Clinical trial results:
A Double Blind, Placebo-Controlled, Phase 2A Mechanistic Study to Evaluate the Effect of ISIS 449884 (ISIS-GCGRRX an Antisense Inhibitor of the Glucagon Receptor) on Hepatic Lipid and Glycogen Content in Patients with Type 2 Diabetes Being Treated with Metformin

Summary

EudraCT number	2015-003337-10
Trial protocol	HU SK AT
Global end of trial date	22 May 2017

Results information

Result version number	v1 (current)
This version publication date	27 November 2019
First version publication date	27 November 2019

Trial information

Trial identification

Sponsor protocol code	ISIS449884-CS3

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02824003
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ionis Pharmaceuticals, Inc.
Sponsor organisation address	2855 Gazelle Court, Carlsbad, United States, CA 92010
Public contact	Ionis Pharmaceuticals, Inc., Ionis Pharmaceuticals, Inc., +1 800-679-4747, patients@ionisph.com
Scientific contact	Ionis Pharmaceuticals, Inc., Ionis Pharmaceuticals, Inc., +1 800-679-4747, patients@ionisph.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	01 June 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the pharmacodynamic (PD) effects of glucagon receptor (GCGR) reduction by ISIS 449884 (100 milligrams [mg]) on hepatic lipid and glycogen content.

Protection of trial subjects:

Each subject, or legally acceptable representative, signed an informed consent form before participating in the study.

Background therapy:

Subjects were on a stable dose of metformin (at least 1000 mg/day) for a minimum of 3 months prior to screening evaluations and continued their stable dose throughout the study.

Evidence for comparator: -

Actual start date of recruitment	16 March 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 15
Worldwide total number of subjects	15
EEA total number of subjects	15

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)	0
Adults (18-64 years)	12
From 65 to 84 years	3

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

15 subjects were randomised at 1 study centre in Austria.

Pre-assignment

Screening details:

50 subjects were screened for the study and 15 were randomised and received study drug.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received ISIS 449884 matching-placebo, by subcutaneous (SC) injection, on Days 1, 3 and 5 of Week 1 as loading doses followed by once weekly from Week 2 through Week 13.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received ISIS 449884 matching-placebo, by SC injection, on Days 1, 3 and 5 of Week 1 as loading doses followed by once weekly from Week 2 through Week 13.

Arm title	ISIS 449884 100 mg

Arm description:

Subjects received 100 milligrams (mg) ISIS 449884, by SC injection, on Days 1, 3 and 5 of Week 1 as loading doses followed by once weekly from Week 2 through Week 13.

Arm type	Experimental
Investigational medicinal product name	ISIS 449884
Investigational medicinal product code	
Other name	IONIS-GCGRRX
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received 100 mg ISIS 449884, by SC injection, on Days 1, 3 and 5 of Week 1 as loading doses followed by once weekly from Week 2 through Week 13.

Number of subjects in period 1	Placebo	ISIS 449884 100 mg
Started	5	10
Per-Protocol Set (PPS)	5	8
Completed	5	8
Not completed	0	2
Adverse event, non-fatal	-	1
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received ISIS 449884 matching-placebo, by subcutaneous (SC) injection, on Days 1, 3 and 5 of Week 1 as loading doses followed by once weekly from Week 2 through Week 13.	
Reporting group title	ISIS 449884 100 mg
Reporting group description:	
Subjects received 100 milligrams (mg) ISIS 449884, by SC injection, on Days 1, 3 and 5 of Week 1 as loading doses followed by once weekly from Week 2 through Week 13.	

Reporting group values	Placebo	ISIS 449884 100 mg	Total
Number of subjects	5	10	15
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 54 ± 10	 57 ± 6	 -
Gender categorical Units: Subjects			
Female	2	5	7
Male	3	5	8

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received ISIS 449884 matching-placebo, by subcutaneous (SC) injection, on Days 1, 3 and 5 of Week 1 as loading doses followed by once weekly from Week 2 through Week 13.	
Reporting group title	ISIS 449884 100 mg
Reporting group description:	
Subjects received 100 milligrams (mg) ISIS 449884, by SC injection, on Days 1, 3 and 5 of Week 1 as loading doses followed by once weekly from Week 2 through Week 13.	
Subject analysis set title	Placebo (PPS)
Subject analysis set type	Per protocol
Subject analysis set description:	
Subjects received ISIS 449884 matching-placebo, by SC injection, on Days 1, 3 and 5 of Week 1 as loading doses followed by once weekly from Week 2 through Week 13.	
Subject analysis set title	ISIS 449884 100 mg (PPS)
Subject analysis set type	Per protocol
Subject analysis set description:	
Subjects received 100 mg ISIS 449884, by SC injection, on Days 1, 3 and 5 of Week 1 as loading doses followed by once weekly from Week 2 through Week 13.	

Primary: Change from Baseline in Fasting Hepatic Glycogen Content (HGC)

End point title	Change from Baseline in Fasting Hepatic Glycogen Content (HGC)
End point description:	
Fasting hepatic glycogen levels were evaluated over time using magnetic resonance spectroscopy (MRS). The Per-Protocol Set (PPS) included all randomised subjects who received at least 11 doses (the first 4 doses must have occurred in the first 14 days) of study drug within 70 days of the first dose, completed protocol-required MRS procedures, and had no significant protocol deviations that would have been expected to affect efficacy assessments.	
End point type	Primary
End point timeframe:	
Baseline, Week 6, and Week 14	

End point values	Placebo (PPS)	ISIS 449884 100 mg (PPS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	8		
Units: millimoles per litre (mmol/L)				
arithmetic mean (standard deviation)				
Baseline	211.50 (± 31.74)	207.55 (± 28.04)		
Change from baseline to Week 6	24.22 (± 30.06)	23.66 (± 24.57)		
Change from baseline to Week 14	-20.16 (± 34.01)	15.11 (± 39.30)		

Statistical analyses

Statistical analysis title	Week 6

Statistical analysis description:

A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	Placebo (PPS) v ISIS 449884 100 mg (PPS)
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.833
Method	Exact Wilcoxon Rank Sum Test

Statistical analysis title	Week 14

Statistical analysis description:

A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	Placebo (PPS) v ISIS 449884 100 mg (PPS)
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.093
Method	Exact Wilcoxon Rank Sum Test

Primary: Percent Change from Baseline in Fasting HGC

End point title	Percent Change from Baseline in Fasting HGC

End point description:

Fasting hepatic glycogen levels were evaluated over time using magnetic resonance spectroscopy (MRS). The Per-Protocol Set (PPS) included all randomised subjects who received at least 11 doses (the first 4 doses must have occurred in the first 14 days) of study drug within 70 days of the first dose, completed protocol-required MRS procedures, and had no significant protocol deviations that would have been expected to affect efficacy assessments.

End point type	Primary

End point timeframe:

Baseline, Week 6, and Week 14

End point values	Placebo (PPS)	ISIS 449884 100 mg (PPS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	8		
Units: percent change in Fasting HGC				
arithmetic mean (standard deviation)				
Percent change from baseline to Week 6	11.5 (± 13.5)	11.4 (± 13.4)		
Percent change from baseline to Week 14	-8.3 (± 15.7)	7.2 (± 18.8)		

Statistical analyses

Statistical analysis title	Week 6

Statistical analysis description:

A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	Placebo (PPS) v ISIS 449884 100 mg (PPS)
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.943
Method	Exact Wilcoxon Rank Sum Test

Statistical analysis title	Week 14

Statistical analysis description:

A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	Placebo (PPS) v ISIS 449884 100 mg (PPS)
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.093
Method	Exact Wilcoxon Rank Sum Test

Primary: Change from Baseline in Fasting Hepatic Lipid Content (HLC)

End point title	Change from Baseline in Fasting Hepatic Lipid Content (HLC)

End point description:

Fasting hepatic lipid levels were evaluated over time using MRS. The PPS included all randomised subjects who received at least 11 doses (the first 4 doses must have occurred in the first 14 days) of study drug within 70 days of the first dose, completed protocol-required MRS procedures, and had no significant protocol deviations that would have been expected to affect efficacy assessments.

End point type	Primary

End point timeframe:

Baseline, Week 6, and Week 14

End point values	Placebo (PPS)	ISIS 449884 100 mg (PPS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	8		
Units: percent lipid content				
arithmetic mean (standard deviation)				
Baseline	23.02 (± 6.31)	13.01 (± 6.04)		
Change from baseline to Week 6	-2.38 (± 2.52)	3.01 (± 2.95)		
Change from baseline to Week 14	-2.68 (± 3.49)	4.15 (± 3.74)		

Statistical analyses

Statistical analysis title	Week 6

Statistical analysis description:

A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	Placebo (PPS) v ISIS 449884 100 mg (PPS)
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012
Method	Exact Wilcoxon Rank Sum Test

Statistical analysis title	Week 14

Statistical analysis description:

A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	Placebo (PPS) v ISIS 449884 100 mg (PPS)
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Exact Wilcoxon Rank Sum Test

Primary: Percent Change from Baseline in Fasting HLC

End point title	Percent Change from Baseline in Fasting HLC

End point description:

Description: Fasting hepatic lipid levels were evaluated over time using MRS. The PPS included all randomised subjects who received at least 11 doses (the first 4 doses must have occurred in the first 14 days) of study drug within 70 days of the first dose, completed protocol-required MRS procedures, and had no significant protocol deviations that would have been expected to affect efficacy assessments.

End point type	Primary

End point timeframe:

Baseline, Week 6, and Week 14

End point values	Placebo (PPS)	ISIS 449884 100 mg (PPS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	8		
Units: percent change in fasting HLC				
arithmetic mean (standard deviation)				
Percent change from baseline to Week 6	-12.5 (± 11.7)	28.2 (± 34.2)		
Percent change from baseline to Week 14	-12.2 (± 16.0)	35.2 (± 35.0)		

Statistical analyses

Statistical analysis title	Week 6

Statistical analysis description:

A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	ISIS 449884 100 mg (PPS) v Placebo (PPS)
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011
Method	Exact Wilcoxon Rank Sum Test

Statistical analysis title	Week 14

Statistical analysis description:

A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	Placebo (PPS) v ISIS 449884 100 mg (PPS)
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	Exact Wilcoxon Rank Sum Test

Primary: Change from Baseline in Fasting Plasma Glucagon

End point title	Change from Baseline in Fasting Plasma Glucagon

End point description:

Fasting plasma glucagon levels were evaluated over time using laboratory analysis. The PPS included all randomised subjects who received at least 11 doses (the first 4 doses must have occurred in the first 14 days) of study drug within 70 days of the first dose, completed protocol-required MRS procedures, and had no significant protocol deviations that would have been expected to affect efficacy assessments. "n" is the number of subjects with data available for analysis at specified timepoint.

End point type	Primary

End point timeframe:

Baseline to Week 14

End point values	Placebo (PPS)	ISIS 449884 100 mg (PPS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	8		
Units: picograms per millilitre (pg/ml)				
arithmetic mean (standard deviation)				
Baseline	160.6 (± 23.0)	114.5 (± 54.5)		
Change from baseline to Week 14 (n= 5,7)	-24.4 (± 27.4)	91.7 (± 140.9)		

Statistical analyses

Statistical analysis title	Week 14

Statistical analysis description:

A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	Placebo (PPS) v ISIS 449884 100 mg (PPS)
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.048
Method	Exact Wilcoxon Rank Sum Test

Primary: Percent Change from Baseline in Fasting Plasma Glucagon

End point title	Percent Change from Baseline in Fasting Plasma Glucagon

End point description:

Fasting plasma glucagon levels were evaluated over time using laboratory analysis. The PPS included all randomised subjects who received at least 11 doses (the first 4 doses must have occurred in the first 14 days) of study drug within 70 days of the first dose, completed protocol-required MRS procedures, and had no significant protocol deviations that would have been expected to affect efficacy assessments.

End point type	Primary

End point timeframe:

Baseline to Week 14

End point values	Placebo (PPS)	ISIS 449884 100 mg (PPS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	7		
Units: percent change in Fasting Glucagon				
arithmetic mean (standard deviation)	-15.8 (± 17.2)	82.7 (± 97.6)		

Statistical analyses

Statistical analysis title	Week 14

Statistical analysis description:

A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	ISIS 449884 100 mg (PPS) v Placebo (PPS)
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	Exact Wilcoxon Rank Sum Test

Primary: Change from Baseline in Fasting Plasma Total Active Glucagon-like Peptide-1 (GLP-1)

End point title	Change from Baseline in Fasting Plasma Total Active Glucagon-like Peptide-1 (GLP-1)

End point description:

Fasting plasma GLP-1 levels were evaluated over time using laboratory analysis. The PPS included all randomised subjects who received at least 11 doses (the first 4 doses must have occurred in the first 14 days) of study drug within 70 days of the first dose, completed protocol-required MRS procedures, and had no significant protocol deviations that would have been expected to affect efficacy assessments. "n" is the number of subjects with data available for analysis at specified timepoint.

End point type	Primary

End point timeframe:

Baseline to Week 14

End point values	Placebo (PPS)	ISIS 449884 100 mg (PPS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	8		
Units: picomoles per litre (pmol/L)				
arithmetic mean (standard deviation)				
Baseline	3.27 (± 1.46)	3.97 (± 2.48)		
Change from baseline to Week 14 (n= 5,7)	1.13 (± 2.65)	1.67 (± 2.73)		

Statistical analyses

Statistical analysis title	Week 14

Statistical analysis description:

A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	Placebo (PPS) v ISIS 449884 100 mg (PPS)
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.755
Method	Exact Wilcoxon Rank Sum Test

Primary: Percent Change from Baseline in Fasting Plasma Total Active GLP-1

End point title	Percent Change from Baseline in Fasting Plasma Total Active GLP-1

End point description:

Fasting plasma GLP-1 levels were evaluated over time using laboratory analysis. The PPS included all randomised subjects who received at least 11 doses (the first 4 doses must have occurred in the first 14 days) of study drug within 70 days of the first dose, completed protocol-required MRS procedures, and had no significant protocol deviations that would have been expected to affect efficacy assessments.

End point type	Primary

End point timeframe:

Baseline to Week 14

End point values	Placebo (PPS)	ISIS 449884 100 mg (PPS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	8		
Units: percent change in fasting total GLP-1				
arithmetic mean (standard deviation)	36.6 (± 65.9)	71.1 (± 146.1)		

Statistical analyses

Statistical analysis title	Week 14

Statistical analysis description:

A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	Placebo (PPS) v ISIS 449884 100 mg (PPS)
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.876
Method	Exact Wilcoxon Rank Sum Test

Primary: Change from Baseline in Glycated Haemoglobin (HbA1c)	
End point title	Change from Baseline in Glycated Haemoglobin (HbA1c)

End point description:

HbA1c levels were evaluated over time using laboratory analysis. The PPS included all randomised subjects who received at least 11 doses (the first 4 doses must have occurred in the first 14 days) of study drug within 70 days of the first dose, completed protocol-required MRS procedures, and had no significant protocol deviations that would have been expected to affect efficacy assessments. The Full Analysis Set (FAS) included all randomised subjects who received at least 1 dose of study drug and had at least 1 post-baseline efficacy or PD assessment.

End point type	Primary

End point timeframe:

Baseline, Week 6, and Week 14

End point values	Placebo	ISIS 449884 100 mg	Placebo (PPS)	ISIS 449884 100 mg (PPS)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	5	10	5	8
Units: percent of HbA1c				
arithmetic mean (standard deviation)				
Baseline	8.7 (± 0.9)	7.9 (± 0.5)	8.7 (± 0.9)	8.1 (± 0.5)
Change from baseline to Week 6	-0.4 (± 0.4)	-0.6 (± 0.3)	-0.4 (± 0.4)	-0.6 (± 0.3)
Change from baseline to Week 14	-0.6 (± 0.4)	-0.9 (± 0.5)	-0.6 (± 0.4)	-1.0 (± 0.6)

Statistical analyses

Statistical analysis title	Week 6 (FAS)

Statistical analysis description:

A superiority test was evaluated using ANOVA to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	Placebo v ISIS 449884 100 mg
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.303
Method	ANOVA

Statistical analysis title	Week 14 (FAS)

Statistical analysis description:

A superiority test was evaluated using ANOVA to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	ISIS 449884 100 mg v Placebo

Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.207
Method	ANOVA

Statistical analysis title	Week 6 (PPS)

Statistical analysis description:

A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	Placebo (PPS) v ISIS 449884 100 mg (PPS)
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.235
Method	Exact Wilcoxon Rank Sum Test

Statistical analysis title	Week 14 (PPS)

Statistical analysis description:

A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	Placebo (PPS) v ISIS 449884 100 mg (PPS)
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.139
Method	Exact Wilcoxon Rank Sum Test

Primary: Percent Change from Baseline in HbA1c

End point title	Percent Change from Baseline in HbA1c

End point description:

HbA1c levels were evaluated over time using laboratory analysis. The PPS included all randomised subjects who received at least 11 doses (the first 4 doses must have occurred in the first 14 days) of study drug within 70 days of the first dose, completed protocol-required MRS procedures, and had no significant protocol deviations that would have been expected to affect efficacy assessments. The FAS included all randomised subjects who received at least 1 dose of study drug and had at least 1 post-baseline efficacy or PD assessment.

End point type	Primary

End point timeframe:

Baseline, Week 6, and Week 14

End point values	Placebo	ISIS 449884 100 mg	Placebo (PPS)	ISIS 449884 100 mg (PPS)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	5	10	5	8
Units: percent change in HbA1c				
arithmetic mean (standard deviation)				
Percent change from baseline to Week 6	-4.2 (± 4.8)	-7.3 (± 3.6)	-4.2 (± 4.8)	-7.6 (± 4.0)
Percent change from baseline to Week 14	-6.3 (± 4.5)	-11.4 (± 6.3)	-6.3 (± 4.5)	-12.4 (± 6.7)

Statistical analyses

Statistical analysis title	Week 6 (FAS)

Statistical analysis description:

A superiority test was evaluated using ANOVA to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	ISIS 449884 100 mg v Placebo
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.185
Method	ANOVA

Statistical analysis title	Week 14 (FAS)

Statistical analysis description:

A superiority test was evaluated using ANOVA to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	ISIS 449884 100 mg v Placebo
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.134
Method	ANOVA

Statistical analysis title	Week 6 (PPS)

Statistical analysis description:

A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	Placebo (PPS) v ISIS 449884 100 mg (PPS)
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.171
Method	Exact Wilcoxon Rank Sum Test

Statistical analysis title	Week 14 (PPS)

Statistical analysis description:

A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	Placebo (PPS) v ISIS 449884 100 mg (PPS)
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.085
Method	Exact Wilcoxon Rank Sum Test

Primary: Change from Baseline in Fasting Plasma Glucose (FPG)

End point title	Change from Baseline in Fasting Plasma Glucose (FPG)

End point description:

FPG was monitored daily by the subject, using a study glucometer. The PPS included all randomised subjects who received at least 11 doses (the first 4 doses must have occurred in the first 14 days) of study drug within 70 days of the first dose, completed protocol-required MRS procedures, and had no significant protocol deviations that would have been expected to affect efficacy assessments. The FAS included all randomised subjects who received at least 1 dose of study drug and had at least 1 post-baseline efficacy or PD assessment. "n" is the number of subjects with data available for analysis at specified timepoint.

End point type	Primary

End point timeframe:

Baseline, Week 6, and Week 14

End point values	Placebo	ISIS 449884 100 mg	Placebo (PPS)	ISIS 449884 100 mg (PPS)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	5	10	5	8
Units: milligrams per decilitre (mg/dL)				
arithmetic mean (standard deviation)				
Baseline	212 (± 17)	171 (± 39)	212 (± 17)	170 (± 43)
Change from baseline to Week 6	-22 (± 36)	-26 (± 26)	-22 (± 36)	-26 (± 27)
Change from baseline to Week 14 (n= 5, 9; 5, 7)	-29 (± 24)	-33 (± 28)	-29 (± 24)	-32 (± 27)

Statistical analyses

Statistical analysis title	Week 6 (FAS)

Statistical analysis description:

A superiority test was evaluated using ANOVA to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	ISIS 449884 100 mg v Placebo

Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.779
Method	ANOVA

Statistical analysis title	Week 14 (FAS)

Statistical analysis description:

A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	Placebo v ISIS 449884 100 mg
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.699
Method	Exact Wilcoxon Rank Sum Test

Statistical analysis title	Week 6 (PPS)

Statistical analysis description:

A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	Placebo (PPS) v ISIS 449884 100 mg (PPS)
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Exact Wilcoxon Rank Sum Test

Statistical analysis title	Week 14 (PPS)

Statistical analysis description:

A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	Placebo (PPS) v ISIS 449884 100 mg (PPS)
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.876
Method	Exact Wilcoxon Rank Sum Test

Primary: Percent Change from Baseline in FPG

End point title	Percent Change from Baseline in FPG

End point description:

FPG was monitored daily by the subject, using a study glucometer. The PPS included all randomised subjects who received at least 11 doses (the first 4 doses must have occurred in the first 14 days) of study drug within 70 days of the first dose, completed protocol-required MRS procedures, and had no significant protocol deviations that would have been expected to affect efficacy assessments. The FAS included all randomised subjects who received at least 1 dose of study drug and had at least 1 post-baseline efficacy or PD assessment. "n" is the number of subjects with data available for analysis at specified timepoint.

End point type	Primary

End point timeframe:

Baseline, Week 6, and Week 14

End point values	Placebo	ISIS 449884 100 mg	Placebo (PPS)	ISIS 449884 100 mg (PPS)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	5	10	5	8
Units: percent change in FPG				
arithmetic mean (standard deviation)				
Percent change from baseline to Week 6	-9.4 (± 16.7)	-13.9 (± 11.4)	-9.4 (± 16.7)	-13.4 (± 11.9)
Percent change from baseline to Week 14(n=5,9;5,7)	-13.3 (± 10.2)	-17.7 (± 13.3)	-13.3 (± 10.2)	-16.9 (± 12.3)

Statistical analyses

Statistical analysis title	Week 6 (FAS)

Statistical analysis description:

A superiority test was evaluated using ANOVA to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	Placebo v ISIS 449884 100 mg
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.543
Method	ANOVA

Statistical analysis title	Week 14 (FAS)

Statistical analysis description:

A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	ISIS 449884 100 mg v Placebo
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.438
Method	Exact Wilcoxon Rank Sum Test

Statistical analysis title	Week 6 (PPS)

Statistical analysis description:

A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	Placebo (PPS) v ISIS 449884 100 mg (PPS)
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.724
Method	Exact Wilcoxon Rank Sum Test

Statistical analysis title	Week 14 (PPS)

Statistical analysis description:

A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	Placebo (PPS) v ISIS 449884 100 mg (PPS)
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.53
Method	Exact Wilcoxon Rank Sum Test

Primary: Change from Baseline in Fasting Plasma Insulin

End point title	Change from Baseline in Fasting Plasma Insulin

End point description:

Fasting plasma insulin levels were evaluated over time using laboratory analysis. The PPS included all randomised subjects who received at least 11 doses (the first 4 doses must have occurred in the first 14 days) of study drug within 70 days of the first dose, completed protocol-required MRS procedures, and had no significant protocol deviations that would have been expected to affect efficacy assessments. The FAS included all randomised subjects who received at least 1 dose of study drug and had at least 1 post-baseline efficacy or PD assessment. "n" is the number of subjects with data available for analysis at specified timepoint.

End point type	Primary

End point timeframe:

Baseline, Week 6, and Week 14

End point values	Placebo	ISIS 449884 100 mg	Placebo (PPS)	ISIS 449884 100 mg (PPS)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	5	10	5	8
Units: micro International Units (µIU)/mL				
arithmetic mean (standard deviation)				
Baseline	11.5 (± 2.7)	11.0 (± 4.2)	11.5 (± 2.7)	10.3 (± 4.4)
Change from baseline to Week 6	1.1 (± 2.2)	-0.9 (± 4.5)	1.1 (± 2.2)	-1.6 (± 4.8)
Change from baseline to Week 14 (n= 5,9; 5,7)	0.1 (± 2.4)	0.5 (± 4.6)	0.1 (± 2.4)	-0.2 (± 4.6)

Statistical analyses

Statistical analysis title	Week 6 (FAS)

Statistical analysis description:

A superiority test was evaluated using ANOVA to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	Placebo v ISIS 449884 100 mg
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.366
Method	ANOVA

Statistical analysis title	Week 14 (FAS)

Statistical analysis description:

A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	Placebo v ISIS 449884 100 mg
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.797
Method	Exact Wilcoxon Rank Sum Test

Statistical analysis title	Week 6 (PPS)

Statistical analysis description:

A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	Placebo (PPS) v ISIS 449884 100 mg (PPS)

Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.414
Method	Exact Wilcoxon Rank Sum Test

Statistical analysis title	Week 14 (PPS)

Statistical analysis description:

A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	Placebo (PPS) v ISIS 449884 100 mg (PPS)
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Exact Wilcoxon Rank Sum Test

Primary: Percent Change from Baseline in Fasting Plasma Insulin

End point title	Percent Change from Baseline in Fasting Plasma Insulin

End point description:

Fasting plasma insulin levels were evaluated over time using laboratory analysis. The PPS included all randomised subjects who received at least 11 doses (the first 4 doses must have occurred in the first 14 days) of study drug within 70 days of the first dose, completed protocol-required MRS procedures, and had no significant protocol deviations that would have been expected to affect efficacy assessments. The FAS included all randomised subjects who received at least 1 dose of study drug and had at least 1 post-baseline efficacy or PD assessment. "n" is the number of subjects with data available for analysis at specified timepoint.

End point type	Primary

End point timeframe:

Baseline, Week 6, and Week 14

End point values	Placebo	ISIS 449884 100 mg	Placebo (PPS)	ISIS 449884 100 mg (PPS)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	5	10	5	8
Units: percent change in fasting plasma Insulin				
arithmetic mean (standard deviation)				
Percent change from baseline to Week 6	11.7 (± 20.7)	-1.7 (± 35.2)	11.7 (± 20.7)	-5.7 (± 38.8)
Percent change from baseline to Week 14(n=5,9;5,7)	2.5 (± 18.3)	8.6 (± 35.3)	2.5 (± 18.3)	5.5 (± 38.0)

Statistical analyses

Statistical analysis title	Week 6 (FAS)

Statistical analysis description:

A superiority test was evaluated using ANOVA to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	ISIS 449884 100 mg v Placebo
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.449
Method	ANOVA

Statistical analysis title	Week 14 (FAS)

Statistical analysis description:

A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	ISIS 449884 100 mg v Placebo
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.699
Method	Exact Wilcoxon Rank Sum Test

Statistical analysis title	Week 6 (PPS)

Statistical analysis description:

A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	Placebo (PPS) v ISIS 449884 100 mg (PPS)
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.524
Method	Exact Wilcoxon Rank Sum Test

Statistical analysis title	Week 14 (PPS)

Statistical analysis description:

A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	Placebo (PPS) v ISIS 449884 100 mg (PPS)
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Exact Wilcoxon Rank Sum Test

Primary: Change from Baseline in Fasting Plasma C-peptide

End point title	Change from Baseline in Fasting Plasma C-peptide

End point description:

Fasting plasma C-peptide levels were evaluated over time using laboratory analysis. The PPS included all randomised subjects who received at least 11 doses (the first 4 doses must have occurred in the first 14 days) of study drug within 70 days of the first dose, completed protocol-required MRS procedures, and had no significant protocol deviations that would have been expected to affect efficacy assessments. The FAS included all randomised subjects who received at least 1 dose of study drug and had at least 1 post-baseline efficacy or PD assessment. "n" is the number of subjects with data available for analysis at specified timepoint.

End point type	Primary

End point timeframe:

Baseline, Week 6, and Week 14

End point values	Placebo	ISIS 449884 100 mg	Placebo (PPS)	ISIS 449884 100 mg (PPS)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	5	10	5	8
Units: nanograms/millilitre (ng/mL)				
arithmetic mean (standard deviation)				
Baseline	3.81 (± 0.98)	3.39 (± 0.56)	3.81 (± 0.98)	3.25 (± 0.53)
Change from baseline to Week 6	0.08 (± 0.28)	-0.25 (± 0.48)	0.08 (± 0.28)	-0.21 (± 0.47)
Change from baseline to Week 14 (n= 5,9; 5,7)	0.07 (± 0.37)	-0.02 (± 0.62)	0.07 (± 0.37)	-0.07 (± 0.52)

Statistical analyses

Statistical analysis title	Week 6 (FAS)

Statistical analysis description:

A superiority test was evaluated using ANOVA to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	Placebo v ISIS 449884 100 mg
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.183
Method	ANOVA

Statistical analysis title	Week 14 (FAS)

Statistical analysis description:

A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	ISIS 449884 100 mg v Placebo

Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.898
Method	Exact Wilcoxon Rank Sum Test

Statistical analysis title	Week 6 (PPS)

Statistical analysis description:

A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	Placebo (PPS) v ISIS 449884 100 mg (PPS)
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.284
Method	Exact Wilcoxon Rank Sum Test

Statistical analysis title	Week 14 (PPS)

Statistical analysis description:

A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	Placebo (PPS) v ISIS 449884 100 mg (PPS)
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.876
Method	Exact Wilcoxon Rank Sum Test

Primary: Percent Change from Baseline in Fasting Plasma C-peptide

End point title	Percent Change from Baseline in Fasting Plasma C-peptide

End point description:

Fasting plasma C-peptide levels were evaluated over time using laboratory analysis. The PPS included all randomised subjects who received at least 11 doses (the first 4 doses must have occurred in the first 14 days) of study drug within 70 days of the first dose, completed protocol-required MRS procedures, and had no significant protocol deviations that would have been expected to affect efficacy assessments. The FAS included all randomised subjects who received at least 1 dose of study drug and had at least 1 post-baseline efficacy or PD assessment. "n" is the number of subjects with data available for analysis at specified timepoint.

End point type	Primary

End point timeframe:

Baseline, Week 6, and Week 14

End point values	Placebo	ISIS 449884 100 mg	Placebo (PPS)	ISIS 449884 100 mg (PPS)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	5	10	5	8
Units: percent change in fasting C-peptide				
arithmetic mean (standard deviation)				
Percent change from baseline to Week 6	3.3 (± 8.6)	-5.9 (± 13.8)	3.3 (± 8.6)	-4.9 (± 14.1)
Percent change from baseline to Week 14(n=5,9;5,7)	0.6 (± 11.6)	-0.7 (± 17.4)	0.6 (± 11.6)	-2.2 (± 15.5)

Statistical analyses

Statistical analysis title	Week 6 (FAS)

Statistical analysis description:

A superiority test was evaluated using ANOVA to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	ISIS 449884 100 mg v Placebo
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.199
Method	ANOVA

Statistical analysis title	Week 14 (FAS)

Statistical analysis description:

A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	Placebo v ISIS 449884 100 mg
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Exact Wilcoxon Rank Sum Test

Statistical analysis title	Week 6 (PPS)

Statistical analysis description:

A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	Placebo (PPS) v ISIS 449884 100 mg (PPS)

Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.284
Method	Exact Wilcoxon Rank Sum Test

Statistical analysis title	Week 14 (PPS)

Statistical analysis description:

A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	Placebo (PPS) v ISIS 449884 100 mg (PPS)
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Exact Wilcoxon Rank Sum Test

Primary: Change from Baseline in Weekly Average Fasting Self-monitored Plasma Glucose (SMPG)

End point title	Change from Baseline in Weekly Average Fasting Self-monitored Plasma Glucose (SMPG)

End point description:

SMPG was measured daily at home using the study glucometer. The PPS included all randomised subjects who received at least 11 doses (the first 4 doses must have occurred in the first 14 days) of study drug within 70 days of the first dose, completed protocol-required MRS procedures, and had no significant protocol deviations that would have been expected to affect efficacy assessments. The FAS included all randomised subjects who received at least 1 dose of study drug and had at least 1 post-baseline efficacy or PD assessment.

End point type	Primary

End point timeframe:

Baseline, Week 6, and Week 14

End point values	Placebo	ISIS 449884 100 mg	Placebo (PPS)	ISIS 449884 100 mg (PPS)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	5	10	5	8
Units: milligrams per decilitre (mg/dl)				
arithmetic mean (standard deviation)				
Baseline	182.94 (± 28.62)	159.70 (± 25.44)	182.94 (± 28.62)	159.26 (± 27.83)
Change from baseline to Week 6	-19.75 (± 37.42)	-21.08 (± 16.05)	-19.75 (± 37.42)	-19.42 (± 14.89)
Change from baseline to Week 14	-30.15 (± 24.79)	-24.39 (± 17.37)	-30.15 (± 24.79)	-26.86 (± 16.16)

Statistical analyses

Statistical analysis title	Week 6 (FAS)
Statistical analysis description:	
A superiority test was evaluated using ANOVA to assess the difference between subjects in the Placebo group and ISIS 449884 group.	
Comparison groups	Placebo v ISIS 449884 100 mg
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.923
Method	ANOVA

Statistical analysis title	Week 14 (FAS)
Statistical analysis description:	
A superiority test was evaluated using ANOVA to assess the difference between subjects in the Placebo group and ISIS 449884 group.	
Comparison groups	Placebo v ISIS 449884 100 mg
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.607
Method	ANOVA

Statistical analysis title	Week 6 (PPS)
Statistical analysis description:	
A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.	
Comparison groups	ISIS 449884 100 mg (PPS) v Placebo (PPS)
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.435
Method	Exact Wilcoxon Rank Sum Test

Statistical analysis title	Week 14 (PPS)
Statistical analysis description:	
A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.	

Comparison groups	Placebo (PPS) v ISIS 449884 100 mg (PPS)
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.833
Method	Exact Wilcoxon Rank Sum Test

Primary: Percent Change from Baseline in Weekly Average Fasting SMPG

End point title	Percent Change from Baseline in Weekly Average Fasting SMPG

End point description:

SMPG was measured daily at home using the study glucometer. The PPS included all randomised subjects who received at least 11 doses (the first 4 doses must have occurred in the first 14 days) of study drug within 70 days of the first dose, completed protocol-required MRS procedures, and had no significant protocol deviations that would have been expected to affect efficacy assessments. The FAS included all randomised subjects who received at least 1 dose of study drug and had at least 1 post-baseline efficacy or PD assessment.

End point type	Primary

End point timeframe:

Baseline, Week 6, and Week 14

End point values	Placebo	ISIS 449884 100 mg	Placebo (PPS)	ISIS 449884 100 mg (PPS)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	5	10	5	8
Units: percent change in fasting SMPG				
arithmetic mean (standard deviation)				
Percent change from baseline to Week 6	-9.3 (± 21.7)	-12.5 (± 8.7)	-9.3 (± 21.7)	-11.6 (± 8.1)
Percent change from baseline to Week 14	-16.3 (± 15.3)	-14.3 (± 8.9)	-16.3 (± 15.3)	-15.9 (± 7.5)

Statistical analyses

Statistical analysis title	Week 6 (FAS)

Statistical analysis description:

A superiority test was evaluated using ANOVA to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	ISIS 449884 100 mg v Placebo
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.684
Method	ANOVA

	Week 14 (FAS)

Statistical analysis title	

Statistical analysis description:

A superiority test was evaluated using ANOVA to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	ISIS 449884 100 mg v Placebo
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.752
Method	ANOVA

Statistical analysis title	Week 6 (PPS)

Statistical analysis description:

A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	Placebo (PPS) v ISIS 449884 100 mg (PPS)
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.622
Method	Exact Wilcoxon Rank Sum Test

Statistical analysis title	Week 14 (PPS)

Statistical analysis description:

A superiority test was evaluated using the Exact Wilcoxon Rank Sum Test to assess the difference between subjects in the Placebo group and ISIS 449884 group.

Comparison groups	Placebo (PPS) v ISIS 449884 100 mg (PPS)
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Exact Wilcoxon Rank Sum Test

Primary: Percentage of Subjects with Treatment-Emergent Adverse Events (TEAEs)

End point title	Percentage of Subjects with Treatment-Emergent Adverse Events (TEAEs)[1]

End point description:

An adverse event (AE) was any unfavourable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the study or use of investigational drug product, whether or not the AE was considered related to the investigational drug product. An AE was considered a treatment-emergent adverse event (TEAE) if it was present prior to the first dose of Study Drug and subsequently worsened or was not present prior to the first dose of Study Drug and subsequently appeared. The Safety Set included all subjects who were randomized and received at least one dose of study drug.

End point type	Primary

End point timeframe:

Up to 13 weeks

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: Descriptive statistics only.

End point values	Placebo	ISIS 449884 100 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	10		
Units: percentage of subjects				
number (not applicable)	100	100		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 13 weeks	
Adverse event reporting additional description:	
The Safety Set included all subjects who were randomised and received at least one dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received ISIS 449884 matching-placebo, by SC injection, on Days 1, 3 and 5 of Week 1 as loading doses followed by once weekly from Week 2 through Week 13.	
Reporting group title	ISIS 449884 100 mg
Reporting group description:	
Subjects received 100 mg ISIS 449884, by SC injection, on Days 1, 3 and 5 of Week 1 as loading doses followed by once weekly from Week 2 through Week 13.	

Serious adverse events	Placebo	ISIS 449884 100 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 5 (20.00%)	0 / 10 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 5 (20.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	ISIS 449884 100 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	10 / 10 (100.00%)	
Vascular disorders			
Hypertension			

subjects affected / exposed	1 / 5 (20.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	0 / 5 (0.00%)	7 / 10 (70.00%)	
occurrences (all)	0	41	
Injection site pain			
subjects affected / exposed	0 / 5 (0.00%)	3 / 10 (30.00%)	
occurrences (all)	0	7	
Injection site pruritus			
subjects affected / exposed	0 / 5 (0.00%)	3 / 10 (30.00%)	
occurrences (all)	0	5	
Injection site swelling			
subjects affected / exposed	0 / 5 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	4	
Injection site discolouration			
subjects affected / exposed	0 / 5 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	2	
Injection site induration			
subjects affected / exposed	0 / 5 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	2	
Reproductive system and breast disorders			
Metrorrhagia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Ovarian cyst			
subjects affected / exposed	0 / 5 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Psychiatric disorders			
Shared psychotic disorder			
subjects affected / exposed	1 / 5 (20.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 5 (20.00%)	3 / 10 (30.00%)	
occurrences (all)	1	4	

Aspartate aminotransferase increased			
subjects affected / exposed	1 / 5 (20.00%)	3 / 10 (30.00%)	
occurrences (all)	1	8	
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	0 / 5 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
White blood cell count increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 5 (20.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Wound			
subjects affected / exposed	1 / 5 (20.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 5 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Eye disorders			
Diabetic retinal oedema			
subjects affected / exposed	1 / 5 (20.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 5 (20.00%)	2 / 10 (20.00%)	
occurrences (all)	1	3	
Abdominal pain upper			

subjects affected / exposed	0 / 5 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 5 (20.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Alopecia areata			
subjects affected / exposed	0 / 5 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Diffuse alopecia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Eczema			
subjects affected / exposed	0 / 5 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	1 / 5 (20.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Azotaemia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Haematuria			
subjects affected / exposed	0 / 5 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Renal impairment			
subjects affected / exposed	1 / 5 (20.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	2 / 5 (40.00%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Back pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Intervertebral disc disorder			

subjects affected / exposed	0 / 5 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Neck pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 5 (60.00%)	0 / 10 (0.00%)	
occurrences (all)	6	0	
Bacteriuria			
subjects affected / exposed	1 / 5 (20.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Acarodermatitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Asymptomatic bacteriuria			
subjects affected / exposed	1 / 5 (20.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Cystitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Herpes zoster			
subjects affected / exposed	0 / 5 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	1 / 5 (20.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hypertriglyceridaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Hypoglycaemia			

subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 July 2015	Clarified inclusion criterion #6 with regard to eligibility of subjects who had been on a stable dose of metformin plus a sulfonylurea (SU) or dipeptidyl peptidase-4 (DPPIV) inhibitor; deleted exclusion criterion #22 for waist circumference because it was not a contraindication for the MRS procedure; added safety monitoring rules for platelet count results for consistency with other ongoing protocols; and to clarify addition of "Initiation of new or change in dose" to Disallowed Concomitant Therapy #5.
23 May 2016	Revised the platelet monitoring criteria to ensure an uninterpretable platelet value was repeated and available for physician review prior to the next scheduled dose per protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported