Clinical trial results:
1-year extension to CICL670A2402 an open-label, multicenter trial on efficacy and safety of long-term treatment with ICL670 (10 - 20 mg/kg/day) in beta-thalassemia patients with transfusional hemosiderosis (Amendment 3: extension prolonged to up to 2 years)

Summary

EudraCT number	2016-004322-42
Trial protocol	Outside EU/EEA
Global end of trial date	04 May 2008

Results information

Result version number	v1 (current)
This version publication date	10 May 2018
First version publication date	10 May 2018

Trial information

Trial identification

Sponsor protocol code	CICL670A2402E1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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	04 May 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 May 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Allow patients treated with ICL670 in the core protocol to continue iron chelation therapy with ICL670

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	16 July 2005
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	Saudi Arabia: 20
Country: Number of subjects enrolled	Egypt: 84
Country: Number of subjects enrolled	Lebanon: 64
Country: Number of subjects enrolled	Oman: 21
Country: Number of subjects enrolled	Syria: 42
Worldwide total number of subjects	231
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)	104
Adolescents (12-17 years)	77

Adults (18-64 years)	50
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This is an Extension to Core Study CICL670A2402 (NCT00171171). 233 participants completed the core study and entered this extension study. 2 subjects in the 16 and older arm did not receive drug.

Pre-assignment

Screening details:

2 participants from the 16 and older group did not receive deferasirox. Thus, the 16 and older group comprises of 69 treated participants.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Deferasirox (Between 2 <16 Years)

Arm description:

Participants age 2 years up to 16 years received a daily oral dose of deferasirox. Dose selection was based on the dose last received in the core study. The individual daily doses of deferasirox and the exact amount of tablets (125, 250, or 500 mg) contributing to each dose were calculated by the investigator based on the patient’s body weight.

Arm type	Experimental
Investigational medicinal product name	Deferasirox
Investigational medicinal product code	ICL670
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Deferasirox was given orally once daily (10 to 20 mg/kg) to participants 2 years and older based on participant's body weight. Deferasirox was available as 125 mg, 250 mg, and 500 mg tablets.

Arm title	Deferasirox (16 Years or Older)

Arm description:

Participants age 16 years or older received a daily oral dose of deferasirox. Dose selection was based on the dose last received in the core study. The individual daily doses of deferasirox and the exact amount of tablets (125, 250, or 500 mg) contributing to each dose were calculated by the investigator based on the patient’s body weight.

Arm type	Experimental
Investigational medicinal product name	Deferasirox
Investigational medicinal product code	ICL670
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Deferasirox was given orally once daily (10 to 20 mg/kg) to participants 2 years and older based on participant's body weight. Deferasirox was available as 125 mg, 250 mg, and 500 mg tablets.

Number of subjects in period 1	Deferasirox (Between 2 <16 Years)	Deferasirox (16 Years or Older)
Started	162	69
Completed	154	60
Not completed	8	9
Adverse event, serious fatal	1	2
Consent withdrawn by subject	-	1
Adverse event, non-fatal	1	2
Lost to follow-up	6	2
Protocol deviation	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Deferasirox (Between 2 <16 Years)
Reporting group description:	
Participants age 2 years up to 16 years received a daily oral dose of deferasirox. Dose selection was based on the dose last received in the core study. The individual daily doses of deferasirox and the exact amount of tablets (125, 250, or 500 mg) contributing to each dose were calculated by the investigator based on the patient's body weight.	
Reporting group title	Deferasirox (16 Years or Older)
Reporting group description:	
Participants age 16 years or older received a daily oral dose of deferasirox. Dose selection was based on the dose last received in the core study. The individual daily doses of deferasirox and the exact amount of tablets (125, 250, or 500 mg) contributing to each dose were calculated by the investigator based on the patient's body weight.	

Reporting group values	Deferasirox (Between 2 <16 Years)	Deferasirox (16 Years or Older)	Total
Number of subjects	162	69	231
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)	104	0	104
Adolescents (12-17 years)	58	19	77
Adults (18-64 years)	0	50	50
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Safety Population consisting of all participants who received study drug in the Extension study n= 231.			
Units: years			
arithmetic mean	9.5	21.2	
standard deviation	± 3.59	± 5.82	-
Gender Categorical			
Safety Population consisting of all participants who received study drug in the Extension study n=231.			
Units: Subjects			
Female	80	34	114
Male	82	35	117

End points

End points reporting groups

Reporting group title	Deferasirox (Between 2 <16 Years)

Reporting group description:

Participants age 2 years up to 16 years received a daily oral dose of deferasirox. Dose selection was based on the dose last received in the core study. The individual daily doses of deferasirox and the exact amount of tablets (125, 250, or 500 mg) contributing to each dose were calculated by the investigator based on the patient’s body weight.

Reporting group title	Deferasirox (16 Years or Older)

Reporting group description:

Participants age 16 years or older received a daily oral dose of deferasirox. Dose selection was based on the dose last received in the core study. The individual daily doses of deferasirox and the exact amount of tablets (125, 250, or 500 mg) contributing to each dose were calculated by the investigator based on the patient’s body weight.

Subject analysis set title	Deferasirox (Between 2 <16 years)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants age 2 years up to 16 years received a daily oral dose of deferasirox. Dose selection was based on the dose last received in the core study. The individual daily doses of deferasirox and the exact amount of tablets (125, 250, or 500 mg) contributing to each dose were calculated by the investigator based on the patient's body weight.

Subject analysis set title	Deferasirox (16 Years or older)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants age 16 years or older received a daily oral dose of deferasirox. Dose selection was based on the dose last received in the core study. The individual daily doses of deferasirox and the exact amount of tablets (125, 250, or 500 mg) contributing to each dose were calculated by the investigator based on the patient's body weight.

Subject analysis set title	Deferasirox (Between 2 <16 years)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants age 2 years up to 16 years received a daily oral dose of deferasirox. Dose selection was based on the dose last received in the core study. The individual daily doses of deferasirox and the exact amount of tablets (125, 250, or 500 mg) contributing to each dose were calculated by the investigator based on the patient's body weight.

Subject analysis set title	Deferasirox (16 Years or older)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants age 16 years or older received a daily oral dose of deferasirox. Dose selection was based on the dose last received in the core study. The individual daily doses of deferasirox and the exact amount of tablets (125, 250, or 500 mg) contributing to each dose were calculated by the investigator based on the patient's body weight.

Subject analysis set title	Deferasirox (Between 2 <16 years)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants age 2 years up to 16 years received a daily oral dose of deferasirox. Dose selection was based on the dose last received in the core study. The individual daily doses of deferasirox and the exact amount of tablets (125, 250, or 500 mg) contributing to each dose were calculated by the investigator based on the patient's body weight.

Subject analysis set title	Deferasirox (16 Years or older)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants age 16 years or older received a daily oral dose of deferasirox. Dose selection was based on the dose last received in the core study. The individual daily doses of deferasirox and the exact amount of tablets (125, 250, or 500 mg) contributing to each dose were calculated by the investigator based on the patient's body weight.

Subject analysis set title	Deferasirox (All Participants)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants received a daily oral dose of deferasirox. Dose selection was based on the dose last received in the core study. The individual daily doses of deferasirox and the exact amount of tablets (125, 250, or 500 mg) contributing to each dose were calculated by the investigator based on the patient's body weight.

Primary: Percentage of Participants with Treatment Success from Core Baseline (BL) to extension end of study, by baseline LIC level and age

End point title	Percentage of Participants with Treatment Success from Core Baseline (BL) to extension end of study, by baseline LIC level and age

End point description:

Success was defined as the percentage of participants with decreased liver iron content (LIC) at the end of extension study compared to core baseline (BL) LIC. Success Criteria: For participants with Baseline LIC from 1 - <7 mg Fe/g dw, success was achieved if LIC level maintained at 1 - <7 mg Fe/g dw. For participants with Baseline LIC ≥7 - <10 mg Fe/g dw, success was achieved if LIC dropped to between 1 and < 7 mg Fe/g dw. For participants with Baseline LIC ≥10 mg Fe/g dw, success was achieved if LIC dropped by at least 3 mg Fe/g dw. LIC was measured by biopsy or magnetic resonance imaging.

End point type	Primary

End point timeframe:

From Core Study Baseline, to Extension End of Study, Up to 3 Years

End point values	Deferasirox (Between 2 <16 years)	Deferasirox (16 Years or older)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	162	71		
Units: percentage of participants				
arithmetic mean (confidence interval 95%)				
Core Baseline LIC 1-<7 mg Fe/g dw (n=20, 2)	75.0 (56.0 to 94.0)	100 (15.8 to 100)		
Core Baseline LIC 7-<10 mg Fe/g dw (n=18, 8)	72.2 (51.5 to 92.9)	50.0 (15.7 to 84.3)		
Core Baseline LIC ≥10 mg Fe/g dw (n=124, 61)	76.6 (69.2 to 84.1)	73.8 (62.7 to 84.8)		

Statistical analyses

Statistical analysis title	treatment success rate
Comparison groups	Deferasirox (Between 2 <16 years) v Deferasirox (16 Years or older)
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided

Primary: Absolute Change in Liver Iron Concentration (LIC)Measured by Liver MRI or Liver Biopsy from Core Study Baseline (BL) to End of Extension Study, by LIC Category

End point title	Absolute Change in Liver Iron Concentration (LIC)Measured by Liver MRI or Liver Biopsy from Core Study Baseline (BL) to End of Extension Study, by LIC Category

End point description:

Liver MRI or Liver Biopsy was performed at the core study baseline (BL) and then 1 year and 2 years in the core study, baseline of the extension study and time of discontinuation from the extension visit (end of study). Liver iron content (LIC) is reported in milligram Iron per gram dry weight (mg Fe/g dw). Absolute change in LIC from core study baseline to the end of the extension study is presented for participants with the following two core study baseline LIC levels: 1-<7 mg Fe/g dw and ≥7 mg Fe/g dw.

End point type	Primary

End point timeframe:

From Baseline of Core Study to End of Extension Study, up to 3 years

End point values	Deferasirox (Between 2 <16 years)	Deferasirox (16 Years or older)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	119	41		
Units: mg Fe/g dw				
arithmetic mean (standard deviation)				
Core Baseline LIC 1-<7 mg Fe/g dw (n=12, 0)	-1.32 (± 3.125)	0 (± 0)		
Core Baseline LIC ≥7 mg Fe/g dw (n=107, 41)	-9.03 (± 9.260)	-8.39 (± 11.312)		

Statistical analyses

Statistical analysis title	Liver Iron Concentraton <7 mg Fd/g dw
Comparison groups	Deferasirox (Between 2 <16 years) v Deferasirox (16 Years or older)
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.172
Method	t-test, 2-sided

Secondary: Absolute Change in Serum Ferritin Level Measured From Core Study Baseline (BL) to End of Extension Study

End point title	Absolute Change in Serum Ferritin Level Measured From Core Study Baseline (BL) to End of Extension Study

End point description:

Serum Levels were assessed at core study baseline (BL), 1 year, 2 years in core study, baseline of extension study and time of discontinuation from the extension visit (end of study) in monthly intervals. Serum Ferritin is reported in micrograms per Liter (µg/L).

End point type	Secondary

End point timeframe:

From Baseline of Core Study to End of Extension Study, up to 3 years

End point values	Deferasirox (Between 2 <16 years)	Deferasirox (16 Years or older)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	120	43		
Units: µg/L				
arithmetic mean (standard deviation)	-1432.51 (± 1969.622)	-1791.91 (± 2712.334)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in Serum Ferritin Level for All Participants Measured from Core Study Baseline (BL) to End of Extension Study, by Baseline Liver Iron Content (LIC)

End point title	Absolute Change in Serum Ferritin Level for All Participants Measured from Core Study Baseline (BL) to End of Extension Study, by Baseline Liver Iron Content (LIC)

End point description:

Serum Levels were assessed at core study baseline (BL) and then 1 year and 2 years in core study, baseline of extension study and time of discontinuation from the extension visit (end of study). Serum Ferritin is reported in micrograms per Liter. Absolute change in Serum Ferritin from core study baseline to the end of the extension study is presented for participants with the following two core study baseline LIC levels: 1-<7 mg Fe/g dw and ≥7 mg Fe/g dw.

End point type	Secondary

End point timeframe:

From Baseline of Core Study to End of Extension Study, up to 3 years

End point values	Deferasirox (All Participants)			
Subject group type	Subject analysis set			
Number of subjects analysed	163			
Units: µg/L				
arithmetic mean (standard deviation)				
Core Baseline LIC 1-<7 mg Fe/g dw (n=12)	-369.83 (± 1349.57)			
Core Baseline LIC ≥ 7 mg Fe/g dw (n=151)	-1619.31 (± 2217.104)			

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

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups

Reporting group title	age group ge 2 - lt 16 years

Reporting group description:

age group ge 2 - lt 16 years

Reporting group title	age group ge 16 years

Reporting group description:

age group ge 16 years

Serious adverse events	age group ge 2 - lt 16 years	age group ge 16 years	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 162 (3.09%)	12 / 69 (17.39%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events	0	0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 162 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 162 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			

subjects affected / exposed	0 / 162 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 162 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perinephric collection			
subjects affected / exposed	0 / 162 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 162 (0.00%)	2 / 69 (2.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 162 (0.00%)	3 / 69 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aneurysm			
subjects affected / exposed	0 / 162 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	0 / 162 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 162 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Arrhythmia			
subjects affected / exposed	0 / 162 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 162 (0.62%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 162 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 162 (0.62%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 162 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coma			
subjects affected / exposed	0 / 162 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	1 / 162 (0.62%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 162 (0.62%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			

subjects affected / exposed	0 / 162 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 162 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 162 (0.00%)	3 / 69 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 162 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 162 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer perforation			
subjects affected / exposed	0 / 162 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 162 (0.62%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 162 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Adenoidal hypertrophy			
subjects affected / exposed	1 / 162 (0.62%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 162 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 162 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 162 (0.62%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Otitis media			
subjects affected / exposed	1 / 162 (0.62%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perinephric abscess			
subjects affected / exposed	0 / 162 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia streptococcal			
subjects affected / exposed	1 / 162 (0.62%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 162 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Subdiaphragmatic abscess			
subjects affected / exposed	1 / 162 (0.62%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 162 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	age group ge 2 - lt 16 years	age group ge 16 years	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	54 / 162 (33.33%)	33 / 69 (47.83%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	13 / 162 (8.02%)	4 / 69 (5.80%)	
occurrences (all)	16	4	
Blood calcium decreased			
subjects affected / exposed	0 / 162 (0.00%)	4 / 69 (5.80%)	
occurrences (all)	0	6	
Blood creatinine increased			
subjects affected / exposed	5 / 162 (3.09%)	9 / 69 (13.04%)	
occurrences (all)	6	12	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	0 / 162 (0.00%)	5 / 69 (7.25%)	
occurrences (all)	0	8	
Pyrexia			
subjects affected / exposed	3 / 162 (1.85%)	6 / 69 (8.70%)	
occurrences (all)	3	7	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 162 (0.62%)	5 / 69 (7.25%)	
occurrences (all)	1	5	
Vomiting			

subjects affected / exposed	17 / 162 (10.49%)	5 / 69 (7.25%)	
occurrences (all)	20	9	
Musculoskeletal and connective tissue disorders			
Osteoporosis			
subjects affected / exposed	1 / 162 (0.62%)	4 / 69 (5.80%)	
occurrences (all)	1	4	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 162 (0.62%)	4 / 69 (5.80%)	
occurrences (all)	1	4	
Influenza			
subjects affected / exposed	26 / 162 (16.05%)	3 / 69 (4.35%)	
occurrences (all)	54	4	
Upper respiratory tract infection			
subjects affected / exposed	3 / 162 (1.85%)	8 / 69 (11.59%)	
occurrences (all)	10	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 March 2005	The purpose of this protocol amendment is 1) to introduce a fixed starting dose of 20 mg/kg for all patients 2) to implement a dose adjustment schedule based on serial serum ferritin measurements 3) to provide further details on the assessment of further potential surrogate markers and the necessity of increasing blood sample volume 4) to introduce safety measures to be taken in case of increased liver parameters 5) to update the liver biopsy laboratory procedures 6) to clarify some protocol discrepancies.
02 May 2005	This amendment extends study CICL670A2402 by means of a separate extension protocol CICL670A2402E1 provided as Post-text supplement 9 to the original protocol. In this extension study, liver MRI will be the reference technique for determination of liver iron concentration (LIC) in all patients. Only in patients in whom liver MRI is not practicable, liver biopsy (the technique used for LIC determination in the core study) will be used.
24 May 2006	The purpose of this protocol amendment is 1) to simplify the dosing and assessment procedures in the core and extension protocol based upon the emerging safety and efficacy profile that has been observed in the clinical development program, 2) to extend the duration of the extension study for another year to give study patients access to the study drug until it will be commercially available, and 3) to correct protocol inconsistencies.
09 October 2007	This amendment is to update the dosing, dose adjustment and assessment procedures in the extension protocol based upon the update of the global periodic safety review (the monitoring of serum creatinine and the dose reduction criteria for increased serum creatinine levels will be updated; dose modification criteria for hypersensitivity reactions, cytopenias and for increased urinary protein/creatinine ratio will be newly introduced), to further clarify dose adjustments due to changes in serum ferritin and due to increased transaminases levels, and skin rash in the extension study. It will allow harmonization of dosing adjustments across multiple clinical studies with ICL670 and to further clarify definition of study population for statistical analysis in the extension study. The changes introduced by amendment 4 will only apply for the extension. Based on the global periodic safety review of the clinical and post-marketing data, the global label for ICL670 has been updated and the following dose adjustments/procedures in ongoing studies have been added/modified. • Monitoring of the serum creatinine has been incorporated for patients with preexisting renal conditions and for patients who are receiving medicinal products that depress renal function. • The dose modification procedure, for adult and pediatric patients has been adjusted: for pediatric patients with increased serum creatinine levels above the age-appropriate ULN and for adult patients with non-progressive increases by >33% above average of pretreatment measures at 2 consecutive visits. • Monthly tests for proteinuria have been added to the visit schedule to monitor the renal safety for all patients. • Cases of serious hypersensitivity reactions, have been reported in patients receiving ICL670, the onset of the reaction occurring in the majority of cases within the first month of treatment. If reactions are severe, ICL670 should be discontinued and appropriate medical intervention instituted.

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.

An internal review revealed major Good Clinical Practice violations at 2 sites in Saudi Arabia: 602 for core + extension, 601 for 2-yr extension. Therefore data was excluded (completely for 602 + partly for 601) from analyses.

Notes: