Clinical trial results:
An Open-Label Study of XOMA 358, with Optional Dose Escalation, in Patients with Congenital Hyperinsulinism

Summary

EudraCT number	2016-001275-80
Trial protocol	DE
Global end of trial date	20 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	X358605

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Xoma (US) LLC
Sponsor organisation address	2200 Powell Street, Suite 310, Emeryville, United States, CA 94608
Public contact	Kirk Jonhson, Xoma (US) LLC, +1 501 204 7439, Kirk.Johnson@xoma.com
Scientific contact	Kirk Jonhson, Xoma (US) LLC, +1 501 204 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	31 October 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 January 2017
Global end of trial reached?	Yes
Global end of trial date	20 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this Phase 2 study was to evaluate the safety, pharmacokinetics and pharmacodynamics of XOMA 358 in patients aged 12 years and older with hypoglycemia associated with congenital hyperinsulinism (CHI).

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. After the subject has ended his/her participation in the trial, the investigator provided appropriate medication and/or arranged access to appropriate care for the patient.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 September 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 4
Worldwide total number of subjects	4
EEA total number of subjects	4

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)	2
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects with blood glucose < 60 mg/dL or with clinically meaningful decrease in blood glucose in conjunction with symptoms during monitored fasts, who could be safely washed out of background medications used to treat CHI and who met all inclusion/exclusion criteria were enrolled. No subjects failed screening.

Period 1

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

Arms

Arm title	Cohort 1

Arm description:

All patients were enrolled in Cohort 1 and received a first dose of 3 mg/kg X358 on Day 1 followed by a second dose of 6 mg/kg X358 on Day 4 or 5

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 dose of X358 followed by a single 6 mg/kg dose. Both doses administered as an IV infusion over 30 minutes.

Number of subjects in period 1	Cohort 1
Started	4
Completed	4

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	4	4	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	2	2	
Adults (18-64 years)	2	2	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	24.5		
standard deviation	± 13.87	-	
Gender categorical Units: Subjects			
Female	1	1	
Male	3	3	
K(ATP) mutation Units: Subjects			
Yes	2	2	
no	2	2	

End points

End points reporting groups

Reporting group title	Cohort 1

Reporting group description:

All patients were enrolled in Cohort 1 and received a first dose of 3 mg/kg X358 on Day 1 followed by a second dose of 6 mg/kg X358 on Day 4 or 5

Primary: Cumulative time blood glucose < 70 mg/dL (< 3.89 mM)

End point title	Cumulative time blood glucose < 70 mg/dL (< 3.89 mM)[1]

End point description:

Duration of hypoglycaemia (blood glucose < 70 mg/dL) is presented for Baseline values collected during the Screening period (where 24-hour CGM was recorded) and Days 1 to D12 post 3 mg/kg X358 and 6 mg/kg X358 administration. Duration of hypoglycaemia is calculated as the sum of the total time in the specified threshold; number of data points < threshold multiplied by 5 minutes.

End point type	Primary

End point timeframe:

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

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	Cohort 1			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: minutes				
arithmetic mean (standard deviation)				
Baseline; 3 mg/kg Dose	558.44 (± 307.699)			
Day 1 to 12; 3 mg/kg Dose	703.85 (± 520.096)			
Baseline; 6 mg/kg Dose	558.44 (± 307.699)			
Day 1 to 12; 6 mg/kg Dose	483.65 (± 323.573)			

Statistical analyses

No statistical analyses for this end point

Primary: Frequency of hypoglycaemic events (< 60 mg/dL)

End point title	Frequency of hypoglycaemic events (< 60 mg/dL)[2]

End point description:

The number of hypoglycemic episodes (< 60 mg/dL) over each 24-hour day was reported, and summarised herein for Baseline (taken as average number of episodes for non-fast days during checkin and Screening where 24-hour CGM was recorded, combined) and post-treatment (average number of episodes for all Days D1 to D12 combined). An instance of hypoglycemia was defined as 3 consecutive

measurements within a 15 minute window that are < 60 mg/dL.

End point type	Primary

End point timeframe:

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

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	Cohort 1			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: Events				
arithmetic mean (standard deviation)				
Baseline; 3 mg/kg Dose	2.81 (± 2.569)			
Day 1 to 12, 3 mg/kg Dose	4.21 (± 3.148)			
Baseline; 6 mg/kg	2.81 (± 2.569)			
Day 1 to 12; 6 mg/kg Dose	3.65 (± 2.461)			

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	Cohort 1			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: Rescue medication required				
Glucose infusion	1			
Paracetamol	1			

Statistical analyses

No statistical analyses for this end point

Primary: Glucose area under the curve (AUC24)

End point title	Glucose area under the curve (AUC24)[4]

End point description:

Glucose (mg/dL) AUC(0-24) via CGMS is presented for Baseline #1 (average of AUC on non-fast days (during checkin and Screening period where 24 hr CGM was recorded), Baseline #2 (average of AUC on all days (checkin and Screening period where 24hr CGM was recorded) and Days 1 to 11 post-dose, checkout [Day 16) and follow-up visits [Day 29 and 33])

End point type	Primary

End point timeframe:

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

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	Cohort 1			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: mg/dL				
arithmetic mean (standard deviation)				
Baseline #1; 3 mg/kg Dose	2023.875 (± 283.2190)			
Baseline #2; 3 mg/kg Dose	1972.454 (± 285.0928)			
Day 1; 3 mg/kg Dose	1898.10 (± 778.72)			
Day 2; 3 mg/kg Dose	1911.73 (± 577.06)			
Day 3; 3 mg/kg Dose	1876.89 (± 450.43)			
Day 4; 3 mg/kg Dose	2600.35 (± 149.46)			
Baseline #1; 6 mg/kg Dose	2023.875 (± 283.2190)			
Baseline #2; 6 mg/kg Dose	1972.454 (± 285.0928)			
Day 1; 6 mg/kg Dose	2286.32 (± 758.49)			
Day 2; 6 mg/kg Dose	2288.27 (± 691.35)			
Day 3; 6 mg/kg Dose	2123.73 (± 710.25)			
Day 4; 6 mg/kg Dose	2219.66 (± 785.31)			
Day 5; 6 mg/kg Dose	2196.83 (± 621.43)			
Day 6; 6 mg/kg Dose	2210.13 (± 517.73)			
Day 7; 6 mg/kg Dose	2110.61 (± 568.05)			
Day 8; 6 mg/kg Dose	2184.74 (± 495.83)			
Day 9; 6 mg/kg Dose	2270.03 (± 976.55)			

Day 10; 6 mg/kg Dose	2209.28 (± 538.09)			
Day 11; 6 mg/kg Dose	2412.12 (± 492.44)			
Check Out; 6 mg/kg Dose	2311.46 (± 461.112)			
Follow-up; 6 mg/kg Dose	1546.44 (± 538.014)			

Statistical analyses

No statistical analyses for this end point

Primary: Fasting and postprandial glucose, insulin, C-peptide

End point title	Fasting and postprandial glucose, insulin, C-peptide[5]

End point description:

Glucose measurements via a bedside glucometer, serum insulin and C-peptide measurements are presented for fasting days (0-hour, pre-breakfast) for both Baseline and post-treatment days. Post-prandial measurements are presented for both Baseline (average of 0-hour, pre-breakfast measurements) and post-treatment (average of 2-hour post-breakfast measurements).

End point type	Primary

End point timeframe:

AM fasting: Baseline (Screening period, and prior to dosing on Day 1) and post-treatment (Days 2, 4, 5, 6, 7, 8, and 9)
Post-prandial: Baseline (Screening period) and post-treatment (Days 2, 4, 5, 6, 7, 8 and 9)

Notes:

[5] - 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	Cohort 1			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: mg/dL; mIU/L; (ng/mL				
arithmetic mean (standard deviation)				
Glucose; AM Fasting; Baseline; 3 mg/kg Dose	66.52 (± 16.282)			
Glucose; AM Fasting; Post-Treatment; 3 mg/kg Dose	66.22 (± 29.243)			
Glucose; AM Fasting; Baseline; 6 mg/kg Dose	69.07 (± 18.923)			
Glucose; AM Fasting; Post-Treatment; 6 mg/kg Dose	73.20 (± 25.810)			
Glucose; Post-prandial; Baseline; 3 mg/kg Dose	68.24 (± 17.382)			
Glucose; Post-prandial; Post-Treatment; 3 mg/kg Do	122.75 (± 70.025)			
Glucose; Post-prandial; Baseline; 6 mg/kg Dose	68.24 (± 17.382)			
Glucose; Post-prandial; Post-Treatment; 6 mg/kg Do	146.40 (± 39.863)			
Insulin; AM Fasting; Baseline; 3 mg/kg Dose	12.383 (± 4.4984)			
Insulin; AM Fasting; Post-Treatment; 3 mg/kg Dose	57.225 (± 43.6895)			

Insulin; AM Fasting; Baseline; 6 mg/kg Dose	41.800 (± 45.5670)			
Insulin; AM Fasting; Post-Treatment; 6 mg/kg Dose	114.604 (± 52.2824)			
Insulin; Post-prandial; Baseline; 3 mg/kg Dose	12.938 (± 5.7387)			
Insulin; Post-prandial; Post-Treatment; 3 mg/kg Do	296.200 (± 210.6859)			
Insulin; Post-prandial; Baseline; 6 mg/kg Dose	12.938 (± 5.7387)			
Insulin; Post-prandial; Post-Treatment; 6 mg/kg Do	559.481 (± 164.0734)			
C-peptide; AM Fasting; Baseline; 3 mg/kg Dose	1.8458 (± 0.43435)			
C-peptide; AM Fasting; Post-Treatment; 3 mg/kg Dos	1.3800 (± 0.63038)			
C-peptide; AM Fasting; Baseline; 6 mg/kg Dose	2.1296 (± 0.77543)			
C-peptide; AM Fasting; Post-Treatment; 6 mg/kg Dos	2.0569 (± 0.56838)			
C-peptide; Post-prandial; Baseline; 3 mg/kg Dose	1.8725 (± 0.52122)			
C-peptide; Post-prandial; Post-Treatment; 3 mg/kg	7.4588 (± 4.75957)			
C-peptide; Post-prandial; Baseline; 6 mg/kg Dose	1.8725 (± 0.52122)			
C-peptide; Post-prandial; Post-Treatment; 6 mg/kg	9.7088 (± 2.11836)			

Statistical analyses

No statistical analyses for this end point

Primary: Time to hypoglycemia during provocation (< 60 mg/dL [< 3.33 mM])

End point title	Time to hypoglycemia during provocation (< 60 mg/dL [< 3.33 mM])[6]

End point description:

First occurrence of glucose < 60 mg/dL (3.33 mM) from the start of fasting challenge post-dosing of 3 and 6 mg/kg X358 on Day 3 (provocation day) is presented.

End point type	Primary

End point timeframe:

Day 3 post dose (Provocation)

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	Cohort 1			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: minutes				
arithmetic mean (standard deviation)				
3 mg/kg Dose	2920.0 (± 3704.70)			

6 mg/kg Dose	5797.5 (± 943.99)			

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Percentage change in glucose measurements (mg/dL) via CGM over 24 hours on non-fast Days 1-7 and 8-12 post 6 mg/kg X358 dose versus Baseline glucose values for non-fast days (S-1 to S4 where 24hr CGM is recorded) 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	Cohort 1			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: Percent change from baseline				
median (full range (min-max))				
Days 1-7 (non-fast)	10.226 (-15.70 to 23.81)			
Days 8-12 post 6 mg/kg X358 (non-fast)	12.738 (-5.82 to 24.22)			

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 post 6 mg/kg X358 dose 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	Cohort 1			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: Percent change from baseline				
median (full range (min-max))				
Days 1-8 post 6 mng/kg X358	12.216 (-10.36 to 24.19)			

Statistical analyses

No statistical analyses for this end point

Post-hoc: Subgroup Analysis: Fasting Blood Glucose -Days 4 and 5 vs. Baseline (2-days)

End point title	Subgroup Analysis: Fasting Blood Glucose -Days 4 and 5 vs. Baseline (2-days)

End point description:

The change in fasting blood glucose (mg/dL) on Days 4 and 5 versus Baseline (2-days) is presented.

End point type	Post-hoc

End point timeframe:

Baseline (S3 or S4) to Day 5 post 2nd dose.

End point values	Cohort 1			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: Change from baseline				
median (full range (min-max))				
Days 4 and 5 post 2nd dose	-1.351 (-4.50 to 37.84)			

Statistical analyses

No statistical analyses for this end point

Post-hoc: Subgroup Analysis: Fasting Blood Glucose- Days 4 and 5 vs. Baseline (3-days)

End point title	Subgroup Analysis: Fasting Blood Glucose- Days 4 and 5 vs. Baseline (3-days)

End point description:

The change in fasting blood glucose (mg/dL) on Days 4 and 5 post 6 mg/kg X358 dose versus Baseline (average of blood glucose on S3, S4 and Day 1 pre-dose) is presented

End point type	Post-hoc

End point timeframe:

Baseline (S3 or S4 and Day pre-dose where fasting blood glucose is recorded) to Day 5 post 2nd dose.

End point values	Cohort 1			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: Change from baseline(3-days)				
median (full range (min-max))				
Days 4 and 5 post 2nd dose	2.252 (-2.10 to 36.04)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from date of informed consent until end of study.

Adverse event reporting additional description:

Pre-treatment adverse events were not related to protocol procedures and were related to underlying disease. All Treatment-Emergent Adverse Events were considered unrelated to study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	X358

Reporting group description: -

Serious adverse events	X358		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	X358		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)		
Investigations			
Eosinophil count increased			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	5		
Headache			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	2		

General disorders and administration site conditions Malaise subjects affected / exposed occurrences (all)	 1 / 4 (25.00%) 2		
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all)	 1 / 4 (25.00%) 1		
Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all) Gastrointestinal infection subjects affected / exposed occurrences (all)	 1 / 4 (25.00%) 1 1 / 4 (25.00%) 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.

Due to the small number of patients enrolled into this study, definitive conclusions cannot be drawn

Notes: