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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ogluo

International non-proprietary name: glucagon

Procedure No. EMEA/H/C/005391/0000

Note

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



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List of abbreviations

AAS	average autonomic symptom
ADA	American Diabetes Association
AET	Analytical evaluation
A/G	albumin-globulin ratio
AI	auto-injector
ANS	average neuroglycopenic symptom
API	active pharmaceutical ingredient
ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical
ATS	average total symptom
AUC(0-∞)	area under the plasma concentration-time curve from time 0 extrapolated to infinity
AUC(0-60)	area under the plasma concentration-time curve from time 0 to 60 minutes
AUC(0-120)	area under the plasma concentration-time curve from time 0 to 120 minutes
AUC(0-240)	area under the plasma concentration-time curve from time 0 to 240 minutes
AUCex	area under the plasma concentration-time excursion curve
BE	bioequivalence/bioequivalent
BGmax	maximum blood glucose concentration
CA	California
CD	Circular dichroism
CHMP	Committee for Medicinal Products for Human Use
Cmax	maximum observed concentration
Configuration A	Ogluo pre-filled pen
Configuration B	Ogluo pre-filled syringe
CQA	Critical Quality Attribute
CRC	Clinical Research Centre
CSR	clinical study report
DB	double-blind
Dht	sample mean of the difference of the success/failure scores between the two treatments
DMSO	dimethyl sulfoxide
DSC	Differential Scanning Calorimetry
ECG	electrocardiogram
ED	emergency department
EMA	European Medicines Agency
ESI-MS	Electrospray ionisation mass spectrometry
ESI-MS-CAD-MS	Electrospray ionisation-mass spectrometry-collision activated dissociation-mass spectrometry
EU	European Union
F	female
FAERS FDA	Adverse Event Reporting System
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GC-MS	Gas chromatography mass spectrometry
GEK	Glucagon Emergency Kit (Eli Lilly)
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practices
G-Pen/Gvoke	Ogluo
H ₂ SO ₄	sulfuric acid
HCl	hydrochloric acid
HF	Human Factors
HK	HypoKit GlucaGen (Novo Nordisk)
HPLC	high performance liquid chromatography
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IRB	institutional review board
IS	internal standard
ISE	Integrated Summary of Efficacy

ISS	Integrated Summary of Safety
ITT	Intent to Treat
LC-MS/MS	liquid chromatography-tandem mass spectrometry
M	male
MAA	Marketing Authorisation Application
MAE	maximum absolute excursion from baseline
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intent to Treat
MO	Major Objection
NDA	New Drug Application
NF	National Formulary
NICE	National Institute for Health and Care Excellence
NLT	not less than
NMT	not more than
NR	non-randomised
OL	open-label
PK	pharmacokinetic
PD	pharmacodynamic
PFS	pre-filled syringe
PGR	Plasma Glucose Response
Ph. Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan
PP	Per Protocol
PT	prothrombin time
PTT	partial thromboplastin time
TPP	Quality target product profile
R	randomised Q
Retic	reticulocytes
rDNA	recombinant deoxyribonucleic acid
RH	Relative Humidity
RIA	radioimmunoassay
RTU	ready to use
SA	Scientific Advice
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAWP	Scientific Advice Working Party
SB	single blind
SC	subcutaneous
SmPC	Summary of Product Characteristics
SOC	System Organ Class
t _{1/2}	half-life
T1D	type 1 diabetes
T2D	type 2 diabetes
TAMC	total aerobic microbial count
TBG _{max}	time to maximum blood glucose concentration
TEAE	treatment-emergent adverse event
Tex	time to maximum excursion from baseline
TFA	trifluoroacetic acid
TK	toxicokinetic
T _{max}	time to maximum observed plasma concentration
TYMC	total yeasts and moulds count
UHPLC	ultrahigh performance liquid chromatography
UK	United Kingdom
US	United States
USP	United States Pharmacopoeia
VAS	Visual Analog Scale

XO crossover
XR(P)D X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Xeris Pharmaceuticals Ireland Limited submitted on 21 November 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Ogluo, 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 27 June 2019. 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: Ogluo is indicated for the treatment of severe hypoglycaemia in adults, adolescents, and children aged 2 years and over with diabetes mellitus.

The legal basis for this application refers to:

Article 10(3) of Directive No 2001/83/EC - Hybrid application

The application submitted is composed of administrative information, complete quality data, a clinical bioequivalent study with the reference medicinal product GlucaGen/GlucaGen HypoKit and with appropriate own applicant's non-clinical and clinical data.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: GlucaGen/GlucaGen HypoKit
- Marketing authorisation holder: Novo Nordisk A/S
- Date of authorisation: (25-10-1962)
- Marketing authorisation granted by:
 - Member State (EEA): Denmark
 - National procedure
- Marketing authorisation number: 04108

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: GlucaGen/GlucaGen HypoKit
- Marketing authorisation holder: Novo Nordisk A/S
- Date of authorisation: (25-10-1962)
- Marketing authorisation granted by:
 - Member State (EEA): Denmark
 - National procedure
- Marketing authorisation number: 04108

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which

bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: GlucaGen/GlucaGen HypoKit
- Marketing authorisation holder: Novo Nordisk A/S
- Date of authorisation: (25-10-1962)
- Marketing authorisation granted by:
 - Member State (EEA): Denmark
 - National procedure
 - Marketing authorisation number(s): 04108
- Bioavailability study number(s): XSGP-304

Information on Paediatric requirements

Not applicable

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.

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 received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
22 October 2015	EMEA/H/SA/3156/1/2015/SME/	Minne Casteels, Peter Mol
26 April 2018	EMEA/H/SA/3156/1/FU/1/2018/SME/III	Elmer Schabel, Kolbeinn Gudmundsson

The scientific advice pertained to the following quality, nonclinical, and clinical aspects:

- Sufficiency of qualification of impurities. Proposed drug substance specifications. Drug product release specifications. The G-Pen manufacturing process. Proposed stability programme with pre-filled syringes.
- Overall adequacy of nonclinical studies to support MAA. Sufficiency of nonclinical and post-marketing data to support safety of excipients. The degradant characterisation profile delineated in a rat toxicology study. Adequacy of the nonclinical pharmacology and toxicology studies to support both the auto-injector and pre-filled syringe presentations of G-Pen.
- Design of two Phase 3 studies (protocol XSGP-303 and XSGP-304), both randomised, blinded, 2-way crossover comparative efficacy and safety studies in adults with T1DM, including duration, population, endpoints, sample size, choice of reference product, and PK analyses. Waiver of immunogenicity and tachyphylaxis evaluation. Human factors studies. Bridging PK/PD study (XSGP-101) to support an MAA of both the auto-injector and pre-filled syringe presentations of G-Pen. Paediatric development.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Karin Janssen van Doorn Co-Rapporteur: Simona Badoi

The application was received by the EMA on	21 November 2019
The procedure started on	2 January 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	23 March 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	23 March 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	6 April 2020
The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC members on	17 April 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	30 April 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	17 July 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	20 August 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	3 September 2020
The Rapporteurs circulated Updated Joint Assessment Report on the responses to the List of Questions to all CHMP members on	10 September 2020

The CHMP agreed on 1 st List of Outstanding Issues in writing to be sent to the applicant on	17 September 2020
The applicant submitted the responses to the CHMP 1 st List of Outstanding Issues on	10 October 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to 1 st List of Outstanding Issues to all CHMP members on	28 October 2020
The Rapporteurs circulated Updated Joint Assessment Report on the responses to 1 st List of Outstanding Issues to all CHMP members on	5 November 2020
The CHMP agreed on 2 nd List of Outstanding Issues in writing to be sent to the applicant on	12 November 2020
The applicant submitted the responses to the CHMP 2 nd List of Outstanding Issues on	17 November 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to 2 nd List of Outstanding Issues to all CHMP members on	25 November 2020
The Rapporteurs circulated Updated Joint Assessment Report on the responses to 2 nd List of Outstanding Issues to all CHMP members on	3 December 2020
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 Ogluo on	10 December 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The proposed indication is for the treatment of severe hypoglycaemia in adults, adolescents, and children aged 2 years and over with diabetes mellitus.

One of the main complications of diabetes treatment with insulin is the emergence of hypoglycaemia. Hypoglycaemia in diabetes is defined by the American Diabetes Association (ADA) as “all episodes of abnormally low plasma glucose concentration that expose the individual to potential harm” [ADA].

The ADA Workgroup recommends that patients with drug-treated diabetes (insulin secretagogue or insulin) become concerned about developing hypoglycaemia at a plasma glucose concentration of ≤ 70 mg/dL (3.9 mmol/L) [ADA]. A blood concentration < 54 mg/dL is the threshold at which neuroglycopenic symptoms begin to occur and requires immediate action to resolve the hypoglycaemic event (Level 2 hypoglycaemia). Level 3 hypoglycaemia is a severe event characterised by altered mental and/or physical functioning that requires assistance from another person for recovery.

2.1.2. Epidemiology and risk factors, screening tools/prevention

Therapy with insulin causes hypoglycaemia during the course of established T1D, and progressively more frequently over time in type 2 diabetes mellitus (T2D). The U.K. Hypoglycaemia Study Group reported an incidence of 110 severe hypoglycaemic episodes per 100 patient-years in patients with T1D treated with insulin for < 5 years, and an incidence of 320 episodes per 100 patient-years in those with T1D treated for > 15 years [U.K. Hypoglycaemia Study Group]. Type 1 diabetics suffer an average of two symptomatic hypoglycaemic events per week, and a severe, temporarily disabling event approximately once a year [McLeod]. Insulin-using T2D patients typically have several hypoglycaemic episodes in a given year, one to two of these being severe episodes. There are currently approximately 1.4 million T1D patients and 3.8 million insulin-using T2D patients in the United States (US), as reported by the US Center for Disease Control [CDC]. On average, the total insulin-using patient population experiences about 3 million severe hypoglycaemic events per year.

2.1.3. Clinical presentation, diagnosis

Hypoglycaemia presents as diaphoresis, pallor, nausea, palpitations, tremors, and anxiety. If hypoglycaemia becomes severe, symptoms may then include confusion, abnormal behaviour, blurred vision, psychomotor abnormalities, loss of consciousness, seizures, and coma [DCCT/EDIC Study Research Group].

2.1.4. Management

The ADA recommends that all insulin- and sulfonylurea-using diabetics carry glucagon emergency kits (GEKs) and use glucagon as first line therapy in the event of a severe hypoglycaemic event [ADA]. The current standard of care for severe hypoglycaemia is an injection of glucagon. Administration of glucagon with current products (i.e. Lilly Glucagon for Injection, and Novo GlucaGen) is a 9-step process including assembly of the kit, aqueous reconstitution of the powdered glucagon, and manual administration of the dose [Glucagon, Novo GlucaGen].

About the product

Ogluo is a sterile, subcutaneous, injectable, non-aqueous formulation of glucagon. The Ogluo pre-filled syringe (PFS) container consists of a 1.0 mL long cyclic olefin polymer syringe with ETFE laminated plunger (plunger stopper) filled with Ogluo glucagon formulation.

The 1 mg PFS is targeted to deliver at least 0.2 mL of glucagon injection, containing 1 mg glucagon. The 0.5 mg PFS is targeted to deliver at least 0.1 mL of formulation, containing 0.5 mg glucagon.

Type of Application and aspects on development

The clinical development programme of Ogluo included 7 clinical trials involving 62 healthy subjects in one phase 1 study (Study XSGP-101), and 300 adult and 31 paediatric subjects with T1D in two Phase 2 studies (Study XSGP-201 and Study XSGP-202) and four Phase 3 studies (XSGP-301, XSGP-303, and XSGP-304 in adults and the open-label study XSGP-302 in paediatric subjects 2-18 years old).

In addition, 7 human factors (HF) studies were sponsored by the applicant which were designed to mimic real-life emergency situations, and tested a total of 5 user groups that included first responders, trained and untrained users, adults and paediatric caregivers of people with diabetes.

The global clinical development programme for Ogluo was officially initiated in the United States in 2013 with dosing of the first subject in Study XSGP-201. EMA Scientific Advice (SA) was received with regards to the design of study XSGP-304. The FDA approved Ogluo on 10 Sep 2019 for the treatment of severe hypoglycaemia in patients with diabetes ages 2 years and above.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a solution for injection in a pre-filled syringe or a pre-filled pen containing 1 or 0.5 mg of glucagon as active substance.

Other ingredients are: trehalose dihydrate, dimethyl sulfoxide (DMSO), sulfuric acid, and water for injections.

The product is available in a pre-filled 1 mL cyclic olefin polymer syringe with ETFE coated chlorobutyl rubber piston, 27-gauge staked stainless steel needle, and bromo butyl rubber rigid needle shield or a pre-filled, single-dose pen containing a 1 mL cyclic olefin polymer syringe with ETFE coated chlorobutyl rubber piston, 27-gauge staked stainless steel needle, and bromo butyl rubber flexible needle shield as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

Glucagon is a synthetic linear 29 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-glutamyl-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-glutamyl-L-aspartyl-L-phenylalanyl-L-valyl-L-glutamyl-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:

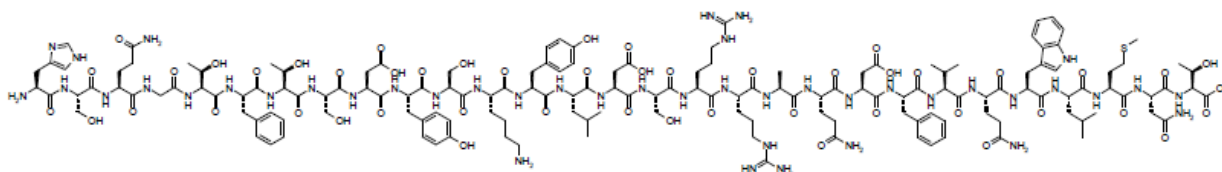


Figure 1: Active substance structure

The chemical structure of glucagon is determined by the route of synthesis based on the structures of the individual amino acids and the order of their stepwise addition. It was further elucidated by a combination of

amino acid analysis, gas chromatography-mass spectrometry (GC-MS), electrospray ionisation mass spectrometry (ESI-MS), electrospray ionisation-mass spectrometry-collision activated dissociation-mass spectrometry (ESI-MS-CAD-MS) and circular dichroism (UV CD). The solid state properties of the active substance were measured by dynamic vapour sorption (DVS), 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, the 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.

The active substance is an amorphous powder, no crystalline or polymorphic forms have been identified to date.

Manufacture, characterisation and process controls

The active substance is manufactured at 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 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 Ph. Eur. monograph and the glucagon USP monograph and it is considered appropriate.

Both individual and total related substances are controlled. The acceptance criteria are appropriate.

The analytical methods used have been adequately described and non-compendial methods 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 from 5 commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 5 commercial 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°C/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. The analytical methods used were the same as for release and were stability indicating.

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

Photostability testing following 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.

Studies under stressed conditions to evaluate the influence of temperature and moisture in the solid state, forced decomposition studies, and hygroscopicity studies were also conducted 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

The finished product is a sterile, subcutaneous, injectable, non-aqueous liquid formulation of glucagon. The finished product contains glucagon at a concentration of 5 mg/mL. The product is available in two strengths: 1 mg and 0.5 mg.

Other ingredients are trehalose dihydrate, dimethyl sulfoxide, sulfuric acid, and water for injections.

The finished product will be offered in two presentations, a pre-filled pen with an auto-injector (Configuration A) and a pre-filled syringe (PFS) (Configuration B). The pre-filled syringe container is common to both presentations. The PFS container consists of a 1.0 mL long cyclic olefin polymer syringe with ETFE laminated plunger (plunger stopper).

This is a hybrid medicinal product for which the reference product is GlucaGen / GlucaGen HypoKit 1 mg powder and solution for injection authorised the 25th October 1962 by Novo Norkisk A/S.

During the assessment, the CHMP requested analytical comparability data to support a hybrid application, which included analytical comparability data from a satisfactory number of finished product batches of Ogluo and the reference product, a risk-based evaluation of these data, and discussion regarding the similarities and differences between the properties of synthetic glucagon used in Ogluo and the recombinantly manufactured active substance used in the reference product as a major objection. In support of this Article 10(3) application, the applicant provided an analytical comparability review, including data on the level of glucagon active substance and on the finished product level, i.e. several batches of both Ogluo and the reference product GlucaGen, tested at various stages of shelf-life. On the active substance level, synthetic glucagon was compared to recombinantly produced glucagon contained in the Chemical Reference Standard (CRS). The finished products Ogluo and the reference product were analysed with respect to content, purity, and impurities and the results evaluated. Test and reference product significantly differ regarding the impurity profile. This is expected due to the different finished product composition. The glucagon assay results for GlucaGen expressed as % label claim were higher than the results for Ogluo. However, a possible connection between quality (declining amounts of glucagon in Ogluo during storage) and clinical response (in terms of time to recovery) could be excluded based on the quality and clinical data provided. Thus, the differences in % label claim between Ogluo and its reference product GlucaGen at the end of shelf-life was deemed acceptable.

Ogluo was developed as a ready-to-use formulation intended for subcutaneous injection. As glucagon is prone to degradation in aqueous solutions, the applicant selected a (nearly) water-free formulation with DMSO as a solvent.

The finished product has been developed to have the following advantages over existing glucagon rescue therapies: ready-to-use (RTU) glucagon treatment with no mixing or manual reconstitution required, precise, reliable, and rapid full-dosing of glucagon, reducing the risk of a partial or failed dose delivery, and room temperature stable, requiring no refrigeration, for convenience and portability. Ogluo addresses the current unmet medical need for a simple and ready-to-use glucagon preparation. It provides a reliable alternative to the existing glucagon powder kits approved for the treatment of severe hypoglycaemia.

For the development of finished product, the physical properties of the active substance, such as particle size and solid-state form, have no impact on the finished product processability or performance and as such are not considered key attributes in accordance with relevant ICH Q6A decision trees.

Compatibility of the glucagon with the excipients and DMSO in the finished product formulation has been confirmed by the stability of the finished product at the proposed commercial storage condition of 25°C.

The excipients used in the formulation are trehalose dihydrate as stabiliser, DMSO as diluent, and sulfuric acid as ionisation control. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Glucagon is known to be prone to aggregate and fibril formation. Aggregate formation in a non-aqueous solvent is not *per se* excluded because glucagon may not adopt its native conformation. Therefore, positive and negative glucagon fibril control samples have been produced. These control samples were used to demonstrate that the EP 2.2.1 Clarity method and ThT Fluorescence can detect samples containing glucagon fibrils. The finished product was stressed under two different conditions designed to exceed worst-case real-world patient handling. Evaluation by EP2.2.1 Clarity and ThT Fluorescence confirmed that no glucagon fibrillation was present. Based on these results it can be concluded that the finished product is not sensitive to aggregation and is not prone to glucagon fibril formation.

Two design of experiments (DoE) studies were conducted in order to confirm the robustness of the proposed formulation. The first study evaluated the variation of amounts of each component formulation. The target formulation is robust, and no significant trends were observed in the study. The second study evaluated the impact of the content of a specific ion in the glucagon active substance on the quality attributes of the final formulation. The results of this study demonstrate that the glucagon final formulation quality is not affected at the ion content levels controlled for in the Ogluo formulation.

The manufacturing process of the finished product has been developed using Quality by Design principles described in ICH Q8 although no design spaces are claimed.

A quality target product profile (QTPP) was developed and critical quality attributes (CQAs) of the final product include appearance (solution), glucagon assay, degradation products, water content, deliverable volume, particulate matter, sterility, endotoxins, and container closure integrity, which are relevant for both configurations. Additional CQAs specific to Configuration A (auto-injector) include injection depth, injection time, activation force, cap removal force, and deliverable volume. No additional CQAs for Configuration B were determined. CQAs are continually monitored to ensure final product outputs remain within acceptable quality limits. Risk assessments were performed throughout the process design stage based on empirical evidence and scientific knowledge to evaluate the impact of material attributes and process parameters on CQAs. High risk attributes and parameters were identified for further study or evaluation until the risk was reduced as low as possible and the proven acceptable ranges (PARs) were identified for each attribute or parameter, where applicable.

The manufacturing process is a stepwise operation consisting of 5 unit operations, compounding, sterilizing filtration, aseptic filling, assembly and final packaging.

Sterile filtration and aseptic processing have been implemented and validated to manufacture the finished product. The choice of the sterilisation method is considered sufficiently justified in accordance with the relevant sterilisation guideline (EMA/CHMP/CVMP/QWP/850374/2015) decision tree.

The primary container closure system is a pre-filled syringe (PFS) with a staked stainless-steel needle, COP syringe barrel, and ETFE laminated plunger stopper (piston). The finished product is offered in two presentations, a pre-filled syringe with an auto-injector (Configuration A) and a pre-filled syringe with an attached manual plunger rod and backstop (Configuration B). The PFS (primary closure system) is identical for both, with the exception of a rigid outer (non-drug product contacting) needle shield on Configuration B. The Configuration A and B have overall been adequately developed and tested according to relevant ISO norms, using the finished product solution, and their suitability has been demonstrated.

For both Configurations A and B, aging studies at 40°C/ 75% RH were performed to demonstrate that functionality of the devices is maintained over the intended shelf-life of 2 years at room temperature. The auto-injector contains a power pack with a complex mechanism. This essential mechanism needs to function properly in an emergency situation for which the drug is intended. The components will be stored before use in manufacture of the finished product.

Extractables testing was performed on the primary packaging components followed by a comprehensive leachable study which has been completed on the primary container system. In that study, analytical evaluation threshold (AET) calculations were provided that demonstrate suitably low and non-toxic levels of all leachables from the primary container system over the shelf-life of the product.

Biocompatibility testing was performed in both configurations. The recommended biocompatibility testing includes cytotoxicity, sensitisation, and irritation or intracutaneous reactivity. Testing was performed on final, finished devices under compliance to the GLP regulation. All tests passed.

Manufacture of the product and process controls

The finished product is manufactured by one manufacturing site.

The manufacturing process consists of 3 main steps: compounding, sterilizing filtration and aseptic filling. The process is considered to be a non-standard manufacturing process.

Process performance qualification (PPQ) according to the master validation plan has been completed. Three PPQ campaigns were performed at scale, delivering 7 batches of finished product. The manufacturing PPQ has demonstrated that commercial batches will be consistently produced to meet the final release specifications. During the evaluation, the CHMP requested the validation results of pen assembly which was not covered by the PPQ campaigns as a major objection. The requested data was provided demonstrating that the pen assembly step has been successfully validated. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release and shelf life specifications include appropriate tests for this kind of dosage form: appearance (visual), colour (Ph. Eur.), clarity (Ph. Eur.), identity (HPLC retention time, molecular weight), assay (HPLC), degradation products (HPLC), water content (Ph. Eur.), subvisible particulate matter (Ph. Eur.), endotoxin (Ph. Eur.), sterility (Ph. Eur.), container closure integrity (dye ingress method), extractable volume (Ph. Eur.), break-loose force (Instron force tester), and glide force (Instron force tester).

During the evaluation, the CHMP insisted that in order to accept the proposed specification limits for assay and impurities, unequivocal evidence needed to be provided that the variability observed in the clinical study batches was not related to a variable or decreasing finished product quality throughout shelf-life. This was raised as a major objection. The applicant argued that the finished product is not sensitive to aggregation and is not prone to glucagon fibril formation. However, the specification was revised. This was considered acceptable based on data provided showing that the lower amount of glucagon is not related to clinical effect (time to recovery).

No residual solvent testing is proposed for the release of the finished product. Solvents which would be considered impurities are controlled by the active substance and excipient specifications. There are no organic solvents used in the manufacturing of the finished product, other than DMSO, which is included as the formulation vehicle.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. The data obtained after 6 months of storage at 40°C/75% RH have demonstrated that elemental impurities are not present at levels exceeding the permitted daily exposure reported in the ICH Q3D. Therefore, no elemental impurities testing is proposed before release of the commercial finished product.

The CHMP requested the submission of a risk evaluation concerning the presence of nitrosamine impurities as a major objection. This information was provided applying the principles outlined in the notice "Information on nitrosamines for marketing authorisation holders (EMA/409815/2020)". No risk was identified.

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

Batch analysis results are provided for 6 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from 6 commercial scale batches of finished product stored for up to 30 months under long term conditions (25°C / 60% RH), 12 months under intermediate conditions (30°C / 65% RH) and for up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided.

Stability studies were performed on pre-filled syringes (PFS) in the primary container/closure system. The PFS batches for primary registration stability are representative of the intended commercial product and process. These PFSs are packaged in pouches consistent with the intended commercial packaging for Configuration A and Configuration B. The pouched PFSs are stored horizontally in the stability chambers. The auto-injector assembly, and the manual plunger and backstop were not included in the stability assessments as they are not in contact with the formulation during storage. The stability data from the PFSs support the registration for both Configuration A and Configuration B. Device Reliability Testing for both configurations stored in pouches was satisfactory.

Samples were tested for appearance, assay, degradants, water content, particulate matter, endotoxins and container closure integrity (CCI). The analytical procedures used are stability indicating.

Under long term, intermediate and accelerated conditions, all stability-indicating attributes remained well within the proposed commercial specifications throughout the study durations.

A freeze-thaw study of 4 batches with three rounds of temperature cycling from -20°C to 40°C (48 hours each) was conducted. No changes to appearance were observed and the minor changes to assay and degradation products were within specification. This study demonstrates that product quality will not be adversely affected by potential temperature excursions during shipping or storage.

In addition, 2 batches were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The PFS with and without the protective pouches was evaluated. The glucagon in PFS exposed to the severe conditions of the ICH study was significantly degraded, indicating that protection from light during long term storage is warranted. The assay and total degradants observed for pouched control PFS demonstrate that the pouch provides adequate protection from light.

Based on available stability data, the proposed shelf-life of 2 years with the following instructions “do not store above 25°C, do not refrigerate or freeze, do not store below 15°C, store in original sealed foil pouch until time of use in order to protect from light and moisture” as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

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

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Ogluo was developed as a ready-to-use formulation intended for subcutaneous injection. As glucagon is prone to degradation in aqueous solutions, a (nearly) water-free formulation was selected with DMSO as a solvent. Ogluo is offered in two configurations sharing a pre-filled plastic syringe as primary container with a staked needle and elastomeric needle shield and a laminated rubber piston. The PFS is integrated in an auto-injector for Configuration A, and equipped with a plunger rod with backstop and an additional rigid needle shield for Configuration B.

Information on development, manufacture, and control of the active substance and finished product has been presented in a satisfactory manner. 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.

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. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Xeris has developed a biocompatible, non-aqueous peptide/protein reformulation technology (Xerisol™) that allows the manufacture of concentrated, low volume, stable peptide formulations which can be pre-mixed and pre-loaded into a pre-filled syringe. Xeris has applied this technology to develop a stable, sterile, non-aqueous liquid formulation for the subcutaneous (SC) injection of glucagon, for the treatment of severe hypoglycaemia in patients with Type 1 diabetes or insulin-dependent Type 2 diabetes (Ogluo [glucagon injection]).

To support this submission, Xeris has conducted 6 nonclinical studies with the Xeris glucagon formulation (hereafter Xeris glucagon) administered SC; 4 studies in Sprague-Dawley rats, 1 study in New Zealand White rabbits, and 1 study in Yorkshire pigs.

In several instances, these studies had multiple endpoints which included a comparison of the pharmacodynamics (PD), pharmacokinetics (PK), and/or toxicity of the Xeris glucagon formulation to the marketed human recombinant glucagon products Glucagon for Injection and GlucaGen (Eli Lilly 2018, Novo Nordisk 2015). The studies were designed to demonstrate the safety of the Xeris glucagon vehicle and glucagon aqueous formulation and to assess the safety, pharmacokinetics, and/or glucose lowering effects of Xeris

glucagon. The pivotal repeat-dose toxicity studies in the rat and the rabbit local tolerance study were conducted in compliance with the GLP regulations.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The primary pharmacodynamics of Xeris glucagon on blood glucose was assessed *in vivo* in 2 PK/PD studies; 1 in Sprague Dawley rats (Report CB12-5015-R-TX) and 1 in Yorkshire pigs (Report PKPD13-GPO-06). In addition, an assessment of Xeris glucagon PD was included in a 2-week GLP rat toxicity study (Report XSGPE-TX02). In each of these studies, a marketed, recombinant glucagon injection drug product was used as a comparator to Xeris glucagon. The rat studies used the Eli Lilly glucagon formulation and Novo Nordisk GlucaGen drug product was used as a comparator in the pig study.

In rats, statistical data performed from 0 to 60 min showed that at clinically relevant doses (based on body weight; 0.016 mg/kg), Xeris glucagon SC injection rose glucose levels that is comparable to the marketed glucagon (Eli Lilly). Although, a trend toward a decrease in blood glucose concentrations can be seen in female rats, statistics demonstrate that there is no gender-related differences. This was confirmed in a second rat study. However, there is a statistically significant difference at shorter times, 5- and 10-minutes post-dosing respectively, which indicate that for the clinical intended dose (1 mg) the Eli Lilly glucagon acts faster and more efficiently than Ogluo (**Figures 2 and 3**). This was considered a concern for an emergency drug.

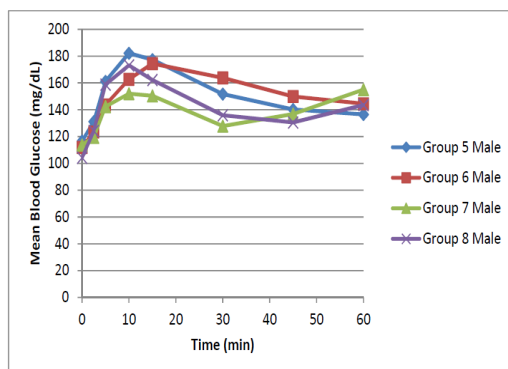


Figure 2: Blood Glucose Time Course, Phase-II Males (Groups 5 to 8)

Group 5 = 2.5µg xeris glucagon, group 6 = 5µg xeris glucagon, group 7= 50 µg xeris glucagon, group 8 = 5µg Eli Lilly Glucagon.

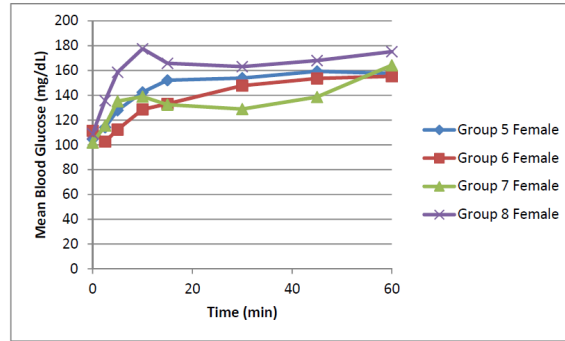


Figure 3 Blood Glucose Time Course, Phase-II Females (Groups 5 to 8)

Group 5 = 2.5µg xeris glucagon, group 6 = 5µg xeris glucagon, group 7= 50 µg xeris glucagon, group 8 = 5µg Eli Lilly Glucagon.

In fasted Yorkshire pigs, the glucose response mediated by glucagon Xeris was identical to the one mediated by glucagon from Novo Nordisk when both compounds were administered SC at a lower dose level (i.e. 8.5-fold) than the recommended dose of glucagon (1 mg for an adult). This is peculiar that the reference product that was used in this study (Novo Nordisk glucagon) is different than the one (Eli Lilly glucagon) used in other studies, which were carried out in rats. The applicant justified that this PKPD13-GPO-06 study was added in the dossier because Novo Nordisk glucagon is approved and marketed for use in the EU, while Eli Lilly glucagon is Xeris reference product in the US. Although it would have been pertinent to compare the three glucagon products in Yorkshire pigs: Ogluo, Novo Nordisk glucagon, and Eli Lilly glucagon, the issue is not pursued.

Secondary pharmacodynamic studies

Considering the long clinical experience with glucagon, which is an authorised product, together with the fact that the formulation does not contain new excipients (i.e. trehalose and DMSO), the applicant did not perform dedicated secondary pharmacodynamics studies with Xeris glucagon; that is agreed.

Safety pharmacology programme

Considering the long clinical experience with glucagon, which is an authorised product, together with the fact that the formulation does not contain new excipients (i.e. trehalose and DMSO), the applicant did not perform dedicated safety pharmacology studies with Xeris glucagon; that is agreed.

Pharmacodynamic drug interactions

No nonclinical pharmacodynamics drug interaction studies were conducted with Ogluo. Absence of pharmacodynamic drug interaction studies is acceptable since glucagon is a well-established substance.

2.3.3. Pharmacokinetics

The pharmacokinetics of Xeris glucagon was assessed *in vivo* in PK/PD studies in Sprague Dawley rats and Yorkshire pigs. In each of these studies, a marketed, recombinant glucagon injection drug product was used as a comparator.

The vehicle formulation was modified during the development of Xeris glucagon drug product. The pharmacokinetics of the 2 formulations was assessed in a single-dose study in rats.

Additionally, Xeris glucagon plasma concentrations were measured in the 2-week toxicity study in rats. The PK/PD study in rats and the 2-week toxicity study in rats were conducted in compliance with the Good Laboratory Practices.

Methods of analysis

Initially, Xeris used a commercial radioimmunoassay (RIA) to quantify glucagon in rodent plasma that was performed per the manufacturer recommendation. The method for analyses was then changed to a robust liquid chromatography-tandem mass spectrometry (LC-MS/MS)-based assay. The LC-MS/MS assay was validated in accordance with the European Medicines Agency Guideline on Bioanalytical Method validation (EMA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2).

To ensure consistency of the bioanalytical results obtained from these assays, Xeris conducted a comparative analysis of glucagon levels measured using LC-MS/MS and RIA and included results from an enzyme linked immunosorbent assay (ELISA). This comparison between the bioanalytical methods showed generally good comparability with sample stabilisation. The glucagon concentrations were generally lower using the RIA method. The observations of lower nominal concentrations with the RIA method was primarily due to background subtraction of endogenous levels of glucagon. No endogenous levels of glucagon were detected using the LC-MS/MS method.

As requested, the applicant provided more in-depth cross validation between methods and its conclusion regarding this aspect, in addition to an explanation on the role of ELISA method in this comparability exercise, which are acceptable. However, in fact the ELISA method was not used in nonclinical studies.

In addition, nonclinical PK studies have little relevance for the comparability exercise between Ogluo and the EU reference product GlucaGen HypoKit, clinical studies being paramount for the demonstration of equivalence regarding safety and efficacy between the above-mentioned medicinal products. Therefore, no further issue has been raised.

Absorption:

The absorption of glucagon was assessed in SD Rats, which were administered with a SC single dose of Xeris glucagon (2.5, 5 or 50 µg) or Eli Lilly glucagon (5 µg). T_{1/2} and T_{max} did not statistically differ between 2.5 and 5 µg Xeris glucagon compared to 5 µg Eli Lilly glucagon. However, C_{max} for 5 µg Xeris glucagon was statistically greater than C_{max} for 5 µg Eli Lilly glucagon, as opposed to C_{max} for 2.5 µg Xeris glucagon. AUC_{0-∞} were statistically similar for the two lower doses of Xeris glucagon and 5 µg Eli Lilly glucagon. One should expect to observe a greater calculated AUC_{0-∞} for 5 µg Xeris glucagon group than for the 2.5 µg one. However, the applicant made the point that very low dose volumes were administered to the rats: 0.5 µL and 1.0 µL (2.5 µg and 5 µg, respectively). So, mis-dosing may most likely occur with such low volumes. As a result, large variabilities can be expected in measurements of glucagon plasma concentrations.

In Yorkshire pigs, no statistical differences were noted for C_{max} and AUC_{0-∞} between Xeris glucagon and the reference control Novo Nordisk glucagon. The tested dose was 8.5-fold lower than the clinical intended dose of 1 mg glucagon.

Being an endogeneous peptide, distribution, metabolism, and excretion studies with Xeris glucagon are not warranted. In view of the clinical experience - no drug-drug interaction studies have been conducted with Xeris glucagon.

Other PK studies:

During development, the formulation of Xeris glucagon was slightly revised before entering into the Phase 3 clinical studies. The new formulation is nearly identical to the formulation tested in earlier nonclinical and in the Phase 2 studies.

Because of this change in formulation, a single-dose, exploratory study was conducted in SD rats to compare the postdose plasma concentrations of Xeris glucagon measured following SC dosing of 1 mg/kg with Formulation A or Formulation B.

Statistical analysis of the glucagon plasma concentrations showed that the 2 formulations were equivalent with the ratio of mean glucagon over 240 minutes of 0.97 (90% CI, 0.81 to 1.17).

2.3.4. Toxicology

Single dose toxicity

No single dose toxicity studies were conducted with Xeris glucagon due to its extensive nonclinical and clinical experience as an endogenous component of glucose homeostasis and glycaemic control. However, no toxicity was noted in the repeat dose toxicity studies following a single dose of up to approximately 2 mg/kg.

Repeat dose toxicity

The toxicity of Xeris glucagon and the reversibility of the treatment effects were evaluated in two repeat-dose studies in rats: a 2-day toxicity study (Report CB12-5015-R-TX) and a 2-week toxicity study (Report XSGPE-TX02). These studies included groups of rats administered the marketed Eli Lilly rDNA glucagon for injection as a comparator. The studies were designed to evaluate the toxicity, toxicokinetics, and/or pharmacodynamics of the Xeris glucagon formulation with the Eli Lilly Glucagon formulation. The 2-day study evaluated a dose of 5 µg/day (approximately 0.02 mg/kg). The 2-week toxicity studies assessed doses of up to approximately 2 mg/kg/day (approximately 1.23 to 1.64 mg/kg/day in males and 1.63 to 1.97 mg/kg/day in females).

In general, the results of the studies showed similar effects among the rats treated with the Xeris Glucagon formulation and the Eli Lilly glucagon formulation. No glucagon-related deaths occurred. Statistical analyses of the body weight and clinical pathology data revealed no adverse effects at any dose assessed. The minor changes seen in these parameters were transient in nature and often occurred among both Xeris and Eli Lilly glucagon-treated rats.

In the 2 day-study, increased incidence of rats with mild inflammation at the injection site was noted in the Xeris-treated animals (9/20) compared to the other treatment groups, including the Xeris-vehicle, which each had 1/20 animals with generally trace to mild injection site inflammation. Thus, this finding might be considered treatment-related.

In the 2-week study, reversible increases in mean absolute and relative (body and brain) liver weights occurred in males and females administered the high dose (Xeris glucagon: approximately 1.23 to 1.64 mg/kg/day in males and 1.63 to 1.97 mg/kg/day in females; Eli Lilly glucagon: 1.16 to 1.60 mg/kg in males and 1.64 to 2.00 mg/kg in females). No hepatic changes were noted microscopically and the changes were attributed to the pharmacology of glucagon. In the 2-week repeated-dose toxicity study there were no major adverse effects

but the development of scabs at the injection sites was noted mainly in the Xeris glucagon, and to a lesser extent in Xeris vehicle-treated rats that were not fully reversible after a 2 week recovery period. Histologically, the findings at the injection site correlated with epidermal necrosis and serocellular crust formation. Since comparable histological findings were also observed in the rat administered the Xeris-vehicle, the applicant suggested a potential vehicle-related effect rather than a Xeris glucagon related effect at the injected site. Nevertheless, injection site lesions in the 2 mg/kg/day Xeris Glucagon dose group animals at Day 15 were considered to be more severe overall. Compared to Xeris-glucagon, no adverse findings were noted at the injection site of rats administered the comparator (Glucagon Emergency Kit from Eli Lilly) or its corresponding vehicle. Based on the results of the 2-day and 14-day toxicity studies, the contribution of the vehicle does not appear sufficient to explain the higher toxicity of Xeris-glucagon at injection site as compared to Eli Lilly glucagon. In the clinical programme, injection site reactions were mild to moderate in severity, self-limited, fully resolved and required no additional medical intervention. Importantly, injection site oedema has been added as a common adverse reaction to the Ogluo SmPC.

Other than the effects observed at the injection sites, there were no systemic toxicities at any Xeris Glucagon dose levels. Comparable effects were observed at equivalent doses of the Lilly Glucagon test article; therefore, with the exception of injection site findings, there are no profound differences with regards to the toxicological profile between the two test articles when administered to male and female rats over a 14-day period.

Genotoxicity

Glucagon has been extensively used in the clinic and the safety profile of this peptide is well known. Furthermore, the excipients used in the Xeris-glucagon drug product formulation (i.e. trehalose and DMSO) are not new. Therefore, genotoxicity studies are not warranted with Xeris glucagon.

Carcinogenicity

Glucagon has been extensively used in the clinic and the safety profile of this peptide is well known. Therefore, carcinogenicity studies are not warranted with Xeris glucagon.

Reproduction Toxicity

Glucagon has been extensively used in the clinic and the safety profile of this peptide is well known. Therefore, reproductive and developmental toxicity studies are not warranted with Xeris glucagon. With regards to fertility, pregnancy, and lactation, section 4.6 of the SmPC of Xeris glucagon was aligned with the information contained in the SmPC of the reference product.

Toxicokinetic data

The 2-week toxicity study included an assessment of the toxicokinetics of Xeris glucagon compared with the Eli Lilly glucagon. No sex-related differences in plasma glucagon levels were noted at any dose. A comparison of Xeris glucagon to Lilly glucagon AUC₀₋₁₂₀ ratios ranged from 1.13 to 1.78 on Day 1 and from 1.49 to 3.08 on Day 14, indicating that plasma levels of glucagon tended to be higher following repeated administration of Xeris glucagon compared to Lilly glucagon. The slight increase in the plasma glucagon levels after repeated doses of the Xeris glucagon did not appear to increase toxicity in the dose groups.

Based on the 14-day repeat dose study, the NOAEL was found to be approximately 1.23 to 1.64 mg/kg in males and 1.63 to 1.97 mg/kg/day in females (safety margins 33.2 to 36.3x based on Cmax for the clinical intended dose of 1 mg/day, study XSGP-301).

Local Tolerance

In a local tolerance study, no Xeris glucagon-related dermal irritation was seen in rabbits following a single SC dose of 1 mg/rabbit. Reversible, mild inflammation, mixed cell in the subcutaneous tissue and minimal degeneration/necrosis, myofiber in the subcutaneous tissue were noted approximately 48-hours postdose for 2 of 3 males administered 1 mg Xeris glucagon. No histopathologic changes were seen at the necropsy conducted on Day 14.

Other toxicity studies

A 14-day rat toxicology study was conducted to qualify potential impurities that may become present during the anticipated 2-year shelf-life of the drug product. In that study animals were administered Xeris glucagon vehicle or Xeris glucagon at dose levels up to 2 mg/kg/day that was deliberately degraded to simulate the impurity profile present at the end of shelf life (forced degradation protocol). This study did not identify unexpected toxicities. The minor changes seen in body weight and clinical pathology data were comparable to those seen with Xeris glucagon and the Eli Lilly glucagon in the previous 2-week toxicity study. Increased liver weights and ratios were noted and were associated with glycogen-type vacuolation in the liver of males and females at ≥ 1 mg/kg/day. These increases in glycogen content in the liver is an expected result of glucagon treatment and its pharmacological mechanism. The NOAEL established in this study was 2 mg/kg/day.

2.3.5. Ecotoxicity/environmental risk assessment

The applicant provided the adequate justification for not submitting ERA studies. The active substance of Ogluo (glucagon for injection) is glucagon, an endogenous peptide hormone, and is thus classified as a peptide; therefore, a detailed Environmental Risk Assessment is not required for this medicinal product.

With regards to disposal, section 6.6 of the Ogluo SmPC appropriately specified that any unused medicinal product or waste material should be disposed of in accordance with local requirements that is consistent with the information available in the SmPC of the reference product (GlucaGen HypoKit).

2.3.6. Discussion on non-clinical aspects

To support this submission, Xeris has conducted 6 nonclinical studies with the Xeris glucagon formulation (4 studies in Sprague-Dawley rats, 1 study in New Zealand White rabbits, and 1 study in Yorkshire pigs. Two of the rat studies compared the pharmacodynamics (PD), pharmacokinetics (PK), toxicokinetics (TK), and/or toxicity of the Xeris glucagon formulation with the Eli Lilly glucagon formulation and a study in Yorkshire pigs compared the PD and PK of Xeris glucagon with the Novo Nordisk's glucagon formulation, which is the EU reference product for Ogluo (Eli Lilly 2018, Novo Nordisk 2015). A 2-week study was conducted in rats to qualify impurities present in the drug substance after forced degradation. Further, a local subcutaneous (SC)

tolerance study was conducted with Xeris glucagon in rabbits. In addition, a single-dose PK study was conducted to assess a change in the formulation of the drug product.

Overall, the *in vivo* pharmacodynamics data show that at clinically relevant doses, Xeris glucagon injection was highly effective in raising glucose levels and produced glucose responses in rats and pigs that were comparable to the marketed glucagon products (Eli Lilly and Novo Nordisk). Nevertheless, in the rat study at short times (5-10 min post-dosing), the Eli Lilly glucagon was found to act faster and more efficiently than Ogluo. Moreover, the applicant used different comparators in the PD studies conducted in the rat (Eli Lilly glucagon) and in the pig (Novo Nordisk glucagon) because Novo Nordisk glucagon is approved and marketed for use in the EU, while Eli Lilly glucagon is Xeris' reference product in the US. Although it would have been pertinent to compare the three glucagon products in Yorkshire pigs: Ogluo, Novo Nordisk glucagon, and Eli Lilly glucagon, this issue was not pursued.

To ensure consistency of the bioanalytical results, Xeris conducted a comparative analysis of glucagon levels measured using LC-MS/MS and RIA and included results from an enzyme linked immunosorbent assay (ELISA). This comparison between the bioanalytical methods showed generally good comparability with sample stabilisation. The glucagon concentrations were generally lower using the RIA method. The observations of lower nominal concentrations with the RIA method were primarily due to background subtraction of endogenous levels of glucagon. No endogenous levels of glucagon were detected using the LC-MS/MS method. It was not clear why the ELISA method was included in this comparative analysis. A rationale regarding the role of the ELISA method in the comparability exercise and a more thorough discussion regarding the comparability between the bioanalytical methods used have been provided. However, in fact ELISA method has not been used in nonclinical studies. Moreover, the little relevance of nonclinical PK studies in the comparability exercise between test article and reference product should be taken into account, paramount trials being represented by clinical studies. In conclusion, the query raised was resolved.

Post-dose plasma glucagon concentrations and absorption parameters (C_{max}, AUC) in Sprague-Dawley rats and Yorkshire pigs administered Xeris glucagon was overall similar to those seen in animals administered the same doses of Eli Lilly glucagon (rats) or Novo Nordisk glucagon (Yorkshire pigs). No statistically significant differences were noted for any group. It is unclear why in the rat study, the AUC_{0-∞} for Xeris glucagon at the dose of 2.5 µg and 5 µg were not statistically different. However, in further discussions, the applicant made the point that very low dose volumes were administered to the rats: 0.5 µL and 1.0 µL (2.5 µg and 5 µg, respectively). So, mis-dosing may most likely occur with such low volumes. As a result, one can expect large variabilities in measurements of glucagon plasma concentrations.

Since the formulation of Xeris glucagon was slightly revised during the clinical development programme, a single-dose, exploratory study was conducted in Sprague-Dawley rats to compare the post-dose plasma concentrations measured following SC dosing with Formulation A or Formulation B. This exploratory PK study confirmed the bioequivalence of the 2 Xeris glucagon formulations.

The Xeris glucagon toxicity programme was comprised of a 2-day toxicity study and a 2-week toxicity study to evaluate the toxicity of the Xeris drug product in rats. These studies included groups of rats administered the marketed Eli Lilly rDNA glucagon for injection as a comparator. No unexpected Xeris glucagon-related systemic toxicities occurred in rats administered 5 µg/day (~ 0.02 mg/kg) for 2 days or up to 2 mg/kg/day. In general, the results of the studies showed similar effects among the rats treated with the Xeris glucagon formulation and the Eli Lilly glucagon formulation. Nevertheless, injection site lesions were observed in the animals administered Xeris glucagon and, to a lesser extent, Xeris vehicle, while no such a finding was observed with the comparator (Glucagon Emergency Kit from Eli Lilly) or its corresponding vehicle. The applicant underlined

that in the clinical programme, injection site reactions were mild to moderate in severity, self-limited, fully resolved and required no additional medical intervention. Importantly, injection site oedema has been added as a common adverse reaction to the Ogluo SmPC, which addresses adequately the concern that was raised both in the nonclinical and clinical studies.

In view of the nonclinical and clinical experience with glucagon, no reproductive and developmental toxicity studies have been conducted with Xeris glucagon.

In a local tolerance study conducted in the rabbit, mild inflammation, mixed cell in the subcutaneous tissue and minimal degeneration/necrosis, myofiber in the subcutaneous tissue were noted approximately 48-hours after the SC administration of 1 mg Xeris glucagon. Those findings were reversible as no histopathologic changes were seen at the necropsy conducted on Day 14.

No unexpected toxicities occurred in a 2-week toxicity study in rats that was conducted to evaluate impurities in the Xeris glucagon drug product. No adverse toxicities occurred in vehicle control animals administered the Xeris DMSO vehicle formulation.

2.3.7. Conclusion on the non-clinical aspects

In conclusion, all nonclinical aspects have been addressed satisfactory.

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***

Table 1 Ogluo clinical studies

Protocol No. Study Start - Stop Date	Study Objective	Primary Endpoint	Population	Total Enrolled	Subjects Treated Gender (M:F)	Age Mean/ Range (years)	Phase	Study Design ^a	Admin.	Dose (mg)	Injection Location
XSGP-101 13Feb2018 19Mar2018	BE of the AI and PFS configurations of Gvoke	Plasma glucagon AUC (0-240 min) and C _{max}	Healthy volunteers	32	16 – M 16 – F	44.6/ 19 – 63	1	R, OL, XO	Gvoke AI vs Gvoke PFS	AI 1 mg PFS 1 mg	Abdomen
XSGP-201 18Sep2013 22Jan2014	Safety and tolerability	Plasma glucose AUC, C _{max} and T _{max}	Healthy volunteers	30	9 – M 21 – F	38.7/ 20 – 57	2	R, DB, XO	Gvoke AI vs GEK	Gvoke 1 GEK 1	Arm
XSGP-202 01May2015 – 29May2015	Pilot Study	Plasma glucose >70 mg/dL within 30min	Adult T1D	7	1 – M 6 – F	42 (median) 23 – 59	2	NR, OL, XO	Gvoke vial and syringe	Gvoke 0.5 Gvoke 1	Arm
XSGP-301 15Mar2017 – 04Aug2017	Plasma Glucose recovery from <50 mg/dL	Plasma glucose >70 mg/dL within 30min	Adult T1D	80	44 – M 36 – F	43.6 / 18 – 74	3	R, DB, XO	Gvoke AI GEK	Gvoke 1 GEK 1	Arm, thigh, abdomen
XSGP-302 17Apr2017 – 04Aug2017	Plasma glucose response from <80 mg/dL	Plasma glucose recovery within 30 min	Paediatric T1D	31	15 – M 16 – F	2 to 6 (N=7) 6 to 12 (N=13) 12 to 18 (N=11)	3	NR, OL, XO	Gvoke AI	Gvoke 1 Gvoke 0.5	Arm, thigh, abdomen
XSGP-303 08Jan2018 18Apr2018	Plasma glucose recovery from <50 mg/dL	Plasma glucose >70 mg/dL within 30 min	Adult T1D	81	44 – M 37 – F	38 / 18-72	3	R, SB, XO	Gvoke AI GEK	Gvoke 1 GEK 1	Abdomen
XSGP-304 19Sep2018 02Apr2019	Plasma glucose recovery from <54 mg/dL	Plasma glucose >70 mg/dL or increase ≥20 mg/dL, within 30 min	Adult T1D	132	70 – M 62 – F	39.5 / 19-72	3	R, SB, XO	Gvoke AI HK	Gvoke 1 HK 1	Abdomen

AI= Auto-Injector, BE=bioequivalence, DB=double-blind, F=Female, GEK=glucagon emergency kit (Lilly), HK=HypoKit (Novo Nordisk), M=Male, NR=Non-randomized, OL=open label, PFS=pre-filled syringe, R=Randomized, SB=single blind, T1D=type 1 diabetes, XO=crossover.

Gvoke=Ogluo

2.4.2. Pharmacokinetics

Pharmacokinetics of Ogluo were evaluated in healthy volunteer studies XSGP-101 and XSGP-201, and phase 3 studies XSGP-301 (adult T1D patients) and XSGP-302 (paediatric T1D patients). The focus of the clinical development programme was, however, on the demonstration of comparable clinical effect of Ogluo to currently marketed versions of glucagon, therefore, PK data are mostly supportive for this application.

Since Ogluo is a synthetic glucagon formulation which contains the same amino acid sequence as native glucagon as well as to recombinant glucagon used in currently marketed glucagon emergency kits, distribution and elimination pathways are expected to be the same as for recombinant glucagon.

Analytical methods

Throughout the clinical programme, two analytical methods were used to quantify glucagon in plasma samples; 1) a radioimmunoassay (RIA) and 2) liquid chromatography tandem mass spectrometry (LC-MS/MS).

The LC-MS/MS method, used for glucagon determination in studies XSGP-101, -301, and -302, was adequately validated, but unexpected issues (low IS response, interfering peak) were encountered during analysis of samples of study XSGP-301 and study XSGP-101, respectively. Although the acidification process during clinical sample processing was suspected to be the root cause for this deviating IS response in study XSGP-301, the applicant reassured that protease activity was sufficiently blocked in all samples.

For study XSGP-101, the presence of an interfering peak in an important portion of study samples could not be clarified. Obviously, the accuracy of a portion of the study samples may have been influenced by the presence of this interfering peak (as reflected by ISR failure), precluding conclusion on PK equivalence (see below).

No bioanalytical issues were reported for paediatric study XSGP-302.

The commercial RIA kit, applied in study XSGP-201, was not revalidated in line with the EMA guideline and cross-reactivity with glucagon-like peptides present in Lilly glucagon was observed. Since the clinical programme focussed on the demonstration of comparable clinical effect, these issues were not pursued.

PK studies

Study XSGP-201

The overall objective of study XSGP-201 was to compare the safety, PK, and efficacy (glucodynamics) of Ogluo administered as 0.5 mg and 1 mg injections, versus the US comparator Lilly glucagon for injection (GEK) 1 mg. The study was designed as a randomised, double-blind, 3-period, 6-sequence crossover study in healthy volunteers (N=30). Treatment were separated with a period of 3-14 days.

Treatment groups differed significantly ($p < 0.001$) with regard to mean glucagon AUC₀₋₂₄₀, mean glucagon C_{max}, and mean glucagon t_{max} and no evidence of bioequivalence between treatments was found with regard to these three parameters. Significantly higher exposure was observed after administration of Lilly glucagon versus Ogluo and t_{max} was longer for Ogluo (mean of 37.6 min versus 18.9 min) (Figure 4).

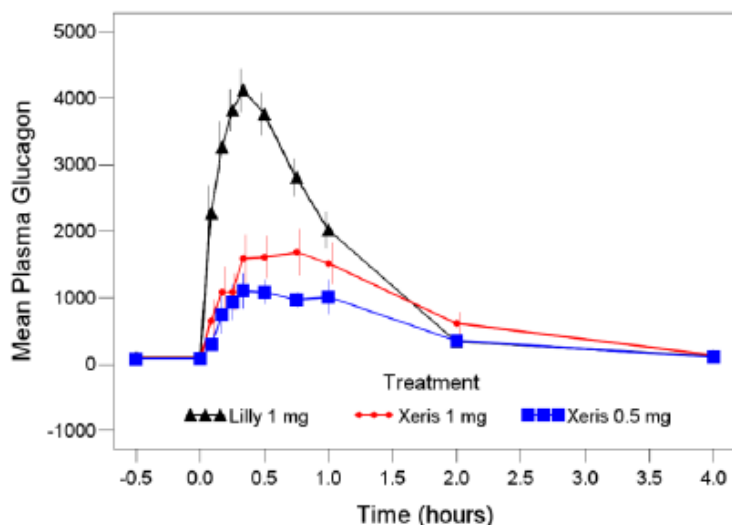


Figure 4. Mean plasma glucagon (ng/mL) by time and treatment

Given the findings of XSGP-201, Phase 3 trials of Ogluo focused on establishing non-inferiority to the US and EU reference product via a clinical efficacy development programme. Comparative PK analyses were not part of the Phase 3 programme. In this context, the lack of BE is not of concern.

Study XSGP-101

Ogluo is offered in two presentations; a pre-filled syringe inserted into an auto-injector (AI, Configuration A) and a pre-filled syringe fitted with a manual plunger rod and backstop (PFS, Configuration B). All phase 3 studies were conducted with Configuration A.

Study XSGP-101 was a Phase 1, single-site, randomised, open-label, two-way crossover study to demonstrate PK and PD equivalence of Ogluo 1 mg when injected SC in the abdomen via auto-injector versus a manual pre-filled syringe, in fasted healthy subjects with low to normal blood glucose (70 to 120 mg/dL). Two single dose treatments were administered 3 to 7 days apart.

Mean plasma glucagon AUC(0-240), C_{max}, and t_{max} were generally similar overall and between treatments, although lower plasma glucagon AUC and C_{max} levels were shown for subjects who received AI (Configuration A) at their second treatment. These lower glucagon levels are neither considered statistical or clinically relevant since they did not correlate to lower plasma glucose levels and did not impact the BE conclusion. It should however be reminded that, as explained above (bioanalytical methods), no definite conclusion on PK equivalence can be drawn due to the potential inaccurate measurements of an important portion of study samples. Since it is acknowledged that the PD response is most relevant for the desired action of Ogluo and PD equivalence was demonstrated between both configurations in this study, this issue was not further pursued.

Table 2. Analysis of plasma glucagon between treatments (study XSGP-101)

Treatment	N	Geometric Mean Estimate ^a (SE)	95% CI	P-Value (Difference)	90% CI	BE Test
AUC₀₋₂₄₀ (ng-min/mL)						
AI (Configuration A)	32	166.4 (1048.16)	146.2, 189.2	--	--	--
PFS (Configuration B)	32	177.4 (1117.88)	156.0, 201.8	--	--	--
Configuration B/ Configuration A ^b	--	106.65% (7.227%)	92.85%, 122.51%	0.3497	95.05%, 119.67%	Satisfied
C_{max} (ng/mL)						
AI (Configuration A)	32	2.1 (15.66)	1.8, 241.8	--	--	--
PFS (Configuration B)	32	2.1 (16.11)	1.8, 248.7	--	--	--
Configuration B/ Configuration A ^b	--	102.87% (9.447%)	85.25%, 124.12%	0.7602	88.01%, 120.24%	Satisfied

Study XSGP-301

Study XSGP-301 was a randomised, double-blinded, 2-way crossover comparative efficacy and safety study comparing Ogluo 1 mg to Glucagon Emergency Kit (GEK, Eli Lilly) 1 mg, in 80 subjects with T1D during an induced state of severe hypoglycaemia. PK parameters were determined after SC administration of Ogluo and analysed descriptively for the different injection sites (randomly assigned): upper arm, leg, or abdomen. Mean plasma glucagon t_{max} was similar regardless of injection site. However, mean plasma glucagon C_{max} and AUC values were highest when Ogluo was administered in the abdomen followed by the arm, followed by the leg. These differences are not considered to be clinically relevant since comparable PD data (time to plasma glucose > 70 mg/dL) were obtained for the different injection sites.

Table 3. Summary PK parameters (Mean (SD)) by injection site

	Abdomen (N=25)	Arm (N=28)	Leg (N=25)
C _{max} (ng/mL)	2761.62 (1324.895)	2567.74 (1156.964)	2104.04 (818.768)
AUC ₀₋₂₄₀ (min*ng/mL)	3834.69 (1274.668)	3583.79 (1401.440)	2929.94 (933.118)
T _{max} (min)	49.28	54.57	45.64

Since study XSGP-301 is the only PK study conducted in adult type 1 diabetes (T1D) patients, the PK parameters for this study were included in section 5.2 of the SmPC.

Absorption

Across-study comparison

Table 4. Mean (SD) PK parameters of Plasma Glucagon Across Studies Following Administration of Ogluo 1 mg Subcutaneous to Adult Subjects (Study XSGP-301)

PK Parameter	Value	XSGP-101		XSGP-201	XSGP-301
		Configuration A	Configuration B	1.0 mg	1.0 mg
C _{max} (ng/mL)	N	32	32	27	78
	Mean (SD)	2.40 (1.253)	2.43 (1.261)	2.06 (2.052) ^a	2.50 (1.14)
T _{max} (h)	N	32	32	27	78
	Mean (SD)	40.5 (19.0)	42.5 (15.8)	37.6 (15.2)	40.5 (18.6)
AUC ₀₋₂₄₀ (ng·min/mL)	N	32	32	28	78
	Mean (SD)	181.8 (71.8)	191.1 (71.5)	195.60 (206.9) ^b	200 (73.3)
AUC ₀₋₁₂₀ (ng·min/mL)	N	32	32	N/A	N/A
	Mean (SD)	154.9 (68.4)	162.8 (71.1)	N/A	N/A

Discrepancies were noted between AUC, C_{max}, and t_{max} values (of the same study) reported in different documents. These discrepancies may partly be explained by the incorrect use of PK parameters units (expressed differently as ng/mL or pg/mL).

The applicant confirmed what is the correct value and unit for C_{max}, AUC₀₋₂₄₀, and t_{max} for study XSGP-301 and adapted the SmPC accordingly.

Bioavailability

Different injection sites (arm, leg, or abdomen) for subcutaneous (SC) administration of Ogluo were used throughout the clinical development programme (see Table 1).

Pharmacokinetics for Ogluo were described by injection site in Study XSGP-301. This study was a Phase 3, non-inferiority, randomised, controlled, double-blinded, 2-treatment, 2-sequence, 2-way crossover comparative efficacy and safety study in adult T1D patients. Following insulin-induced hypoglycaemia (<50

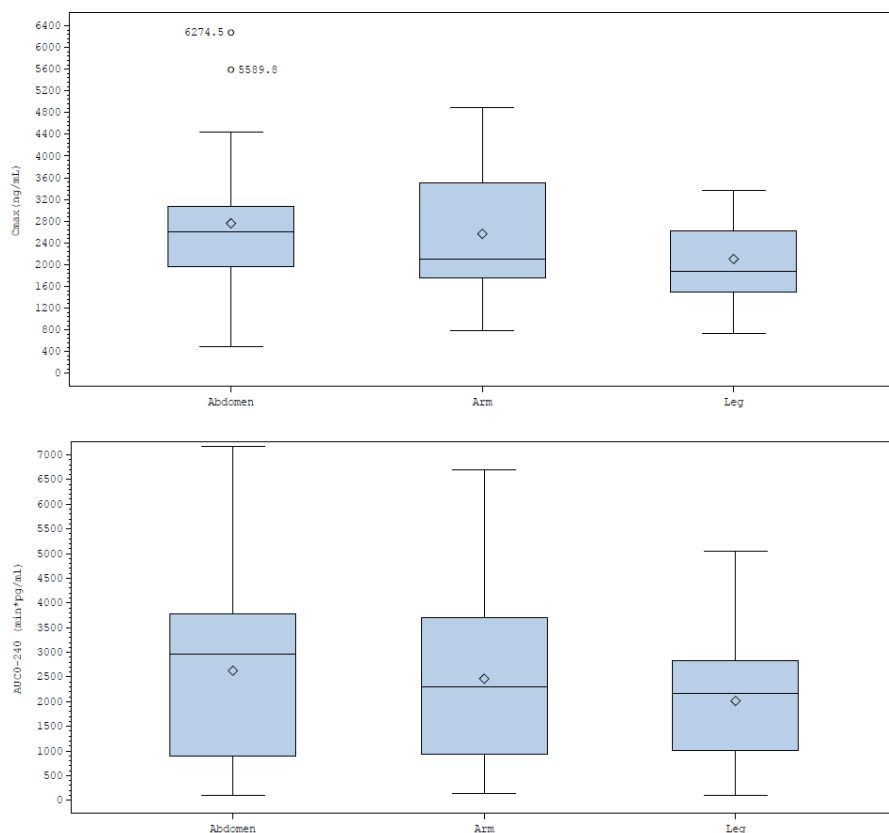
mg/dL plasma glucose), subjects were treated SC in the upper arm, leg, or abdomen with either 1 mg Lilly Glucagon or 1 mg Ogluo. The injection site for each subject was randomly assigned and remained fixed between the two treatment visits. Treatments were separated by a wash-out of 7 to 28 days.

A total of 80 subjects (44 male, 36 female) were randomised; 77 subjects received the Ogluo treatment. As a post-hoc analysis, the PK parameters (only determined for Ogluo) were analysed descriptively by injection site.

Results

Mean plasma glucagon concentration (Ogluo glucagon) over time was highest when administered in the abdomen, followed by the arm, followed by the leg from approximately 20 to 60 minutes after administration. After 60 minutes, plasma glucagon concentration over time showed little separation between curves by injection site.

Assessment of different injection site locations showed that mean plasma glucagon Cmax and AUC values were highest when Ogluo was administered in the abdomen followed by the arm, followed by the leg. However, mean plasma glucagon tmax was similar regardless of injection site location.



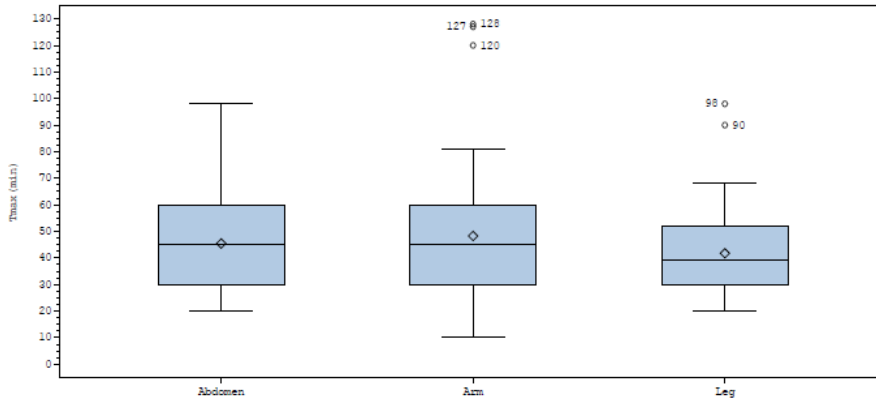


Figure 5. Plasma glucagon Cmax (ng/mL), AUC0-240 (ng*min/mL) and tmax (min) (above, middle, below) by injection site in subjects administered Ogluo

Table 5. Summary PK parameters (Mean (SD)) by injection site

	Abdomen (N=25)	Arm (N=28)	Leg (N=25)
Cmax (ng/mL)	2761.62 (1324.895)	2567.74 (1156.964)	2104.04 (818.768)
AUC0-240 (min*ng/mL)	3834.69 (1274.668)	3583.79 (1401.440)	2929.94 (933.118)
tmax (min)	49.28	54.57	45.64

Since study XSGP-301 was primarily an efficacy and safety study, only PK-related aspects of this study are described here. For more details on the study, reference is made to the clinical efficacy section.

PK parameters for the different injection sites were only analysed descriptively and hence, no statistical analysis was performed. Neither did the applicant provide a plasma concentration time curve by injection site. In general, tmax was the least impacted by the location of injection, which is important for a rescue medication. Larger mean differences (and more variability) was observed between injection sites for the parameters Cmax and AUC. The applicant discussed the observed differences are not clinically relevant.

Distribution

The apparent volume of distribution was determined in studies XSGP-101, XSGP-201 and XSGP-301.

	V/F (L) (mean (range))
study XSGP-101 (Configuration A)	4,2
study XSGP-101 (Configuration B)	2,5
study XSGP-201	754 (36-6005)
study XSGP-301	272 (77.8-1050)

Ogluo is a formulation of synthetic glucagon that is structurally identical to native glucagon as well as to recombinant glucagon used in currently marketed glucagon emergency kits. Once absorbed, distribution and elimination pathways are expected to be the same as for recombinant glucagon. Limited information on Ogluo distribution has been provided, which was considered acceptable. Across studies, a very broad range of values were reported for the apparent volume of distribution. Considering these data, the applicant clarified the origin of the range of 137-2425 L for apparent volume of distribution reported in the SmPC.

Elimination

Glucagon is extensively degraded in the liver, kidney, and plasma.

In **study XSGP-301**, the mean apparent clearance was determined to be 340 L/h (range 144 -800 L/h) and the mean half-life was 31.9 minutes.

In **study XSGP-201**, the mean half-life was 63.7 minutes following administration of 1 mg Ogluo and 51.0 minutes following administration of 1 mg Lilly glucagon.

In **study XSGP-101**, the mean half-life was 41.4 minutes (Configuration A) and 35.9 minutes (Configuration B).

Elimination pathways are expected to be the same for Ogluo as for other glucagon formulations. Compared to the patient information for Lilly glucagon (half-life of 8-18 minutes after IV administration), a longer half-life was observed for Ogluo and for Lilly glucagon following SC administration. This likely reflects residual appearance from the injection site, so called flip-flop kinetics. The value for half-life obtained in study XSGP-301 is used for labelling purposes, which is supported since this is the only PK study conducted in T1D patients.

Dose proportionality and time dependencies

In study **XSGP-201**, dose linearity and proportionality of Ogluo 0.5 mg and Ogluo 1 mg were investigated by fitting a simple linear model with dose as the factor: $Y = \theta_0 + \theta_1 * (Dose)$.

Dose linearity could not be established statistically for any glucagon parameter (AUC₀₋₂₄₀ and C_{max}) because the slope θ_1 of dose was not significantly different from zero (P-values: AUC₀₋₂₄₀: 0.19, C_{max}: 0.30). Due to the inability to statistically support dose linearity, dose proportionality could not be demonstrated for any glucagon parameters (AUC₀₋₂₄₀, C_{max}, and t_{max}).

AUC and C_{max} were less than dose proportional after administration of a single 1 mg and 0.5 mg dose of Ogluo in study XSGP-201. Since Ogluo is proposed as a single dose rescue treatment in case of severe hypoglycaemia, the lack of dose-proportionality was not of concern.

Special populations

Study XSGP-302

Study XSGP-302 was a Phase 3 study to evaluate the glucose response of Ogluo in paediatric patients with T1D. The PK of Ogluo for each age group (2 to < 6 years, 6 to < 12 years, and 12 to < 18 years) were analysed descriptively as a secondary objective. Subjects were administered insulin to induce a low normal glycaemic

state and then received an age appropriate dose of Ogluo. Subjects aged 2 to < 12 years received a single 0.5 mg dose of Ogluo. Subjects aged 12 to < 18 years received a 1 mg dose of Ogluo at the first visit, and the 0.5 mg dose at a second visit occurring 1 to 4 weeks later. The applicant states that the transition to the adult dose (i.e. 1 mg) at 12 years (corresponding to average weight of 40-45 kg) is based on a weight-exposure model using data from study XSGP-201. The applicant was asked to provide the details of this modelling exercise as well as a discussion on the reliability of the conclusion as no subjects weighing less than 58 kg were included in study XSGP-201. The applicant's responses clarified that the paediatric dose selection was not based on modelling and simulation and it was based on the ISPAD 2014 guidelines. Based on PK data available from study XSGP-201 in adults a weight-based exposure modelling analysis has been performed in adolescents weighing above 40 kg, including the median, the 5th and 95th percentiles for glucagon AUC and concentration. No simulations were performed in children below 12 years and weighing below 40 kg.

From the figures provided for glucagon concentration the 5th percentile after 1 mg dose crosses with the 95th percentile after 0.5 mg dose at the point corresponding to the weight cut-off of 45 kg. However, the values for glucagon AUC corresponding to this weight cut-off after the 0.5 mg dose are below those obtained after 1 mg dose.

The applicant assumed that at this weight cut-off (45 kg) similar exposures for both Cmax and AUC would be expected in paediatric population as to that of 1 mg dose in adults weighing 70 kg, but simulations have not been performed in support of that assumption. In addition, no information about the simulations for Ctau is included.

Based on PK data observed in the conducted paediatric study XSGP-302 lower exposures were noticed in adolescents either after 0.5 mg or 1 mg dose than in children 2-6 years of age. In addition, a lower exposure was noticed in children 6-12 years of age comparative with the one observed in children 2-6 years of age after administration of a fixed 0.5 mg dose of glucagon.

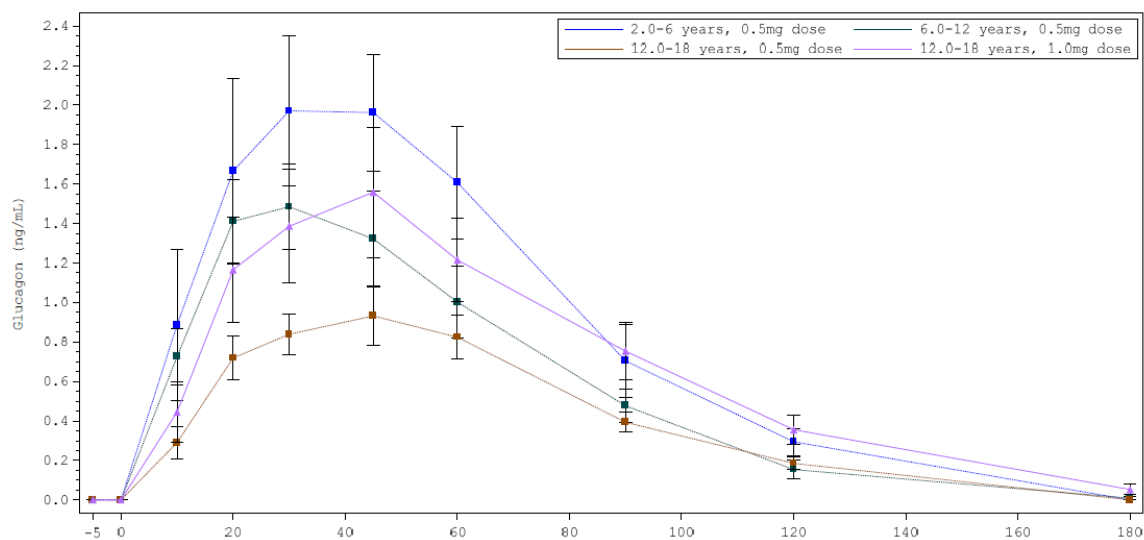


Figure 6. Mean (SE) plasma glucagon at each time point for age/dose group

Table 6. Summary PK parameters for age/dose groups

PK parameter		2.0-<6.0 years 0.5 mg	6.0-<12.0 years 0.5 mg	12.0-<18.0 years 0.5 mg	12.0-<18.0 y 1 mg
C _{max} (ng/mL)	N	7	13	11	11
	Mean (SD)	2.3 (1.08)	1.6 (0.84)	1.1 (0.49)	1.9 (1.18)
t _{max} (min)	N	7	13	11	11
	Mean (SD)	41.4 (12.82)	33.8 (14.96)	40.4 (15.38)	51.0 (22.96)
AUC ₀₋₁₈₀ (ng/mL * min)	N	5	12	11	10
	Mean (SD)	138.9 (77.59)	104.7 (55.24)	73.4 (28.05)	134.3 (56.03)

The predictions from the performed weight-based modelling analysis indicate a decreasing in exposure with the increasing of the body weight, given the high volume of distribution of glucagon, in a similar way with the lower exposures observed with increasing of age group after subcutaneous administration of glucagon.

Although it should be kept in mind that subject numbers for each age group were low and the secondary PD endpoints were similar between age groups with regard to mean plasma glucose AUC(0-90), C_{max}, and T_{max}, there seems to be a trend for decreasing mean glucagon levels with increasing age group after administration of a fixed 0.5 mg dose, thus, the proposed weight cut-off at 45 kg for the transition to adult dose does not support an optimal dose based on glucagon PK parameters in children 6-12 years. Therefore, a weight cut-off at 25 kg was recommended for the transition to adult dose.

The applicant revised the paediatric dosage including a weight cut-off at 25 kg, for transition to adult dose, 1 mg, and the SmPC was updated accordingly.

PK data obtained in paediatric subjects have been included in section 5.2 of the SmPC.

Other special populations

No studies with Ogluo were performed in renal and/or hepatic impaired patients. The applicant relays on the labelling information for the reference product Glucagen in these subpopulations. Hence, the proposed SmPC does not include any dose adjustments. This is considered acceptable in view of the short-time emergency use of Ogluo.

Study XSGP-301 included 9 T1D patients aged 65 years and above, but PK parameters were not presented separately for these elderly patients. In general, no changes in PK parameters are expected due to advanced age in line with what is known for other glucagon products.

The PK of Ogluo were analysed descriptively for different ethnicities/races in studies XSGP-301 and XSGP-101 and suggest no significant difference in Ogluo PK among subgroups.

Pharmacokinetic interaction studies

The interaction properties of Ogluo proposed for labelling are based on published data for the injectable glucagon formulation, which is acceptable.

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

Studies XSGP-301 and XSGP-303 used GEK (the US reference product) as comparator, therefore these studies are less relevant for Europe. Study XSGP-302 had no control arm and was mainly intended to justify the use in children and to determine the dose in children. Study XSGP-304 is the pivotal study. Overall, Ogluo seems to act slower than the reference product, but Cmax and Glucose AUC (0-90) is slightly higher.

Plasma glucose was assessed for different periods of time across studies (ie, 90, 180, or 240 minutes). In addition, study investigators had discretion to restart a subject's insulin if medically necessary after the 90-minute timepoint, which required censoring of glucose values from after that point due to the potential confounding effect of this glucose lowering medication.

Therefore, to standardise results for comparison of pharmacodynamics across studies, time to reach two specified plasma glucose levels was analysed (from time of study drug injection), as opposed to only using Cmax, tmax and AUC:

1. Time to plasma glucose > 70 mg/dL.
2. Time to a plasma glucose increase over baseline of ≥ 20 mg/dL.

Data were pooled for the Study XSGP-301 and Study XSGP-303 Phase 3 studies. Data from Study XSGP-304 is presented as a comparison to pooled data. Study drug preparation time for Ogluo in Study XSGP-304 was 0.76 minutes vs 1.76 minutes for HK; this time advantage for Ogluo would shorten time to plasma glucose recovery.

In pooled Studies XSGP-301 and XSGP-303, and in Study XSGP-304, the time to specified plasma glucose (>70 mg/dL or increase ≥ 20 mg/dL) was approximately 4 minutes longer following Ogluo treatment in patients with T1D. However, in the pooled studies, time to hypoglycaemia symptom relief (clinical correlate) was similar and not statistically different between Ogluo and GEK. Overall, the average time to plasma glucose recovery was well below the threshold of 30 minutes from study drug injection (13.8 minutes following Ogluo administration and 10.0 minutes following GEK).

In Study XSGP-304, the time to specified plasma glucose response was approximately 4 minutes longer following Ogluo treatment in patients with T1D. However, time to hypoglycaemia symptom relief (clinical correlate) was similar between Ogluo and HK in the mITT population and statistically significantly faster for Ogluo in the PP population. Overall, the average time to plasma glucose recovery was well below the threshold of 30 minutes from study drug injection (14.8 minutes after Ogluo administration and 10.4 minutes after HK).

Overall, across all adult Phase 3 studies the average time to plasma glucose recovery was below the threshold of 30 minutes from study drug injection, in any treatment arm.

2.4.4. Discussion on clinical pharmacology

In general, for the PK data provided in this application issues were observed with the bioanalytical methods questioning the reliability of the data reported (see below). The discrepancies found between PK parameter values for the same study reported in different documents have been clarified by the applicant.

The LC-MS/MS method, used for glucagon determination in studies XSGP-101, -301, and -302, was adequately validated, but unexpected issues (low IS response, interfering peak) were encountered during analysis of samples of study XSGP-301 and study XSGP-101, respectively. The applicant was asked to justify the reliability of the results obtained in these studies. The fact that an important portion of samples from both Configuration A and B could not be determined accurately (as reflected in the failed ISR), precluded conclusion on PK equivalence. However, it is acknowledged that only the PD response is relevant for the desired action of Ogluo and PD equivalence was demonstrated between both configurations in this study. No bioanalytical issues were reported for paediatric study XSGP-302.

Deficiencies identified for the commercial RIA kit, applied in study XSGP-201, are not further questioned since no bioequivalence (BE) between Ogluo and Lilly glucagon could be demonstrated in this study, which changed the focus of the clinical programme to the demonstration of comparable clinical effect.

Besides the significant differences in exposure between Ogluo 1 mg injections and the Lilly glucagon emergency kit 1 mg in **study XSGP-201**, there was also a shift in t_{max}. The observed delayed t_{max} for Ogluo (mean of 37.6 min versus 18.9 min) is also reflected in the PD response.

Assessment of the use of different injection sites in **Study XSGP-301** showed that mean plasma glucagon t_{max} was similar regardless of injection site. However, mean plasma glucagon C_{max} and AUC values were highest when Ogluo was administered in the abdomen followed by the arm, followed by the leg. These differences are not clinically significant since the corresponding plasma glucose responses are comparable.

In view of the proposed indication in children of 2 years and above, a paediatric **study XSGP-302** was performed to compare the PK after Ogluo administration in T1D patients between 3 age groups (2 to <6, 6 to <12, and 12 to <18 year). Subjects aged 2 to <12 years received a single 0.5 mg dose of Ogluo, whereas subjects aged 12 to < 18 years initially received a 1 mg dose. The transition to the 1 mg dose at 40-45 kg (corresponding to +/-12 years old subjects) has been proposed based on a weight-exposure model using data from study XSGP-201. The applicant was asked to provide the details of this modelling exercise as well as a discussion on the reliability of the conclusion as no subjects weighing less than 58 kg were included in study XSGP-201. The applicant's responses clarified that the paediatric dose selection was not based on modelling and simulation and it was based on the ISPAD 2014 guidelines. In addition, based on PK data available from study XSGP-201 in adults, a weight-based exposure modelling analysis has been performed in adolescents weighing above 40 kg. No simulations were performed in children below 12 years and weighing below 40 kg.

The predictions from the performed weight-based modelling analysis indicate a decreasing in exposure with the increasing of the body weight, given the high volume of distribution of glucagon, in a similar way with the lower exposures observed with increasing of age group after subcutaneous administration of glucagon.

Although it should be kept in mind that subject numbers for each age group were low and the secondary PD endpoints were similar between age groups with regard to mean plasma glucose AUC(0-90), C_{max}, and t_{max}, there seems to be a trend for decreasing mean glucagon levels with increasing age group after administration of a fixed 0.5 mg dose, thus, the proposed weight cut-off at 45 kg for the transition to adult dose does not support an optimal dose based on glucagon PK parameters in children 6-12 years. Therefore, a weight cut-off

at 25 kg was recommended for the transition to adult dose. As recommended, the applicant revised the paediatric dosage including a weight cut-off at 25 kg for transition to adult dose. The PK data obtained in paediatric subjects have been included in section 5.2 of the SmPC.

No studies have been performed to investigate PK of Ogluo in patients with T2D. However, the applicant intends to conduct a post-marketing actual-use study and include both T1DM and T2DM subjects (see efficacy).

Ogluo is structurally identical to currently marketed recombinant glucagon formulations. The absence of specific DDI studies is thus acceptable. Similarly, no renal and/or hepatic impairment studies were conducted, which is accepted.

Study XSGP-301 included 9 T1D patients aged 65 years and above, but PK parameters were not presented separately for these elderly patients. In general, no changes in PK parameters are expected due to advanced age, in line with what is known for other glucagon products.

The PK of Ogluo were analysed descriptively for different ethnicities/races in studies XSGP-301 and XSGP-101 and suggest no significant difference in Ogluo PK among subgroups.

The PD was evaluated in studies XSGP-301 and 303 where GEK (the US reference product) was used as comparator, therefore these studies are less relevant for Europe. Study XSGP-302 had no control arm and was mainly intended to justify the use in children and to determine the dose in children. Study XSGP-304 is the pivotal study. Overall, Ogluo seems to act slower than the reference product, but C_{max} and Glucose AUC (0-90) is a little bit higher.

2.4.5. Conclusions on clinical pharmacology

PK data are supportive for this application. All other concerns have been addressed by the applicant and are considered resolved.

In general, the PD data indicate that Ogluo acts around 4 minutes slower than the reference product GlucaGen HypoKit. However, Ogluo has ease-of-use as the main added value. It is pre-mixed and pre-loaded into a pre-filled syringe and auto-injector pen ready-to-use with no reconstitution required. In addition, it has enhanced portability and availability due to room-temperature stability. These are all considerable advantages when compared to the existing EU product, HK, that needs to be reconstituted in a multi-step process and for which the cold chain should be maintained (under clinical efficacy).

2.5. Clinical efficacy

The efficacy of Ogluo was evaluated for 2 pooled study population groups:

1. Adult Phase 3 Studies: Studies XSGP-301 and XSGP-303 examined the use of Ogluo, Configuration A, in adult subjects with T1D in comparison to GEK.
2. Paediatric Phase 3 Study: Study XSGP-302 examined the glucose response of subjects ages 2≤18 years with T1D following administration of Ogluo, Configuration A.

Simple pooling of Studies XSGP-301 and XSGP-303 was carried out with the assumption that the studies were weighted equally because they employed similar study designs and methodology; had identical selection criteria, a comparable number of clinical sites, and similar patient demographics and number of subjects; and used the identical active comparator (GEK).

Of important note, both Phase 3 studies (XSGP-301, -303) were crossover studies; therefore, the number of subjects receiving each treatment presented does not represent unique subjects, but rather Ogluo or comparator administrations.

Study XSGP-304 was not pooled with Studies XSGP-301 and XSGP-303 because of dissimilarity of the study designs, i.e. different target blood glucose level (54 mg/dL to meet IHSG guidelines, rather than 50 mg/dL), the insulin-induction procedure itself (continued for an additional 5 minutes after plasma glucose confirmation to align with EMA SA), and the active comparator reference drug used HK (instead of GEK).

The applicant provided the required clarifications regarding the numbers of drug product batches and auto-injectors (pens) batches used in all clinical studies.

2.5.1. Dose response study(ies)

There were no real dose-selection studies for Ogluo. The applicant used the doses of the RLDs (Eli Lilly glucagon and GlucaGen HypoKit) for adults, i.e. 1 mg. However, for children, different cut-offs for the choice between the 0.5 and the 1 mg dose were used than for the RLDs, which required further justification.

As stated in Abraham 2018, the recommended glucagon dosing is weight based: 1 mg for adults and children >25 kg and 0.5 mg for children <25 kg (according to Novo Nordisk manufacturer guidelines) while Eli Lilly uses a weight cut-off of 20 kg. In the EU SmPC of GlucaGen HypoKit, the 1 mg dose is already recommended as of 25 kg and 6-8 years old while for Ogluo, this is only as of 12 years old or 45 kg.

The applicant refers to the ISPAD 2014 guidelines for the use of 12 years as a cut-off to choose between 0.5 mg and 1 mg. The applicant also refers to the results of XSGP-201 study, based on which – through a weight-exposure model - the transition to the adult dose of Ogluo is proposed at 40 to 45 kg, corresponding to the average weight at 12 years of age (see also PK section). Moreover, as the paediatric study XSGP-302 only included 13 patients ages $6 \leq 12$ years, the data are limited and it cannot be excluded that there is a risk of under dosage which could be dangerous as Ogluo is a rescue-treatment, and which could be more dangerous than the risk of over dosage which is mainly nausea and vomiting.

Therefore, further justification was requested for the higher cut-offs (age 12 years and body weight 45 kg) for the 1 mg glucagon dose than for GlucaGen HypoKit (6-8 years old and 25 kg). Although the secondary PD endpoints were similar between age groups with regard to mean plasma glucose AUC(0-90), C_{max}, and t_{max}, the proposed weight cut-off at 45 kg for the transition to adult dose did not support an optimal dose based on glucagon PK parameters in children 6-12 years, indicating a decrease in exposure with increasing age group after administration of a fixed 0.5 mg dose, therefore a weight cut-off at 25 kg was recommended for the transition to adult dose. As recommended, the applicant revised the paediatric dosage including a weight cut-off at 25 kg, for transition to adult dose.

2.5.2. Main study(ies)

Adult studies

There were 3 studies executed in adults: the European pivotal study (study XSGP-304), and studies XSGP-301 and XSGP-303 for which the results are pooled.

XSGP-304

Methods

Study design

Study XSGP-304 is a phase 3 multicentre, randomised, controlled, single-blind, 2-way crossover study to compare the efficacy and safety of Ogluo with GlucaGen HypoKit (Glucagon) for induced hypoglycaemia rescue in adults with T1DM.

Subjects were randomised to one of two treatment sequences below and received one dose within each treatment period separated by a washout period of 7 to 28 days.

Table 6 Randomised Treatment Sequence

Treatment Sequence	Treatment 1	Treatment 2
1	G-Pen 1 mg	GlucaGen Hypokit 1 mg
2	GlucaGen Hypokit 1 mg	G-Pen 1 mg

In each period subjects were confined to clinic at Day -1 before dosing, will undergo the following procedures and were discharged at Day 1.

Day -1: Clinic arrival, assessments specified by protocol, evening meal in clinic.

Day 1:

- Overnight monitoring and Morning Procedures. Subjects will be monitored by glucose and will be given glucose and/or insulin to optimise plasma glucose levels.
- Baseline Euglycaemic Steady State (early morning).

Prior to starting the hypoglycaemia induction procedure, the subject must have stable plasma glucose for at least 30 minutes at 95 ± 20 mg/dL (75 to 115 mg/dL [4.17 to 6.38 mmol/L]) at a stable IV insulin infusion rate varying no more than $\pm 20\%$ during which plasma glucose must be measured at least every 15 ± 2 minutes (i.e., at least 3 consecutive values in the target range at 0, 15, and 30 minutes).

- Hypoglycaemia Induction Procedure (following baseline euglycemic steady state). See 'Treatments'.
- Randomisation to one of the treatment sequences shown in the above table.
- Confirmation of Hypoglycaemic Steady State.
- Decision to Dose. Once the hypoglycaemic steady state is confirmed, the Investigator will confirm that it is appropriate to administer study drug to the subject. The clock time of this "Decision to Dose" will be captured in the source documents.
- Preparation and Administration of Study Drug. Following a decision to dose, subjects were administered a subcutaneous injection around the umbilicus with either 1 mg GlucaGen HypoKit or 1 mg Ogluo.
- Post-dose assessments. Blood glucose levels will be monitored for up to 180 minutes post-dosing. Subjects will also complete a questionnaire about symptoms of hypoglycaemia during the hypoglycaemia

induction phase and for up to 180 minutes after treatment with glucagon.

Plasma glucose monitoring

Venous plasma glucose was measured via rapid glucose analyser (YSI 2300 or 2900) before and during hypoglycaemia induction, and every 5 minutes post study drug dose through 90 minutes, with ± 2 minutes for all collections, and at 120, 150, and 180 minutes with ± 5 minutes for collections.

The crossover design of this study is considered valuable in order to decrease between-subject variability. The single dose approach to assess efficacy and safety of Ogluo versus GlucaGen HypoKit is adequate as Ogluo is not intended to be used regularly but only as rescue medication. The study is not placebo-controlled which is acceptable as the use of a placebo would not be ethical in hypoglycaemic patients. The washout-period of minimum 7 days (up to 28 days) between the 2 treatment administrations is largely sufficient to prevent a carry-over taking into account the quite short half-life of glucagon.

However, blood glucose monitoring post-dose was not continuous so the time to achieve glucose recovery was measured with intervals of 5 minutes.

Study Participants

	Inclusion Criteria
Study XSGP-304	<ol style="list-style-type: none"> 1. Males and females diagnosed with T1D for at least 24 months. Women of childbearing potential required a negative urine pregnancy test and must have used medically accepted contraception throughout the study and for 7 days after the last dose of study drug. Nursing mothers were allowed to participate in the study. However, breast feeding during the inpatient study visits (Visits 2 and 3) and for 48 hours after each dose of study drug was not allowed. 2. Current usage of daily insulin treatment that included having an assigned "correction factor" for managing hyperglycaemia. 3. Age 18 to 75 years, inclusive. 4. Random serum C-peptide concentration < 0.6 ng/mL. 5. Subjects reporting active marijuana use or testing positive for tetrahydrocannabinol (THC) via rapid urine test were allowed to participate in the study at the discretion of the investigator. 6. Willingness to follow all study procedures, including attending all clinic visits. 7. Provided informed consent as evidenced by a signed and dated ICF completed before any trial-related activities occurred.
	Exclusion Criteria
	<ol style="list-style-type: none"> 1. Pregnancy. 2. Glycated haemoglobin (HbA1c) $> 10\%$ at Screening. 3. Body mass index (BMI) > 40 kg/m². 4. Renal insufficiency (serum creatinine > 3.0 mg/dL) or end-stage renal disease requiring renal replacement therapy. 5. Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3 times the upper limit of normal (ULN). 6. Hepatic synthetic insufficiency as defined as a serum albumin of < 3.0 g/dL. 7. Haematocrit $< 30\%$. 8. Blood pressure (BP) readings at Screening: systolic blood pressure (SBP) < 90 or > 150 mm Hg, and diastolic blood pressure (DBP) < 50 or > 100 mm Hg. 9. Clinically significant electrocardiogram (ECG) abnormalities. 10. Use of total insulin dose per day > 2 U/kg. 11. Inadequate venous access. 12. Congestive heart failure, New York Heart Association (NYHA) Class III or IV. 13. History of myocardial infarction, unstable angina, or revascularisation within the 6 months prior to Screening. 14. History of a cerebrovascular accident in the 6 months prior to Screening or with major neurological deficits. 15. Active malignancy within 5 years from Screening, except basal cell or squamous cell skin cancers. Any history of breast cancer or malignant melanoma was exclusionary. 16. Major surgical operation within 30 days prior to Screening. 17. History of or seizure disorder at Screening (other than with suspect or documented hypoglycaemia).

	<p>18. Bleeding disorder, treatment with warfarin, or platelet count below 50×10^9 per liter at Screening.</p> <p>19. History of pheochromocytoma or disorder with increased risk of pheochromocytoma (multiple endocrine neoplasia type 2 [MEN 2], neurofibromatosis, or Von Hippel-Lindau disease).</p> <p>20. History of insulinoma.</p> <p>21. History of allergies to glucagon or glucagon-like products, or any history of significant hypersensitivity to glucagon or any related products or to any of the excipients (DMSO and trehalose) in the investigational formulation.</p> <p>22. History of glycogen storage disease.</p> <p>23. Positive tests for human immunodeficiency virus [HIV], hepatitis C virus [HCV], or hepatitis B virus [HBV] infection (hepatitis B surface antigen positive [HBsAg+]) at Screening.</p> <p>24. Active substance abuse other than THC or alcohol abuse (more than 21 drinks per week for male subjects or 14 drinks per week for female subject).</p> <p>25. Administration of glucagon within 7 days of Screening.</p> <p>26. Participation in other studies involving administration of an investigational drug or device within 30 days or 5 half-lives (whichever was longer) prior to Screening and during participation in the current study.</p> <p>27. Any other reason the investigator deemed exclusionary.</p>
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The inclusion and exclusion criteria are generally considered appropriate.

The applicant provided explanations regarding the country specific protocol amendments concerning changes in inclusion and exclusion criteria. The applicant's explanations that these changes had no impact on subject safety or study outcome are considered acceptable. The applicant updated the CSR of study XSGP-304 identifying country specific changes in the inclusion and exclusion criteria.

Moreover, while the targeted indication enholds the complete diabetes mellitus group, only T1DM patients and no T2DM patients were included. What's more, there were many types of patients excluded from the Clinical study, which is accepted for this setting, but the actual-use study is planned to include the use of Ogluo in these excluded patients.

In addition, insulinoma was an exclusion criterion in the Phase 3 studies. In the EU proposed SmPC, the following warning is included: "Glucagon reacts antagonistically towards insulin and caution should be observed if Ogluo is used in patients with insulinoma.". However, the below warning is considered more informative:

"In patients with insulinoma, administration of glucagon may produce an initial increase in blood glucose. However, glucagon administration may directly or indirectly (through an initial rise in blood glucose) stimulate exaggerated insulin release from an insulinoma and cause hypoglycaemia. A patient developing symptoms of hypoglycaemia after a dose of glucagon should be given glucose orally or intravenously." This has been implemented by the applicant. The risk of "Hypoglycaemia in patients with insulinoma or glucagonoma" has been reclassified by the applicant as a risk not considered important for inclusion in the list of safety concerns.

There was only 1 European study site i.e. Austria (besides 4 in the US) in the 'European Phase 3 study' XSGP-304 and it was not clear how many patients were recruited at this EU site. It was clarified by applicant that the only Investigational Site was in Austria, where 35 Subjects were screened and 32 enrolled. The XSGP-304 study utilised European marketed comparator product (GlucaGen HypoKit; Novo Nordisk) at all clinical study sites in Europe and North America.

Treatments

Hypoglycaemia was induced through an insulin induction procedure to a target glucose level of <54 mg/dL (3.0 mmol/L). This target level is adequate as in line with the ADA 2019 paper which states that a blood

concentration <54 mg/dL is the threshold at which neuroglycopenic symptoms begin to occur and requires immediate action to resolve the hypoglycaemic event (Level 2 hypoglycaemia). An insulin dosing algorithm was used in order to maintain a steady state of hypoglycaemia.

Additionally, the IV insulin infusion was not stopped until 5 minutes after the subject's first plasma glucose was <54 mg/dL, per European Medicines Agency (EMA) scientific advice 2018, to mimic potential real-world scenarios in which insulin may cause clinically important hypoglycaemia. The EMA SA recommended this in order to be more open to the use of the 30-minute time point for measurement of the primary endpoint; however, the provided earlier time points were also assessed and analysed (see statistical comments).

After a confirmatory plasma glucose of <54 mg/dL and a hypoglycaemic steady state was obtained, the subject was administered (time point of administered dose) study drug SC to the abdomen around the umbilicus with either Ogluo or HK per the randomised assignment. The time point of the investigator's "decision to dose" was also documented.

However, study glucagon was not administered in more severe hypoglycaemic episodes (if the PG was below 42 mg/dL). Consequently, the effect of Ogluo in more severe situations seen in clinical practice, such as loss of consciousness or seizures, was not examined. Although this is endorsed for ethical/safety reasons, during the EMA SA, it was recommended to perform an actual-use study.

In this study, Configuration A (auto-injector) was used. During the EMA SA, it was indicated that if it could be shown in XSGP-101 that the PK and PD parameters of both configurations were similar within the usual bioequivalence margins, extrapolation of efficacy and safety data from Configuration A (auto-injector) to Configuration B (pre-filled syringe) is possible. Since chromatographic interference was observed during sample analysis, the applicant was asked to justify the reliability of the measured glucagon concentrations. The applicant could not exclude that a portion of the study samples are not determined accurately, precluding a definite conclusion on PK equivalence. However, it is acknowledged that the PD response is most relevant for the desired action of Ogluo and PD equivalence was demonstrated between both configurations in this study.

Objectives

Primary:

To demonstrate that Ogluo 1 mg (test) was not inferior to GlucaGen HypoKit 1 mg (reference), in subjects with T1D in a state of insulin-induced hypoglycaemia.

Secondary:

To evaluate the safety and tolerability of Ogluo 1 mg versus GlucaGen HypoKit 1 mg in the study population.

Outcomes/endpoints

The *primary* endpoint is an alternate combined endpoint: PGR as defined by

- either a plasma glucose concentration ≥ 70 mg/dL (≥ 3.88 mmol/L) within 30 minutes of study drug injection (PGR 1) OR
- an increase in plasma glucose concentration ≥ 20 mg/dL (≥ 1.11 mmol/L) within 30 minutes of study drug injection (PGR 2).

For the primary endpoint, treatment groups were compared for rates of achieving a positive PGR.

Secondary:

1. Rate of achieving a plasma glucose concentration ≥ 70 mg/dL (≥ 3.88 mmol/L) within 30 minutes from injection of study drug.
2. Rate of achieving an increase in plasma glucose concentration ≥ 20 mg/dL (≥ 1.11 mmol/L) within 30 minutes from injection of study drug.
3. Rates of positive symptomatic response, defined as relief of neuroglycopenic symptoms 30 minutes from a decision to dose.
4. Rates of positive treatment response, defined as exhibiting either a positive PGR or a positive symptomatic response.
5. Time to a positive PGR from injection of study drug.
6. Time to administer study drug from time to a decision to dose.
7. PD characteristics of mean plasma glucose concentration (0 to 90 minutes post dose), C_{max} , t_{max} , AUC_{0-90min}, and area under the concentration versus time curve from time 0 to 180 minutes (AUC_{0-180min}).
8. Time to (a) initial relief and (b) complete resolution of autonomic and neuroglycopenic symptoms of hypoglycaemia from a decision to dose.
9. Time to resolution of the overall feeling of hypoglycaemia from a decision to dose.
10. Safety endpoints, including AE/SAE rates, and changes in vital signs, laboratory variables, and PE/ECG findings.
11. Tolerability endpoints measured at 30, 90, and 180 minutes post dosing, including Draize scale scores for injection site erythema and oedema as assessed by the investigator, and injection site discomfort and duration as assessed by subject questionnaire responses.

To describe and compare hypoglycaemia symptom relief/resolution of the 2 treatments, a hypoglycaemia questionnaire was used that measured severity of 4 neuroglycopenic symptoms (dizziness, blurred vision, difficulty in thinking, and faintness), and 4 autonomic symptoms (sweating, tremor, palpitations, and feeling of nervousness), as well as a global feeling of hypoglycaemia.

The secondary endpoints take both time points into account, in line with the EMA SA: from decision to dose and from administered dose.

In addition there were some comments about the use of symptomatic scores a.o. whether they are reliable as it might be difficult for patients to assess symptoms as they are in a state of induced hypoglycaemia or recovering from it.

Sample size

The described method for the sample size calculation does not take into account clinical aspects as required in the guideline EMEA/CPMP/EWP/2158/99.

The sample size calculation is based on assumptions with respect to rates 0.20 and 0.25, which are clearly not realistic cfr. Clinical study report XSCP-304 p62-63. The guideline on the choice of the non-inferiority

margin stipulates that contingencies have to be made in case the rates are not realistic, there is no alternate plan for testing to be found in the SAP. The unrealistic rates have resulted in an endpoint that could not be tested in a valid manner (success rates near to 100%).

Sample size calculations are based on rate ratios, testing is performed on differences. The sample size calculation should correspond with the testing procedure or, if this is not the case, a reasoning has to be provided to show that the approach was conservative in the sense that the sample is most likely to be higher than if a corresponding calculation was performed. The sample size calculation was deemed not acceptable. Therefore, a rationale for the rates 0.20 and 0.25 used to calculate the sample size in study XSCP-304 was required. The applicant provided a rationale for the choices of 0.20 and 0.25 in the sample size calculation, which was accepted.

Randomisation

Randomisation was a permuted random block assignment, stratified by clinical site. The subjects were randomly assigned to receive either Treatment Sequence 1 (Ogluo → GlucaGen HypoKit) or Treatment Sequence 2 (GlucaGen HypoKit → Ogluo).

Blinding (masking)

The subject, but not the investigator and clinical staff, was blinded (single-blind design). There were no unblinding requirements needed for the study. The subject's ability to see the injection equipment and procedure also was obstructed by use of a blindfold placed prior to dosing.

The results of the Subject Study Drug Assignment Questionnaire used to demonstrate the success of the blinding as presented in the Listing of study drug assignment Questionnaire Per-Protocol Population showed that 78 of subjects (67.8%) were able to guess the actual study treatment per sequence. This finding questioned the success of the blinding. The applicant discussed the possible impact of this finding on the clinical trial results, i.e. hypoglycaemia symptoms relief/resolution endpoints. It is acknowledged that the applicant had put in place several measures to assure the blinding, but taking into account the results of the Subject Study Drug Assignment Questionnaire and the fact that the symptoms scores for hypoglycaemia/neuroglycopenia are subjective, the possible impact of this finding on the clinical trial results, could not be excluded. However, taking into account that the primary and secondary objectives endpoints of the study has been achieved, the issue is not further pursued.

Statistical methods

The treatment of missing data has to be related to the (presumed) mechanism of missing data generation and conservative with respect to the decision in favour of the treatment proposed. It is unclear how the assumption of failure would be conservative with respect to the statistical test.

Therefore, an explanation is required regarding how the missing data approach is linked to the possible missing data mechanism. The missing data is most likely to a missing data mechanism related to the efficiency of the treatment. The missing data approach that consists of not taking into account the missing data might therefore introduce a bias and results need to be confirmed through a robustness analysis. However, this issue is not pursued.

The method of transition from the glucose concentration measures every five minutes to the time to PGR. Such a transition underlies the time to event analysis and is also relevant for the frequency tables with 5 min time interval classes. The method of transition can be influential with respect to the tables and time to event analysis.

Therefore, a specification on how mathematically technical the sequential data from the discrete measurements of glucose concentration about every five minutes were transformed into time to PGR event data and used to generate frequency tables with 5 min time interval classes is required. However, data represented in tables provided were in contradiction with data represented in post-hoc figure provided. The data represented in some provided tables as the basis for the B/R analysis are an underestimate when compared to data represented in certain figures. Therefore, the applicant was requested to provide discretisation's based on different interpolation strategies on patient level in order to provide robustness for the B/R analysis. Changes to the interval $30 \leq$ and ≤ 35 into $30 \leq$ and < 35 to make intervals more equilibrated were provided. And the applicant was also requested to clarify how the discretisation, refinements, and interpolations have been performed for each of the figure, post hoc table, and the tables created.

Due to the extremely high percentage of recovery at 30 min, no valid statistical comparison can be made based on the used primary endpoint between Ogluo and HypoKit in responder rate.

Despite the 5 min continuation of insulin administration after hypoglycaemia threshold (54 mg/dL) has been reached, and the alteration to take into account the effect of this continuation, the endpoint has proven to be insensitive to the detection of potential differences between Ogluo and HypoKit.

If incidence rates at a fixed moment cannot be estimated with enough precision, the resulting confidence intervals are unreliable and thus the comparison with thresholds to establish non-inferiority, independent of the procedure to establish the intervals and thresholds.

In the SA it was suggested based on available data that the original endpoint would be insensitive to detect any potential differences between Ogluo and HypoKit. Therefore, a suggestion was made to provide assessment and analysis of earlier time points. The CSR nor in the SAP analysis of earlier type points was subject to confirmatory testing strategy.

A difference in failure rate of 5% at 30 min is rather arbitrary and does not reflect the degree of failure which is of utmost importance with respect to the condition intended to treat. Therefore the test can only be accessory to a positive benefit risk analysis if a clinical relevant amount of patients have a high degree of failure. From the data provided in the study report of trial XSGP-304, it is clear that a rather substantial amount of an estimated 7.9% of patients only had sufficient response (positive PGR) after more than 20 min. Also the reported average time to first positive plasma glucose response after study drug injection showed an estimated increase of 4.12 min with a high variability for the Ogluo (SD = 4.9 min). The latter is a relatively rough indicator of possible individual problems - outliers in agreement with data presented. It is paramount to investigate why a substantial amount of individuals might not benefit from treatment due to the possible consequences in the benefit/risk assessment.

If the average of 14.57 min and standard deviation of 4.905 min are considered to be good estimates of the true mean and standard deviation of the time to first plasma glucose response after study drug injection, and one assumes a normal distribution for Ogluo, then 5% of patients will have a first positive plasma glucose response after 22.638 min, the HypoKit value being 13.579 min. The estimated time to have 95% of patients to reach first positive plasma glucose response after drug injection is 9.059 min earlier for HypoKit compared

to Ogluo. Clarity was needed with respect to the distributions of the time to PGR its distribution. There was no clear characterisation of patients with a high time to PGR time for Ogluo.

Testing the non-inferiority at an earlier stage as suggested in the SA (20 min) would not solve the problem of the presence of cases with a substantial time to response or give insight in the high observed variability of the response to Ogluo, making it an unreliable treatment when comparing it with HypoKit (estimated standard deviation 4.905 min for Ogluo compared to 1.902 min for the HypoKit). At the time point of 20 min suggested by SA all treatments with HypoKit were successful, therefore testing would be relevant only as from 15 min, but it would not reflect the risk of prolonged delay in treatment effect.

The log rank test used to compare the time to event endpoints is a test for non-parametric comparison of hazard functions developed in the context of survival analysis in the presence of censoring. It is standard practice to compare continuous repeated measures data with a paired t-test, if the difference is sufficiently normal distributed or if the sample size is sufficiently large to claim robustness with respect to deviations from normality.

The applicant was requested to perform a t-test based on a two-sided 95% CI for non-inferiority margins of 3 min for time from decision to dose to positive plasma glucose response. These analyses have been provided.

The cross-over design is adequate to filter out the interindividual variability but cannot filter out starting conditions.

A substantial amount of patients have to wait 20 min or more before positive plasma glucose level is reached: 21.1% time from dose and 16.7% time from decision to dose. The number of patients that had to wait 30 minutes or more is 3.1%, also when considering time from decision to dose. When extrapolating to the diabetic patient population these percentages can result in a substantial amount of patients.

The individual glucose level curves for study XSGP-304 are provided accompanying the study report of trial XSGP-304. From the individual glucose level curves provided one can observe that the glucose concentration curve is reasonably linear in the period of interest [0 min; 30min]. Therefore, the angle of a linear approximation of the measurement points within this interval represent a rate of cure. It makes sense to analyse the slope, the rate with which the patient recovers due to treatment through regression modelling based on glucose concentration measurements between administration and 30 min after administration. This analysis has the advantage to separate the effect of the dosing from the initial effect of delay in dosing and can be combined with expected and possibly failed treatment from literature (systematic literature review and meta-analysis).

Results

Participant flow

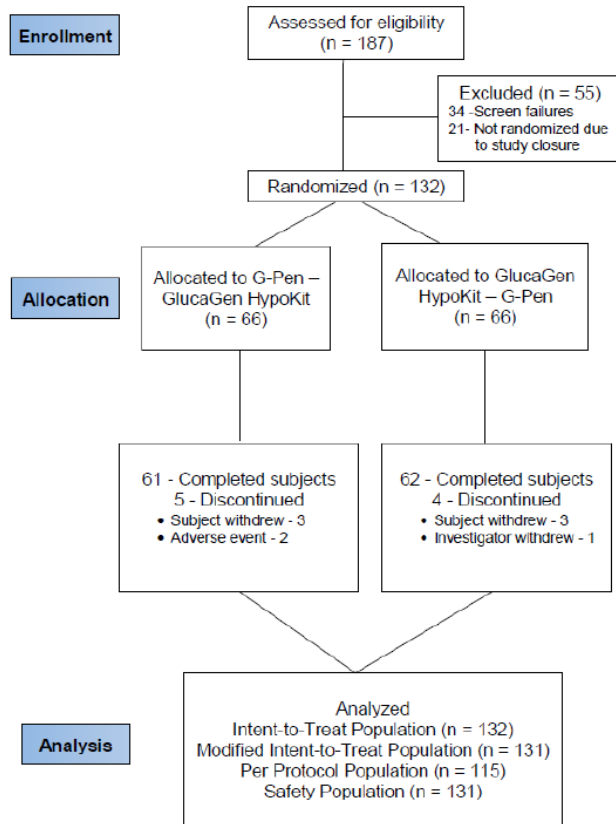


Figure 7 Subject Disposition in Study XSGP-304

Recruitment

Of the 132 patients that were randomised, 123 patients completed the study. Nine (9/132; 6.8%) subjects withdrew early from the study (5/66 [7.6%] subjects in the Ogluo arm and 4/66 [6.1%] subjects in the GlucaGen HypoKit arm). For the 5 subjects in the Ogluo arm, reasons for early withdrawal were subject withdrawal (3 subjects withdrew for personal reasons) and AE (abdominal pain in 1 subject and hypoglycaemia in 1 subject). Four subjects in the GlucaGen HypoKit arm discontinued early from the study (3 subjects withdrew for personal reasons and 1 subject was withdrawn by the investigator [unable to reach hypoglycaemia]).

Conduct of the study

Protocol amendments

The CSR mentioned that two protocol amendments have been made to the original protocol dated 06 August 2018, as presented in the following table:

Table 7 Summary of Protocol Amendments

Version no./ Date	Summary of Changes	Rationale
Version 1.1 (Site Specific for Austria) 06 Nov. 2018	<ul style="list-style-type: none"> Exclusion Criterion No. 17 was changed to include subjects with a <u>history</u> of seizure disorder (other than with suspect or documented hypoglycemia) in addition to subject who had current seizure disorder. 	<ul style="list-style-type: none"> To satisfy Austrian Regulatory Authority's concern of Exclusion Criteria (This change was later incorporated into global protocol Version 2.0).
Version 2 17 Dec. 2018	<ul style="list-style-type: none"> Study Phase was changed from 3B to 3. For clarity, secondary endpoint expanded into 2 endpoints: <ol style="list-style-type: none"> Rate of achieving a plasma glucose concentration ≥ 70 mg/dL (≥ 3.88 mmol/L) within 30 minutes from injection of study drug. Rate of achieving an increase in plasma glucose concentration ≥ 20 mg/dL (≥ 1.11 mmol/L) within 30 minutes from injection of study drug. Study overview updated to clarify types of blood glucose meters to be used and note that results were to be entered into EDC. Hypoglycemia induction procedure and justification section updated to note that although the investigator could override the insulin dosing algorithm at their discretion, they did not have discretion to give bolus doses once plasma glucose was ≤ 65 mg/dL (3.3 mmol/L). Drug storage updated to note that excursions between in drug storage temperatures of 15° C and 30° C (59° F and 86 °F) allowed. Day 1 procedures updated to note that symptom assessment to occur every 5±2 minutes after glucagon was administered until 90 minutes post dosing, and every 30 minutes (coinciding with plasma glucose measurements) between 90 and 180 minutes post study drug administration. 	<ul style="list-style-type: none"> To provide clarifications of study phase and various study procedures.

According to this table, the last version of the protocol is Version 2 dated 17 Dec. 2018. The CSR mentions as the last version of the protocol as Version 2.1 dated 17 Dec. 2018 (submitted in the MAA documentation). The applicant was required to clarify this taking also into account that several inconsistencies related to inclusion and exclusion criteria between the CSR and Version 2.1 of the protocol dated 17 Dec. 2018 have been found. The applicant provided explanations regarding the country specific protocol amendments. In the further responses provided, the applicant updated the CSR of study XSGP-304 identifying country specific changes in the inclusion and exclusion criteria.

Baseline data

The study included 37 males (53.0%) and 29 (47.0%) females. Patients ranged from 19 to 72 years of age, with a mean age of 39.5 years. The duration of T1DM ranged from 2 to 56 years. Overall, 123/132 (93.2%) were white, and mean BMI was 27.0 kg/m². Demographic and baseline characteristics were similar between

treatment groups. However, taking into account the cross-over design of the study, balance between treatment arms is not an issue. Only 7 (6.8% of) the included subjects were non-white of which 2 Black or African American, 6 Asian, and 1 Native Hawaiian or Other Pacific Islander.

No data on baseline characteristics related to the T1DM (like HbA1c, insulin modality/use/dose, history of severe hypoglycaemia event – except for some exclusion criteria) are provided in the MA dossier.

No patients with T2DM were included in the study population while the intended indication is both T1DM and T2DM patients with severe hypoglycaemia. During the EMA SA, it was recommended to perform an actual-use study to explore how T2DM patients may benefit from Ogluo. The detailed plan of a post-marketing trial with including T1DM and T2DM patients was indeed performed.

The number of elderly patients included in the clinical trial was small (only six patients [4.5%]); taking into account their increased hypoglycaemia risk, their reduced ability to recognise hypoglycaemia symptoms and communicate their needs it would have been relevant for the intended population to include more elderly patients. Studies XSGP-301 and XSGP-303 included 15 patients of 65 years old, no patients 75 years old and above were included. Therefore, the SmPC mentions that efficacy and safety data for Ogluo are very limited in patients aged 65 years and absent in patients aged 75 and above and a sufficient number of elderly patients will be included in the planned actual-use study.

Numbers analysed

Table 8 Summary of Analysis Populations (All Randomised Subjects)

Analysis Population	G-Pen n (%) (N=132)	GlucaGen Hypokit n (%) (N=132)	All Subjects n (%) (N=132)
Intent-to-Treat Population	128 (97.0)	123 (93.2)	132 (100.0)
Modified Intent-to-Treat Population	127 (96.2)	123 (93.2)	131 (99.2)
Per-Protocol Population	115 (87.1)	115 (87.1)	115 (87.1)
Safety Population	127 (96.2)	123 (93.2)	131 (99.2)

Percentages are based on number of subjects randomized to treatment.

ITT Population defined as all subjects randomized.

mITT population defined as all ITT subjects who received at least 1 dose of study drug.

PP Population defined as all randomized subjects who during both study periods successfully received their assigned study drugs and had no major protocol deviations.

Safety Population defined as all subjects randomized and who received at least 1 dose of study drug.

Planned treatment was used for ITT Population and actual treatment was used for mITT, PP and Safety Population.

Of the ITT Population consisting of 132 patients, 17 patients were excluded from the PP population consisting then of 115 patients: 1 patient who received 2 doses of GlucaGen HypoKit (also excluded from the mITT population), 6 patients with a major protocol deviation, 9 patients who withdrew early. For one patient, the reason for the exclusion from the PP population was not found in the dossier.

Outcomes and estimation

Primary endpoint: Positive PGR

The numbers of subjects achieving a plasma glucose >70 mg/dL or rise ≥20 mg/dL within 30 minutes of dosing were similar between treatment groups: 99% for Ogluo subjects and 100% for HK subjects for the mITT population, and 100% of subjects in both treatment groups for the PP population.

Table 9 Number of Subjects with Plasma Glucose >70 mg/dL or ≥20 mg/dL Rise Within 30 Minutes of Dosing: Adult Phase 3 Type 1 Diabetic Subjects (mITT Population)

Gvoke (N=127) n (%)	HK (N=123) n (%)
126 (99.2)	123 (100.0)

Non-inferiority analysis

In accordance with EMA SAWP 2018, for the primary endpoint, treatment groups were compared for failure rate differences for plasma glucose response (PGR). Risk difference in rates of failing to achieve the primary endpoint were assessed for Ogluo versus HK (used as reference) and the associated 95% CIs presented. For non-inferiority testing, calculations were conducted with stratification by site taken into consideration. Non-inferiority was declared if the upper limit of the 95% confidence interval for the difference in failure rates is ≤5%. Analysis of the primary endpoint (plasma glucose >70 mg/dL or rise ≥20 mg/dL within 30 minutes of dosing) by population and treatment for all randomised subjects met the predefined criteria for non-inferiority (difference in failure rates is ≤5%; see table below).

Table 10 Non-Inferiority Analysis of Primary Endpoint by Population and by Treatment (All Randomised Subjects), Phase 3 Study XSGP-304

Population	N	Ratio of Failing		Risk Difference	95% CI for Risk Difference	Non-Inferiority Satisfied?
		Gvoke	HK			
Intent-to-Treat Population	132	0.038	0.068	-0.030	(-0.094, 0.027)	Yes
Modified Intent-to-Treat Population	131	0.038	0.061	-0.023	(-0.085, 0.035)	Yes
Per-Protocol Population	115	0.000	0.000	0.000	(-0.033, 0.033)	Yes

N=number of subjects in analysis population; CI=confidence intervals

Table 11 Summary of Subjects Having Positive Plasma Glucose Response from Time of Study Drug Administration by Treatment (mITT)

Time Point	G-Pen (N=127)		Glucagen Hypokit (N=123)	
	Time Point Summary n (%)	Cumulative Summary n (%)	Time Point Summary n (%)	Cumulative Summary n (%)
5 Min post dose	3 (2.4)	3 (2.4)	4 (3.3)	4 (3.3)
10 Mins post dose	44 (34.6)	47 (37.0)	105 (85.4)	109 (88.6)
15 Mins post dose	52 (40.9)	99 (78.0)	14 (11.4)	123 (100.0)
20 Mins post dose	18 (14.2)	117 (92.1)	0	123 (100.0)
25 Mins post dose	5 (3.9)	122 (96.1)	0	123 (100.0)
30 Mins post dose	4 (3.1)	126 (99.2)	0	123 (100.0)
35 Mins post dose	1 (0.8)	127 (100.0)	0	123 (100.0)

Abbreviations: Mins = minutes

N = Number of subjects in analysis population which are available for analysis.

Percentages are based on N.

Non-inferiority declared if the upper limit of the 95% CI for the difference in failure rates is ≤5%.

For primary endpoint, positive PGR defined as reaching PGR1 or PGR2.

PGR1 defined as reaching a plasma glucose concentration ≥70 mg/dL (≥3.88 mmol/L) within 30 minutes of study drug injection (actual time).

PGR2 defined as reaching an increase in plasma glucose concentration ≥20 mg/dL (≥1.11 mmol/L) within 30 minutes of study drug injection (actual time).

Table 12 Summary of Subjects Having Positive Plasma Glucose Response from Time of Study Drug Administration by Treatment (PP)

Time Point	G-Pen (N=115)		Glucagen Hypokit (N=115)	
	Time Point Summary n (%)	Cumulative Summary n (%)	Time Point Summary n (%)	Cumulative Summary n (%)
5 Mins post dose	3 (2.6)	3 (2.6)	4 (3.5)	4 (3.5)
10 Mins post dose	39 (33.9)	42 (36.5)	97 (84.3)	101 (87.8)
15 Mins post dose	49 (42.6)	91 (79.1)	14 (12.2)	115 (100.0)
20 Mins post dose	17 (14.8)	108 (93.9)	0	115 (100.0)
25 Mins post dose	4 (3.5)	112 (97.4)	0	115 (100.0)
30 Mins post dose	3 (2.6)	115 (100.0)	0	115 (100.0)

Abbreviations: Mins = minutes

N = Number of subjects in analysis population which are available for analysis.

Percentages are based on N.

Non-inferiority declared if the upper limit of the 95% CI for the difference in failure rates is $\leq 5\%$.

For primary endpoint, positive PGR defined as reaching PGR1 or PGR2.

PGR1 defined as reaching a plasma glucose concentration ≥ 70 mg/dL (≥ 3.88 mmol/L) within 30 minutes of study drug injection (actual time).

PGR2 defined as reaching an increase in plasma glucose concentration ≥ 20 mg/dL (≥ 1.11 mmol/L) within 30 minutes of study drug injection (actual time).

In the PP Population, 100% of subjects in both treatment groups had achieved a positive PGR at 30 minutes post dose.

Sensitivity analysis

Results of a sensitivity analysis (in which all missing data were considered a success) also supported the predefined criteria for non-inferiority (see table below).

Table 13 Sensitivity Analysis of Primary Endpoint by Population and by Treatment (All Randomised Subjects)

Population	N	Ratio of Failing		Risk Difference	95% CI for Risk Difference	Non-Inferiority Satisfied?
		Gvoke	HK			
Intent-to-Treat Population	132	0.008	0.000	0.008	(-0.021, 0.042)	Yes
Modified Intent-to-Treat Population	131	0.008	0.000	0.008	(-0.022, 0.043)	Yes

N=number of subjects in analysis population; CI=confidence intervals.

Secondary endpoints

Plasma Glucose at 30 Minutes Post-dose

A comparison of the mean plasma glucose concentration at 30 minutes post-dose in Study XSGP-304 is shown in the table below. Overall Ogluo and HK were similar for this endpoint and both groups had mean and median values that were well above 70 mg/dL. The mean plasma glucose in the Ogluo group was 2 standard deviations above 70 mg/dL, indicating a robust response.

Table 14 Mean Plasma Glucose (mg/dL) at 30 Minutes Post-dose: Phase 3 Study XSGP-304

Statistics	Phase 3 Study XSGP-304	
	Gvoke (N=127)	HK (N=123)
n	125	121
Mean	129.26	144.03
SD	25.237	20.789
Median	129.87	144.50
Min	60.5	90.8
Max	196.4	205.4

N=number of subjects in analysis population; SD=standard deviation.

Rate of achieving a positive PGR1 – rate of achieving a positive PGR2

The number of subjects with a positive PGR 1 at 30 minutes post dose was similar between treatment groups: 99% (n=126) for Ogluo subjects and 100% (n=123) for GlucaGen HypoKit subjects in the mITT Population and 100% in both treatment groups in the PP Population. Analysis of positive PGR 1 by population and treatment for all randomised subjects met the predefined criteria for non-inferiority (difference in failure rates is $\leq 5\%$).

The exact same results were observed for PGR2.

Rates of Positive Symptomatic Response

Positive symptomatic response was defined as relief of neuroglycopenic symptoms within 30 minutes from a decision to dose. Rates of positive symptomatic response from time of decision to dose were similar between treatment groups at all time points for the mITT Population. At 30 minutes post dose, 34/39 subjects (87.2%) in the Ogluo group and 29/35 subjects (82.9%) in the GlucaGen HypoKit group had achieved positive symptomatic response. Similar results were observed with the ITT Population., Rates of positive symptomatic response from time of decision to dose were higher in the Ogluo group compared to the GlucaGen group at all time points for the PP Population. At 30 minutes post dose, 33/35 subjects (94.3%) in the Ogluo group had achieved positive symptomatic response while 29/35 subjects (82.9%) in the GlucaGen HypoKit group had achieved positive symptomatic response. Analysis of positive symptomatic response by population and treatment for all randomised subjects did not meet the predefined criteria for non-inferiority due to a greater ratio of failing in the GlucaGen HypoKit group.

Rates of Positive Treatment Response

Positive treatment response was defined as exhibiting either a positive PGR (within 30 minutes from injection of study drug) or a positive symptomatic response (within 30 minutes from a decision to dose).

The number of subjects having a positive treatment response by 30 minutes post dose was similar between treatment groups: 99% for Ogluo subjects and 100% for GlucaGen HypoKit subjects in the mITT Population; similar results in the ITT Population and 100% in both treatment groups in the PP Population.

Analysis of positive treatment response by population and treatment for all randomised subjects met the predefined criteria for non-inferiority (difference in failure rates is $\leq 5\%$).

Time to Positive PGR

Mean time to achieving plasma glucose of ≥ 70 mg/dL or ≥ 20 mg/dL increase in plasma glucose concentration within 30 minutes of study drug administration was greater in the Ogluo treatment group compared to the HK treatment group:

Table 15 Mean time to (Minutes) achieving plasma glucose of ≥ 70 mg/dL or ≥ 20 mg/dL increase in plasma glucose concentration within 30 minutes of study drug administration

Mean time to achieving PG of ≥ 70 mg/dL or ≥ 20 mg/dL increase in PG within 30 minutes of study drug administration (minutes)	mITT		PP	
	Gvoke	HK	Gvoke	HK
	14.8 min (± 5.3)	10.4 min (± 1.8)	14.57 min (± 4.9)	10.45 min (± 1.9)

Similar results were observed with the ITT Population.

Table 16 Summary of Time (Minutes) to First Positive Plasma Glucose Response After Study Drug Injection by Treatment (mITT)

Statistics	G-Pen (N=127)	Glucagen Hypokit (N=123)
n	127	123
Mean	14.80	10.41
SD	5.349	1.846
CV (%)	36.15	17.73
Geometric Mean	13.93	10.26
Geometric CV (%)	36.01	17.92
Median	15.00	10.00
Min	5.0	5.0
Max	35.0	15.0

SD = Standard Deviation; CV = Coefficient of Variation.
 N = Number of subjects in analysis population.
 For primary endpoint, positive PGR defined as reaching PGR1 or PGR2.
 PGR1 defined as reaching a plasma glucose concentration ≥ 70 mg/dL (≥ 3.88 mmol/L) within 30 minutes of study drug injection (actual time).
 PGR2 defined as reaching an increase in plasma glucose concentration ≥ 20 mg/dL (≥ 1.11 mmol/L) within 30 minutes of study drug injection (actual time).

However, all were well within the clinically meaningful timeframe of 30 minutes of study drug administration.

Study Drug Preparation Time

Time required from a decision to dose to complete preparation and administration of study drug was statistically significantly faster in the Ogluo group compared to the HK group (P-value < 0.05 , Log rank Test) in all 3 populations:

Table 17 Mean preparation time

Mean preparation time	mITT		PP	
	Gvoke	HK	Gvoke	HK
Absolute	46.8 sec (0.78 min)	105.1 sec (1.76 min)	44.9 sec (0.75 min)	106.0 sec (1.78 min)
Difference between both groups	58,3 sec (0,97 min)		61,1 sec (1,02 min)	

Table 18 Summary of Glucagon Preparation Time (Seconds) by Treatment (mITT and PP Populations), Phase 3 Study XSGP-304

Statistic	mITT Population		PP Population	
	Gvoke (N=127)	HK (N=123)	Gvoke (N=115)	HK (N=115)
n	127	123	115	115
Mean	46.76 ^a	105.1 ^a	44.89 ^a	106.03 ^a
SD	31.576	40.561	31.288	40.579
CV (%)	67.52	38.59	69.70	38.27
Geometric Mean	37.30	101.22	35.65	101.07
Geometric CV (%)	78.68	33.18	78.66	33.99
Median	40.00	101.00	39.00	101.00
Min	8.0	0.0	8.0	0.0
Max	197.0	322.0	197.0	322.0

^a $P < 0.001$, hazard ratio of the 2 groups was compared for each population using the Log rank test with stratification by treatment.

These findings have important ramifications during real-world use of the product by laymen caregivers of diabetic patients who would likely need even more time to prepare HK than the licensed and trained pharmacists in this study. Additionally, the rate of successful preparation and delivery of full dose glucagon by caregivers in pre-hospital, emergency situations is low (<13%) with lyophilised powder glucagon kits (Yale *et al.*, 2017).

Time to Symptom Relief

Time to symptom relief was evaluated with symptom relief of hypoglycaemia being defined as a return to a score (average neuroglycopenic symptom score [ANS], average autonomic symptom score [AAS], and average total symptom score [ATS]) no more than one unit above baseline symptoms during the euglycemic baseline period, where the baseline symptom is the last values of score (ANS, AAS, and ATS) just before IV push dose of insulin.

a) Time to initial relief

For the mITT Population, mean time to relief of autonomic and neuroglycopenic symptoms of hypoglycaemia were similar between treatment groups.

Table 19 Mean time to relief

Mean time to relief (minutes)	mITT		PP	
	Gvoke	HK	Gvoke	HK
Neuroglycopenic symptoms	10.77 min (±8.644)	10.43 min (±5.790)	9.32 min (±6.229)	10.43 min (±5.790)
Autonomic symptoms	11.22 min (±6.173)	10.54 min (±7.150)	10.50 min (±5.471)	10.70 min (±7.203)
Total symptoms	12.5 min (±7.419)	11.08 min (±7.218)	11.42 min (±5.898)	11.08 min (±7.218)

Overall, times to symptom relief after a decision to dose were generally similar between treatment groups. However, for the Per-Protocol Population, subjects who received Ogluo had statistically significantly faster neuroglycopenic symptom relief compared to subjects who received HK (10.51 minutes vs.13.98 minutes, respectively; $P=0.023$).

b) Time to Complete Resolution

Time to symptom resolution was defined as a return to a score (ANS, AAS, and ATS) of 1.0, meaning all individual symptom scores within the domain had a score of 1 = absent.

For the mITT and PP Population, mean times to complete resolution of autonomic and neuroglycopenic symptoms of hypoglycaemia from a decision to dose were similar between treatment groups:

Table 20 Mean time to complete resolution

Mean time to complete resolution (minutes)	mITT		PP	
	Gvoke	HK	Gvoke	HK
Neuroglycopenic symptoms	17.24 min (±9.323)	16.06 min (±8.412)	17.25 min (±9.376)	16.11 min (±8.484)
Autonomic symptoms	20.03 min (±12.779)	17.04 min (±10.695)	19.55 min (±12.798)	16.73 min (±10.674)
Total symptoms	21.06 min (±12.013)	18.21 min (±10.126)	21.09 min (±12.171)	18.02 min (±10.169)

Analysis of time to complete resolution of neuroglycopenic, autonomic and total hypoglycaemia symptoms by population and treatment for all randomised subjects met the criteria for non-inferiority based on non-significant ($P>0.05$) findings for all hazard ratio comparisons.

Time to Resolution of the Overall Feeling of Hypoglycaemia

Analysis of time to resolution of the overall feeling of hypoglycaemia by population and treatment for all randomised subjects met the criteria for non-inferiority based on non-significant ($P>0.05$) findings for all hazard ratio comparisons. Mean time to complete resolution of overall feeling of hypoglycaemia from a decision to dose was similar between treatment groups:

Mean time to complete resolution of overall feeling of hypoglycemia (minutes)	mITT		PP	
	Gvoke	HK	Gvoke	HK
	15.53 min (±7.295)	15.32 min (±8.479)	15.21 min (±7.344)	15.42 min (±8.520)

In the ITT Population analyses, similar results were observed in all efficacy endpoints.

In summary, the study demonstrated that Ogluo was non-inferior when compared to GlucaGen HypoKit based on analysis of positive PGR: 99% for Ogluo patients and 100% for HK patients in the mITT Population and 100% of subjects in both treatment groups in the PP Population achieved positive PGR within 30 minutes post-dose.

However, the time to achieve positive PGR as of administration of study drug was 4-4.5 minutes longer (14.5-15 versus 10.5 minutes) for Ogluo versus HK and more HK subjects achieved positive PGR earlier than Ogluo:

- at 10 minutes post-dose, more than 2 times the number of HK subjects (cumulative: 109 patients (88.6%)) achieved a positive PGR than Ogluo patients (cumulative: 47 patients (37.0%)).
- at 15 minutes post-dose, all mITT patients (100%) treated with HK had a positive PGR, while still 28 patients (22.0%) in the mITT and 26 patients (20.9%) in the PP Ogluo group had not yet achieved a positive PGR
- at 20 minutes post-dose, still 10 patients (7.9%) in the mITT and 7 patients (6.1%) in the PP Ogluo group had not yet achieved a positive PGR = delay of >5 minutes
- at 25 minutes post-dose, still 5 (3.9%) patients in the mITT and 5 patients (2.6%) in the PP Ogluo group had not yet achieved a positive PGR = delay of >10 minutes
- at 30 minutes post-dose, still 1 (3.9%) patient in the mITT Ogluo group had not yet achieved a positive PGR = delay of >15 minutes (all achieved this in the PP group)
- only at 35 minutes post-dose, all Ogluo mITT patients had achieved this so the last patient had a delay of up to 20 minutes.

This longer time is not considered clinically relevant by the applicant as they were all still within the predefined 30 minutes after dosing, and will be shortened in clinical practice thanks to the about 1 minute shorter time to prepare study drug between the ready-to-use Ogluo and the to-be-reconstituted HK. Although analysis of symptomatic responses by treatment did not meet the predefined criteria for non-inferiority because of a greater ratio of HK patients not achieving sufficient symptomatic response, analysis of positive treatment response (successful plasma glucose recovery or successful symptom recovery) by treatment did meet the predefined criteria for non-inferiority in all analysed populations.

This slower effect (4-4.5 minutes longer in time to achieve recovery) has been properly reflected in the SmPC.

The gain considering no reconstitution is necessary is estimated to be only 1 minute which would mean that there still is a delay of 3 to 3.5 minutes. Moreover, the time to recovery of 14.8 minutes (versus 10.4 minutes for HK) is only a mean value with important variability as the standard deviations were respectively 5.4 and 1.9 minutes.

When looking at the responders per time interval for Ogluo (mITT): 18 (14.2%) patients took 15 to 20 minutes, 5 patients (3.9%) took 20 to 25 minutes, 4 patients (3.1%) took 25 to 30 minutes and 1 patient (0.8%) took 30 to 35 minutes to recover. This is in contrast to the HK patients who all took maximum 15 minutes to recover (and 88.6% took only up to 10 minutes, which was the case for merely 37% of Ogluo patients). This means that for more than 20% of Ogluo patients there was a delay of 5 to 20 minutes which can put them at risk of serious consequences.

The SmPC of Glucagen HK mentions that if the patient does not respond within 10 minutes, intravenous glucose should be given. If this would be applied to Ogluo patients, this means that 63% of them would need to receive IV glucose.

For the time-point 'from decision to dose', only subjective symptomatic results have been submitted and there were some comments regarding the use of symptom relief scores;

- the questionnaires were not validated
- there are no data on the symptom scores in the dossier (only on the time to relief of symptoms): e.g. whether they were high or low in the study, comparable or not in both treatment groups, if there were patients without hypoglycaemia symptoms
- it was questionable whether the results are reliable as it might be difficult for patients to assess symptoms as they are in a state of induced hypoglycaemia or recovering from it, and no patients with symptoms of severe hypoglycaemia were included.

The applicant clarified that the not validated score was used as a PRO and that in most of the Phase 3 adult T1D subjects, the change in symptom scores results were consistent with glucose effects. It is addressed that the symptom relief scores still are not validated. However, across trials the symptom scores results were consistent with glucose effects, therefore issue was resolved.

Throughout the phase 3 clinical development programme adult subjects in the Lilly glucagon group or the GlucaGen HypoKit group achieved plasma glucose > 70 mg/dL or plasma glucose increase to >20 mg/ dL, approx. 4 minutes faster as compared to adult subjects in the Ogluo group, based on 'Receiving Glucagon' or 'Decision to Dose', respectively. In the SmPC of the reference product, under Method of administration Section 4.2 based on the onset of glucagon action in the GlucaGen HypoKit, there are specific recommendations, as follows:

“The patient will normally respond within 10 minutes. When the patient has responded to the treatment, give oral carbohydrate to restore the liver glycogen and prevent relapse of hypoglycaemia. If the patient does not respond within 10 minutes, intravenous glucose should be given”. There were no specific recommendations based on the onset of glucagon action in the Ogluo proposed SmPC.

Because Ogluo has not been re-administered in the clinical trials performed, the recommendation regarding the re-administration was not supported by clinical data. However, it is acknowledged that it is a risk mitigation measure for the delay in response observed throughout the clinical trials for Ogluo as compared to the reference product. Thus, the following recommendation in section 4.2 of the SmPC was added:

“The patient will normally respond within 15 minutes. When the patient has responded to the treatment, give oral carbohydrate to restore the liver glycogen and prevent relapse of hypoglycaemia. If the patient does not respond within 15 minutes, an additional dose of Ogluo from a new device may be administered while waiting for emergency assistance.”

However, the applicant should take into account that a second dose of glucagon can stimulate further GLP-1 receptor and it may cause additional nausea and other adverse drug reactions.

In the responses provided, the applicant removed this recommendation regarding re-administration of Ogluo. However, taking into account the number of subjects who do not responded in 15 minutes in clinical trials and the fact that the patient can be in an area where the emergency cannot reach him/her, recommendation was the applicant to keep this recommendation.

Ancillary analyses

No subgroup analyses were performed based on intrinsic factors. The rationale is supported by EMA Guideline on the Investigation of Subgroups in Confirmatory Clinical Trials (EMA, 2019) and based on the following categories:

1. There was no strong reason to expect an inconsistent response to treatment across the different intrinsic factors as the treatment response had been extremely consistent across the Phase 3 adult studies and the Phase 3 paediatric study (across all age groups).
2. There was no reason to justify an expectation that an inconsistent treatment response across the different intrinsic factors would be observed.

Therefore, no further investigations were required and none were performed.

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 (see later sections).

Table 21 Summary of efficacy for trial 304

Title: Study XSGP-304 is a phase 3 multicenter, randomized, controlled, single- blind, 2-way crossover study to compare the efficacy and safety of Ogluo with Glucagen HypoKit (Glucagon) for induced hypoglycaemia rescue in adults with T1DM.
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Study identifier	XSGP-304		
Design	Phase 3 Multicentre, Randomised, Controlled, Single-Blind, 2-Way Crossover		
	Duration of main phase:	2 treatm seq separated by washout of 7-28 d	
	Duration of Run-in phase:	Screening up to 30 d before randomisation	
	Duration of Extension phase:	Not applicable	
Hypothesis	Non-inferiority		
Treatments groups	Ogluo	Ogluo 1 mg, single administration, N=132 (but cross-over design, so 66 first Ogluo, then HK – and 66 first HK, then Ogluo)	
	GlucaGen HypoKit (HK)	HK 1 mg, single administration, N=132 (but cross-over design, so 66 first Ogluo, then HK – and 66 first HK, then Ogluo)	
Endpoints and definitions	Primary endpoint	<i>alternate combined</i> endpoint (PGR): either a plasma glucose concentration ≥ 70 mg/dL (≥ 3.88 mmol/L) (PGR 1) OR an increase in plasma glucose concentration ≥ 20 mg/dL (≥ 1.11 mmol/L) (PGR 2) within 30 minutes of study drug injection	
	Secondary endpoint	mean time to positive PGR (min) from study drug administration	
	Secondary endpoint	mean drug preparation time (sec) from a decision to dose	
Database lock	Last subject completed 02/04/2019 – CSR 07/10/2019		
Results and analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	mITT for some, PP for others		
Descriptive statistics and estimate variability	Treatment group	Ogluo	HK
	Number of subjects	mITT: 127 PP: 115	mITT: 123 PP: 115
	Primary: Achieving positive PGR < 30 minutes (mITT)	126 (=99.2%)	123 (=100%)
	Secondary: mean time to positive PGR (min)	14.80 (SD: 5.349)	10.41 (SD: 1.846)
	Secondary: mean drug preparation time (sec)	mITT: 46.76 (SD: 31.576) PP: 44.89 (SD: 31.288)	mITT: 105.1 (SD: 40.561) PP: 106.03 (SD: 40.579)
Effect estimate per comparison	Primary endpoint	Comparison	Ogluo vs HK
		Risk difference in failing to achieve positive	mITT: -0.023 PP: 0.000
		95% CI	mITT (-0.085, 0.035) PP (-0.033, 0.033)
		Non-inferiority	Satisfied as upper limit of 95% CI of the difference in failure rates is $\leq 5\%$

XSGP-301 and XSGP-303

Methods

Study design

Study XSGP-301

This is a Phase 3 non-inferiority, randomised, double-blind, 2-way crossover efficacy and safety trial involving 80 adult subjects with T1D ages 18 to 75 years to determine the failure rate of Ogluo 1 mg relative to GEK 1 mg, predominantly White.

Study XSGP-303

This is a Phase 3 non-inferiority, randomised, single-blind, 2-way crossover comparative efficacy and safety study in 81 adult subjects with T1D ages 18 to 74, predominantly White.

Both studies involved 2 daytime CRC visits 7 to 28 days apart, with random assignment to treatment sequence (i.e., administration of Ogluo 1 mg during one session and GEK 1 mg during the other).

Study Participants

Treatments

In general, the treatment administration procedure (including an insulin induction procedure to induce hypoglycaemia) in studies XSGP-301 and XSGP-303 was similar to the one in study XSGP-304. However, there were also some differences including a different comparator (GEK) and the target plasma glucose concentration after the insulin induction procedure at which administration of glucagon could occur: 50 mg/dL in studies XSGP-301 and XSGP-303 versus 54 mg/dL in study XSGP-304 to be in line with the IHSG guidelines.

Moreover, as recommended during the EMA SA, in study XSGP-304, the insulin infusion was continued for 5 minutes after the target plasma glucose concentration of 54 mg/dL was achieved, while in studies XSGP-301 and XSGP-303, insulin dose was stopped immediately once the target plasma glucose concentration was achieved.

Other differences were the timing of the screening procedures before randomisation (60 days in XSGP-301 and XSGP-303, and 30 days in XSGP-304), the time of plasma glucose monitoring after study drug administration (180 in XSGP-304 and XSGP-303, and 90/240 minutes in XSGP-301), and the fact that time to response from the decision was measured in studies XSGP-303 and XSGP-304 but not in study XSGP-301.

The applicant used the data from study XSGP-301 to implement an insulin dose adjustment algorithm in study XSGP-303 in order to avoid achieving nadirs <40 mg/dL that were observed in study XSGP-301.

Objectives

XSGP-301

The primary objective was assessed by the comparison of failure rates of plasma glucose to have a measured value >70 mg/dL within 30 minutes of study drug administration.

Secondary objectives of the study were to compare the PD characteristics of Ogluo vs. GEK, describe and compare hypoglycaemia symptom relief of the 2 treatments, describe Ogluo PK in the major ethnicities and races in the United States, and compare the safety and tolerability of Ogluo vs. GEK in T1D subjects who were in a state of insulin-induced hypoglycaemia.

XSGP-303

The primary objective of this study was to demonstrate that the efficacy (return to plasma glucose > 70 mg/dL) of Ogluo 1 mg (test) was non-inferior to Lilly Glucagon 1 mg (reference) in T1D subjects who are in a state of insulin-induced hypoglycaemia. Study results were assessed by the comparison of failure rates of both the test and reference products to have measured plasma glucose values > 70 mg/dL within 30 minutes of administration of treatment.

The secondary objectives of this study were: to demonstrate the efficacy (return to plasma glucose >70.0 mg/dL or an increase in plasma glucose \geq 20 mg/dL at 30 minutes post study drug injection); demonstrate the efficacy (return to plasma glucose >70.0 mg/dL or alleviation of all neuroglycopenic symptoms at 30 minutes post study drug injection); compare the pharmacodynamic characteristics of Ogluo versus Lilly Glucagon; describe and compare hypoglycaemia symptom relief of the two products (including a hypoglycaemia questionnaire that measured severity of 4 neuroglycopenic symptoms (dizziness, blurred vision, difficulty in thinking, and faintness), and 4 autonomic symptoms (sweating, tremor, palpitations, and feeling of nervousness), as well as a global feeling of hypoglycaemia); describe and compare the two products for preparation time required to inject to the abdomen from a decision to treat; and compare the safety and tolerability of Ogluo.

During evaluation of Study XSGP-301, it was noted that in some instances subjects reported resolution of the overall sensation of hypoglycaemia, while still reporting individual symptoms. Consequently, both the "time to complete resolution of symptoms" was considered in Study XSGP-303, along with "relief" of symptoms, which required aggregate symptoms to return to a level no more than 1 unit higher than the maximum score reported during the baseline observation period.

Outcomes/endpoints

XSGP-301 and XSGP-303

Primary endpoint: an increase in plasma glucose concentration from below 50.0 mg/dL to greater than 70.0 mg/dL within 30 minutes after receiving glucagon.

XSGP-301

The combined primary endpoint in study XSGP-304, was not a pre-specified endpoint in study XSGP-301. However, it was added in study XSGP-301 ad-hoc before un-blinding as an alternate combined glucose-response endpoint i.e. an increase in plasma glucose concentration from below 50.0 mg/dL to > 70.0 mg/dL or increased > 20 mg/dL within 30 minutes after receiving glucagon

The reason for this was that, in about 30% of procedures, nadir glucose of less than 40 mg/dL with an impact on the evaluation of the primary endpoint was observed.

Secondary endpoints:

- Pharmacodynamic characteristics, including: plasma glucose AUC, C_{max}, T_{max} and time to reach >70.0 mg/dL.
- Symptoms of hypoglycaemia (if present) as documented using the hypoglycaemia symptom questionnaire.
- Pharmacokinetic parameters including: descriptive analysis of AUC, C_{max} and T_{max} of the different ethnicities.

XSGP-303

The combined primary endpoint in study XSGP-304, was included as a secondary endpoint in study XSGP-303 but was also analysed as an alternate combined endpoint for comparison with study XSGP-304.

In study XSGP-303 (not in XSGP-301), like in study XSGP-304, some secondary endpoints also used the time-point 'from decision to dose' (although again for symptomatic endpoints, not for objective endpoints related to plasma glucose) and a time-to-event analysis; the total preparation time was also measured. The same issues regarding the use of symptom relief scores as formulated for study XSGP-304 are applicable here.

Secondary endpoints:

- Return of plasma glucose to > 70 mg/dL or clearance of all neuroglycopenic symptoms within 30 minutes after receiving glucagon.
- Return of plasma glucose to > 70 mg/dL or an increase in plasma glucose by ≥ 20 mg/dL within 30 minutes after receiving glucagon.
- Increase in plasma glucose by ≥ 20.0 mg/dL within 30 minutes after receiving glucagon.
- Relief within 30 minutes after receiving glucagon of all neuroglycopenic symptoms present immediately after the decision to dose.
- Pharmacodynamic characteristics, including: plasma glucose AUC, C_{max}, and t_{max}, time to achieve a 20.0 mg/dL increase, and time to reach >70.0 mg/dL, both from time of glucagon administration and from time of the decision to dose.
- Total preparation time required to inject to the abdomen from a decision to treat, as measured between the time of "decision to dose" and time of injection.
- Hypoglycaemia symptom relief using the hypoglycaemia symptom questionnaire, from just after the decision to dose to 180 minutes post-injection of glucagon.
- Safety-related parameters including: Change in Vital signs from just prior to dosing to 180 minutes post-injection of glucagon, in physical exam findings from Screening to Follow-up, in ECG findings from Screening to Follow-up, in standard safety laboratory parameters (e.g., haematology and serum chemistry) from Screening to Follow-up; incidence of adverse events (AEs) and serious adverse events (SAEs); subjective injection site discomfort as reported by subjects using a 100-mm VAS and other questionnaires; Erythema and/or oedema formation at site of injection assessed by an Investigator using the modified Draize scale.

Results

Participant flow

Table 22 Subject Disposition Across Studies XSGP-301 and XSGP-303

Disposition	Adult Phase 3 Type 1 Diabetic Subjects Pool		
	Gvoke → GEK n (%)	GEK → Gvoke n (%)	All Subjects n (%)
Randomized subjects	85	76	161
Completed study	82 (96.5)	71 (93.4)	153 (95.0)
Discontinued the study	3 (3.5)	5 (6.6)	8 (5.0)
Reason for study discontinuation ^a			
Adverse event	0	0	0
Investigator decision	0	0	0
Lost to follow-up	0	1	1
Withdrawal by investigator	0	1	1
Study terminated by sponsor	0	0	0
Subject withdrawal	3	3	6

GEK=Glucagon Emergency Kit, HK=HypoKit, ND=no data.

^a Percentages are based on the number of subjects randomized.

Of the 161 randomised subjects in studies XSGP-301 and XSGP-303, 153 (95.0%) completed the studies. There were 2 discontinuations in XSGP-301, and there were 6 discontinuations in XSGP-303. None of the discontinuations was due to an adverse event (AE) or intolerance to study drug.

Of the 6 (7.4%) subjects who terminated early in XSGP-303, 2 (2.5%) withdrew from the study before the first treatment (one due to the subject's decision to withdraw and one due to the investigator's decision to withdraw) and 4 (4.9%) withdrew from the study before the second treatment (all due to the subjects' decision to withdraw).

Baseline data

Overall, the majority of subjects in the Phase 3 Pool were male (57.1% Ogluo; 55.4% GEK). Mean age was 41.1 years (both treatment groups). The majority had a mean duration of diabetes from 11 to 30 years. Like in study XSGP-304, the majority of patients was White (89.6% Ogluo; 89.2% GEK). Overall, the demographic characteristics between Ogluo and GEK were comparable but taking into account the cross-over design of the study, balance between treatment arms was not an issue.

Numbers analysed

XSGP-301

Table 23 Data sets analysed

Disposition	C-Pen 1 mg n (%)	Lilly Glucagon 1 mg n (%)
Randomized	80 (100)	80 (100)
Intent-to-Treat	80 (100)	80 (100)
Randomized treatment received, analyzed as treated	77 (96.3)	78 (97.5)
Reverse treatment sequence, analyzed as treated	1 (1.3)	1 (1.3)
Incorrect treatment received, (Primary Endpoint imputed)	1 (1.3)	0
Missed visits (Primary Endpoint imputed) ¹	1 (1.3)	1 (1.3)
Modified Intent-to-Treat (mITT)²	80 (100)	80 (100)
Randomized treatment received	77 (96.3)	78 (97.5)
Reverse treatment sequence, analyzed as treated	1 (1.3)	1 (1.3)
Incorrect treatment set to missing (Primary Endpoint imputed)	1 (1.3)	0
Missed visits (Primary Endpoint imputed) ¹	1 (1.3)	1 (1.3)
Pre-specified Per-Protocol Population³	80 (100)	80 (100)
Randomized treatment received, no Protocol violation	71 (88.8)	74 (92.5)
Randomized treatment received, Protocol violations (Primary Endpoint imputed)	6 (7.5)	4 (5.0)
Reverse treatment sequence analyzed as treated	1 (1.3)	1 (1.3)
Incorrect treatment set to missing (Primary Endpoint imputed)	1 (1.3)	0
Missed visits (Primary Endpoint imputed) ¹	1 (1.3)	1 (1.3)
Revised Per-Protocol (evaluable population, hereafter referred to as the Per-Protocol Population)⁴	80 (100)	80 (100)
Randomized treatment received, no Protocol violation	76 (95.0)	77 (96.3)
Randomized treatment received, Protocol violations (Primary Endpoint imputed)	1 (1.3)	1 (1.3)
Reverse treatment sequence analyzed as treated	1 (1.3)	1 (1.3)
Incorrect treatment received (Primary Endpoint imputed)	1 (1.3)	0
Missed visits (Primary Endpoint imputed) ¹	1 (1.3)	1 (1.3)

¹ Imputed endpoints used in the analysis.

² Defined as subjects who received at least 1 dose of study drug with sequence group based on actual treatment received.

³ Having either an increase in basal rate insulin or a bolus insulin dose within 20 min of glucagon injection.

⁴ Subjects in whom the basal rate was increased by at least 20% < 20 minutes pre-glucagon.

In study XSGP-301, 80 subjects were randomised to one of the two sequence groups and were included in the ITT population; 79 subjects (98.75%) completed the visits. All 80 subjects (100.0%) received at least one dose of study drug and were included in the mITT population. Of the subjects in the mITT population, 77 subjects (96.25%) received the randomised Ogluo treatment and 78 subjects (97.50%) received the randomised Lilly Glucagon treatment; of the subjects randomised to receive Ogluo, 1 subject (1.25%) received treatment in the reverse order, 1 subject (1.25%) received Lilly Glucagon at both visits, and 1 subject (1.25%) withdrew from the study.

The CSR (section 10.2) mentions that there were 10 major protocol deviations which were excluded from the PP analyses, consistent with the SAP approved on 08 August 2017 and according to the *Protocol Violation Assessment of Protocol XSGP-301* Appendix 16.1.9.1 - Version 1.0, approved by the applicant on 10 August 2017. However, elsewhere, the CSR (section 11.1) mentions only 2 exclusions from the PP population due to major protocol deviations. This is due to the fact that, after completion of the SAP and adjudication/unblinding by the sponsor and the monitor, a subsequent adjudication was performed and the PP population used for the primary efficacy analysis was modified by non-considering as a major protocol

violation any bolus within 20 minutes prior to administration of the study drug. Thus, these subjects have not been excluded from the PP population, although Section 7 of Version 1.6 of the protocol mentions that "late bolus doses (i.e., within 20 minutes of dosing) should be avoided" and in *Protocol Violation Assessment of Protocol XSGP-301* both "late bolus doses (i.e., within 20 minutes of dosing)" and "subject's insulin basal rate increased within 20 minutes prior to the study drug administration when the glucose dropping rate of change was >1 mg/dl/min" are considered as major protocol violations. As such, only "subject's insulin basal rate increased within 20 minutes prior to the study drug administration" was kept as a major protocol violation and only two subjects, one from Ogluo treated and one from GEK treated, have been excluded from the primary analysis.

The impact of the change of the protocol violation classification on the primary efficacy analysis has been presented by the applicant. Calculations for the primary endpoint of Dht were done with the PP population (i.e., where treatments outcomes were set to missing for visits where Pre-Specified protocol violations occurred – that is excluding the 9 subjects) and with the RPP population (i.e., treatments outcomes were set to missing for visits where Revised protocol violations occurred – that is including the 9 subjects).

Based on the test result difference for of Dht failure scores, Ogluo did not satisfy the non-inferiority criterion for the pre-specified PP population but did satisfy the non-inferiority criterion for the revised PP population.

Table 24

Summary of the Analysis of Dht by Population
All Patients

Analysis Type	N	Dht	SE	Dht + 2.6 * SE	Non-Inferiority Satisfied?
ITT	80	0.054	0.025	0.118	No
MITT	80	0.054	0.025	0.118	No
PPFROT	80	0.051	0.022	0.109	No
RPPROT	80	0.043	0.022	0.099	Yes

Taking into account the result for the alternate combined glucose-response endpoint which satisfy the non-inferiority criterion for both pre-specified PP- and revised PP population, the failure to achieve a steady state hypoglycaemia for a third of the procedures, and the fact that study XSGP-301 is only supportive for the assessment, this issue was not pursued.

XSGP-303

Table 25 Analysis Population by Treatment

Population	All Randomized Subjects N=81	
	G-Pen n (%)	Lilly Glucagon n (%)
ITT (For binary endpoints, missing data imputed)	81 (100)	81 (100)
ITT (For all other endpoints, missing data not imputed)	76 (93.8)	78 (96.3)
PP	73 (90.1)	73 (90.1)
Safety	76 (93.8)	78 (96.3)

ITT=intent-to-treat, PP=per-protocol

In study XSGP-303, of the ITT Population consisting of 81 patients, 8 patients were excluded from the PP population consisting then of 73 patients: 2 patients with a major protocol deviation and 6 patients who withdrew early. For a last patient, the reason for the exclusion from the PP population was not found in the dossier.

Outcomes and estimation

Primary endpoint:

Of subjects treated with Ogluo, 97.4% of subjects in the mITT Population and 98% of subjects in the PP Population achieved a plasma glucose level >70 mg/dL within 30 minutes of dosing, comparable to treatment with GEK in which 100% of subjects achieved the primary endpoint (see table below). Thus, simple pooling showed that Ogluo and GEK were comparable with respect to success/failure rates on the primary endpoint.

Table 26 Number of Subjects with Plasma Glucose >70 mg/dL Within 30 Minutes of Dosing: Adult Phase 3 Type 1 Diabetic Subjects

Adult Phase 3 Subjects with Type 1 Diabetes Pool			
mITT		Per Protocol	
Gvoke (N=154) n (%)	GEK (N=157) n (%)	Gvoke (N=150) n (%)	GEK (N=153) n (%)
150 (97.4)	157 (100.0)	147 (98.0)	153 (100.0)

Secondary endpoints:

Plasma Glucose at 30 Minutes Post-dose

Overall Ogluo and GEK were similar for this endpoint in the adult Phase 3 studies and both groups had mean and median values that were well above 70 mg/dL. The mean plasma glucose in the pooled Ogluo group was 2 standard deviations above 70 mg/dL, indicating a robust response.

Table 27 Mean Plasma Glucose (mg/dL) at 30 Minutes Post-dose: Adult Phase 3 Subjects with Type 1 Diabetes Pool

Statistics	Adult Phase 3 Subjects with Type 1 Diabetes Pool	
	Gvoke (N=154)	GEK (N=157)
n	154	156
Mean	119.93	132.00
SD	24.906	21.934
Median	121.80	131.00
Min	55.9	80.5
Max	184.5	184.5

N=number of subjects in analysis population; SD=standard deviation.

Plasma Glucose Increase ≥ 20 mg/dL Within 30 Minutes of Dosing

Of the subjects treated with Ogluo within these studies, 98.7% (n=152/154) achieved a plasma glucose increase ≥ 20 mg/dL within 30 minutes, which was comparable to GEK (100%, n=157).

Mean Time to Plasma Glucose Increase >70 mg/dL or ≥ 20 mg/dL Increase

Of the subjects treated with Ogluo within these studies, the mean time to achieve plasma glucose >70 mg/dL or increase in plasma glucose >20 mg/dL was 13.8 minutes versus 10.0 minutes for GEK.

Neuroglycopenic Symptom Relief Within 30 Minutes

The analyses of the Adult Phase 3 Subjects with Type 1 Diabetes Pool demonstrated that Ogluo was comparable to GEK based on achieving relief of neuroglycopenic symptoms within 30 minutes after dosing.

For the mITT analysis, 85.1% (131/154) of the subjects on Ogluo had symptom relief within 30 minutes after dosing, while 82.2% (129/157) on GEK experienced relief within 30 minutes.

Plasma Glucose >70 mg/dL or Neuroglycopenic Symptom Relief Within 30 Minutes

The analyses of the Adult Phase 3 Subjects with Type 1 Diabetes Pool demonstrated that Ogluo was comparable to GEK based on an increase in plasma glucose concentration >70 mg/dL or neuroglycopenic symptom relief within 30 minutes after dosing.

Of the subjects treated with Ogluo within these studies, 99.4% (153/154) had a plasma glucose >70 mg/dL or neuroglycopenic symptom relief within 30 minutes, which was comparable to GEK (100%).

XSGP-301

Primary endpoint:

Overall, Ogluo did not satisfy the criterion for non-inferiority to GEK based on analysis of failure scores for the ITT Population for the primary endpoint (increase in plasma glucose concentration from below 50 mg/dL to >70 mg/dL within 30 minutes after receiving study drug). Contributing to the difference in mean failure scores were 4 subjects in the Ogluo arm who did not achieve a plasma glucose >70 mg/dL within 30 minutes, but, rather, within an average time of 43.2 minutes without receiving glucose or additional intervention beyond Ogluo. It was noted that these 4 subjects had a nadir glucose in the range of 26.2 to 40.6 mg/dL, well below the protocol-defined plasma glucose target of just under 50 mg/dL. The procedure relied heavily on investigator discretion. In some cases, the investigators infused an excessive amount of insulin and even increased insulin infusion rates when the plasma glucose rate was on target at 1 mg/(dL*min). This undercut the ability to achieve the desired steady state. About a third of the procedures across the treatment groups had post-dose glucose concentrations less than 40 mg/dL, illustrating the lack of steady state. Nevertheless, only 4 subjects in the study failed to achieve the primary endpoint of plasma glucose above 70 mg/dL in 30 minutes, a testament to the effectiveness of both products.

Among the 4 subjects who failed to achieve plasma glucose >70 mg/dL within 30 minutes was 1 of the 2 subjects with a major protocol violation. When this treatment visit was set to "missing" as per the study Statistical Analysis Plan, Ogluo satisfied the criterion for non-inferiority to GEK based on analysis of failure scores for the PP Population for the primary endpoint.

Table 28 Test Result of the Difference of Failure Scores (Study XSGP-301)

	D_{ht}	$SE_{D(ht)}$	$D_{ht} + 2.6 \times SE_{D(ht)}$	Non-Inferiority Criterion
ITT Population	0.054	0.025	0.118	Not Satisfied
PP Population	0.043	0.022	0.099	Satisfied

D_{ht} =sample mean of the difference of the success/failure scores between the 2 treatments (derived for each subject from the treatment score minus the control failure score), where success was defined as glucose >70 mg/dL within 30 minute of injection. $SE_{D(ht)}$ =standard error of D_{ht} .

Noninferiority Criterion: Gvoke non-inferiority criterion was satisfied if $D_{ht} + 2.6 \times SE_{D(ht)}$ was ≤ 0.1 .

The PP Population is presented in the data source as the Revised PP Population.

Alternate combined endpoint:

Ogluo satisfied the criterion for non-inferiority to GEK based on analysis of failure scores for both the ITT and PP Populations for the alternate combined glucose-response endpoint (an increase in plasma glucose concentration >70 mg/dL or increased ≥ 20 mg/dL within 30 minutes after study drug administration). Two of the subjects who failed to achieve a plasma glucose value >70 mg/dL within 30 minutes did exhibit a rise in plasma glucose of ≥ 20 mg/dL within 30 minutes of receiving Ogluo.

Table 29 Summary of the Analysis of Return of Plasma Glucose to >70 mg/dL or an Increase in Plasma Glucose by ≥ 20 mg/dL within 30 minutes after Dosing, Study XSGP-301

Analysis Set	D_{htex}	$SE_{D(htex)}$	$D_{htex} + 2.6 \times SE_{D(htex)}$	Non-Inferiority Criterion
ITT Population	0.029	0.018	0.075	Satisfied
PP Population	0.030	0.018	0.077	Satisfied

D_{htex} =sample mean of the difference of the success/failure scores between the two treatments (derived for each subject from the treatment score minus the control failure score), where success was defined as glucose >70 mg/dL or increased >20 mg/dL within 30 minutes of injection; $SE_{D(htex)}$ =standard error of D_{htex} .

Noninferiority Criterion: Gvoke non-inferiority was satisfied if $D_{htex} + 2.6 \times SE_{D(htex)}$ ≤ 0.1

Secondary endpoints:

In general, subjects in the GEK treatment group reached a plasma glucose concentration >70 mg/dL earlier than subjects in the Ogluo treatment group (GEK: mean of 14.2 minutes [standard deviation: 4.26], Ogluo: 19.9 minutes [8.51]), from time of study drug administration.

Median times to achieve this endpoint were 15.0 and 18.5 minutes for GEK and Ogluo, respectively, also from time of study drug administration. These differences were not clinically meaningful, given that both the time course and extent of relief of symptomatic hypoglycaemia was similar for Ogluo compared with GEK.

However, these minor differences warranted examination of drug preparation time in further clinical studies, to examine plasma glucose recovery times from a decision to dose.

Mean time to response was longer in both groups, relative to the mean time of just under 12 minutes observed for Ogluo in Study XSGP-202. Delays in dosing caused by operational considerations of maintaining double-blinding led to the lower nadir plasma glucoses observed in the study, due to the carryover effect of IV insulin used to induce hypoglycaemia, likely contributing to this effect.

Resolution of hypoglycaemia symptoms was similar between the groups. In almost all cases, the resolution of these clinical symptoms preceded the return of documented euglycemia. Average hypoglycaemia symptom scores were similar between Ogluo and GEK from 0 to 90 minutes post study drug injection.

Median time to a first response of "No" to the question, "Do you currently feel hypoglycaemic?" and median time to resolution of the aggregate hypoglycaemia symptom scores were comparable for Ogluo and GEK.

Average time to resolution of the global feeling of hypoglycaemia did not differ significantly between Ogluo and GEK. Consequently, it can be concluded that any differences between Ogluo and GEK with respect to PD parameters, including mean time to plasma glucose >70 mg/dL, had no effect on resolution of symptoms, an important consideration when comparing the clinical efficacy of the products, where restoration of neurologic function and oral intake is critical to further medically manage severe hypoglycaemia.

XSGP-303

Primary endpoint:

Ogluo satisfied the criterion for non-inferiority to GEK based on analysis of the primary endpoint (an increase in plasma glucose concentration from below 50 mg/dL to >70 mg/dL within 30 minutes after receiving glucagon) for both the ITT and PP Populations. The percentage of subjects meeting the primary endpoint was 100% for both groups within both analytical populations (see table below).

Analysis Set	D_{htex}	$SE_{D(ht)}$	$D_{ht} + 2.8 \times SE_{D(ht)}$	Non-Inferiority Criterion
ITT Population	0.009	0.005	0.022	Satisfied
PP Population	0.009	0.000	0.000	Satisfied

D_{htex} =sample mean of the difference of the success/failure scores between the two treatments (derived for each subject from the treatment score minus the control failure score), where success was defined as glucose >70 mg/dL or increased ≥ 20 mg/dL within 30 minutes of injection; $SE_{D(htex)}$ =standard error of D_{htex}
 Noninferiority Criterion: Gvoke non-inferiority was satisfied if $D_{ht} + 2.8 \times SE_{D(ht)} \leq 0.1$

All evaluable subjects had successful plasma glucose recovery (> 70 mg/dL) within 30 minutes based on both starting point evaluations: Receiving Glucagon and Decision to Dose (see table below).

Table 30 Number and Percentage of Subjects with Plasma Glucose > 70 mg/dL within 30 Minutes After Glucagon Treatment (ITT Population)

	Subjects with Plasma Glucose > 70 mg/dL within 30 Minutes after Treatment n (%)			
	G-Pen (N=76)		Lilly Glucagon (N=78)	
	Timepoint	Cumulative	Timepoint	Cumulative
Time (minutes) from Receiving Glucagon Treatment				
5	0	0	2 (2.6)	2 (2.56)
10	25 (32.9)	25 (32.9)	56 (71.8)	58 (74.4)
15	35 (46.1)	60 (78.9)	20 (25.6)	78 (100)
20	12 (15.8)	72 (94.7)	0	78 (100)
25	4 (5.3)	76 (100)	0	78 (100)
30	0	76 (100)	0	78 (100)
Time (minutes) from Decision to Dose				
5	0	0	0	0
10	14 (18.4)	14 (18.4)	29 (37.2)	29 (37.2)
15	37 (48.7)	51 (67.1)	45 (57.7)	74 (94.9)
20	21 (27.6)	72 (94.7)	4 (5.1)	78 (100)
25	4 (5.3)	76 (100)	0	78 (100)
30	0	76 (100)	0	78 (100)

Alternate combined endpoint:

Ogluo satisfied the criterion for non-inferiority to GEK based on analysis of failure scores for both the ITT and PP Populations for the alternate combined glucose-response endpoint (an increase in plasma glucose concentration >70 mg/dL or increased ≥ 20 mg/dL within 30 minutes after study drug administration).

Table 31 Summary of the Analysis of Return of Plasma Glucose to >70 mg/dL or an Increase in Plasma Glucose by ≥ 20 mg/dL within 30 minutes after Dosing, Study XSGP-303

Analysis Set	D_{htex}	$SE_{D(\text{htex})}$	$D_{\text{ht}} + 2.8 \times SE_{D(\text{ht})}$	Non-Inferiority Criterion
ITT Population	0.009	0.005	0.022	Satisfied
PP Population	0.009	0.000	0.000	Satisfied

D_{htex} =sample mean of the difference of the success/failure scores between the two treatments (derived for each subject from the treatment score minus the control failure score), where success was defined as glucose >70 mg/dL or increased ≥ 20 mg/dL within 30 minutes of injection; $SE_{D(\text{htex})}$ =standard error of D_{htex}

Noninferiority Criterion: Gvoke non-inferiority was satisfied if $D_{\text{ht}} + 2.8 \times SE_{D(\text{ht})} \leq 0.1$

Secondary endpoints:

Ogluo satisfied the criterion for non-inferiority to Ogluo based on analysis of the secondary endpoint of relief of neuroglycopenic symptoms by 30 minutes after study drug administration for both the ITT and PP Populations.

Ogluo was therapeutically equivalent to GEK in clinically meaningful effects (i.e. successful restoration of normal plasma glucose levels within 30 minutes of drug administration, from a state of insulin-induced severe hypoglycaemia) and in terms of the key PD endpoints: plasma glucose Cmax, tmax, and AUC, and plasma glucose concentration-by-time curves showed little separation between treatments, when administered SC.

Time to initial relief of autonomic or neuroglycopenic symptoms was comparable for Ogluo compared to GEK from both a decision to dose and from the point of receiving glucagon. Time to a first "No" for the global question "Do you currently feel hypoglycaemic?" (i.e. resolution of the global sensation of hypoglycaemia) was statistically shorter (by 2.5 minutes), for Ogluo compared to GEK from a decision to dose, but not the point of receiving glucagon. Time to resolution of autonomic and neuroglycopenic hypoglycaemia symptoms did not differ significantly between Ogluo and GEK from either administration a decision to dose or from administration of glucagon. Mean symptom scores over time did not differ significantly between Ogluo and GEK. These findings also highlight the fact that any differences between the groups with respect to PD variables have no meaningful clinical significance.

The mean time for plasma glucose recovery after administration of Ogluo was rapid, 12.5 minutes for a concentration >70 mg/dL, and 11.4 minutes for a 20 mg/dL increase from baseline. Time to a plasma glucose concentration >70 mg/dL was about 2.5 minutes faster from a decision to dose, and about 3.5 minutes faster following injection of GEK, compared to Ogluo.

These differences had no impact on relief/resolution of symptoms. Mean time for plasma glucose >70 mg/dL following injection of Ogluo was about 6 minutes faster in Study XSGP-303, compared to Study XSGP-301 and more similar to the results of Study XSGP-202. This finding indicated that the precision of the single investigator in Study XSGP-202 was achieved in a multi-centre study, Study XSGP-303, and validated the use of the single-blind study design.

Ogluo required significantly less drug preparation time than did GEK (27.3 vs. 97.2 sec), which required reconstitution, based on comparison of means in both the mITT and PP Populations.

Table 32 Mean Drug Preparation Time (Seconds) (ITT Population) XSGP-303

Statistics	Adult Subjects with Type 1 Diabetes Phase 3 Study XSGP-303		P-value ^a
	Gvoke (N=76)	GEK (N=78)	
n	76	78	N/A
Mean	27.3	97.2	
SD	19.66	45.06	
Median	23.0	93.5	
Min	12	40	
Max	130	257	
Equivalence ^b	Gvoke vs GEK		

^a Comparison of mean time for preparation of study drug as determined by stopwatch.

^b equivalence calculation applied a mixed model for the LA mean difference. Fixed factors: Treatment, Period, Treatment*Period; Repeat: Subject ID; Covariance Structure: Unstructured.

In study XSGP-301, the criterion for non-inferiority based on the primary endpoint versus GEK was not achieved. This was explained by the applicant by the fact that 4 patients in the Ogluo group had a nadir below 40 mg/dL. However, the FDA CDER Clinical Review Template (page 47) mentions 5 patients with a nadir <40 mg/dL with patients both in the Ogluo and in the GEK group. According to the applicant, these patients had an average time to response of 43.2 minutes without receiving glucose or additional intervention beyond study drug administration.

Therefore, the applicant was requested to provide the information for all patients in XSGP-301 with a pre-dose or post-dose nadir <40 mg/dL and for all patients with a failure to reach the primary endpoint. The applicant provided a Post-hoc table Listing of patients with a nadir plasma glucose <40 mg/dL All Randomised Subjects as asked.

These patients approach the setting of severe hypoglycaemia (which is the indication of Ogluo) better than the other studies in which patients with a plasma glucose <42 mg/dL could not be treated with glucagon, and these appear to have an additional risk as they require a long time to achieve a BG > 70 mg/dL. The applicant discussed the risk accompanying the long time to achieve a glucose > 70mg/dL adequately.

In order to align the primary endpoint across the 3 Phase 3 adult studies (301, 303, and 304), the data from studies XSGP-301 and XSGP-303 were analysed according to the primary endpoint of study XSGP-304: an alternate combined endpoint consisting of plasma glucose >70 mg/dL or increase ≥ 20 mg/dL within 30 minutes of dosing. For this alternate endpoint, the non-inferiority margin was achieved in studies XSGP-301 and XSGP-303.

Although all patients in XSGP-303 achieved plasma glucose recovery (> 70 mg/dL) or increase ≥ 20 mg/dL within 30 minutes, the mean time to achieve this was longer for Ogluo than for GEK, both for time from administration and for time from decision to dose:

- plasma glucose >70 mg/dL:

about 3.5 minutes longer (12.2 minutes versus 8.6 minutes) for time from administration and about 2.5 minutes longer (13.3 minutes versus 10.7 minutes) for time from decision to dose

- increase ≥ 20 mg/dL:

about 3.5 minutes longer (11.4 minutes versus 8.0 minutes) for time from administration and about 2.5 minutes longer (12.5 minutes versus 10.1 minutes) for time from decision to dose.

In XSGP-303 (ITT), more GEK patients achieved plasma glucose >70 mg/dL earlier than Ogluo patients, both for time from administration of study drug and for time from decision to dose:

- at 10 minutes, more than 2 times the number of GEK patients (cumulative: 58 patients (74.4%) achieved this than Ogluo patients (cumulative: 25 patients (32.9%)).
- at 15 minutes post-dose and 20 minutes from decision to dose, all GEK patients (100%) achieved this, while still resp. 16 patients (21.1%) and 4 patients (5.3%) in the Ogluo group had not yet achieved this
- at 25 minutes post-dose and 25 minutes from decision to dose, all Ogluo patients had achieved this.

Like for study XSGP-304, this was not considered clinically relevant by the applicant as the mean values to achieve this for Ogluo were all within 15 minutes, the drug preparation time was 70 seconds shorter (27.3 vs. 97.2 sec) for Ogluo and the time to achieve relief of symptoms was overall similar for Ogluo as for GEK. However, like for study XSGP-304 there were some comments regarding the use of symptom relief scores which were resolved (see above).

Clinical studies in special populations

There are only limited data for Ogluo in paediatric patients (31) with only 7 in the 2-<6, 13 in the 6-<12 and 11 patients in the 12≤18 years old group, all from study XSGP-302. The number of included patients in each age group was mentioned in the SmPC.

For elderly patients, the pooled analysis based on results from studies XSGP-301 and XSGP-303, showed that 14 out of 15 patients of 65 years or older achieved plasma glucose levels > 70 mg/dL within 30 minutes post-dose. However, there are only very limited data for Ogluo in elderly patients 65 years and above (21 patients of which 6 in the pivotal study), and none in elderly 75 years and above. This should be reflected in the SmPC by stating that efficacy and safety data for Ogluo are very limited in patients aged 65 years and above, and absent in patients aged 75 and above. A sufficient number of elderly patients will be included in the planned actual-use study.

Ogluo was not investigated in patients with hepatic or renal impairment. The SmPC states that it can be used in these patients and that no dose adjustment is required, which can be supported as it is a rescue-treatment, and it is in line with another recently approved glucagon product as well as GlucaGen HypoKit.

XSGP-302

Methods

Study design

Study XSGP-302 is an open-label, sequential treatment efficacy and safety Phase 3 study to evaluate the glucose response of Ogluo (Glucagon Injection) in 31 paediatric patients ages 2 to 18 years with T1DM. There was no comparison versus a reference product in this study (while a comparator was included in the paediatric study of a recently approved glucagon product).

Treatments

Subjects were administered insulin to induce a low-normal glycaemic state and then received an age-appropriate dose of Ogluo in a CRC. During the treatment phase, subjects ages 2 to <12 years completed a single treatment visit and received Ogluo 0.5 mg. Subjects ages 12 to <18 years received Ogluo 1 mg at an initial treatment visit and were administered Ogluo 0.5 mg at a second visit occurring 1 to 4 weeks later (table below).

Table 33 Treatment sequence

Subject Age	Dose 1	Dose 2
2 to < 12 years	G-Pen 0.5 mg	Not applicable
12 to < 18 years	G-Pen 1 mg	G-Pen 0.5 mg

For safety reasons in this paediatric population, severe hypoglycaemia was not induced in this study; instead, a low-normal glycaemic state was induced by administration of insulin: a decrease of plasma glucose to a target <80 mg/dL. A glucose increase from these low-normal blood glucose values can be accepted as a surrogate for the treatment of severe hypoglycaemia.

Per the RLD, Eli Lilly Glucagon, 1 mg is the approved dose for treating severe hypoglycaemia in adults, while a dose of 0.5 mg is indicated for patients weighing less than 20 kg. The applicant states that results from study XSGP-201 have been used based on which – through a weight-exposure model - the transition to the adult dose of Ogluo is proposed at 40 to 45 kg, corresponding to the average weight at 12 years of age. As per data presented in response, the weight-based exposure modelling analysis has been performed in adolescents weighing above 40 kg. No simulations were performed in children below 12 years and weighing below 40 kg. (see also PK section). The proposed weight cut-off at 45 kg for the transition to adult dose did not support an optimal dose based on glucagon PK parameters in children 6-12 years, indicating a decrease in exposure with increasing age group after administration of a fixed 0.5 mg dose, although the secondary PD endpoints were similar between age groups with regard to mean plasma glucose $AUC_{(0-90)}$, C_{max} , and T_{max} . Therefore a weight cut-off at 25 kg was recommended for the transition to adult dose.

The duration of study participation for individual subjects was approximately 2 to 6 weeks, and the duration of the study was 5 months.

Objectives

Primary objective:

To assess the increase in plasma glucose of subjects from baseline to 30 minutes in subjects in a low normal glycaemic state after injection of an age-appropriate dose of Ogluo (glucagon injection), in each of three age groups (2 to < 6 years, 6 to < 12 years, and 12 to < 18 years) of paediatric subjects with T1DM.

Secondary objectives:

- In the 12 to < 18-year-old age group, to additionally assess the plasma glucose change from baseline to 30 minutes after administration of Ogluo at a dose of 0.5 mg.
- Determine Ogluo PK for each age group.
- Determine the safety and tolerability of Ogluo for each age group.

Outcomes/endpoints

Primary endpoint:

The change in plasma glucose following treatment with Ogluo, with an emphasis on the increase from baseline to 30 minutes post-dosing.

Secondary endpoints:

- Pharmacokinetic parameters, including: descriptive analysis of AUC_{0-120m}, C_{max} and t_{max} of the different age cohorts.
- Pharmacodynamic characteristics, including: plasma glucose AUC_{0-120m}, C_{max}, t_{max} and time to achieve an increase in plasma glucose of at least 25 mg/dL.
- Safety-related parameters including: – Vital signs – Incidence of adverse events (AEs) and serious adverse events (SAEs) – Subjective injection site discomfort using the Faces Pain Scale [FPS-R] – Subjects with sufficient comprehension will further describe the nature and duration of any injection site discomfort using a second questionnaire – Erythema and/or oedema formation at site of injection assessed by an investigator using the modified Draize scale.

Statistical methods

Results

Participant flow

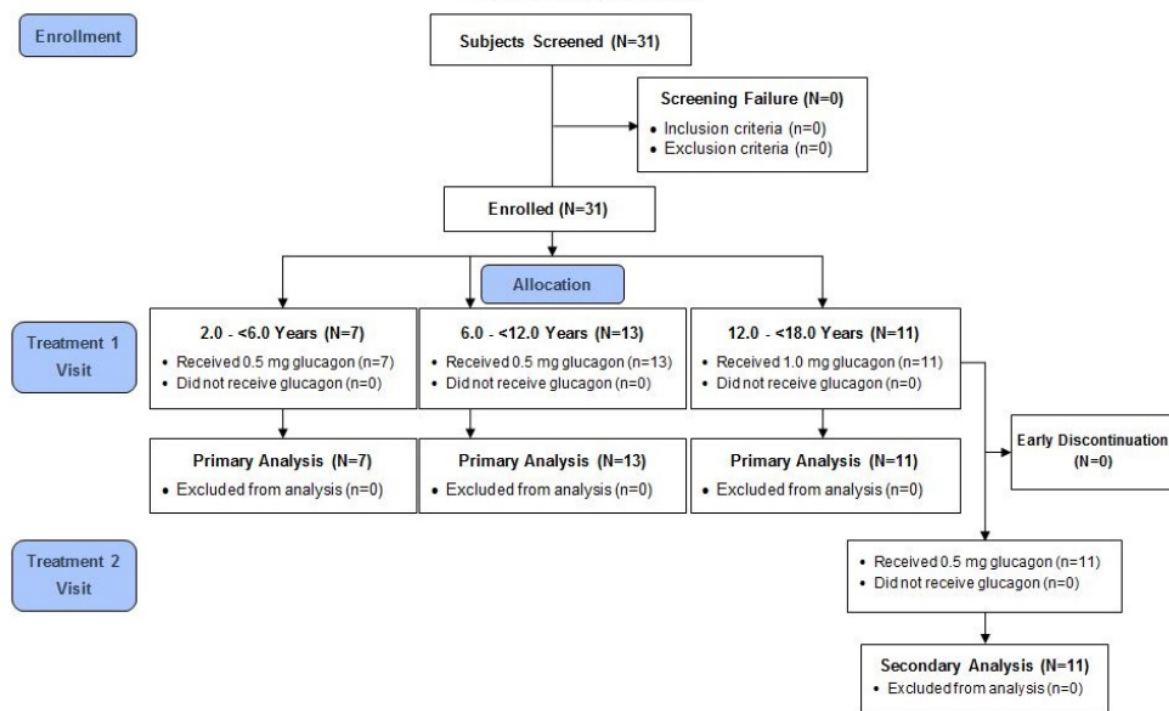


Figure 8 Disposition of subjects

Thirty-one subjects were enrolled in this study, of which 7 subjects were in the 2 to < 6 years age group, 13 subjects were in the 6 to < 12 years age group, and 11 subjects were in the 12 to < 18 years age group which is considered low. No subjects discontinued treatment and there were no screen failures.

Baseline data

The median ages of enrolled subjects in each age group were 5.3 years (2 to < 6 years group), 11.4 years (6 to < 12 years group), and 15.6 years (12 to < 18 years group). All subjects were not Hispanic/Latino and the majority of subjects in each age group were White (71.4%, 92.3%, and 100% of subjects in the 2 to < 6 years, 6 to < 12 years, and 12 to < 18 years age groups, respectively). There were more female subjects than male subjects in the 2 to < 6 years and 12 to < 18 years age groups (71.4% and 54.5%, respectively), and more male subjects than female subjects in the 6 to < 12 years age group (61.5%).

Numbers analysed

The applicant states that the mITT and PP population are identical as there was no protocol violation while there was one major protocol deviation which concerned a study nurse not being documented as having received the hands-on training with Ogluo.

Outcomes and estimation

Primary endpoint

Statistically significant increases from Baseline in mean plasma glucose were observed in each age group ($p < 0.001$ for all groups) at 30 minutes following administration of an age-appropriate dose of Ogluo (change from Baseline of 81.4 mg/dL [SD=18.3], 84.2 mg/dL [SD=25.3], and 54.0 mg/dL [SD=27.3] in the 2 to < 6 years, 6 to < 12 years, and 12 to < 18 years [1 mg dose] age groups, respectively) (see table below).

Table 34 Plasma Glucose Before and 30 Minutes After Administration of Ogluo by Age Group

Age Group	G-Pen dose	Plasma Glucose (mg/dL) Mean (SD), Median, [Min – Max]			p-value ^a
		Baseline	30 minutes	Change	
2 to < 6 years (N=7)	0.5 mg	68.1 (8.3), 71, [55-77.5]	149.6 (15.2), 152, [130-174]	81.4 (18.3), 82.5, [59-111.5]	< 0.001
6 to < 12 years (N=13)	0.5 mg	71.6 (7.6), 75, [51.5-78.5]	155.8 (26.5), 156, [107-203]	84.2 (25.3), 87, [43-126]	< 0.001
12 to < 18 years (N=11)	1 mg	75.5 (3.6), 76.5, [65-78]	129.5 (29.5), 138, [70-163]	54.0 (27.3), 61, [5-88]	< 0.001

max=maximum; min=minimum; SD=standard deviation

^a p-value was computed using a t-test for testing whether the change in glucose from baseline to 30 minutes was zero.

Mean (SD) plasma glucose levels for subjects in the 3 age groups (2 to < 6 years, 6 to < 12 years, and 12 to < 18 years age groups) plotted by time showed little separation between age groups.

In the 12 to < 18 years age group, plasma glucose-response curves did not vary greatly for subjects who received 0.5 mg and 1 mg of Ogluo.

Secondary endpoints:

Plasma Glucose Response in Paediatric Subjects

Paediatric subjects receiving an age-appropriate dose of Ogluo consistently achieved an increase in plasma glucose >25 mg/dL within 30 minutes. All remaining subjects reached this secondary endpoint without glucose therapy or additional intervention.

Table 35 Number of Subjects with Plasma Glucose Increase ≥ 25 mg/dL Within 30 Minutes

Gvoke 1 mg (N=11) n (%)	Gvoke 0.5 mg (N=31) n (%)
9 (81.8%)	30 (96.8)

Across all 31 subjects the mean time to plasma glucose increase ≥ 25 mg/dL from baseline was 19 minutes.

Table 36 Mean Time to Plasma Glucose Increase of ≥ 25 mg/dL from Baseline: Phase 3 Paediatric Study (XSGP-302)

Statistic	Gvoke 0.5 mg		Gvoke 1 mg	All Subjects
	2 to <6 YR (N=7)	6 to <12 YR (N=13)	12 to <18 YR (N=11)	(N=31)
n	7	13	11	31
Mean	16.4	16.2	23.6	18.9
SD	3.78	4.63	9.51	7.38
Median	15.0	15.0	20.0	20.0
Min	10	10	15	10
Max	20	25	45	45

Plasma Glucose Response in Paediatric Subjects

Age groups were generally similar to each other in mean plasma glucose AUC(0-90), C_{max}, and t_{max}. There were no clinically meaningful differences between age groups.

The Baseline-adjusted mean (SD) AUC(0-90) values were 8147.71 (2162.379), 8001.59 (2510.799), and 6377.54 (2700.448) min*mg/dL in the 2 to < 6 years, 6 to < 12 years, and 12 to < 18 years age groups, respectively.

The median times to increase by ≥ 25 mg/dL from Baseline in plasma glucose did not differ substantially in the 2 to < 6 years, 6 to < 12 years, and 12 to < 18 years age groups (15.0, 15.0, and 20.0 minutes, respectively).

For subjects in the 12 to < 18 years age group, mean plasma glucose AUC(0-90), C_{max}, and t_{max} were similar after dosing with 0.5 mg or 1 mg.

The Baseline-adjusted mean (SD) AUC(0-90) was similar for the 1 mg G-Pen treatment (6377.54 [2700.448] min*mg/dL) compared with 0.5 mg Ogluo treatment (7042.85 [2011.071] min*mg/dL) in subjects 12 to < 18 years. The median time to increase by ≥ 25 mg/dL from Baseline was the same after 0.5 mg and 1 mg treatment (20 minutes each).

Although the increase from baseline in mean plasma glucose at 30 minutes post-dose was statistically significant in all age groups, there are some unexpected observations in the age group 12-<18 years versus the other age groups even though the administered dose of 1 mg was the double of the 0.5 mg used in the other age groups:

- the glucose increase from baseline (54.0 mg/dL) was much lower than for the other age groups (2-<6 and 6-<12), (81.4 and 84.2 mg/dL), and this cannot only be explained by a higher baseline glucose level
- only 81.8% of patients in this group achieved a glucose increase ≥ 25 mg/dL within 30 minutes while of those having received 0.5 mg (other age groups together with the second administration in age group 12-<18 yo) 96.8% achieved this

- mean time to plasma glucose increase ≥ 25 mg/dL from baseline was also higher (23.6 minutes versus 16.4 and 16.2 minutes)
- lower glucose AUC(0-90) (6377.54 (2700.448) versus 8147.71 (2162.379) and 8001.59 (2510.799) min*mg/dL
- glucose response did not vary greatly after receiving the 0.5 mg dose compared to the 1 mg dose of Ogluo, and overall similar PD was observed.

The applicant was requested to explain and to discuss whether this is due to outliers or not. According to the applicant the differences could be explained as follows: subjects (2 to <6 years and 6 to <12 years) likely received more glucagon by weight-based exposure. The difference in success rates is likely due to the administration of excess residual insulin from the insulin pumps during the 1 mg treatment visits, related to the individual study procedures. No outliers were identified.

Supportive studies

Human Factors Studies

The Human Factors Studies were designed to mimic real-life emergency situations, and tested a total of 5 user groups that included first responders, trained and untrained users, adults and paediatric (adolescent) caregivers of people with diabetes.

The Human Factors Studies submitted for Ogluo only mimic emergency situations without the pressure on uninstructed caregivers caused by real-life stress (as would be the case in actual-use studies).

However, although an emergency situation can never be perfectly simulated, these human factor studies do provide some useful information:

In summary, multiple comparative studies conducted by Xeris and other pharmaceutical companies have demonstrated significant usability issues and a lack of functional efficacy with existing glucagon emergency kits.

Conversely, summative human factors studies with Ogluo have validated both product presentations as safe, effective, and usable for the intended users in the context of a severe hypoglycaemia emergency.

Almost all participants in all Human Factors Studies were able to successfully administer Ogluo, in 1 small study also in a much higher number of patients than for the comparator GEK:

- HF2: 14 of 16 participants (88%) were able to successfully administer a rescue injection using Ogluo compared with 5 of 16 participants (31%) with the GEK (chi-square test = 10.49, $P < 0.05$)
- HF3: 74 of 75 participants (98.7%) successfully administered the rescue injection using the Ogluo
- HF7 and HF5: All participants (15/15 and 75/75, 100%) performed a successful rescue and injected glucagon into the subcutaneous tissue at the labelled injection site.

Some of the Human Factors Studies for Ogluo also included untrained adolescent users (as young as 12 years old) which were able to successfully use Ogluo to carry out the full rescue injection procedure during an emergency use context.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The objective of the clinical development programme was to evaluate glycaemic response of Ogluo compared to other glucagon products in adult patients; for paediatric patients the glycaemic response in itself was examined without a comparison to other products.

The clinical development programme of Ogluo included 7 clinical trials involving 62 healthy subjects in 1 phase 1 study (Study XSGP-101), and 300 adult and 31 paediatric subjects with T1D in 2 Phase 2 studies (Study XSGP-201 and Study XSGP-202) and 4 Phase 3 studies (XSGP-301, XSGP-303, and XSGP-304 in adults and the open-label study XSGP-302 in paediatric subjects 2-18 years old). The **3** controlled Phase 3 adult clinical studies used other injectable glucagon products as a comparator: the earlier studies XSGP-301 and XSGP-303 versus the US product Eli Lilly glucagon (=GEK) and the pivotal study XSGP-304, designed and conducted based on the recommendations of the EMA SA, versus the European product GlucaGen HypoKit (=HK).

There were also 7 human factors studies designed to mimic real-life emergency situations which tested a total of 5 user groups including first responders, trained and untrained users, adults and paediatric (adolescent) caregivers of people with diabetes.

However, no actual-use studies were performed yet to investigate the use of Ogluo in stressful real-life circumstances while these could have provided data about the effectiveness of Ogluo in a stressful setting which is not the case in the Human Factors studies submitted for Ogluo, which only mimic these kind of situations without the pressure on uninstructed caregivers caused by real-life stress.

There were no real dose-selection studies for Ogluo. For adults and adolescents, and for children 2≤6 years old the applicant simply used the doses of the reference products (GEK and HK) i.e. resp. 1 mg and 0.5 mg. However, for children 6≤12 years old and 25≤45 kg, the dose selection was not well justified and the proposed dose differs from the one for the reference products with higher cut-offs proposed for the 1 mg glucagon dose for Ogluo (age 12 years and body weight 45 kg) than for the EU product HK (6-8 years old and 25 kg). As recommended, the applicant revised the paediatric dosage including a weight cut-off at 25 kg, for transition to adult dose, 1 mg.

The pivotal study in adult study XSGP-304 was conducted to compare the efficacy and safety of Ogluo with the EU reference product HK for induced hypoglycaemia rescue in adults with T1DM. It was a Phase 3 multicentre, randomised, controlled, single-blind, 2-way crossover in 132 patients ages 19 to 72 years with T1DM, predominantly White. This study was called the 'European Phase 3 study' in the EMA SA documents although there was only 1 European study site i.e. Austria while there were 4 in the US. T. 35 European subjects were screened and 32 enrolled.

There was no placebo control group which is acceptable as the use of a placebo would not be ethical in hypoglycaemic patients. The crossover design of this study was considered valuable in order to decrease between-subject variability. The single dose approach is adequate as Ogluo is not intended to be used regularly but only as rescue medication. The washout-period of minimum 7 days (up to 28 days) between the 2 treatment administrations is largely sufficient to prevent a carry-over taking into account the quite short half-life of glucagon. Several issues that have been identified with regard to study conduct with potential impact on study results regarding blinding and protocol amendments as well as inconsistencies between documents regarding batch numbers, inclusion/exclusion criteria and protocol versions have been clarified by the applicant.

In addition, an Errata memorandum to the clinical study report XSGP-304 including correct numbering of the country-specific changes has been provided.

The primary endpoint was an alternate combined endpoint (PGR) as defined by either a plasma glucose concentration ≥ 70 mg/dL (≥ 3.88 mmol/L = PGR1) OR an increase in plasma glucose concentration ≥ 20 mg/dL (≥ 1.11 mmol/L = PGR2) within 30 minutes of study drug injection.

Hypoglycaemia was induced through an insulin induction procedure to a target glucose level of < 54 mg/dL (3.0 mmol/L). However, for ethical/safety reasons, study glucagon was not administered if the PG was < 42 mg/dL which means that the effect of Ogluo in more severe hypoglycaemia seen in clinical practice leading to an altered mental and/or physical status requiring assistance was not examined. For this, the CHMP recommended to perform an actual-use study. The actual-use study will provide data in T2DM patients which were not included and in patient types that were excluded in the clinical studies, and in elderly patients. A detailed plan of an actual-use post marketing study will include these particular patient populations, and study is included in the RMP.

The SmPC warning regarding insulinoma has been included in the SmPC in line with another glucagon containing product as considered more informative.

Although some of the secondary endpoints take both time points into account ('from decision to dose' and 'from administered dose'), in line with the EMA SA, the objective endpoints regarding positive PGR are only foreseen for the time-point 'post-dose' but not 'from decision to dose' and there were some comments about the use of symptomatic scores (see further).

Another study in **adults study XSGP-301** was conducted (before study XSGP-304) to determine the failure rate of Ogluo 1 mg relative to GEK 1 mg in adults with T1DM. It was a Phase 3 non-inferiority, randomised, double-blind, 2-way crossover efficacy and safety trial involving 80 adult subjects with T1D ages 18 to 75 years, predominantly White.

Another study in **adults study XSGP-303** was conducted (before study XSGP-304) to compare efficacy and safety of Ogluo 1 mg with GEK 1 mg in adults with T1DM. It was a Phase 3 non-inferiority, randomised, single-blind, 2-way crossover comparative efficacy and safety study in 81 adult subjects with T1D ages 18 to 74, predominantly White.

Although the treatment administration procedure (including an insulin induction procedure to induce hypoglycaemia) in studies XSGP-301 and XSGP-303 was quite similar to the one in study XSGP-304, there were also some differences including another comparator (GEK vs HK), a different target plasma glucose concentration after the insulin induction procedure at which administration of glucagon could occur (50 mg/dL vs 54 mg/dL) and the fact that insulin dose was stopped immediately once the target plasma glucose concentration was achieved (vs continuation for 5 minutes).

The applicant used the data from study XSGP-301 to implement an insulin dose adjustment algorithm in study XSGP-303 in order to avoid achieving nadirs < 40 mg/dL like those observed in study XSGP-301. Consequently, like in study XSGP-304, the use of Ogluo was not examined in more severe hypoglycaemia in study XSGP-303 (see above).

The primary endpoint in XSGP-301 and XSGP-303 was an increase in plasma glucose concentration from below 50.0 mg/dL to greater than 70.0 mg/dL within 30 minutes after receiving glucagon.

The combined primary endpoint in study XSGP-304, was not a pre-specified endpoint in study XSGP-301 but it was added ad-hoc before un-blinding as an alternate combined glucose-response endpoint i.e. an increase

in plasma glucose concentration from below 50.0 mg/dL to > 70.0 mg/dL or increased > 20 mg/dL within 30 minutes after receiving glucagon. This was also analysed as an alternate combined endpoint in study XSGP-303 for comparison with study XSGP-304, and was also a secondary endpoint in study XSGP-303. In study XSGP-303 (not in XSGP-301), like in study XSGP-304, some secondary endpoints also used the timepoint 'from decision to dose' (although again for symptomatic endpoints, not for objective endpoints related to plasma glucose) and a time-to-event analysis; the total preparation time was also measured. Both studies XSGP-301 and XSGP-303 also used symptomatic relief scores as secondary endpoints for which the same comments as listed for study XSGP-304 were applicable and resolved.

In study XSGP-301, an issue has been identified with regard to study conduct at the level of major protocol violations with potential impact on study results. As such, based on the test result difference for Dht failure scores, Ogluo did not satisfy the non-inferiority criterion for the pre-specified PP population, defined in the protocol based on the initial definitions of the major protocol violations, but did satisfy the non-inferiority criterion for the revised PP population, defined after the unblinding and additional adjudication and subsequent modification of the major protocol violations. However, taking into account that the result for the alternate combined glucose-response endpoint did satisfy the non-inferiority criterion for both pre-specified PP- and revised PP population, the failure to achieve a steady state hypoglycaemia for a third of the procedures, and the study XSGP-301 is only supportive for the assessment, this issue was not pursued.

Overall in the **3 adult Phase 3 studies**, there are only very limited data in elderly patients 65 years and above (21 of which 6 in the pivotal study), and even none in elderly 75 years and above.

A last study, **study XSGP-302**, in the paediatric population was conducted to evaluate the glucose response of Ogluo (Glucagon Injection) in paediatric patients with T1DM. It was a Phase 3, open-label, sequential treatment efficacy and safety study in 31 paediatric subjects with T1DM ages 2 to 18 years, predominantly White.

For ethical reasons, subjects were administered insulin to induce a low-normal glycaemic state (blood glucose < 80 mg/dL), instead of the hypoglycaemic state in the adult studies, and then received an age-appropriate dose of Ogluo in a CRC.

During the treatment phase, subjects ages 2 to <12 years completed a single treatment visit and received Ogluo 0.5 mg. Subjects ages 12 to <18 years received Ogluo 1 mg at an initial treatment visit and were administered Ogluo 0.5 mg at a second visit occurring 1 to 4 weeks later.

The study had some limitations as the number of patients per age group was low with only 7 in the 2≤6, 13 in the 6≤12 and 11 patients in the 12≤18 years old group, there was no comparison versus a reference product and no hypoglycaemia was induced in the paediatric population (which however can be accepted as a surrogate for the treatment of severe hypoglycaemia).

According to the applicant, results from study XSGP-201 have been used through a weight-exposure model to propose a transition to the adult dose of Ogluo at 40 to 45 kg, corresponding to the average weight at approximately 12 years of age but these data have not been provided nor discussed (see also PK section), the doses used in this study were age-based, not weight based.

As recommended, the applicant revised the paediatric dosage including a weight cut-off at 25 kg, for transition to adult dose.

Human Factors Studies

The Human Factors Studies submitted for Ogluo only mimic emergency situations without the pressure on uninstructed caregivers caused by real-life stress (as would be the case in actual-use studies).

Almost all participants in all Human Factors Studies were able to successfully administer Ogluo, in 1 small comparative study also in a much higher number of patients than for the comparator GEK (88% vs 31%).

Some of the Human Factors Studies for Ogluo also included untrained adolescent users (as young as 12 years old) which were able to successfully use Ogluo to carry out the full rescue injection procedure during an emergency use context.

Efficacy data and additional analyses

Adult Pivotal Phase 3 study XSGP-304

In this study, 99% (mITT) and 100% (PP) of Ogluo subjects achieved the primary endpoint (plasma glucose >70 mg/dL or rise \geq 20 mg/dL within 30 minutes of dosing), comparable to treatment with HK subjects in which 100% of subjects achieved this. This study demonstrated that Ogluo was non-inferior to HK for achieving the primary endpoint.

However, the mean time to achieve positive PGR as of administration of study drug was 4-4.5 minutes longer for Ogluo versus HK. Moreover, more HK subjects achieved positive PGR earlier than Ogluo: at 15 minutes post-dose, all HK subjects had achieved a positive PGR while still 28 patients (22.0%) in the mITT and 26 patients (20.9%) in the PP Ogluo group had not; at 20 minutes post-dose, still 10 patients (7.9%) in the mITT and 7 patients (6.1%) in the PP Ogluo group had not; at 25 minutes post-dose, still 5 (3.9%) patients in the mITT and 4 patients (2.6%) in the PP Ogluo group had not; at 30 minutes post-dose, still 1 (3.9%) patient in the mITT Ogluo group had not (all achieved this in the PP group); it is only at 35 minutes post-dose, that all Ogluo subjects achieved this.

The applicant considers this not clinically relevant as they were all still within the predefined 30 minutes after dosing, and it will be shortened in clinical practice thanks to the about 1 minute shorter time to prepare study drug. In addition, when measuring as of the decision to dose (instead of as of administration of study drug) and using symptom relief scores, several results were similar or even better for Ogluo versus HK, and analysis of positive treatment response (successful plasma glucose recovery or successful symptom recovery) by treatment did meet the predefined criteria for non-inferiority in all analysed populations.

The 4-4.5 minutes longer time to achieve positive PGR have been properly reflected in the SmPC. The gain considering that no reconstitution is necessary is estimated to be only 1 minute which would mean that there still is a delay of 3 to 3.5 minutes. Moreover, as the time to recovery of 14.8 minutes (versus 10.4 minutes for HK) is only a mean value (with important variability as the standard deviations were respectively 5.4 and 1.9 minutes), it was useful to look at the time interval of the individual patients through the responders per time interval for Ogluo: 18 (14.2%) patients took 15 to 20 minutes, 5 patients (3.9%) took 20 to 25 minutes, 4 patients (3.1%) took 25 to 30 minutes and 1 patient (0.8%) took 30 to 35 minutes to recover versus maximum 15 minutes to recover for HK patients (and 88.6% took only up to 10 minutes, which was the case for merely 37% of Ogluo patients).

This means that for many patients (>20%) there is a delay of 5 to 20 minutes versus HK which should be reflected in the SmPC. In this context the CHMP proposed to make a SmPC amendment in section 4.4:

Delay in response

Please take into account that in +/- 15% of patients a delay in glucose response of more than 20 minutes was observed in the pivotal trial.

The SmPC of the reference product mentions specific recommendations regarding the onset of action which should normally be within 10 minutes and the fact that, if this is not the case, IV glucose should be given. As requested, specific recommendation have been proposed for Ogluo SmPC specifying that the onset of action should normally be within 15 minutes and the fact that, if it is not the case an additional dose of Ogluo from a new device may be administered while waiting for emergency assistance.

Adult Phase 3 studies XSGP-301 and XSGP-303

For the pooled data from studies XSGP-301 and XSGP-303, 97.4% of Ogluo subjects (mIIT) and 98% (PP) achieved the primary endpoint (plasma glucose level >70 mg/dL within 30 minutes of dosing), comparable to treatment with GEK in which 100% of subjects achieved this.

However, when looking at the results of study XSGP-301 separately, the criterion for non-inferiority based on the primary endpoint versus GEK was not achieved which was explained by the applicant by the fact that 4 patients in the Ogluo group had a nadir below 40 mg/dL and an average time of 43.2 minutes. Nevertheless, these patients approach the setting of severe hypoglycaemia (which is the indication of Ogluo) better than the other studies in which patients with a plasma glucose <42 mg/dL could not be treated with glucagon, and they appear to have an additional risk as they require a long time to achieve a plasma glucose >70 mg/dL.

The data from studies XSGP-301 and XSGP-303 were analysed according to the primary endpoint of study 304 using an alternate combined endpoint (plasma glucose >70 mg/dL or increase ≥ 20 mg/dL within 30 minutes of dosing) for which the non-inferiority margin was achieved in both studies.

However, like in study XSGP-304, also in study XSGP-303, the mean time to achieve plasma glucose recovery (>70 mg/dL) or increase ≥ 20 mg/dL was longer for Ogluo than for GEK: about 3.5 minutes for time from administration (resp. 12.2 minutes versus 8.6 minutes and 11.4 minutes versus 8.0 minutes) and about 2.5 minutes for time from decision to dose (resp. 11.4 minutes versus 8.0 minutes and 12.5 minutes versus 10.1 minutes). Moreover, also like in study XSGP-304, more GEK patients (ITT) achieved plasma glucose >70 mg/dL earlier than Ogluo patients, both for time from drug administration and for time from decision to dose: at 15 minutes post-dose and 20 minutes from decision to dose, all GEK patients (100%) achieved this, while still resp. 16 patients (21.1%) and 4 patients (5.3%) in the Ogluo group had not; it is only at 25 minutes post-dose and from decision to dose, that all Ogluo patients had achieved this.

Nonetheless, like for study XSGP-304, this is not considered clinically relevant by the applicant as the mean values to achieve this for Ogluo were all within 15 minutes, the drug preparation time was 70 seconds shorter (27.3 vs. 97.2 sec) for Ogluo and the time to achieve relief of symptoms was overall similar for Ogluo as for GEK.

In study XSGP-301, there was a modification in the PP population used for the primary efficacy analysis after completion of the SAP and adjudication/unblinding by the sponsor and the monitor, by non-considering as a major protocol violation any bolus within 20 minutes prior to administration of the study drug, which had an impact on the primary efficacy analysis in the pre-specified PP population, but no impact on the alternate combined endpoint efficacy analysis conducted in the pre-specified PP population.

Assessment of paediatric data on clinical efficacy

Paediatric Phase 3 study 302

In each age group, statistically significant ($p < 0.001$) increases from Baseline in mean plasma glucose were observed at 30 minutes post-dose. All 30 evaluable patients achieved a target glucose increase of at least 25 mg/dL and the mean time to achieve plasma glucose increase ≥ 25 mg/dL from baseline was 19 minutes.

However, although the increase from Baseline in mean plasma glucose at 30 minutes post-dose was statistically significant in the age group $12 \leq 18$ years, there were some uncertainties due to the unexpected observations versus the other age groups (even though the administered dose of 1 mg was the double of the 0.5 mg used in the other age groups) regarding the following parameters: lower glucose increase from baseline, lower number of patients achieving a glucose increase ≥ 25 mg/dL within 30 minutes, higher mean time to plasma glucose increase ≥ 25 mg/dL from baseline, lower glucose AUC(0-90) and a glucose response that did not vary greatly after receiving the 0.5 mg dose compared to the 1 mg dose of Ogluo. This was not due to outliers and explained by subjects until 12 years who received more glucagon by weight-based exposure and the administration of excess residual insulin from the insulin pumps during the 1 mg treatment visits, related to the individual study procedures.

2.5.4. Conclusions on the clinical efficacy

The efficacy of injectable glucagon in the rescue treatment of severe hypoglycaemia is well established. The applicant has developed Ogluo as a ready-to-use SC glucagon product with the purpose of eliminating the time and stress that accompanies reconstitution and withdrawal of the solution before administration with the current injectable glucagon products.

No actual-use studies have been performed yet to investigate the effectiveness of Ogluo in a setting with the pressure on uninstructed caregivers caused by real-life stress and a detailed plan is performed for the post-marketing setting.

There are no real dose-response studies for Ogluo, and there were some uncertainties about the appropriate dose for children 6-12 years old and $25 \leq 45$ kg (0.5 mg or 1 mg), as the dose selection was not well justified and the proposed dose differs from the one for the reference product regarding the cut-offs proposed for Ogluo (age 12 years and body weight 45 kg) for the 1 mg glucagon dose which are higher than for Glucagen HypoKit (6-8 years old and 25 kg). As recommended, the applicant revised the paediatric dosage including a weight cut-off at 25 kg, for transition to adult dose, 1 mg.

Overall, the Phase 3 adult studies demonstrated that Ogluo treated severe hypoglycaemia within 30 minutes post-dose in a manner that was non-inferior to the comparators, GEK and HK.

However, in the pivotal study versus the EU reference product, Ogluo required about 4 to 4.5 minutes longer to achieve plasma glucose recovery. This should be reflected in the SmPC though the applicant considered this of limited relevance as there is the shorter preparation time for Ogluo and the fact that several results were similar or even better for Ogluo versus HK when measuring 'from decision to dose' and using symptom relief scores, and that analysis of positive treatment response did meet the predefined criteria for non-inferiority.

The gain due to the fact that no reconstitution is necessary is estimated to be only 1 minute so there still is a mean delay of 3 to 3.5 minutes.

Therefore the following was agreed to be included in the SmPC:

Section 4.4

“– Recovery Time

Please take into account that approximately 15% of patients achieved glucose recovery after 20 minutes or more in the pivotal trial.”

- Section 4.2

– “The patient will normally respond within 15 minutes. When the patient has responded to the treatment, give oral carbohydrate to restore the liver glycogen and prevent relapse of hypoglycaemia. If the patient does not respond within 15 minutes, an additional dose of Ogluo from a new device may be administered while waiting for emergency assistance. It is recommended that the patients are prescribed two Ogluo devices.”.

2.6. Clinical safety

Safety assessments presented are based on available data from all study participants who were treated with at least 1 dose of Ogluo or the active comparator, Lilly Glucagon or GlucaGen HypoKit. The applicant performed an integrated safety data analysis in the relevant population for two study pools: Adult Subjects with T1D Pool from studies XSGP-202, XSGP-301 and XSGP-303 and Phase 3 Pool from studies XSGP-301 and XSGP-303. According to the applicant, studies XSGP-302 and XSGP-304 were analysed separately due to their specific characteristics.

Patient exposure

Ogluo is indicated for the treatment of severe hypoglycaemia in patients with diabetes ages 2 years and above. However, safety assessment is only available in patients with T1D.

The 3 well-controlled Phase 3 studies in adult subjects (Studies XSGP-301, XSGP-303, XSGP-304), and 1 open-label Phase 3 study in paediatric subjects (Study XSGP-302) are main topic for the safety assessment. All studies except Study XSGP-302 were full crossover studies, while in Study XSGP-302, crossover was limited to subjects in the age 12 to < 18 years category.

The number of subjects receiving each treatment (with the exception of paediatric subjects < 12 years of age) does represent administration of Ogluo or comparator, Ogluo 1 mg or 0.5 mg, or Ogluo Configuration A or Configuration B, which is accepted.

Table 37 Patient exposure

	Patients enrolled	Patients exposed	Patients exposed to the proposed dose range	Patients with long term* safety data
Placebo-controlled	N/A	N/A	N/A	N/A
Active –controlled				
XSGP-301	80	77	77	0
XSGP-303	81	75	75	0
XSGP-304	132	123	123	0

Open studies					
XSGP-202		7	7	7	0
XSGP-302		32	31	31	0
Post marketing	N/A	N/A	N/A	N/A	
Compassionate use	N/A	N/A	N/A	N/A	

* In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.

A total of 362 adult subjects received at least 1 dose of Ogluo 1 mg, including 300 adult subjects with T1D (Studies XSGP-202, -301, -303, and -304), and 62 healthy adult subjects (Studies XSGP-101 and -201) in single-dose studies. In addition, a total of 31 paediatric subjects with T1D received at least 1 dose of Ogluo 0.5 mg, 11 of whom also received at least 1 dose of Ogluo 1 mg (Study XSGP-302) in a crossover fashion.

Exposure to study drug in the Ogluo development programme is consistent with real-world use of glucagon, where the estimated incidence of hypoglycaemic events requiring glucagon rescue treatment is 1.1 events per year for patients with type 1 diabetes of <5 years duration. This is in line with daily practical life.

Regarding exposure in children, the safety database by age group is limited: 7 patients in the 2 to <6 years age group and 13 patients in the 6 to <12 years age group exposed to 0.5 mg dose and 11 patients in the 12 to <18 years age group exposed to 0.5 mg dose and 1.0 mg dose.

Ogluo is intended as rescue medication in severe hypoglycaemic episodes. However, hypoglycaemia is a common adverse drug reaction in diabetic patients treated with insulin and sulfonylureas, leading to repeated administration of glucagon as rescue medication. Due to the clinical studies design, no information on exposure after repeated administration is available and would have been useful. The EMA SAWP advised the applicant to conduct a post-marketing actual-use study in which patients could receive more than one Ogluo injection, and which could provide immunogenicity information. The applicant provided a plan for the post-authorisation Actual Use Study to evaluate the effectiveness, safety, and ease of use of Xeris glucagon to treat severe hypoglycaemic events in children, adolescents, and adults with diabetes, in a real world setting. Included patient populations and the design are adequately addressed.

However, as pointed out in the questions regarding statistics above, it seems that a significant amount of patients recover after approx. 20 minutes. The applicant stated that they can't identify in advance the patients who will response late. Therefore, it was considered that the post-marketing phase III trial will not be informative to further clarify.

Adverse events

Phase 3 Adult Subjects (Pooled Studies XSGP-301 and XSGP-303, and Study XSGP-304)

The overall incidence of TEAEs was higher across the Ogluo groups versus comparator groups in the pooled Phase 3 Studies (46.1% Ogluo vs 33.1% GEK) and in Study XSGP-304 (52.8% Ogluo vs 46.3% HK) The higher incidence was partially driven by the incidences of nausea and vomiting, both known adverse class effects of glucagon. The insulin induction procedure itself likely was a cause of nausea: subjects fasted from midnight

before the insulin induction procedure to the following morning and continued to fast for 4 to 6 hours during and after the procedure. Furthermore, in Study XSGP-304, the insulin induction *procedure was revised from previous studies to include a longer period of insulin infusion. Thus, subjects in the studies were in an unbalanced metabolic state by the time the glucagon was administered; the resultant incidence rates of nausea and vomiting are therefore not unexpected.*

All the Phase 3 Adult Studies used the same commercial formulation and batch of Ogluo; thus, there was consistency of the drug product across all studies.

Nearly all TEAEs during the Phase 3 studies were determined by the investigator to be of mild or moderate intensity. One (0.8%) subject treated with Ogluo, 1 (0.6%) subject treated with GEK, and 1 (0.8%) subject treated with HK experienced a TEAE judged to be of severe intensity.

The majority of events that occurred in both the pooled Phase 3 studies and Study XSGP-304 were deemed related to the study drug (T-S1). These events primarily comprised nausea, vomiting, and headache, and each of these events is a known adverse effect of glucagon.

No serious TEAEs occurred following treatment with Ogluo in Phase 3 studies; although there was 1 SAE related to Ogluo (vasovagal reaction) in Study XSGP-202. One (0.6%) subject experienced a serious TEAE (hyperinsulinaemic hypoglycaemia) following treatment with GEK in Study XSGP-301. In general, TEAEs related to Ogluo were mild to moderate in severity, required no additional medical intervention, and were self-limited (Table below).

Table 38 Overview of TEAEs Across Pooled Phase 3 Adult Studies XSGP-301 and XSGP-303, and Phase 3 Adult Study XSGP-304 (Safety Population)

	Phase 3 Adult Pooled Studies (Studies 301 and 303)		Phase 3 Adult Study 304	
	Gvoke 1 mg (N=154)	GEK 1 mg (N=157)	Gvoke 1 mg (N=127)	HK 1 mg (N=123)
	n (%)	n (%)	n (%)	n (%)
Number of subjects with AE	71 (46.1)	53 (33.8)	69 (54.3)	60 (48.8)
Number of subjects with TEAE	71 (46.1)	52 (33.1)	67 (52.8)	57 (46.3)
Subjects who had a TEAE that was:				
Mild	60 (39.0)	40 (25.5)	56 (44.1)	50 (40.7)
Moderate	18 (11.7)	15 (9.6)	15 (11.8)	10 (8.1)
Severe	0	1 (0.6)	1 (0.8)	1 (0.8)
Number of subjects who had a TEAE related to study drug	60 (39.0)	45 (28.7)	58 (45.7)	55 (44.7)
Number of subjects who had a treatment-emergent SAE	0	1 (0.6)	0	0
Number of subjects who had SAE related to study drug	0	0	0	0
Number of subjects who had SAE leading to death	0	0	0	0
Number of subjects who had TEAE leading to study discontinuation	0	0	2 (1.6)	0

Headache was a commonly reported-related TEAE in adult subjects treated with either the Ogluo or the Lilly Glucagon or the GlucaGen HypoKit, respectively. As headache is a side effect not mentioned in the SmPC of GlucaGen HypoKit. However, it is included by the applicant in the tabulated summary of adverse reactions of Ogluo SmPC.

Phase 3 Paediatric Subjects

In the Phase 3 Paediatric Subjects, the incidence of subjects who reported TEAEs was similar in subjects age 2 to < 6 years and those age 12 to < 18 years (71.4% and 72.7%, respectively), and higher in the 6 to < 12 years age group (92.3%). Fewer TEAEs were reported in subjects age 12 to < 18 years when they received Ogluo 0.5 mg (54.5%) compared with when these same subjects received Ogluo 1 mg (72.7%). None of the TEAEs reported were considered severe, and there were no deaths, SAEs, or TEAEs leading to discontinuation.

Among the 31 Ogluo injections in paediatric subjects, 42 TEAEs occurred, for a rate of 1.35 TEAEs per injection; 83.3% (35/42) were mild, 16.7% (7/42) were moderate and 0% (0/42) severe (see table below).

Table 39 Treatment-Emergent Adverse Events Occurring in \geq 2 Ogluo-Treated Subjects in the Phase 3 Paediatric Subjects Pool (Study XSGP-302)

System Organ Class Preferred Term	Gvoke 0.5 mg						Gvoke 1 mg			
	2 to < 6 years		6 to <12 years		12 to <18 years		All		12 to < 18 years	
	Subject N=7 n (%)	No. of Events	Subject N=13 n (%)	No. of Events	Subject N=11 n (%)	No. of Events	Subject N=31 n (%)	No. of Events	Subject N=11 n (%)	No. of Events
Gastrointestinal disorders	3 (42.9)	4	7 (53.8)	11	4 (36.4)	4	14 (45.2)	19	6 (54.5)	6
Nausea	3 (42.9)	3	7 (53.8)	7	4 (36.4)	4	14 (45.2)	14	4 (36.4)	4
Vomiting	1 (14.3)	1	3 (23.1)	3	0	0	4 (12.9)	4	2 (18.2)	2
Metabolism and nutrition disorders	2 (28.6)	3	8 (61.5)	9	3 (27.3)	3	13 (41.9)	15	3 (27.3)	3
Hyperglycaemia	1 (14.3)	1	1 (7.7)	1	0	0	2 (6.5)	2	0	0
Hypoglycaemia	2 (28.6)	2	7 (53.8)	8	3 (27.3)	3	12 (38.7)	13	3 (27.3)	3

Common Adverse Events

Phase 3 Adult Subjects (Pooled Studies XSGP-301 and XSGP-303, and Study XSGP-304).

The most commonly occurring TEAEs in adult studies were nausea (29.9%, Ogluo vs 22.9%, GEK [pooled studies] and 42.5%, Ogluo vs 44.7%, HK [Study XSGP-304]); vomiting (16.2% vs 9.6%, pooled studies and 12.6% vs 13.8%, Study XSGP-304); and headache (5.2% vs 3.8%, pooled studies and 5.5% vs 7.3%, Study XSGP-304) (See table below). In all clinical studies of Ogluo, events of nausea and vomiting that occurred during or after the insulin induction procedure were treated primarily with ondansetron. All of these events were transient, and all resolved fully.

There were 2 incidences of tachycardia (2 [1.6%]) and 1 incidence of supraventricular extrasystoles (1 [0.8%]) after treatment with Ogluo 1 mg. However, glucagon is not known as arrhythmogenic, and they were likely a result of the insulin induction.

Both events of tachycardia were judged as mild and related to study drug; both events resolved spontaneously. The event of supraventricular extrasystoles was judged as mild and not related to study drug; it resolved spontaneously. The subject with supraventricular extrasystoles had a medical history of pulmonary valve insufficiency.

Overall, there were no remarkable differences in the incidence of TEAEs between Ogluo-treated subjects and GEK-treated subjects in the Adult T1D Subjects pool. Overall, the majority of events were judged as mild or moderate, and all events were self-limiting, and resolved fully by the end of the studies. When treatments were compared on a gross level, there were no apparent and significant differences in incidence rates for TEAEs, no apparent data inconsistencies, no apparent safety signals.

Table 40 Analysis of TEAEs Occurring in ≥ 2 Subjects Across Pooled Phase 3 Adult Studies XSGP-301 and XSGP-303, and Phase 3 Adult Study XSGP-304 (Safety Population)

	Phase 3 Adult Pooled Studies (Studies 301 and 303)		Phase 3 Adult Study 304	
	Gvoke 1 mg (N=154)	GEK 1 mg (N=157)	Gvoke 1 mg (N=127)	HK 1 mg (N=123)
	n (%)	n (%)	n (%)	n (%)
Number of subjects with at least 1 TEAE	71 (46.1)	52 (33.1)	67 (52.8)	57 (46.3)
Gastrointestinal disorders	58 (37.7)	45 (28.7)	57 (44.9)	55 (44.7)
Nausea	46 (29.9)	36 (22.9)	54 (42.5)	55 (44.7)
Vomiting	25 (16.2)	15 (9.6)	16 (12.6)	17 (13.8)
Diarrhoea	2 (1.3)	1 (0.6)	2 (1.6)	1 (0.8)
Nervous system disorders	11 (7.1)	7 (4.5)	8 (6.3)	11 (8.9)
Headache	8 (5.2)	6 (3.8)	7 (5.5)	9 (7.3)
Dizziness	2 (1.3)	1 (0.6)	2 (1.6)	2 (1.6)
General disorders and administration site conditions	4 (2.6)	4 (2.5)	3 (2.4)	0
Injection site pain	2 (1.3)	1 (0.6)	2 (1.6)	0
Infections and infestations	5 (3.2)	0	2 (1.6)	2 (1.6)
Nasopharyngitis	0	0	2 (1.6)	1 (0.8)
Upper respiratory tract infection	2 (1.3)	0	0	0
Cardiac disorders	2 (1.3)	0	3 (2.4)	0
Tachycardia	1 (0.6)	0	2 (1.6)	0
Metabolism and nutrition disorders	1 (0.6)	1 (0.6)	2 (1.6)	0
Hypoglycaemia	0	0	2 (1.6)	0

Phase 3 Paediatric Subjects

Nausea was reported at a slightly higher rate in younger paediatric subjects (7/13 [53.8%] in 6 to <12-year-old group) compared with older paediatric subjects (36.4% at both the 0.5 and 1 mg dose levels for 12 to <18-year-old group). Vomiting was reported in younger paediatric subjects (3/13 [23.1%] in 6 to <12-year-old group) and in the older group that received 1 mg Ogluo (2/11 [18.2%] in 12 to <18-year-old group).

Hypoglycaemia was more reported in the paediatric population compared to the adults. There was a total of 10 events of hypoglycaemia in the 2 to <12 years age group and 3 events of hypoglycaemia in the 12 to <18 years age group; hypoglycaemia was judged to be related to the insulin induction procedure of the study, and the episodes were recorded as adverse events by the investigator. However, 2 cases of moderate hypoglycaemia were late-onset events that occurred after an initial rise in plasma glucose, occurring at 120 or 150 minutes after administration of Ogluo. All cases of hypoglycaemia resolved without sequelae.

The applicant was requested to explain the higher amount of hypoglycaemic events in paediatric patients compared to adults which is unexpected as in children, no hypoglycaemia was induced, compared to adults where hypoglycaemia < 54 mg/dL was induced. The applicant referred to the artificial and no real-world trial scenarios where paediatric subjects would immediately ingest fast-acting oral carbohydrates after initial plasma glucose recovery from glucagon, which was not allowed during the trial, because of the need to monitor the sole effects of the study drug upon blood glucose response.

The frequency of adverse events were not equally reported in the different age groups in the paediatric population.

The applicant explained that different rates of TEAEs across age-groups could be related to the "higher glucagon exposure in younger age groups". However, in the Phase 3 Paediatric Subjects, after administration

of Ogluo 0.5 mg dose the overall incidence of related TEAEs was slightly higher for subjects 6 to < 12 years (76.9%) than subjects 2 to < 6 years (57.1%) or subjects 12 to < 18 years (36.4%), although the exposure appeared to be higher in subjects aged 2 to < 6 years.

It is agreed that that none of the TEAEs reported were considered severe, and that the number of children included in the Phase 3 Paediatric trial is small.

In section 4.8 of the Ogluo SmPC submitted in response to Day 120 LoQs, the applicant proposed to add the following under "Paediatric population":

"Paediatric population

The most frequently reported adverse reactions are nausea (45.2%), vomiting (12.9%), and hyperglycaemia (6.5%). Hypoglycaemia (38.7%) was observed in clinical trials but was not considered drug-related. Based on data from a clinical trial, the frequency, type and severity of adverse reactions observed in children are similar as in adults."

However, the applicant's proposal for section 4.8 of the Ogluo SmPC reflects the overall rates of TEAEs occurring in Phase 3 Paediatric for subjects treated with 0.5 mg dose and does not reflect the different rates of TEAEs between the same age group (12 to <18 years) treated with 0.5 mg and 1 mg, respectively. Moreover, relevant for children ages 12 to <18 years are drug-related TEAEs reported after administration of 1 mg dose of Ogluo as this is the dose proposed for this age group. As requested, in the responses submitted to Day 180 LoOIs, the applicant included in section 4.8 Paediatric population of the SmPC the most frequently reported drug-related TEAEs by the relevant dose for the respective age groups.

In general, a high number of patients reported at least 1 of (T)SAE's, both in children and adults. Patients with DT2 are not represented in the trials, but would be included in the future actual-use study.

The overall incidence of TEAEs was higher across the Ogluo groups versus comparator groups in the pooled Phase 3 Studies (46.1% Ogluo vs 33.1% GEK) and in Study XSGP-304 (52.8% Ogluo vs 46.3% HK). The higher incidence was partially driven by the incidences of nausea and vomiting that are known as adverse class effects of glucagon. However, both Ogluo and the comparator are glucagon and both groups underwent the same insulin induction procedure. The applicant could not sufficiently clarify the difference.

Tolerability

Modified Draize Scale Scores

The Modified Draize Scale measured oedema and erythema at the injection site(s) during the Phase 3 studies. Both oedema and erythema scores range from 0 (no oedema/erythema) to 4 (severe oedema/erythema). The Modified Draize Scale was measured by the investigator at 30, 90, and 180 minutes post-injection. Only those subjects with oedema/erythema at the 30-minute time point were evaluated at 180 minutes. Overall Draize Scale mean scores were low in all Phase 3 studies across both the Ogluo and comparator treatments (GEK and HK), and for the majority of subjects, oedema/erythema resolved by the 90-minute time point, and by the 180-minute time-point, all oedema/erythema had resolved.

Table 41 Oedema in Adult Phase 3 Type 1 Diabetic Subjects (Pooled Studies XSGP-301 and XSGP-303)

Time	Oedema	Gvoke N=154 n (%)	GEK N=157 n (%)
10 minutes	None	97 (63.0)	128 (81.5)
	Very slight	31 (20.1)	20 (12.7)
	Well defined	21 (13.6)	8 (5.1)
	Moderate	4 (2.6)	0
	Severe	1 (0.6)	0
30 minutes	None	78 (50.6)	134 (85.4)
	Very slight	46 (29.9)	15 (9.6)
	Well defined	20 (13.0)	7 (4.5)
	Moderate	8 (5.2)	0
	Severe	2 (1.3)	0
End of Visit ^a	None	78 (50.6)	58 (36.9)
	Very slight	11 (7.1)	2 (1.3)
	Well defined	1 (0.6)	1 (0.6)
	Moderate	0 (0.0)	0
	Severe	2 (1.3)	0

Note: Subjects with missing value assume to have none. For subjects with multiple values for the same treatment and time point, maximum value is used.

^a Subjects measured at 180 minutes, 240 minutes, or prior to exiting clinic.

Injection site oedema was evaluated in subjects administered study drug to the abdomen around the umbilicus, outer arm, and outer thigh. Overall, oedema was self-limited, and a majority of subjects had complete resolution by the end of the treatment visit for all injection sites evaluated. Subjects who received study drug by abdominal injection tended to have less and milder oedema, with earlier onset and resolution than subjects who received study drug by injection to the outer arm or outer thigh. Although injection site oedema was self-limited with complete resolution, mostly oedema appeared earlier and more intensive in the Ogluo treatment groups. The applicant could not clarify this, but injection site oedema has been added as a common adverse reaction to the Ogluo SmPC.

In the Phase 3 Adult Study XSGP-304, at 30 minutes post dose, a higher percentage of subjects in the HK group had no oedema compared to subjects administered Ogluo (see Table below). However, at 90 and 180 minutes after administration of study drug, oedema scores were similar between the treatment groups. Additionally, at 90 minutes post-administration, most oedema had resolved in both groups.

Table 42 Summary of Local Tolerability - Draize Scale for Oedema (Safety Population) (Study XSGP-304)

Time Point	Category	Scale	Gvoke (N=127) n (%)	HK (N=123) n (%)
30 mins post dose	Oedema Formation	No oedema	44 (34.6)	74 (60.2)
		Very slight oedema, barely perceptible	21 (16.5)	4 (3.3)
		Well-defined oedema	8 (6.3)	0
		Moderate oedema, raised approx. 1mm	3 (2.4)	0
		Severe oedema, raised >1mm and beyond exposure area	0	0
90 mins post dose	Oedema Formation	No oedema	105 (82.7)	119 (96.7)
		Very slight oedema, barely perceptible	14 (11.0)	3 (2.4)
		Well-defined oedema	8 (6.3)	0
		Moderate oedema, raised approx. 1mm	0	0
		Severe oedema, raised >1mm and beyond exposure area	0	0
180 mins post dose	Oedema Formation	No oedema	118 (92.9)	119 (96.7)
		Very slight oedema, barely perceptible	7 (5.5)	1 (0.8)
		Well-defined oedema	0	0
		Moderate oedema, raised approx. 1mm	0	0
		Severe oedema, raised >1mm and beyond exposure area	0	0

In the Phase 3 Paediatric Subjects (XSGP-302) the overall incidences of oedema and erythema were low and given the small sample size, no review of oedema and erythema by injection site was performed (see Table below).

Table 43 Incidence of Oedema After Administration of Ogluo by Age Group (Paediatric Study XSGP-302)

Age Group	Gvoke Dose	Incidence of Oedema ^a n (%)		
		10 Minutes	30 Minutes	180 Minutes
2 to <6 years (N=7)	0.5 mg	3 (42.9)	3 (42.9)	1 (16.7)
6 to <12 years (N=13)	0.5 mg	9 (69.2)	8 (61.5)	4 (30.8)
12 to <18 years (N=11)	0.5 mg	6 (54.5)	5 (45.5)	1 (9.1)
12 to <18 years (N=11)	1 mg	5 (45.5)	5 (45.5)	1 (9.1)

^a Oedema formation is defined as Modified Draize Scale score for oedema >0.

Injection Site Discomfort Measured via VAS

Injection site discomfort was measured by the 100 mm Visual Analog Scale (VAS), on which 0 indicated no discomfort and 100 indicated the worst possible discomfort. The VAS was evaluated at 30, 90, and 180 minutes post injection.

Overall, mean VAS scores were low across all Phase 3 studies across both Ogluo and comparator treatments; few subjects overall described pain post-injection. The majority of subjects who reported discomfort after the injection had no discomfort by the 90-minute post-dose time point. The survey was to evaluate discomfort over time, and not many reports of discomfort were elevated to the status of an adverse events. In the Phase 3

Adult Pooled Studies XSGP-301 and XSGP-303, 2 (1.3%) subjects treated with Ogluo and 1 (0.6%) subject treated with GEK and in Adult Phase 3 Study XSGP-304, 2 (1.6%) subjects treated with Ogluo had TEAEs of injection site pain. Overall, by the end of the studies, VAS scores tended to normalise to baseline levels.

In particular for the Phase 3 Adult Study XSGP-304 at 30 minutes post dose, a higher percentage of subjects in the HK group had no erythema compared to subjects administered Ogluo 1 mg (see Table below). However, at 90 and 180 minutes after administration of study drug, erythema scores were similar. Additionally, at 90 minutes post-administration, most erythema had resolved in both groups.

Table 44 Summary of Local Tolerability – Draize Scale for Erythema (Safety Population) (Study XSGP-304)

Time Point	Category	Scale	Gvoke (N=127) n (%)	HK (N=123) n (%)
30 mins post dose	Erythema Formation	No erythema	37 (29.1)	56 (45.5)
		Very slight erythema, barely perceptible	24 (18.9)	20 (16.3)
		Well-defined erythema	14 (11.0)	1 (0.8)
		Moderate erythema, raised approx. 1mm	1 (0.8)	1 (0.8)
		Severe erythema, raised >1mm and beyond exposure area	0	0
90 mins post dose	Erythema Formation	No erythema	102 (80.3)	110 (89.4)
		Very slight erythema, barely perceptible	17 (13.4)	12 (9.8)
		Well-defined erythema	7 (5.5)	0
		Moderate erythema, raised approx. 1mm	1 (0.8)	0
		Severe erythema, raised >1mm and beyond exposure area	0	0
180 mins post dose	Erythema Formation	No erythema	113 (89.0)	114 (92.7)
		Very slight erythema, barely perceptible	10 (7.9)	6 (4.9)
		Well-defined erythema	2 (1.6)	0
		Moderate erythema, raised approx. 1mm	0	0
		Severe erythema, raised >1mm and beyond exposure area	0	0

In the Phase 3 Paediatric Subjects pool where subjects received SC administration of Ogluo 0.5 or 1 mg by the 180-minute at post-dose time point, there were no subjects with erythema among those who received Ogluo 0.5 mg, and only 1 (9.1%) subject with measurable erythema among those who received the 1 mg dose.

Injection Site Discomfort

Subjects in adult studies were evaluated using a visual analogue scale (VAS) that characterised injection site discomfort on a scale ranging from 0 mm (no pain) to 100 mm (maximum pain).

VAS scores are summarised for the Adult Subjects with T1D Pool in (see table below). Overall, VAS scores in the Adult Subjects with T1D Pool were low (indicating minimal pain) in subjects treated with both Ogluo 1 mg and GEK 1 mg, and decreased from the 10-minute post-dose time point to 30-minute and End of Visit time points.

Table 45 Visual Analog Scale Results for Adult Subjects with T1D Pool (Safety Population) (Pooled Studies XSGP-202, XSGP-301, and XSGP-303)

Postdose Time Point	Statistic	Gvoke 1 mg (N=161)	GEK 1 mg (N=157)
10 minutes	n	160	156
	Mean (SD)	19.4 (23.46)	6.1 (12.41)
	Median	9.0	0.0
	Min - Max	0 – 100	0 – 89
30 minutes	n	159	156
	Mean (SD)	9.7 (18.43)	1.3 (5.07)
	Median	0.0	0.0
	Min – Max	0 – 79	0 - 40
End of Visit (90, 180, or 240 minutes)	n	68	36
	Mean (SD)	5.3 (9.55)	1.6 (7.53)
	Median	0.0	0.0
	Min – Max	0 – 50	0 – 45

Note: Results are expressed in millimetres on a 100-mm VAS scale.

At each time point, injection site discomfort in the Phase 3 Adult Study XSGP-304 was reported by more subjects receiving Ogluo than by those receiving HK. However, overall the incidence of injection site discomfort was low. The level of injection site discomfort was highest at 30 minutes following Ogluo administration (38.5 on a 100-mm scale). By 90 and 180 minutes post-dose, mean injection site discomfort for subjects receiving Ogluo was 15.8 and 8.4 mm, respectively.

Injection site discomfort in paediatric subjects (Study XSGP-302) was measured by the 10-point Faces Pain Scale – Revised (FPS-R) at 10, 30, and 180-minutes post-injection. The majority of paediatric subjects reported injection site discomfort at 10 minutes post-dose, but this statistic diminished over time.

By 180 minutes post-dose, only 1 subject in each of the 2 to <6 years and 6 to <12 years groups reported discomfort, and in the 12 to <18 years group, no subjects reported discomfort.

In general: No new safety or tolerability concerns are raised. Injection site discomfort and oedema is initially higher in patients who received Ogluo. These tolerability discomfort resolves equally with the non Ogluo patients. Injection site oedema has been added as an undesirable effect in SmPC section 4.8 and in PL section 4.

For both treatment populations adults and children, nothing is known about the repetitive side effects after different administrations of Ogluo in patients with repetitive hypoglycaemic events. The applicant will examine this in the post-marketing setting e.g. and it is included in the actual-use study. An evaluation for usability and drug administration errors is incorporated into the study design, in order to help examine the potential risk of “Drug administration error leading to loss of drug benefit”.

The proposed Ogluo SmPC mentions that “based on data from clinical trials and post-marketing experience, the frequency, type and severity of adverse reactions observed in children are expected to be the same as in adults”. However, the results of study XSGP-302 showed that:

-Some TEAEs considered related to treatment with the Ogluo which have been reported in children are not mentioned in the proposed Ogluo SmPC in adults, e.g. hyperglycaemia, urticaria;

-There are different rates of TEAEs across age-groups, generally, with a higher incidence in younger subjects (<12 years old), compared with the 12 to <18-year-old group of subjects.

As requested, the applicant included in section 4.8 Paediatric population of the SmPC the most frequently reported drug-related TEAEs by the relevant dose for the respective age groups.

Serious adverse event/deaths/other significant events

There were no deaths among the Phase 3 adult subjects, or among the Phase 3 paediatric subjects.

The rates of SAE’s seen in all clinical trials are low; only two SAEs have been reported. A narrative description did not show a relationship with the study drug.

In the Phase 3 Adult Subjects, there was 1 (0.6%) subject who experienced an SAE of severe hyperinsulinaemic hypoglycaemia following treatment with GEK in Study XSGP-301. This event was judged as not related to study drug (it occurred the evening following discharge from the study site); the subject received rescue treatment (type of treatment unknown) from a friend, and was also treated by emergency medical technicians, and the subject recovered without hospitalisation (CSR XSGP-301).

There were no paediatric subjects who experienced an SAE during Study XSGP-302.

Laboratory findings

The safety assessment of Ogluo based upon an evaluation of changes from baseline in clinical haematology laboratory evaluations was performed in the Phase 3 clinical studies.

In Study XSGP-202, clinical haematology laboratory evaluations were not performed.

Phase 3 Adult Subjects with T1D: There were no clinically significant mean haematology laboratory evaluations noted.

Phase 3 Adult Study XSGP-304: There was no evidence of mean population changes during the study and, while a few individual values changed across the normal range boundaries, none were found to be of clinical significance. No clinically significant mean changes from baseline were observed across the measured haematology laboratory values.

In Study XSGP-302, clinical haematology laboratory evaluations were performed only for screening, without follow-up laboratory evaluations.

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.

Scheduled laboratory tests were performed in the adult phase 3 studies. In Study XSGP-302, clinical chemistry laboratory evaluations were performed only for screening, without follow-up laboratory evaluations. Except for mean fasting glucose elevation at baseline, which is expected for the patient population, there were no relevant abnormalities in the clinical chemistry or haematology evaluations.

In general, analysis of laboratory parameters in this patient population is not a major concern.

Vital signs

Vital signs, which included heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP), were monitored in the clinical studies conducted with G-Pen. Comparisons were performed at various time in the clinical studies (e.g., 30, 60, 90, 120, and 180/240 minutes post drug injection), and evaluation shifts from baseline/screening to post-treatment follow-up was performed.

Overall, there were no clinically significant changes in vital signs in the Adult T1D Subjects pool and in Phase 3 Adult Subjects with T1D pool.

In study XSGP-304, the majority of measurements for BP (diastolic and systolic), heart rate, weight, respiratory rate, and temperature were within normal limits. However, treatment-emergent high SBP was observed after Ogluo (maximum SBP of 172 mmHg 30 minutes post-dose and 176 mmHg 120 minutes post-dose). However, no trends were observed between treatment arms.

It is known that after glucagon administration increases in mean heart rate and blood pressure are possible. CSR XSGP-302 is presenting vital signs after administration of the Ogluo by age group and by treatment, according to the values presented it appears that SPB values (mean values approx. 60 mmHg) are lower than DPB (mean values ranging from approx. 100 to 115 mmHg) for all age groups and doses. As requested, the applicant provided the corrected values.

Safety in special populations

Elderly

In the studies across 154 Adult Phase 3 T1D Subjects who received at least 1 dose of Ogluo, 15 subjects were ≥ 65 years of age, and 139 subjects were < 65 years of age. The small number of subjects ≥ 65 years of age makes interpretation difficult. However, the incidence of TEAEs was generally similar between age groups and there were no apparent dose-related trends.

No safety data have been generated for patients with hepatic or renal impairment nor with hypertension; only limited data are available for patients > 65 years old and no data for patients > 75 years old.

However, the risk profile of Ogluo 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.

MedDRA Terms	Age <65 number (percentage)	Age 65-74 number (percentage)	Age 75-84 number (percentage)	Age 85+ number (percentage)
Total AEs	198 (55.0%)	6 (28.6%)	n/a	n/a
Serious AEs – Total	1 (0.3%)	0	n/a	n/a
- Fatal	0	0	n/a	n/a
- Hospitalization/prolong existing hospitalization	0	0	n/a	n/a
- Life-threatening	0	0	n/a	n/a
- Disability/incapacity	0	0	n/a	n/a
- Other (medically significant)	0	0	n/a	n/a
AE leading to drop-out	2 (0.6%)	0	n/a	n/a
Psychiatric disorders	0	0	n/a	n/a
Nervous system disorders	35 (9.7%)	0	n/a	n/a
Accidents and injuries	2 (0.6%)	0	n/a	n/a
Cardiac disorders	5 (1.4%)	0	n/a	n/a
Vascular disorders	1 (0.3%)	0	n/a	n/a
Cerebrovascular disorders	0	0	n/a	n/a
Infections and infestations	6 (1.7%)	1 (4.8%)	n/a	n/a
Anticholinergic syndrome	0	0	n/a	n/a
Quality of life decreased	n/a	n/a	n/a	n/a
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	9 (2.5%)	0	n/a	n/a
<other AE appearing more frequently in older patients>	n/a	n/a	n/a	n/a

n/a = not applicable

Paediatric subjects

In paediatric subjects who received Ogluo in Study XSGP-302, there were no age-related trends seen in adverse events or safety laboratory evaluations.

Other special populations

Sex subgroups were evaluated for male and female categories. Overall, the incidence of TEAEs was higher in female subjects than in male subjects. This may be attributed to differences in exposure due to lower body mass in female subjects.

Race subgroups included: African American, Asian, White, and Other (American Indian, Alaska native, native Hawaiian, or other Pacific Islander). Interpretation of the data was limited due to the small sample size of subjects with race other than White.

The incidence of other TEAEs was generally similar between body mass (≤ 80 kg, 81 to 109 kg, and ≥ 110 kg) subgroups.

Adult subgroups for diabetes duration included: < 10 years, 11-20 years, 21-30 years, 31-40 years, and > 41 years.

Paediatric subgroups for diabetes duration included: ≤ 3 years, and ≥ 4 years.

Overall, the incidence of TEAEs was generally similar across the disease duration subgroups.

Subjects with a disease duration of 0-10 years had the highest incidence of nausea (35.0%) versus a maximum of 32% in the other subgroups. Subjects with a disease duration of 21-30 years had the highest incidence of vomiting (23.1%) versus a maximum of 20.0% in the other subgroups. The incidence of other TEAEs was low across the subgroups.

Studies of the effects of extrinsic factors on the safety of Ogluo have not been conducted.

Glucagon does not cross the human placental barrier. The use of Ogluo 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).

Available data from case reports and a small number of observational studies with glucagon use in pregnant women over decades of use have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or foetal outcomes. Multiple small studies have demonstrated a lack of transfer of pancreatic glucagon across the human placental barrier during early gestation.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognised pregnancies is 2%-4% and 15%-20%, respectively.

The safety and effectiveness of Ogluo in paediatric patients younger than 2 years of age is not known.

There is no information available on the presence of glucagon in human or animal milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. 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).

However, glucagon is a peptide and would be expected to be broken down to its constituent amino acids in the infant's digestive tract, and is therefore, unlikely to cause harm to an exposed infant.

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 hypokalaemia. If the patient develops a dramatic increase in BP, non-selective alpha-adrenergic blockade has been shown to be effective in lowering BP for the short time that control would be needed.

There have been no reports of abuse of Ogluo in clinical investigations. There is no evidence of potential for abuse or misuse of Ogluo for illegal purposes. No studies to assess the abuse potential of Ogluo have been conducted. Ogluo is not likely to be abused and does not produce dependence effects.

There have been no studies of the effects of Ogluo on the ability to drive or operate machinery or on impairment of mental ability. There is no evidence to suggest that Ogluo would affect the ability to drive or operate machinery. The patient's ability to concentrate or react may be impaired as a result of hypoglycaemia. Until

hypoglycaemia 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 SmPC. No separate interaction studies for Ogluo are required.

Immunological events

The concern that frequent administration of Ogluo would yield more information about the immunogenic potential is not withheld by the applicant, due to the fact that the applicant has not seen any immunogenicity risks to date in its chronic glucagon development programs, as discussed during the scientific advice process.

However, as discussed in the EMA SA, a relevant aspect regarding safety and tolerability of peptides and proteins is immunogenicity.

See Quality regarding the fact that glucagon is known to be prone to aggregation or formation of fibrils. Due to the special formulation used in Ogluo, the notion that immunogenicity of glucagon is usually low may not apply for the Xeris product.

Taking into account that no data regarding the immunogenicity potential have been submitted, the applicant was asked to submit a risk-assessment in line with section 10 of the EMA Guideline on Immunogenicity assessment of therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev 1). If this risk-assessment concludes to the need of immunogenicity assays, a thorough discussion justifying the strategy used and the suitability of the bioanalytical methods selected, the validation reports of the immunogenicity assays used as well as the bioanalytical reports with clinical sample results should be submitted. The applicant's answer was mainly based on clinical arguments and not related to immunogenicity assays.

No data about actual-use planned study are submitted in the dossier. Therefore, this was asked to be provided (see higher) including a discussion about how it will be ensured to include a sufficient number of patients who will have administration of multiple doses for analysis of potential immunogenicity. Moreover, in line with the above cited EMA guideline, it was asked how an actual-use study will deal with the pre-existing antibodies. This question, related to pre-existing antibodies has not been addressed, however the clinical argumentation is considered acceptable and no further immunogenicity data were considered necessary.

Safety related to drug-drug interactions and other interactions

All adult subjects in the pooled Studies XSGP-301 and XSGP-303 reported 1 or more drugs used in diabetes, including multiple brands and forms of insulin. The next most frequently reported prior medications belonged in the following ATC categories: Multivitamins, Thyroid Therapy, Agents Acting on the Renin-Angiotensin System, and Lipid-Modifying Agents.

During Studies XSGP-301 and XSGP-303, the most frequently-reported concomitant medication was ondansetron, which was administered to treat adverse events of nausea and vomiting.

In Study XSGP-304 prior and concomitant medications were collected at the same time. Overall, all subjects reported insulin treatment (multiple brands of insulin were used). The next most frequently-reported ATC categories of medications were the same as for the pooled studies, with the addition of ondansetron, which was administered for adverse events of nausea and vomiting during and after the insulin induction procedure.

The majority of paediatric subjects received ondansetron during the study for at least 1 adverse event of nausea.

No interaction between Ogluo and the most frequently reported concomitant medications used in the Phase 3 studies was observed, although a formal analysis was not conducted. Warfarin was a prohibited medication in all studies due to glucagon's potential to increase its anticoagulant effect.

The pharmacological profile of glucagon is well established after decades of widespread clinical use. Drug related changes in serum chemistry and haematology have not been expected for glucagon. Therefore, drug interaction studies were not performed for Ogluo; however, interaction with other medicinal products is available through class labelling. The current US and EU labels for GlucaGen (GlucaGen HypoKit UK SmPC 2015; GlucaGen HypoKit USPI 2015) list the following drug interactions relevant to treatment of severe hypoglycaemia:

- Beta-blockers: Patients taking beta-blockers may have a transient increase in pulse and blood pressure when given Ogluo, which will be temporary because of glucagon's short half-life.
- Indomethacin: In patients taking indomethacin, Ogluo may lose its ability to raise blood glucose, or may even produce hypoglycaemia
- Warfarin: Ogluo may increase the anticoagulant effect of warfarin.

In clinical studies of Ogluo, there have been no reports of adverse events of overdoses. Administration of Ogluo at 1 mg in healthy subjects with T1D has been adequately tolerated. In cases of overdose, the patient may experience nausea and vomiting; however, due to the short half-life of Ogluo (31.9 minutes; CSR XSGP-101), these adverse events should be transient.

However, glucagon plays a role in antagonizing the effects of insulin and maintaining glucose homeostasis by promoting hepatic gluconeogenesis and glycogenolysis and inhibiting glycogen synthesis and in other pathways. In the adipocyte for example, glucagon activates the phosphorylation and activation of hormone-sensitive lipase and the lipolysis, which further may influence the gluconeogenesis.

Discontinuation due to adverse events

Phase 3 Adult Subjects

No subject discontinued treatment due to TEAE in the pooled Studies 301 and 303. Two (1.6%) subjects treated with Ogluo withdrew from Study XSGP-304 due to TEAEs. One (0.8%) subject withdrew due to abdominal pain and 1 (0.8%) subject withdrew due to hypoglycaemia. The subject who withdrew due to hypoglycaemia received an additional bolus of 0.40 IU insulin with a plasma glucose of 64.4 mg/dL in order to induce the last decline of blood glucose to the target level prior to receiving the dose of study drug. Although the protocol noted that no additional bolus was allowed when plasma glucose level was <65 mg/dL, the subject showed a high degree of insulin resistance (HbA1c 9.1% and high insulin rate needed during hypoglycaemia induction). This bolus was at the investigator's discretion to overcome counter-regulation and reach target plasma glucose as the subject was experiencing progressive hypoglycaemic symptoms. This subject also received IV glucose after dosing with study drug, but before 30 minutes post-glucagon administration due to safety reasons (further progression of hypoglycaemic symptoms) (CSR XSGP-304). Of note, this investigator discretion was deemed a major protocol deviation, per study protocol and the statistical analysis plan. The progressive hypoglycaemic symptoms were determined not to be study drug related.

Both of these adverse events leading to study discontinuation resolved.

Paediatric patients

No subjects discontinued in the Phase 3 Paediatric Study XSGP-302.

Post marketing experience

Currently there is no post marketing experience in the EU.

2.6.1. Discussion on clinical safety

A total of 300 adult subjects with T1D (Studies XSGP-202, -301, -303, and -304) received at least 1 dose of Ogluo 1 mg, in single-dose studies. In addition, a total of 31 paediatric subjects with T1D received at least 1 dose of Ogluo 0.5 mg, 11 of whom also received at least 1 dose of Ogluo 1 mg (Study XSGP-302) in a crossover fashion. Doses analysed in the population were 0.5 mg and 1 mg; these doses are proposed in the MAA. The issue regarding the dose in children aged 6 to <12 years was solved.

The issues regarding patient exposure as well as regarding relatedness of the TEAEs in Adult Phase 3 Subjects with T1D Pool have been clarified.

The safety profile of Ogluo includes well-known effects of glucagon treatment (vomiting, nausea) as well as local tolerability effects (injection pain, oedema). Headache, which was a commonly reported-related TEAE in adult subjects treated with either the Ogluo or the Lilly Glucagon or the GlucaGen HypoKit, respectively, was included in the listing of adverse events in the Ogluo SmPC, although it is not included among adverse events in the GlucaGen HypoKit SmPC. Because these adverse effects are transient and are non-serious in nature, they are not considered to have a negative impact for the patient.

Next to the already well known adverse events, in Ogluo treated patients, there was initially after administration a higher injection site discomfort and oedema compared with the comparator arm; this discomfort resolves equally. Injection site oedema is added as an undesirable effect in SmPC section 4.8 and in PL section 4.

There were several differences with the observed reporting in children in study XSGP-302 versus adults. Firstly regarding hypoglycaemia which was unexpectedly more reported in the paediatric population in study XSGP-302 compared to the adults. Some TEAEs considered related to treatment with Ogluo which have been reported in children are not mentioned in the proposed Ogluo SmPC in adults, e.g. hyperglycaemia, urticarial and there are different rates of TEAEs across age-groups, generally, with a higher incidence in younger subjects (<12 years old), compared with the 12 to <18-year-old group of subjects. The most common TEAEs across age and dose groups were nausea and vomiting. These issues are satisfactorily discussed.

The rates of SAEs seen in all clinical trials are low; only two SAEs have been reported.

Overall, across the clinical development programme, the majority of adverse events were self-limiting and resolved fully by the end of the study.

The safety database for Ogluo was sufficient in scope to adequately characterise the safety profile of Ogluo in adults (mostly <65 years) and paediatric patients (all ≥ 2 years) with diabetes given the intended use of Ogluo and the history of safe use with the currently approved injectable glucagon products. However, elderly patients and others than Caucasian patients were rarely included in the safety database.

Patients with T2D were not investigated in the trials, although they represent the highest diabetes population in general daily practice. This patient population will be included in the post marketing trial.

Analysis of laboratory parameters was minimal but this is not a concern due to the fact that the pharmacological profile of glucagon is well established after decades of widespread clinical use. Drug related changes in serum chemistry and haematology have not been expected for glucagon.

It is known that after glucagon administration increases in mean heart rate and blood pressure are possible. An issue has been identified regarding the SBP and DBP for all age groups and doses in study XSGP-302. The applicant provided the corrected values for SPB and DPB. There were 2 incidences of tachycardia and 1 incidence of supraventricular extrasystoles after treatment with Ogluo 1 mg. However, glucagon is not known as arrhythmogenic, and they were likely due to the insulin induction, and the incidences were manageable with positive outcome.

The safety evaluation for Ogluo 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 Ogluo because the treatment indication is for acute potentially life-saving episodic use and not for chronic administration.

For both treatment populations adults and children, nothing is known about the repetitive side effects after different administrations of Ogluo in patients with repetitive hypoglycaemic events. Therefore, it was advised to supply safety data from Ogluo in chronic use. The applicant discussed how this will be examined in the post-marketing setting e.g. will this be included in the actual-use study. An evaluation for usability and drug administration errors is incorporated into the study design, in order to help examine the potential risk of "Drug administration error leading to loss of drug benefit".

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

Very elderly patients and patients with renal or hepatic impairment were not included in the clinical trials. These special patient groups are not excluded from Ogluo treatment according to the current SmPC, and no dose adjustment is recommended. Additional data regarding adverse effects in the different age groups < 65 years old and ≥65 years old would be examined in the actual use postmarketing trial.

Only two adults and no paediatric patients discontinued treatment due to TEAE.

No drug-drug interaction studies were conducted with Ogluo. The interactions included in the Ogluo SmPC are in line with the SmPC of the reference product; this is agreed.

Immunogenicity is a relevant aspect regarding safety and tolerability of peptides and proteins. The notion that immunogenicity of glucagon is usually low may not apply for Ogluo due to its special formulation. Taking into account that no immunogenicity-related data have been submitted, the applicant submitted a risk-assessment in line with section 10 of the EMA Guideline on Immunogenicity assessment of therapeutic proteins (EMA/CHMP/BMWP/14327/2006 Rev 1). Eventually, the risk-assessment was based on clinical arguments and not related to immunogenicity assays and seemed acceptable.

Moreover, during the EMA SA, it was recommended to conduct an actual-use study in which patients could receive more than 1 Ogluo injection, possibly providing valuable immunogenicity information. Data about this planned study were asked to be submitted including a discussion on how it will be ensured to include a sufficient number of patients with multiple dosing as well as elderly patients as well as how an actual-use study will deal with the pre-existing antibodies in line with the above cited EMA guideline and this issue was solved.

2.6.2. Conclusions on the clinical safety

Overall, the safety profile of Ogluo is consistent with the currently approved injectable glucagon products. The most commonly reported AEs in adults and children were nausea, vomiting and headache.

Except for headache and oedema at the injection site, and hypoglycaemia, hyperglycaemia and urticaria reported in children, the current product labelling for injectable glucagon provides the reported adverse effects. Currently, the product labelling is accordingly adapted.

Based upon all the available data within the development programme, Ogluo is considered to be safe and well tolerated for the rescue treatment of severe hypoglycaemia in adult and paediatric patients ≥ 2 years old with diabetes.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Drug administration error leading to loss of drug benefit
Missing information	None

Pharmacovigilance plan

No additional pharmacovigilance activities are considered necessary for the product. Routine pharmacovigilance is considered sufficient to identify and characterise the risks of the product.

Risk minimisation measures

Safety concern	Risk minimisation measures
Drug administration error leading to loss of drug benefit	<p>Routine risk minimisation measures:</p> <ul style="list-style-type: none">• SmPC sections 4.2 (Posology and method of administration) and 6.6 (Special precautions for disposal and other handling)• PLs section 2 (What you need to know before you use Ogluo) and 3 (How to use Ogluo)• 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 to use Ogluo, Assist step)• Prescription drug requiring patient training by HCP <p>Additional risk minimisation measures:</p> <ul style="list-style-type: none">• Administration leaflet• Audio Visual training materials

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

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.

2.9. New Active Substance

The CHMP, based on the available data, considers that glucagon is not a new active substance, as it is a constituent of a medicinal product previously authorised within the European Union. Glucagon is contained in the marketing authorisation GlucaGen which was authorised in the European Union since October 1962.

2.10. Product information

2.10.1. 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*.

2.10.2. Quick Response (QR) code

The administration leaflet to patients, which aims at minimising the important potential risk in the RMP of inappropriate use of the device leading to loss of drug benefit, and which will be given from healthcare professionals to patients upon initial Ogluo prescription and after training, should contain a URL and QR code to a website where patients can access the instructional video which aims at providing step-by-step instructions on the appropriate use of Ogluo.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed indication is:

“Ogluo is indicated for the treatment of severe hypoglycaemia in adults, adolescents, and children aged 2 years and over with diabetes mellitus.”

Hypoglycaemia is the limiting factor in the glycaemic management of diabetes (Cryer, 2008; Cryer, 2014) and causes recurrent morbidity in most patients with type 1 diabetes mellitus (T1D) and advanced type 2 diabetes mellitus (T2D).

The working group of the EASD and ADA describes that severe hypoglycaemia denotes severe cognitive impairment requiring external assistance for recovery and also describes a serious, clinically important low glucose level of <3.0 mmol/L (<54 mg/dL) as sufficiently low to greatly increase the risk of severe hypoglycaemia.

Severe hypoglycaemia may present itself with symptoms such as cognitive impairment, behavioural changes and psychomotor abnormalities, and loss of consciousness, seizure, and coma. If severe hypoglycaemia is left untreated it may result in death.

3.1.2. Available therapies and unmet medical need

The majority of severe hypoglycaemic events are treated on an emergency basis, outside of a healthcare facility. Injectable glucagon is currently the only treatment option for severe hypoglycaemia for patients and

their caregivers in this setting, which is available as GEK (Lilly, 2018) and HK (Novo, 2015), with only HK being marketed in the EU. However, their administration tends to be complex as it requires a multistep process in which the lyophilised glucagon powder must be manually reconstituted with the liquid diluent at the time of use, then withdrawn from a vial into a syringe, and then dose calibrated before injection. Further downsides are the fact that the glucagon must be used immediately after reconstitution, and that it should be stored in the refrigerator.

Under a stressed environment, the complexity of preparing the drug for administration may lead to drug administration failures due to either partial doses or missed doses all together: company-owned studies with currently marketed emergency glucagon kits have shown that only 6% to 31% of users were able to successfully prepare and administer the full dose of glucagon, while in a published study (Yale *et al.*, 2017) this was shown to be only 0% to 13%. This leads the applicant to conclude that there is an *unmet clinical need* for a ready-to-use glucagon formulation that can be administered with reliability and ease when needed by caregivers or family members. Recently, a ready-to-use glucagon formulation for intranasal administration was authorised in the EU.

The proposed Ogluo Configuration A (auto-injector) is a 2-step process and Configuration B (pre-filled syringe) requires 3 steps to administer the rescue dose, proposed to simplify the complexity of the rescue treatment of severe hypoglycaemia.

3.1.3. Main clinical studies

The clinical development programme of Ogluo included 7 clinical trials involving 62 healthy subjects in one phase 1 study (Study XSGP-101), and 300 adult and 31 paediatric subjects with T1D in two Phase 2 studies (Study XSGP-201 and Study XSGP-202) and four Phase 3 studies (XSGP-301, XSGP-303, and XSGP-304 in adults and the open-label study XSGP-302 in paediatric subjects 2-18 years old).

Table 46 Overview of Clinical Efficacy Studies

Protocol No. Study Start - Stop Date	Study Objective	Primary Endpoint	Population	Total Enrolled	Subjects Treated Gender (M:F)	Age Mean/ Range (years)	Phase	Study Design ^a	Admin.	Dose (mg)	Injection Location
XSGP-101 13Feb2018 19Mar2018	BE of the AI and PFS configurations of Gvoke	Plasma glucagon AUC (0-240 min) and C _{max}	Healthy volunteers	32	16 - M 16 - F	44.6/ 19 - 63	1	R, OL, XO	Gvoke AI vs Gvoke PFS	AI 1 mg PFS 1 mg	Abdomen
XSGP-201 18Sep2013 22Jan2014	Safety and tolerability	Plasma glucose AUC, C _{max} , and T _{max}	Healthy volunteers	30	9 - M 21 - F	38.7/ 20 - 57	2	R, DB, XO	Gvoke AI vs GEK	Gvoke 1 GEK 1	Arm
XSGP-202 01May2015 - 29May2015	Pilot Study	Plasma glucose >70 mg/dL within 30min	Adult T1D	7	1 - M 6 - F	42 (median) 23 - 59	2	NR, OL, XO	Gvoke vial and syringe	Gvoke 0.5 Gvoke 1	Arm
XSGP-301 15Mar2017 - 04Aug2017	Plasma Glucose recovery from <50 mg/dL	Plasma glucose >70 mg/dL within 30min	Adult T1D	80	44 - M 36 - F	43.6 / 18 - 74	3	R, DB, XO	Gvoke AI GEK	Gvoke 1 GEK 1	Arm, thigh, abdomen
XSGP-302 17Apr2017 - 04Aug2017	Plasma glucose response from <80 mg/dL	Plasma glucose recovery within 30 min	Paediatric T1D	31	15 - M 16 - F	2 to 6 (N=7) 6 to 12 (N=13) 12 to 18 (N=11)	3	NR, OL, XO	Gvoke AI	Gvoke 1 Gvoke 0.5	Arm, thigh, abdomen
XSGP-303 08Jan2018 18Apr2018	Plasma glucose recovery from <50 mg/dL	Plasma glucose >70 mg/dL within 30 min	Adult T1D	81	44 - M 37 - F	38 / 18-72	3	R, SB, XO	Gvoke AI GEK	Gvoke 1 GEK 1	Abdomen
XSGP-304 19Sep2018 02Apr2019	Plasma glucose recovery from <54 mg/dL	Plasma glucose >70 mg/dL or increase ≥20 mg/dL, within 30 min	Adult T1D	132	70 - M 62 - F	39.5 / 19-72	3	R, SB, XO	Gvoke AI HK	Gvoke 1 HK 1	Abdomen

AI= Auto-Injector, BE=bioequivalence, DB=double-blind, F=Female, GEK=glucagon emergency kit (Lilly), HK=HypoKit (Novo Nordisk), M=Male, NR=Non-randomized, OL=open label, PFS=pre-filled syringe, R=Randomized, SB=single blind, T1D=type 1 diabetes, XO=crossover.

In addition, 7 Human Factors (HF) Studies were designed to mimic real-life emergency situations, and tested a total of 5 user groups that included first responders, trained and untrained users, adults and paediatric (adolescent) caregivers of people with diabetes.

3.2. Favourable effects

In the pivotal adult study XSGP-304, 99% (mITT) and 100% (PP) of Ogluo subjects achieved the primary endpoint (plasma glucose >70 mg/dL or rise ≥20 mg/dL within 30 minutes of dosing), comparable to treatment with HK subjects in which 100% of subjects achieved this. This study demonstrated that Ogluo was non-inferior to HK for achieving the primary endpoint.

For the pooled data from studies XSGP-301 and XSGP-303, 97.4% of Ogluo subjects (mITT) and 98% (PP) achieved the primary endpoint (plasma glucose level >70 mg/dL within 30 minutes of dosing), comparable to treatment with GEK in which 100% of subjects achieved this.

The data from studies XSGP-301 and XSGP-303 were analysed according to the primary endpoint of study XSGP-304 using an alternate combined endpoint (plasma glucose >70 mg/dL or increase ≥20 mg/dL within 30 minutes of dosing) for which the non-inferiority margin was achieved in both studies.

In the paediatric study XSGP-302, statistically significant ($p < 0.001$) increases from Baseline in mean plasma glucose were observed at 30 minutes post-dose in each age group. All 30 evaluable patients achieved

a target glucose increase of at least 25 mg/dL and the mean time to achieve plasma glucose increase \geq 25 mg/dL from baseline was 19 minutes.

Ogluo is pre-mixed and pre-loaded into a pre-filled syringe and auto-injector pen ready-to-use with no reconstitution required. In addition, it has enhanced portability and availability due to room-temperature stability, while the existing EU product HK needs to be reconstituted in a multi-step process and the cold chain should be maintained.

In the Human Factors Studies, almost all participants succeeded to successfully administer Ogluo: percentages varied from 88% in comparison to 31% for the comparator in one study, 98.7% and 100% in the other studies. Some of these studies also included untrained adolescent users (as young as 12 years old) which were able to successfully use Ogluo to carry out the full rescue injection procedure during an emergency use context.

3.3. Uncertainties and limitations about favourable effects

In Study XSGP-201, the PK profile was distinctly different between Ogluo and Lilly glucagon with significantly higher glucagon exposure in the comparator group and a shift in t_{max} , indicating a slower rate of absorption for Ogluo, which seems to be reflected in a delay in PD response. It was suggested that this shift could result from the different formulations (aqueous solution in Lilly glucagon vs. DMSO preparation used in Ogluo).

This is also reflected in the fact that Ogluo required about 4 to 4.5 minutes longer versus the EU reference product in the pivotal study XSGP-304 to achieve plasma glucose recovery. This difference was considered of limited relevance as it will be decreased in clinical practice thanks to the shorter preparation time for Ogluo. Additionally the mean times to achieve plasma glucose recovery were all still within the predefined 30 minutes post-dose, and that, when measuring 'from decision to dose' (instead of as of administration of study drug) and using the not validated symptom relief scores as a PRO, several results were similar or even better for Ogluo versus HK, and analysis of positive treatment response (successful plasma glucose recovery or successful symptom recovery) by treatment did meet the predefined criteria for non-inferiority in all analysed populations. Across trials the symptom relief scores were consistent with glucose effects. This was addressed by additional warnings in the SmPC.

3.4. Unfavourable effects

Overall, the safety profile of Ogluo is consistent with the currently approved injectable glucagon products in both adult and paediatric patients with diabetes. There are no key unfavourable effects noticed which have an impact on the benefit-risk balance.

3.5. Uncertainties and limitations about unfavourable effects

A post-authorisation actual use study is planned to evaluate the real-world effectiveness and ease of use to treat severe hypoglycaemic episodes in children, adolescents, and adults with insulin dependent diabetes (T1D or T2D). In this study an evaluation of drug administration error will be included. However, there are no remaining limitations and uncertainties that have an impact on the benefit-risk balance.

3.5.1. Effects Table

Table 47 Effects Table for Ogluo in the treatment of severe hypoglycaemia in adults, adolescents and children aged 2 years and over with diabetes mellitus (data cut-off: 02/04/2019).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Treatment success	Adults: rates of achieving a positive PGR (plasma glucose ≥ 70 mg/dL (≥ 3.88 mmol/L) OR increase ≥ 20 mg/dL (≥ 1.11 mmol/L) within 30 min post-dose	%	99.2%	100%	Non-inferiority of Ogluo to HK was demonstrated. BUT * There are statistical comments/questions *Only about 1 minute gain due to shorter drug preparation time *Not examined in T2DM patients, in more severe hypoglycaemia leading to an altered mental and/or physical status requiring assistance, and in patients with multiple glucagon administrations (for immunogenicity)	Study XSGP-304
Treatment success	Children: change in plasma glucose with an emphasis on the increase from baseline to 30 min post-dose	mg/dL	2 \leq 6: 81.4 6 \leq 12: 84.2 12 \leq 18: 54.0 P<0.001	N/A	Statistically significant increases from Baseline in mean plasma glucose BUT *Low number of patients *No comparator	Study XSGP-302 – study XSGP-201
Usability	Successful administration	% of participants	HF2: 88% HF3: 98.7% HF7: 100% HF5: 100%	HF2: 31% Others: no comparator		Human Factors Studies
Unfavourable Effects						

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Nausea	Incidence	%	22,9 vs 29,9 ⁽¹⁾ 54,7 vs 44,9 ⁽²⁾ 36,4 ⁽³⁾		In general, these events were mild to moderate in severity, and never led to discontinuation. Rates of occurrence were similar between treatments.	Comparator vs Pooled adult studies ¹ XSGP-301, ¹ XSGP-303, and comparator vs adult study ² XSGP-304), and paediatric Study ³ XSGP-302)
Vomiting			9,6 vs 16,2 ⁽¹⁾ 13,8 vs 12,6 ⁽²⁾ 18,2 ⁽³⁾			
Hypoglycemia	Incidence	%	0 vs 0 ⁽¹⁾ 0 vs 1,6 ⁽²⁾ 27,3 ⁽³⁾		In general, these events were mild to moderate in severity, and infrequently led to discontinuation.	idem
Injection site discomfort	Incidence		*See Tolerability section		No anaphylaxis or serious hypersensitivity AEs were reported. There were no discontinuations for the related events of injection site discomfort.	idem

Notes: *Overall, at 30 minutes post dose, a higher percentage of subjects in the GlucaGen HypoKit group had no oedema or erythema compared to subjects administered Ogluo. However, at 90 and 180 minutes after administration of study drug, oedema and erythema scores were similar and at 90 minutes post-administration, most oedema had resolved in both groups.

At each time-point, injection site discomfort was reported by more subjects receiving Ogluo than GlucaGen HypoKit and the mean total duration of injection site discomfort was longer for subjects receiving Ogluo than GlucaGen HypoKit. The level of injection site discomfort was highest at 30 minutes following Ogluo.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

Time to glucose recovery

The glucose recovery after Ogluo administration is delayed by average 4 to 4.5 minutes compared to the EU reference product (study XSGP-304), while prompt recovery is critical in the acute treatment of severe hypoglycaemia. The risk from this delay may be partially mitigated by the time gained due to the fact that no reconstitution is needed for Ogluo in contrast to HypoKit. However, this gain in preparation time appeared to be only 1 minute in the pivotal study which would mean that there still is a delay of 3 to 3.5 minutes.

Moreover, the delay based on the time to recovery of 14.8 minutes versus 10.4 minutes for HK is only a mean value with an important variability. At 15 minutes post-dose, all HK patients had achieved recovery, while for Ogluo there was a delay of 5 to 20 minutes for many (>20%) patients (outliers).

However, it is possible that caregivers of diabetic patients during real-world use of the product would need even more time to prepare HK than the trained, licensed pharmacists in this study which would decrease the delay for Ogluo versus HK.

Successful administration

Another important parameter to take into account is successful administration of glucagon. If a dose is not successfully administered in a severe hypoglycaemic event, the recommended action for HK is to call emergency medical services and wait for them to arrive which also creates an important delay to recovery. The recommended action for Ogluo is to call emergency medical services immediately after administration; an additional dose of Ogluo from a new device may be administered while waiting for emergency assistance.

This appears to be a problem with the existing injectable glucagon as e.g. only 12.5% of the 16 caregivers and none of the 15 acquaintances delivered a full dose of glucagon from the GEK in a simulation study (Yale *et al.*, 2017) that evaluated a glucagon nasal powder versus a marketed GEK.

This is in contrast to Ogluo for which its ease-of-use is the main added value. It is pre-mixed and pre-loaded into a pre-filled syringe and auto-injector pen ready-to-use with no reconstitution required. In addition, it has enhanced portability and availability due to room-temperature stability. These are all considerable advantages when compared to the existing EU product HK that needs to be reconstituted in a multi-step process and for which the cold chain should be maintained.

The ease-of-use of Ogluo was demonstrated in the Human Factors Studies by the fact that almost all participants had a successful administration of Ogluo, also in a small comparative study versus HK (88% successful administration for Ogluo and only 31% for the GEK); it might even be administered by adolescents to their siblings or parents with diabetes, which would be unfeasible with HK.

3.6.2. Balance of benefits and risks

There was a delay in response in a non-negligible amount of patients with Ogluo compared to the comparator in the pivotal study. This has been reflected in the SmPC:

Section 4.4

– Recovery Time

Please take into account that approximately 15% of patients achieved glucose recovery after 20 minutes or more in the pivotal trial.

• Section 4.2

– The patient will normally respond within 15 minutes. When the patient has responded to the treatment, give oral carbohydrate to restore the liver glycogen and prevent relapse of hypoglycaemia. If the patient does not respond within 15 minutes, an additional dose of Ogluo from a new device may be administered while waiting for emergency assistance. It is recommended that the patients are prescribed two Ogluo devices.

Additional educational materials are also agreed (annex II and RMP) aimed at providing guidance on how to minimise the important potential risk of inappropriate use of the device leading to loss of drug benefit. Healthcare professionals and patients/caregivers who are expected to prescribe, supply, or use the product have access to the administration leaflet and instructional video.

Ogluo has ease-of-use as the main added value. It is pre-mixed and pre-loaded into a pre-filled syringe and auto-injector pen ready-to-use with no reconstitution required. In addition, it has enhanced portability and availability due to room-temperature stability. These are all considerable advantages when compared to the existing EU product HK that needs to be reconstituted in a multi-step process and for which the cold chain should be maintained.

The benefit/risk ratio is considered positive.

3.6.3. Additional considerations on the benefit-risk balance

Not applicable.

3.7. Conclusions

The overall B/R of Ogluo 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 Ogluo is favourable in the following indication:

Ogluo is indicated for the treatment of severe hypoglycaemia in adults, adolescents, and children aged 2 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 on 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.

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 Ogluo (glucagon), for the treatment of severe hypoglycaemia in adults, adolescents, and children aged 2 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 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 Ogluo is marketed, all healthcare professionals and patients/caregivers who are expected to prescribe, supply, or use the product have access to the following:

- Administration leaflet;
- Instructional video.

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

- Patients should receive the administration leaflet from their healthcare professionals upon initial Ogluo prescription and after training;
- It is important not to test the single-dose device in advance, not to remove the single-dose device from the foil pouch in advance and to ensure that the patient understands that each Ogluo single-dose device can only be used once;
- The PL should be referenced for more detailed information regarding administration and handling of Ogluo;
- Patients can use the leaflet to teach those around them how to correctly handle and administer Ogluo;
- If the patient does not respond within 15 minutes, an additional dose of Ogluo from a new device may be administered while waiting for emergency assistance;
- The leaflet should contain a URL and QR code to a website where patients can access the instructional video.

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

- To reinforce the correct Ogluo handling and administration, step-by-step instructions on the appropriate use of Ogluo should be provided;
- If the patient does not respond within 15 minutes, an additional dose of Ogluo from a new device may be administered while waiting for emergency assistance.