

**Clinical trial results:****A Multiple Center, Open Label, Prospective Study to Evaluate the Effectiveness and Ease-Of-Use of AMG504-1 Administered in the Home or School Environments for Treating Hypoglycemia in Children and Adolescents with T1D****Summary**

EudraCT number	2015-003732-12
Trial protocol	Outside EU/EEA
Global end of trial date	21 August 2015

**Results information**

Result version number	v1
This version publication date	18 June 2017
First version publication date	18 June 2017

**Trial information****Trial identification**

Sponsor protocol code	16423
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**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02402933
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 16423, Trial Alias: I8R-MC-B001, Other: AMG109

Notes:

**Sponsors**

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 1901/2006 apply to this trial?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 August 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	21 August 2015
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

Up to fifty (50) children and adolescents with type 1 diabetes (T1D) aged 4 to less than 18 years at time of enrolment will be selected for inclusion in the study. The target is to obtain treatment response and user-experience data following use of AMG504-1 (LY900018) in treating episodes of hypoglycemia.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 March 2015
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: 26
Worldwide total number of subjects	26
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)	11
Adolescents (12-17 years)	15
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Participants and their principal caregiver(s) (such as parents, family member, roommate, teacher, and coach) will be trained in the use of AMG504-1 (Dry-Mist nasal glucagon powder).

### Pre-assignment

Screening details:

No Text Entered

### Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

<b>Arm title</b>	Nasal Glucagon
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Arm description:

Four doses of AMG504-1 (3 mg glucagon powder per dose) were dispensed to participants and each participant/caregiver were encouraged to keep one dose with them at all times and the other doses in a convenient location.

Arm type	Experimental
Investigational medicinal product name	Nasal Glucagon
Investigational medicinal product code	
Other name	Dry-Mist nasal glucagon, AMG504-1, LY900018
Pharmaceutical forms	Inhalation solution
Routes of administration	Nasal use

Dosage and administration details:

3 mg glucagon powder

<b>Number of subjects in period 1</b>	Nasal Glucagon
Started	26
Received at least one dose of study drug	22
Completed	12
Not completed	14
Consent withdrawn by subject	4
Sponsor Decision	10

## Baseline characteristics

### Reporting groups

Reporting group title	Nasal Glucagon
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Reporting group description:

Four doses of AMG504-1 (3 mg glucagon powder per dose) were dispensed to participants and each participant/caregiver were encouraged to keep one dose with them at all times and the other doses in a convenient location.

Reporting group values	Nasal Glucagon	Total	
Number of subjects	26	26	
Age categorical			
Units: Subjects			

Age Continuous			
Units: years			
arithmetic mean	11.7		
standard deviation	± 3.73	-	
Gender, Male/Female			
Units: participants			
Female	15	15	
Male	11	11	
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	1	1	
White	25	25	
More than one race	0	0	
Unknown or Not Reported	0	0	
Region of Enrollment			
Units: Subjects			
United States	26	26	

## End points

### End points reporting groups

Reporting group title	Nasal Glucagon
Reporting group description: Four doses of AMG504-1 (3 mg glucagon powder per dose) were dispensed to participants and each participant/caregiver were encouraged to keep one dose with them at all times and the other doses in a convenient location.	

### Primary: Number of Participants Awakening or Returning to a Normal Status Within 30 Minutes Following Studied Drug of Administration

End point title	Number of Participants Awakening or Returning to a Normal Status Within 30 Minutes Following Studied Drug of Administration <sup>[1]</sup>
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#### End point description:

Number of participants with effectiveness of nasal glucagon administered under clinical use in treating episodes of hypoglycemia in children and adolescents with T1D, as defined by clinical recovery following studied drug administration. Responses to questions completed by the caregiver are used to assess this outcome.

An episode of severe hypoglycemia is generally defined as an event associated with severe neuroglycopenia usually resulting in coma or seizure and requiring parenteral therapy (glucagon or intravenous glucose) administered by a third party. In this study moderate hypoglycemia is defined as an episode wherein the child/adolescent with diabetes has symptoms and/or signs of neuroglycopenia and has a blood glucose  $\leq 3.9$  millimole per liter (mmol/L) (70 milligram per deciliter [mg/dL]) based on a blood sample taken at or close to the time of treatment.

End point type	Primary
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#### End point timeframe:

Within 30 minutes after each drug administration for an episode of hypoglycemia

#### 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: this is a single arm study and no statistical comparison was planned.

End point values	Nasal Glucagon			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: participants				
number (not applicable)	14			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Assessment of Ease-of-use of Dry-Mist Nasal Glucagon by Completion of Questionnaires by the Caregiver

End point title	Assessment of Ease-of-use of Dry-Mist Nasal Glucagon by Completion of Questionnaires by the Caregiver
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#### End point description:

Assess ease-of-use of intranasally administered glucagon in the hands of caregivers of participants who may be called upon to treat episodes of hypoglycemia.

Measurement for Degree of difficulty: opening the kit, Degree of difficulty: understanding the

instructions on how to use the kit, Degree of difficulty: administering the medication into the nostril, Degree of satisfaction is 1 (Very Difficult) to 7 (Very Easy). Measurement for Dry Mist Nasal Glucagon will be easy to teach other caregivers, Nasal formulation of glucagon is less intimidating for caregivers, Dry Mist Nasal Glucagon is easy to carry and would be willing to carry it, Intranasal delivery of glucagon is preferable: level of agreement 1 (Strongly Disagree) to 7 (Strongly Agree).

Population: Proportions and n are based on the total number of hypoglycemic events (N=33) of 14 participants.

End point type	Secondary
End point timeframe:	After each drug administration for an episode of hypoglycemia

End point values	Nasal Glucagon			
Subject group type	Reporting group			
Number of subjects analysed	14 <sup>[2]</sup>			
Units: percentage of event				
number (not applicable)				
Difficulty: opening the kit (Easy) (n=6)	18.2			
Difficulty: opening the kit (Very Easy) (n=27)	81.8			
Difficulty: instructions (Average) (n=4)	12.1			
Difficulty: instructions (Relatively Easy) (n=1)	3			
Difficulty: instructions (Easy) (n=6)	18.2			
Difficulty: instructions (Very Easy) (n=22)	66.7			
Difficulty: administering (Average) (n=2)	6.1			
Difficulty: administering (Easy) (n=11)	33.3			
Difficulty: administering (Very Easy) (n=20)	60.6			
Time to administer (<30 seconds) (n=20)	60.6			
Time to administer (30-<60 seconds) (n=9)	27.3			
Time to administer (1-<2 minutes) (n=4)	12.1			
Degree of satisfaction (Average) (n=2)	6.1			
Degree of satisfaction (Relatively Easy) (n=1)	3			
Degree of satisfaction (Easy) (n=8)	24.2			
Degree of satisfaction (Very Easy) (n=22)	66.7			
Compare of administration (Not Applicable) (n=25)	75.8			
Compare of administration (Much Easier) (n=2)	25			
Compare of administration (Easier) (n=2)	25			
Compare of administration (About the Same) (n=4)	50			
Ease to teach other (Easy) (n=4)	12.1			
Ease to teach other (Very Easy) (n=29)	87.9			

Notes:

[2] - Except compare of administration (much easier, easier, about the same) is based on n=8 events.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants With Adverse Events Solicited through Nasal Score Questionnaire

End point title	Percentage of Participants With Adverse Events Solicited through Nasal Score Questionnaire
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End point description:

An adverse event is a clinical event is a health change from the participant's normal state, as defined during the pre-trial evaluation and enrollment. Adverse events were assessed based on participant's responses to the Nasal Score Questionnaire administered within 2 hours of recovery after the dosing event.

End point type	Secondary
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End point timeframe:

Within 2 hours of full recovery from a hypoglycemic event

End point values	Nasal Glucagon			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: percentage of participants				
number (not applicable)	100			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in Blood Glucose Level Over Time

End point title	Change in Blood Glucose Level Over Time
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End point description:

Glucometer-based measurements of blood glucose after the studied drug administration. The participants' change in blood glucose level from baseline was measured by the caregiver using a glucometer at 15, 30 and 45 minutes after IN glucagon administration.

End point type	Secondary
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End point timeframe:

Baseline, 15, 30 and 45 minutes after drug administration for an episode of hypoglycemia

<b>End point values</b>	Nasal Glucagon			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: milligram/deciliter (mg/dL)				
arithmetic mean (standard deviation)				
15 minutes drug administration	58.2 (± 21.16)			
30 minutes drug administration	106.8 (± 39.57)			
45 minutes drug administration	124.1 (± 49.09)			

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Entire Study

Adverse event reporting additional description:

Adverse events were collected systematically by the Caregiver using the Hypoglycemia Questionnaire, and by the Participant using the Nasal Score Questionnaire.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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### Reporting groups

Reporting group title	Nasal Glucagon
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Reporting group description:

3 mg glucagon powder

<b>Serious adverse events</b>	Nasal Glucagon		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 22 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

<b>Non-serious adverse events</b>	Nasal Glucagon		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 22 (90.91%)		
Investigations			
Caregiver-Incomplete Dose Administered	Additional description: Hypoglycemia Questionnaire		
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Caregiver-Face Injury	Additional description: Hypoglycemia Questionnaire		
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	4		
Nervous system disorders			

Caregiver-Dizziness subjects affected / exposed occurrences (all)	Additional description: Hypoglycemia Questionnaire	
	1 / 22 (4.55%) 1	
Caregiver-Somnolence subjects affected / exposed occurrences (all)	Additional description: Hypoglycemia Questionnaire	
	1 / 22 (4.55%) 1	
Caregiver-Tremor subjects affected / exposed occurrences (all)	Additional description: Hypoglycemia Questionnaire	
	1 / 22 (4.55%) 1	
General disorders and administration site conditions		
Caregiver-Headache subjects affected / exposed occurrences (all)	Additional description: Hypoglycemia Questionnaire	
	14 / 22 (63.64%) 26	
Caregiver-Fatigue subjects affected / exposed occurrences (all)	Additional description: Hypoglycemia Questionnaire	
	1 / 22 (4.55%) 1	
Caregiver-Product Taste Abnormal subjects affected / exposed occurrences (all)	Additional description: Hypoglycemia Questionnaire	
	1 / 22 (4.55%) 2	
Ear and labyrinth disorders		
Participant-Itching of Ears subjects affected / exposed occurrences (all)	Additional description: Nasal Score Questionnaire	
	1 / 22 (4.55%) 1	
Eye disorders		
Caregiver-Watery Eyes subjects affected / exposed occurrences (all)	Additional description: Hypoglycemia Questionnaire	
	18 / 22 (81.82%) 37	
Participant-Itchy Eyes subjects affected / exposed occurrences (all)	Additional description: Nasal Score Questionnaire	
	4 / 22 (18.18%) 10	
Participant-Redness of Eyes subjects affected / exposed occurrences (all)	Additional description: Nasal Score Questionnaire	
	8 / 22 (36.36%) 15	
Participant-Watery Eyes subjects affected / exposed occurrences (all)	Additional description: Nasal Score Questionnaire	
	17 / 22 (77.27%) 37	

Gastrointestinal disorders			
Caregiver-Abdominal Pain Upper subjects affected / exposed occurrences (all)	Additional description: Hypoglycemia Questionnaire 2 / 22 (9.09%) 2		
Caregiver-Nausea subjects affected / exposed occurrences (all)	Additional description: Hypoglycemia Questionnaire 6 / 22 (27.27%) 10		
Caregiver-Vomiting subjects affected / exposed occurrences (all)	Additional description: Hypoglycemia Questionnaire 1 / 22 (4.55%) 1		
Respiratory, thoracic and mediastinal disorders			
Caregiver-Nasal Discomfort subjects affected / exposed occurrences (all)	Additional description: Hypoglycemia Questionnaire 19 / 22 (86.36%) 41		
Caregiver-Paranasal Sinus Hypersecretion subjects affected / exposed occurrences (all)	Additional description: Hypoglycemia Questionnaire 1 / 22 (4.55%) 1		
Caregiver-Rhinorrhoea subjects affected / exposed occurrences (all)	Additional description: Hypoglycemia Questionnaire 2 / 22 (9.09%) 2		
Participant-Itching of Throat subjects affected / exposed occurrences (all)	Additional description: Nasal Score Questionnaire 2 / 22 (9.09%) 4		
Participant-Nasal Congestion subjects affected / exposed occurrences (all)	Additional description: Nasal Score Questionnaire 12 / 22 (54.55%) 19		
Participant-Nasal Itching subjects affected / exposed occurrences (all)	Additional description: Nasal Score Questionnaire 7 / 22 (31.82%) 9		
Participant-Sneezing subjects affected / exposed occurrences (all)	Additional description: Nasal Score Questionnaire 11 / 22 (50.00%) 16		
Participant-Runny Nose subjects affected / exposed occurrences (all)	Additional description: Nasal Score Questionnaire 15 / 22 (68.18%) 27		
Skin and subcutaneous tissue disorders			

Caregiver-Hyperhidrosis subjects affected / exposed occurrences (all)	Additional description: Hypoglycemia Questionnaire	
	1 / 22 (4.55%)	
	1	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Participants from non-GCP compliant site were excluded from the analysis.
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Notes: