Clinical trial results:
An open-label phase 2 study to evaluate the safety and efficacy of CCX168 in subjects with IgA Nephropathy on stable RAAS blockade.

Summary

EudraCT number	2014-003402-33
Trial protocol	BE SE
Global end of trial date	13 September 2015

Results information

Result version number	v1
This version publication date	21 October 2022
First version publication date	21 October 2022

Trial information

Trial identification

Sponsor protocol code	CL005_168

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	IND Number: 123187

Notes:

Sponsors

Sponsor organisation name	Chemocentryx Inc
Sponsor organisation address	835 Industrial Rd. Suite 600, San Carlos, United States, 94070
Public contact	Clinical Operations Manager, ChemoCentryx, Inc. , 1 6502102900,
Scientific contact	Clinical Operations Manager, ChemoCentryx, Inc. , 1 6502102900,

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 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 September 2015
Global end of trial reached?	Yes
Global end of trial date	13 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary safety objective of this study is to evaluate the safety and tolerability of CCX168 in subjects with IgAN on background supportive therapy with a maximally tolerated dose of RAAS blockade.
The primary efficacy objective is to evaluate the efficacy of CCX168 based on an improvement in proteinuria.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki and with all applicable laws and regulations of the locale and country where the study was conducted, and in compliance with Good Clinical Practice Guidelines. Only subjects that met all the study inclusion and none of the exclusion criteria were entered in the study. The rationale of the study, procedural details, and investigational goals were explained to each subject, along with potential risks and benefits. Each subject was assured of his/her right to withdraw from the study at any time.

Background therapy:

At screening, subjects ideally were taking one or two RAAS blocker(s) and had BP <140/90 mmHg. If the blood pressure target of <125/75 mmHg was not achieved during the titration period (up to 4 weeks), additional anti-hypertension medication (non-ACE-I or ARBs) was considered to achieve this blood pressure goal (<125/75 mmHg). Once titrated to the optimal RAAS dose, all subjects participated in an 8-week run-in period during which they were required to take a stable MTD of an RAAS blocker before starting treatment with CCX168 on Day 1. If a subject was on two RAAS blockers (any combination of ACE inhibitor, ARB, and aldosterone blocker) at the time of screening, the subject was required to remain on stable doses of those medications throughout the 8-week run-in period. Titration to an MTD for both RAAS blockers was not needed in this case if the blood pressure goal of <125 / 75 mmHg was achieved.

Evidence for comparator: -

Actual start date of recruitment	27 March 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 4
Country: Number of subjects enrolled	Sweden: 3
Worldwide total number of subjects	7
EEA total number of subjects	3

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	7
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening took place for 14 days. Screening was following by a combined renin-angiotensin-aldosterone system (RAAS) titration (up to 4 weeks) plus run-in period (8 weeks) with an additional up to 7-day eligibility confirmation.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	CCX168

Arm description:

Modified Intent-to-Treatment (mITT) Population included all subjects who received at least one dose of study drug and who had at least one post baseline urinary PCR assessment.

Arm type	Experimental
Investigational medicinal product name	ccx168
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

CCX168 30 mg, twice daily (b.i.d.) orally for 84 days (12 weeks). The CCX168 dose was taken in the morning, optimally within one hour after breakfast, and in the evening, optimally within one hour after dinner.

Number of subjects in period 1	CCX168
Started	7
Completed	7

Baseline characteristics

Reporting groups	
Reporting group title	Overall study
Reporting group description:	
Safety Population included of all subjects who received at least one dose of study drug.	

Reporting group values	Overall study	Total	
Number of subjects	7	7	
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)	0	0	
Adults (18-64 years)	7	7	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	44.1		
standard deviation	± 13.20	-	
Gender categorical Units: Subjects			
Female	4	4	
Male	3	3	
Race Units: Subjects			
Asian	1	1	
White (Caucasian)	6	6	
Ethnic Group Units: Subjects			
Hispanic or Latino	1	1	
Other	6	6	
BMI			
BMI = Body Max Index			
Units: kg/m 2			
arithmetic mean	30.05		
standard deviation	± 8.29	-	
Mean time since diagnosis of IgAN			
IgAN = IgA Nephropathy			
Units: month			
arithmetic mean	17.3		
full range (min-max)	1 to 42	-	
PCR			

urinary PCR = protein:creatinine ratio			
Units: mg/g			
arithmetic mean	1906.84		
full range (min-max)	1181.06 to 3392.25	-	
ACR			
Urinary ACR = Albumin to Creatinine Ratio			
Units: mg/g			
arithmetic mean	1528.42		
full range (min-max)	921.76 to 2898.18	-	
eGFR			
eGFR = estimated Glomerular Filtration Rate			
Units: mL/min/1.73m²			
arithmetic mean	65.89		
full range (min-max)	48.91 to 93.91	-	
MCP-1 to Creatinine ratio			
MCP-1 = Monocyte Chemoattractant Protein-1			
Units: pg/mg crea			
arithmetic mean	577.44		
full range (min-max)	224.79 to 974.70	-	

End points

End points reporting groups

Reporting group title	CCX168
Reporting group description: Modified Intent-to-Treatment (mITT) Population included all subjects who received at least one dose of study drug and who had at least one post baseline urinary PCR assessment.	
Subject analysis set title	8-week Run-in period
Subject analysis set type	Safety analysis
Subject analysis set description: 8-week RAAS run-in period	
Subject analysis set title	12-week treatment period
Subject analysis set type	Safety analysis
Subject analysis set description: 12-week CCX168 treatment period	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: Safety Population included of all subjects who received at least one dose of study drug.	

Primary: Change in slope of first morning urinary PCR from the 8-week RAAS blocker run-in period to the 12-week CCX168 treatment period

End point title	Change in slope of first morning urinary PCR from the 8-week RAAS blocker run-in period to the 12-week CCX168 treatment period
End point description: The mean change in the slope of the urinary protein:creatinine ratio (UPCR, in mg/g/week) between the 8-week run-in period and the 12-week treatment period	
End point type	Primary
End point timeframe: Week -8 to -1 (Run-in period) and Week 1 to 12 (treatment period)	

End point values	CCX168	8-week Run-in period	12-week treatment period	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	7	7	7	
Units: mean slope change in UPCR				
arithmetic mean (standard deviation)	-2.4 (± 141.77)	8.6 (± 76.85)	6.1 (± 82.47)	

Statistical analyses

Statistical analysis title	Change in slope uPCR
Statistical analysis description: P-value is for the comparison between Slope of Week -8 to -5 and Slope of Week -4 to -1 using random coefficients regression.	

Comparison groups	8-week Run-in period v 12-week treatment period
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.965
Method	t-test, 2-sided
Parameter estimate	Slope
Point estimate	-2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-133.6
upper limit	128.7
Variability estimate	Standard deviation
Dispersion value	141.77

Primary: Subject incidence of adverse events (AE's)

End point title	Subject incidence of adverse events (AE's)[1]

End point description:

Acronyms use: Adverse Events (AE's) Serious Adverse Events (SAE's)

End point type	Primary

End point timeframe:

Day 0 - Day 169 (throughout the trial)

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: No inferential statistical analysis was performed on Adverse Event or other safety data.

End point values	Safety Population			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: Patients				
Subjects who had any AE	7			
Subjects who had an SAE	1			
AE leading to interruption of treatment	1			
AE leading to permanent discontinuation of study	0			
Withdrawals due to AE	0			
Deaths	0			
AE of grade 3 ≥	1			
Related AE grade 3≥	0			
Subjects who had an AE possibly related	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects achieving renal response from baseline to day 85

End point title	Proportion of subjects achieving renal response from baseline to day 85

End point description:

Renal Response defined as an improvement in proteinuria based on a decrease from baseline to Day 85 in proteinuria to a level <300 mg/g creatinine and maintaining eGFR within 15% of baseline.

End point type	Secondary

End point timeframe:

Baseline and Day 85

End point values	CCX168			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: Participants				
Patients with a renal response by Day 85	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects achieving a partial renal response from baseline to day 85

End point title	Proportion of subjects achieving a partial renal response from baseline to day 85

End point description:

A partial renal response, defined as an improvement in proteinuria based on a decrease from baseline to Day 85 in proteinuria to a level <1 g/g creatinine and maintaining eGFR within 15% of baseline.

End point type	Secondary

End point timeframe:

Baseline and Day 85

End point values	CCX168			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: Participants				
Patients with a partial renal response at day 85	2			
Patients with no partial renal response at day 85	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to day 85 in Vital Signs

End point title	Change from Baseline to day 85 in Vital Signs

End point description:

End point type	Secondary

End point timeframe:

Baseline to day 85

End point values	Safety Population			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: Change from baseline				
arithmetic mean (standard deviation)				
Heart rate (BPM)	1.3 (± 8.56)			
Systolic BP (mmHg)	-1.4 (± 12.11)			
Diastolic BP (mmHg)	2.1 (± 8.45)			
Temperature (C)	0.2 (± 0.68)			
Weight (kg)	-0.6 (± 2.39)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From Baseline up to 169 days	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1
Reporting groups	
Reporting group title	Safety population
Reporting group description:	
Safety population included all subjects who received any CCX168	

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 7 (14.29%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Angina unstable			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	3		
Blood creatine phosphokinase			

increased			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	3		
Blood creatinine increased			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Blood thyroid stimulating hormone increased			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Eosinophil count increased			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Wound			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 7 (42.86%)		
occurrences (all)	3		
Migraine			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Localized oedema			

subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Peripheral swelling			
subjects affected / exposed	3 / 7 (42.86%)		
occurrences (all)	3		
Pyrexia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	3		
Inguinal hernia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	4		
Vomiting			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Dyspnoea			

subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Wheezing			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Hair growth abnormal			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Skin swelling			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Polyuria			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	4		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	3 / 7 (42.86%)		
occurrences (all)	3		
Parotitis			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Rhinovirus infection			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 November 2014	The main changes that made Amendment 1.0 to the protocol included the following: - Exclusion criterion number 12 was added to exclude subjects with infection requiring antibiotic treatment that has not cleared prior to starting CCX168 treatment on Day 1. - Stopping criteria were added regarding liver enzyme elevations and WBC decreases. -Modification to the Safety Monitoring Plan. - Wording added to indicate that the slope of the last 4 weeks of the run-in period may be used as baseline slope instead of the full 8 weeks if steady state has not been reached in the first 4 weeks of the run-in period. - A statement was added to that if the blood pressure target of <125/75 mmHg is not achieved during the titration period, additional anti-hypertension medication (non-ACE-I or ARBs) should be considered to achieve this blood pressure goal. - Several sections were revised to reflect addition of PK assessment in patients with IgA nephropathy.
13 May 2015	The main changes that Amendment 2.0 made to the protocol included the following: - Inclusion of serum amylase and lipase monitoring over the course of the study. - Monitoring of central nervous system function
17 July 2015	The main change that Amendment 3.0 made to the protocol included the following: -Modified stopping rules for individual subjects, based on white blood cell, neutrophil, and lymphocyte counts, as well as hepatic aminotransferase or bilirubin elevations

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported