Clinical trial results:
A phase II, single centre, randomised, placebo-controlled, 3-part trial to assess the safety, tolerability and efficacy of Zibotentan in patients with renal disease secondary to scleroderma

Summary

EudraCT number	2013-003200-39
Trial protocol	GB
Global end of trial date	19 October 2017

Results information

Result version number	v2 (current)
This version publication date	13 June 2025
First version publication date	05 July 2019
Version creation reason	• Correction of full data set Updated statistical analysis, there is no change in the overall conclusion, or for any of the numerical endpoint data, there are some minor changes, for example, one additional AE was identified in the placebo arm of ZEBRA 1 .

Trial information

Trial identification

Sponsor protocol code	13/0077

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02047708
WHO universal trial number (UTN)	-
Other trial identifiers	IRAS number : 136274

Notes:

Sponsors

Sponsor organisation name	UCL
Sponsor organisation address	Joint Research Office , Gower Street , London , United Kingdom, WC1E 6BT
Public contact	Dr Edward Stern, UCL Joint Research office , ctimps@ucl.ac.uk
Scientific contact	Dr Edward Stern, UCL Joint Research office , ctimps@ucl.ac.uk

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	14 December 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 October 2017
Global end of trial reached?	Yes
Global end of trial date	19 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectives for this study is to see how safe Zibotentan is in patients with scleroderma and kidney damage and whether it has any effect on their kidney function

Protection of trial subjects:

Zibotentan has been well tolerated but has been associated with minor side effects including headache, low blood pressure, nausea, vomiting and nasal congestion.These side effects were minimised by keeping within the dosage range as well as regular safety monitoring while on the study.

Participants with severe hepatic impairment were excluded as a clinical study detailed in the Zibotentan Investigator's Brochure indicated reduced clearance of Zibotentan in these patients.

Participants may experience some local discomfort whilst blood samples are taken. This may include pain,
inflammation, infection or a small bruise at the puncture site. The study doctor will follow up if any of these side effects occur.

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, single centre, randomised, placebo controlled, 3 part trial designed to evaluate the safety, tolerability and efficacy of
Zibotentan in patients with renal disease secondary to scleroderma . As there is no approved drug for DcSSC, a placebo arm is the relevant comparator.

Actual start date of recruitment	03 February 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	United Kingdom: 23
Worldwide total number of subjects	23
EEA total number of subjects	23

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)	14
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment window was 02/10/2014 to 02/02/2017

Pre-assignment

Screening details:

Zebra 1: 16 participants screened (3 were screen failures, 13 randomised).
Zebra 2A: 4 participants screened (0 screen failures).
Zebra 2B: 8 participants screened (2 screen failures, 6 randomised).

Pre-assignment period milestones

Number of subjects started	23
Number of subjects completed	23

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:

Zebra 1- Double blind
Zebra 2A- Single blind
Zebra 2B- Open label

Arms

Are arms mutually exclusive?	Yes
Arm title	Zebra 1 - Active Treatment

Arm description:

A 1:1 randomised parallel group placebo-controlled, double-blind, single centre trial comparing Zibotentan 10 mg once daily orally (with possible dose reductions to a minimum dose of 5mg once daily) with matched placebo in Scleroderma patients with CKD2 and CKD3 (and GFR >45 ml/min) over 26 weeks with a 26 weeks follow up.

Arm type	Experimental
Investigational medicinal product name	Zibotentan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Zibotentan 2.5, 5, 7.5, 10 mg taken orally or placebo

Arm title	Zebra 2A - Active Treatment

Arm description:

A parallel group placebo-controlled, single blind, single centre trial comparing Zibotentan once daily orally over 26 weeks, with a 26 week follow up, with matched placebo using 2:1 (active:placebo) randomisation in patients within 1-12 months of SRC (Scleroderma Renal Crisis) not requiring ongoing dialysis. Individual patients will start at 2.5 mg once daily and following weekly monitoring will be dose escalated by 2.5 mg weekly to a maximum of 10 mg once daily over the course of the first 4 weeks.

Arm type	Experimental

Investigational medicinal product name	Zibotentan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Zibotentan 2.5, 5, 7.5, 10 mg taken orally or placebo

Arm title	Zebra 2B - Active Treatment

Arm description:

An open label single ascending dose administration pharmacokinetic study of Zibotentan 2.5 mg to 10 mg orally in patients requiring dialysis. Individual patients can receive up to two single doses of Zibotentan (at different dose levels).

Arm type	Experimental
Investigational medicinal product name	Zibotentan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Zibotentan 2.5, 5, 7.5, 10 mg taken orally

Arm title	Zebra 1 - Placebo

Arm description:

A 1:1 randomised parallel group placebo-controlled, double-blind, single centre trial comparing Zibotentan 10 mg once daily orally (with possible dose reductions to a minimum dose of 5mg once daily) with matched placebo in Scleroderma patients with CKD2 and CKD3 (and GFR >45 ml/min) over 26 weeks with a 26 weeks follow up.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo

Arm title	Zebra 2A - Placebo

Arm description:

A parallel group placebo-controlled, single blind, single centre trial comparing Zibotentan once daily orally over 26 weeks, with a 26 week follow up, with matched placebo using 2:1 (active:placebo) randomisation in patients within 1-12 months of SRC (Scleroderma Renal Crisis) not requiring ongoing dialysis. Individual patients will start at 2.5 mg once daily and following weekly monitoring will be dose escalated by 2.5 mg weekly to a maximum of 10 mg once daily over the course of the first 4 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo

Number of subjects in period 1	Zebra 1 - Active Treatment	Zebra 2A - Active Treatment	Zebra 2B - Active Treatment
Started	6	2	6
Completed	6	1	6
Not completed	0	1	0
Adverse event, serious fatal	-	1	-

Number of subjects in period 1	Zebra 1 - Placebo	Zebra 2A - Placebo
Started	7	2
Completed	7	2
Not completed	0	0
Adverse event, serious fatal	-	-

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	23	23	
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)	14	14	
From 65-84 years	9	9	
85 years and over	0	0	
Age continuous Units: years			
median	61		
full range (min-max)	34 to 75	-	
Gender categorical Units: Subjects			
Female	14	14	
Male	9	9	

Subject analysis sets

Subject analysis set title	Zebra 1 - Active Treatment
Subject analysis set type	Sub-group analysis

Subject analysis set description:

A 1:1 randomised parallel group placebo-controlled, double-blind, single centre trial comparing Zibotentan 10 mg once daily orally (with possible dose reductions to a minimum dose of 5mg once daily) with matched placebo in Scleroderma patients with CKD2 and CKD3 (and GFR >45 ml/min) over 26 weeks with a 26 weeks follow up.

Subject analysis set title	Zebra 2A - Active Treatment
Subject analysis set type	Sub-group analysis

Subject analysis set description:

A parallel group placebo-controlled, single blind, single centre trial comparing Zibotentan once daily orally over 26 weeks, with a 26 week follow up, with matched placebo using 2:1 (active:placebo) randomisation in patients within 1-12 months of SRC (Scleroderma Renal Crisis) not requiring ongoing dialysis. Individual patients will start at 2.5 mg once daily and following weekly monitoring will be dose escalated by 2.5 mg weekly to a maximum of 10 mg once daily over the course of the first 4 weeks.

Subject analysis set title	Zebra 2B - Active Treatment
Subject analysis set type	Sub-group analysis

Subject analysis set description:

An open label single ascending dose administration pharmacokinetic study of Zibotentan 2.5 mg to 10 mg orally in patients requiring dialysis. Individual patients can receive up to two single doses of

Zibotentan (at different dose levels).

Subject analysis set title	Zebra 1 - Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

A 1:1 randomised parallel group placebo-controlled, double-blind, single centre trial comparing Zibotentan 10 mg once daily orally (with possible dose reductions to a minimum dose of 5mg once daily) with matched placebo in Scleroderma patients with CKD2 and CKD3 (and GFR >45 ml/min) over 26 weeks with a 26 weeks follow up.

Subject analysis set title	Zebra 2A - Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

A parallel group placebo-controlled, single blind, single centre trial comparing Zibotentan once daily orally over 26 weeks, with a 26 week follow up, with matched placebo using 2:1 (active:placebo) randomisation in patients within 1-12 months of SRC (Scleroderma Renal Crisis) not requiring ongoing dialysis. Individual patients will start at 2.5 mg once daily and following weekly monitoring will be dose escalated by 2.5 mg weekly to a maximum of 10 mg once daily over the course of the first 4 weeks.

Reporting group values	Zebra 1 - Active Treatment	Zebra 2A - Active Treatment	Zebra 2B - Active Treatment
Number of subjects	6	2	6
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	3	1	5
From 65-84 years	3	1	1
85 years and over	0	0	0
Age continuous Units: years			
median	64	64	52
full range (min-max)	53 to 70	63 to 65	39 to 68
Gender categorical Units: Subjects			
Female	4	1	1
Male	2	1	5

Reporting group values	Zebra 1 - Placebo	Zebra 2A - Placebo	
Number of subjects	7	2	
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)	3	2	

From 65-84 years	4	0	
85 years and over	0	0	

Age continuous Units: years			
median	68	45.5	
full range (min-max)	54 to 75	34 to 57	
Gender categorical Units: Subjects			
Female	6	2	
Male	1	0	

End points

End points reporting groups

Reporting group title	Zebra 1 - Active Treatment

Reporting group description:

A 1:1 randomised parallel group placebo-controlled, double-blind, single centre trial comparing Zibotentan 10 mg once daily orally (with possible dose reductions to a minimum dose of 5mg once daily) with matched placebo in Scleroderma patients with CKD2 and CKD3 (and GFR >45 ml/min) over 26 weeks with a 26 weeks follow up.

Reporting group title	Zebra 2A - Active Treatment

Reporting group description:

A parallel group placebo-controlled, single blind, single centre trial comparing Zibotentan once daily orally over 26 weeks, with a 26 week follow up, with matched placebo using 2:1 (active:placebo) randomisation in patients within 1-12 months of SRC (Scleroderma Renal Crisis) not requiring ongoing dialysis. Individual patients will start at 2.5 mg once daily and following weekly monitoring will be dose escalated by 2.5 mg weekly to a maximum of 10 mg once daily over the course of the first 4 weeks.

Reporting group title	Zebra 2B - Active Treatment

Reporting group description:

An open label single ascending dose administration pharmacokinetic study of Zibotentan 2.5 mg to 10 mg orally in patients requiring dialysis. Individual patients can receive up to two single doses of Zibotentan (at different dose levels).

Reporting group title	Zebra 1 - Placebo

Reporting group description:

A 1:1 randomised parallel group placebo-controlled, double-blind, single centre trial comparing Zibotentan 10 mg once daily orally (with possible dose reductions to a minimum dose of 5mg once daily) with matched placebo in Scleroderma patients with CKD2 and CKD3 (and GFR >45 ml/min) over 26 weeks with a 26 weeks follow up.

Reporting group title	Zebra 2A - Placebo

Reporting group description:

A parallel group placebo-controlled, single blind, single centre trial comparing Zibotentan once daily orally over 26 weeks, with a 26 week follow up, with matched placebo using 2:1 (active:placebo) randomisation in patients within 1-12 months of SRC (Scleroderma Renal Crisis) not requiring ongoing dialysis. Individual patients will start at 2.5 mg once daily and following weekly monitoring will be dose escalated by 2.5 mg weekly to a maximum of 10 mg once daily over the course of the first 4 weeks.

Subject analysis set title	Zebra 1 - Active Treatment
Subject analysis set type	Sub-group analysis

Subject analysis set description:

A 1:1 randomised parallel group placebo-controlled, double-blind, single centre trial comparing Zibotentan 10 mg once daily orally (with possible dose reductions to a minimum dose of 5mg once daily) with matched placebo in Scleroderma patients with CKD2 and CKD3 (and GFR >45 ml/min) over 26 weeks with a 26 weeks follow up.

Subject analysis set title	Zebra 2A - Active Treatment
Subject analysis set type	Sub-group analysis

Subject analysis set description:

A parallel group placebo-controlled, single blind, single centre trial comparing Zibotentan once daily orally over 26 weeks, with a 26 week follow up, with matched placebo using 2:1 (active:placebo) randomisation in patients within 1-12 months of SRC (Scleroderma Renal Crisis) not requiring ongoing dialysis. Individual patients will start at 2.5 mg once daily and following weekly monitoring will be dose escalated by 2.5 mg weekly to a maximum of 10 mg once daily over the course of the first 4 weeks.

Subject analysis set title	Zebra 2B - Active Treatment
Subject analysis set type	Sub-group analysis

Subject analysis set description:

An open label single ascending dose administration pharmacokinetic study of Zibotentan 2.5 mg to 10 mg orally in patients requiring dialysis. Individual patients can receive up to two single doses of Zibotentan (at different dose levels).

Subject analysis set title	Zebra 1 - Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

A 1:1 randomised parallel group placebo-controlled, double-blind, single centre trial comparing Zibotentan 10 mg once daily orally (with possible dose reductions to a minimum dose of 5mg once daily) with matched placebo in Scleroderma patients with CKD2 and CKD3 (and GFR >45 ml/min) over 26 weeks with a 26 weeks follow up.

Subject analysis set title	Zebra 2A - Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

A parallel group placebo-controlled, single blind, single centre trial comparing Zibotentan once daily orally over 26 weeks, with a 26 week follow up, with matched placebo using 2:1 (active:placebo) randomisation in patients within 1-12 months of SRC (Scleroderma Renal Crisis) not requiring ongoing dialysis. Individual patients will start at 2.5 mg once daily and following weekly monitoring will be dose escalated by 2.5 mg weekly to a maximum of 10 mg once daily over the course of the first 4 weeks.

Primary: Zebra 1: Serum VCAM-1 Level at Week 26 compared to baseline

End point title	Zebra 1: Serum VCAM-1 Level at Week 26 compared to baseline[1][2]

End point description:

Summary statistics for the serum Vascular cell adhesion molecule-1 (VCAM-1) level at baseline and at week 26, stratified by treatment group.

End point type	Primary

End point timeframe:

26 weeks after baseline

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: Summary statistics only, due to small number of trial participants.

[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: This is the primary endpoint for the ZEBRA 1 sub-study only.

End point values	Zebra 1 - Active Treatment	Zebra 1 - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	7		
Units: ODU				
arithmetic mean (standard deviation)				
Baseline	0.19 (± 0.09)	0.28 (± 0.19)		
26 weeks	0.20 (± 0.05)	0.28 (± 0.22)		

Statistical analyses

No statistical analyses for this end point

Primary: Zebra 2A: eGFR level at week 26 compared to baseline

End point title	Zebra 2A: eGFR level at week 26 compared to baseline[3][4]

End point description:

Estimated glomerular filtration rate (eGFR) (ml/min/1.73m2) at baseline and at week 26, by treatment group (ZEBRA 2A). Results given are participant results.
NOTE: Results given the the end point values table below are participant results. Active Treatment Arm participants are Z2A002 and Z2A004 (no reading was available at week 26 for Z2004), Placebo arm participants are Z2A001 and Z2A003. Where a reading in not applicable for that participant a zero has been added to the end point value table below.

End point type	Primary

End point timeframe:

26 weeks after baseline visit

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Summary statistics only, due to small number of trial participants.

[4] - 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: This is the primary endpoint for the ZEBRA 2A sub-study only.

End point values	Zebra 2A - Active Treatment	Zebra 2A - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2[5]	2[6]		
Units: ml/min/1.73m2				
Z2A001 (Placebo) - Baseline	0	57		
Z2A003 (Placebo) - Baseline	0	34		
Z2A002 (Active Treatment) - Baseline	27	0		
Z2A004 (Active Treatment) - Baseline	21	0		
Z2A001 (Placebo) - Week 26	0	65		
Z2A003 (Placebo) - Week 26	0	43		
Z2A002 (Active Treatment) - Week 26	26	0		

Notes:

[5] - Results are participant results, where a reading is not applicable a zero has been added.

[6] - Results are participant results, where a reading is not applicable a zero has been added.

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 Zibotentan in CKD2/3 patients assessed by ECG, Physical examination, vital signs, haematology, clinical chemistry and Urinalysis. 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	Zebra 1: Active Treatment

Reporting group description:

1:1 randomised parallel group placebo-controlled, double-blind, single centre trial comparing Zibotentan 10 mg once daily orally (with possible dose reductions to a minimum dose of 5mg once daily) with matched placebo in Scleroderma patients with CKD2 and CKD3 (and GFR >45 ml/min) over 26 weeks with a 26 weeks follow up.

Reporting group title	Zebra 2A: Active Treatment

Reporting group description:

A parallel group placebo-controlled, single blind, single centre trial comparing Zibotentan once daily orally over 26 weeks, with a 26 week follow up, with matched placebo using 2:1 (active:placebo) randomisation in patients within 1-12 months of SRC (Scleroderma Renal Crisis) not requiring ongoing dialysis. Individual patients will start at 2.5 mg once daily and following weekly monitoring will be dose escalated by 2.5 mg weekly to a maximum of 10 mg once daily over the course of the first 4 weeks

Reporting group title	Zebra 2B - Active Treatment

Reporting group description:

An open label single ascending dose administration pharmacokinetic study of Zibotentan 2.5 mg to 10 mg orally in patients requiring dialysis. Individual patients can receive up to two single doses of Zibotentan (at different dose levels).

Reporting group title	Zebra 1: Placebo

Reporting group description:

1:1 randomised parallel group placebo-controlled, double-blind, single centre trial comparing Zibotentan 10 mg once daily orally (with possible dose reductions to a minimum dose of 5mg once daily) with matched placebo in Scleroderma patients with CKD2 and CKD3 (and GFR >45 ml/min) over 26 weeks with a 26 weeks follow up.

Reporting group title	Zebra 2A: Placebo

Reporting group description:

A parallel group placebo-controlled, single blind, single centre trial comparing Zibotentan once daily orally over 26 weeks, with a 26 week follow up, with matched placebo using 2:1 (active:placebo) randomisation in patients within 1-12 months of SRC (Scleroderma Renal Crisis) not requiring ongoing dialysis. Individual patients will start at 2.5 mg once daily and following weekly monitoring will be dose escalated by 2.5 mg weekly to a maximum of 10 mg once daily over the course of the first 4 weeks

Serious adverse events	Zebra 1: Active Treatment	Zebra 2A: Active Treatment	Zebra 2B - Active Treatment
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	1 / 2 (50.00%)	1 / 6 (16.67%)
number of deaths (all causes)	0	1	0
number of deaths resulting from	0	1	0

adverse events			
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Pseudoaneurysm	Additional description: Pseudoanuerysm left arteriovenous fistula (AVF)		
subjects affected / exposed	0 / 6 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
High INR	Additional description: Raised international normalised ratio (INR)		
subjects affected / exposed	0 / 6 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumonia Community Acquired	Additional description: Community acquired pneumonia		
subjects affected / exposed	0 / 6 (0.00%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Pneumonia	Additional description: Hospital acquired pneumonia (Streptococcus Pneumoniae)		
subjects affected / exposed	0 / 6 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Zebra 1: Placebo	Zebra 2A: Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 7 (14.29%)	1 / 2 (50.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 2 (50.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Pseudoaneurysm	Additional description: Pseudoanuerysm left arteriovenous fistula (AVF)		
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
High INR	Additional description: Raised international normalised ratio (INR)		
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonia Community Acquired	Additional description: Community acquired pneumonia		
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia	Additional description: Hospital acquired pneumonia (Streptococcus Pneumoniae)		
subjects affected / exposed	1 / 7 (14.29%)	0 / 2 (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: 1 %

Non-serious adverse events	Zebra 1: Active Treatment	Zebra 2A: Active Treatment	Zebra 2B - Active Treatment
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 6 (83.33%)	2 / 2 (100.00%)	3 / 6 (50.00%)
General disorders and administration site conditions			
General symptom			
subjects affected / exposed	5 / 6 (83.33%)	2 / 2 (100.00%)	3 / 6 (50.00%)
occurrences (all)	20	4	3

Non-serious adverse events	Zebra 1: Placebo	Zebra 2A: Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 7 (85.71%)	2 / 2 (100.00%)	
General disorders and administration site conditions			
General symptom			

subjects affected / exposed occurrences (all)	6 / 7 (85.71%) 27	2 / 2 (100.00%) 4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 May 2014	1. All patients will have pre and treatment echocardiogram in all parts of the study. Patients in ZEBRA 1 and ZEBRA 2A will also have an end of treatment echocardiogram. Updated following MHRA review. 2. All patients will have NT pro-BNP measured as part of the panel of monthly safety bloods. Updated following MHRA review. 3. End of treatment (week 26) pharmacokinetics analysis is to be omitted from ZEBRA 1 and ZEBRA 2A. Additional PK testing at this stage would not have any safety value for study participants or add to the scientific quality of the study.
06 July 2016	1. Update to the Investigator's brochure (current version 15). 2. Minor changes to the layout of the Scleroderma Health assessment questionnaire. 3. Updates to the Protocol to reflect change in named statistician and contact details as well as update to sponsor's representative's contact details.
07 December 2016	1. Changes to the inclusion criteria for the ZEBRA 2B sub-study, removing the requirement that patients have a diagnosis of scleroderma or scleroderma renal crisis. 2. At all study visits where a 24-hour urine collection was mandated, will be replaced by a spot urine sample for protein:creatinine ratio. It is well established in clinical practice that this measurement method is at least as accurate as 24-hour collection and it is much better tolerated by patients. 3. The visit schedules for all three studies contain an error that has persisted through earlier protocol versions: as described in the endpoints for these studies, the trial design requires experimental biomarkers to be collected at start of treatment visit (visit 1), end of treatment visit (26 weeks) and end of follow-up visit (52 weeks), but the protocol shows biomarker sample collection at all study visits. This error been corrected in the latest version. Only routine safety blood and urine samples will be collected at interim study visits.
25 July 2017	1. The removal of follow up visits for Zebra 2B renal crisis patients which are not relevant for either safety or research outcomes as well as clarification on dose escalation. 2. Updated the information sheet and Protocol in line with the previously REC approved substantial amendment 5 i.e. the removal of Echocardiograms for 2B patients which is not relevant for non-Scleroderma patients.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
10 August 2015	Recruitment freeze due to potential interruption of IMP supply	03 September 2015
01 November 2015	Decision by sponsor to freeze recruitment to allow data to be migrated from one database to another. Initial database shut down unexpectedly.	11 March 2016

Notes:

Limitations and caveats

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

Challenging to recruit patients within the recruitment window due to limitations mentioned above. Recruitment target in the 2 arms of the study therefore not met. Statistical analysis plan updated accordingly.

Notes: