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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Zegalogue (SRD)

Dasiglucagon

Procedure no: EMA/PAM/0000324523

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	CHMP Rapporteur AR	30 March 2026	9 April 2026
☐	CHMP comments	13 April 2026	13 April 2026
☐	Updated CHMP Rapporteur AR	16 April 2026	16 April 2026
☒	CHMP outcome	23 April 2026	23 April 2026

Table of contents

1. Introduction

On 20 January 2026, the MAH submitted a completed paediatric study for Zegalogue, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that "Phase 3, Randomised, Open-label, Cross-over Study to Confirm the Clinical Efficacy and Safety of Dasiglucagon Versus Glucagon for the Treatment of Severe Hypoglycaemia in Asian Adults with Type 1 Diabetes (T1D) Including an Investigation of Dasiglucagon in a Japanese Adolescent Cohort" is part of a clinical development program.

2.2. Information on the pharmaceutical formulation used in the study

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study ID: NN9515-7675; A Phase 3, Randomised, Open-label, Cross-over Study to Confirm the Clinical Efficacy and Safety of Dasiglucagon Versus Glucagon for the Treatment of Severe Hypoglycaemia in Asian Adults with Type 1 Diabetes (T1D) Including an Investigation of Dasiglucagon in a Japanese Adolescent Cohort.

2.3.2. Clinical study

Phase 3, Randomised, Open-label, Cross-over Study to Confirm the Clinical Efficacy and Safety of Dasiglucagon Versus Glucagon for the Treatment of Severe Hypoglycaemia in Asian Adults with Type 1 Diabetes (T1D) Including an Investigation of Dasiglucagon in a Japanese Adolescent Cohort.

Description

The study was conducted as part of the development programme for dasiglucagon, to investigate effect on glycaemic response of a single 0.6 mg s.c. injection of dasiglucagon for treatment of insulin-induced hypoglycaemia in adult Asian non-Japanese and Japanese participants with T1D, including an investigation of dasiglucagon in a Japanese adolescent cohort with T1D. Data from this study will support the regulatory applications of dasiglucagon for the treatment of severe hypoglycaemia in Japan and other Asian countries.

Methods

Study participants

Inclusion criteria:

- For adult participants: Asian male or female.

- For adolescent participants: Japanese male or female

- Diagnosed with T1D >1 year before screening.

- HbA1c <10.0% (86 mmol/mol) as assessed by subcontracted laboratory by the site on the day of screening.

- Treated with stable insulin treatment (based on the investigator's discretion preferably no more than a 10-unit daily variation in total daily insulin dose) 30 days prior to screening.

- For adult participants: Body mass index (BMI) between 18.5 and 29.9 kg/m2 (both inclusive).

- For adolescent participants: Body weight ≥ 33.4 kg

Exclusion criteria:

1. Known or suspected hypersensitivity to study intervention(s) or related products (glucagon or its derivatives).

2. Exposure to an IMP within 30 days or 5 times the half-life of the IMP (if known), whichever is longer before screening.

3. Severe hypoglycaemia in the last month prior to screening.

4. Hospitalisation for diabetic ketoacidosis in the last month prior to screening.

5. Presence or history of any clinically relevant respiratory, metabolic, renal, hepatic, gastrointestinal, endocrinological conditions (except conditions associated with diabetes mellitus).

6. History of epilepsy or seizure disorder.

7. Known presence or history of pheochromocytoma/paraganglioma (i.e., adrenal gland tumour/neuroendocrine neoplasm) or insulinoma (i.e., insulin-secreting pancreas tumour).

8. Clinically significant abnormal ECG at screening as evaluated by investigator.

9. Any disorder, unwillingness or inability which in the investigator's opinion, might jeopardise the participant's safety or compliance with the protocol.

Treatments

S.c. injection of dasiglucagon 0.6 mg versus i.m. injection of glucagon 1 mg.

Objective(s)

Primary: To confirm the effect on glycaemic response of a single 0.6 mg s.c. injection of dasiglucagon for the treatment of insulin-induced hypoglycaemia in Asian adults with T1D. This includes comparing the difference in time to plasma glucose (PG) recovery between dasiglucagon s.c. and glucagon i.m. to a non-inferiority margin of 3 minutes.

Secondary: To investigate the clinical efficacy of dasiglucagon assessed by the glycaemic response of a single 0.6 mg s.c. injection of dasiglucagon for the treatment of insulin-induced hypoglycaemia in Asian participants with T1D.

To investigate the pharmacokinetic properties of a single 0.6 mg s.c. injection of dasiglucagon for the treatment of insulin-induced hypoglycaemia in Asian participants with T1D.

To investigate the safety of a single 0.6 mg s.c. injection of dasiglucagon for the treatment of insulin-induced hypoglycaemia in Asian participants with T1D.

Main Outcomes/endpoints

Time to PG recovery, where PG recovery is defined as the first increase in PG of ≥20 mg/dL (1.1 mmol/L) from baseline.

PG change from baseline at 15 minutes after IMP injection.

AUC0-30min: Area under the plasma dasiglucagon concentration time curve from 0 to 30 minutes after IMP injection.

Cmax: Maximum observed plasma dasiglucagon concentration.

Number of adverse events (AEs).

Sample size

Thirty-four (34) adult Asian participants (with at least 27 Japanese participants).

Four (4) adolescent Japanese participants.

Randomisation and blinding (masking)

The randomisation of the participants took place on the first dosing visit (visit 2 day 1).

Statistical Methods

The primary hypothesis to be tested is that dasiglucagon s.c. is non-inferior to glucagon i.m. in terms of the primary endpoint, time to PG recovery, for adults with T1D.

Formally, let D be the treatment difference 'dasiglucagon s.c.' minus 'glucagon i.m.' of time to PG recovery. The null hypothesis (H0) will be tested against the alternative hypothesis (HA) of non-inferiority as given by, H0: $D \geq 3$ minutes against HA: $D < 3$ minutes.

Non-inferiority of dasiglucagon will be considered confirmed if the upper boundary of the 2-sided 95% confidence interval for D is below 3 minutes.

The non-inferiority margin of 3 minutes ensures that a large fraction of the glucagon treatment effect against placebo on time to PG recovery is preserved. In a confirmatory trial in adults with T1D comparing dasiglucagon to glucagon s.c. and placebo (ZP4207-16137), the median time to PG recovery was 12 minutes for glucagon s.c. and 40 minutes for placebo. The effect of glucagon on the blood glucose response has been seen to be similar for s.c. and i.m. administration routes.

No confirmatory testing was performed for the secondary endpoints nor the adolescent cohort.

Results

Participant flow

Table 1. Participant disposition - summary - adults - all participants

	Total	
	N	(%)
Screened	40	
Screening failures	6	
Withdrawn before randomisation	0	
Randomised	34	(100.0)
Exposed	33	(97.1)
Full analysis set	33	(97.1)
Safety analysis set	33	(97.1)
Completed	33	(97.1)
Withdrawn after randomisation	1	(3.0)
Adverse event	0	(0.0)
Protocol deviation	0	(0.0)
Lost to follow-up	0	(0.0)
Met eligibility criteria but not needed	0	(0.0)
Met eligibility criteria but missed visit window	0	(0.0)
Site/closure	0	(0.0)
Epi/pandemic	0	(0.0)
Physician decision	1	(3.0)
Withdrawal of consent by subject	0	(0.0)
Other	0	(0.0)

N: Number of participants, %: Percentage of participants.

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Table 2. Participant disposition - summary - adolescents - all participants

	Total	
	N	(%)
Screened	4	
Screening failures	0	
Withdrawn before randomisation	0	
Randomised	0	(0.0)
Exposed	4	(100.0)
Full analysis set	4	(100.0)
Safety analysis set	4	(100.0)
Completed	4	(100.0)
Withdrawn after randomisation	0	(0.0)
Adverse event	0	(0.0)
Protocol deviation	0	(0.0)
Lost to follow-up	0	(0.0)
Met eligibility criteria but not needed	0	(0.0)
Met eligibility criteria but missed visit window	0	(0.0)
Site/closure	0	(0.0)
Epi/pandemic	0	(0.0)
Physician decision	0	(0.0)
Withdrawal of consent by subject	0	(0.0)
Other	0	(0.0)

N: Number of participants, %: Percentage of participants.

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Recruitment

Thirty-four (34) adult Asian participants (with at least 27 Japanese participants) were randomised 1:1 to each treatment sequence, receiving a single s.c. injection of 0.6 mg dasiglucagon and a single i.m. injection of 1 mg glucagon in an insulin-induced hypoglycaemic state (using a manual hypoglycaemic clamp procedure). Among them, at least 30 participants (with at least 24 Japanese participants) were planned to complete the dosing visits. Four (4) adolescent Japanese participants received a single s.c. injection of 0.6 mg dasiglucagon in an insulin-induced hypoglycaemic state (using a manual hypoglycaemic clamp procedure).

Baseline data

Table 3. Demography and baseline characteristics - categorical - summary - adults - safety analysis set

	Total	
	N	(%)
Number of subjects	33	
Age group		
N	33	(100.0)
Adults (18-64 years)	32	(97.0)
Elderly 65 to 84 years	1	(3.0)
Sex		
N	33	(100.0)
Male	21	(63.6)
Female	12	(36.4)
Race		
N	33	(100.0)
Asian	33	(100.0)
Ethnicity		
N	33	(100.0)
Not Hispanic or Latino	33	(100.0)
Country/area of residence		
N	33	(100.0)
Japan	33	(100.0)

N: Number of participants, %: Percentage of participants.

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Number analysed

For adults: Full analysis set 33 (97.1%), Safety analysis set 33 (97.1%).

For adolescents: Full analysis set 4 (100.0), Safety analysis set 4 (100.0).

Efficacy results

Efficacy summary for adults

- Estimated mean Time to PG recovery (first increase in plasma glucose of ≥20 mg/dL (1.1 mmol/L) from baseline) for adults was 8.73 min with dasiglucagon and 8.15 min with glucagon, confirming non-inferiority of dasiglucagon vs. glucagon. Estimated treatment difference 0.58 [0.03; 1.14]95% CI.
- All adults were recovered within 15 min after IMP injection in both treatment arms.
- Estimated mean PG change from baseline at 15 min after IMP injection for adults was 48.01 mg/dL with dasiglucagon and 51.30 mg/dL with glucagon. Estimated treatment difference -3.29 [-6.98; 0.40]95% CI.
- Estimated mean PG change from baseline at 20 min after IMP injection for adults was 63.25 mg/dL with dasiglucagon and 65.40 mg/dL with glucagon. Estimated treatment difference -2.15 [-6.05; 1.75]95% CI.

- Estimated geometric mean of AUE PG, 0-30min, baseline adj for adults with dasiglucagon was 21.70 h*mg/dL and 22.61 h*mg/dL for glucagon. Estimated treatment ratio 0.96 [0.90; 1.02]95% CI.

- Estimated geometric mean of AUE PG, 0-60min, baseline adj for adults with dasiglucagon was 82.17 h*mg/dL and 78.43 h*mg/dL for glucagon. Estimated treatment ratio 1.05 [1.00; 1.10]95% CI.

- Estimated geometric mean of AUE PG, 0-90min, baseline adj for adults with dasiglucagon was 162.31 h*mg/dL and 146.43 h*mg/dL for glucagon. Estimated treatment ratio 1.11 [1.05; 1.17]95% CI.

- Estimated geometric mean of maximum observed baseline adjusted PG values for adults with dasiglucagon was 176.02 mg/dL and 145.65 mg/dL for glucagon. Estimated treatment ratio 1.21 [1.12; 1.30]95% CI.

Efficacy summary for adolescents

- Mean Time to PG recovery for adolescents with dasiglucagon was 7.22 min.

- All adolescents were recovered within 15 min after IMP injection.

- Mean PG change from baseline at 15 min after IMP injection for adolescents with dasiglucagon was 51.50 mg/dL and 69.00 mg/dL at 20 min after IMP injection.

- Geometric mean of AUE PG, 0-30min, baseline adj for adolescent with dasiglucagon was 24.05 h*mg/dL, 88.03 h*mg/dL for AUE PG, 0-60min, baseline adj and 172.15 mg/dL for AUE PG, 0-90min, baseline adj.

- Geometric mean of maximum observed baseline adjusted PG values for adolescents with dasiglucagon was 183.33 mg/dL.

PK summary for adults

- Geometric mean of AUC 0-30min for dasiglucagon in adults was 346.39 h*pmol/L with CV% 46.22.

- Geometric mean of maximum observed dasiglucagon concentrations in adults was 1230.24 h*pmol/L with CV% 33.47.

PK summary for adolescents

Due to a bioanalytical issue in the adolescent dasiglucagon analytical method, PK endpoints could not be derived for the adolescent participants. The analytical method used for the analysis of adolescent plasma samples was shown to perform acceptably and was reproducible when applied to adult incurred plasma samples. Reproducibility was not observed when the method was applied to adolescent incurred plasma samples. Although the reason for this could not be definitively identified, the MAH suspected that the difference in sample collection procedure, affected the integrity of the samples and this was the reason for inconsistency in quantification of dasiglucagon.

Primary endpoint – time to PG recovery, adults

From 0 to 90 minutes after IMP injection, the estimated mean time to PG recovery, where PG recovery is defined as the first increase in PG of ≥20 mg/dL (1.1 mmol/L) from baseline, was: 8.73 minutes with dasiglucagon, 8.15 minutes with glucagon.

The ETD for dasiglucagon versus glucagon for time to PG recovery from 0 to 90 minutes after IMP injection was: 0.58 [0.03;1.14] 95% CI.

As determined by the analysis detailed in the SAP, non-inferiority of dasiglucagon vs glucagon on time to PG recovery was confirmed.

Figure 1. PD - Plasma glucose - mean profiles - adults - full analysis set

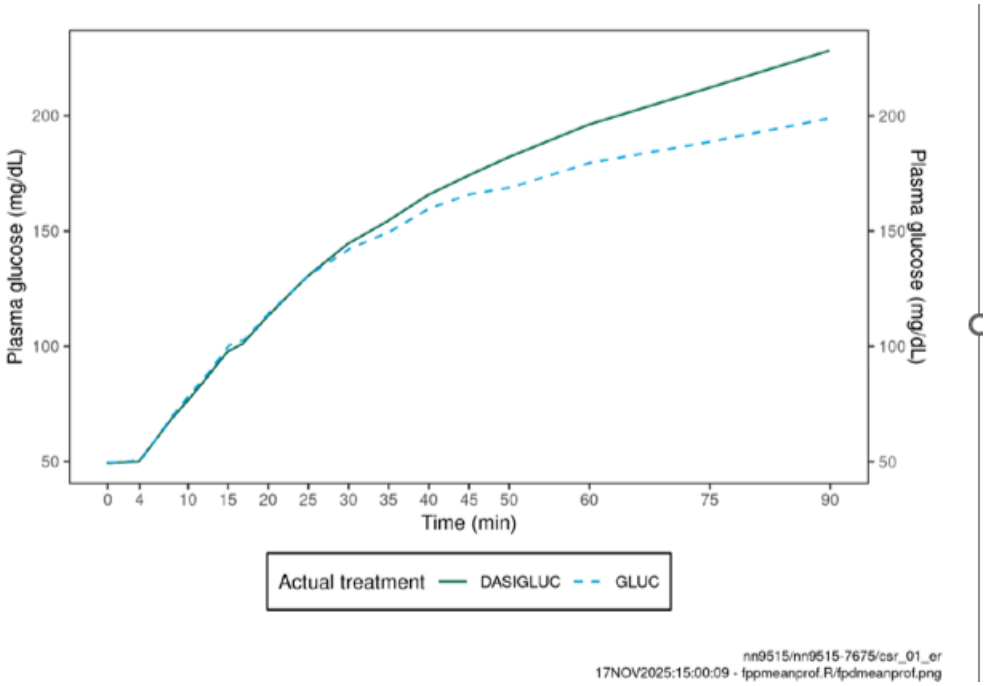
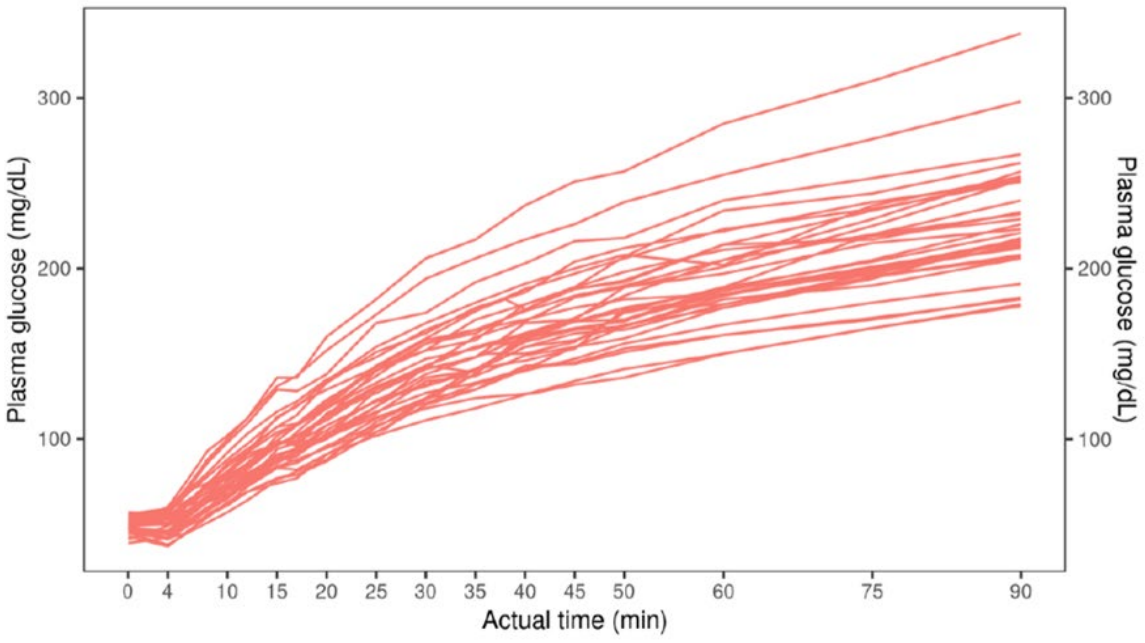


Figure 2. PD - Plasma glucose - Dasiglucagon - individual profiles - adults - full analysis set



Supportive secondary endpoint - time to PG recovery, adolescents

From 0 to 90 minutes after IMP injection, the observed mean (SD) time to PG recovery, where PG recovery is defined as the first increase in PG of ≥20 mg/dL (1.1 mmol/L) from baseline, was 7.22 (0.87) minutes with dasiglucagon.

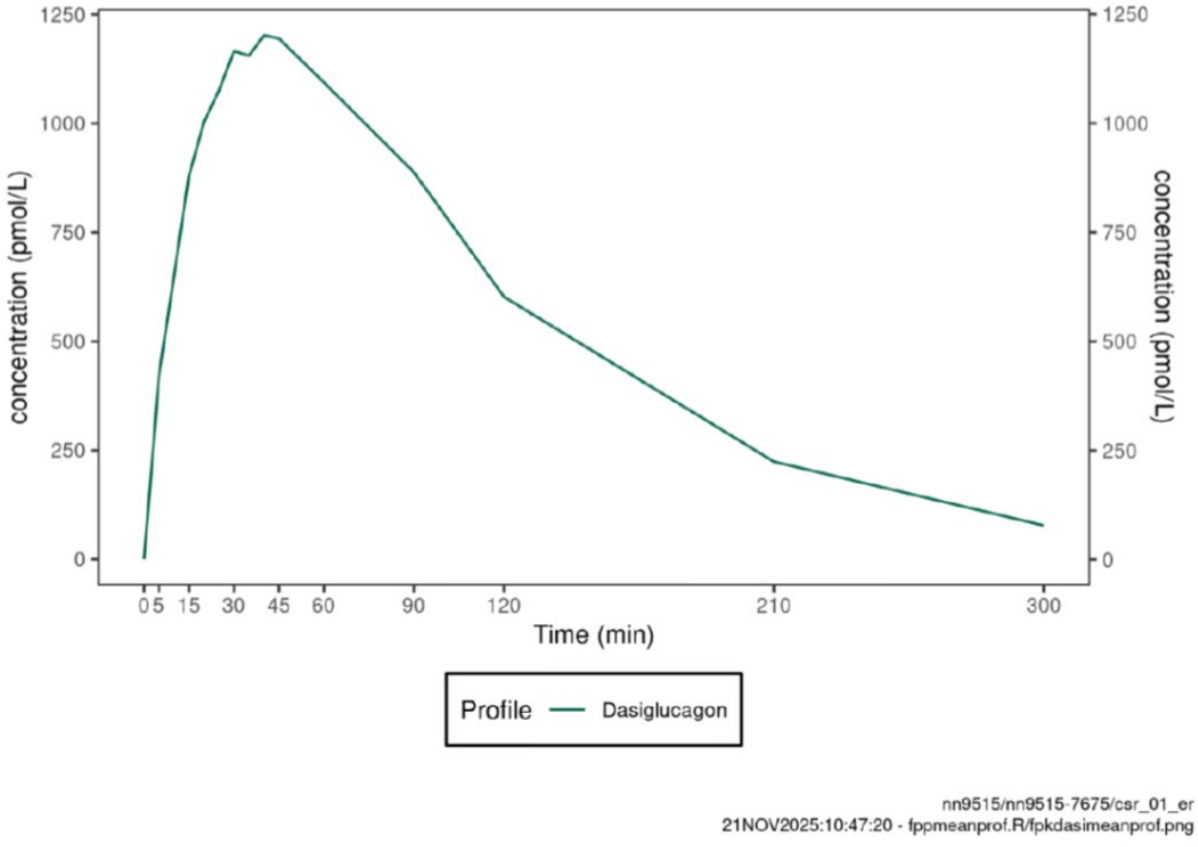
PK Dasiglucagon profile

From 0 to 30 minutes after IMP injection, the observed geometric mean (CV%) AUC of dasiglucagon after a single dose was: 346.39 (46.22) h*pmol/L.

From 0 to 5 hours after IMP injection, the observed geometric mean (CV%) Cmax of dasiglucagon after a single dose was: 1230.24 (33.47) pmol/L.

Data for this section are presented in Figure 3.

Figure 3. PK - Dasiglucagon - mean profile - linear-scale - adults - full analysis set



Safety results

The reported adverse events were limited to the expected gastrointestinal disorders: nausea, vomiting, and diarrhoea.

- The number and proportion of participant with treatment emergent adverse events were higher with dasiglucagon than with glucagon.

- All reported AEs were of mild intensity.

- All AEs were resolved completely.

- 2 adult participants, 1 in each of the dasiglucagon and glucagon groups, and one adolescent participant experienced severe (level 3) or clinically significant hypoglycaemia (level 2). All the episodes resolved without sequalae.

- No clinically significant changes were observed in laboratory parameters, vital signs, or injection site reaction.

- None of the participants was anti-drug antibody (ADA) positive.

Number of adverse events, adults

The number of adverse events from IMP injection (visit 2 day 1 and visit 3 day 1) until 28 days after IMP injection was: 29 events in 16 (48.5%) participants with dasiglucagon, 18 events in 9 (27.3%) participants with glucagon.

Number of adverse events, adolescents

The number of adverse events from IMP injection (visit 2 day 1 and visit 3 day 1) until 28 days after IMP injection was: 3 events in 2 (50.0%) participants with dasiglucagon.

Number of hypoglycaemic episodes, adults

The number of hypoglycaemic episodes from IMP injection (visit 2 day 1 and visit 3 day 1) until 12 hours after IMP injection is presented in the next table:

Table 4. Hypoglycaemic episodes - treatment-emergent - summary - adults - safety

	DASIGLUC			GLUC			Total		
	N	(%)	E	N	(%)	E	N	(%)	E
Number of participants	33			33			33		
Hypoglycaemia alert value (level 1)	0			2	(6.1)	2	2	(6.1)	2
Clinically significant hypoglycaemia (level 2)	0			1	(3.0)	1	1	(3.0)	1
Severe hypoglycaemia (level 3)	1	(3.0)	1	0			1	(3.0)	1
Severe (level 3) or clinically significant (level 2) hypoglycaemia	1	(3.0)	1	1	(3.0)	1	2	(6.1)	2

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of events

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Cross-reference: TFL 8.3.1.15

Table 5. TEAEs - by system organ class and preferred term - summary - adults - safety analysis set

	DASIGLUC			GLUC			Total		
	N	(%)	E	N	(%)	E	N	(%)	E
Number of participants	33			33			33		
Events	16	(48.5)	29	9	(27.3)	18	19	(57.6)	47
Gastrointestinal disorders	16	(48.5)	29	9	(27.3)	18	19	(57.6)	47
Nausea	15	(45.5)	15	9	(27.3)	9	18	(54.5)	24
Vomiting	13	(39.4)	13	8	(24.2)	8	15	(45.5)	21
Diarrhoea	1	(3.0)	1	1	(3.0)	1	2	(6.1)	2

%: Percentage of participants, E: Number of events, N: Number of participants.
In-study period: the period from the time of drug administration until 28 days after.
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Cross-reference: TFL 8.3.1.3

2.3.3. Discussion on clinical aspects

The study was conducted to evaluate efficacy and safety of dasiglucagon in a population (n=33) of adult Asian non-Japanese and Japanese participants with type 1 diabetes mellitus (T1D), and in a Japanese adolescent cohort (n=4) with T1D. The main aims of the study were to confirm the effect on glycaemic response of a single 0.6 mg s.c. injection of dasiglucagon for the treatment of insulin-induced hypoglycaemia in Asian adults with T1D, and investigation of dasiglucagon in a Japanese adolescent cohort.

Dasiglucagon showed non-inferiority at the primary endpoint, that was time to plasma glucose (PG) recovery in Japanese adults (recovery from a condition of hypoglycaemia induced by insulin administration). After IMP injection, the estimated mean time to plasma glucose recovery, were 8.73 minutes with subcutaneous dasiglucagon vs 8.15 minutes with intramuscular glucagon, the difference being less than the non-inferiority margin calculated for the primary objective (a difference lower than 3 minutes was calculated as non-inferiority margin). The other efficacy endpoints showed results with a similar trend: dasiglucagon increased blood glucose levels in a manner similar to glucagon, but with small numerical differences usually in favour of the comparator glucagon.

In a small cohort (n=4) of Japanese adolescents with T1D, dasiglucagon demonstrated its effect with a mean time to plasma glucose recovery of 7.22 minutes. There was no comparator arm in this case, but the fact that the recovery time was shorter than what observed in the adult population should be reassuring regarding efficacy in adolescents.

The safety profile was overall tolerable, however dasiglucagon had a higher incidence of AEs compared to glucagon; moreover, in dasiglucagon arm was observed a case of severe hypoglycaemia (i.e. level 3, severe cognitive impairment requiring external assistance for recovery) whereas glucagon had at most a case of clinically significant hypoglycaemia (i.e. level 2). The Level 3 event was probably related to low liver glycogen storage. Gastrointestinal AEs in adults, such as nausea and vomiting, were more frequent with dasiglucagon compared to glucagon.

The MAH provided more details of the level 3 hypoglycaemia event. The participant with BMI above 20 kg/m²was enrolled. The participant received the IMP; a single 0.6 mg subcutaneous injection of dasiglucagon. The participant experienced severe hypoglycaemia (Level 3, severe cognitive impairment requiring external assistance for recovery). The hypoglycaemic event occurred approximately 3.5 hours after the previous dasiglucagon administration. Adverse events nausea and vomiting preceded the hypoglycaemic event. The lowest recorded plasma glucose level was in the range 50-55 mg/dL. The patient received glucose as a rescue treatment. The investigator did not consider the event as a Serious Adverse Event.

In the glucagon period of the sequence in adults there were 1 treatment emergent hypoglycaemic episode (level 2). The participants' BMI is above 20 kg/m². The participant received the IMP; a single intramuscular injection of 1 mg glucagon. On the same day, the participant experienced an adverse event of clinically significant hypoglycaemia (level 2, the participant did not need assistance). The lowest recorded plasma glucose level was in the range of 50-55 mg/dL. There were no other treatment emergent adverse events, and the patient did not receive any rescue medication for the event. The investigator did not consider the event as a Serious Adverse Event. Even if the Investigator did not consider the AE as a SAE, however it can be argued that a level 3 hypoglycaemia, requiring rescue therapy administered by another person, could be considered as a potential life-threatening condition and thus it might warrant the status of SAE.

The AE occurred about 3.5 hours after the administration of dasiglucagon, however no further information was provided. From the figure showing the plasma glucose in individual patients, it seems that all the adult patients responded to dasiglucagon, therefore it can be deduced that in this patient the administration of dasiglucagon elicited a correct response of increasing plasma glucose but after 3 hours an event of hypoglycaemia occurred.

In conclusion, it is not completely clear the relationship between the observed AE of severe hypoglycaemia (Level 3, severe cognitive impairment requiring external assistance for recovery) in 1 patient and dasiglucagon administration; however, the efficacy data seems to show the effect of dasiglucagon in all patients, therefore, probably, the hypoglycaemic event was due to low liver glycogen storages, with consequent relapsing hypoglycaemia (carbohydrates should be given to restore liver glycogen; see point 5 at SmPC 4.2 section, and 4.4 section). Since the SmPC well describes the measure to be taken (i.e. carbohydrates should be given to restore liver glycogen) the issue is not further pursued.

The PK results showed that dasiglucagon exposure in Japanese adults with T1D seems in line with previous studies. PK in adolescents was not determined, due to a bioanalytical issue affecting the reproducibility of PK samples.

In conclusion, dasiglucagon showed non-inferiority, compared to glucagon, in increasing blood glucose levels, in the experimental setting of an insulin-induced hypoglycaemic state in an Asian adult population. The safety profile was slightly worse than the comparator glucagon.

3. Rapporteur's CHMP overall conclusion and recommendation

Dasiglucagon showed non-inferiority compared to glucagon in increasing blood glucose levels in the experimental setting of an insulin-induced hypoglycaemic state in adults. No new safety concerns are raised. No regulatory action is required.

☒ **Fulfilled:**

No regulatory action required.