Clinical trial results:
A Single-Dose Open-Label Study of XOMA 358 in Patients with Congenital Hyperinsulinism (CHI)

Summary

EudraCT number	2015-002847-32
Trial protocol	GB
Global end of trial date	13 January 2017

Results information

Result version number	v1 (current)
This version publication date	04 May 2018
First version publication date	04 May 2018

Trial information

Trial identification

Sponsor protocol code	X358602

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02604485
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Xoma (US) LLC
Sponsor organisation address	220 Powell Street, Suite 310, Emeryville, United States, CA 94608
Public contact	Kirk Johnson, Xoma (US) LLC, +1 510 204 7439, Kirk.Johnson@xoma.com
Scientific contact	Kirk Johnson, Xoma (US) LLC, +1 510 204 7439, Kirk.Johnson@xoma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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	02 November 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 January 2017
Global end of trial reached?	Yes
Global end of trial date	13 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety , pharmacokinetics and pharmacodynamics of a single dose of XOMA 358 in patients with hypoglycaemia associated with congenital hyperinsulinism.

Protection of trial subjects:

This study was conducted in accordance with Good Clinical Practice standards, ethical principles stated in the Declaration of Helsinki and applicable local regulatory requirements. Patients were assured that they could withdraw from the study at any time without jeopardizing their medical care. Close monitoring of all subjects was adhered to throughout the trial conduct.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 November 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 Kingdom: 3
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	10
EEA total number of subjects	3

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)	0
Adolescents (12-17 years)	2
Adults (18-64 years)	8
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects ≥12 years (UK) or at ≥18 years (US) with a clinical diagnosis of CHI, who could be safely washed out of background CHI medications and met all inclusion/exclusion criteria were enrolled. There were two screen failures. The hypoglycemia inclusion criteria was modified during the study via protocol amendments (see More Information section).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	X358 1 mg/kg

Arm description:

Single dose X358 1 mg/kg

Arm type	Experimental
Investigational medicinal product name	X358
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Single 1 mg/kg IV dose of X358 as an infusion over 30 minutes on 1 occasion.

Arm title	X358 3 mg/kg

Arm description:

Single dose X358 3 mg/kg

Arm type	Experimental
Investigational medicinal product name	X358
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Single 3 mg/kg IV dose of X358 as an infusion over 30 minutes on 1 occasion

Arm title	X358 6 mg/kg

Arm description:

Single dose X358 6 mg/kg

Arm type	Experimental
Investigational medicinal product name	X358
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Single 6 mg/kg IV dose of X358 as an infusion over 30 minutes on 1 occasion

Arm title	X358 9 mg/kg

Arm description:

Single dose X358 9 mg/kg

Arm type	Experimental
Investigational medicinal product name	X358
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Single 9 mg/kg IV dose of X358 as an infusion over 30 minutes on 1 occasion.

Number of subjects in period 1	X358 1 mg/kg	X358 3 mg/kg	X358 6 mg/kg
Started	2	3	4
Completed	2	3	4

Number of subjects in period 1	X358 9 mg/kg
Started	1
Completed	1

Baseline characteristics

Reporting groups	
Reporting group title	X358 1 mg/kg
Reporting group description: Single dose X358 1 mg/kg	
Reporting group title	X358 3 mg/kg
Reporting group description: Single dose X358 3 mg/kg	
Reporting group title	X358 6 mg/kg
Reporting group description: Single dose X358 6 mg/kg	
Reporting group title	X358 9 mg/kg
Reporting group description: Single dose X358 9 mg/kg	

Reporting group values	X358 1 mg/kg	X358 3 mg/kg	X358 6 mg/kg
Number of subjects	2	3	4
Age categorical Units: Subjects			
Adolescents (12-17 years)	0	1	1
Adults (18-64 years)	2	2	3
Age continuous Units: years			
median	22.5	23.7	20.8
standard deviation	± 2.12	± 11.50	± 7.63
Gender categorical Units: Subjects			
Female	2	0	3
Male	0	3	1
K(ATP) mutation Units: Subjects			
Yes	0	2	3
No	2	1	1

Reporting group values	X358 9 mg/kg	Total	
Number of subjects	1	10	
Age categorical Units: Subjects			
Adolescents (12-17 years)	0	2	
Adults (18-64 years)	1	8	
Age continuous Units: years			
median	32.0		
standard deviation	± 0	-	
Gender categorical Units: Subjects			
Female	0	5	
Male	1	5	

K(ATP) mutation Units: Subjects			
Yes	0	5	
No	1	5	

End points

End points reporting groups

Reporting group title	X358 1 mg/kg
Reporting group description: Single dose X358 1 mg/kg	
Reporting group title	X358 3 mg/kg
Reporting group description: Single dose X358 3 mg/kg	
Reporting group title	X358 6 mg/kg
Reporting group description: Single dose X358 6 mg/kg	
Reporting group title	X358 9 mg/kg
Reporting group description: Single dose X358 9 mg/kg	
Subject analysis set title	Subgroup Analysis 1
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects with duration of hypoglycemia < 70 mg/dL >= 120 minutes at Baseline (non-fast). Subjects in 1 mg/kg cohort are excluded	
Subject analysis set title	Subgroup Analysis 2
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects with average duration of hypoglycemia of < 70 mg/dL >= 120 minutes at Baseline (4-5 days). Subjects in 1 mg/kg cohort are excluded.	
Subject analysis set title	Subgroup Analysis 3
Subject analysis set type	Sub-group analysis
Subject analysis set description: All subjects excluding 1 mg/kg cohort	

Primary: Fasting glucose, insulin, C-peptide, ketones, free fatty acids

End point title	Fasting glucose, insulin, C-peptide, ketones, free fatty acids[1]
End point description: End of fast values for glucose, insulin, C-peptide, ketones, free fatty acids are presented for Baseline (Day -5) and post dose value (Day 3, 5 or 11). The fast began after the consumption of dinner on the night before each listed day and continued for 24 hours or until blood glucose dropped to < 60 mg/dL or until other parameters were met Blood glucose and ketones were measured with a bedside glucometer, every 3 hours until blood glucose was < 70 mg/dL and every hour until blood glucose was < 60 mg/dL. The fast ended when set criteria was met: Pre-determined fasting time of 24 hours was reached, or Blood glucose was less than 60 mg/dL, or bedside ketones was > 2.5 mmol/L on 2 separate readings, or patient was symptomatic.	
End point type	Primary
End point timeframe: Day -11 prior to dosing and post dose up to Day 11	

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: Due to the small sample size, only a descriptive analysis and documentation of data listings of this endpoint was specified.

End point values	X358 1 mg/kg	X358 3 mg/kg	X358 6 mg/kg	X358 9 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	3	4	1
Units: mg/dL; mIU/L; ng/mL; mmol/L; mEq/L				
arithmetic mean (standard deviation)				
Glucose; Baseline	74.0 (± 0)	68.3 (± 5.51)	67.8 (± 4.72)	74.0 (± 0)
Glucose; post-dose	79.0 (± 0)	62.0 (± 0)	67.5 (± 3.42)	52.0 (± 0)
insulin; Baseline	9.30 (± 0)	4.23 (± 3.465)	7.85 (± 1.353)	9.90 (± 0)
insulin; post-dose	52.40 (± 0)	9.50 (± 0)	69.95 (± 26.831)	51.00 (± 0)
C-peptide; Baseline	1.200 (± 0)	0.663 (± 0.3667)	1.203 (± 0.1841)	1.320 (± 0)
C-peptide; post-dose	2.090 (± 0)	0.690 (± 0)	1.568 (± 0.5881)	1.360 (± 0)
ketones; Baseline	0.540 (± 0)	0.480 (± 0.3659)	0.255 (± 0.0929)	0.090 (± 0)
ketones; post-dose	0.100 (± 0)	1.410 (± 0)	0.625 (± 0.3516)	0.060 (± 0)
free fatty acids; Baseline	0.90 (± 0)	1.10 (± 0.400)	0.88 (± 0.150)	0.20 (± 0)
free fatty acids; post-dose	0.40 (± 0)	2.10 (± 0)	1.13 (± 0.538)	0.20 (± 0)

Statistical analyses

No statistical analyses for this end point

Primary: Glucose area under the curve for each day (AUC24)

End point title	Glucose area under the curve for each day (AUC24)[2]

End point description:

Glucose area under the curve for each day (AUC24) for non-provocation days (patient did not have OGTT, protein or fasting challenges) are presented.
No statistical data is included for patients in the 1 mg/kg group because both patients received diazoxide on Day 5.

End point type	Primary

End point timeframe:

Glucose was followed via the continuous glucose monitor from Baseline (Day -6 to Day -1 prior to dosing) until post dose Day 29.

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: Due to the small sample size, only a descriptive analysis and documentation of data listings of this endpoint was specified.

End point values	X358 1 mg/kg	X358 3 mg/kg	X358 6 mg/kg	X358 9 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	4	1
Units: mg/dL*hr				
arithmetic mean (standard deviation)				
Day -2	2011.95 (± 173.178)	2596.56 (± 353.453)	2400.8 (± 401.154)	1475.15 (± 0)
Day -1	1906.97 (± 171.307)	2588.14 (± 356.522)	2234.17 (± 578.298)	1513.05 (± 0)

Day 1	2017.87 (± 108.686)	2816.83 (± 619.072)	2708.45 (± 165.641)	1685.62 (± 0)
Day 2	2267.18 (± 819.726)	3017.17 (± 1190.837)	3033.67 (± 234.912)	1959.78 (± 0)
Day 6	0 (± 0)	2690.68 (± 598.16)	2819.47 (± 575.821)	1802.8 (± 0)
Day 7	0 (± 0)	2511.89 (± 564.422)	2579.3 (± 792.292)	1869.84 (± 0)
Day 8	0 (± 0)	2599.48 (± 469.251)	2964.46 (± 216.42)	1881.66 (± 0)
Day 9	0 (± 0)	2633.45 (± 725.526)	2977.29 (± 336.804)	1802.72 (± 0)
Day 10	0 (± 0)	2635.97 (± 571.989)	2954.02 (± 375.741)	2101.95 (± 0)
Day 15	0 (± 0)	2187.55 (± 103.928)	2828.65 (± 182.06)	0 (± 0)
Day 29	0 (± 0)	1237.89 (± 1578.544)	1185.99 (± 45.871)	0 (± 0)

Statistical analyses

No statistical analyses for this end point

Primary: Concomitant treatment/medications used during rescue

End point title	Concomitant treatment/medications used during rescue[3]

End point description:

Rescue medication taken by subjects for hypoglycaemia during the study is presented.

End point type	Primary

End point timeframe:

Concomitant treatment used during rescue were reported from Baseline until the end of the study.

Notes:

[3] - 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: Due to the small sample size, only a descriptive analysis and documentation of data listings of this endpoint was specified.

End point values	X358 1 mg/kg	X358 3 mg/kg	X358 6 mg/kg	X358 9 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	4	1
Units: Number of subjects rescued by medication				
Number of subjects rescued by medication	2	1	0	1

Statistical analyses

No statistical analyses for this end point

Primary: Number of hypoglycemic events per day with glucose < 70 mg/dL, <60 mg/dL, and <50 mg/dL

End point title	Number of hypoglycemic events per day with glucose < 70

	mg/dL, <60 mg/dL, and <50 mg/dL[4]

End point description:

The number of hypoglycemic episodes (< 70 mg/dL, <60 mg/dL, and <50 mg/dL) per day was reported over each 24-hour day and summarised herein for Baseline and post-dose Day 1 to 12, grouped by day Non-Provocation Days are Days -2, -1, 1 (dosing day), 2, 6 through 10, 15 and 29. The protein challenge was performed 4 hours after the breakfast time on Day -4 and Day 4. If the patient did not demonstrate hypoglycemia during the screening fast and demonstrated hypoglycemia during the Day -4 protein challenge, then additional protein challenges occurred on Days -3, 3, 5 and 11 and the fasts were not performed. * Non-provocation days.
An instance of hypoglycemia started when there were 3 consecutive measurements within a 15 minute window that were less than the threshold value. The duration was the sum of the total time the patient was in the specified threshold.

End point type	Primary

End point timeframe:

Glucose was followed via the continuous glucose monitor from Baseline (Day -6 to Day -1 prior to dosing) until post dose Day 29.

Notes:

[4] - 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: Due to the small sample size, only a descriptive analysis and documentation of data listings of this endpoint was specified.

End point values	X358 1 mg/kg	X358 3 mg/kg	X358 6 mg/kg	X358 9 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2[5]	3	4	1
Units: Hypoglycemia				
geometric mean (standard deviation)				
Threshold < 50 mg/dL, Day -2 & Day -1	0.25 (± 0.354)	0.17 (± 0.289)	0.13 (± 0.250)	4.50 (± 0)
Threshold < 50 mg/dL, Day 1	1.00 (± 1.414)	0.00 (± 0.000)	0.00 (± 0.000)	7.00 (± 0)
Threshold < 50 mg/dL, Day 2 & Day 6*	0.50 (± 0.707)	0.00 (± 0.000)	0.50 (± 0.408)	5.00 (± 0)
Threshold < 50 mg/dL, Day -4 & Day -1	0.25 (± 0.354)	0.00 (± 0.000)	0.13 (± 0.250)	4.50 (± 0)
Threshold < 50 mg/dL, Day 2 to Day 12	1.50 (± 1.650)	0.36 (± 0.315)	0.43 (± 0.155)	4.55 (± 0)
Threshold < 60 mg/dL, Day -2 & Day -1	1.75 (± 0.354)	0.17 (± 0.289)	0.75 (± 0.500)	6.00 (± 0)
Threshold < 60 mg/dL, Day 1	2.50 (± 2.121)	0.00 (± 0.000)	0.75 (± 0.957)	8.00 (± 0)
Threshold < 60 mg/dL, Day 2 & Day 6*	1.50 (± 2.121)	0.33 (± 0.577)	0.63 (± 0.250)	6.50 (± 0)
Threshold < 60 mg/dL, Day -4 & Day -1	2.50 (± 0.707)	0.00 (± 0.000)	0.88 (± 0.854)	7.50 (± 0)
Threshold < 60 mg/dL, Day 2 to Day 12	2.50 (± 3.064)	0.61 (± 0.410)	0.84 (± 0.114)	5.64 (± 0)
Threshold < 70 mg/dL, Day -2 & Day -1	4.50 (± 2.828)	0.50 (± 0.000)	1.75 (± 1.190)	7.50 (± 0)
Threshold < 70 mg/dL, Day 1	4.00 (± 1.414)	1.00 (± 1.000)	1.75 (± 0.500)	4.00 (± 0)
Threshold < 70 mg/dL, Day 2 & Day 6*	3.50 (± 4.590)	1.50 (± 1.732)	1.25 (± 0.645)	8.00 (± 0)
Threshold < 70 mg/dL, Day -4 & Day -1	3.75 (± 2.475)	0.50 (± 0.500)	1.25 (± 0.957)	7.50 (± 0)
Threshold < 70 mg/dL, Day 2 to Day 12	3.33 (± 2.828)	1.42 (± 0.584)	1.77 (± 0.436)	6.36 (± 0)

Notes:

[5] - Both patients received Diazoxide on Day 5. Data collected Day 5 onwards are excluded from analysis

Statistical analyses

No statistical analyses for this end point

Primary: Average time per day of blood glucose < 70 mg/dL

End point title	Average time per day of blood glucose < 70 mg/dL[6]

End point description:

Average time per day of blood glucose < 70 mg/dL was reported over each 24-hour day and is summarised herein for Baseline values collected during the Screening period and Days 1 to D12 post dose, grouped by day

Non-Provocation Days are Days -2, -1, 1 (dosing day), 2, 6 through 10, 15 and 29. The protein challenge was performed 4 hours after the breakfast time on Day -4 and Day 4. If the patient did not demonstrate hypoglycemia during the screening fast and demonstrated hypoglycemia during the Day -4 protein challenge, then additional protein challenges occurred on Days -3, 3, 5 and 11 and the fasts were not performed. * Non-provocation days.

End point type	Primary

End point timeframe:

Glucose was followed via the continuous glucose monitor from Baseline (Day -6 to Day -1 prior to dosing) until post dose Day 29.

Notes:

[6] - 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: Due to the small sample size, only a descriptive analysis and documentation of data listings of this endpoint was specified.

End point values	X358 1 mg/kg	X358 3 mg/kg	X358 6 mg/kg	X358 9 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	4	1
Units: minutes				
arithmetic mean (standard deviation)				
Day -2 & Day -1	303.75 (± 132.583)	22.50 (± 18.028)	105.00 (± 47.697)	920.00 (± 0)
Day 1	290.00 (± 134.350)	71.67 (± 67.885)	115.00 (± 41.833)	905.00 (± 0)
Day 2 & Day 6*	375.00 (± 494.975)	109.17 (± 163.274)	80.00 (± 50.662)	652.50 (± 0)
Day -4 & Day -1	318.75 (± 164.402)	15.00 (± 10.000)	96.88 (± 56.361)	1042.50 (± 0)
Day 2 to Day 12	464.17 (± 555.079)	128.48 (± 119.190)	130.57 (± 43.229)	608.18 (± 0)

Statistical analyses

No statistical analyses for this end point

Primary: Postprandial glucose, insulin, C-peptide, ketones and free fatty acids (FFA)

End point title	Postprandial glucose, insulin, C-peptide, ketones and free fatty acids (FFA)[7][8]

End point description:

Protein challenge measurements were conducted prior to dosing (Day -4) and post dose (Day4) for glucose, insulin, C-peptide, ketones and free fatty acids. The protein challenge was performed 4 hours after the breakfast time on Day -4 and Day 4. Bedside glucose and serum PD blood draws took every 30 minutes during the protein challenge procedure, until the rescue criteria were met.Time-matched Day 4 change from Baseline (most recent, non-missing protein profile conducted during Screening period) is presented.

End point type	Primary

End point timeframe:

Day -11 prior to dosing and post dose up to Day 11

Notes:

[7] - 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: Due to the small sample size, only a descriptive analysis and documentation of data listings of this endpoint was specified.
[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to the small sample size, only a descriptive analysis and documentation of data listings

of this endpoint was specified.

End point values	X358 3 mg/kg	X358 6 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	3		
Units: mg/dL; mIU/L; ng/mL; mmol/L; mEq/L				
arithmetic mean (standard deviation)				
Glucose; Day 4; 0 hr before start of provocation	15.00 (± 0)	20.33 (± 75.182)		
Glucose; Day 4; 30 minutes after provocation	4.00 (± 0)	11.00 (± 13.115)		
insulin; Day 4; 0 hr before start of provocation	19.300 (± 0)	256.133 (± 239.5830)		
insulin; Day 4; 30 minutes after provocation	36.600 (± 0)	300.233 (± 218.3129)		
C-peptide; Day 4; 0 hr before start of provocation	0.6000 (± 0)	0.3700 (± 2.22178)		
C-peptide; Day 4; 30 minutes after provocation	0.2000 (± 0)	0.2200 (± 1.54793)		
ketones; Day 4; 0 hr before start of provocation	0.3200 (± 0)	0.0133 (± 0.02517)		
ketones; Day 4; 30 minutes after provocation	0 (± 0)	0 (± 0)		
FFA; Day 4; 0 hr before start of provocation	0.600 (± 0)	0.167 (± 0.3055)		
FFA; Day 4; 30 minutes after provocation	0 (± 0)	0 (± 0)		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Subgroup Analysis: Glucose Non-fast days 1-7 and 8-12 vs. Baseline (nonfast)

End point title	Subgroup Analysis: Glucose Non-fast days 1-7 and 8-12 vs. Baseline (nonfast)

End point description:

Percentage change in glucose measurements (mg/dL) via CGM over 24 hours on non-fast Days 1-7 and 8-12 versus Baseline glucose values for non-fast days (Day -5 to Day -1 where 24 hour CGM is recorded) is presented. Subjects in 1 mg/kg cohort are excluded from this analysis

End point type	Post-hoc

End point timeframe:

Glucose was followed via the continuous glucose monitor from check in (5 days prior to dosing) until Day 29 post dose.

End point values	Subgroup Analysis 1			
Subject group type	Subject analysis set			
Number of subjects analysed	3			
Units: Percent Change from baseline (non-fast)				
median (full range (min-max))				
Days 1-7 (non-fast)	14.079 (5.47 to 22.10)			
Days 8-12 (non-fast)	10.887 (9.37 to 27.07)			

Statistical analyses

No statistical analyses for this end point

Post-hoc: Subgroup Analysis: Glucose Days 1-8 vs. Baseline (4-5 Days)

End point title	Subgroup Analysis: Glucose Days 1-8 vs. Baseline (4-5 Days)

End point description:

Percentage change in glucose measurements (mg/dL) via CGMS over 24 hours on Days 1-8 versus Baseline (4-5 days) is presented.

End point type	Post-hoc

End point timeframe:

Glucose was followed via the continuous glucose monitor from check in (5 days prior to dosing) until Day 29 post dose.

End point values	Subgroup Analysis 2			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: Percent Change from baseline				
median (full range (min-max))				
Days 1-8	11.181 (5.98 to 21.74)			

Statistical analyses

No statistical analyses for this end point

Post-hoc: Fasting Blood Glucose -Days 4 and 6 vs. Baseline (2- days)

End point title	Fasting Blood Glucose -Days 4 and 6 vs. Baseline (2- days)

End point description:

The change in fasting blood glucose (mg/dL) on Days 4 and 6 versus Baseline (2-days; Day -2 and Day -1) is presented.

End point type	Post-hoc

End point timeframe:

Baseline (Day -2) to Day 6

End point values	Subgroup Analysis 3			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: Change from baseline (2-days)				
median (full range (min-max))				
Days 4 and 6	9.255 (-7.50 to 24.50)			

Statistical analyses

No statistical analyses for this end point

Post-hoc: Subgroup Analysis: Fasting Blood Glucose- Days 4 and 6 vs. Baseline (3-days)

End point title	Subgroup Analysis: Fasting Blood Glucose- Days 4 and 6 vs. Baseline (3- days)

End point description:

The change in fasting blood glucose (mg/dL) on Days 4 and 6 versus Baseline (average of fasting blood glucose on Day -2, Day -1 and Day 1 pre-dose) is presented

End point type	Post-hoc

End point timeframe:

Baseline (Day -2) to to Day 6

End point values	Subgroup Analysis 3			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: Change from baseline (3-days)				
median (full range (min-max))				
Days 4 and 6	-3.333 (-13.51 to 14.50)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event data were to be collected throughout the study beginning at the time the patient had signed the ICF

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	X358 1 mg/kg
Reporting group description:	
Single dose X358 1 mg/kg	
Reporting group title	X358 3 mg/kg
Reporting group description:	
Single dose X358 3 mg/kg	
Reporting group title	X358 6 mg/kg
Reporting group description:	
Single dose X358 6 mg/kg	
Reporting group title	X358 9 mg/kg
Reporting group description:	
Single dose X358 9 mg/kg	

Serious adverse events	X358 1 mg/kg	X358 3 mg/kg	X358 6 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Myoclonus			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Headache			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Depressed level of consciousness			

subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Skin and subcutaneous tissue disorders			
Cold sweat			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 4 (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	X358 9 mg/kg		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Myoclonus			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Depressed level of consciousness			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Cold sweat			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	X358 1 mg/kg	X358 3 mg/kg	X358 6 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)	3 / 3 (100.00%)	4 / 4 (100.00%)
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Thrombophlebitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Catheter site related reaction			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Feeling hot			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Infusion site induration			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Lethargy			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0

Upper respiratory tract congestion			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Nervousness			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Investigations			
Body temperature increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Injection site bruising			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Injection site pain			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	2 / 2 (100.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Depressed level of consciousness			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	1 / 2 (50.00%)	2 / 3 (66.67%)	1 / 4 (25.00%)
occurrences (all)	1	3	1
Headache			

subjects affected / exposed	2 / 2 (100.00%)	3 / 3 (100.00%)	3 / 4 (75.00%)
occurrences (all)	5	4	9
Lethargy			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Muscular weakness			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Myoclonus			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	1 / 4 (25.00%)
occurrences (all)	0	1	2
Vision blurred			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Mental impairment			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Somnolence			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Abdominal pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			

subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	2 / 2 (100.00%)	2 / 3 (66.67%)	0 / 4 (0.00%)
occurrences (all)	3	2	0
Vomiting			
subjects affected / exposed	1 / 2 (50.00%)	1 / 3 (33.33%)	2 / 4 (50.00%)
occurrences (all)	1	1	2
Dyspepsia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hypoaesthesia oral			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Paraesthesia oral			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Skin and subcutaneous tissue disorders			
Cold sweat			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Skin irritation			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Hyperhidrosis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Pharyngitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1

Non-serious adverse events	X358 9 mg/kg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Thrombophlebitis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Catheter site related reaction			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Feeling hot			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Infusion site induration			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Lethargy			

subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Upper respiratory tract congestion			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Nervousness			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Investigations			
Body temperature increased			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Injection site bruising			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Injection site pain			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Tachycardia			

subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Depressed level of consciousness			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	4		
Lethargy			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Muscular weakness			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Myoclonus			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Vision blurred			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Mental impairment			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	2		
Eye disorders			
Vision blurred			

subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Abdominal pain upper			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Hypoaesthesia oral			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Paraesthesia oral			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Cold sweat			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	2		
Skin irritation			

subjects affected / exposed occurrences (all) Hyperhidrosis subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0 1 / 1 (100.00%) 1		
Musculoskeletal and connective tissue disorders Musculoskeletal chest pain subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Pharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 July 2015	The amendment includes the following substantial changes:The scope of data to be reviewed by the DSRC before additional patients exposure or and changing the dose level was increased from Day 12 to all available data through Day 29.Two different Screening schedule options (Option A and Option B) were added to accommodate different availability and convenience needs of individual patients. The Schedules of Events were changed for logistic efficiency or to collect additional safety and drug characterization data.
12 August 2015	The amendment includes the following substantial changes: Protocol sections referring to pregnancy were clarified.
08 December 2015	The amendment includes the following substantial changes:A final safety follow-up visit, beyond Day 43, was added at Day 105 and collection of blood samples for hematology, chemistry, and urinalysis panels was added at Day 43. Subject inclusion criteria was modified to remove weight ≤ 90 kg at Screening to allow for the inclusion of patients who had a clinically meaningful decrease in blood glucose with symptoms during hypoglycaemia inducing procedures. If a patient did not demonstrate blood glucose values < 60 mg/dL during the Screening fast, yet demonstrated blood glucose values < 60 mg/dL during the Day -4 Protein Challenge, then a Protein Challenge was performed in lieu of a monitored fast on Days -3, 3, 5, and 11.
22 February 2016	The amendment includes the following substantial changes: The dose level for Cohort B was confirmed at 3 mg/kg, by recommendation of the DSRC and patients were permitted to participate in more than 1 cohort.
26 May 2016	The amendment includes the following substantial changes: The OGTT was omitted throughout the protocol. A third cohort, "Cohort C," was added at a dose level of 6 mg/kg, and the resulting sample size was increased to up to a total of approximately 18 patients.An optional inpatient hypoglycemia provocation test (fasting procedure OR Protein Challenge procedure) was added at Day 22
26 August 2016	The amendment includes the following substantial changes: The hypoglycemia inclusion criterion was changed by replacing the required decrease in glucose levels during provocation with a required duration of decreased glucose levels as measured by CGM over a fixed period of time without provocation. The exclusion criterion "Use of any long-acting somatostatin analogs or glucose-affecting medications that require > 72-hour washout" was deleted. Screening options "A" and "B" were replaced with a single screening and Baseline schedule, and the Protein Challenge provocations have been omitted from the protocol. Cohort D with a single dose at 9 mg/kg X358 was added. Outcome measures were added for duration of hypoglycemia and number of episodes at relevant glucose levels.

Notes:

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.

None reported

Notes: