Sponsor

Novartis

Generic Drug Name

Deferasirox

Trial Indication

Myelodysplastic Syndrome

Protocol Number

CICL670AUS03

Protocol Title

An Open Label, Safety and Tolerability Study of Deferasirox for Treatment of Transfusional Iron Overload in Low-risk and INT-1, Myelodysplastic Patients Using Serum Ferritin Monitoring

Clinical Trial Phase

Phase IV

Phase of Drug Development

Phase IV

Study Start/End Dates

25-Jul-2005 to 28-Mar-2008

Reason for Termination

NA

Study Design/Methodology

This was an open-label, multi-center, single-arm trial designed to assess the safety and tolerability of oral Exjade in adult transfusion-dependent MDS patients with iron overload. A screening period lasting up to 4 weeks after the initial screening visit was used to assess patient eligibility. Approximately 150 patients were to be enrolled in the trial.

Centers

45 centers in 2 countries: Canada (6), United States (39)

Objectives:

Primary objective

- The primary objective was to evaluate the safety and tolerability of deferasirox (ICL670, marketed as Exjade®) administered orally at 20 mg/kg/day for 1 year to patients with MDS

Secondary objective

- To evaluate the efficacy of Exjade based on changes in serum ferritin from baseline to 3, 6, 9 and 12 months after initiation of treatment
- To evaluate the role of non-transferrin bound iron (labile plasma iron [LPI] and directly chelatable iron [DCI]), serum iron, transferrin, and transferrin saturation on the safe administration of Exjade
- To evaluate change in transfusion requirements and estimate the frequency of hematologic improvement using the International Working Group (IWG) criteria in patients who were not receiving growth factors or chemotherapy for their underlying MDS
- To evaluate trough pharmacokinetic (PK) parameters of Exjade in MDS patients
- To assess compliance with administration of oral Exjade
- To describe the prevalence of hereditary hemochromatosis gene (HFE) gene mutations in this population and to observe any relationship between the presence of these mutations and the rate of change in serum ferritin.

Test Product (s), Dose(s), and Mode(s) of Administration

Dispersible tablets of Exjade were supplied in dosage strengths of 125 mg, 250 mg and 500 mg per tablet. Registered patients initiated treatment with Exjade 20 mg/kg/day. The appropriate daily dose (i.e., number of tablets of each strength to be taken each day) was calculated by the investigator based on the patient's actual body weight. In order to simplify administration, only single strength tablets were used. Therefore doses were rounded to the nearest single strength dose. Exjade was to be taken every morning 30 minutes before breakfast, preferably around the same time between 7:00 and 9:00 AM each day. The tablets were to be dropped into water, orange juice, or apple juice and gently stirred for 1 to 3 minutes until completely dispersed.

Reference Product(s), Dose(s), and Mode(s) of Administration

Not applicable.

Criteria for Evaluation

Efficacy: Efficacy was assessed through examination of serum ferritin, transferrin, transferrin saturation, total iron, and LPI. Additional exploratory endpoints examined were transfusion requirements and hematologic response (as determined according to International Working Group
[IWG] criteria).

Safety: Safety assessments consisted of recording and monitoring all adverse events, including serious adverse events, and the regular monitoring of hematology and blood chemistry values. Additional assessments included vital signs, body weight, ECGs, echocardiograms, evaluations of urine protein/creatinine ratios, ocular examinations, and audiometry.

Pharmacokinetics: Blood collections for ICL670 blood levels were performed only in patients who had been on treatment without dose adjustment or treatment interruption for at least 4 days prior to scheduled sampling. Trough blood samples were collected just prior to the next dose administration at
Weeks 13, 25, 37 and 49 (Months 3, 6, 9 and 12). Plasma concentrations of both deferasirox (ICL670) and the iron-complex Fe-[deferasirox]2 (Fe-[ICL670]2) were measured.

Statistical Methods

Data from all centers were pooled so that an adequate number of patients would be available for analysis. Continuous variables were summarized using univariate statistics (n, mean, median, standard deviation [SD], standard error of the mean [SEM], minimum, and

maximum); categorical variables were summarized using frequencies and percents. For iron marker parameters, change from baseline was calculated. Descriptive statistics were used to summarize the prevalence of HFE gene mutations. Safety data were analyzed descriptively.

Study Population: Key Inclusion/ Exclusion Criteria

Inclusion Criteria:

- Male or female patients with low or intermediate (INT-1) risk MDS
- Patients can be EITHER naïve to iron chelation OR have had prior treatment with deferoxamine (DFO).
- Age greater than or equal to 18 years
- Availability of transfusion records for the 12 weeks prior to registration
- A lifetime minimum of 30 previous packed red blood cell transfusions
- Availability of at least three CBC values (pretransfusion) during the 12 weeks prior to registration
- Serum Ferritin:

For entry into the screening period, serum ferritin ≥ 1000 ng/mL on at least two occasions, at least two weeks apart, during the prior year.
Serum ferritin ≥ 1000 ng/mL at screening via the central lab.

- Life expectancy ≥ 6 months
- Sexually active women must use an effective method of contraception, or must have undergone clinically documented total hysterectomy and/or oophorectomy, or tubal ligation or be postmenopausal (defined as amenorrhea for at least 12 months)
- Able to provide written informed consent

Exclusion Criteria:

- Serum creatinine above the upper limit of normal
- ALT > 500 U/L during screening
- Clinical or laboratory evidence of active Hepatitis B or C
- Urinary protein/creatinine ratio > 0.5 mg/mg
- History of HIV positive test result (ELISA or Western blot)
- ECOG Performance Status > 2
- Patients with uncontrolled systemic hypertension
- Unstable cardiac disease not controlled by standard medical therapy
- Patients with a diagnosis of or history of clinically relevant ocular toxicity related to iron chelation
- Systemic diseases (cardiovascular, renal, hepatic, etc.) which would prevent study treatment
- Pregnancy or breast feeding
- Treatment with systemic investigational drug within the past 4 weeks or topical investigational drug within the past 7 days

- Other surgical or medical condition which might significantly alter the absorption, distribution, metabolism or excretion of study drug
- History of non-compliance to medical regimens or patients who are considered potentially unreliable and/or not cooperative

Participant Flow Table

Patient disposition

	All Patients (N=173)	Baseline Serum Creatinine	
		≤ULN (N=149)	>ULN (N=24)
Number (%) of patients who completed study	95 (54.9)	87 (58.4)	8 (33.3)
Number (%) of patients who prematurely discontinued study	78 (45.1)	62 (41.6)	16 (66.7)
Primary reason for discontinuation, n (%)			
Adverse events	27 (15.6)	21 (14.1)	6 (25.0)
Abnormal laboratory value(s)	15 (18.7)	9 (6.0)	6 (25.0)
Unsatisfactory therapeutic effect	2 (1.2)	2 (1.3)	0 (0.0)
Patient's condition no longer requires study drug	1 (0.6)	1 (0.7)	0 (0.0)
Patient withdrew consent	16 (9.2)	14 (9.4)	2 (8.3)
Death	17 (9.8)	15 (10.1)	2 (8.3)

Baseline Characteristics

Demographic summary by treatment group (FAS population)

		All Patients N = 173
Age (years)	N	173
	Mean	69.9
	SD	11.45
	Median	71.0
	Min, max	21, 90
Age group (years) – n (%)	18 to < 50	9 (5.2)
	50 to < 65	37 (21.4)
	≥ 65	127 (73.4)
Gender – n (%)	Male	103 (59.5)
	Female	70 (40.5)
Race – n (%)	Caucasian	159 (91.9)
	Black	4 (2.3)
	Oriental	4 (2.3)
	Other	6 (3.5)
Weight (kg)	N	173
	Mean	76.4
	SD	16.21
	Median	74.4
	Min, max	41, 125
Weight group (kg)	< 15	0 (0.0)
	15 to < 35	0 (0.0)
	35 to < 55	13 (7.5)
	55 to < 75	79 (45.7)
	≥ 75	81 (46.8)

Baseline disease characteristics (FAS population)

		All Patients N = 173
Myelodysplastic Syndrome (MDS) staging risk group – n (%)	Low (Score=0)	46 (26.6)
	INT - 1 (Score=0.5 - 1.0)	124 (71.7)
	Other	3 (1.7)
Time since initial diagnosis – n (%)	< 1 year	15 (8.7)
	≥ 1 year to < 3 years	59 (34.1)
	≥ 3 years	99 (57.2)
Lifetime number of previous packed red blood cell transfusions	N	57
	Mean	68.5
	SD	73.13
	Median	41.0
	Min, max	17, 435
Minimum number of previous transfusions	N	116
	Mean	59.8
	SD	53.24
	Median	41.5
	Min, max	20, 349
Total number of years on transfusions	N	173
	Mean	3.5
	SD	3.18
	Median	3.0
	Min, max	1, 34
Pre-screening ferritin values (µg/L)	N	173
	Mean	3080.3
	SD	1991.83
	Median	2535.0
	Min, max	1000, 16490

Primary Outcome Result(s)

Refer to Safety Result section for primary outcome result.

Secondary Outcome Result(s)

Serum ferritin and change from baseline (absolute and percent) in serum ferritin during study (FAS population)

Visit		Serum Ferritin (µg/L)	Absolute change from baseline (µg/L)	% change from baseline
Baseline	n	172		
	Mean	3202.5		
	SD	1826.87		
	Median	2771.5		
	Min, Max	863, 9993		
Week 13	n	143	142	142
	Mean	3087.3	-169.9	-1.61
	SD	1797.22	1062.36	27.093
	Median	2736.0	-146.5	-4.68
	Min, Max	769, 10592	-6679, 3260	-66.8, 141.9
Week 25	n	125	124	124
	Mean	2811.8	-403.7	-6.98
	SD	1401.65	1149.67	32.466
	Median	2551.0	-167.5	-8.14
	Min, Max	601, 7132	-5034, 2265	-63.8, 147.4
Week 37	N	111	110	110
	Mean	2636.0	-558.9	-13.28
	SD	1535.34	1249.69	38.029
	Median	2309.0	-505.0	-19.47
	Min, Max	387, 8495	-3699, 4132	-75.0, 163.9
Week 53	N	91	91	91
	Mean	2532.7	-716.5	-14.21
	SD	1652.14	1781.31	47.082
	Median	2201.0	-592.0	-23.21
	Min, Max	468, 10311	-5752, 5948	-80.1, 136.3

Serum ferritin and change from baseline (absolute and percent) in serum ferritin during study (per-protocol population)

Visit		Serum Ferritin (µg/L)	Absolute change from baseline (µg/L)	% change from baseline
Baseline	N	91		
	Mean	3247.9		
	SD	1767.63		
	Median	2882.0		
	Min, Max	863, 9993		
Week 13	N	88	88	88
	Mean	3101.9	-186.8	-1.85
	SD	1627.18	1102.34	23.832
	Median	2824.5	-27.5	-1.75
	Min, Max	834, 9313	-6679, 3260	-66.8, 60.9
Week 25	N	89	89	89
	Mean	2808.4	-479.4	-7.50
	SD	1322.39	1189.68	32.903
	Median	2570.0	-169.0	-8.18
	Min, Max	701, 6586	-5034, 2265	-63.8, 147.4
Week 37	N	85	85	85
	Mean	2591.9	-604.5	-14.28
	SD	1471.64	1238.72	34.067
	Median	2197.0	-457.0	-18.28
	Min, Max	387, 8495	-3699, 4132	-75.0, 94.7
Week 53	N	91	91	91
	Mean	2532.7	-716.5	-14.21
	SD	1652.14	1781.31	47.082
	Median	2201.0	-592.0	-23.21
	Min, Max	468, 10311	-5752, 5948	-80.1, 136.3

Absolute change from baseline to Week 49/Month 12 in LPI (LPI unit) during study (FAS population)

Visit		FAS Patients N=173
Week 13	n	117
	Mean	-0.31
	SD	0.657
	SEM	0.061
	Median	-0.10
	P25, P75	-0.60, 0.00
	Min, Max	-3.3, 2.2
Week 25	n	107
	Mean	-0.34
	SD	0.557
	SEM	0.054
	Median	-0.20
	P25, P75	-0.70, 0.00
	Min, Max	-2.4, 1.2
Week 37	n	89
	Mean	-0.41
	SD	0.594
	SEM	0.063
	Median	-0.30
	P25, P75	-0.70, 0.00
	Min, Max	-3.4, 0.6
Week 49	n	64
	Mean	-0.52
	SD	0.665
	SEM	0.083
	Median	-0.45
	P25, P75	-0.90, 0.00
	Min, Max	-3.6, 0.9

DCI (DCI unit) during study (FAS population)

Visit		FAS Patients N=173
Baseline	n	163
	Mean	0.06
	SD	0.180
	SEM	0.014
	Median	0.00
	P25, P75	0.00, 0.00
	Min, Max	0.0, 1.3
Week 13	n	126
	Mean	0.22
	SD	0.429
	SEM	0.038
	Median	0.00
	P25, P75	0.00, 0.20
	Min, Max	0.0, 2.2
Week 25	n	112
	Mean	0.19
	SD	0.493
	SEM	0.047
	Median	0.00
	P25, P75	0.00, 0.10
	Min, Max	0.0, 2.6

Week 37	n	93
	Mean	0.17
	SD	0.397
	SEM	0.041
	Median	0.00
	P25, P75	0.00, 0.00
	Min, Max	0.0, 1.7
Week 49	n	70
	Mean	0.16
	SD	0.387
	SEM	0.046
	Median	0.00
	P25, P75	0.00, 0.00
	Min, Max	0.0, 1.7

Absolute change from baseline to Week 49/Month 12 in DCI (DCI unit) during study (FAS population)

Visit		FAS Patients N=173
Week 13	n	117
	Mean	0.15
	SD	0.403
	SEM	0.037
	Median	0.00
	P25, P75	0.00, 0.10
	Min, Max	-0.5, 2.2
Week 25	n	107
	Mean	0.14
	SD	0.500
	SEM	0.048
	Median	0.00
	P25, P75	0.00, 0.10
	Min, Max	-0.6, 2.6
Week 37	n	89
	Mean	0.13
	SD	0.388
	SEM	0.041
	Median	0.00
	P25, P75	0.00, 0.00
	Min, Max	-0.6, 1.4

Visit		FAS Patients N=173
Week 49	n	64
	Mean	0.12
	SD	0.400
	SEM	0.050
	Median	0.00
	P25, P75	0.00, 0.05
	Min, Max	-0.6, 1.6

Total iron (µg/dL) during study (FAS population)

Visit		FAS Patients N=173
Baseline	n	173
	Mean	197.02
	SD	60.518
	SEM	4.601
	Median	194.00
	P25, P75	166.00, 230.00
	Min, Max	48.0, 409.0
Week 5	n	156
	Mean	245.61
	SD	84.583
	SEM	6.772
	Median	239.00
	P25, P75	194.50, 286.00
	Min, Max	54.0, 661.0
Week 9	n	156
	Mean	241.63
	SD	98.109
	SEM	7.855
	Median	231.50
	P25, P75	190.00, 288.50
	Min, Max	54.0, 889.0

Visit		FAS Patients N=173
Week 13	n	140
	Mean	236.15
	SD	88.447
	SEM	7.475
	Median	230.50
	P25, P75	192.50, 286.50
	Min, Max	54.0, 863.0
Week 17	n	136
	Mean	237.88
	SD	77.290
	SEM	6.628
	Median	235.50
	P25, P75	191.50, 276.00
	Min, Max	32.0, 594.0
Week 21	n	132
	Mean	250.42
	SD	135.942
	SEM	11.832
	Median	233.00
	P25, P75	191.00, 282.50
	Min, Max	27.0, 1188.0

Visit		FAS Patients N=173
Week 13	n	140
	Mean	236.15
	SD	88.447
	SEM	7.475
	Median	230.50
	P25, P75	192.50, 286.50
	Min, Max	54.0, 863.0
Week 17	n	136
	Mean	237.88
	SD	77.290
	SEM	6.628
	Median	235.50
	P25, P75	191.50, 276.00
	Min, Max	32.0, 594.0
Week 21	n	132
	Mean	250.42
	SD	135.942
	SEM	11.832
	Median	233.00
	P25, P75	191.00, 282.50
	Min, Max	27.0, 1188.0

Visit		FAS Patients N=173
Week 13	n	140
	Mean	236.15
	SD	88.447
	SEM	7.475
	Median	230.50
	P25, P75	192.50, 286.50
	Min, Max	54.0, 863.0
Week 17	n	136
	Mean	237.88
	SD	77.290
	SEM	6.628
	Median	235.50
	P25, P75	191.50, 276.00
	Min, Max	32.0, 594.0
Week 21	n	132
	Mean	250.42
	SD	135.942
	SEM	11.832
	Median	233.00
	P25, P75	191.00, 282.50
	Min, Max	27.0, 1188.0

Visit		FAS Patients N=173
Week 49	n	92
	Mean	227.23
	SD	104.476
	SEM	10.892
	Median	218.00
	P25, P75	180.00, 279.00
	Min, Max	48.0, 929.0
Week 53	n	91
	Mean	233.67
	SD	77.639
	SEM	8.139
	Median	221.00
	P25, P75	186.00, 275.00
	Min, Max	16.0, 455.0

Transferrin (mg/dL) during study (FAS population)

Visit		FAS Patients N=173
Baseline	n	171
	Mean	158.77
	SD	30.707
	SEM	2.348
	Median	156.00
	P25, P75	137.00, 183.00
	Min, Max	83.0, 244.0
Week 5	n	152
	Mean	161.51
	SD	30.711
	SEM	2.491
	Median	161.00
	P25, P75	136.00, 182.00
	Min, Max	88.0, 239.0
Week 9	n	157
	Mean	162.54
	SD	32.784
	SEM	2.616
	Median	157.00
	P25, P75	140.00, 180.00
	Min, Max	92.0, 256.0

Visit		FAS Patients N=173
Week 13	n	143
	Mean	165.76
	SD	31.027
	SEM	2.595
	Median	161.00
	P25, P75	140.00, 190.00
	Min, Max	108.0, 257.0
Week 17	n	136
	Mean	163.43
	SD	31.609
	SEM	2.710
	Median	161.00
	P25, P75	140.50, 185.00
	Min, Max	83.0, 253.0
Week 21	n	132
	Mean	163.27
	SD	33.154
	SEM	2.886
	Median	156.00
	P25, P75	138.00, 186.00
	Min, Max	90.0, 263.0

Visit		FAS Patients N=173
Week 25	n	123
	Mean	163.46
	SD	31.898
	SEM	2.876
	Median	160.00
	P25, P75	143.00, 184.00
	Min, Max	107.0, 266.0
Week 29	n	119
	Mean	160.32
	SD	30.194
	SEM	2.768
	Median	158.00
	P25, P75	140.00, 178.00
	Min, Max	98.0, 257.0
Week 33	n	118
	Mean	164.42
	SD	31.712
	SEM	2.919
	Median	161.00
	P25, P75	141.00, 184.00
	Min, Max	103.0, 257.0

Visit		FAS Patients N=173
Week 37	n	110
	Mean	160.16
	SD	34.846
	SEM	3.322
	Median	158.00
	P25, P75	133.00, 184.00
	Min, Max	88.0, 272.0
Week 41	n	103
	Mean	163.57
	SD	34.140
	SEM	3.364
	Median	163.00
	P25, P75	138.00, 180.00
	Min, Max	95.0, 283.0
Week 45	n	95
	Mean	165.35
	SD	34.563
	SEM	3.546
	Median	159.00
	P25, P75	140.00, 189.00
	Min, Max	102.0, 255.0

Visit		FAS Patients N=173
Week 49	n	92
	Mean	165.70
	SD	37.952
	SEM	3.957
	Median	160.00
	P25, P75	136.50, 188.50
	Min, Max	90.0, 289.0
Week 53	n	90
	Mean	165.49
	SD	35.966
	SEM	3.791
	Median	161.00
	P25, P75	137.00, 195.00
	Min, Max	99.0, 253.0

Absolute change from baseline to Week 53 in transferrin saturation (%) during study (FAS population)

Visit		FAS Patients N=173
Week 5	n	154
	Mean	-22.09
	SD	19.656
	SEM	1.584
	Median	-25.00
	P25, P75	-36.00, -13.00
	Min, Max	-69.0, 66.0
Week 9	n	155
	Mean	-21.63
	SD	22.104
	SEM	1.775
	Median	-27.00
	P25, P75	-37.00, -7.00
	Min, Max	-65.0, 45.0
Week 13	n	139
	Mean	-10.88
	SD	19.593
	SEM	1.662
	Median	-11.00
	P25, P75	-21.00, -1.00
	Min, Max	-73.0, 57.0

Visit		FAS Patients N=173
Week 17	n	135
	Mean	-20.85
	SD	20.874
	SEM	1.797
	Median	-21.00
	P25, P75	-34.00, -8.00
	Min, Max	-73.0, 43.0
Week 21	n	131
	Mean	-21.05
	SD	22.240
	SEM	1.943
	Median	-22.00
	P25, P75	-37.00, -8.00
	Min, Max	-67.0, 63.0
Week 25	n	124
	Mean	-12.17
	SD	22.701
	SEM	2.039
	Median	-11.00
	P25, P75	-27.00, -1.00
	Min, Max	-66.0, 58.0

Visit		FAS Patients N=173
Week 29	n	117
	Mean	-19.24
	SD	22.414
	SEM	2.072
	Median	-18.00
	P25, P75	-34.00, -5.00
	Min, Max	-70.0, 62.0
Week 33	n	116
	Mean	-21.65
	SD	22.636
	SEM	2.102
	Median	-24.50
	P25, P75	-36.00, -9.00
	Min, Max	-68.0, 64.0
Week 37	n	110
	Mean	-14.09
	SD	23.474
	SEM	2.238
	Median	-12.50
	P25, P75	-31.00, -2.00
	Min, Max	-68.0, 57.0

Visit		FAS Patients N=173
Week 41	n	102
	Mean	-18.75
	SD	22.872
	SEM	2.265
	Median	-22.50
	P25, P75	-33.00, -5.00
	Min, Max	-57.0, 72.0
Week 45	n	96
	Mean	-23.08
	SD	25.082
	SEM	2.560
	Median	-26.00
	P25, P75	-39.00, -6.00
	Min, Max	-77.0, 57.0
Week 49	n	91
	Mean	-13.91
	SD	21.851
	SEM	2.291
	Median	-12.00
	P25, P75	-27.00, -1.00
	Min, Max	-72.0, 65.0

Visit		FAS Patients N=173
Week 53	n	89
	Mean	-17.22
	SD	23.113
	SEM	2.450
	Median	-18.00
	P25, P75	-32.00, -4.00
	Min, Max	-69.0, 64.0

Transfusion requirements overall and by subgroups (FAS population)

		Screening (N=171)	Week 1 through 13 (N=147)	Week 14 through 26 (N=128)	Week 27 through 39 (N=113)	Week 40 through 52 (N=83)
Number of Patients Receiving Transfusions [n (%)]		163 (95.3%)	136 (92.5%)	119 (93.0%)	98 (86.7%)	72 (86.7%)
Number of Transfusions per Patient [n (%)]	0	8 (4.7%)	11 (7.5%)	9 (7.0%)	15 (13.3%)	11 (13.3%)
	>0-<5	99 (57.9%)	59 (40.1%)	54 (42.2%)	38 (33.6%)	29 (34.9%)
	5-<10	53 (31.0%)	69 (46.9%)	57 (44.5%)	54 (47.8%)	33 (39.8%)
	10-<15	10 (5.8%)	7 (4.8%)	8 (6.3%)	6 (5.3%)	10 (12.0%)
	>=15	1 (0.6%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

IWG hematologic response overall (Per Protocol Set)

	PPS Patients (N=91) n (%)
Did Patient Have A Hematologic Improvement While On Study	
Yes - Any Response	7 (7.7%)
- Major Response	6 (6.6%)
- Minor Response	1 (1.1%)
No Response	74 (81.3%)
Missing	10 (11.0%)

Trough Plasma ICL670 concentration (µmol/L) (FAS population)

Visit		FAS Patients N=173
Week 13	n	129
	Mean	34.471
	SD	38.6767
	SEM	3.4053
	Median	21.200
	Min, Max	0.00, 209.00
Week 25	n	114
	Mean	45.290
	SD	52.1370
	SEM	4.8831
	Median	26.700
	Min, Max	0.00, 331.00
Week 37	n	99
	Mean	42.831
	SD	46.4170
	SEM	4.6651
	Median	25.200
	Min, Max	0.00, 242.00
Week 49	n	77
	Mean	42.464
	SD	40.1061
	SEM	4.5705
	Median	30.700
	Min, Max	0.00, 223.00

Exposure to study drug (safety population)

	All Patients N = 173
Compliance – n (%)	
N	173
Mean (SD)	102 (26.74)
Median	99.6
Min, Max	28, 292

Prevalence of HFE Genetic Mutations

Number of Patients Tested [N]	Total	94
C282Y [n(%)]	Negative	85 (90.43%)
	Heterozygous	9 (9.57%)
	Homozygous	0 (0.00%)
H63D [n(%)]	Negative	70 (74.47%)
	Heterozygous	24 (25.53%)
	Homozygous	0 (0.00%)
S65C [n(%)]	Negative	92 (97.87%)
	Heterozygous	2 (2.13%)
	Homozygous	0 (0.00%)

Safety Results

Number (%) of patients with AEs overall and by system organ class (Safety Population)

	All Patients N = 173
No. (%) of patients studied	173 (100)
No. (%) of patients with AE(s)	171 (98.8)
System organ class affected – n (%)	
Blood and lymphatic system disorders	38 (22.0)
Cardiac disorders	24 (13.9)
Ear and labyrinth disorders	17 (9.8)
Endocrine disorders	2 (1.2)
Eye disorders	28 (16.2)
Gastrointestinal disorders	141 (81.5)
General disorders and administration site disorders	120 (69.4)
Hepatobiliary disorders	9 (5.2)
Immune system disorders	7 (4.0)
Infections and infestations	104 (60.1)
Injury, poisoning and procedural complications	37 (21.4)
Investigations	64 (37.0)
Metabolism and nutrition disorders	63 (36.4)
Musculoskeletal and connective tissue disorders	88 (50.9)
Neoplasms benign, malignant and unspecified	15 (8.7)
Nervous system disorders	66 (38.2)
Psychiatric disorders	38 (22.0)
Renal and urinary disorders	44 (25.4)
Reproductive system and breast disorders	13 (7.5)
Respiratory, thoracic, and mediastinal disorders	94 (54.3)
Skin and subcutaneous tissue disorders	82 (47.4)
Surgical and medical procedures	4 (2.3)
Vascular disorders	29 (16.8)

Summary of moderate or severe treatment-emergent adverse events occurring in 5% or more of patients (Safety Population)

	All Patients N = 173	
	Total (%)	**Moderate/Severe**
Fatigue	68 (39.3)	43 (24.9)
Diarrhea	104 (60.1)	34 (19.7)
Pneumonia	19 (11.0)	18 (10.4)
Pyrexia	32 (18.5)	18 (10.4)
Dyspnea	39 (22.5)	17 (9.8)
Blood creatinine increased	34 (19.7)	15 (8.7)
Urinary tract infection	21 (12.1)	14 (8.1)
Rash	32 (18.5)	14 (8.1)
Nausea	63 (36.4)	14 (8.1)
Edema peripheral	40 (23.1)	13 (7.5)
Thrombocytopenia	12 (6.9)	12 (6.9)
Anorexia	25 (14.5)	11 (6.4)
Back pain	20 (11.6)	10 (5.8)
Arthralgia	21 (12.1)	9 (5.2)
Neutropenia	10 (5.8)	9 (5.2)

Summary of treatment-related serious adverse events (Safety Population)

	Intensity	All Patients N = 173 n (%)
Any primary system organ class		
	Total	9 (5.2)
	Moderate	6 (3.5)
	Severe	3 (1.7)
AE preferred term		
Edema peripheral	Moderate	2 (1.2)
Thrombocytopenia	Moderate	1 (0.6)
Cardiac failure congestive	Moderate	1 (0.6)
Eyelid edema	Moderate	1 (0.6)
Diarrhea	Moderate	1 (0.6)
Diarrhea	Severe	1 (0.6)
Nausea	Moderate	1 (0.6)
Vomiting	Moderate	1 (0.6)
Chest pain	Mild	1 (0.6)
Pyrexia	Mild	1 (0.6)
Jaundice cholestatic	Severe	1 (0.6)
Drug hypersensitivity	Moderate	1 (0.6)
Anorexia	Moderate	1 (0.6)
Dehydration	Moderate	1 (0.6)
Presyncope	Moderate	1 (0.6)
Acute prerenal failure	Mild	1 (0.6)
Renal failure acute	Moderate	1 (0.6)
Renal impairment	Mild	1 (0.6)
Dyspnea	Mild	1 (0.6)
Rash macular	Severe	1 (0.6)
Rash popular	Severe	1 (0.6)
Rash pruritic	Severe	1 (0.6)
Urticaria	Moderate	1 (0.6)

Number (%) of patients with serious or significant adverse events (Safety Population)

	All Patients N = 173
Number (%) of patients with serious or other significant events	
Death	17 (9.8)
SAE	78 (45.1)
AE leading to discontinuation	54 (31.2)
AE leading to a dose adjustment or temporary interruption	82 (47.4)
AE leading to concomitant medication or non-drug therapy	154 (89.0)

Other Relevant Findings:

N/A

Conclusion:

Relative to the study objectives, the following conclusions are drawn:

- The median duration of exposure was 358 days and the mean duration was 267 days
- The mean dose (19.8 mg/kg/day) of Exjade taken over the study duration was close to the protocol-specified target dose of 20 mg/kg/day.
- 57 patients (32.9%) had dose increases from 20 to 30 mg/kg/day and 4 patients (2.3%) had dose increases from 30 to 40 mg/kg/day. 32 patients (18.5%) had dose reductions from 20 to 10 mg/kg/day.
- Exjade led to reductions in mean serum ferritin levels at most timepoints throughout the study. Median decreases of 4.7%, 8.1%, 19.5%, and 23.2% were observed in the FAS patients at Weeks 13, 25, 37, and 53, respectively. The observed serum ferritin values at these same timepoints in the per-protocol population corresponded to median decreases of 1.8%, 8.2%, 18.3%, and 23.2%, respectively,.
- 68 patients (39.3%) had abnormal LPIs at baseline. 90% of these patients normalized over the course of the study.
- Hematologic improvement was observed in 7 patients of 91 per-protocol evaluable patients. Six of these responses were major and 1 was minor. Four patients had an erythroid response, and 2 patients each had a platelet and neutrophil response. The lone minor response occurred among the erythroid responses.
- The most commonly observed treatment-related AEs were diarrhea, nausea, increased blood creatinine, rash, abdominal pain, vomiting, and anorexia.

Date of Clinical Study Report:

16-Jun-2009