



Clinical trial results:

An open-label, phase II, randomized, pilot study to assess the effect in terms of erythroid improvement of deferasirox combined with erythropoietin compared to erythropoietin alone in patients with low- and int-1-risk myelodysplastic syndrome

Summary

EudraCT number	2013-000981-12
Trial protocol	IT SE GB ES
Global end of trial date	22 March 2017

Results information

Result version number	v1 (current)
This version publication date	06 April 2018
First version publication date	06 April 2018

Trial information

Trial identification

Sponsor protocol code	CICL670A2421
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01868477
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, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 March 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 March 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to assess the effect of treatment with deferasirox (DFX) + erythropoietin (EPO) vs. erythropoietin (EPO) alone on erythropoiesis after 12 weeks of treatment

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	28 January 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	China: 6
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Korea, Republic of: 1
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	United Kingdom: 2
Worldwide total number of subjects	23
EEA total number of subjects	14

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	3
From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Twenty-three patients were randomized into the trial

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	Erythropoietin alpha

Arm description:

Starting dose was erythropoietin 40,000 units/week. If after 4 weeks erythroid improvement was inadequate, dose was escalated to 60,000 units/week. If after 12 weeks of treatment, erythroid improvement was inadequate, participants were switched to the combination arm. At any time when erythroid response was achieved, erythropoietin treatment was stopped until end of study.

Arm type	Experimental
Investigational medicinal product name	Erythropoietin alpha
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Erythropoietin alpha (EPO): provided as available in the respective country and is delivered subcutaneous injection

Arm title	Deferasirox + Erythropoietin alpha
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Arm description:

Starting dose was deferasirox dispersible tablet (DT) 10 mg/kg/day or deferasirox film-coated tablet (FCT) 7 mg/kg/day in combination with erythropoietin 40,000 units/week. If after 4 weeks erythroid improvement was inadequate, erythropoietin dose was escalated to 60,000 units/week. If after 12 weeks of treatment, erythroid improvement was inadequate, participants were discontinued from the study. At any time when erythroid response was achieved, erythropoietin treatment was stopped study and Deferasirox treatment was continued until end of study

Arm type	Experimental
Investigational medicinal product name	deferasirox dispersible tablets
Investigational medicinal product code	DFX DT
Other name	
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

supplied in 125, 250, 500 mg dispersible tablets

Investigational medicinal product name	deferasirox film-coated tablets
Investigational medicinal product code	
Other name	DFX FCT
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:
supplied in 90,180, 360 mg film-coated tablets

Number of subjects in period 1	Erythropoietin alpha	Deferasirox + Erythropoietin alpha
Started	12	11
Completed	8	6
Not completed	4	5
Consent withdrawn by subject	1	-
Disease progression	1	1
Adverse event, non-fatal	2	4

Baseline characteristics

Reporting groups

Reporting group title	Erythropoietin alpha
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Reporting group description:

Starting dose was erythropoietin 40,000 units/week. If after 4 weeks erythroid improvement was inadequate, dose was escalated to 60,000 units/week. If after 12 weeks of treatment, erythroid improvement was inadequate, participants were switched to the combination arm. At any time when erythroid response was achieved, erythropoietin treatment was stopped until end of study.

Reporting group title	Deferasirox + Erythropoietin alpha
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Reporting group description:

Starting dose was deferasirox dispersible tablet (DT) 10 mg/kg/day or deferasirox film-coated tablet (FCT) 7 mg/kg/day in combination with erythropoietin 40,000 units/week. If after 4 weeks erythroid improvement was inadequate, erythropoietin dose was escalated to 60,000 units/week. If after 12 weeks of treatment, erythroid improvement was inadequate, participants were discontinued from the study. At any time when erythroid response was achieved, erythropoietin treatment was stopped study and Deferasirox treatment was continued until end of study

Reporting group values	Erythropoietin alpha	Deferasirox + Erythropoietin alpha	Total
Number of subjects	12	11	23
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age Continuous			
Units: years			
arithmetic mean	74.5	71.1	
standard deviation	± 5.84	± 7.54	-
Sex: Female, Male			
Units: Subjects			
Female	8	5	13
Male	4	6	10
Race/Ethnicity, Customized			
Units: Subjects			
Caucasian	8	7	15
Asian	4	4	8

End points

End points reporting groups

Reporting group title	Erythropoietin alpha
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Reporting group description:

Starting dose was erythropoietin 40,000 units/week. If after 4 weeks erythroid improvement was inadequate, dose was escalated to 60,000 units/week. If after 12 weeks of treatment, erythroid improvement was inadequate, participants were switched to the combination arm. At any time when erythroid response was achieved, erythropoietin treatment was stopped until end of study.

Reporting group title	Deferasirox + Erythropoietin alpha
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Reporting group description:

Starting dose was deferasirox dispersible tablet (DT) 10 mg/kg/day or deferasirox film-coated tablet (FCT) 7 mg/kg/day in combination with erythropoietin 40,000 units/week. If after 4 weeks erythroid improvement was inadequate, erythropoietin dose was escalated to 60,000 units/week. If after 12 weeks of treatment, erythroid improvement was inadequate, participants were discontinued from the study. At any time when erythroid response was achieved, erythropoietin treatment was stopped and Deferasirox treatment was continued until end of study

Subject analysis set title	EPO+DFX (12 weeks)
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Patients randomized to EPO alone with inadequate response at 12 weeks who had been switched over to combination EPO+DFX

Subject analysis set title	EPO (24 weeks)
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Patients who were in EPO alone group and were not switched to EPO+DFX after 12 weeks,

Subject analysis set title	EPO+DFX at 12
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Patients randomized to EPO alone with inadequate response at 12 weeks who had been switched over to combination EPO+DFX

Subject analysis set title	EPO+DFX at 12 weeks
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

This analysis included patients randomized either to EPO or DFX+EPO at baseline as well as patients who did not have erythroid response at week 12 in the EPO group and switched to combination therapy. The time-course of Hb and its absolute changes from baseline was summarized by descriptive statistics by visit and erythroid response. Patients randomized to EPO and not switching after 12 weeks to EPO+DFX would consist of only responders

Primary: Summary of erythroid response within 12 weeks, by treatment group (Full Analysis Set)

End point title	Summary of erythroid response within 12 weeks, by treatment group (Full Analysis Set)
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End point description:

Difference in percentage of patients achieving an erythroid response within 12 weeks of treatment between the two arms according to modified IWG 2006 criteria increase in hemoglobin (Hb) ≥ 1.5 g/dL. Erythroid response is defined as the increase in Hb from baseline ≥ 1.5 g/dL. Patients achieving erythroid response at least once within 12 weeks were considered responders

End point type	Primary
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End point timeframe:

Baseline up to 12 weeks

End point values	Erythropoietin alpha	Deferasirox + Erythropoietin alpha		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	11		
Units: percentage of participants				
number (confidence interval 95%)	41.7 (15.2 to 72.3)	27.3 (6.02 to 61.0)		

Statistical analyses

Statistical analysis title	EPO vs EPO + DFX
Comparison groups	Erythropoietin alpha v Deferasirox + Erythropoietin alpha
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Mean difference (final values)
Point estimate	14.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24
upper limit	48.16

Secondary: Summary of hematologic response in patients randomized to EPO+DFX and EPO alone, within 24 weeks of treatment (Full Analysis Set)

End point title	Summary of hematologic response in patients randomized to EPO+DFX and EPO alone, within 24 weeks of treatment (Full Analysis Set)
End point description:	
Hematological response criteria defined as: Erythroid response: hemoglobin (Hb) increase from baseline ≥ 1.5 g/dL (baseline < 11 g/dL), neutrophil response: increase from baseline $\geq 100\%$ and increase $> 0.5 \times 10^9/L$ (baseline $< 1 \times 10^9/L$), platelet response: increase from baseline $\geq 30 \times 10^9/L$ (baseline $< 100 \times 10^9/L$) according to modified IWG 2006 criteria	
End point type	Secondary
End point timeframe:	
Baseline up to 24 weeks	

End point values	Erythropoietin alpha	Deferasirox + Erythropoietin alpha		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	11		
Units: participants				
arithmetic mean (standard deviation)	1.8 (± 0.21)	2.1 (± 0.61)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of hematologic improvement in patients randomized to EPO+DFX and EPO alone, within 24 weeks of treatment (Full Analysis Set)

End point title	Summary of hematologic improvement in patients randomized to EPO+DFX and EPO alone, within 24 weeks of treatment (Full Analysis Set)
End point description:	Percentage of participants achieving an hematologic improvement defined as: neutrophil improvement: increase from baseline $>0.5 \times 10^9/L$ (baseline = $1.0 \times 10^9/L$), platelet improvement: increase from baseline $\geq 30 \times 10^9/L$ (baseline = $100 \times 10^9/L$), hemoglobin improvement: Hb increase from baseline $\geq 1 \text{ g/dL}$ (baseline $<11 \text{ g/dL}$)
End point type	Secondary
End point timeframe:	Baseline up to 24 weeks

End point values	Erythropoietin alpha	Deferasirox + Erythropoietin alpha		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	11		
Units: percentage of participants				
Hematologic improvement	100	46		
Neutropil improvement	67	80		
Platelet improvement	50	80		
Hemoglobin improvement	67	60		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in hemoglobin values up to 24 weeks

End point title	Absolute change in hemoglobin values up to 24 weeks
End point description:	Absolute change in hemoglobin values for patients showing improvement: Hemoglobin improvement Hb increase from baseline $\geq 1 \text{ g/dL}$ (baseline $<11 \text{ g/dL}$)
End point type	Secondary

End point timeframe:
Baseline up to 24 weeks

End point values	Erythropoietin alpha	Deferasirox + Erythropoietin alpha		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	3		
Units: g/dL				
arithmetic mean (standard deviation)	1.3 (± 0.37)	1.4 (± 0.55)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in platelets and neutrophil levels up to 24 weeks

End point title	Absolute change in platelets and neutrophil levels up to 24 weeks
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End point description:

Absolute change in platelets and neutrophil levels for patients showing improvement: neutrophil improvement: increase from baseline $>0.5 \times 10^9/L$ (baseline = $1.0 \times 10^9/L$), platelet improvement: increase from baseline $\geq 30 \times 10^9/L$ (baseline = $100 \times 10^9/L$)

End point type	Secondary
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End point timeframe:

Baseline up to 24 weeks

End point values	Erythropoietin alpha	Deferasirox + Erythropoietin alpha		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	11		
Units: $10^9/L$				
arithmetic mean (standard deviation)				
Platelets n=6,4 Neutrophils n=8,4	58.7 (± 23.93) 1.2 (± 1.16)	66.3 (± 22.74) 2.4 (± 1.57)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of erythroid response in participants randomized to EPO alone at baseline and switched to EPO+DFX after 12 weeks of treatment (Full Analysis Set)

End point title	Summary of erythroid response in participants randomized to EPO alone at baseline and switched to EPO+DFX after 12 weeks of treatment (Full Analysis Set)
End point description: Erythroid response: hemoglobin increase from baseline ≥ 1.5 g/dL (baseline <11 g/dL). Percentages are based on N. Confidence intervals are calculated using Clopper-Pearson method. Hemoglobin value is at time of first response	
End point type	Secondary
End point timeframe: Week 13 up to 24 weeks	

End point values	EPO+DFX (12 weeks)			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of erythroid response within 24 weeks in participants randomized to EPO at baseline and not switched to EPO+DFX after 12 weeks of treatment (Full Analysis set)

End point title	Summary of erythroid response within 24 weeks in participants randomized to EPO at baseline and not switched to EPO+DFX after 12 weeks of treatment (Full Analysis set)
End point description: Erythroid response: hemoglobin increase from baseline ≥ 1.5 g/dL (baseline <11 g/dL). Percentages are based on N. Confidence intervals are calculated using Clopper-Pearson method. Hemoglobin value is at time of first response	
End point type	Secondary
End point timeframe: baseline up to 24 weeks	

End point values	EPO (24 weeks)			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: percentage of participants				
number (confidence interval 95%)	71.4 (47.8 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in serum ferritin up to 24 weeks for erythropoietin alpha arm (Full Analysis Set)

End point title	Absolute change in serum ferritin up to 24 weeks for erythropoietin alpha arm (Full Analysis Set) ^[1]
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End point description:

Absolute change in serum ferritin from baseline

End point type	Secondary
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End point timeframe:

Baseline up to 24 weeks

Notes:

[1] - 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 was done

End point values	Erythropoietin alpha			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: ng/mL				
median (full range (min-max))				
Responders - Week 5 n=5	-98.5 (-323 to -73.5)			
Responders - Week 9 n=5	-79.0 (-381 to 54.0)			
Responders - Week 13 n=4	24.8 (-179 to 104)			
Responders - Week 17 n=4	-57.8 (-140 to 258.0)			
Responders - Week 21 n=2	-39.8 (-44.0 to -35.5)			
Non-responders - Week 5 n=2	-352 (-523 to -182)			
Non-responders - Week 9 n=2	-189 (-572 to 194.5)			
Non-responders - Week 13 n=2	-44.5 (-621 to 531.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in serum ferritin up to 24 weeks for Deferasirox + erythropoietin alpha arm (Full Analysis Set)

End point title	Absolute change in serum ferritin up to 24 weeks for Deferasirox + erythropoietin alpha arm (Full Analysis Set) ^[2]
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End point description:

Absolute change in serum ferritin from baseline

End point type	Secondary
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End point timeframe:

Baseline up to 24 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 was done

End point values	Deferasirox + Erythropoietin alpha			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: ng/mL				
median (full range (min-max))				
Responders - Week 5 n=3	-82.5 (-243 to 1068)			
Responders - Week 9 n=3	-139 (-292 to 702.0)			
Responders - Week 13 n=3	-121 (-338 to 0.0)			
Responders - Week 17 n=3	16.5 (-143 to 722.0)			
Responders - Week 21 n=3	-95.5 (-189 to 173.0)			
Non-responders - Week 5 n=7	-38.0 (-315 to 111.0)			
Non-responders - Week 9 n=4	-144 (-435 to 1.0)			
Non-responders - Week 13 n=3	-155 (-225 to -127)			
Non-responders - Week 17 n=2	-123 (-154 to -91.0)			
Non-responders - Week 21 n=1	-291 (-291 to -291)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in serum ferritin up to 24 weeks for EPO+DFX at 12 weeks arm (Full Analysis Set)

End point title	Absolute change in serum ferritin up to 24 weeks for EPO+DFX at 12 weeks arm (Full Analysis Set)
End point description:	
Absolute change in serum ferritin from baseline	
End point type	Secondary
End point timeframe:	
Baseline up 24 weeks	

End point values	EPO+DFX at 12			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: ng/mL				
median (full range (min-max))				
Responders - Week 5 n=1	-116 (-116 to -116)			
Responders - Week 9 n=1	-136 (-136 to -136)			
Responders - Week 13 n=1	59.5 (59.5 to 59.5)			
Responders - Week 17 n=1	74.5 (74.5 to 74.5)			
Non-responders - Week 5 n=4	-68.3 (-144 to 221.3)			
Non-responders - Week 9 n=3	-148 (-319 to 321.3)			
Non-responders - Week 13 n=4	220.4 (-228 to 635.3)			
Non-responders - Week 17 n=2	-16.6 (-28.5 to -4.7)			
Non-responders - Week 21 n=3	-10.5 (-463 to 367.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in hemoglobin (Hb) from baseline for erythropoietin alpha arm (Full Analysis Set)

End point title	Absolute change in hemoglobin (Hb) from baseline for erythropoietin alpha arm (Full Analysis Set) ^[3]
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End point description:

This analysis included patients randomized either to EPO or DFX+EPO at baseline as well as patients who did not have erythroid response at week 12 in the EPO group and switched to combination therapy. The time-course of Hb and its absolute changes from baseline was summarized by descriptive statistics by visit and erythroid response. Patients randomized to EPO and not switching after 12 weeks to EPO+DFX, would consist of only responders.

End point type	Secondary
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End point timeframe:

Baseline up to 24 weeks

Notes:

[3] - 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 was done

End point values	Erythropoietin alpha			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: g/dL				
median (full range (min-max))				
Responders - Week 5 n=5	1.5 (1.1 to 3.2)			
Responders - Week 9 n=5	1.9 (1.3 to 4.4)			

Responders - Week 13 n=4	1.7 (1.5 to 3.4)			
Responders - Week 17 n=4	1.6 (-0.3 to 1.8)			
Responders - Week 21 n=3	0.8 (-0.7 to 1.8)			
Non-responders - Week 5 n=2	-0.9 (-1.7 to -0.1)			
Non-responders - Week 9 n=2	-1.7 (-2.0 to -1.4)			
Non-responders - Week 13 n=2	-2.5 (-2.8 to -2.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in hemoglobin (Hb) from baseline for Deferasirox + erythropoietin alpha arm (Full Analysis Set)

End point title	Absolute change in hemoglobin (Hb) from baseline for Deferasirox + erythropoietin alpha arm (Full Analysis Set) ^[4]
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End point description:

This analysis included patients randomized either to EPO or DFX+EPO at baseline as well as patients who did not have erythroid response at week 12 in the EPO group and switched to combination therapy. The time-course of Hb and its absolute changes from baseline was summarized by descriptive statistics by visit and erythroid response. Patients randomized to EPO and not switching after 12 weeks to EPO+DFX would consist of only responders.

End point type	Secondary
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End point timeframe:

Baseline up to 24 weeks

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was done

End point values	Deferasirox + Erythropoietin alpha			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: g/dL				
median (full range (min-max))				
Responders - Week 5 n= n=3	0.7 (0.6 to 2.0)			
Responders - Week 9 n=3	1.6 (1.0 to 2.6)			
Responders - Week 13 n=3	2.9 (2.8 to 3.0)			
Responders - Week 17 n=3	2.4 (0.6 to 3.0)			
Responders - Week 21 n=3	1.7 (-1.3 to 2.4)			
Non-responders - Week 5 n=7	-0.1 (-2.3 to 0.1)			
Non-responders - Week 9 n=4	0.0 (-0.8 to 0.5)			
Non-responders - Week 13 n=3	0.2 (0.1 to 0.5)			
Non-responders - Week 17 n=1	-0.5 (-0.5 to 0.5)			

Non-responders - Week 21 n=1	-0.6 (-0.6 to 0.6)			
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Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in hemoglobin (Hb) from baseline for EPO+DFX at 12 weeks arm (Full Analysis Set)

End point title	Absolute change in hemoglobin (Hb) from baseline for EPO+DFX at 12 weeks arm (Full Analysis Set)
End point description: This analysis included patients randomized either to EPO or DFX+EPO at baseline as well as patients who did not have erythroid response at week 12 in the EPO group and switched to combination therapy. The time-course of Hb and its absolute changes from baseline was summarized by descriptive statistics by visit and erythroid response. Patients randomized to EPO and not switching after 12 weeks to EPO+DFX would consist of only responders.	
End point type	Secondary
End point timeframe: Baseline up to 24 weeks	

End point values	EPO+DFX at 12 weeks			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: g/dL				
median (full range (min-max))				
Responders - Week 5 n= n=1	1.2 (1.2 to 1.2)			
Responders - Week 9 n=1	1.8 (1.8 to 1.8)			
Responders - Week 13 n=1	0.7 (0.7 to 0.7)			
Responders - Week 17 n=1	-0.6 (-0.6 to -0.6)			
Non-responders - Week 5 n=4	0.3 (-0.5 to 0.6)			
Non-responders - Week 9 n=3	0.5 (-0.4 to 0.8)			
Non-responders - Week 13 n=3	0.4 (0.2 to 1.0)			
Non-responders - Week 17 n=3	0.0 (-0.1 to 0.9)			
Non-responders - Week 21 n=3	0.0 (-0.7 to 0.8)			

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 are reported in this record from First Patient First Treatment until Last Patient Last Visit up to approximately 24 weeks

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	EPO a
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Reporting group description:

EPO alpha

Reporting group title	EPO+DFX DT
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Reporting group description:

EPO+DFX DT

Reporting group title	EPO+DFX FCT
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Reporting group description:

EPO+DFX FCT

Reporting group title	Switched to DFX+EPO after 12 weeks
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Reporting group description:

Switched to DFX+EPO after 12 weeks

Serious adverse events	EPO a	EPO+DFX DT	EPO+DFX FCT
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 7 (14.29%)	1 / 10 (10.00%)	1 / 1 (100.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
C-reactive protein increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 1 (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
Cardiac disorders			

Tachycardia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 1 (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			
Syncope			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	1 / 1 (100.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 1 (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	1 / 7 (14.29%)	0 / 10 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Diverticulitis			

subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	1 / 1 (100.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Switched to DFX+EPO after 12 weeks		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 5 (20.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
C-reactive protein increased			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	1 / 5 (20.00%)		
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	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal pain			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Diverticulitis			
subjects affected / exposed	0 / 5 (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	EPO a	EPO+DFX DT	EPO+DFX FCT
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 7 (57.14%)	10 / 10 (100.00%)	1 / 1 (100.00%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			

subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 1 (0.00%)
occurrences (all)	0	2	0
Blood uric acid increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Haemoglobin decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Heart rate increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 7 (28.57%)	2 / 10 (20.00%)	0 / 1 (0.00%)
occurrences (all)	2	2	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 1 (0.00%)
occurrences (all)	0	2	0
Gravitational oedema			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Injection site bruising			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Pyrexia			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 10 (0.00%) 0	0 / 1 (0.00%) 0
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 10 (0.00%) 0	0 / 1 (0.00%) 0
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 10 (0.00%) 0	0 / 1 (0.00%) 0
Anal fissure subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 10 (0.00%) 0	0 / 1 (0.00%) 0
Constipation subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 10 (10.00%) 1	0 / 1 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	3 / 10 (30.00%) 3	1 / 1 (100.00%) 1
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 10 (10.00%) 1	0 / 1 (0.00%) 0
Inguinal hernia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 10 (0.00%) 0	0 / 1 (0.00%) 0
Toothache subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 10 (0.00%) 0	0 / 1 (0.00%) 0
Hepatobiliary disorders Hepatic function abnormal subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 10 (10.00%) 1	0 / 1 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 10 (10.00%) 1	0 / 1 (0.00%) 0

Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Rash maculo-papular			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	1 / 7 (14.29%)	1 / 10 (10.00%)	0 / 1 (0.00%)
occurrences (all)	1	1	0
Neck pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Herpes zoster			

subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Hordeolum			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Localised infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Lung infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Switched to DFX+EPO after 12 weeks		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Blood creatinine increased			

subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Blood uric acid increased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Haemoglobin decreased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Heart rate increased subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Weight decreased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Gravitational oedema subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Injection site bruising subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Oedema peripheral subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Pyrexia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 2		
Ear and labyrinth disorders			

Vertigo subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Gastrointestinal disorders			
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 2		
Anal fissure subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Constipation subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Diarrhoea subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Inguinal hernia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Toothache subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Hepatobiliary disorders			
Hepatic function abnormal subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Skin and subcutaneous tissue disorders			
Alopecia			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Rash</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Rash maculo-papular</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 5 (20.00%)</p> <p>1</p> <p>1 / 5 (20.00%)</p> <p>1</p> <p>0 / 5 (0.00%)</p> <p>0</p>		
<p>Renal and urinary disorders</p> <p>Renal impairment</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 5 (20.00%)</p> <p>1</p>		
<p>Musculoskeletal and connective tissue disorders</p> <p>Arthralgia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Back pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Neck pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pain in extremity</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 5 (20.00%)</p> <p>1</p> <p>1 / 5 (20.00%)</p> <p>1</p> <p>1 / 5 (20.00%)</p> <p>1</p> <p>0 / 5 (0.00%)</p> <p>0</p>		
<p>Infections and infestations</p> <p>Conjunctivitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Gastroenteritis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Herpes zoster</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hordeolum</p>	<p>0 / 5 (0.00%)</p> <p>0</p> <p>0 / 5 (0.00%)</p> <p>0</p> <p>0 / 5 (0.00%)</p> <p>0</p>		

subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Localised infection			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Lung infection			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 November 2013	<ul style="list-style-type: none">- Change inclusion criteria of lower hemoglobin (Hb) threshold value of > 6 g/dl to ≥ 8 g/dL- Clarify that patients with performance status (PS) > 2 must not be enrolled in the study- Clarify that patients with need of transfusion must not be enrolled in the study and they must be withdrawn from the study anytime when transfusion as rescue therapy is needed- Delete prophylactic hydrocortisone to prevent transfusion reaction from the list of allowed concurrent therapy- Standardize term for trial design from exploratory to pilot- Addition of inflammatory biomarkers IL-1, IL-6 and IFN-γ
14 November 2014	<ul style="list-style-type: none">- Changed the inclusion criterion of upper limit of documented diagnosis of MDS disease from < 2 years to < 3 years- Changed the inclusion criterion of lower limit of creatinine clearance from ≥ 60 mL/min to above the concentration limit in locally approved prescribing information- Inclusion of patients with stable steroid treatment for other chronic medical conditions than adrenal failure was allowed- Excluded patients with hepatic impairment fulfilling criteria of Child-Pugh Class B or C- Guidance on treating patients with Stevens-Johnson syndrome- Guidance on concomitant administration of deferasirox with CYP1A2 substrates that have a narrow therapeutic index and the concomitant use of bile acid sequestrates- Introduction of Per Protocol set, grouping for safety analyses and supportive analyses- Revision of analysis sets of primary and secondary objectives
06 August 2015	<ul style="list-style-type: none">- Addition of DFX FCT as optional study medication- Patients with creatinine clearance between 40 mL/min and < 60 mL/min, who do not present with additional risk factors that may impair renal function, might have been eligible at the discretion of the investigator.- Changed the inclusion criterion of upper limit of Serum Ferritin from 1,000 ng/mL to 1,500 ng/mL (Values within 10% difference above 1500 ng/mL or 10% difference below 300 ng/mL might have been accepted at discretion of the investigator if the patient represented the investigational population.

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.

This study did not meet the original enrollment objective of 60 patients and was terminated without extending enrollment past original planned LPFV of 31-Oct-2016.

Notes:

