



Clinical trial results:

A Randomized, Double Blind, Placebo-Controlled, Phase 2 Study to Assess the Safety, Tolerability and Efficacy of ISIS 426115 (an Antisense Glucocorticoid Receptor Antagonist) Administered Subcutaneously Once Weekly for 6 Weeks to Patients with Type 2 Diabetes Mellitus Being Treated with Metformin

Summary

EudraCT number	2013-002172-40
Trial protocol	RO
Global end of trial date	09 April 2015

Results information

Result version number	v1 (current)
This version publication date	07 November 2019
First version publication date	07 November 2019

Trial information

Trial identification

Sponsor protocol code	ISIS426115-CS2
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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, Ionis Pharmaceuticals, 011 800-679-4747, patients@ionisph.com
Scientific contact	Ionis Pharmaceuticals, Ionis Pharmaceuticals, 011 800-679-4747, 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	09 April 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	09 April 2015
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 safety and tolerability of ISIS-GCCRx subcutaneous injection (dosage: 210 milligrams per week [mg/wk]) in combination with metformin vs. metformin + placebo.

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	03 March 2014
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	Canada: 7
Country: Number of subjects enrolled	Romania: 13
Country: Number of subjects enrolled	South Africa: 18
Worldwide total number of subjects	38
EEA total number of subjects	13

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)	26
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects must have been on a stable dose of metformin (at least 1000 mg/day) alone for a minimum of 3 months prior to screening evaluations and were required to continue their stable doses of metformin treatment throughout the study.

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-GCCRRx-matching placebo on alternate days during the first week and then once weekly for 5 weeks, plus daily metformin per individual regimen.

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-GCCRRx placebo-matching, subcutaneous (SC) injections, on alternate days during the first week and then once weekly for 5 weeks, plus daily metformin per individual regimen.

Arm title	ISIS-GCCRRx, 210 mg
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Arm description:

Subjects received ISIS-GCCRRx, 210 mg, administered by SC on alternate days during the first week and then once weekly for 5 weeks, plus daily metformin per individual regimen.

Arm type	Experimental
Investigational medicinal product name	ISIS-GCCRRx
Investigational medicinal product code	
Other name	ISIS 426115
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subject received ISIS-GCCRRx, 210 mg, administered by SC on alternate days during the first week and then once weekly for 5 weeks, plus daily metformin per individual regimen.

Number of subjects in period 1	Placebo	ISIS-GCCRRx, 210 mg
Started	13	25
Completed	13	22
Not completed	0	3
Voluntary Withdrawal	-	1
Adverse Events	-	1
Ineligibility	-	1

Baseline characteristics

Reporting groups

Reporting group title	Placebo
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Reporting group description:

Subjects received ISIS-GCCRRx-matching placebo on alternate days during the first week and then once weekly for 5 weeks, plus daily metformin per individual regimen.

Reporting group title	ISIS-GCCRRx, 210 mg
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Reporting group description:

Subjects received ISIS-GCCRRx, 210 mg, administered by SC on alternate days during the first week and then once weekly for 5 weeks, plus daily metformin per individual regimen.

Reporting group values	Placebo	ISIS-GCCRRx, 210 mg	Total
Number of subjects	13	25	38
Age categorical Units: Subjects			
< 18	0	0	0
18 <= and <= 41	1	1	2
41 < and <= 65	6	20	26
> 65	6	4	10
Age continuous Units: years			
arithmetic mean	59.92	56.84	
standard deviation	± 12.57	± 8.63	-
Gender categorical Units: Subjects			
Female	4	16	20
Male	9	9	18

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Subjects received ISIS-GCCRRx-matching placebo on alternate days during the first week and then once weekly for 5 weeks, plus daily metformin per individual regimen.	
Reporting group title	ISIS-GCCRRx, 210 mg
Reporting group description: Subjects received ISIS-GCCRRx, 210 mg, administered by SC on alternate days during the first week and then once weekly for 5 weeks, plus daily metformin per individual regimen.	

Primary: Change from Baseline in Serum Fasting Fructosamine

End point title	Change from Baseline in Serum Fasting Fructosamine
End point description: The Per-Protocol Set (PPS) included randomised subjects with a measure at Baseline and at least 1 post-baseline serum fructosamine measure; received 3 loading doses of ISIS-GCCRRx or placebo in the first week and all 8 doses of ISIS-GCCRRx or placebo within 49 days of the first dose; had no dose adjustments; and had no significant protocol deviations that would be expected to affect efficacy assessments.	
End point type	Primary
End point timeframe: Baseline to Week 7	

End point values	Placebo	ISIS-GCCRRx, 210 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	22		
Units: micromoles per litre ($\mu\text{mol/L}$)				
arithmetic mean (standard error)	4.85 (\pm 7.42)	3.00 (\pm 6.07)		

Statistical analyses

Statistical analysis title	Placebo vs ISIS-GCCRRx 210 mg
Comparison groups	Placebo v ISIS-GCCRRx, 210 mg
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.851
Method	ANOVA

Secondary: Percentage of Subjects with Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point title	Percentage of Subjects with Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)
End point description:	
An adverse event (AE) is 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 is considered related to the investigational drug product. TEAE was defined as an event that occurred during or after initiation of study treatment and before the end of follow-up period. SAE, as determined by the Investigator or Sponsor, meets any of the following criteria: results in death; is life-threatening; requires inpatient hospitalisation or prolongation of existing hospitalisation; results in persistent or significant incapacity or substantial disruption of ability to conduct normal life functions; or results in congenital anomaly or birth defect in the offspring of the subject (whether the subject is male or female). The Safety Set included all randomised subjects who received at least 1 dose of ISIS-GCCRRx or placebo.	
End point type	Secondary
End point timeframe:	
Up to 18 weeks	

End point values	Placebo	ISIS-GCCRRx, 210 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	25		
Units: percentage of subjects				
number (not applicable)				
TEAEs	38.5	88.0		
SAEs	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 18 weeks

Adverse event reporting additional description:

The Safety Set included all subjects who were randomized and received at least one dose of study drug.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Subjects received ISIS-GCCRRx-matching placebo on alternate days during the first week and then once weekly for 5 weeks, plus daily metformin per individual regimen.

Reporting group title	ISIS-GCCRRx, 210 mg
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Reporting group description:

Subjects received ISIS-GCCRRx, 210 mg, administered by subcutaneous injections (SC) on alternate days during the first week and then once weekly for 5 weeks, plus daily metformin per individual regimen.

Serious adverse events	Placebo	ISIS-GCCRRx, 210 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Placebo	ISIS-GCCRRx, 210 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 13 (38.46%)	20 / 25 (80.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 13 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Orthostatic hypotension			
subjects affected / exposed	0 / 13 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	9	

Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 13 (7.69%)	0 / 25 (0.00%)	
occurrences (all)	3	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 13 (7.69%)	2 / 25 (8.00%)	
occurrences (all)	2	2	
Injection site erythema			
subjects affected / exposed	0 / 13 (0.00%)	14 / 25 (56.00%)	
occurrences (all)	0	54	
Injection site nodule			
subjects affected / exposed	0 / 13 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	4	
Injection site oedema			
subjects affected / exposed	0 / 13 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	6	
Injection site pain			
subjects affected / exposed	0 / 13 (0.00%)	11 / 25 (44.00%)	
occurrences (all)	0	55	
Injection site pruritus			
subjects affected / exposed	0 / 13 (0.00%)	9 / 25 (36.00%)	
occurrences (all)	0	36	
Injection site swelling			
subjects affected / exposed	0 / 13 (0.00%)	4 / 25 (16.00%)	
occurrences (all)	0	20	
Vessel puncture site haematoma			
subjects affected / exposed	1 / 13 (7.69%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 13 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Diarrhoea			
subjects affected / exposed	1 / 13 (7.69%)	2 / 25 (8.00%)	
occurrences (all)	1	2	

Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	1 / 25 (4.00%) 1	
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	1 / 25 (4.00%) 1	
Infections and infestations Conjunctivitis subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) Lower respiratory tract infection subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1 1 / 13 (7.69%) 3	0 / 25 (0.00%) 0 1 / 25 (4.00%) 1 0 / 25 (0.00%) 0 2 / 25 (8.00%) 2 2 / 25 (8.00%) 4	
Metabolism and nutrition disorders Hyperkalaemia subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 25 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 April 2014	<ul style="list-style-type: none">- Clarified existing eligibility requirements for renal function and included an exclusion criterion based on glycaemic parameters.- Simplified compliance with screening procedures: the screening fasting plasma glucose (FPG) assessment period was lengthened, and the screening visit window was shortened.- Revised the Safety Monitoring and Stopping Rules for Liver Chemistry Tests for increased surveillance of subject safety.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported