations: IMG = intramuscular glucagon; max = maximum; min = minimum; N = number of patients in the Efficacy Analysis Set; NG = nasal glucagon; SD = standard deviation.
Sources: CLUWE//statsclstr/lillyce/prd/ly900018/i8r_mc_igbi/csr1/output/shared/tfl/igbi_smpgluc_mg.rtf; CLUWE//statsclstr/lillyce/prd/ly900018/i8r_mc_igbi/csr1/output/shared/tfl/igbi_smpgluc_mmol.rtf.

Proportion of Patients with Treatment Success

The proportions of patients in the NG and IMG treatment groups achieving treatment success were 100% and 100%, respectively in the Efficacy Analysis Set, as presented in

Table 22. Nasal glucagon demonstrated non-inferiority to IMG in reversing insulin-induced hypoglycaemia since the upper limit of the 2-sided 95% CI for the difference is less than the non-inferiority margin of 10%. The proportions of patients achieving other glucose criteria are also presented by treatment group in this table. These results confirm the efficacy of NG commercial drug product to IMG.

Of the 66 patients in the Efficacy Analysis set, 3 patients in each group had glucose nadir <50 mg/dL (2.8 mmol/L) prior to glucagon dosing in both dosing visits. All these patients achieved treatment success within 30 minutes in both dosing visits.

Table 15 Proportion of Patients with Treatment Success in Study IGBI

	Efficacy Analysis (T1D) Set N=66[a]	
	NG 3 mg	**IMG 1 mg**
Treatment Success – n (%)	66 (100.0)	66 (100.0)
Treatment Difference (95% confidence limit)[b,c]	0.0% (-1.5%, 1.5%)	
Glucose Criterion Met – n (%)		
(i) ≥70 mg/dL (3.9 mmol/L)	66 (100.0)	66 (100.0)
(ii) Increase by ≥20 mg/dL (1.1 mmol/L) from nadir	66 (100.0)	66 (100.0)
Both (i) and (ii)	66 (100.0)	66 (100.0)

Abbreviations: CI = confidence interval; CSR = clinical study report; IMG = intramuscular glucagon; n = number of patients in the specified group; N = number of patients in the Efficacy Analyses Set; NG = nasal glucagon; T1D = type 1 diabetes mellitus.

a The Efficacy Analysis Set consisted of all patients who received both doses of the study drug with evaluable primary outcome.

b Difference calculated as (percentage with success in IMG) – (percentage with success in NG).

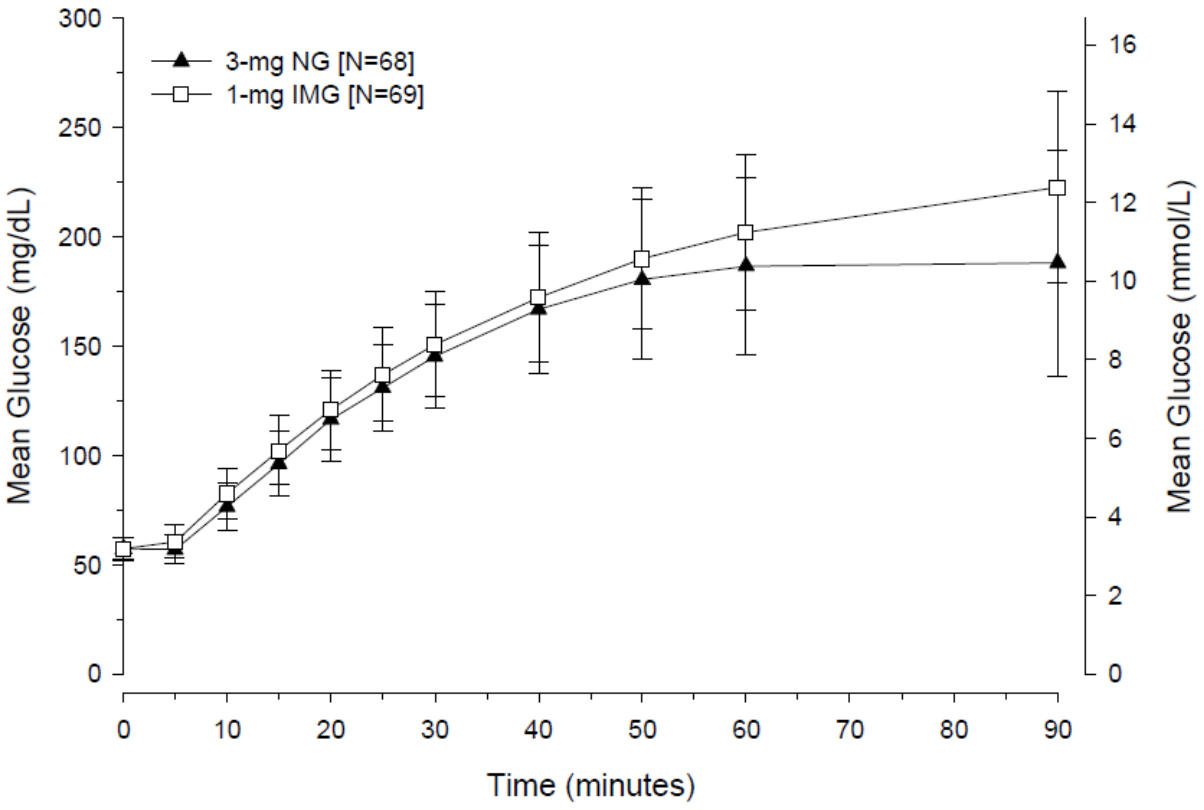
c 2-sided 95% CI from Wald method with continuity correction.

Sources: Study IGBI CSR, Table IGBI.7.1, Table IGBI.7.2.

Blood Glucose Change Over Time

For patients in the Full Analysis Set, nadir glucose levels were 55.2 mg/dL (3.1 mmol/L) and 56 mg/dL (3.1 mmol/L) for NG and IMG respectively.

Both NG 3 mg and IMG 1 mg rapidly raised glucose levels and produced mean glucose levels above 70 mg/dL (3.9 mmol/L) by 10 minutes post-glucagon dosing (Figure 20). Glucose levels of both treatment groups continued to rise thereafter. Nasal glucagon 3 mg demonstrated a similar glycemic response to IMG 1 mg through 40 minutes post-glucagon dosing. After the 40-minute time point the glucose profiles began to diverge; whereas the glucose profile with NG began to plateau by 60 minutes, the glucose profile with IMG continued to increase.



Abbreviations: IMG = intramuscular glucagon; N = number of patients; NG = nasal glucagon; SD = standard deviation; T1D = type 1 diabetes mellitus.

Figure 18 Mean (+/-SD) observed glucose concentration over time after glucagon administration by treatment groups in patients with T1D in Study IGBI, Full Analysis Set.

Time to Treatment Success

Time to treatment success represents time from glucagon administration to patients achieving treatment success; it does not include glucagon dose preparation time (for example, reconstitution time for IMG).

For patients in the Efficacy Analysis set, the mean time to treatment success was 11.4 and 9.9 minutes in the NG and IMG treatment groups, respectively . The time to reach an increase of ≥20 mg/dL (1.1 mmol/L) from glucose nadir was 12.4 and 11.2 minutes in the NG and IMG treatment groups, respectively.

Edinburgh Hypoglycemia Symptom Questionnaire

In this study, the Edinburgh Hypoglycemia Symptom Questionnaire was administered to patients to collect data of 13 signs and symptoms of hypoglycemia.

Symptoms of hypoglycemia, as represented by mean total scores, were mild and similar for both the NG (16.6) and IMG (16.2) groups prior to glucagon administration. There were no statistically significant differences between treatments in total score or subscale scores at either baseline or at any postdose time point. Furthermore, the total score and subscale scores were low compared to the maximum possible scores.

Summary of Study IGBI

Results from this clinical bridging and confirmatory study are consistent with what was observed in pivotal Study IGBC. Nasal glucagon commercial product raised glucose levels rapidly and demonstrated non-inferiority in treatment success compared to IMG for the correction of insulin-induced hypoglycemia in T1D patients.

Table 16. Summary of Efficacy for trial I8R-MC-IGBI

Title: Comparison of Glucagon Administered by Either the Nasal (LY900018) or Intra-Muscular (GlucaGen®) Routes in Adult Patients with Type 1 Diabetes Mellitus During Controlled Insulin-Induced Hypoglycaemia			
Study identifier	**I8R-MC-IGBI**		
Design	Multicentre, randomised, open-label, 2-treatment, 2-period, single-dose crossover study in patients with T1D that compared glucagon administered by either the nasal route (LY900018; nasal glucagon) or the IM route in reversing insulin-induced hypoglycaemia (insulin infusion was stopped when glucose was <60 mg/dL [3.3 mmol/L]) in adult patients with type 1 diabetes (T1D).		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase		Two dosing visits ≥1 to 7 days apart, each with a single dose of glucagon (NG or IMG) Not applicable Not applicable
Hypothesis	Non-inferiority		
Treatments groups (Randomised patients receiving study drug)	A single dose of nasal glucagon (NG) 3mg		70
	A single dose of intramuscular glucagon (IMG) 1mg		69
Endpoints and definitions	Primary endpoint	Percentage of patients achieving treatment success	Percentage of patients who achieved either an increase in glucose to ≥70 mg/dL (3.9 mmol/L) or an increase of ≥20 mg/dL (1.1 mmol/L) from nadir[a] within 30 minutes after receiving study glucagon.
	Other endpoints	Increase in glucose to ≥70 mg/dL (3.9 mmol/L)	Percentage of patients who achieved an increase in glucose to ≥70 mg/dL (3.9 mmol/L) from nadir[a] within 30 minutes after receiving study glucagon
		Increase of ≥20 mg/dL (1.1 mmol/L)	Percentage of patients who achieved a glucose increase of ≥20 mg/dL (1.1 mmol/L) from nadir[a] within 30 minutes after receiving study glucagon
		Increase in glucose to ≥70 mg/dL (3.9 mmol/L) and an increase of ≥20 mg/dL (1.1 mmol/L)	Percentage of patients who achieved both an increase in glucose to ≥70 mg/dL (3.9 mmol/L) and an increase of ≥20 mg/dL (1.1 mmol/L) from nadir[a] within 30 minutes after receiving study glucagon

		Time to achieving treatment success	Time to achieving either an increase in glucose to ≥70 mg/dL (3.9 mmol/L) or an increase of ≥20 mg/dL (1.1 mmol/L) from nadir[a] within 30 minutes after receiving study glucagon
Database lock	December 17, 2017		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Efficacy population: all randomised patients who received both NG and IMG with evaluable primary outcome. Timepoint: within 30 minutes after receiving study glucagon		
Treatment Group (number of patients)	NG 3mg (N=66)	IMG 1mg (N=66)	
Treatment success n (%)	66 (100 %)	66 (100 %)	
Treatment Difference (2-sided 95 % confidence interval)	0 % (-5.4%, 5.4%)		
Other endpoints			
Increase in glucose to ≥70 mg/dL (3.9 mmol/L)	66 (100%)	66 (100%)	
Increase of ≥20 mg/dL (1.1 mmol/L)	66 (100%)	66 (100%)	
Increase in glucose to ≥70 mg/dL (3.9 mmol/L) and an increase of ≥20 mg/dL (1.1 mmol/L)	66 (100%)	66 (100%)	
Time to treatment success (minutes)	11.4	9.9	

a. Nadir is defined as the minimum glucose value at the time of or within 10 minutes following glucagon administration

b Difference calculated as (percentage in IMG) – (percentage in NG).

c 2-sided 95 % confidence interval (CI) using the unconditional profile likelihood method based on 'exact' tail areas; non-inferiority margin = 10 %.

Study B002

In an adult actual use study (B002), patients with type 1 diabetes and their caregivers were dispensed Baqsimi to treat moderate or severe hypoglycaemic events in the home or work setting. A total of 157 moderate or severe hypoglycaemic events reported by 69 patients were included in the efficacy analysis. In 151 (96.2 %) of these events, patients awoke or returned to normal status within 30 minutes following Baqsimi administration. In all (100 %) 12 severe hypoglycaemic events, patients awoke, stopped convulsions or returned to normal status within 5 to 15 minutes following Baqsimi administration.

Study B001

In a paediatric actual use study (B001), patients aged 4 to < 18 years old with type 1 diabetes and their caregivers were dispensed 3 mg Baqsimi to treat moderate or severe hypoglycaemic events in the home or school setting. A total of 33 moderate hypoglycaemic events reported by 14 patients were included in the efficacy analysis. In all events, including clinically significant hypoglycaemia with a glucose level < 3.0 mmol/L (< 54 mg/dL), patients returned to normal status within 5 to 30 minutes following Baqsimi administration.

Study IGBE

Study IGBE was a single-center, open-label, 2-period, parallel study that assessed the impact of nasal decongestant and common cold on NG 3 mg PK and PD in 36 otherwise healthy adults. Common cold symptoms were assessed using the 8-item Jackson cold scale and peak nasal flow measurements were done before each glucagon administration.

Subjects with nasal congestion and/or nasal discharge associated with a common cold were randomly assigned to cohort 1 or 2. In Cohort 1, 18 subjects (9 males, 9 females, mean age [SD]: 32 [9]) received a single NG 3 mg dose. After a 7- to 28-day washout period, and after being cold-symptom-free for at least 2 days, these subjects received a second NG 3 mg dose. In total, 17 of 18 subjects completed both periods. In Cohort 2, 18 subjects (8 males, 10 females, mean age [SD]: 29 [8]) were given a dose (i.e. 2 sprays) of oxymetazoline, a nasal decongestant, in both nostrils 2 hours before a single NG 3 mg dose. This cohort did not receive a second dose of NG. In both cohorts, subjects fasted overnight for at least 10 hours before glucagon administration and continued fasting for at least 3 hours postdose. Blood samples were collected to measure baseline glucagon and glucose levels 30, 15, and ≤5 minutes (time 0) before NG dosing, and further samples were collected 5, 10, 15, 20, 30, 40, 60, 90, 120, 150, and 180 minutes after dosing.

Table 17 Summary of PK and PD Parameters – Study IGBE

	Change from Baseline Glucagon (PK) Parameters			Glucose (PD) Parameters		
Treatment (N_{PK}/N_{PD})	C_{max}[a] (pg/mL)	$AUC(0\text{-}t_{last})$[a] (pg.h/mL)	T_{max}[a] (hours)	BG_{max}[a] (mg/dL)	ΔBG_{max}[a] (mg/dL)	T_{BGmax}[a] (hours)
3 mg NG Cold (18/18)	1150 [87]	1040 [98]	0.3 (0.08, 1.50)	144 [23]	52.2 [54]	0.5 (0.25, 1.00)
3 mg NG Cold+Decongestant (18/18)	812 [74]	868 [72]	0.3 (0.17, 1.00)	158 [18]	61.2 [41]	0.7 (0.33,1.00)
3 mg NG No Cold (17/17)	746 [74]	632 [63]	0.3 (0.25, 0.67)	139 [19]	48.6 [50]	0.6 (0.33, 1.00)

Abbreviations: $AUC(0\text{-}t_{last})$ = area under the concentration curve from time 0 to the last quantifiable concentration (C_{last}); BG = blood glucose; BG_{max} = maximum observed blood glucose concentration; ΔBG_{max} = maximum change from baseline blood glucose concentration; C_{max} = maximum observed concentration; IMG = intramuscular glucagon; NG = nasal glucagon; N_{PD} = number of subjects in the PD analysis; N_{PK} = number of subjects in the PK analysis; PD = pharmacodynamics; PK = pharmacokinetics; T_{BGmax} = time to maximum blood glucose concentration; T_{max} = time to maximum drug concentration.

[a] Arithmetic mean [% coefficient of variation] is presented for C_{max}, BG_{max}, ΔBG_{max}, and $AUC(0\text{-}t_{last})$. Median (minimum, maximum) is presented for T_{max} and T_{BGmax}.

2.5.4. Discussion on clinical efficacy

Design and conduct of clinical studies

One pivotal study was conducted to compare the response of NG 3 mg with IMG 1 mg in a controlled clinical setting in adult patients. Study IGBC was a randomized, multicenter, open-label, in-patient, insulin-induced hypoglycemia study in 83 patients 18 to 65 years of age with T1D or T2D. The study was conducted at sites in the US. The patient population was predominantly white; the majority were diagnosed with T1D.

The primary efficacy outcome measure was the proportion of patients achieving treatment success, which was defined as either an increase in blood glucose to ≥70 mg/dL (3.9 mmol/L) or an increase of ≥20 mg/dL (1.1 mmol/L) from glucose nadir within 30 minutes after receiving study glucagon without receiving additional actions to increase the blood glucose level.

One pivotal study was conducted to compare the response of NG with IMG in a controlled clinical setting in pediatric patients. In addition to the comparison of NG 3 mg to weight-based IMG, the study also included a comparison of NG 2 mg with NG 3 mg as well as a comparison of NG 2 mg to weight-based IMG. Study IGBB was a multicenter, randomized, in-patient, crossover study in 48 patients 4 to <17 years of age with T1D. The study was conducted at sites in the US. Study IGBB was conducted in accordance with the iPSP agreed to by the Sponsor and the US FDA, and was agreed to by EMA/Paediatric Committee (PDCO) as part of the PIP.

A margin of 10% was used in Study IGBC to assess the non-inferiority of NG to IMG. The Applicant`s justification for the non-inferiority margin of 10% is considered not adequate (according to the Applicant the margin of 10% was chosen based on data for glucagon injection in a simulated emergency study where 10% of children and adolescents did not receive any glucagon at all due to difficulties in reconstituting the IM preparation). Albeit a difference in 10% between anti-hypoglycaemic treatments may be clinically relevant, the magnitude of the non-inferiority margin will not be further discussed (no implication in light of the well comparable results).

Efficacy data and additional analyses

In the NG clinical development program, doses ranging from 0.5 mg to 6 mg have been studied. In essence, a clear dose-response has not been established in the pharmacology and clinical studies. All studies investigating more than one dose of NG, were performed with a formulation distinct from the commercial formulation. The latter showed considerable differences in PK (Cmax about twice as high in adults, and extrapolated about 4-fold as high in children). An integrated dose-response analysis performed across studies estimated that NG 3 mg produced 87% of the maximal response (estimated as 81 mg/dl glucose increase), whereas NG 2 mg produced 73%. However, considerable variability between studies renders this integrated analysis difficult to interpret.

Taken together, as the primary goal of rescue treatment is to quickly restore blood glucose and safety concerns associated with high exposure will -in most instances – be less significant than therapeutic failure, use of the NG 3 mg dose in adults and adolescents is supported.

Existing data indicate that 3 mg nasal glucagon fully occupies the glucagon receptors for a short period of time and that any excess glucagon has no biological effects (maybe except for GLP-1 receptor stimulation which is not considered hazardous; it may cause additional nausea). Therefore, using the adult dose also for young children is acceptable. In the pivotal study in adults (IGBC) in the primary analysis population, comprised of patients with T1D with a glucose nadir of <70 mg/dl (N=75), the proportions of patients in the NG 3 mg and IMG 1 mg treatment groups who achieved treatment success were 98.7% and 100%, respectively. The difference in the proportion of patients who achieved treatment success was 1.3%, with the 1-sided upper 97.5% confidence interval of 4.0%, which is below the non-inferiority margin of 10%; thus, in principle, NG demonstrated non-inferiority to IMG in reversing insulin-induced hypoglycemia (still, a definite conclusion is subject to the clarification of the a. m. methodological shortcomings with respect to the primary analysis; in particular, missing pre-specification and validity of the primary analysis).

The critical findings in the GCP inspection of Study IGBB in respect to source data handling most likely also apply for the pivotal adult study IGBC because data handling was similar. PK data cannot be relied upon due to inadequate sample processing; this impacts PD data to a lesser extent, which therefore seem to be reliable.

In the primary analysis population, 97.3% of patients in the NG 3 mg treatment group and 98.7% of patients in the IMG 1 mg treatment group achieved both glucose criteria of treatment success. Of the five patients with T2D included in the efficacy analysis, 100% achieved treatment success with NG and IMG within 30 minutes of glucagon administration. The sensitivity analysis conducted in patients with T1D with a glucose nadir of <50 mg/dl at both dosing visits (n=39 [52%]) also demonstrated non-inferiority to IMG in the proportion of patients achieving treatment success.

Patients in the primary analysis population had a mean time to treatment success of 16.2 minutes and 12.2 minutes in the NG and IMG treatment groups, respectively. In clinical practice, time starts at the caregiver`s decision to dose. Therefore, the time needed to reconstitute the IMG would delay administration. Hence, the 4 min difference in study IGBC is unlikely to occur in the real-world setting.

Symptom scores in the hypoglycemia questionnaire were similar for the NG (20.6) and IMG (20.0) groups prior to glucagon administration. Most patients in both treatment groups had mild symptoms. At 30 minutes, both treatment groups had a 20% decrease in symptoms from baseline, indicating similar improvement of symptoms of hypoglycemia. Hypoglycemia symptoms for both treatment groups continued to improve through 45 minutes.

In the pivotal study in the pediatric population (study IGBB) all (100%) patients in both treatment arms across all age groups achieved an increase in glucose ≥20 mg/dl from nadir within 30 minutes of glucagon administration. All patients across all treatment and age groups achieved this increase in glucose within 20 minutes post-glucagon administration. This was confirmed by an analysis applying the original response criterion: all patients achieved an increase in glucose ≥25mg/dL by 20 minutes post glucagon administration.

An additional post-hoc analysis of a subgroup of patients (n=6 IMG; n=9 NG 3 mg) whose glucose nadir was <70 mg/dl was performed using the same primary endpoint criteria used in the adult efficacy integrated analysis. All 6 patients (100%) in the injectable glucagon group (mean glucose nadir of 58.2 mg/dl) and all 9 patients (100%) in the NG group (mean glucose nadir of 60.7 mg/dl) achieved treatment success of a glucose increase to ≥70 mg/dl or an increase of ≥20 mg/dl from nadir within 30 minutes of glucagon administration. In addition, all 6 patients (100%) in IMG group and all 9 patients (100%) in the NG 3 mg group met both of the glucose criteria.

The average time to achieve glucose increase of ≥20 mg/dl and ≥25 mg/dl, respectively, was determined. Results were similar for NG 3mg and IMG across all age groups (for an increase ≥20 mg/dl: young children IMG 10.0 minutes, NG 10.8 minutes; children IMG 12.5 minutes, NG 11.3 minutes; adolescents IMG 12.5 minutes, NG 14.2 min).

The clinical bridging and confirmatory study (IGBI) served to compare the commercial and the clinical trial drug products.

The proportions of patients in the NG and IMG treatment groups achieving treatment success were 100% and 100%, respectively, and non-inferiority was shown. Three patients in each group had a glucose nadir <50 mg/dl prior to glucagon dosing in both dosing visits. All these patients achieved treatment success within 30 minutes in both dosing visits. The mean time to treatment success was 11.4 and 9.9 minutes in the NG and IMG treatment groups, respectively

Symptoms of hypoglycemia as assessed in the hypoglycemia questionnaire, as represented by mean total scores, were similar for both the NG (16.6) and IMG (16.2) groups prior to glucagon administration. At 30 min post-dose mean total scores were 14.3 (-2.3) for NG and 14.5 (-1.7) for IMG. Scores are considered generally low (reflecting a population with milder forms of hypoglycaemia), compared with the maximum possible scores (7x13=91).

In the actual use study in adults (B002) 157 hypoglycemic events (from 69 patients) were evaluable, of which 151 (96.2%) met the primary endpoint, defined as patients awakened or returned to normal status within 30 minutes following NG administration. The six events (3.8%) not resolved within 30 minutes were all moderate hypoglycemic events; 1 had a blood glucose level that returned to normal (>70mg/dl) by 30 minutes but had a persistent headache, and 5 events had returned to normal status between 30 and 45 minutes without the use of additional measures to raise glucose levels. Importantly, all severe hypoglycemic events (n=12) resolved. No caregivers called for external professional emergency medical assistance. In 80.5% of events caregivers reported that it was easy to administer NG and that they were satisfied with the use of NG (94.4% of events).

In the pediatric actual use study (B001) all moderate hypoglycemic events (n=33, 100%) from all 14 patients in the efficacy analysis met the primary endpoint. No severe hypoglycemic events were reported. This may be due to the fact that symptoms of hypoglycemia and physiological hormone responses may occur at a higher glucose level in children compared to adults (Ly et al., 2014) and that most caregivers intervene before severe hypoglycemia sets in. Clinically significant hypoglycemia or major hypoglycemia, defined as a blood glucose level of <54mg/dl was, however, reported; all these events (n = 17) were resolved within 30 minutes. In this study, no caregivers called for external professional emergency medical assistance. No patients ingested oral carbohydrates or used an injectable glucagon kit before the hypoglycemic event was resolved. For most of the hypoglycemic events (93.9%), caregivers reported that it was easy or very easy to administer NG and that they were satisfied with the use of NG.

As an additional analysis an indirect between-study comparison was conducted between study IGBC and IGBI which showed a comparable efficacy in terms of treatment success between the NG 3 mg clinical trial drug product in the and the NG 3 mg commercial drug product. Difference in time to treatment success between NG and IMG (NG minus IMG) was 1.5 min for study IGBI, which was slightly shorter than what was observed in study IGBC (4 min). The shorter time to treatment success shown in this between study comparison may well be due to the difference in Cmax (tmax was however comparable, please refer to PK section of this report). Overall, this additional analysis shows that the clinical implications of the observed differences in PK are likely to be modest and justify the conclusion of comparable efficacy in adults and adolescents.

Elderly patients were not sufficiently represented in the clinical studies. In studies IGBC and IGBI patients up to 65 and 64 years, respectively, were enrolled; the study population was young (mean age: 32.9 years IGBC, 42.7 years IGBI). In the adult actual use study B002 patients up to 75 years could be included, the oldest patient included was 71 years. Older patients are at increased risk of hypoglycemia since they tend to be frail and on polypharmacy.

It is agreed that the available data (including newly submitted data of study ICGJ) in patients above 65 years of age (no patient above the age of 70 was included in the study program) hint at an efficacy and safety profile in line with the one in younger patients. The issue, that data in patients above the age of 70 are missing, is now reflected in section 4.2 of the SmPC by the following sentence:

"There are only limited data on the safety and efficacy of X in patients aged 65 years and above and no such data in patients aged 70 and above."

Adults

In the primary analysis population, comprised of patients with T1D with a glucose nadir of <70 mg/dL (3.9 mmol/L) (N=75), the proportions of patients in the NG 3 mg and IMG 1 mg treatment groups who achieved treatment success were 98.7% and 100%, respectively. The difference in the proportion of patients who achieved treatment success was 1.3%, with the 1-sided upper 97.5% confidence interval of 4.0%, which is below the NIM of 10%; thus, NG demonstrated non-inferiority to IMG in reversing insulin-induced hypoglycemia.

Paediatric patients

All (100%) patients in both treatment arms across all age groups achieved a glucose increase of ≥20 mg/dL (1.1 mmol/L) and ≥25 mg/dL (1.4 mmol/L) from nadir within 20 minutes of glucagon administration. The mean times to achieve these increases were similar for NG and IMG across all age groups. In both treatment groups across all age groups, glucose levels started to rise quickly. Across all age groups, NG 3 mg demonstrated a glycemic response similar to IMG, and glucose levels continued to rise through 60 minutes post glucagon administration.

2.5.5. Conclusions on the clinical efficacy

The efficacy of glucagon is unquestionable; in this application the focus is on demonstrating efficacy of the intranasal administration.

The pivotal adult study (Study IGBC) enrolled limited number of patients with T2D but their glucose response over time following NG administration was similar to adult patients with T1D.

In the primary analysis population, comprised of patients with T1D with a glucose nadir of <70 mg/dL (3.9 mmol/L) (N=75), the proportions of patients in the NG 3 mg and IMG 1 mg treatment groups who achieved treatment success were 98.7% and 100%, respectively.

The time to treatment success was 2 to 4 minutes longer for patients treated with NG 3 mg compared to patients treated with IMG 1 mg.

All (100%) pediatric patients in both treatment arms across all age groups in Study IGBB achieved a glucose increase of ≥20 mg/dL (1.1 mmol/L) and ≥25 mg/dL (1.4 mmol/L) from nadir within 20 minutes of glucagon administration.

In the pivotal controlled studies, NG 3 mg produced clinically relevant increases in response to insulin-induced (moderate) hypoglycaemia, showing comparable success rates as IMG. These findings are supported by actual-use studies which evaluated effectiveness of NG in the treatment of moderate to severe hypoglycaemia in a real world setting. In these studies, the caregivers successfully delivered NG in a stressful setting, and no caregivers called for external professional emergency medical assistance. In addition, for most of the hypoglycaemic events, caregivers reported that it was easy to administer NG compared to injectable glucagon and that they were satisfied with the use of NG.

Albeit the number of T2DM patients included in the development program was low, an indication comprising both types of diabetes is considered justified, as the mechanism of action is unlikely to be different in T2DM patients. The time to treatment success was 2 to 4 minutes longer for patients treated with NG 3 mg compared to patients treated with IMG 1 mg; however, the time required for the multistep preparation of injectable glucagon was not included, thereby disfavouring NG.

The adult and pediatric pivotal studies did not assess efficacy in severe hypoglycaemia, since induction of this condition is unethical (even more so in children). However, increases in glucose from normoglycemic baseline have likewise been used as a biomarker to support approval of injectable glucagon products. Extrapolation of results to severe hypoglycaemia is considered eligible.

A routine GCP inspection of the paediatric study IGBB yielded critical findings related to sample processing and data handling which cannot be corrected post-hoc. In the paediatric study IGBB the data recording system provided by the sponsor was not GCP compliant. Part of the information stored in the eCFRs could be verified by independent recordings at the individual study sites.

The results of the newly performed analysis taking these data detected at the individual study sites into account (including patients for whom >90% of source data were available) are in agreement with the previous analysis including the entire patient population. The MO pertaining to GCP non-compliance of the data recording system for study IGBB has been considered addressed

The critical findings in the GCP inspection of Study IGBB in respect to source data handling may also apply for the pivotal adult study IGBC because data handling was similar. but according to the inspectors this impacts PD data of Study IGBC to a lesser extent. The Applicant has provided convincing evidence that the newer studies, using the commercial Baqsimi product, are sufficient to support MAA of Baqsimi in adults.

2.6. Clinical safety

Patient exposure

The Table below shows the diagram of primary, clinical bridging, confirmatory, and supportive analysis datasets for safety analyses of nasal glucagon studies.

Study	Population Studied	NG vs Active Comparator (Y or N)	NG 3 mg Exposure n	In Setting of Reduced Glucose (Y or N)	Study Purpose
IGBC	Adult T1D and T2D	Y	83	Y	Pivotal Study
IGBA	Adult T1D	Y	8	Y	Dose Finding
IGBD	Healthy Adult Volunteers	Y	0	N	First Human Dose
IGBE	Healthy Adult Volunteers	N	36	N	Common Cold
IGBF	Adult T1D and T2D	Y	49	N	Immunogenicity
IGBG	Adult T1D and T2D	N	27	N	Double Dose
IGBI	Adult T1D	Y	70	Y	Clinical Bridging to Commercial Product
B002	Adult T1D	N	87	N	Actual-Use
IGBB	Pediatric T1D	Y	36	Y	Pivotal Study
B001	Pediatric T1D	N	22	N	Actual-Use

Abbreviations: n = number of patients; N = no; NG = nasal glucagon; T1D = type 1 diabetes mellitus; T2D = type 2 diabetes mellitus; Y = yes.
Note: Study IGBH was terminated early and is not included in this figure. Three patients received NG 3 mg. The safety data from this study are presented in the IGBH clinical study report. Study IGBH was repeated under a new trial alias, Study IGBG, and data from Study IGBG are included in the Adult Integrated Safety Population.

A total of 499 patients, including 70 patients <18 years of age, received the study drug (either NG or IMG) in the 11 completed clinical studies (Table 25) Of these patients, 461 received NG, with 421 patients receiving the 3 mg dose proposed for registration. Additionally, of these 461 NG-treated patients, 365 were patients with T1D, 44 were patients with T2D, and 52 were adults without diabetes. A total of 234 patients received IMG at the approved dose of 0.5 mg or 1 mg.

Since most studies employed a crossover design, many patients received both NG and IMG, so the total number of patients is less than the sum of NG patients and IMG patients.

Table 18 Summary of Adult and Pediatric Exposure to Study Drug in the Nasal Glucagon Clinical Studies (IGBA, IGBB, IGBC, IGBD, IGBE, IGBF, IGBG, IGBH, IGBI, B001, and B002)

Population	Total (N)	CG[a] (Total) (N)	NG (Total) (N)	NG 3 mg (N)	NG (T1D) (N)	NG (T2D) (N)	NG (HV) (N)
Adult patients[b]	429	210	403	363	307	44	52
Pediatric patients[b]	70	24	58	58	58	--	--
Total[b]	**499**	**234**	**461**	**421**	**365**	**44**	**52**

Abbreviations: CG = control glucagon; CSR = clinical study report; HV = adults without diabetes; N = total number of patients; NG = nasal glucagon; T1D = type 1 diabetes mellitus; T2D = type 2 diabetes mellitus.

a Included 1 mg intramuscular injection of glucagon or 1 mg subcutaneous injection of glucagon in adult studies, and 0.5 or 1 mg intramuscular injection of glucagon in the pediatric study.

b Number of total patients is not the sum of NG- and CG-treated patients because a patient may have received both NG and CG in a crossover study and is counted in each respective treatment group, but is only counted once in the total.

Sources: CLUWE: //statsclstr//lillyce/prd/ly900018/idb/output/shared/smexp111.rtf;
CLUWE: //statsclstr//lillyce/prd/ly900018/idb/output/shared/smexp112.rtf;
CLUWE: //statsclstr//lillyce/prd/ly900018/idb/output/shared/smdem121.rtf;
CSR synopses for Studies IGBA, IGBB, IGBC, IGBD, IGBE, IGBF, IGBG, IGBH, IGBI, B001, and B002.

Overall Adult Exposure

Table 26 presents a summary of exposure to NG and IMG by dose for all adult patients in the 9 NG clinical studies. A total of 403 adult patients received at least 1 dose of NG in the adult studies.

Approximately 45% of the patients (178/403) received more than 1 dose of NG (maximum of 11 doses), and the majority of patients (363/403 [90.1%]) received the 3 mg dose proposed for registration. In addition, 210 patients received at least 1 dose of IMG, which was either a subcutaneous or intramuscular injection of 1 mg glucagon, dependent on the study.

Table 19 Summary of Exposure Adult Patients in the Nasal Glucagon Clinical Studies (IGBA, IGBC, IGBD, IGBE, IGBF, IGBG, IGBH, IGBI, and B00

	CG (N=210)		NG_all (N=403)				
	IMG 1 mg n (%)	SCG 1 mg n (%)	NG 0.5 mg n (%)	NG 1 mg n (%)	NG 2 mg n (%)	NG 3 mg n (%)	NG 6 mg n (%)
Total number of patients	177 (84.3)	33 (15.7)	15 (3.7)	26 (6.5)	34 (8.4)	363 (90.1)	41 (10.2)
Total number of doses	227	33	15	26	34	597	91

Abbreviations: CG = control glucagon; CSR = clinical study report; IMG = intramuscular glucagon; N = total number of patients; n = number of patients in the specified category; NG = nasal glucagon; SCG = subcutaneous injection of glucagon.

Note 1: The number of patients in NG_all group is not the sum of each NG dose because a patient may have received different NG doses due to crossover design, but is only counted once in the NG_all group.

Note 2: Control glucagon included 1 mg intramuscular injection of glucagon, and 1 mg subcutaneous injection of glucagon.

Sources: CLUWE: //statsclstr//lillyce/prd/ly900018/idb/output/shared/smexp111.rtf; Study B002 CSR, Table B002.8.1; Study IGBH CSR, Appendix 16.2.5;
CLUWE: //statsclstr//lillyce/prd/ly90018/i8r_mc_igbi/csr1/output/shared/l_exi.doc;
CLUWE: //statsclstr//lillyce/prd/ly90018/i8r_mc_igbi/csr1/output/shared/l_exn.doc.

Although data are limited for the pediatric subgroup of the target population, the CHMP agreed that safety data generated in both, adults and younger patients can provide reassurance regarding the safety of NG in the total target population.

Hypoglycemia is a common side effect in patients treated with insulin, which potentially leads to repetitive administration of glucagon. This was also seen in different trials, where patients received up to 11 administrations of the study drug.

While patients with DT2 are more prevalent in the society, they were less represented in the trials. It is accepted that both groups of patients with DT1 or DT2 have similar side effects due to exposure from administration of glucagon.

Adverse events

Adverse events were collected and assessed in 2 complementary ways: as spontaneously reported AEs and as symptoms solicited through questionnaires.

The percentage of patients suffering at least one AE differed between the studies. In study **IGBC**, **55.4%** and **45.1%** reported at least one AE with Baqsimi and GlucaGen, respectively; in Study **IGBI** the percentages were **44.3%** vs. **46.4%** (nasal vs. IM) and in Study **IGBF 100%** vs. **80.8%** (nasal vs. injected). The higher AE incidence in Study IGBF is probably due to the fact that in the latter the participants received three glucagon administrations instead of one as in the other studies.

Adverse Events in Adults

Table **27** presents a summary of TEAEs reported in at least 2% of patients in either the NG 3 mg or IMG treatment groups at the preferred term level, by SOC and treatment group.

Table 20 Summary of Treatment-Emergent Adverse Events in At Least 2% of Patients in Either Treatment Group by System Organ Class, Preferred Term and Treatment Group Study IGBC

System Organ Class Preferred Term	CG (N=82) n (%)	NG 3 mg (N=83) n (%)
Patients reporting ≥1 TEAE	37 (45.1)	46 (55.4)
Gastrointestinal disorders	30 (36.6)	29 (34.9)
Nausea	22 (26.8)	18 (21.7)
Vomiting	9 (11.0)	13 (15.7)
Nervous system disorders	8 (9.8)	18 (21.7)
Headache	7 (8.5)	17 (20.5)
Head discomfort	0	2 (2.4)
Somnolence	0	2 (2.4)
Respiratory, thoracic, and mediastinal disorders	1 (1.2)	16 (19.3)
Nasal discomfort	0	8 (9.6)
Nasal congestion	1 (1.2)	7 (8.4)
Rhinorrhea	1 (1.2)	2 (2.4)
Eye disorders	1 (1.2)	8 (9.6)
Lacrimation increased	1 (1.2)	7 (8.4)
Eye pruritus	1 (1.2)	2 (2.4)
General disorders and administration site conditions	7 (8.5)	8 (9.6)
Fatigue	7 (8.5)	7 (8.4)
Facial pain	0	2 (2.4)
Skin and subcutaneous tissue disorders	2 (2.4)	4 (4.8)
Pruritus	1 (1.2)	3 (3.6)
Musculoskeletal and connective tissue disorders	0	3 (3.6)
Muscular weakness	0	2 (2.4)
Ear and labyrinth disorders	1 (1.2)	2 (2.4)
Ear pain	1 (1.2)	2 (2.4)

Abbreviations: CG = control glucagon (intramuscular glucagon); N = total number of patients; n = number of patients in the specified category; NG = nasal glucagon; TEAE = treatment-emergent adverse event.
Source: CLUWE: //statsclstr//lillyce/prd/ly900018/i8r_mc_igbc/final/output/shared/tfl/igbc_smtea111.rtf.

At least 1 TEAE was reported by 55.4% of NG-treated patients and 45.1% of IMG-treated patients. Very commonly reported TEAEs (≥10% of patients) in the NG 3 mg group were nausea, headache, and vomiting. Nausea and vomiting were reported with similar incidences in the NG 3 mg and IMG groups.

In addition, nasal/respiratory/anosmia TEAEs (a subset of all TEAEs) were very commonly reported (≥10% of patients) in the NG 3 mg group. Only TAE's from the upper respiratory tract (the area of the nose) are observed.

Supportive Analyses from Additional Integrated Datasets

Eye Disorders

Lacrimation Increased

One hundred twenty-two (52.1%) NG-treated patients and 2 (1.4%) IMG-treated patients reported lacrimation increased. Four events (NG) were severe, but none of the events were considered serious. In all studies the events were resolved within 1 day.

Ocular Hyperemia

Fifty-two (22.2%) NG-treated patients and 2 (1.4%) IMG-treated patients reported ocular hyperemia. One event (NG) was severe but was not considered serious. In all studies, approximately 95% of the events resolved within 1 day.

Eye Pruritus

Thirty-four (14.5%) NG-treated patients and 3 (2.1%) IMG-treated patients reported eye pruritus. Two events (NG) were severe, but none of the events were considered serious. In all studies, all events resolved within a day.

Nervous System Disorders

Headache

Eighty-six (36.8%) NG-treated patients reported 114 TEAEs of headache, and 14 (9.9%) IMG-treated patients reported 16 events. Two events (NG) were severe, but none of the events were considered serious. Three events (NG, 1; IMG, 2) did not have a documented resolution during the study. In Study IGBC, where TEAE start date/time and end date/time were only recorded as a date, 18 of the 24 TEAEs of headache resolved within 1 day, 5 events (NG, 2; IMG, 3) resolved in 1 to 2 days, and 1 event (NG) resolved in 2 to 3 days. In the other studies that recorded time in addition to date, approximately 50% of events resolved within 4 hours, approximately 92% of events resolved within 1 day, and approximately 8% of events took longer than 1 day to resolve.

Headache is not a mentioned side effect in the SmPC of IMG. The Applicant explained the different manifestations of headache and the possible relationship with passing of glucagon through the blood-brain barrier. These explanations were accepted.

Gastrointestinal Disorders

Nausea and Vomiting

Sixty-four (27.4%) NG-treated patients and a similar proportion of IMG-treated patients (38 [27.0%] patients) reported nausea. Four events (NG, 3; IMG, 1) were severe, but none were considered serious. In all studies, approximately 98% of events resolved within 1 day.

Thirty-nine (16.7%) NG-treated patients and a similar proportion of IMG-treated patients (19 [13.5%] patients) reported vomiting. Three TEAEs (NG, 2; IMG, 1) of severe vomiting were reported by 2 patients; none of the events were considered serious. In all studies, approximately 97% of events resolved within 1 day.

Hypersensitivity Reactions

Terms identified from the search were: urticaria, rash, pruritus, eyelid edema, eye swelling, chest discomfort, and erythema. Ten (4.3%) NG-treated patients and 2 (1.4%) IMG-treated patients reported these events. All events were mild or moderate, with the exception of a TEAE of severe pruritus in Study IGBC, which began on the date of NG 3 mg administration. The event was considered related to study treatment and completely resolved within 4 days of receiving NG.

While pruritus was the predominantly reported event (NG, 4; IMG, 1), it is not possible to determine whether these events were localized or systemic in nature based on the event terms reported. None of these events led to discontinuation or were reported as serious. Furthermore, none of these events occurred in patients who were treatment-emergent anti-drug antibody positive.

Adverse Events in Pediatrics

The NG 3 mg dose in pediatric pivotal Study IGBB is the primary dataset used for determining the AE profile of NG. The combined NG 2 mg and NG 3 mg doses (NG_all) is used as a supportive dataset when a population-wide perspective is considered to be more informative. Therefore the labelling in the SmPC was modified accordingly. This approach was accepted by the CHMP. . Therefore the labelling in the SmPC was modified accordingly. This approach was accepted by the CHMP

Table 28 presents a summary of all TEAEs reported in the pediatric pivotal study, by preferred term and treatment group. Events are presented by decreasing frequency at the SOC level for the NG 3 mg group, and within each SOC, by decreasing frequency at the preferred term level for the NG 3 mg group.

In the pediatric pivotal study, 55.6% of NG 3 mg-treated patients and 75.0% of IMG-treated patients reported at least 1 TEAE. Very commonly reported TEAEs (≥10% of patients) in the NG 3 mg group at the preferred term level were vomiting, headache, and nausea. In the IMG group, nausea, vomiting, headache, and injection site discomfort were very commonly reported TEAEs, with similar incidences of nausea and vomiting as reported in the NG 3 mg group.

In addition, nasal/respiratory/anosmia TEAEs were very commonly reported (≥10% of patients) in the NG 3 mg group. The population in the Pediatric Pivotal Study IGBB is small though (60 patients, with 36 in the NG 3 mg group). Adverse event are less reported in children compared to adults. It is not excluded that younger patients do not report side effects because of their limited cognitive functions and therefore the difficulties to report adverse events correctly. Therefore the labelling in the SmPC was modified accordingly. This approach was accepted by the CHMP

Table 21 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Treatment Group Pediatric Pivotal Study IGBB

System Organ Class Preferred Term	CG (N=24) n (%)	NG 3 mg (N=36) n (%)
Patients with ≥1 TEAE	18 (75.0)	20 (55.6)
Gastrointestinal disorders	16 (66.7)	17 (47.2)
Vomiting	9 (37.5)	11 (30.6)
Nausea	8 (33.3)	6 (16.7)
Abdominal pain upper	1 (4.2)	1 (2.8)
Diarrhoea	1 (4.2)	0
Nervous system disorders	3 (12.5)	9 (25.0)
Headache	3 (12.5)	9 (25.0)
Dizziness	1 (4.2)	0
Respiratory, thoracic, and mediastinal disorders	0	6 (16.7)
Nasal discomfort	0	3 (8.3)
Nasal congestion	0	2 (5.6)
Sneezing	0	1 (2.8)
Eye disorders	0	2 (5.6)
Eye irritation	0	1 (2.8)
Ocular discomfort	0	1 (2.8)
General disorders and administration site conditions	5 (20.8)	0
Catheter site pain	1 (4.2)	0
Injection site discomfort	5 (20.8)	0
Metabolism and nutrition disorders	1 (4.2)	0
Hypoglycaemia	1 (4.2)	0

Abbreviations: CG = control glucagon (intramuscular glucagon); N = total number of patients; n = number of patients in the specified category; NG = nasal glucagon; TEAE = treatment-emergent adverse event.
Note: CG refers to a 0.5 mg or 1 mg intramuscular injection of glucagon.
Source: CLUWE: //statsclstr//lillyce/prd/ly900018/idb/output/shared/smtea112.rtf.

Of the nervous system disorders, headache was the most important side effect observed in children in the NG group.

Serious adverse event/deaths/other significant events

The rates of SAE's seen in all trials were low, both in children and adults. One SAE was reported in the 9 completed adult studies. The event was an SAE of cellulitis (right leg), reported by a 54-year-old male patient with T2D in Study IGBG. The SAE was considered severe, unexpected, and not related to study treatment, but did lead to discontinuation of the patient from the study.

One SAE was reported in the pediatric studies. The SAE of severe hypoglycemia, in pediatric pivotal Study IGBB, was reported by a 7-year-old male patient with T1D after receiving IMG in Study IGBB. The SAE was not considered related to study treatment, but was determined to be related to study procedures.

One death was reported across the 9 completed adult studies (in Study B002 a patient experienced a Klebsiella infection approximately 5 weeks after his last dose of NG; developed acidosis, sepsis, and multiple organ failure and died 3 days later). No deaths occurred in the pediatric studies.

Laboratory findings

Based on the intended use as an intermittent rescue medication and the decades of clinical experience with glucagon therapy according to the Applicant comprehensive laboratory assessments were not considered necessary and therefore, available laboratory data are limited.

Only hematology parameters provided post baseline results. Additionally, the adult and pediatric pivotal studies, clinical bridging and confirmatory study, and actual-use studies provided no relevant clinical laboratory data because laboratory measurements were either collected only at baseline or not collected at all (in actual-use studies). No abnormal postdose laboratory values were judged to be clinically significant.

Electrocardiograms were performed in some studies, but not for pediatric pivotal Study IGBB, the actual-use studies, or Study IGBI because these studies did not collect ECGs. There were no abnormal ECG findings in the NG program.

Safety in special populations

No safety data have been generated for special populations (patients with liver of renal impairment), or patients with hypertension. The risk profile of nasally applied glucagon in elderly, hepatic or renal impairment is considered to correspond to the risk profile of intravenously applied glucagon for which no specific measures are necessary.

Immunological events

Consistent with the immunogenic properties of protein and peptide therapeutics, individuals exposed to NG could develop an immune response, including formation of antidrug antibodies (ADA).

Data from 3 studies of the NG development program (Studies IGBF, IGBG, and B002) demonstrated minimal incidence of treatment-emergent antidrug antibodies (TE ADA) for NG. The assays measured anti-glucagon antibodies in human serum using a ligand-binding assay, which had a target sensitivity of 250 to 500 ng/mL ADA. None of the patients with TE ADA experienced a hypersensitivity AE, and no patient developed neutralizing antibodies.

The Applicant developed the US FDA- and European Medicines Agency (EMA)-compliant assays, and retested samples from Studies IGBF, IGBG, and B002. Results from these new assays showed minimal (2%) incidence of TE ADA, with a maximum titer of 1:80. No neutralizing antibodies were detected. There was no correlation between positive TE ADA results and AEs.

Treatment-emergent (TE) ADA-positive patients have been defined by the Applicant as the sum of treatment-boosted ADA positive plus the treatment-induced ADA positive patients. Originally, the following definition was given by the Applicant for TE ADA-positive patient: If baseline result is 'ADA Detected', at least 1 postbaseline titer that is a 4-fold or greater increase in titer from baseline measurement has been observed for treatment-boosted ADA-positive patients. If baseline result is 'ADA Not Detected', at least 1 post-baseline ADA 'Detected' sample with a corresponding titer that is one 2-fold dilution higher than the minimal required dilution has been observed for treatment induced ADA-positive patients. Three patients from the three studies with immunogenicity data for NG glucagon were found to comply with this definition.

The original definition of the treatment-induced ADA-positive has been questioned since only the patients showing a titer twice the minimum required dilution (MRD) were considered. However, it is expected that putative ADA positive samples, further confirmed positive and showing a titer equal to the MRD at one or several postbaseline time points are considered in the integrated analysis of the clinical significance of immunogenicity. If patients showing 1 MRD positive results are also considered as TE ADA positive patients, four patients should be added. In total, 7 out of 124 ADA evaluable patients (5.6%) can be included in the TE ADA-positive patients group. The ADA incidence can be considered to be low and should be reported in the SmPC. All available clinical data indicate that there is no effect on PD, efficacy, or safety endpoints.

With the responses to the D120 LoQ, an additional study with immunogenicity data was provided by the Applicant from the study IGBJ. In this study, one patient had an ADA titer of 1:40 at pre-hypoglycemia induction but ADA were not detected at early discontinuation (38 days postdose) and 1 patient had a positive ADA titer of 1:40 at pre-hypoglycemia induction and was also positive for ADA with a titer of 1:40 at follow-up (36 days postdose). No rise in ADA titer were observed after glucagon administration. Thus, these observations do not support the development of an immune response following the administration of glucagon in this study.

In summary, overall 5.6% of patients developed treatment-emergent anti-glucagon antibodies. These antibodies were not neutralising and did not lower the efficacy of glucagon nor were they associated with the development of treatment-emergent adverse reactions.

Safety related to drug-drug interactions and other interactions

No drug-drug interaction studies were conducted with NG.

The label for GlucaGen (GlucaGen HypoKit UK SmPC 2015; GlucaGen HypoKit USPI 2015) list the following drug interactions relevant to treatment of severe hypoglycemia:

- Warfarin: glucagon may increase the anticoagulant effect of warfarin
- Beta-blockers: Patients taking beta-blockers might be expected to have a greater increase in both pulse and BP, which will be temporary because of glucagon's short half-life.
- Indomethacin: When used with indomethacin, glucagon may lose its ability to raise blood glucose or paradoxically may even produce hypoglycemia.

No reproductive and developmental toxicity studies of NG have been conducted in animals.

Glucagon does not cross the human placental barrier. The use of NG during pregnancy, if needed, is not precluded (Glucagon for Injection Product Monograph, 2012; GlucaGen HypoKit UK SmPC, 2015; GlucaGen HypoKit Product Monograph, 2016; Glucagon for Injection USPI, 2017).

It is not known whether glucagon is excreted in human milk. Glucagon nasal powder is a peptide and intact glucagon is not absorbed from the GI tract. Therefore, even if the infant ingested glucagon it would be unlikely to have any effect on the infant (GlucaGen HypoKit UK SmPC, 2015; GlucaGen HypoKit USPI, 2015; GlucaGen HypoKit Product Monograph, 2016).

If over-dosage of glucagon occurs, the patient may experience nausea, vomiting, inhibition of gastrointestinal tract motility, increases in BP and pulse rate, and a decrease in serum potassium. Because glucagon has a short half-life, treatment of overdose is symptomatic, primarily for nausea, vomiting, and hypokalemia. If the patient develops a dramatic increase in BP, non-selective alpha-adreneric blockade has been shown to be effective in lowering BP for the short time that control would be needed.

Neither NG nor the active comparators have a known profile as a drug of abuse. There were no reported instances of intended drug abuse in the NG clinical program.

No studies on the effects on the ability to drive and use machines have been performed. The patient's ability to concentrate or react may be impaired as a result of hypoglycemia. Until hypoglycemia has been adequately treated, the ability to drive vehicles or to operate machinery may be impaired.

These issues are adequately reflected under sections 4.5, 4.6 and 4.7 respectively of the SPC No separate interaction studies for NG are required.

Discontinuation due to adverse events

With the exception of Study IGBI, discontinuations due to AEs were not captured in study case report forms (CRFs) or reported in CSRs; therefore, all study discontinuations were retrospectively reviewed to identify any that may have been due to an AE.

Overall Adult Disposition

Forty of 403 (9.9%) NG-treated patients and 2 of 210 (1.0%) IMG-treated patients discontinued prematurely from the 9 completed studies in adult patients (please refer to

Table 29).

One patient (NG) died due to an AE not considered related to study drug, and another 9 patients (NG, 7 [1.7%]; IMG, 2 [1.0%]) discontinued due to AEs. Four of the 7 NG discontinuations due to AE occurred in NG studies without a IMG comparator.

Other reasons for discontinuation of NG-treated patients were withdrawal by patient (6 [1.5%]), physician decision (2 [0.5%]), Sponsor's decision (19 [4.7%]), and protocol violation (5 [1.2%]). Thirty of the 32 discontinuations for other reasons occurred in NG studies without a IMG comparator. No IMG-treated patients discontinued due to reasons other than AE.

It is noted that discontinuation of treatment during the trials in adults is lower than in paediatric patients in both groups (NG versus IMG). However, discontinuation rate 10 times higher was observed in the NG treated group and subsequent to adverse events due to sponsor`s decision. The Applicant explained that there is a comparable rate for discontinuation between NG and injectable glucagon in the trials where both NG and IMG are used. The remaining discontinuations of treatment are in the trials, where only NG was used, without possibility to compare with IMG, which gives the impression that the discontinuations in NG are higher. This explanation was accepted by the CHMP.

Table 22 Proportion of Patients Discontinued from Study and Reasons for Discontinuation Adult Patients in the Nasal Glucagon Clinical Studies (IGBA, IGBC, IGBD, IGBE, IGBF, IGBG, IGBH, IGBI, and B002)

	CG (N=210) n (%)	NG_all (N=403) n (%)
Study Disposition		
Completed	208 (99.0)	363 (90.1)
Discontinued	2 (1.0)	40 (9.9)
Reasons for Discontinuation		
Adverse Event	2 (1.0)	7 (1.7)
Death	0	1 (0.2)
Protocol Violation[a]	0	5 (1.2)
Withdrawal by Patient	0	6 (1.5)
Physician Decision	0	2 (0.5)
Sponsor Decision[b]	0	19 (4.7)

Abbreviations: CG = control glucagon; CSR = clinical study report; N = total number of patients; n = number of patients in the specified category; NG = nasal glucagon.

a Sponsor terminated a site in Study B002 due to good clinical practice (GCP) noncompliance.

b Study IGBH terminated and Study B002 temporarily placed on hold due to potential subtarget dosing (IGBH CSR; B002 CSR, Sections 5.4 and 6.1; Section 3.2.P.2.3).

Note: Control glucagon included 1 mg intramuscular injection of glucagon and 1 mg subcutaneous injection of glucagon.

Sources: Table APP.2.7.4.1; IGBI CSR, Table IGBI.6.2; IGBH CSR; CLUWE:\prd\ly900018\i8r_mc_b002\final\output\shared\AMG108 Listings_12AUG2016_v5.0.pdf.

Overall Pediatric Disposition

Twelve of 58 (20.7%) NG-treated patients and no IMG-treated patients discontinued from Study IGBB or B001 prematurely.

There were 4 discontinuations due to AEs (NG, 4 [6.9%]; IMG, 0). Three of the 4 discontinuations due to AEs (nasal discomfort) occurred in uncontrolled NG Study B001. The other reason for discontinuation of NG-treated patients was Sponsor's decision to terminate a site because of good clinical practice (GCP) noncompliance in uncontrolled Study B001.

In children the discontinuation rate is much higher than in adults and 20 times higher in the NG than in the IMG group, also mostly due to sponsor`s decision. The Applicant was requested to clarify this high amount of withdrawals by the sponsor in children. The Applicant explained that there is a comparable rate for discontinuation between NG and injectable glucagon in the trial where both NG and IMG were studied. The remaining discontinuations of treatment are in the trial where only NG was used, without possibility to compare with IMG, which gives the impression that the discontinuations in NG are higher. This explanation was accepted by the CHMP.

2.6.1. Discussion on clinical safety

The safety profile of NG includes well-known effects of glucagon treatment and no important identified risks have been observed in the NG program. Moreover, the safety results were consistent across the different studies. Glucagon administration caused GI side effects irrespective of the route of administration. In case of nasal administration, local symptoms were frequently observed which were not confined to the nose but also encompassed irritation of eyes and throat as well as headache. These symptoms were transient and were not considered serious. No major differences were observed between children and adults. Local nasal and non-nasal symptoms were systematically collected via a questionnaire.

However, next to the already well known adverse events as mentioned in the SmPC of IMG, in NG treated patients was headache a common adverse events.

It cannot be excluded that the observed irritation of the upper airways may in some cases be accompanied by potentially hazardous events such as bronchoconstriction, dyspnoea, difficulty to breathe or suffocation fear. The AE reports as submitted by the Applicant do not give a hint for this, but such events obviously were not systematically collected. Only one case of anxiety was spontaneously reported in the NG group of Study IGBC. The applicant considers it unlikely that hazardous events related to the airways (e.g. dyspnoea, bronchoconstriction) were overlooked, noting that study participants were instructed to carefully report any relevant event and that studies in animals did not show distribution of Baqsimi powder to the lower airways. On the other hand, under-reporting of events related to respiration cannot fully be excluded because the applicant confirmed that such events were not specifically followed as AEs of special interest. Thus, some uncertainties remain, but in general it can be agreed to the applicant's position that serious respiratory events most likely would have been reported. Further information will be obtained from post-marketing observations.

The safety database for NG was sufficient in scope to adequately characterize the safety profile of NG in the elderly adult (mostly <65 years) and pediatric patients (all >4 years) with diabetes given the intended use of NG and the history of safe use with the currently approved injectable glucagon products. Others than Caucasian patients were not included in the safety database. Moreover, the patients who received only 3mg NG are only a small amount of the investigated patient group. Patients with DT2 were under-investigated in the trials, although they represent the highest diabetes population in general daily practice. However, it is accepted that no difference in adverse events in both type I and type II diabetes is expected.

It is noticed that the adverse events are not different between children and adults, although adverse events are less reported in children than in adults. This could be due to the way of symptom collection via a questionnaire which obviously was developed for adults and which could be difficult to understand for children. It is not excluded that children were not able to answer the questions adequately in the used questionnaires. Thus, AEs in younger children could be under-reported. The applicant could not exclude under-reporting of AEs in children and therefore suggests modifying the labelling in the SmPC accordingly. This approach is accepted.

Furthermore, it has to be assumed that the maximal plasma level (Cmax) of glucagon will be higher with the current Baqsimi preparation intended for marketing than with the preparation used in the paediatric study IGBB because higher glucagon Cmax has been observed in the most recently conducted studies in adults (IGBJ and IGBI) which utilized commercial process drug product. This could be a safety problem because children down to the age of four years are intended to receive the same dose as adults, i.e. 3 mg. This is justified by the acceptable tolerability of 3 mg in children in Study IGBB. However, comparison of the PK results of the adult studies IGBC and IGBI shows that the newer powder leads to a nearly doubled Cmax. A routine GCP inspection of the paediatric study IGBB yielded critical findings related to data handling which cannot be corrected post-hoc.

In the paediatric study IGBB the data recording system provided by the sponsor was not GCP compliant. Part of the information stored in the eCFRs could be verified by independent recordings at the individual study sites. The applicant was asked for how many patients ≥90% of data are available for both visits and to perform a re-evaluation of the study results using these patients only. According to the applicant's response to the GCP inspection report, data from around 60% of the visits could be rescued to a large extent (≥90% of data verified). The re-analyses based on source documentation availability in Study IGBB demonstrate a benefit/risk profile consistent with the one determined based on the complete dataset. The MO pertaining to GCP non-compliance of the data recording system could be addressed through the availability of independent recordings of eCFR data at the individual study sites. The results of the newly performed analysis taking these data detected at the individual study sites into account (including patients for whom >90% of source data were available) are in agreement with the previous analysis including the entire patient population.

As with all development programs, the safety evaluation for NG could not detect very rare adverse effects, adverse effects with long latency, or adverse effects caused by prolonged or cumulative exposure. It is accepted that these limitations are less meaningful for NG because the treatment indication is for acute potentially life-saving episodic use and not for chronic administration. However, several patients received several administrations of NG during a short time period.

The adverse effects and the potential risk associated with NG will be managed through routine measures including labelling and pharmacovigilance activities, which are planned for the post-marketing period.

Mean systolic and diastolic blood pressure were consistently higher after administration of NG as compared to injected glucagon, by around 6 mmHg. The reason for this finding is not clear; local irritation might play a role, but this BP increase is not considered a concern since Baqsimi is not intended for chronic use.

Elderly patients and patients with renal or hepatic impairment were largely excluded from the main clinical trials because induction of hypoglycaemia could pose a hazard for this population. These special patient groups are not excluded from NG treatment according to the current SmPC, and no dose adjustment is recommended.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

In order to minimise the potential risk of inappropriate use of the device (which might lead to loss of the drug dose by inadvertent priming of the single dose container), the Marketing Authorisation Holder must ensure that healthcare professionals and patients/carers who are expected to prescribe, supply or use the product have access to educational materials, i.e. and administration leaflet, instructional video and a demonstration kit that includes a trainer device.

2.6.2. Conclusions on the clinical safety

Nasal administration of glucagon NG frequently leads to local side effects which appear more intense than the injection site reactions after IM/SC administration of an injectable glucagon. Moreover, adverse events were more commonly seen in adults than in children. The most commonly reported AEs were headache, nausea, vomiting, and "upper respiratory tract irritation." Except for headache, the current product labelling for injectable glucagon provides the reported adverse effects due to intra nasal glucagon.

To minimise a potential risk of inappropriate use of the device, routine and additional risk minimisation measures are recommended to minimise a potential risk of inappropriate use of the device (see section 2.7 Risk Management Plan).

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Inappropriate use of the device leading to loss of drug benefit
Missing information	None

Pharmacovigilance plan

There are no planned or ongoing additional pharmacovigilance activities.

Routine pharmacovigilance is considered sufficient to identify and characterise the important potential risk of "inappropriate use of the device leading to loss of drug benefit". In this respect, specific targeted adverse event follow-up questionnaires around lack of drug benefit are developed.

Risk minimisation measures

Safety Concern	Risk Minimisation Measures
Inappropriate use of the device leading to loss of drug benefit (important potential risk)	**Routine risk minimisation measures:** SmPC Sections 4.2 (Posology and method of administration) and 6.6 (Special precaution for disposal and other handling), PL Section 3 (How Baqsimi is to be given), and IFU (Important points to know and preparing the dose). Routine risk minimisation activities recommending specific clinical measures to address the risk: Instructions for patients to discuss the proper use of glucagon with family and friends before it is needed—PL Section 2 (What you need to know before you receive Baqsimi) and IFU (Initial statement). Instructions for users to call for medical help right away after administering glucagon—SmPC Section 4.2 (Posology and method of administration), PL Section 3 (How Baqsimi is to be given), and IFU (After giving the dose). Other routine risk minimisation measures beyond the Product Information: Instructions for proper use are highlighted on the device carton and tube container to state 'Do not press the plunger prior to insertion as you will lose the dose' and 'Do not press plunger before insertion', respectively. **Additional risk minimisation measures:** • Administration leaflet • Instructional video • Demonstration kit that includes a trainer device

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.5 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

Based on the fact that this application concerns both a new formulation and a novel method of administration of glucagon, the CHMP is of the opinion that a separate entry in the EURD list for BAQSIMI is needed, as it cannot follow the already existing entry for glucagon. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request the alignment of the new PSUR cycle with the international birth date (IBD). The IBD is 24.07.2019. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

In view of the important potential risk of inappropriate use of the device (see RMP above), other routine risk minimisation measures beyond the Product Information were introduced, i.e. instructions for proper use are highlighted on the device carton and tube container to state 'Do not press the plunger prior to insertion as you will lose the dose' and 'Do not press plunger before insertion', respectively.

Furthermore, additional risk minimisation measures (administration leaflet, instructional video and a demonstration kit with a trainer device) will be made available.

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Severe hypoglycemia is one of the most significant complications of diabetes treatment, occurring more frequently in patients with profound endogenous insulin deficiency—type 1 diabetes mellitus (T1D) and advanced type 2 diabetes mellitus.

Episodes of severe hypoglycemia are characterized by neurological impairment that, if left untreated, can lead to serious consequences, such as loss of consciousness, seizures, coma, adverse cardiovascular outcomes, and even death. Severe hypoglycemia requires the assistance from another person to actively administer carbohydrates, glucagon, or take other corrective actions (IHSG 2015).

3.1.2. Available therapies and unmet medical need

Injectable glucagon is a safe and efficacious emergency treatment for severe hypoglycemia and, together with administration of carbohydrates, is currently the only treatment option for patients and their caregivers outside of the hospital or emergency medical setting. However, practical considerations, such as the multistep preparation of the solution for administration and injection by untrained users, have limited the use of injectable glucagon and can lead to delays in treatment and increased use of costly emergency medical services.

Peptide hormones are typically administered via a parenteral route such as intravenous, intramuscular, or subcutaneous. Oral administration is not practical since they undergo digestion and inactivation in the gastrointestinal tract and significant first pass metabolism, resulting in significant loss of efficacy). To overcome the usability challenges of injectable therapy while preserving efficacy, intranasal administration of peptide hormones has been developed. Known examples of intranasal peptides include desmopressin, oxytocin, and calcitonin. This application is for the use of a nasal glucagon (NG) for treatment of severe hypoglycaemia providing an administration of glucagon via a ready to use needle-free device, and could represent an improvement in the evolution of the treatment of severe hypoglycaemia outside of the hospital or emergency medical setting. .

3.1.3. Main clinical studies

The pharmacokinetic and pharmacodynamic profile of nasal glucagon (NG) was characterised in healthy subjects (study IGBD) and in adults with type 1 or type 2 diabetes (Study IGBA and study IGBG).

As main evidence of efficacy in the adult population, **two controlled clinical studies** (**IGBC, IGBI**) were submitted. Effectiveness was investigated in a **non-controlled actual-use study** (**B002**).

Studies IGBC and IGBI were single dose, multicenter, randomized, open-label, 2-treatment, 2 period crossover, non-inferiority studies. Efficacy in reversing insulin-induced hypoglycemia in patients with T1DM was assessed compared to injectable glucagon. The primary efficacy outcome was the proportion of patients achieving treatment success, which was defined as either an increase in blood glucose to ≥70 mg/dl or an increase of ≥20 mg/d from glucose nadir within 30 minutes after receiving study glucagon without receiving additional actions to increase the blood glucose level. Time to treatment success was investigated as an additional endpoint. Since there were relevant qualitative differences between the clinical trial drug product and commercial drug product, a clinical bridging study (IGBI) was conducted using NG commercial drug product, which mimicked the design of study IGBC. Symptoms of hypoglycemia were captured in studies IGBC and IGBI by using the Edinburgh Hypoglycemia Questionnaire. Patients were asked to rate the intensity of each symptom included in the questionnaire on a 1 =no symptoms to 7 =severe symptoms scale.

The actual use study was a single-arm open-label study in adults with T1D. A single dose of NG was administered in case of moderate or severe hypoglycemia for up to 6 months. The endpoint was the proportion of hypoglycemic events in which patients awakened or returned to normal status within 30 min after NG administration. The purpose of this study was to evaluate effectiveness and safety of NG when administered by caregivers for treatment of severe or moderate hypoglycemia in adult patients with T1D. The caregiver's perception on the use of NG was captured by an unvalidated questionnaire addressing usability issues.

As main evidence of efficacy in the pediatric population, two multicenter studies in patients with T1D using the clinical trial drug product were submitted. The pivotal study (**IGBB**) was a randomized study with the purpose to assess safety, tolerability, and PK and PD properties of NG. The exploratory efficacy analyses investigated the proportion of patients with treatment response defined as a rise ≥25 mg/dl above nadir by 30 minutes.

The **actual use study in children** (**B001**) mimicked the design of study B002. The endpoint was the proportion of patients who achieved an increase in glucose ≥20 mg/dl from nadir within 30 min after administration of NG. Usability was assessed as in the adult actual use study.

3.2. Favourable effects

In the adult pivotal **study IGBC** the proportions of patients in the NG 3 mg and IMG 1 mg treatment groups who achieved treatment success were 98.7% and 100%, respectively, in the primary analysis population (patients with T1D). The treatment difference in the proportions of patients achieving treatment success (IMG-NG) was 1.3%, with the 1-sided upper 97.5% confidence limit of 4.0%, which is below the non-inferiority margin of 10%. Of the five patients with T2D included in the efficacy analysis, 100% achieved treatment success with NG and IMG. The sensitivity analysis conducted in patients with T1D with a glucose nadir of <50 mg/dl at both dosing visits (n=39 [52%]) also demonstrated non-inferiority to IMG in the proportion of patients achieving treatment success (100% treatment success with IMG, 97.4% treatment success with NG).

These favourable effects observed in the pivotal study were confirmed with the commercial drug product in **study IGBI** (clinical bridging study). In this study, 100% of all patients in both treatment arms achieved treatment success.

Patients in **study IGBC** had a mean time to treatment success of 16.2 minutes and 12.2 minutes in the NG and IMG treatment groups, respectively (study IGBI: 11.4 minutes and 9.9 minutes in the NG and IMG treatment groups, respectively; study IGBB: young children IMG 10.0 minutes, NG 10.8 minutes; children IMG 12.5 minutes, NG 11.3 minutes; adolescents IMG 12.5 minutes, NG 14.2 min). Time to treatment success was slightly shorter with IMG across studies.

In both studies (IGBC and IGBI) the rise in blood glucose was accompanied by an improvement in hypoglycemia symptoms (Edinburgh Hypoglycemia Questionnaire). In both studies and both treatment groups, a moderate decrease in mean total score was demonstrated at the 30 min time-point and symptoms continued to improve through 45 minutes. The perception of hypoglycaemic recovery was similar between the two treatment modalities.

The favorable blood glucose restoring ability of NG was confirmed in children from 4 to 18 years of age: in the pivotal pediatric **study IGBB** 100% of patients with T1D achieved an increase in glucose of ≥25 mg/dl within 30 minutes of NG administration in all age cohorts in both treatment arms.

Two uncontrolled actual use studies in adults and children (**B002 and B001**) demonstrated real-world effectiveness and good acceptability by caregivers. Among adult patients with T1D who used NG to treat moderate or severe (n=12) hypoglycemic events, patients awoke, ceased convulsions, or returned to normal status within 30 minutes for 96.2% of hypoglycemic events. In the pediatric study, all patients returned from moderate hypoglycemia (no severe hypoglycemia was reported) to normal status within 30 minutes. In these studies, the caregiver successfully delivered NG in a stressful setting, and no caregiver called for external professional emergency medical assistance. In addition, for most of the hypoglycemic events in both actual use studies, caregivers reported (un-validated questionnaire) that it was easy to administer NG compared to injectable glucagon (93.9% pediatric study, 80.5% adult study) and that they were satisfied with the use of NG.

3.3. Uncertainties and limitations about favourable effects

The patient populations of the NG clinical studies were generally homogenous and largely composed of white, non-elderly adult (<65 years) and pediatric patients from the US, Canada, and Germany. Therefore, one could argue that there is a lack of diversity in the study population. However, there is no reason to assume that glucagon would not work or would work differently in older patients or in patients of different ethnic background. The fact that elderly patients are insufficiently represented in the clinical studies has been reflected in the product information. This is considered a limitation of the clinical development since older patients are at increased risk of hypoglycemia since they tend to be frail and on polypharmacy . In the proposed product information a warning with respect to age has been added.

The studied patient population were mainly T1DM patients and the number of T2DM patients that received NG was limited (n=44). Also the number of pediatric patients (4-18 years) included in the trials was limited (n=70).However, this is not of concern for efficacy since the mechanism of action of glucacon is the same in T1DM and T2DM patients and in adult and paediatric patients with diabetes and the same dose will be used across the age spectrum.

The proposed use of nasal glucagon is for treatment of severe hypoglycaemia but the controlled studies did not induce severe hypoglycaemia in study subjects. This is acceptable because of ethical considerations and because non-inferior efficacy of NG was shown compared to injectable glucagon, which is also licensed for treatment of severe hypoglycaemia.

A routine GCP inspection of the paediatric study IGBB yielded critical findings related to sample processing and data handling. The data recording system provided by the sponsor was not GCP compliant. However, this issue could be addressed during the procedure as part of the information stored in the eCFRs could be verified by independent recordings at the individual study sites. Data from about 60% of the visits could be rescued to a large extent (≥90% of data verified). Re-analyses of these data showed consistencv with the complete dataset.

The critical findings in the GCP inspection of Study IGBB with respect to source data handling may also apply for the pivotal adult study IGBC because data handling was similar. PK data cannot be relied upon due to inadequate sample processing. PD data were affected to a lesser extent. However, the Applicant has provided convincing evidence that the newer studies, using the commercial Baqsimi product (IGBI), are sufficient to support efficacy of Baqsimi in adults. Therefore, study IGBI is considered pivotal for showing efficacy in adults.

Time from glucagon administration to treatment success was slightly shorter (1 to 4 minutes) with injectable glucagon across studies. However, in the real-world setting, time starts at the caregiver`s decision to administer glucagon. Since injectable glucagon requires a multistep preparation, one can safely assume that the small differences are without relevance in clinical practice.

PK-results with NG are heterogeneous and a drift of PK-values was observed during the development program which could be attributed to the change in drug product. Lower glucagon exposure mainly appeared in early clinical studies with the clinical trial drug product (IGBA, IGBE). In contrast, Cmax increased markedly with the commercial formulation (IGBI and IGBJ) compared to the older formulation used in the pivotal studies IGBC (adult) and IGBB (paediatric). Due to critical GCP findings in study IGBB, only PD results of this study are considered reliable. However, it is concluded that PK data are only of supportive value to the B/R analysis.

3.4. Unfavourable effects

The main adverse effects reported were ocular irritation (lacrimation, pruritus), nausea, vomiting, headache and upper respiratory tract symptoms. The safety profile of NG includes well-known effects of glucagon treatment and no important identified risks have been observed in the NG program. Adverse effects were transient and non-serious in nature.

However, next to the already well known adverse events as mentioned in the SmPC of IMG, in NG treated patients was headache a common adverse events. Although, this effect was transient in both adults and children, it is not clear if there is a relation between the severity of the hypoglycemia or if it is purely related with the intra nasal admission of the investigated drug.

It is noticed that the adverse events are not different between children and adults, although adverse events are less reported in children than in adults. It is not excluded that children were not able to answer the questions adequately in the used questionnaires. The applicant could not exclude under-reporting of AEs in children and therefore suggested modifying the labelling in the SmPC accordingly. This approach is accepted.

Overall, the safety profile of NG is consistent with the currently approved injectable glucagon products, with the exception of additional effects related to its nasal route of administration. The most commonly reported AEs were headache, nausea, vomiting, and "upper respiratory tract irritation." Except for headache, the current product labelling for injectable glucagon provides the reported adverse effects due to intra nasal glucagon.

Adverse events were more commonly seen in adults than in children.

Overall, the safety data presented in this dossier demonstrate that NG is safe for the treatment of severe hypoglycemia in adult and pediatric patients. However, the commercial formulation may have a markedly increased Cmax compared to the clinical trial formulation.

To minimise a potential risk of inappropriate use of the single dose container, risk minimisation measures will be implemented. These include a demonstration kit with a training device, an administration leaflet and an instructional video.

3.5. Uncertainties and limitations about unfavourable effects

The safety database for NG was sufficient to adequately characterize the safety profile of NG in the elderly adult (mostly <65 years) and pediatric patients (all >4 years) with diabetes given the intended use of NG and the history of safe use with the currently approved injectable glucagon products. However, only Caucasian patients were included in the safety database. Moreover, patients who received 3mg NG are only a part of the investigated patient group. Patients with T2DM were underrepresented in the trials, although they represent the highest diabetes population in general daily practice. On the other hand, patients with T1DM generally carry a higher risk for hypoglycaemia. No difference in adverse events in both T1DM and T2DM is expected.

The safety database is considered sufficient in size , except for some subgroups of patients such as patients >65 years, children and non-white patients. However, the safety profile can be extrapolated to these patient populations also.

Children down to four years of age are intended to receive the same dose of Baqsimi as adults (3 mg). Safety and tolerability of this dose (older formulation) were investigated in the paediatric study IGBB, albeit in a rather low number of subjects. Adult studies revealed that the commercial Baqsimi preparation may lead to markedly higher Cmax than the preparation used in most studies including IGBB. The applicant provided a comprehensive analysis which suggests that no harm is expected from transiently high plasma levels of glucagon when using the adult dose in children.

The possibility to generalize to clinical practice is acceptable, however

-Information of NG in breastfeeding patients is lacking but because glucagon is not absorbed in the gastrointestinal tract, this is not a problem even if glucagon is excreted in the milk.

-There is no subgroup analysis of AE's by gender, race, and ethnicity. However, no difference in safety profile is expected.

-No safety data have been generated for special populations (patients with liver of renal impairment), or patients with hypertension. However, glucagon is intended to be administered as a single dose in an emergency situation. Therefore, lack of such data is considered acceptable.

As with all development programs, the safety evaluation for NG could not detect very rare adverse effects, adverse effects with long latency, or adverse effects caused by prolonged or cumulative exposure. It is accepted that these limitations are less meaningful for NG because the treatment indication is for acute potentially life-saving episodic use and not for chronic administration. However, several patients received several administrations of NG during a short time period.

3.6. Effects Table

Table 23 Effects Table for Nasal Glucagon in the Treatment of Severe Hypoglycemia in Adult and Pediatric Patients with Diabetes Mellitus

Effect	Short Description	Unit	Treatment		Uncertainties/ Strength of evidence	References
			NG 3 mg	IMG a		
Favourable Effects						
Treatment Success	Adults: Proportion of patients with an increase in glucose to ≥70 mg/dL (3.9 mmol/L) or an increase of ≥20 mg/dL (1.1 mmol/L) from glucose nadir[b] within 30 minutes after receiving glucagon for insulin-induced hypoglycemia, without receiving additional actions to increase the glucose level. Insulin infusion was stopped when glucose was <60 mg/dL (3.3 mmol/L).	%	98.7(1) 100(2)	100(1) 100(2)	Non-inferiority of NG to IMG was demonstrated in 2 active comparator-controlled adult studies. Hypoglycemia with blood glucose <60 mg/dL (3.3 mmol/L) was used as a surrogate for severe hypoglycemia.	(1)Adult Pivotal Study IGBC; (2)Adult Clinical Bridging and Confirmatory Study IGBI
Treatment Success	Pediatrics: Proportion of patients with an increase in glucose ≥20 mg/dL (1.1 mmol/L) from glucose nadir[b] within 30 minutes of glucagon administration, without receiving additional actions to increase the glucose level. Insulin was used if necessary to attain a glucose <80 mg/dL (4.4 mmol/L).		100	100	Consistent efficacy between the 2 treatments. Limited data on patients with blood glucose <70 mg/dL (3.9 mmol/L).	Pediatric Pivotal Study IGBB
Effectiveness	Adults and Pediatrics: Proportion of moderate or severe hypoglycemic events for which patients awakened or returned to a normal status within 30 minutes following NG administration.		96.2(1) 100(2)	N/A	Assessment based on caregiver's judgment. NG was administered by intended users (caregivers) in the real-world setting. No active comparator was included.	(1)Adult Actual-Use Study B002[d]; (2)Pediatric Actual-Use Study B001[e]
	Proportion of caregivers who administered full doses of glucagon in a simulated use study after receiving training and instructions.		94	13	Although a simulated study, distracting sounds and other stressors were used to model the urgency	Simulation Study[f]

Effect	Short Description	Unit	Treatment		Uncertainties/ Strength of evidence	References
			NG 3 mg	IMG a		
Usability	Proportion of untrained acquaintances who administered full doses of glucagon in a simulated use study	%	93	0	and stress of a real-life severe hypoglycemic event.	
	Adults and Pediatrics: Proportion of hypoglycemic events for which caregivers reported that NG was easy or very easy to administer.		80.5(1) 93.9(2)		An unvalidated questionnaire was used to evaluate the caregivers assessment of the degree of difficulty using NG.	1)Adult Actual-Use Study B002[d]; (2)Pediatric Actual-Use Study B001[e]
	Adults and Pediatrics: Proportion of hypoglycemic events for which caregivers were relatively satisfied, satisfied, or very satisfied with NG use		94.4(1) 93.9(2)		An unvalidated questionnaire was used to evaluate the caregivers assessment of the degree of satisfaction using NG.	
Unfavourable Effects						
Nausea	Incidence	%	21.7(1) 31.4(2) 16.7(3)	26.8(1) 42.0(2) 33.3(3)	In general, these events were mild to moderate in severity, and infrequently led to discontinuation. Rates of occurrence were similar between treatments.	(1)Adult Pivotal Study IGBC; (2)Adult Bridging and Confirmatory Study IGBI; (3)Pediatric Pivotal Study IGBB
Vomiting	Incidence		15.7(1) 14.3(2) 30.6(3)	11.0(1) 17.4(2) 37.5(3)		
Headache	Incidence		20.5(1) 15.7(2) 25.0(3)	8.5(1) 10.1(2) 12.5(3)	In general, these events were mild to moderate in severity, and infrequently led to discontinuation.	
URTI[c]	Incidence		19.3(1) 4.3(2) 16.7(3)	1.2(1) 1.4(2) 0(3)		
Pruritus	Incidence		3.6(1) 0(2) 0(3)	1.2(1) 0(2) 0(3)	No anaphylaxis or serious hypersensitivity AEs were reported. There were no discontinuations for the related event of pruritus.	

Abbreviations: AEs = adverse events; NG = nasal glucagon; IMG = intramuscular glucagon; N/A = not applicable; URTI = upper respiratory tract irritation.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Severe hypoglycaemia is an emergency situation. Nasal glucagon was shown to restore blood glucose levels in hypoglycemic adult and paediatric subjects to a similar extent and within a similar time frame as injectable glucagon. Further important favourable effects are the comparability in terms of time to treatment success with IMG, and with respect of improvement of hypoglycemic symptom perception. Two uncontrolled actual use studies in adults and children demonstrated real-world effectiveness and good acceptability by caregivers, which is clearly beneficial in light of the unmet medical need for a ready-to-use device.

Adverse events frequently occurred after administration of Baqsimi, consisting of GI effects and local symptoms affecting nose, eyes, throat and head in general. GI effects were also observed with injected glucagon so that they do not contribute to B/R considerations of Baqsimi when compared to available IM glucagon kits. The local symptoms were occasionally reported as severe and were in general more frequent than injection site reactions following IM glucagon. However, local symptoms were not regarded serious . Local symptoms are not considered an important risk in the light of the life-threatening situation in which Baqsimi is used. Under these circumstances, the need for reliable administration (in terms of easy delivery) outweighs the frequently observed local discomfort.

In order to minimise the potential risk of inappropriate use of the device (which might lead to loss of the drug dose by inadvertent priming of the single dose container), the Marketing Authorisation Holder must ensure that healthcare professionals and patients/carers who are expected to prescribe, supply or use the product have access to educational materials, i.e. and administration leaflet, instructional video and a demonstration kit that includes a trainer device.Overall, the safety profile of NG is consistent with the currently approved injectable glucagon products, with the exception of additional effects related to its nasal route of administration and is acceptable.

3.7.2. Balance of benefits and risks

Severe hypoglycaemia is a serious acute complication of diabetes treatment.

In the pivotal controlled studies, NG 3 mg produced clinically relevant increases in blood-glucose in response to insulin-induced hypoglycaemia, showing comparable success rates to IMG in paediatric patients aged 4-18 and adults. These findings are supported by actual-use studies, which demonstrated effectiveness of NG in the treatment of moderate to severe hypoglycaemia. These findings underscore the benefit of nasal glucagon. The safety profile of NG is consistent with the currently approved injectable glucagon products, with the exception of additional effects related to its nasal route of administration. Additional risk minimisation measures will be implemented (educational materials) to minimise a potential risk of inappropriate use of the device.

In summary, NG 3 mg has the potential to serve as a valuable asset in the treatment of hypoglycaemia in adults and children with the potential advantage of an easy delivery of glucagon in an emergency situation.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of BAQSIMI is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of BAQSIMI is favourable in the following indication:

Treatment of severe hypoglycaemia in adults, adolescents, and children aged 4 years and over with diabetes mellitus.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Prior to launch of Baqsimi (glucagon), for the treatment of severe hypoglycaemia in adults, adolescents, and children aged 4 years and over with diabetes mellitus, in each EU Member State, the Marketing Authorisation Holder (MAH) must agree on the content and format of the educational materials, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational materials are aimed at providing guidance on how to minimise the important potential risk in the RMP of inappropriate use of the device leading to loss of drug benefit.

The MAH shall ensure that in each Member State where Baqsimi is marketed, all healthcare professionals and patients/carers who are expected to prescribe, supply or use the product have access to the following:

- Administration leaflet;
- Instructional video;
- Demonstration kit that includes a trainer device with an administration leaflet unique to the trainer device.

The **administration leaflet** should contain the following key elements:

- Patients should receive the administration leaflet from their healthcare professionals upon initial Baqsimi prescription and after training.
- The demonstration kit should include a leaflet unique to the trainer device.
- It is important not to prime the single-dose container in advance, not to remove the shrink wrapping or to remove the single-dose container from the tube in advance and to ensure that the patient understands that while the trainer device used during demonstration can be reset/reused, each Baqsimi single-dose container can only be used once.
- The PL/IFU should be referenced for more detailed information regarding administration and handling of Baqsimi.
- Patients can use the leaflet to teach those around them how to correctly handle and administer Baqsimi.
- The leaflet should contain a URL and, where required, a password to a website where patients can access the instructional video.

The **instructional video** should contain the following key elements:

- To reinforce the correct Baqsimi handling and administration, step-by-step instructions on the appropriate use of Baqsimi should be provided.

The **demonstration kit that includes a trainer device** should contain the following key elements:

- The demonstration kit consists of a trainer device, which is a non-drug containing device, and a box with instructions on how to use Baqsimi.

- An administration leaflet unique to the trainer device should be included within the demonstration kit that includes the trainer device.
- The trainer device should be used by healthcare professionals who prescribe and supply Baqsimi to educate patients and/or caregivers.
- In addition to instructions for correct handling and administration, the demonstration kit should contain key points that healthcare professionals who prescribe and supply Baqsimi should emphasise when training patients and/or caregivers on Baqsimi (importance of not priming the single-dose container in advance, not removing the shrink wrapping or removing the single-dose container from the tube in advance and ensuring that the patient understands that while the trainer device used during demonstration can be reset/reused, each Baqsimi single-dose container can only be used once).
- The trainer device should not be inserted into a patient's nostril when demonstrating (that is, to observe prudent hygiene measures).

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0184/2015 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.