



Clinical trial results:

A Randomized, Open-label, Multi-center, Phase II Study to Evaluate the Safety and Efficacy of Deferasirox (ICL670) 20 mg/kg/Day Relative to Subcutaneous Deferoxamine in Sickle Cell Disease Patients With Iron Overload From Repeated Blood Transfusions

Summary

EudraCT number	2016-002583-14
Trial protocol	Outside EU/EEA
Global end of trial date	08 April 2008

Results information

Result version number	v1 (current)
This version publication date	11 November 2017
First version publication date	11 November 2017

Trial information

Trial identification

Sponsor protocol code	CICL670A2201
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00110617
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 April 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 April 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the safety of ICL670 compared to deferoxamine, during 24 weeks, in patients with sickle cell disease and iron overload from repeated blood transfusions.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 May 2005
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	United States: 201
Worldwide total number of subjects	203
EEA total number of subjects	0

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)	73
Adolescents (12-17 years)	67
Adults (18-64 years)	63
From 65 to 84 years	0

85 years and over	0
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Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

212 participants were enrolled in the study; however, 9 participants from Site 512 were excluded due to severe Good Clinical Practice (GCP) violations. 203 participants are included in the Full Analysis Set 1.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Deferasirox (ICL670)

Arm description:

Deferasirox (ICL670) 20 mg/kg orally once daily for 104 weeks.

Arm type	Experimental
Investigational medicinal product name	Deferasirox
Investigational medicinal product code	ICL670
Other name	
Pharmaceutical forms	Chewable/dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

Provided in 125 mg, 250 mg, and 500 mg dispersible tablets and were administered orally at an initial dose of 20 mg/kg/day.

Arm title	Deferoxamine (DFO) then ICL670
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Arm description:

Deferoxamine (DFO) subcutaneously for a weekly dose of 175 mg/kg for 24 weeks then crossed over to receive Deferasirox (ICL670) orally 20 mg/kg for a total of 104 weeks on therapy.

Arm type	Active comparator
Investigational medicinal product name	Deferoxamine
Investigational medicinal product code	Deferoxamine
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Supplied in vials of 500 mg and 2000 mg administered subcutaneously for a weekly doses of 175 mg/kg/day.

Investigational medicinal product name	Deferasirox
Investigational medicinal product code	ICL670
Other name	
Pharmaceutical forms	Chewable/dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

Provided in 125 mg, 250 mg, and 500 mg dispersible tablets and were administered orally at an initial dose of 20 mg/kg/day.

Number of subjects in period 1	Deferasirox (ICL670)	Deferoxamine (DFO) then ICL670
Started	135	68
Safety Set 1; Received Study Drug	135	56
Full Analysis 2; Received ICL670	135	53
On Going at Week 24	126	53
Completed	96	39
Not completed	39	29
Adverse event, serious fatal	1	1
Consent withdrawn by subject	10	4
Adverse event, non-fatal	2	4
Abnormal Laboratory Value	4	2
Administrative problems	6	5
Patient no longer requires study drug	1	-
Did not receive study drug	-	12
Lost to follow-up	9	1
Lack of efficacy	1	-
Protocol deviation	5	-

Baseline characteristics

Reporting groups

Reporting group title	Deferasirox (ICL670)
Reporting group description: Deferasirox (ICL670) 20 mg/kg orally once daily for 104 weeks.	
Reporting group title	Deferoxamine (DFO) then ICL670
Reporting group description: Deferoxamine (DFO) subcutaneously for a weekly dose of 175 mg/kg for 24 weeks then crossed over to receive Deferasirox (ICL670) orally 20 mg/kg for a total of 104 weeks on therapy.	

Reporting group values	Deferasirox (ICL670)	Deferoxamine (DFO) then ICL670	Total
Number of subjects	135	68	203
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)	48	25	73
Adolescents (12-17 years)	44	23	67
Adults (18-64 years)	43	20	63
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	16.4	16.2	
standard deviation	± 10.31	± 10.15	-
Gender, Male/Female			
Units: Subjects			
Female	56	33	89
Male	79	35	114

End points

End points reporting groups

Reporting group title	Deferasirox (ICL670)
Reporting group description:	
Deferasirox (ICL670) 20 mg/kg orally once daily for 104 weeks.	
Reporting group title	Deferoxamine (DFO) then ICL670
Reporting group description:	
Deferoxamine (DFO) subcutaneously for a weekly dose of 175 mg/kg for 24 weeks then crossed over to receive Deferasirox (ICL670) orally 20 mg/kg for a total of 104 weeks on therapy.	

Primary: The number of participants with Adverse Events (AEs) in the first 24 weeks of treatment

End point title	The number of participants with Adverse Events (AEs) in the first 24 weeks of treatment ^[1]
End point description:	
The number of participants with Adverse Events (AEs) overall and according to Medical Dictionary for Regulatory Activities (MedDRA) preferred term greater than or equal to 5% participants in any group by treatment in the first 24 weeks.	
End point type	Primary
End point timeframe:	
24 Weeks	

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 as the primary endpoint as safety.

End point values	Deferasirox (ICL670)	Deferoxamine (DFO) then ICL670		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	56		
Units: participants				
Headache	30	17		
Sickle cell anaemia with crisis	30	8		
Diarrhoea	30	5		
Vomiting	21	9		
Pyrexia	19	9		
Nausea	20	4		
Abdominal pain	16	6		
Upper respiratory tract infection	10	9		
Rash	14	3		
Cough	10	7		
Constipation	11	2		
Pain in Extremity	10	3		
Back Pain	8	4		
Chest Pain	7	5		
Oropharyngeal pain	7	5		
Pruritus	7	5		
Abdominal pain upper	8	3		
Nasal congestion	6	4		

Urinary tract infection	9	0		
Arthralgia	7	1		
Nasopharyngitis	4	3		
Insomnia	3	3		
Dizziness	2	3		
Injection site pain	0	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in serum ferritin from baseline to week 24

End point title	Absolute change in serum ferritin from baseline to week 24
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End point description:

Absolute change from baseline serum ferritin after 24 weeks of treatment with Deferasirox (ICL670) and absolute change from baseline serum ferritin after 24 weeks of treatment with Deferoxamine. Means were adjusted for the amount of transfused blood.

End point type	Secondary
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End point timeframe:

Baseline, 24 Weeks

End point values	Deferasirox (ICL670)	Deferoxamine (DFO) then ICL670		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	50		
Units: mg/mL				
least squares mean (confidence interval 95%)	-173.2 (-691.5 to 345.1)	-868.7 (-1661.9 to 75.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in serum ferritin after start of treatment with Deferasirox (ICL670) to week 24 and to week 52

End point title	Absolute change in serum ferritin after start of treatment with Deferasirox (ICL670) to week 24 and to week 52
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End point description:

Absolute change in serum ferritin after start of treatment with Deferasirox (ICL670) to week 24 and the absolute change in serum ferritin after start of treatment with Deferasirox (ICL670) to week 52 for the Deferasirox treatment group and the Deferoxamine then Deferasirox treatment group. Means were adjusted for the amount of transfused blood.

End point type	Secondary
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End point timeframe:

Start of Deferasirox (ICL670) treatment, 24 Weeks, 52 Weeks

End point values	Deferasirox (ICL670)	Deferoxamine (DFO) then ICL670		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	49		
Units: mg/mL				
least squares mean (confidence interval 95%)				
24 weeks from ICL670 treatment start (n=111,47)	-146.7 (-673.7 to 380.2)	-204.7 (-1014.7 to 605.3)		
52 weeks from ICL670 treatment start (n=113,40)	-487.3 (-761.6 to -213.0)	-545.7 (-1007.1 to -84.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in serum ferritin after start of treatment with Deferasirox (ICL670) to week 104

End point title	Absolute change in serum ferritin after start of treatment with Deferasirox (ICL670) to week 104 ^[2]
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End point description:

Absolute change in serum ferritin after start of treatment with Deferasirox (ICL670) to week 104 for the Deferasirox treatment group. Means were adjusted for the amount of transfused blood.

End point type	Secondary
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End point timeframe:

Start of Deferasirox (ICL670) treatment, 104 Weeks

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: No statistical analysis as the primary endpoint as safety.

End point values	Deferasirox (ICL670)			
Subject group type	Reporting group			
Number of subjects analysed	87			
Units: mg/mL				
least squares mean (confidence interval 95%)	-682.6 (-1090.3 to -274.9)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	11.0
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Reporting groups

Reporting group title	Safety-1 Set ICL670
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Reporting group description:

Safety-1 Set ICL670

Reporting group title	Safety-1 Set DFO
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Reporting group description:

Safety-1 Set DFO

Reporting group title	Safety-2 Set ICL670
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Reporting group description:

Safety-2 Set ICL670

Reporting group title	Safety-2 Set Crossover
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Reporting group description:

Safety-2 Set Crossover

Serious adverse events	Safety-1 Set ICL670	Safety-1 Set DFO	Safety-2 Set ICL670
Total subjects affected by serious adverse events			
subjects affected / exposed	40 / 135 (29.63%)	20 / 56 (35.71%)	78 / 135 (57.78%)
number of deaths (all causes)	1	0	1
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Poor peripheral circulation			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	0 / 135 (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
Superior vena caval occlusion			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	0 / 135 (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

Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	0 / 135 (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
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 135 (0.00%)	1 / 56 (1.79%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site pain			
subjects affected / exposed	0 / 135 (0.00%)	1 / 56 (1.79%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 135 (0.74%)	0 / 56 (0.00%)	7 / 135 (5.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	0 / 135 (0.00%)	1 / 56 (1.79%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device breakage			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	0 / 135 (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
Device malfunction			
subjects affected / exposed	0 / 135 (0.00%)	1 / 56 (1.79%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Implant site reaction			

subjects affected / exposed	0 / 135 (0.00%)	1 / 56 (1.79%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	1 / 135 (0.74%)	0 / 56 (0.00%)	2 / 135 (1.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	2 / 135 (1.48%)	0 / 56 (0.00%)	3 / 135 (2.22%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	6 / 135 (4.44%)	3 / 56 (5.36%)	17 / 135 (12.59%)
occurrences causally related to treatment / all	0 / 6	0 / 3	0 / 19
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchospasm			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	2 / 135 (1.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	3 / 135 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			

subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 135 (0.00%)	1 / 56 (1.79%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infiltration			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	0 / 135 (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
Oropharyngeal pain			
subjects affected / exposed	1 / 135 (0.74%)	0 / 56 (0.00%)	3 / 135 (2.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngeal inflammation			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 135 (0.00%)	1 / 56 (1.79%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wheezing			

subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	0 / 135 (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
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	1 / 135 (0.74%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	2 / 135 (1.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood culture positive			
subjects affected / exposed	2 / 135 (1.48%)	0 / 56 (0.00%)	2 / 135 (1.48%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood pressure diastolic decreased			
subjects affected / exposed	1 / 135 (0.74%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Culture throat positive			
subjects affected / exposed	1 / 135 (0.74%)	0 / 56 (0.00%)	2 / 135 (1.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin decreased			
subjects affected / exposed	0 / 135 (0.00%)	1 / 56 (1.79%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heart rate increased			
subjects affected / exposed	1 / 135 (0.74%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	2 / 135 (1.48%)	0 / 56 (0.00%)	2 / 135 (1.48%)
occurrences causally related to treatment / all	2 / 3	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test abnormal			
subjects affected / exposed	2 / 135 (1.48%)	0 / 56 (0.00%)	2 / 135 (1.48%)
occurrences causally related to treatment / all	2 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oxygen saturation decreased			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Serum ferritin increased			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urine protein/creatinine ratio increased			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cells urine positive			

subjects affected / exposed	1 / 135 (0.74%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	0 / 135 (0.00%)	1 / 56 (1.79%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 135 (0.74%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibula fracture			
subjects affected / exposed	0 / 135 (0.00%)	1 / 56 (1.79%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 135 (0.00%)	1 / 56 (1.79%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury			
subjects affected / exposed	0 / 135 (0.00%)	1 / 56 (1.79%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patella fracture			
subjects affected / exposed	0 / 135 (0.00%)	1 / 56 (1.79%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			
subjects affected / exposed	1 / 135 (0.74%)	1 / 56 (1.79%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			

subjects affected / exposed	1 / 135 (0.74%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Sickle cell anaemia			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	0 / 135 (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
Sickle cell anaemia with crisis			
subjects affected / exposed	27 / 135 (20.00%)	6 / 56 (10.71%)	38 / 135 (28.15%)
occurrences causally related to treatment / all	0 / 51	0 / 13	0 / 150
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardio-respiratory arrest			
subjects affected / exposed	1 / 135 (0.74%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Conduction disorder			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	0 / 135 (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
Intracardiac thrombus			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	0 / 135 (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
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	1 / 135 (0.74%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ataxia			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Balance disorder			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid artery occlusion			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	0 / 135 (0.00%)	1 / 56 (1.79%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Convulsion			
subjects affected / exposed	1 / 135 (0.74%)	0 / 56 (0.00%)	4 / 135 (2.96%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysarthria			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	2 / 135 (1.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	2 / 135 (1.48%)	2 / 56 (3.57%)	5 / 135 (3.70%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokinesia			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			

subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	2 / 135 (1.48%)	0 / 56 (0.00%)	2 / 135 (1.48%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Moyamoya disease			
subjects affected / exposed	1 / 135 (0.74%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorder			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	0 / 135 (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
Syncope			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	2 / 135 (1.48%)	0 / 56 (0.00%)	2 / 135 (1.48%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Acute chest syndrome			
subjects affected / exposed	0 / 135 (0.00%)	2 / 56 (3.57%)	2 / 135 (1.48%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukocytosis			
subjects affected / exposed	1 / 135 (0.74%)	0 / 56 (0.00%)	3 / 135 (2.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Photophobia			
subjects affected / exposed	0 / 135 (0.00%)	1 / 56 (1.79%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 135 (1.48%)	0 / 56 (0.00%)	6 / 135 (4.44%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	1 / 135 (0.74%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	2 / 135 (1.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	5 / 135 (3.70%)	0 / 56 (0.00%)	6 / 135 (4.44%)
occurrences causally related to treatment / all	1 / 5	0 / 0	1 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 135 (0.74%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	4 / 135 (2.96%)	0 / 56 (0.00%)	7 / 135 (5.19%)
occurrences causally related to treatment / all	1 / 4	0 / 0	1 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

Cholelithiasis			
subjects affected / exposed	0 / 135 (0.00%)	1 / 56 (1.79%)	3 / 135 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin ulcer			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 135 (0.74%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal papillary necrosis			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenocortical insufficiency acute			

subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	0 / 135 (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
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	2 / 135 (1.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthropathy			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	1 / 135 (0.74%)	1 / 56 (1.79%)	2 / 135 (1.48%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	2 / 135 (1.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			
subjects affected / exposed	1 / 135 (0.74%)	1 / 56 (1.79%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	0 / 135 (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
Pain in extremity			
subjects affected / exposed	2 / 135 (1.48%)	0 / 56 (0.00%)	5 / 135 (3.70%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			

Bacteraemia			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	0 / 135 (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
Bacterial infection			
subjects affected / exposed	1 / 135 (0.74%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	2 / 135 (1.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site infection			
subjects affected / exposed	0 / 135 (0.00%)	1 / 56 (1.79%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 135 (0.00%)	2 / 56 (3.57%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	1 / 135 (0.74%)	0 / 56 (0.00%)	3 / 135 (2.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 135 (0.74%)	0 / 56 (0.00%)	3 / 135 (2.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected skin ulcer			

subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lobar pneumonia			
subjects affected / exposed	1 / 135 (0.74%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mycoplasma infection			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parvovirus infection			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	3 / 135 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis streptococcal			
subjects affected / exposed	1 / 135 (0.74%)	1 / 56 (1.79%)	2 / 135 (1.48%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	4 / 135 (2.96%)	0 / 56 (0.00%)	9 / 135 (6.67%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia klebsiella			
subjects affected / exposed	1 / 135 (0.74%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia streptococcal			

subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	0 / 135 (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
Rotavirus infection			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	2 / 135 (1.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 135 (0.74%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal infection			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth abscess			

subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	0 / 135 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 135 (0.00%)	2 / 56 (3.57%)	4 / 135 (2.96%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 135 (1.48%)	0 / 56 (0.00%)	4 / 135 (2.96%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	1 / 135 (0.74%)	1 / 56 (1.79%)	2 / 135 (1.48%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 135 (0.74%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemosiderosis			
subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemic hyperosmolar nonketotic syndrome			
subjects affected / exposed	1 / 135 (0.74%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			

subjects affected / exposed	0 / 135 (0.00%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 135 (0.74%)	0 / 56 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Safety-2 Set Crossover		
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 53 (41.51%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Vascular disorders			
Poor peripheral circulation			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Superior vena caval occlusion			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Catheter site pain			

subjects affected / exposed	0 / 53 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	4 / 53 (7.55%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 0			
Chills				
subjects affected / exposed	1 / 53 (1.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Device breakage				
subjects affected / exposed	1 / 53 (1.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Device malfunction				
subjects affected / exposed	1 / 53 (1.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Implant site reaction				
subjects affected / exposed	0 / 53 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				
subjects affected / exposed	0 / 53 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	1 / 53 (1.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				

subjects affected / exposed	6 / 53 (11.32%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchospasm			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cough			
subjects affected / exposed	2 / 53 (3.77%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Epistaxis			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung infiltration			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oropharyngeal pain			

subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pharyngeal inflammation			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia aspiration			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	2 / 53 (3.77%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pulmonary oedema			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wheezing			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Delirium			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mental status changes			

subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood culture positive			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood pressure diastolic decreased			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Culture throat positive			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemoglobin decreased			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Heart rate increased			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic enzyme increased			

subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Liver function test abnormal			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oxygen saturation decreased			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Serum ferritin increased			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urine protein/creatinine ratio increased			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
White blood cells urine positive			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fibula fracture			

subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Patella fracture			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Procedural pain			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Sickle cell anaemia			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sickle cell anaemia with crisis			
subjects affected / exposed	11 / 53 (20.75%)		
occurrences causally related to treatment / all	0 / 51		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			

Cardio-respiratory arrest			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Conduction disorder			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intracardiac thrombus			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ataxia			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Balance disorder			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Carotid artery occlusion			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebral ischaemia			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			

subjects affected / exposed	1 / 53 (1.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Convulsion				
subjects affected / exposed	0 / 53 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dysarthria				
subjects affected / exposed	0 / 53 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	1 / 53 (1.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypokinesia				
subjects affected / exposed	0 / 53 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Loss of consciousness				
subjects affected / exposed	0 / 53 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Migraine				
subjects affected / exposed	0 / 53 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Moyamoya disease				
subjects affected / exposed	0 / 53 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorder				

subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Acute chest syndrome			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Leukocytosis			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Photophobia			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Diarrhoea			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin ulcer			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal failure acute			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal papillary necrosis			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenocortical insufficiency acute			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Arthropathy			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Back pain			

subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal pain			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neck pain			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Osteonecrosis			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacteraemia			
subjects affected / exposed	2 / 53 (3.77%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Bacterial infection			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Catheter site infection			

subjects affected / exposed	1 / 53 (1.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	0 / 53 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	0 / 53 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	1 / 53 (1.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis viral				
subjects affected / exposed	0 / 53 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infected skin ulcer				
subjects affected / exposed	0 / 53 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lobar pneumonia				
subjects affected / exposed	0 / 53 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mycoplasma infection				
subjects affected / exposed	0 / 53 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Parvovirus infection				

subjects affected / exposed	0 / 53 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pharyngitis				
subjects affected / exposed	0 / 53 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pharyngitis streptococcal				
subjects affected / exposed	0 / 53 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	4 / 53 (7.55%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Pneumonia klebsiella				
subjects affected / exposed	0 / 53 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia streptococcal				
subjects affected / exposed	0 / 53 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	1 / 53 (1.89%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Rotavirus infection				
subjects affected / exposed	0 / 53 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				

subjects affected / exposed	0 / 53 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	0 / 53 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sinusitis				
subjects affected / exposed	0 / 53 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Staphylococcal bacteraemia				
subjects affected / exposed	1 / 53 (1.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Streptococcal infection				
subjects affected / exposed	0 / 53 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tooth abscess				
subjects affected / exposed	1 / 53 (1.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	1 / 53 (1.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	1 / 53 (1.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Viral infection				

subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemosiderosis			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemic hyperosmolar nonketotic syndrome			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety-1 Set ICL670	Safety-1 Set DFO	Safety-2 Set ICL670
Total subjects affected by non-serious adverse events			
subjects affected / exposed	97 / 135 (71.85%)	39 / 56 (69.64%)	118 / 135 (87.41%)
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	6 / 135 (4.44%)	5 / 56 (8.93%)	16 / 135 (11.85%)
occurrences (all)	6	5	24
Injection site pain			
subjects affected / exposed	0 / 135 (0.00%)	3 / 56 (5.36%)	0 / 135 (0.00%)
occurrences (all)	0	3	0
Oedema peripheral			
subjects affected / exposed	3 / 135 (2.22%)	0 / 56 (0.00%)	7 / 135 (5.19%)
occurrences (all)	4	0	11
Pain			
subjects affected / exposed	4 / 135 (2.96%)	2 / 56 (3.57%)	11 / 135 (8.15%)
occurrences (all)	4	2	17
Pyrexia			
subjects affected / exposed	14 / 135 (10.37%)	7 / 56 (12.50%)	34 / 135 (25.19%)
occurrences (all)	15	7	52
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	3 / 135 (2.22%)	0 / 56 (0.00%)	7 / 135 (5.19%)
occurrences (all)	3	0	7
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	10 / 135 (7.41%)	7 / 56 (12.50%)	29 / 135 (21.48%)
occurrences (all)	11	9	37
Dyspnoea			
subjects affected / exposed	2 / 135 (1.48%)	2 / 56 (3.57%)	7 / 135 (5.19%)
occurrences (all)	2	3	8
Epistaxis			
subjects affected / exposed	4 / 135 (2.96%)	2 / 56 (3.57%)	8 / 135 (5.93%)
occurrences (all)	6	2	18
Nasal congestion			
subjects affected / exposed	6 / 135 (4.44%)	4 / 56 (7.14%)	20 / 135 (14.81%)
occurrences (all)	8	4	27

Oropharyngeal pain subjects affected / exposed occurrences (all)	6 / 135 (4.44%) 6	5 / 56 (8.93%) 5	24 / 135 (17.78%) 33
Rhinorrhoea subjects affected / exposed occurrences (all)	4 / 135 (2.96%) 5	1 / 56 (1.79%) 1	9 / 135 (6.67%) 10
Wheezing subjects affected / exposed occurrences (all)	0 / 135 (0.00%) 0	0 / 56 (0.00%) 0	3 / 135 (2.22%) 3
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	3 / 135 (2.22%) 3	3 / 56 (5.36%) 4	7 / 135 (5.19%) 9
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	3 / 135 (2.22%) 5	0 / 56 (0.00%) 0	7 / 135 (5.19%) 10
Blood pressure diastolic increased subjects affected / exposed occurrences (all)	6 / 135 (4.44%) 6	2 / 56 (3.57%) 2	8 / 135 (5.93%) 8
Injury, poisoning and procedural complications Transfusion reaction subjects affected / exposed occurrences (all)	0 / 135 (0.00%) 0	0 / 56 (0.00%) 0	2 / 135 (1.48%) 2
Congenital, familial and genetic disorders Sickle cell anaemia with crisis subjects affected / exposed occurrences (all)	7 / 135 (5.19%) 10	4 / 56 (7.14%) 5	17 / 135 (12.59%) 51
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	2 / 135 (1.48%) 2	3 / 56 (5.36%) 3	8 / 135 (5.93%) 11
Headache subjects affected / exposed occurrences (all)	28 / 135 (20.74%) 31	15 / 56 (26.79%) 18	47 / 135 (34.81%) 76
Gastrointestinal disorders			

Abdominal discomfort subjects affected / exposed occurrences (all)	1 / 135 (0.74%) 1	0 / 56 (0.00%) 0	4 / 135 (2.96%) 4
Abdominal pain subjects affected / exposed occurrences (all)	14 / 135 (10.37%) 15	6 / 56 (10.71%) 9	30 / 135 (22.22%) 40
Abdominal pain upper subjects affected / exposed occurrences (all)	7 / 135 (5.19%) 8	3 / 56 (5.36%) 3	13 / 135 (9.63%) 21
Constipation subjects affected / exposed occurrences (all)	11 / 135 (8.15%) 13	2 / 56 (3.57%) 2	24 / 135 (17.78%) 30
Diarrhoea subjects affected / exposed occurrences (all)	30 / 135 (22.22%) 33	5 / 56 (8.93%) 5	36 / 135 (26.67%) 51
Nausea subjects affected / exposed occurrences (all)	16 / 135 (11.85%) 19	4 / 56 (7.14%) 4	33 / 135 (24.44%) 56
Vomiting subjects affected / exposed occurrences (all)	18 / 135 (13.33%) 19	9 / 56 (16.07%) 10	30 / 135 (22.22%) 39
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	7 / 135 (5.19%) 8	5 / 56 (8.93%) 5	13 / 135 (9.63%) 27
Rash subjects affected / exposed occurrences (all)	14 / 135 (10.37%) 15	3 / 56 (5.36%) 3	21 / 135 (15.56%) 26
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all)	3 / 135 (2.22%) 3	0 / 56 (0.00%) 0	7 / 135 (5.19%) 7
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	7 / 135 (5.19%) 12	1 / 56 (1.79%) 1	20 / 135 (14.81%) 33

Back pain			
subjects affected / exposed	7 / 135 (5.19%)	3 / 56 (5.36%)	20 / 135 (14.81%)
occurrences (all)	13	3	35
Musculoskeletal pain			
subjects affected / exposed	2 / 135 (1.48%)	1 / 56 (1.79%)	9 / 135 (6.67%)
occurrences (all)	2	1	10
Pain in extremity			
subjects affected / exposed	10 / 135 (7.41%)	3 / 56 (5.36%)	31 / 135 (22.96%)
occurrences (all)	11	3	48
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 135 (0.74%)	1 / 56 (1.79%)	1 / 135 (0.74%)
occurrences (all)	1	1	1
Influenza			
subjects affected / exposed	3 / 135 (2.22%)	0 / 56 (0.00%)	4 / 135 (2.96%)
occurrences (all)	4	0	5
Nasopharyngitis			
subjects affected / exposed	4 / 135 (2.96%)	3 / 56 (5.36%)	18 / 135 (13.33%)
occurrences (all)	4	3	23
Otitis media			
subjects affected / exposed	3 / 135 (2.22%)	1 / 56 (1.79%)	4 / 135 (2.96%)
occurrences (all)	3	1	4
Pharyngitis streptococcal			
subjects affected / exposed	0 / 135 (0.00%)	1 / 56 (1.79%)	6 / 135 (4.44%)
occurrences (all)	0	1	7
Pneumonia			
subjects affected / exposed	1 / 135 (0.74%)	0 / 56 (0.00%)	2 / 135 (1.48%)
occurrences (all)	1	0	2
Sinusitis			
subjects affected / exposed	3 / 135 (2.22%)	1 / 56 (1.79%)	9 / 135 (6.67%)
occurrences (all)	4	2	13
Upper respiratory tract infection			
subjects affected / exposed	10 / 135 (7.41%)	7 / 56 (12.50%)	25 / 135 (18.52%)
occurrences (all)	11	9	32
Urinary tract infection			

subjects affected / exposed	7 / 135 (5.19%)	0 / 56 (0.00%)	17 / 135 (12.59%)
occurrences (all)	7	0	21

Non-serious adverse events	Safety-2 Set Crossover		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 53 (83.02%)		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	9 / 53 (16.98%)		
occurrences (all)	12		
Injection site pain			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Oedema peripheral			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	15 / 53 (28.30%)		
occurrences (all)	32		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	14 / 53 (26.42%)		
occurrences (all)	28		
Dyspnoea			
subjects affected / exposed	2 / 53 (3.77%)		
occurrences (all)	2		
Epistaxis			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		

Nasal congestion subjects affected / exposed occurrences (all)	7 / 53 (13.21%) 11		
Oropharyngeal pain subjects affected / exposed occurrences (all)	5 / 53 (9.43%) 5		
Rhinorrhoea subjects affected / exposed occurrences (all)	2 / 53 (3.77%) 3		
Wheezing subjects affected / exposed occurrences (all)	3 / 53 (5.66%) 4		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 5		
Blood pressure diastolic increased subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1		
Injury, poisoning and procedural complications Transfusion reaction subjects affected / exposed occurrences (all)	3 / 53 (5.66%) 3		
Congenital, familial and genetic disorders Sickle cell anaemia with crisis subjects affected / exposed occurrences (all)	7 / 53 (13.21%) 19		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0		
Headache			

subjects affected / exposed occurrences (all)	13 / 53 (24.53%) 28		
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	4 / 53 (7.55%) 6		
Abdominal pain subjects affected / exposed occurrences (all)	8 / 53 (15.09%) 14		
Abdominal pain upper subjects affected / exposed occurrences (all)	5 / 53 (9.43%) 8		
Constipation subjects affected / exposed occurrences (all)	4 / 53 (7.55%) 6		
Diarrhoea subjects affected / exposed occurrences (all)	9 / 53 (16.98%) 14		
Nausea subjects affected / exposed occurrences (all)	10 / 53 (18.87%) 13		
Vomiting subjects affected / exposed occurrences (all)	11 / 53 (20.75%) 21		
Skin and subcutaneous tissue disorders			
Pruritus subjects affected / exposed occurrences (all)	2 / 53 (3.77%) 4		
Rash subjects affected / exposed occurrences (all)	4 / 53 (7.55%) 6		
Renal and urinary disorders			
Dysuria subjects affected / exposed occurrences (all)	2 / 53 (3.77%) 3		
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	5 / 53 (9.43%)		
occurrences (all)	7		
Back pain			
subjects affected / exposed	11 / 53 (20.75%)		
occurrences (all)	16		
Musculoskeletal pain			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	9 / 53 (16.98%)		
occurrences (all)	11		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	4 / 53 (7.55%)		
occurrences (all)	4		
Influenza			
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	3		
Nasopharyngitis			
subjects affected / exposed	6 / 53 (11.32%)		
occurrences (all)	9		
Otitis media			
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	5		
Pharyngitis streptococcal			
subjects affected / exposed	5 / 53 (9.43%)		
occurrences (all)	6		
Pneumonia			
subjects affected / exposed	4 / 53 (7.55%)		
occurrences (all)	4		
Sinusitis			
subjects affected / exposed	2 / 53 (3.77%)		
occurrences (all)	2		
Upper respiratory tract infection			

subjects affected / exposed	7 / 53 (13.21%)		
occurrences (all)	12		
Urinary tract infection			
subjects affected / exposed	6 / 53 (11.32%)		
occurrences (all)	8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 April 2005	The main purpose of this amendment was to incorporate changes which served the following purposes: • Change the cardiac exclusion criteria; Amend the preparation of ICL670; Clarify assignment of patient numbering; Change procedures for collection of ECGs; Increase the potential number of sites to participate in the liver biopsy / MRI sub-study. Change the name of the Central laboratory for biopsy processing.
09 October 2005	The main purpose of this amendment was to clarify the exclusion of lactose-intolerant patients noted in Amendment 1. Such exclusion was neither intended nor necessarily based on available clinical evidence.
28 November 2006	The main purpose of this amendment was to incorporate changes which served the following purpose: Describe the cancellation of the planned interim analysis at Week 24 due to sufficient efficacy and safety data being available from other trials; Clarify dosing adjustments due to rash, and changes in body weight, serum ferritin, and serum creatinine. Inform about the change to the timing of the Program Safety Board meeting; Clarify documenting compliance.
08 June 2007	The main purpose of this amendment was to clarify the collection of additional urine samples and shipping of urine samples to the Central laboratory for testing. All protocol amendments were made before database lock. These amendments were not considered to affect the interpretation of the study results.

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.

Due to severe good clinical practice violations, data from 9 participants recruited for Center 512 was excluded from the main analysis of the study.

Notes: