



Clinical trial results: Assessment of Intranasal Glucagon in Children and Adolescents with Type 1 Diabetes Summary

EudraCT number	2015-003252-40
Trial protocol	Outside EU/EEA
Global end of trial date	13 January 2015

Results information

Result version number	v1
This version publication date	22 October 2017
First version publication date	22 October 2017

Trial information

Trial identification

Sponsor protocol code	I8R-MC-IGBB
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01997411
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Alias: I8R-MC-IGBB, Trial Number : 16418, Additional Trial Identifier: AMG103

Notes:

Sponsors

Sponsor organisation name	Jaeb Center for Health Research
Sponsor organisation address	15310 Amberly Drive, Tampa, United States,
Public contact	Study Principal Investigator, Jaeb Center for Health Research, kruedy@jaeb.org
Scientific contact	Study Principal Investigator, Jaeb Center for Health Research, kruedy@jaeb.org
Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, IN, United States, 46285
Public contact	Available Mon - Fri 9 AM - 5 PM EST , Eli Lilly and Company, 1 877-CTLilly,
Scientific contact	Available Mon - Fri 9 AM - 5 PM EST , Eli Lilly and Company, 1 877-285-4559,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-001657-PIP01-14
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No	No

1901/2006 apply to this trial?	
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Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 January 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to assess how glucagon administered as a puff into the nose (AMG504-1) works in children and adolescents compared with commercially-available glucagon given by injection. In addition, the safety and tolerability of glucagon given as a puff into the nose was evaluated.

Protection of trial subjects:

Guidelines as drawn up by the institutional review board were followed with regard to the treatment of human subjects in the study. These guidelines meet the requirements of the Declaration of Helsinki; they also meet the requirements of the United States Code of Federal Regulations (Title 21, Part 56), the Directive 2001/20/EC (Europe) and the Tri-Council Policy Statement (Canada). This study was performed in compliance with Good Clinical Practice.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 December 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 48
Worldwide total number of subjects	48
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	35
Adolescents (12-17 years)	13
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

No Text Entered

Pre-assignment

Screening details:

No Text Entered

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	No
Arm title	4 to<8 Years Old Intramuscular Glucagon Visit

Arm description:

Participants who weighed at least 25 kilograms (kg) were dosed 1 milligram (mg) of recombinant human glucagon United States Pharmacopeia (USP) which was constituted in the commercially provided prefilled disposable syringe containing 1milliliter (mL) of diluting solution. For participants who weighed less than 25 kg, the dose was 0.5 mg constituted in 1 mL of diluting solution. This was completed at one visit and was the only visit for this cohort.

Arm type	Active comparator
Investigational medicinal product name	Intramuscular Glucagon
Investigational medicinal product code	
Other name	Glucagon, GlucaGen HypoKit
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

Participants who weighed at least 25 kg were dosed 1 mg of recombinant human glucagon USP which was constituted in the commercially provided prefilled disposable syringe containing 1 mL of diluting solution. For participants who weighed less than 25 kg, the dose was 0.5 mg constituted in 1 mL of diluting solution. This was completed at one visit and was the only visit for this cohort.

Arm title	4 to <8 Years IN Glucagon 2.0 mg 1st Visit/3.0 mg 2nd Visit
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Arm description:

At the first visit, a glucagon dose of 2.0 mg for participants 4 to less than 8 years of age (equivalent to 20 mg of AMG504-1 dry powder) was administered in a nostril with a prefilled delivery device that delivers a single dose upon activation.

At the second visit, a glucagon dose of 3.0 mg for participants 4 to less than 8 years of age (equivalent to 30 mg of AMG504-1 dry powder) was administered in a nostril with a prefilled delivery device that delivers a single dose upon activation.

Arm type	Experimental
Investigational medicinal product name	Intranasal Glucagon
Investigational medicinal product code	
Other name	AMG504-1
Pharmaceutical forms	Nasal powder
Routes of administration	Intranasal use

Dosage and administration details:

At the first visit, a glucagon dose of 2.0 mg for participants 4 to less than 8 years of age (equivalent to 20 mg of AMG504-1 dry powder) was administered in a nostril with a prefilled delivery device that delivers a single dose upon activation.

At the second visit, a glucagon dose of 3.0 mg for participants 4 to less than 8 years of age (equivalent to 30 mg of AMG504-1 dry powder) was administered in a nostril with a prefilled delivery device that delivers a single dose upon activation.

Arm title	4 to <8 Years IN Glucagon 3.0 mg 1st Visit/2.0 mg 2nd Visit
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Arm description:

At the first visit, a glucagon dose of 3.0 mg for participants 4 to less than 8 years of age (equivalent to 30 mg of AMG504-1 dry powder) was administered in a nostril with a prefilled delivery device that delivers a single dose upon activation.

At the second visit, a glucagon dose of 2.0 mg for participants 4 to less than 8 years of age (equivalent to 20 mg of AMG504-1 dry powder) was administered in a nostril with a prefilled delivery device that delivers a single dose upon activation.

Arm type	Experimental
Investigational medicinal product name	Intranasal Glucagon
Investigational medicinal product code	
Other name	AMG504-1
Pharmaceutical forms	Nasal powder
Routes of administration	Intranasal use

Dosage and administration details:

At the first visit, a glucagon dose of 3.0 mg for participants 4 to less than 8 years of age (equivalent to 30 mg of AMG504-1 dry powder) was administered in a nostril with a prefilled delivery device that delivers a single dose upon activation.

At the second visit, a glucagon dose of 2.0 mg for participants 4 to less than 8 years of age (equivalent to 20 mg of AMG504-1 dry powder) was administered in a nostril with a prefilled delivery device that delivers a single dose upon activation.

Arm title	8 to <12 Years Old Intramuscular Glucagon Visit
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Arm description:

Participants who weighed at least 25 kg were dosed 1 mg of recombinant human glucagon USP which was constituted in the commercially provided prefilled disposable syringe containing 1 mL of diluting solution. For participants who weighed less than 25 kg, the dose was 0.5 mg constituted in 1 mL of diluting solution. This was completed at one visit and was the only visit for this cohort.

Arm type	Active comparator
Investigational medicinal product name	Intramuscular Glucagon
Investigational medicinal product code	
Other name	Glucagon, GlucaGen HypoKit
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

Participants who weighed at least 25 kg were dosed 1 mg of recombinant human glucagon USP which was constituted in the commercially provided prefilled disposable syringe containing 1 mL of diluting solution. For participants who weighed less than 25 kg, the dose was 0.5 mg constituted in 1 mL of diluting solution. This was completed at one visit and was the only visit for this cohort.

Arm title	8 to <12 Years IN Glucagon 2.0 mg 1st Visit/3.0 mg 2nd Visit
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Arm description:

At the first visit, a glucagon dose of 2.0 mg for participants 4 to less than 8 years of age (equivalent to 20 mg of AMG504-1 dry powder) was administered in a nostril with a prefilled delivery device that delivers a single dose upon activation.

At the second visit, a glucagon dose of 3.0 mg for participants 4 to less than 8 years of age (equivalent to 30 mg of AMG504-1 dry powder) was administered in a nostril with a prefilled delivery device that delivers a single dose upon activation.

Arm type	Experimental
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Investigational medicinal product name	Intranasal Glucagon
Investigational medicinal product code	
Other name	AMG504-1
Pharmaceutical forms	Nasal powder
Routes of administration	Intranasal use

Dosage and administration details:

At the first visit, a glucagon dose of 2.0 mg for participants 4 to less than 8 years of age (equivalent to 20 mg of AMG504-1 dry powder) was administered in a nostril with a prefilled delivery device that delivers a single dose upon activation.

At the second visit, a glucagon dose of 3.0 mg for participants 4 to less than 8 years of age (equivalent to 30 mg of AMG504-1 dry powder) was administered in a nostril with a prefilled delivery device that delivers a single dose upon activation.

Arm title	8 to <12 Years IN Glucagon 3.0 mg 1st Visit/2.0 mg 2nd Visit
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Arm description:

At the first visit, a glucagon dose of 3.0 mg for participants 4 to less than 8 years of age (equivalent to 30 mg of AMG504-1 dry powder) was administered in a nostril with a prefilled delivery device that delivers a single dose upon activation.

At the second visit, a glucagon dose of 2.0 mg for participants 4 to less than 8 years of age (equivalent to 20 mg of AMG504-1 dry powder) was administered in a nostril with a prefilled delivery device that delivers a single dose upon activation.

Arm type	Experimental
Investigational medicinal product name	Intranasal Glucagon
Investigational medicinal product code	
Other name	AMG504-1
Pharmaceutical forms	Nasal powder
Routes of administration	Intranasal use

Dosage and administration details:

At the first visit, a glucagon dose of 3.0 mg for participants 4 to less than 8 years of age (equivalent to 30 mg of AMG504-1 dry powder) was administered in a nostril with a prefilled delivery device that delivers a single dose upon activation.

At the second visit, a glucagon dose of 2.0 mg for participants 4 to less than 8 years of age (equivalent to 20 mg of AMG504-1 dry powder) was administered in a nostril with a prefilled delivery device that delivers a single dose upon activation.

Arm title	12 to <17 Years IN Glucagon 1st Visit/IM Glucagon 2nd Visit
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Arm description:

At the first visit, a glucagon dose of 3.0 mg (equivalent to 30 mg of AMG504-1 dry powder) was administered in a nostril with a prefilled delivery device that delivers a single dose upon activation.

At the second visit, participants who weighed at least 25 kg were dosed 1 mg of recombinant human glucagon USP which was constituted in the commercially provided prefilled disposable syringe containing 1 mL of diluting solution. For participants who weighed less than 25 kg, the dose was 0.5 mg constituted in 1 mL of diluting solution.

Arm type	Experimental
Investigational medicinal product name	Intramuscular Glucagon
Investigational medicinal product code	
Other name	Glucagon, GlucaGen HypoKit
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

At the first visit, a glucagon dose of 3.0 mg (equivalent to 30 mg of AMG504-1 dry powder) was administered in a nostril with a prefilled delivery device that delivers a single dose upon activation.

At the second visit, participants who weighed at least 25 kg were dosed 1 mg of recombinant human glucagon USP which was constituted in the commercially provided prefilled disposable syringe containing 1 mL of diluting solution. For participants who weighed less than 25 kg, the dose was 0.5 mg constituted in 1 mL of diluting solution.

Investigational medicinal product name	Intranasal Glucagon
Investigational medicinal product code	
Other name	AMG504-1
Pharmaceutical forms	Nasal powder
Routes of administration	Intranasal use

Dosage and administration details:

At the first visit, a glucagon dose of 3.0 mg (equivalent to 30 mg of AMG504-1 dry powder) was administered in a nostril with a prefilled delivery device that delivers a single dose upon activation.

At the second visit, participants who weighed at least 25 kg were dosed 1 mg of recombinant human glucagon USP which was constituted in the commercially provided prefilled disposable syringe containing 1 mL of diluting solution. For participants who weighed less than 25 kg, the dose was 0.5 mg constituted in 1 mL of diluting solution.

Arm title	12 to <17 Years IM Glucagon 1st Visit/IN Glucagon 2nd Visit
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Arm description:

At the first visit, participants who weighed at least 25 kg were dosed 1 mg of recombinant human glucagon USP which was constituted in the commercially provided prefilled disposable syringe containing 1 mL of diluting solution. For participants who weighed less than 25 kg, the dose was 0.5 mg constituted in 1 mL of diluting solution.

At the second visit, a glucagon dose of 3.0 mg (equivalent to 30 mg of AMG504-1 dry powder) was administered in a nostril with a prefilled delivery device that delivers a single dose upon activation.

Arm type	Active comparator
Investigational medicinal product name	Intramuscular Glucagon
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Other name	Glucagon, GlucaGen HypoKit
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

At the first visit, participants who weighed at least 25 kg were dosed 1 mg of recombinant human glucagon USP which was constituted in the commercially provided prefilled disposable syringe containing 1 mL of diluting solution. For participants who weighed less than 25 kg, the dose was 0.5 mg constituted in 1 mL of diluting solution.

At the second visit, a glucagon dose of 3.0 mg (equivalent to 30 mg of AMG504-1 dry powder) was administered in a nostril with a prefilled delivery device that delivers a single dose upon activation.

Investigational medicinal product name	Intranasal Glucagon
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Other name	AMG504-1
Pharmaceutical forms	Nasal powder
Routes of administration	Intranasal use

Dosage and administration details:

At the first visit, participants who weighed at least 25 kg were dosed 1 mg of recombinant human glucagon USP which was constituted in the commercially provided prefilled disposable syringe containing 1 mL of diluting solution. For participants who weighed less than 25 kg, the dose was 0.5 mg constituted in 1 mL of diluting solution.

At the second visit, a glucagon dose of 3.0 mg (equivalent to 30 mg of AMG504-1 dry powder) was administered in a nostril with a prefilled delivery device that delivers a single dose upon activation.

Number of subjects in period 1	4 to <8 Years Old Intramuscular Glucagon Visit	4 to <8 Years IN Glucagon 2.0 mg 1st Visit/3.0 mg 2nd Visit	4 to <8 Years IN Glucagon 3.0 mg 1st Visit/2.0 mg 2nd Visit
Started	6	6	6
Completed	6	6	6
Not completed	0	0	0
Consent withdrawn by subject	-	-	-

Number of subjects in period 1	8 to <12 Years Old Intramuscular Glucagon Visit	8 to <12 Years IN Glucagon 2.0 mg 1st Visit/3.0 mg 2nd Visit	8 to <12 Years IN Glucagon 3.0 mg 1st Visit/2.0 mg 2nd Visit
Started	6	6	6
Completed	6	6	5
Not completed	0	0	1
Consent withdrawn by subject	-	-	1

Number of subjects in period 1	12 to <17 Years IN Glucagon 1st Visit/IM Glucagon 2nd Visit	12 to <17 Years IM Glucagon 1st Visit/IN Glucagon 2nd Visit
Started	6	6
Completed	6	6
Not completed	0	0
Consent withdrawn by subject	-	-

Baseline characteristics

Reporting groups

Reporting group title	Overall Study
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Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	48	48	
Age categorical			
Units: Subjects			

Age Continuous			
Units: years			
arithmetic mean	10.2		
standard deviation	± 3.5	-	
Gender, Male/Female			
Units:			
Female	16	16	
Male	32	32	
Region of Enrollment			
Units: Subjects			
United States	48	48	
Duration of Diabetes			
Units: years			
median	3.9		
inter-quartile range (Q1-Q3)	2.6 to 6	-	
Local HbA1c (glycated haemoglobin)			
Units: Percentage			
arithmetic mean	8		
standard deviation	± 1	-	

Subject analysis sets

Subject analysis set title	4 to<8 Years Old Intramuscular Glucagon
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Participants who were 4 to < 8 years old at the time of enrollment into the study randomized to receive only the intramuscular glucagon at one visit.

Subject analysis set title	4 to<8 Years Old Intranasal Glucagon 2mg then 3mg
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Participants who were 4 to < 8 years old at the time of enrollment into the study randomized to receive 2.0 then 3.0 mg of intranasal glucagon at two separate visits.

Subject analysis set title	4 to<8 Years Old Intranasal Glucagon 3mg then 2mg
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Participants who were 4 to < 8 years old at the time of enrollment into the study randomized to receive 3.0 then 2.0 mg of intranasal glucagon at two separate visits.

Subject analysis set title	8 to <12 Intramuscular Glucagon
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Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants who were 8 to < 12 years old at the time of enrollment into the study randomized to receive only the intramuscular glucagon at one visit.	
Subject analysis set title	8 to <12 Years Old Intranasal Glucagon 2mg then 3mg
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants who were 8 to < 12 years old at the time of enrollment into the study randomized to receive 2.0 then 3.0 mg of intranasal glucagon at two separate visits.	
Subject analysis set title	8 to <12 Years Old Intranasal Glucagon 3mg then 2mg
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants who were 8 to < 12 years old at the time of enrollment into the study randomized to receive 3.0 then 2.0 mg of intranasal glucagon at two separate visits.	
Subject analysis set title	12 to <17 Years Old Intranasal then Intramuscular Glucagon
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants who were 12 to < 17 years old at the time of enrollment into the study randomized to receive intranasal glucagon then intramuscular glucagon at two separate visits.	
Subject analysis set title	12 to <17 Years Old Intramuscular Glucagon then Intranasal
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants who were 12 to < 17 years old at the time of enrollment into the study randomized to receive intramuscular glucagon then intranasal glucagon at two separate visits.	

Reporting group values	4 to<8 Years Old Intramuscular Glucagon	4 to<8 Years Old Intranasal Glucagon 2mg then 3mg	4 to<8 Years Old Intranasal Glucagon 3mg then 2mg
Number of subjects	6	12	12
Age categorical Units: Subjects			

Age Continuous Units: years arithmetic mean standard deviation	6.1 ± 1.6	6.7 ± 1	±
Gender, Male/Female Units:			
Female	0	3	
Male	6	9	
Region of Enrollment Units: Subjects			
United States	6	12	
Duration of Diabetes Units: years median inter-quartile range (Q1-Q3)	3.1 2.1 to 3.8	2.7 1.8 to 3.6	
Local HbA1c (glycated haemoglobin) Units: Percentage arithmetic mean standard deviation	7.6 ± 0.5	8.3 ± 0.8	±

Reporting group values	8 to <12 Intramuscular	8 to <12 Years Old Intranasal Glucagon	8 to <12 Years Old Intranasal Glucagon
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	Glucagon	2mg then 3mg	3mg then 2mg
Number of subjects	6	12	12
Age categorical			
Units: Subjects			

Age Continuous			
Units: years			
arithmetic mean			
standard deviation	±	±	±
Gender, Male/Female			
Units:			
Female			
Male			
Region of Enrollment			
Units: Subjects			
United States			
Duration of Diabetes			
Units: years			
median			
inter-quartile range (Q1-Q3)			
Local HbA1c (glycated haemoglobin)			
Units: Percentage			
arithmetic mean			
standard deviation	±	±	±

Reporting group values	12 to <17 Years Old Intranasal then Intramuscular Glucagon	12 to <17 Years Old Intramuscular Glucagon then Intranasal	
Number of subjects	12	12	
Age categorical			
Units: Subjects			

Age Continuous			
Units: years			
arithmetic mean			
standard deviation	±	±	
Gender, Male/Female			
Units:			
Female			
Male			
Region of Enrollment			
Units: Subjects			
United States			
Duration of Diabetes			
Units: years			
median			
inter-quartile range (Q1-Q3)			
Local HbA1c (glycated haemoglobin)			
Units: Percentage			
arithmetic mean			
standard deviation	±	±	

End points

End points reporting groups

Reporting group title	4 to <8 Years Old Intramuscular Glucagon Visit
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Reporting group description:

Participants who weighed at least 25 kilograms (kg) were dosed 1 milligram (mg) of recombinant human glucagon United States Pharmacopeia (USP) which was constituted in the commercially provided prefilled disposable syringe containing 1 milliliter (mL) of diluting solution. For participants who weighed less than 25 kg, the dose was 0.5 mg constituted in 1 mL of diluting solution. This was completed at one visit and was the only visit for this cohort.

Reporting group title	4 to <8 Years IN Glucagon 2.0 mg 1st Visit/3.0 mg 2nd Visit
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Reporting group description:

At the first visit, a glucagon dose of 2.0 mg for participants 4 to less than 8 years of age (equivalent to 20 mg of AMG504-1 dry powder) was administered in a nostril with a prefilled delivery device that delivers a single dose upon activation.

At the second visit, a glucagon dose of 3.0 mg for participants 4 to less than 8 years of age (equivalent to 30 mg of AMG504-1 dry powder) was administered in a nostril with a prefilled delivery device that delivers a single dose upon activation.

Reporting group title	4 to <8 Years IN Glucagon 3.0 mg 1st Visit/2.0 mg 2nd Visit
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Reporting group description:

At the first visit, a glucagon dose of 3.0 mg for participants 4 to less than 8 years of age (equivalent to 30 mg of AMG504-1 dry powder) was administered in a nostril with a prefilled delivery device that delivers a single dose upon activation.

At the second visit, a glucagon dose of 2.0 mg for participants 4 to less than 8 years of age (equivalent to 20 mg of AMG504-1 dry powder) was administered in a nostril with a prefilled delivery device that delivers a single dose upon activation.

Reporting group title	8 to <12 Years Old Intramuscular Glucagon Visit
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Reporting group description:

Participants who weighed at least 25 kg were dosed 1 mg of recombinant human glucagon USP which was constituted in the commercially provided prefilled disposable syringe containing 1 mL of diluting solution. For participants who weighed less than 25 kg, the dose was 0.5 mg constituted in 1 mL of diluting solution. This was completed at one visit and was the only visit for this cohort.

Reporting group title	8 to <12 Years IN Glucagon 2.0 mg 1st Visit/3.0 mg 2nd Visit
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Reporting group description:

At the first visit, a glucagon dose of 2.0 mg for participants 4 to less than 8 years of age (equivalent to 20 mg of AMG504-1 dry powder) was administered in a nostril with a prefilled delivery device that delivers a single dose upon activation.

At the second visit, a glucagon dose of 3.0 mg for participants 4 to less than 8 years of age (equivalent to 30 mg of AMG504-1 dry powder) was administered in a nostril with a prefilled delivery device that delivers a single dose upon activation.

Reporting group title	8 to <12 Years IN Glucagon 3.0 mg 1st Visit/2.0 mg 2nd Visit
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Reporting group description:

At the first visit, a glucagon dose of 3.0 mg for participants 4 to less than 8 years of age (equivalent to 30 mg of AMG504-1 dry powder) was administered in a nostril with a prefilled delivery device that delivers a single dose upon activation.

At the second visit, a glucagon dose of 2.0 mg for participants 4 to less than 8 years of age (equivalent to 20 mg of AMG504-1 dry powder) was administered in a nostril with a prefilled delivery device that delivers a single dose upon activation.

Reporting group title	12 to <17 Years IN Glucagon 1st Visit/IM Glucagon 2nd Visit
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Reporting group description:

At the first visit, a glucagon dose of 3.0 mg (equivalent to 30 mg of AMG504-1 dry powder) was administered in a nostril with a prefilled delivery device that delivers a single dose upon activation.

At the second visit, participants who weighed at least 25 kg were dosed 1 mg of recombinant human glucagon USP which was constituted in the commercially provided prefilled disposable syringe containing 1 mL of diluting solution. For participants who weighed less than 25 kg, the dose was 0.5 mg constituted in 1 mL of diluting solution.

Reporting group title	12 to <17 Years IM Glucagon 1st Visit/IN Glucagon 2nd Visit
Reporting group description:	
At the first visit, participants who weighed at least 25 kg were dosed 1 mg of recombinant human glucagon USP which was constituted in the commercially provided prefilled disposable syringe containing 1 mL of diluting solution. For participants who weighed less than 25 kg, the dose was 0.5 mg constituted in 1 mL of diluting solution.	
At the second visit, a glucagon dose of 3.0 mg (equivalent to 30 mg of AMG504-1 dry powder) was administered in a nostril with a prefilled delivery device that delivers a single dose upon activation.	
Subject analysis set title	4 to<8 Years Old Intramuscular Glucagon
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants who were 4 to < 8 years old at the time of enrollment into the study randomized to receive only the intramuscular glucagon at one visit.	
Subject analysis set title	4 to<8 Years Old Intranasal Glucagon 2mg then 3mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants who were 4 to < 8 years old at the time of enrollment into the study randomized to receive 2.0 then 3.0 mg of intranasal glucagon at two separate visits.	
Subject analysis set title	4 to<8 Years Old Intranasal Glucagon 3mg then 2mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants who were 4 to < 8 years old at the time of enrollment into the study randomized to receive 3.0 then 2.0 mg of intranasal glucagon at two separate visits.	
Subject analysis set title	8 to <12 Intramuscular Glucagon
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants who were 8 to < 12 years old at the time of enrollment into the study randomized to receive only the intramuscular glucagon at one visit.	
Subject analysis set title	8 to <12 Years Old Intranasal Glucagon 2mg then 3mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants who were 8 to < 12 years old at the time of enrollment into the study randomized to receive 2.0 then 3.0 mg of intranasal glucagon at two separate visits.	
Subject analysis set title	8 to <12 Years Old Intranasal Glucagon 3mg then 2mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants who were 8 to < 12 years old at the time of enrollment into the study randomized to receive 3.0 then 2.0 mg of intranasal glucagon at two separate visits.	
Subject analysis set title	12 to <17 Years Old Intranasal then Intramuscular Glucagon
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants who were 12 to < 17 years old at the time of enrollment into the study randomized to receive intranasal glucagon then intramuscular glucagon at two separate visits.	
Subject analysis set title	12 to <17 Years Old Intramuscular Glucagon then Intranasal
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants who were 12 to < 17 years old at the time of enrollment into the study randomized to receive intramuscular glucagon then intranasal glucagon at two separate visits.	

Primary: Percentage of Participants with \geq 25 mg/dL Rise in Plasma Glucose

End point title	Percentage of Participants with \geq 25 mg/dL Rise in Plasma Glucose ^[1]
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End point description:

One participant in the 4 to <8 year old 2.0 mg Intranasal Glucagon group was excluded since the participant did not receive glucagon due to blowing nose after IN administration. One participant in the 8 to <12 group withdrew after completion of the 3.0 mg Intranasal Glucagon visit and did not complete

the 2.0 mg Intranasal Glucagon visit.

End point type	Primary
End point timeframe:	
0 to 20 minutes following administration of glucagon	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Inferential statistics were calculated only as exploratory analysis for the maximum observed concentration (Cmax).

End point values	4 to<8 Years Old Intramuscular Glucagon	4 to<8 Years Old Intranasal Glucagon 2mg then 3mg	4 to<8 Years Old Intranasal Glucagon 3mg then 2mg	8 to <12 Intramuscular Glucagon
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	11	12	6
Units: percentage of participants				
number (not applicable)	100	100	100	100

End point values	8 to <12 Years Old Intranasal Glucagon 2mg then 3mg	8 to <12 Years Old Intranasal Glucagon 3mg then 2mg	12 to <17 Years Old Intranasal then Intramuscular Glucagon	12 to <17 Years Old Intramuscular Glucagon then Intranasal
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	12	12	12
Units: percentage of participants				
number (not applicable)	100	100	100	100

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Observed Concentration (Cmax) of Glucagon

End point title	Maximum Observed Concentration (Cmax) of Glucagon
End point description:	
One participant in the 4 to <8 year old 2.0 mg Intranasal Glucagon group was excluded since the participant did not receive glucagon due to blowing nose after IN administration. One participant in the 8 to <12 group withdrew after completion of the 3.0 mg Intranasal Glucagon visit and did not complete the 2.0 mg Intranasal Glucagon visit.	
End point type	Primary
End point timeframe:	
0 to 90 minutes following glucagon administration.	

End point values	4 to<8 Years Old Intramuscular Glucagon	4 to<8 Years Old Intranasal Glucagon 2mg then 3mg	4 to<8 Years Old Intranasal Glucagon 3mg then 2mg	8 to <12 Intramuscular Glucagon
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	11	12	6
Units: picogram per milliliter (pg/mL)				
arithmetic mean (standard deviation)	6343 (± 2029)	3531 (± 1762)	4033 (± 2435)	4817 (± 3086)

End point values	8 to <12 Years Old Intranasal Glucagon 2mg then 3mg	8 to <12 Years Old Intranasal Glucagon 3mg then 2mg	12 to <17 Years Old Intranasal then Intramuscular Glucagon	12 to <17 Years Old Intramuscular Glucagon then Intranasal
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	12	12	12
Units: picogram per milliliter (pg/mL)				
arithmetic mean (standard deviation)	2952 (± 1024)	5832 (± 2106)	4382 (± 3771)	3186 (± 2294)

Statistical analyses

Statistical analysis title	Cmax (2mg versus 3mg; 4 to 8 Years Old)
Comparison groups	4 to<8 Years Old Intranasal Glucagon 2mg then 3mg v 4 to<8 Years Old Intranasal Glucagon 3mg then 2mg
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9333
Method	ANOVA

Statistical analysis title	Cmax (IM versus 3mg; 4 to 8 Years Old)
Comparison groups	4 to<8 Years Old Intramuscular Glucagon v 4 to<8 Years Old Intranasal Glucagon 3mg then 2mg
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1156
Method	ANOVA

Statistical analysis title	Cmax (2mg versus 3mg; 8 to 12 Years Old)
Comparison groups	8 to <12 Years Old Intranasal Glucagon 2mg then 3mg v 8 to <12 Years Old Intranasal Glucagon 3mg then 2mg

Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0027
Method	ANOVA

Statistical analysis title	Cmax (IM versus 3mg; 8 to 12 Years Old)
Comparison groups	8 to <12 Intramuscular Glucagon v 8 to <12 Years Old Intranasal Glucagon 3mg then 2mg
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3599
Method	ANOVA

Statistical analysis title	Cmax (IM versus 3mg; 12 to 17 Years Old)
Comparison groups	12 to <17 Years Old Intramuscular Glucagon then Intranasal v 12 to <17 Years Old Intranasal then Intramuscular Glucagon
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1229
Method	ANOVA

Primary: Time to Maximum Concentration (Tmax) of glucagon

End point title	Time to Maximum Concentration (Tmax) of glucagon ^[2]
End point description: One participant in the 4 to <8 year old 2.0 mg Intranasal Glucagon group was excluded since the participant did not receive glucagon due to blowing nose after IN administration. One participant in the 8 to <12 group withdrew after completion of the 3.0 mg Intranasal Glucagon visit and did not complete the 2.0 mg Intranasal Glucagon visit.	
End point type	Primary
End point timeframe: 0 to 90 minutes following glucagon administration.	

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Inferential statistics were calculated only as exploratory analysis for the maximum observed concentration (Cmax).

End point values	4 to<8 Years Old Intramuscular Glucagon	4 to<8 Years Old Intranasal Glucagon 2mg then 3mg	4 to<8 Years Old Intranasal Glucagon 3mg then 2mg	8 to <12 Intramuscular Glucagon
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	11	12	6
Units: minutes				
arithmetic mean (inter-quartile range (Q1-Q3))	17 (5 to 30)	15 (10 to 20)	17 (10 to 60)	17 (5 to 30)

End point values	8 to <12 Years Old Intranasal Glucagon 2mg then 3mg	8 to <12 Years Old Intranasal Glucagon 3mg then 2mg	12 to <17 Years Old Intranasal then Intramuscular Glucagon	12 to <17 Years Old Intramuscular Glucagon then Intranasal
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	12	12	12
Units: minutes				
arithmetic mean (inter-quartile range (Q1-Q3))	15 (10 to 20)	15 (10 to 30)	17 (5 to 30)	20 (15 to 30)

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve from Time Zero to the Last Quantifiable Concentration (AUC0-t) of Glucagon

End point title	Area Under the Curve from Time Zero to the Last Quantifiable Concentration (AUC0-t) of Glucagon
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End point description:

One participant in the 4 to <8 year old 2.0 mg Intranasal Glucagon group was excluded since the participant did not receive glucagon due to blowing nose after IN administration. One participant in the 8 to <12 group withdrew after completion of the 3.0 mg Intranasal Glucagon visit and did not complete the 2.0 mg Intranasal Glucagon visit.

End point type	Secondary
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End point timeframe:

0 to 90 minutes following administration of glucagon

End point values	4 to<8 Years Old Intramuscular Glucagon	4 to<8 Years Old Intranasal Glucagon 2mg then 3mg	4 to<8 Years Old Intranasal Glucagon 3mg then 2mg	8 to <12 Intramuscular Glucagon
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	11	12	6
Units: hour (hr) per pg/mL				
arithmetic mean (standard deviation)	4158.18 (± 2051.23)	1844.86 (± 99.2)	2583.9 (± 1426.27)	3747.02 (± 2051.71)

End point values	8 to <12 Years Old Intranasal Glucagon 2mg then 3mg	8 to <12 Years Old Intranasal Glucagon 3mg then 2mg	12 to <17 Years Old Intranasal then Intramuscular Glucagon	12 to <17 Years Old Intramuscular Glucagon then Intranasal
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	12	12	12
Units: hour (hr) per pg/mL				
arithmetic mean (standard deviation)	1767.92 (\pm 683.33)	3191.44 (\pm 1139.19)	3267.09 (\pm 2841.57)	2123.19 (\pm 1318.94)

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum concentration (Cmax) of glucose

End point title	Maximum concentration (Cmax) of glucose
End point description:	
One participant in the 4 to <8 year old 2.0 mg Intranasal Glucagon group was excluded since the participant did not receive glucagon due to blowing nose after IN administration. One participant in the 8 to <12 group withdrew after completion of the 3.0 mg Intranasal Glucagon visit and did not complete the 2.0 mg Intranasal Glucagon visit.	
End point type	Secondary
End point timeframe:	
0 to 90 minutes following glucagon administration.	

End point values	4 to<8 Years Old Intramuscular Glucagon	4 to<8 Years Old Intranasal Glucagon 2mg then 3mg	4 to<8 Years Old Intranasal Glucagon 3mg then 2mg	8 to <12 Intramuscular Glucagon
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	11	12	6
Units: mg/dL				
arithmetic mean (standard deviation)	210.33 (\pm 28.08)	188.36 (\pm 51.55)	207 (\pm 43.27)	205.33 (\pm 24.34)

End point values	8 to <12 Years Old Intranasal Glucagon 2mg then 3mg	8 to <12 Years Old Intranasal Glucagon 3mg then 2mg	12 to <17 Years Old Intranasal then Intramuscular Glucagon	12 to <17 Years Old Intramuscular Glucagon then Intranasal
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	12	12	12
Units: mg/dL				
arithmetic mean (standard deviation)	201.27 (\pm)	205.83 (\pm)	193.83 (\pm)	178.17 (\pm)

27.95)	31.98)	33.32)	27.27)
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Statistical analyses

No statistical analyses for this end point

Secondary: Nasal and Non-Nasal Effects/Symptoms

End point title	Nasal and Non-Nasal Effects/Symptoms
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End point description:

Symptoms of runny nose, nasal congestion and/or itching, sneezing, watery and/or itchy eyes, redness of eyes, and itching of ears and/or throat will be assessed 15, 30, 60 and 90 minutes following administration of glucagon. This is done via the "Nasal Non-nasal Score Questionnaire". Each of the 9 symptoms is assigned an integer value from 0 to 3; higher values indicate more severe symptoms (a score of 0 indicates no symptoms). The reported results indicate the cohort median out of a possible maximum value of 27 (summing all 9 questions for each subject and reporting the median/ interquartile range across participants).

Analysis Population Description: One participant in the 8 to <12 group withdrew from the study after completion of the 3.0 mg Intranasal Glucagon visit and did not complete the 2.0 mg Intranasal Glucagon visit.

End point type	Secondary
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End point timeframe:

Timepoints of 15 minutes, 30 minutes, 60 minutes, and 90 minutes post glucagon administration.

End point values	4 to<8 Years Old Intramuscular Glucagon	4 to<8 Years Old Intranasal Glucagon 2mg then 3mg	4 to<8 Years Old Intranasal Glucagon 3mg then 2mg	8 to <12 Intramuscular Glucagon
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	12	12	6
Units: units on a scale				
median (inter-quartile range (Q1-Q3))				
Visit Arrival	0.5 (0 to 1)	0 (0 to 2)	0 (0 to 1)	0 (0 to 0)
15 minutes post glucagon administration	0 (0 to 1)	1 (0 to 3)	0.5 (0 to 2)	0 (0 to 1)
30 minutes post glucagon administration	0 (0 to 1)	1 (0 to 1.5)	0.5 (0 to 1.5)	0 (0 to 1)
60 minutes post glucagon administration	0 (0 to 0)	0.5 (0 to 2)	0 (0 to 1)	0 (0 to 0)
90 minutes post glucagon administration	0 (0 to 0)	0 (0 to 1.5)	0 (0 to 0.5)	0 (0 to 0)

End point values	8 to <12 Years Old Intranasal Glucagon 2mg then 3mg	8 to <12 Years Old Intranasal Glucagon 3mg then 2mg	12 to <17 Years Old Intranasal then Intramuscular Glucagon	12 to <17 Years Old Intramuscular Glucagon then Intranasal
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Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	12	12	12
Units: units on a scale				
median (inter-quartile range (Q1-Q3))				
Visit Arrival	0 (0 to 1)	0 (0 to 0.5)	0 (0 to 0.5)	0.5 (0 to 1)
15 minutes post glucagon administration	3 (0 to 4)	3 (1 to 4.5)	0 (0 to 0)	2 (1 to 4)
30 minutes post glucagon administration	2 (0 to 2)	2.5 (0.5 to 3.5)	0 (0 to 0)	1 (1 to 3)
60 minutes post glucagon administration	0 (0 to 1)	0.5 (0 to 1.5)	0 (0 to 0)	1 (0 to 2)
90 minutes post glucagon administration	0 (0 to 1)	0 (0 to 1)	0 (0 to 0)	1 (0 to 1)

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Effect Concentration Time Curve (AUEC0-1.5) of Glucose from Time Zero up to 90 Minutes

End point title	Area Under the Effect Concentration Time Curve (AUEC0-1.5) of Glucose from Time Zero up to 90 Minutes
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End point description:

One participant in the 4 to <8 year old 2.0 mg Intranasal Glucagon group was excluded since the participant did not receive glucagon due to blowing nose after IN administration. One participant in the 8 to <12 group withdrew after completion of the 3.0 mg Intranasal Glucagon visit and did not complete the 2.0 mg Intranasal Glucagon visit.

End point type	Secondary
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End point timeframe:

0 to 90 minutes following glucagon administration.

End point values	4 to<8 Years Old Intramuscular Glucagon	4 to<8 Years Old Intranasal Glucagon 2mg then 3mg	4 to<8 Years Old Intranasal Glucagon 3mg then 2mg	8 to <12 Intramuscular Glucagon
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	11	12	6
Units: hr.mg/dL				
arithmetic mean (standard deviation)	254.07 (± 32.75)	223.45 (± 69.43)	246.51 (± 54.4)	244.46 (± 27.51)

End point values	8 to <12 Years Old Intranasal Glucagon 2mg then 3mg	8 to <12 Years Old Intranasal Glucagon 3mg then 2mg	12 to <17 Years Old Intranasal then Intramuscular Glucagon	12 to <17 Years Old Intramuscular Glucagon then Intranasal
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	12	12	12
Units: hr.mg/dL				

arithmetic mean (standard deviation)	243.06 (\pm 34.4)	247.5 (\pm 39.39)	232.86 (\pm 39.63)	215.02 (\pm 29.29)
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Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Concentration (Tmax) of Glucose

End point title	Time to Maximum Concentration (Tmax) of Glucose
End point description:	
One participant in the 4 to <8 year old 2.0 mg Intranasal Glucagon group was excluded since the participant did not receive glucagon due to blowing nose after IN administration. One participant in the 8 to <12 group withdrew after completion of the 3.0 mg Intranasal Glucagon visit and did not complete the 2.0 mg Intranasal Glucagon visit.	
End point type	Secondary
End point timeframe:	
0 to 90 minutes following glucagon administration.	

End point values	4 to<8 Years Old Intramuscular Glucagon	4 to<8 Years Old Intranasal Glucagon 2mg then 3mg	4 to<8 Years Old Intranasal Glucagon 3mg then 2mg	8 to <12 Intramuscular Glucagon
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	11	12	6
Units: hours				
median (full range (min-max))	1 (0.67 to 1.5)	0.67 (0.33 to 1)	1 (0.5 to 1.5)	1.5 (1 to 1.5)

End point values	8 to <12 Years Old Intranasal Glucagon 2mg then 3mg	8 to <12 Years Old Intranasal Glucagon 3mg then 2mg	12 to <17 Years Old Intranasal then Intramuscular Glucagon	12 to <17 Years Old Intramuscular Glucagon then Intranasal
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	12	12	12
Units: hours				
median (full range (min-max))	1 (0.67 to 1.5)	1 (0.5 to 1.5)	1 (0.67 to 1.5)	1 (0.5 to 1.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Number and 99% Confidence Interval of Participants Achieving at least

a 25 mg/dl Rise in Blood Glucose above Basal Level

End point title	Number and 99% Confidence Interval of Participants Achieving at least a 25 mg/dl Rise in Blood Glucose above Basal Level
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End point description:

One participant in the 4 to <8 year old 2.0 mg Intranasal Glucagon group was excluded since the participant did not receive glucagon due to blowing nose after IN administration. One participant in the 8 to <12 group withdrew after completion of the 3.0 mg Intranasal Glucagon visit and did not complete the 2.0 mg Intranasal Glucagon visit.

End point type	Secondary
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End point timeframe:

0 to 90 minutes following glucagon administration.

End point values	4 to<8 Years Old Intramuscular Glucagon	4 to<8 Years Old Intranasal Glucagon 2mg then 3mg	4 to<8 Years Old Intranasal Glucagon 3mg then 2mg	8 to <12 Intramuscular Glucagon
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	11	12	6
Units: number of participants				
number (confidence interval 99%)	1 (0.4 to 1)	1 (0.6 to 1)	1 (0.6 to 1)	1 (0.4 to 1)

End point values	8 to <12 Years Old Intranasal Glucagon 2mg then 3mg	8 to <12 Years Old Intranasal Glucagon 3mg then 2mg	12 to <17 Years Old Intranasal then Intramuscular Glucagon	12 to <17 Years Old Intramuscular Glucagon then Intranasal
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	12	12	12
Units: number of participants				
number (confidence interval 99%)	1 (0.6 to 1)	1 (0.6 to 1)	1 (0.6 to 1)	1 (0.6 to 1)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Achieving ≥ 25 mg/dl Rise in Plasma Glucose above Basal Level

End point title	Time to Achieving ≥ 25 mg/dl Rise in Plasma Glucose above Basal Level
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End point description:

Time (in minutes) when all participants experienced a rise in glucose ≥ 25 mg/dL. This is an absolute number and is not a calculated statistic. There is no distribution per cohort.

Analysis Population Description: One participant in the 4 to <8 year old 2.0 mg Intranasal Glucagon group was excluded since the participant did not receive glucagon due to blowing nose after IN administration. One participant in the 8 to <12 group withdrew after completion of the 3.0 mg Intranasal Glucagon visit and did not complete the 2.0 mg Intranasal Glucagon visit.

End point type	Secondary
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End point timeframe:

0 to 90 minutes following glucagon administration.

End point values	4 to<8 Years Old Intramuscular Glucagon	4 to<8 Years Old Intranasal Glucagon 2mg then 3mg	4 to<8 Years Old Intranasal Glucagon 3mg then 2mg	8 to <12 Intramuscular Glucagon
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	11	12	6
Units: minutes				
number (not applicable)	10	20	15	20

End point values	8 to <12 Years Old Intranasal Glucagon 2mg then 3mg	8 to <12 Years Old Intranasal Glucagon 3mg then 2mg	12 to <17 Years Old Intranasal then Intramuscular Glucagon	12 to <17 Years Old Intramuscular Glucagon then Intranasal
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	12	12	12
Units: minutes				
number (not applicable)	20	15	20	20

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Entire Study

Adverse event reporting additional description:

One participant in the 8 to <12 group withdrew from the study after completion of the 3.0 mg Intranasal Glucagon visit and did not complete the 2.0 mg Intranasal Glucagon visit.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1 & 17
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Reporting groups

Reporting group title	4 to<8 Years Old Intramuscular Glucagon
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Reporting group description: -	
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Reporting group title	4 to<8 Years Old Intranasal Glucagon 2.0 mg
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Reporting group description: -	
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Reporting group title	4 to<8 Years Old Intranasal Glucagon 3.0 mg
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Reporting group description: -	
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Reporting group title	8 to <12 Years Old Intramuscular Glucagon
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Reporting group description: -	
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Reporting group title	8 to<12 Years Old Intranasal Glucagon 2.0mg
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Reporting group description: -	
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Reporting group title	8 to<12 Years Old Intranasal Glucagon 3.0mg
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Reporting group description: -	
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Reporting group title	12 to <17 Years Old Intramuscular Glucagon
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Reporting group description: -	
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Reporting group title	12 to<17 Years Old Intranasal Glucagon 3.0mg
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Reporting group description: -	
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Serious adverse events	4 to<8 Years Old Intramuscular Glucagon	4 to<8 Years Old Intranasal Glucagon 2.0 mg	4 to<8 Years Old Intranasal Glucagon 3.0 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 12 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Endocrine disorders			
Hypoglycemia	Additional description: Experienced a hypoglycemic event after receiving a bolus of insulin with lunch. Received 90 grams oral carbohydrates and made a full recovery.		
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	8 to <12 Years Old	8 to<12 Years Old	8 to<12 Years Old
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	Intramuscular Glucagon	Intranasal Glucagon 2.0mg	Intranasal Glucagon 3.0mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 12 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Endocrine disorders			
Hypoglycemia	Additional description: Experienced a hypoglycemic event after receiving a bolus of insulin with lunch. Received 90 grams oral carbohydrates and made a full recovery.		
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	12 to <17 Years Old Intramuscular Glucagon	12 to<17 Years Old Intranasal Glucagon 3.0mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Endocrine disorders			
Hypoglycemia	Additional description: Experienced a hypoglycemic event after receiving a bolus of insulin with lunch. Received 90 grams oral carbohydrates and made a full recovery.		
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	4 to<8 Years Old Intramuscular Glucagon	4 to<8 Years Old Intranasal Glucagon 2.0 mg	4 to<8 Years Old Intranasal Glucagon 3.0 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 6 (83.33%)	6 / 12 (50.00%)	5 / 12 (41.67%)
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Catheter site pain			

subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 12 (8.33%) 1	0 / 12 (0.00%) 0
Injection site discomfort subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Dizziness subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Eye disorders Eye irritation subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Lacrimation increase subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Ocular discomfort subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 12 (8.33%) 1	0 / 12 (0.00%) 0
Diarrhea subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Nausea subjects affected / exposed occurrences (all)	4 / 6 (66.67%) 4	4 / 12 (33.33%) 4	2 / 12 (16.67%) 2
Vomiting subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 12 (8.33%) 1	3 / 12 (25.00%) 3
Respiratory, thoracic and mediastinal disorders Nasal congestion subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Nasal discomfort			

subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Sneezing			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Rhinalgia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Headache			
subjects affected / exposed	0 / 6 (0.00%)	2 / 12 (16.67%)	1 / 12 (8.33%)
occurrences (all)	0	2	1

Non-serious adverse events	8 to <12 Years Old Intramuscular Glucagon	8 to<12 Years Old Intranasal Glucagon 2.0mg	8 to<12 Years Old Intranasal Glucagon 3.0mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	5 / 11 (45.45%)	6 / 12 (50.00%)
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Injection site discomfort			
subjects affected / exposed	3 / 6 (50.00%)	0 / 11 (0.00%)	0 / 12 (0.00%)
occurrences (all)	3	0	0
Dizziness			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Eye irritation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Lacrimation increase			

subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 11 (9.09%) 1	0 / 12 (0.00%) 0
Ocular discomfort subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 11 (0.00%) 0	1 / 12 (8.33%) 1
Diarrhea subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Nausea subjects affected / exposed occurrences (all)	3 / 6 (50.00%) 3	1 / 11 (9.09%) 1	1 / 12 (8.33%) 1
Vomiting subjects affected / exposed occurrences (all)	3 / 6 (50.00%) 3	3 / 11 (27.27%) 3	4 / 12 (33.33%) 4
Respiratory, thoracic and mediastinal disorders			
Nasal congestion subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Nasal discomfort subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Sneezing subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 11 (0.00%) 0	1 / 12 (8.33%) 1
Rhinalgia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Headache subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2	2 / 11 (18.18%) 2	4 / 12 (33.33%) 4

Non-serious adverse events	12 to <17 Years Old Intramuscular Glucagon	12 to<17 Years Old Intranasal Glucagon 3.0mg	
Total subjects affected by non-serious adverse events subjects affected / exposed	7 / 12 (58.33%)	9 / 12 (75.00%)	
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	
General disorders and administration site conditions Catheter site pain subjects affected / exposed occurrences (all) Injection site discomfort subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0	0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0	
Eye disorders Eye irritation subjects affected / exposed occurrences (all) Lacrimation increase subjects affected / exposed occurrences (all) Ocular discomfort subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0	1 / 12 (8.33%) 1 0 / 12 (0.00%) 0 1 / 12 (8.33%) 1	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Diarrhea subjects affected / exposed occurrences (all) Nausea	0 / 12 (0.00%) 0 0 / 12 (0.00%) 0	0 / 12 (0.00%) 0 0 / 12 (0.00%) 0	

subjects affected / exposed	1 / 12 (8.33%)	3 / 12 (25.00%)	
occurrences (all)	1	2	
Vomiting			
subjects affected / exposed	5 / 12 (41.67%)	4 / 12 (33.33%)	
occurrences (all)	5	4	
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	0 / 12 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
Nasal discomfort			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Sneezing			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Rhinalgia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Headache			
subjects affected / exposed	1 / 12 (8.33%)	4 / 12 (33.33%)	
occurrences (all)	1	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported