Clinical trial results:
An Open-Label Phase II Study in anti-GBM disease (Goodpasture's disease) with Adverse Renal Prognosis to Evaluate the Efficacy and Safety of IdeS --GOOD-IDES

Summary

EudraCT number	2016-004082-39
Trial protocol	SE DK AT FR
Global end of trial date	24 July 2020

Results information

Result version number	v1 (current)
This version publication date	11 January 2022
First version publication date	11 January 2022

Trial information

Trial identification

Sponsor protocol code	GOOD-IDES-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03157037
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Linköping University
Sponsor organisation address	Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden, SE-581 83
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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	23 November 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 July 2020
Global end of trial reached?	Yes
Global end of trial date	24 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary efficacy objective is to evaluate the efficacy of an IdeS based regimen to salvage independent renal function defined as no need for dialysis at 6 months and after IdeS treatment.

Protection of trial subjects:

Details of the goals of the research and the risk and benefits of the protocol were reviewed with each potential study subject.
In the event of adverse effects from the study, full resources of the hospital were available to intervene as medically necessary.
Licensed physicians expert in the care of patients with vasculitis were available at all times at each study site.
To mitigate the risk of infections all patients received antibiotic prophylaxis.
Prophylactic medication against Pneumocystis jiroveci pneumonia (PCP) was strongly recommended.
Before administration of imlifidase all patients received solu-medrol and loratadine (or equivalent).
All patients received glucocorticoids as part of standard-of-care. Prophylaxis against peptic ulcers and osteoporosis was given at the discretion of the investigator.
All patients were treated with cyclophosphamide and were therefore monitored for full blood counts according to local practice with a minimum schedule recommended in the study protocol.

Background therapy:

All patients received standard-of-care consisting of plasma exchange (PLEX), glucocorticoids (GC) and cyclophosphamide (CYC), as detailed below:

PLEX: Administered according to local practice, and given at a dose considered necessary to keep anti-GBM antibodies below a toxic level. A standard session usually consisted of 60 ml/kg (based on actual body weight) using albumin (3-5% with or without crystalloid) as a replacement solution. More than 36 hours had to pass after administration of imlifidase before PLEX could be initiated. More than 15 hours following an IV dose of CYC had to pass before PLEX could be given and more than 12 hours if CYC was administered orally. On days when PLEX was given CYC was given after completed PLEX.

GC: Commenced with IV methylprednisolone as 3 daily pulse doses. Each pulse was between 0.5 g and 1 g at the discretion of the investigator. Any dose given to the patient prior to study inclusion was subtracted from the total dose. Additional pulses of methyl prednisolone were allowed to curb resistant pulmonary haemorrhage. Oral GC therapy with prednisolone (dosing according to local practice) was initiated after stopping methylprednisolone. Oral GC was given as a single daily dose. An equivalent daily IV dose applied for patients intolerant to oral GC or if oral GC was contraindicated.

CYC: Induction therapy with CYC was prescribed for at least 13 weeks in patients with independent renal function, but could be withdrawn earlier in patients considered to have reached end-stage renal disease. The study protocol allowed the use of either IV or oral CYC. Concomitant use of mesna was optional and at the discretion of the investigator.

Evidence for comparator:

N/A

Actual start date of recruitment	16 June 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Czechia: 1
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	France: 5
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)	8
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited between 16-Jun-2017 and 22-Jan-2020.

Pre-assignment

Screening details:

A total of 26 patients were screened and 15 were enrolled in the study. Five patients were not eligible due to an eGFR above 15 mL/min/1.73 m2 and another 6 patients were excluded based on one or more exclusion criteria.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

N/A

Arms

Arm title	All patients

Arm description:

All 15 patients (i.e., both patients who were dialysis dependent and patients who were dialysis independent at baseline)

Arm type	Experimental
Investigational medicinal product name	Imlifidase
Investigational medicinal product code	
Other name	IdeS, IgG endopeptidase
Pharmaceutical forms	Concentrate for solution for infusion, Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

After dilution imfilidase was administered as an IV infusion over 30 minutes using a syringe or an infusion bag, an infusion pump and a particle filter.
All patients received a dose of 0.25 mg/kg.
The protocol allowed slowing down or stopping and restarting the infusion if required.

Number of subjects in period 1	All patients
Started	15
Completed	14
Not completed	1
Adverse event, serious fatal	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	15	15	
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)	8	8	
From 65-84 years	7	7	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	61		
full range (min-max)	19 to 77	-	
Gender categorical Units: Subjects			
Female	6	6	
Male	9	9	
Dialysis status Units: Subjects			
Dialysis	10	10	
Not on dialysis but eGFR <15ml/min/1.73m2	5	5	
Occurrence of pulmonary symptoms Units: Subjects			
Yes	9	9	
No	3	3	
Not reported	3	3	
Double positive for Anti-GBM antibodies and ANCA Units: Subjects			
Yes	6	6	
No	9	9	
Time since anti-GBM diagnosis Units: Days			
median	2		
full range (min-max)	0 to 40	-	
Anti-GBM concentration Units: U/mL			

median	130.0		
full range (min-max)	2 to 1090	-	
Time since first renal symptom Units: Days			
median	10		
full range (min-max)	4 to 76	-	
Time since first pulmonary symptom Units: Days			
median	32		
full range (min-max)	1 to 113	-	

End points

End points reporting groups

Reporting group title	All patients

Reporting group description:

All 15 patients (i.e., both patients who were dialysis dependent and patients who were dialysis independent at baseline)

Subject analysis set title	Dialysis Dependent Patients at Baseline
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subgroup of all patients who were on dialysis at baseline

Subject analysis set title	Dialysis Independent Patients at Baseline
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subgroup of all patients who were not on dialysis at baseline

Primary: Proportion of Patients with Independent Renal Function at 6 Months

End point title	Proportion of Patients with Independent Renal Function at 6 Months[1]

End point description:

Number of patients without need for dialysis at 6 months. A patient with independent renal function is defined as a patient without need for dialysis.

End point type	Primary

End point timeframe:

6 months after imlifidase administration

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 statistical analysis was specified. This study is a single arm study.

End point values	All patients	Dialysis Dependent Patients at Baseline	Dialysis Independent Patients at Baseline	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	15	10	5	
Units: Patients	10	5	5	

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Patients with Independent Renal Function at 3 Months

End point title	Proportion of Patients with Independent Renal Function at 3 Months

End point description:

Number of patients without need for dialysis at 3 months. A patient with independent renal function is defined as a patient without need for dialysis.

End point type	Secondary

End point timeframe:

3 months after imlifidase administration

End point values	All patients	Dialysis Dependent Patients at Baseline	Dialysis Independent Patients at Baseline	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	15	10	5	
Units: Patients	9	4	5	

Statistical analyses

No statistical analyses for this end point

Secondary: Renal Function at 3 Months as Measured by eGFR

End point title	Renal Function at 3 Months as Measured by eGFR

End point description:

eGFR is a measure of kidney function. eGFR has been calculated based on p-creatinine according to the modification of diet in renal disease (MDRD) equation. eGFR for a kidney with normal function is above 90 mL/min/1.73m2. Reduced kidney function is characterised by a decreased eGFR value.

End point type	Secondary

End point timeframe:

3 months after imlifidase administration

End point values	All patients	Dialysis Dependent Patients at Baseline	Dialysis Independent Patients at Baseline	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	7	3	4	
Units: mL/min/1.73m2				
arithmetic mean (standard deviation)	23.8 (± 8.9)	20.3 (± 4.7)	26.5 (± 11.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Renal Function at 6 Months as Measured by eGFR

End point title	Renal Function at 6 Months as Measured by eGFR

End point description:

eGFR is a measure of kidney function. eGFR has been calculated based on p-creatinine according to the modification of diet in renal disease (MDRD) equation. eGFR for a kidney with normal function is above

90 mL/min/1.73m2. Reduced kidney function is characterised by a decreased eGFR value.

End point type	Secondary

End point timeframe:

6 months after imlifidase administration

End point values	All patients	Dialysis Dependent Patients at Baseline	Dialysis Independent Patients at Baseline	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	10	5	5	
Units: mL/min/1.73m2				
arithmetic mean (standard deviation)	30.9 (± 13.9)	24.8 (± 6.6)	36.9 (± 17.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Renal Function over Time as Measured by eGFR

End point title	Change in Renal Function over Time as Measured by eGFR

End point description:

eGFR is a measure of kidney function. eGFR has been calculated based on p-creatinine according to the modification of diet in renal disease (MDRD) equation. Reduced kidney function is characterised by a decreased eGFR value. A positive change in eGFR from baseline indicates improved renal function.

End point type	Secondary

End point timeframe:

Pre-imlifidase up to 6 months

End point values	All patients	Dialysis Dependent Patients at Baseline	Dialysis Independent Patients at Baseline	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	10[2]	5[3]	5[4]	
Units: Patients				
Pre-imlifidase eGFR=0-15	6	1	5	
Pre-imlifidase eGFR=15-30	0	0	0	
Pre-imlifidase eGFR=30-60	0	0	0	
Pre-imlifidase eGFR ≥60	0	0	0	
1 month eGFR=0-15	2	1	1	
1 month eGFR=15-30	3	1	2	
1 month eGFR=30-60	2	0	2	
1 month eGFR ≥60	0	0	0	
3 month eGFR=0-15	0	0	0	
3 month eGFR=15-30	6	3	3	
3 month eGFR=30-60	1	0	1	

3 month eGFR ≥60	0	0	0	
6 month eGFR=0-15	0	0	0	
6 month eGFR=15-30	6	4	2	
6 month eGFR=30-60	4	1	3	
6 month eGFR ≥60	0	0	0	

Notes:

[2] - Pre-imlifidase: 6 patients
1 month: 7 patients
3 months: 7 patients
6 months: 10 patients
[3] - Pre-imlifidase: 1 patients
1 month: 2 patients
3 months: 3 patients
6 months: 5 patients
[4] - Pre-imlifidase: 5 patients
1 month: 5 patients
3 months: 4 patients
6 months: 5 patients

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Study Visits with Anti-GBM Antibodies Above a Toxic Level

End point title	Number of Study Visits with Anti-GBM Antibodies Above a Toxic Level

End point description:

Very few patients had anti-GBM antibodies >20 U/mL on the assessment timepoints following imlifidase. PLEX was performed at any time throughout the study when the Investigator judged it necessary, without requirement of recording the anti-GBM antibody level prior to initiation. Hence it was not possible to analyse number of patient days with an anti-GBM level >20 U/mL as was the original plan. Instead number of study visits with a toxic level after imlifidase treatment are presented.

End point type	Secondary

End point timeframe:

Pre-imlifidase up to 6 months after imlifidase administration

End point values	All patients	Dialysis Dependent Patients at Baseline	Dialysis Independent Patients at Baseline	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	15	10	5	
Units: Patients				
0 visits	2	1	1	
1 visit	7	3	4	
2 visits	1	1	0	
3 visits	1	1	0	
5 visits	2	2	0	
6 visits	1	1	0	
9 visits	1	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Haematuria (Blood in urine)

End point title	Haematuria (Blood in urine)

End point description:

Haematuria was assessed using urine dipstick. The result was presented as:
Negative/Trace/+1/+2/+3/+4. In the analysis results being +2 or above are considered as relevant.
Haematuria was an inclusion criterion. All 15 patients had haematuria when included in the study.

End point type	Secondary

End point timeframe:

At 6 months after imlifidase administration

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Positive				
number (not applicable)				
Day 180	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Proteinuria During the Study

End point title	Change in Proteinuria During the Study

End point description:

Change in proteinuria measured as u-albumin/creatinine (g/mol) in morning void during the study .

End point type	Secondary

End point timeframe:

Up to 6 months after imlifidase administration

End point values	All patients	Dialysis Dependent Patients at Baseline	Dialysis Independent Patients at Baseline	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	14[5]	9[6]	5[7]	
Units: g/mol				
arithmetic mean (standard deviation)				
Pre-imlifidase	700 (± 1197)	1117 (± 1544)	199 (± 166)	
3 Months	190 (± 178)	220 (± 197)	153 (± 172)	
6 Months	161 (± 198)	183 (± 231)	122 (± 133)	

Notes:

[5] - Pre-imlifidase: 11 patients
3 Months: 9 patients
6 Months: 14 patients
[6] - Pre-imlifidase: 6 patients
3 Months: 5 patients
6 Months: 9 patients
[7] - Pre-imlifidase: 5 patients
3 Months: 4 patients
6 Months: 5 patients

Statistical analyses

No statistical analyses for this end point

Secondary: Number of PLEXs Needed over Time

End point title	Number of PLEXs Needed over Time

End point description:

Number of PLEXs needed before anti-GBM antibodies are below toxic levels. PLEX was initiatied at the discretion of the investigator throughout the study.

End point type	Secondary

End point timeframe:

Before imlifidase was administered and up to 3 months after imlifidase was administered

End point values	All patients	Dialysis Dependent Patients at Baseline	Dialysis Independent Patients at Baseline	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	15	10	5	
Units: Number of PLEX sessions				
Pre-Screening	33	10	23	
Post-Screening to Pre-imlifidase	5	5	0	
Pre-imlifidase to Day 3	1	0	1	
Day 3 to Day 7	8	8	0	
Day 7 to Day 10	14	14	0	
Day 10 to Day 15	22	20	2	
Day 15 to Day 22	23	18	5	
Day 22 to Day 29	6	5	1	
Day 29 to Day 50	8	5	3	
Day 50 to 3 Months	1	0	1	
Total (Post-imlifidase to 3 Months)	83	70	13	
Total (Pre-Screening to 3 Months)	121	85	36	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics of Imlifidase (AUC, Cmax, CL, Vz)

End point title	Pharmacokinetics of Imlifidase (AUC, Cmax, CL, Vz)

End point description:

AUC=Area under the plasma concentration of imlifidase versus time curve
Cmax=Maximum observed plasma concentration of imlifidase following dosing
CL=Clearance is a measure of the ability of the body to clear imlifidase from plasma
Vz=Volume of distribution of imlifidase during the elimination phase

End point type	Secondary

End point timeframe:

Pre-imlifidase to Day 14 after administration

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: See below				
geometric mean (full range (min-max))				
AUC (h x microgram/mL)	158 (73 to 304)			
Cmax (microgram/mL)	4.7 (2.6 to 8.0)			
CL (mL/h/kg)	1.6 (0.8 to 3.4)			
Vz (L/kg)	0.13 (0.07 to 0.21)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics of Imlifidase (t1/2)

End point title	Pharmacokinetics of Imlifidase (t1/2)

End point description:

The half-life is the time it takes for the concentration of the drug to be reduced by 50%.
Half-life during distribution phase (Alpha-t1/2) Half-life during elimination phase (Beta-t1/2).

End point type	Secondary

End point timeframe:

Pre-dose to Day 14 after administration of imlifidase

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	15[8]			
Units: hours				
arithmetic mean (full range (min-max))				
Alpha-t1/2	2.6 (0.9 to 7.5)			
Beta-t1/2	53 (26 to 115)			

Notes:

[8] - The results refers to harmonic mean. Arithmetic was used since harmonic was not a selectable option.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacodynamics (IgG Degradation)

End point title	Pharmacodynamics (IgG Degradation)

End point description:

Imlifidase specifically cleaves all subclasses of human IgG rapidly and efficiently. The cleaving process involves two steps: (i) intact IgG to single cleaved IgG followed by (ii) single cleaved IgG to completely cleaved IgG (one F(ab')2- and one homodimeric Fc-fragment) The electroluminescence analysis method used measures the sum of intact and single cleaved IgG in serum. The efficacy of imlifidase is evaluated as remaining concentration of intact and single cleaved IgG in serum after treatment.

End point type	Secondary

End point timeframe:

Pre-imlifidase up to 6 months after imlifidase administration

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	15[9]			
Units: mg/mL				
arithmetic mean (standard deviation)				
Pre-imlifidase	6.66 (± 2.94)			
2 hours	0.17 (± 0.12)			
6 hours	0.08 (± 0.05)			
24 hours	0.08 (± 0.05)			
Day 3	0.09 (± 0.05)			
Day 7	0.85 (± 1.56)			
Day 10	1.58 (± 1.69)			
Day 15	2.64 (± 2.42)			
Day 22	2.94 (± 2.34)			
Day 29	3.94 (± 2.18)			
Day 50	4.29 (± 2.05)			
6 Months	6.76 (± 2.49)			

Notes:

[9] - 15 patients at all time points except for 24h, Day 50 and 6 months when 14 patients were analysed

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-imlifidase Antibodies

End point title	Anti-imlifidase Antibodies

End point description:
Concentration of anti-imlifidase antibodies

End point type	Secondary

End point timeframe:

Pre-imlifidase up to 6 months following imlifidase administration

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	15[10]			
Units: mg/L				
arithmetic mean (standard deviation)				
Pre-imlifidase	9.00 (± 4.17)			
Day 7	4.32 (± 5.29)			
Day 15	752 (± 728)			
Day 22	744 (± 736)			
Day 29	609 (± 493)			
Day 50	547 (± 580)			
3 Months	327 (± 263)			
6 Months	242 (± 280)			

Notes:

[10] - Pre-imlifidase, D7, D15, D22, D29: 15 patients
D50 and 6 Months: 14 patients
3 Months: 12 patients

Statistical analyses

No statistical analyses for this end point

Secondary: Renal Histology

End point title	Renal Histology

End point description:

Kidney biopsies classified according to Berden et al. 2010 (focal, crescentic, mixed and sclerotic) and provide information on the histological activity and kidney outcome. Focal class is associated with favourable kidney outcome, whereas sclerotic carries a poor outcome. Crescentic/mixed class could have an intermediate outcome between focal and sclerotic.
Immunofluorescence performed at the local hospitals was also used to assess linear IgG deposits which is a hallmark of anti-GBM antibody disease.

End point type	Secondary

End point timeframe:

Before administration of imlifidase (0-33 days) and after administration of imlifidase (3-6 days)

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	10[11]			
Units: Biopsies				
Crescentic	9			
Mixed	4			
Sclerotic	1			

Linear IgG deposits	11			

Notes:

[11] - 14 biopsies from 10 patients were analysed.
10 biopsies were collected pre-imlifidase and 4 after.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were collected for 6 months (i.e., from the timepoint the patient signed the informed consent form (ICF) until end of study.

Adverse event reporting additional description:

AEs were obtained if spontaneously reported by the patient, if reported in response to an open question from the study personnel, or if revealed by observation.
A TEAE is any AE occurring after imlifidase and within the time of the residual drug effect period i.e. 28 days.
All SAEs were post-TEAEs.
The listed non-serious AEs presents TEAEs only.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Safety Analysis Set

Reporting group description:

All patients who have received imlifidase.

Serious adverse events	Safety Analysis Set		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 15 (33.33%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Viral infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 15 (6.67%)		
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 Analysis Set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 15 (86.67%)		
Vascular disorders			

Hypertension			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Pelvic venous thrombosis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Thrombophlebitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Immune system disorders			
Cryoglobulinaemia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hypogammaglobulinaemia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Bronchial obstruction			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Sinus pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Investigations			
Blood iron decreased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Red blood cell count decreased			

subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Nervous system disorders Cognitive disorder subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	 6 / 15 (40.00%) 6		
Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all)	 2 / 15 (13.33%) 2		
Eye disorders Foreign body sensation in eyes subjects affected / exposed occurrences (all)	 1 / 15 (6.67%) 1		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 1 / 15 (6.67%) 1 4 / 15 (26.67%) 4 2 / 15 (13.33%) 2		
Skin and subcutaneous tissue disorders Ecchymosis			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hyperhidrosis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Rash erythematous			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Infections and infestations			
Clostridium difficile infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Herpes zoster			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pneumonia klebsiella			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hyperglycaemia			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Hyperphosphataemia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Steroid diabetes			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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.

N/A

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31563334