Clinical trial results:
Sclero XIII: A phase II ,double-blind, randomized, placebo-controlled study to investigate pharmacokinetics (PK), safety and efficacy of intravenous factor XIII treatment in patients with systemic sclerosis

Summary

EudraCT number	2014-001101-40
Trial protocol	GB
Global end of trial date	06 September 2018

Results information

Result version number	v1
This version publication date	19 December 2019
First version publication date	19 December 2019
Summary attachment (see zip file)	Sclero XIII study report (Sclero XIII study report FINAL3.pdf)

Trial information

Trial identification

Sponsor protocol code	13/0417

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02551042
WHO universal trial number (UTN)	-
Other trial identifiers	IRAS: 150751

Notes:

Sponsors

Sponsor organisation name	University College London, Joint Research Office
Sponsor organisation address	149 Tottenham Court Road, London, United Kingdom,
Public contact	Prof Christopher Denton, University College London, +44 02073177544, c.denton@ucl.ac.uk
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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	30 September 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 September 2018
Global end of trial reached?	Yes
Global end of trial date	06 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1.To identify any effects of factor XIII treatment on clinical manifestations of Sleroderma (SSc)
2.To investigate factor XIII safety
3.To measure individual factor XIII levels in patients with SSc
4.To measure the effects of factor XIII treatment on factor XIII PK parameters.
5.To explore effects of factor XIII on thrombospondin expression

Protection of trial subjects:

The study involved an initial PK open label arm to assess the safety and tolerability of the IMP in the patient population as well as generating a dosing algorithm that would be used in the double blind, randomized placebo-controlled treatment arm. This was built into the study in order to to minimize safety issues .

Background therapy:

Immunosuppressants such as mycophenolate, cyclophosphamide, and methotrexate are prescribed to manage disease symptoms as there is currently no approved medication.

Evidence for comparator:

This is a phase II, double-blind, randomised, placebo-controlled study to investigate the pharmacokinetics, safety and efficacy of intravenous factor XIII treatment in patients with systemic sclerosis, as there is no approved drug for Diffuse Systemic Sclerosis (DcSSC) a placebo arm is the relevant comparator

Actual start date of recruitment	09 August 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 26
Worldwide total number of subjects	26
EEA total number of subjects	26

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)	19
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment window was 24/11/2015 to 22/01/2018

Pre-assignment

Screening details:

PK arm- 8 participants were screened and randomized
Treatment arm- 22 participants were screened and 18 randomized. There were 4 screen failures and 1 withdrawal

Period 1

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

Blinding implementation details:

Both the investigators and subject were blinded to treatment group allocation. Only the pharmacy staff and designated unblinded nurse were unblinded in order for them to review study participants Factor XIII levels.

Arms

Are arms mutually exclusive?	Yes
Arm title	Active treatment

Arm description:

6 participants with diffuse and 6 with limited SSc were randomly allocated to receive active treatment;

Arm type	Experimental
Investigational medicinal product name	Fibrogammin®P, coagulation factor XIII concentrate (Human)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Individual dosing to 220% of normal every 14 days for 24 weeks. FXIII levels to be measured before and after injection

Arm title	Placebo

Arm description:

3 participants with diffuse SSc and 3 with limited SSc were randomly allocated to receive placebo.

Arm type	Placebo
Investigational medicinal product name	Sodium Chloride, 0,9%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Intravascular use

Dosage and administration details:

Standardised placebo administration every 14 days for 24 weeks total

Arm title	PK arm

Arm description:

4 patients with limited and 4 patients with diffuse systemic sclerosis received a single dose of factor XIII and levels were monitored over a six-week period

Arm type	PK safety
Investigational medicinal product name	Fibrogammin®P, coagulation factor XIII concentrate (Human)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants will receive a single intravenous injection of factor XIII concentrate either 20 or 40 IU/kg, depending on starting levels. Participants with starting levels great than or equal to 90% of normal will receive 20 IU/kg. Participants with starting levels less than 90% of normal will receive 40 IU/kg

Number of subjects in period 1	Active treatment	Placebo	PK arm
Started	12	6	8
Completed	11	6	8
Not completed	1	0	0
poor vascular access	1	-	-

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	26	26	
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)	19	19	
From 65-84 years	7	7	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	0		
standard deviation	± 0	-	
Gender categorical Units: Subjects			
Female	25	25	
Male	1	1	

Subject analysis sets

Subject analysis set title	PK
Subject analysis set type	Safety analysis

Subject analysis set description:

(PK) phase of the trial aimed to assess the safety and tolerability of the IMP in the SSc patient. It also aimed to generate data to produce a dosing algorithm that could be used in the Treatment Phase.

Subject analysis set title	Active Treatment
Subject analysis set type	Per protocol

Subject analysis set description:

12 patients on active treatment, 6 with limited disease and 6 with diffuse disease

Subject analysis set title	Placebo
Subject analysis set type	Per protocol

Subject analysis set description:

6 participants on Placebo, 3 with limited disease and 3 diffuse

Reporting group values	PK	Active Treatment	Placebo
Number of subjects	8	12	6

Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	6	13	
From 65-84 years	2	5	
85 years and over			
Age continuous Units: years			
arithmetic mean	59	59.8	57.5
standard deviation	±	±	±
Gender categorical Units: Subjects			
Female	7	12	6
Male	1	0	0

End points

End points reporting groups

Reporting group title	Active treatment
Reporting group description:	
6 participants with diffuse and 6 with limited SSc were randomly allocated to receive active treatment;	
Reporting group title	Placebo
Reporting group description:	
3 participants with diffuse SSc and 3 with limited SSc were randomly allocated to receive placebo.	
Reporting group title	PK arm
Reporting group description:	
4 patients with limited and 4 patients with diffuse systemic sclerosis received a single dose of factor XIII and levels were monitored over a six-week period	
Subject analysis set title	PK
Subject analysis set type	Safety analysis
Subject analysis set description:	
(PK) phase of the trial aimed to assess the safety and tolerability of the IMP in the SSc patient. It also aimed to generate data to produce a dosing algorithm that could be used in the Treatment Phase.	
Subject analysis set title	Active Treatment
Subject analysis set type	Per protocol
Subject analysis set description:	
12 patients on active treatment, 6 with limited disease and 6 with diffuse disease	
Subject analysis set title	Placebo
Subject analysis set type	Per protocol
Subject analysis set description:	
6 participants on Placebo, 3 with limited disease and 3 diffuse	

Primary: Skin involvement

End point title	Skin involvement
End point description:	
Skin involvement measured with modified Rodnan skin score	
End point type	Primary
End point timeframe:	
Baseline to 24 weeks	

End point values	Active Treatment	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	6		
Units: whole numbers	12	6		

Attachments (see zip file)	Capture.PNG

Statistical analyses

Statistical analysis title	Skin Involvement
Comparison groups	Placebo v Active Treatment
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %

Notes:

[1] - Please see attached chart

Primary: Raynaud condition score	
End point title	Raynaud condition score
End point description: Raynaud condition score	
End point type	Primary
End point timeframe: Baseline to week 24	

End point values	Active Treatment	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	6		
Units: whole numbers	12	6		

Attachments (see zip file)	Capture.PNG

Statistical analyses

Statistical analysis title	Raynauds condition score
Comparison groups	Active Treatment v Placebo
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)

Secondary: Pulmonary function	
End point title	Pulmonary function[2]

End point description:

End point type	Secondary

End point timeframe:

From baseline to week 24

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pulmonary function not assessed in the PK arm, see attached report for full information.

End point values	Active treatment	Placebo	Active Treatment	Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	12	6	12	6
Units: whole numbers	12	6	12	6

Attachments (see zip file)	Secondary endpoints /Secondary endpoints.PNG

Statistical analyses

Statistical analysis title	Pulmonary function
Comparison groups	Placebo v Active treatment
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)

Notes:

[3] - Descriptive analysis

Secondary: Hand function measured with Cochin hand function

End point title	Hand function measured with Cochin hand function

End point description:

End point type	Secondary

End point timeframe:

Baseline to 24 weeks

End point values	Active Treatment	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed				
Units: whole numbers	12	6		

Attachments (see zip file)	Secondary endpoints.PNG

Statistical analyses

No statistical analyses for this end point

Secondary: • Quality of life measured with SF36 quality of life questionnaire

End point title	• Quality of life measured with SF36 quality of life questionnaire

End point description:

End point type	Secondary

End point timeframe:

Baseline to 24 weeks

End point values	Active Treatment	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed				
Units: whole numbers	12	6		

Attachments (see zip file)	Secondary endpoints.PNG

Statistical analyses

No statistical analyses for this end point

Secondary: Prevention of new DU (Digital Ulcers)

End point title	Prevention of new DU (Digital Ulcers)

End point description:

End point type	Secondary

End point timeframe:

Baseline to 24 weeks

End point values	Active Treatment	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed				
Units: whole numbers	12	6		

Attachments (see zip file)	Secondary endpoints.PNG

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to end of study

Adverse event reporting additional description:

Safety and tolerability of Factor XIII assessed by physical examination (including digital ulcer characterization),Vital signs (heart rate, blood pressure, pulse, body weight) and Clinical laboratory parameters. Study doctor also enquired about adverse events
at every study visit between baseline and end of study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Active Treatment
Reporting group description: -	
Reporting group title	PK arm

Reporting group description: -

Serious adverse events	Placebo	Active Treatment	PK arm
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)	1 / 12 (8.33%)	0 / 8 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Chest pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	Active Treatment	PK arm
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 6 (83.33%)	12 / 12 (100.00%)	0 / 8 (0.00%)
General disorders and administration site conditions			

Diarrhea, DU, Dizziness subjects affected / exposed occurrences (all)	5 / 6 (83.33%) 0	12 / 12 (100.00%) 0	0 / 8 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 June 2016	Main updates to Protocol detailed below: -Addition of routine blood tests -Clarification in urine pregnancy tests "to women of childbearing potential" -Clarification to avoid unnecessary capillaroscopy testing. -Patients will be monitored for a minimum of one house after dosing. -Updates to Concomitant medications to ensure patient safety i.e use of Bosentan included as an exclusion criteria - Dosing algorithm for treatment phase explained in detail -Update to dose modifications

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

As this was a small trial, all analysis is descriptive and no robust conclusion about efficacy can be drawn from the data. therefore this study confirms feasibility of recruitment to the designed trial and provides a platform for future studies.

Notes: