

**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	v2 (current)
This version publication date	10 June 2018
First version publication date	18 June 2017
Version creation reason	<ul style="list-style-type: none">• Correction of full data set Updates need to be made to FDS to align data and ClinicalTrials.gov.

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 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)	EMEA-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 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 moderate or severe 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) were trained in the use of nasal glucagon.

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

Arm title	Nasal Glucagon
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Arm description:

3 mg glucagon powder.

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 powder
Routes of administration	Nasal use

Dosage and administration details:

A single dose of 3mg glucagon nasal powder administered using a nasal powder delivery device for the treatment of moderate or severe hypoglycemic events; a maximum of 4 events per patient during the study.

Number of subjects in period 1	Nasal Glucagon
Started	26
Received at least one dose of study drug	22
Completed	12
Not completed	14
Consent withdrawn by subject	4
Discontinued; Site Termination	10

Baseline characteristics

Reporting groups

Reporting group title	Nasal Glucagon
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Reporting group description:

3 mg glucagon powder.

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:	
3 mg glucagon powder.	

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 ^[1]
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End point description:

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 ≤ 3.9 millimoles 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 ^[2]			
Units: participants				
number (not applicable)	14			

Notes:

[2] - Number (not applicable) = number achieving successful recovery.

Statistical analyses

No statistical analyses for this end point

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

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

Assess ease-of-use of intranasal 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 moderate or severe 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			
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			
Ease to teach other (Easy) (n=4)	12.1			
Ease to teach other (Very Easy) (n=29)	87.9			
Compare to Injectable (Not Applicable) (n=25)	75.8			
Compare to Injectable (Much Easier) (n=2)	12.1			
Compare to Injectable (Easier) (n=2)	6.1			
Compare to Injectable (About the Same) (n=4)	12.1			

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:

Adverse events solicited through the Nasal Score Questionnaire included: runny nose, nasal congestion (nostrils plugged), nasal itching, sneezing, watery eyes, itchy eyes, redness of eyes, itching of ears, itching of throat, and other.

A summary of other non-serious AEs, and all SAE's, regardless of causality, is located in the Reported Adverse Events section.

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

Other pre-specified: 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. The change in glucose was calculated from each time point (15, 30 and 45 minutes) minus the baseline.

End point type	Other pre-specified
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End point timeframe:

Baseline (just prior to dosing or right after study drug administration), 15, 30 and 45 minutes after drug administration for an episode of hypoglycemia.

End point values	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

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Entire Study

Adverse event reporting additional description:

All participants who received at least one dose of NG, including GCP non-compliance site.
Adverse events were collected systematically using the Hypoglycemia Questionnaire.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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Reporting groups

Reporting group title	Nasal Glucagon
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Reporting group description:

3 mg glucagon powder

Serious adverse events	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 %

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

Dizziness subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Somnolence subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Tremor subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Headache subjects affected / exposed occurrences (all)	14 / 22 (63.64%) 26		
Product Taste Abnormal subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 2		
Eye disorders Watery Eyes alternative dictionary used: Questionnaire 1 subjects affected / exposed occurrences (all)	18 / 22 (81.82%) 37	Additional description: Hypoglycemia Questionnaire	
Gastrointestinal disorders Abdominal Pain Upper subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Nausea subjects affected / exposed occurrences (all)	6 / 22 (27.27%) 10		
Vomiting subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Respiratory, thoracic and mediastinal disorders			

<p>Nasal Discomfort</p> <p>alternative dictionary used: Questionnaire 1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	Additional description: Hypoglycemia Questionnaire		
	19 / 22 (86.36%)		
41			
<p>Rhinorrhoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	2 / 22 (9.09%)		
	2		
<p>Paranasal Sinus Hypersecretion</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	1 / 22 (4.55%)		
	1		
<p>Sneezing</p> <p>alternative dictionary used: Questionnaire 1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	Additional description: Hypoglycemia Questionnaire		
	1 / 22 (4.55%)		
1			
<p>Skin and subcutaneous tissue disorders</p> <p>Hyperhidrosis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	1 / 22 (4.55%)		
	1		

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

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.

Notes: