

FIGURE 1

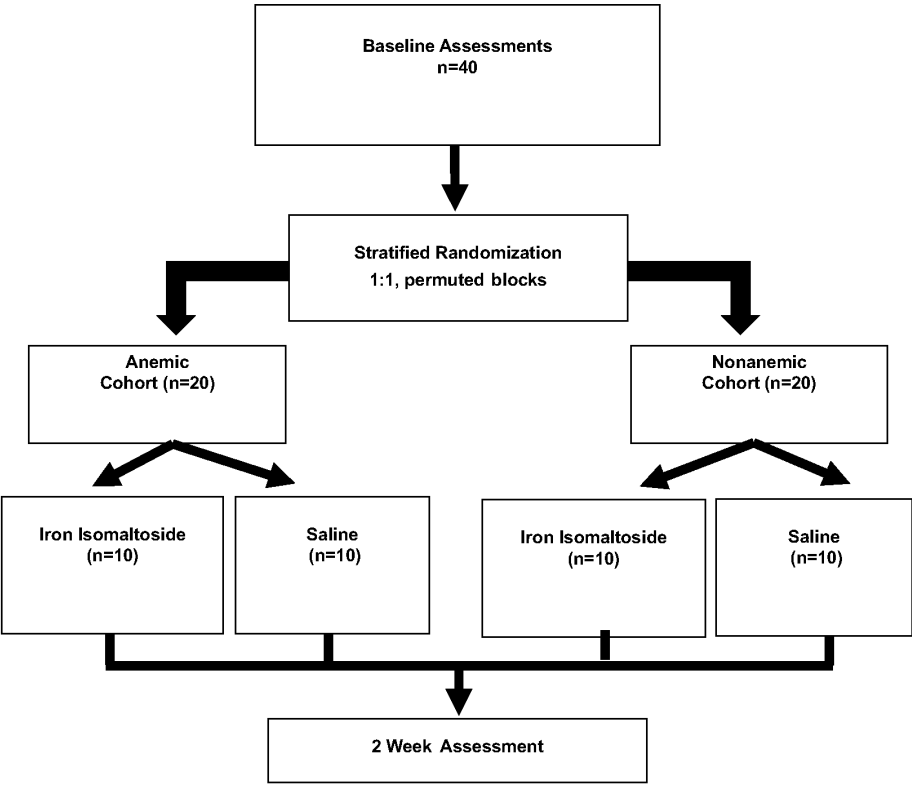


FIGURE 3

Variable	Total (n=25)	Iron (n=10)	Placebo (n=15)	P-value
Age, years	64 (58-77)	63 (57-72)	73.5 (64-79)	0.080
Male	18 (72)	8 (80)	10 (67)	0.659*
Body surface area (BSA), m ²	2.0 (1.8-2.1)	2.1 (1.8-2.2)	2.0 (1.8-2.1)	0.699
NYHA class				
II	14 (56)	2 (70)	7 (47)	0.424*
III	11 (44)	3 (30)	8 (53)	
Ischaemic aetiology	13 (52)	6 (60)	7 (47)	0.688*
Diabetes	12 (48)	5 (50)	7 (47)	0.999*
Hypertension	17 (68)	7 (70)	10 (67)	0.999*
Kidney disease	5 (20)	3 (30)	2 (13)	0.358*
ACE inhibitor/ARB	22(87)	8 (80)	14 (93)	0.543*
Beta Blocker	21 (84)	9 (90)	12 (80)	0.626*
Eplerenone/Spironolactone	16 (64)	6 (60)	10 (67)	0.999*
Amiodarone	2 (8)	0 (0)	2 (13)	0.500*
Anticoagulants	2 (8)	1 (10)	1 (7)	0.999*
Antiplatelets	19 (76)	9 (90)	10 (67)	0.345*
Systolic BP, mmHg	124 (113-134)	127 (113-139)	121 (111-134)	0.560
Diastolic BP, mmHg	70 (61-74)	70 (60-74)	70 (61-82)	0.868
Haemoglobin, g/L	127 (121 – 141)	122 (117-141)	133 (121-142)	0.454
Ferritin, ng/mL	52 (29-70)	32 (28-55)	61 (43-79)	0.063
TSAT, %	19 (14-32)	21 (19-33)	16 (12-32)	0.374
Creatinine, micromol/L	111 (87-142)	136 (104-149)	92 (80-142)	0.090
LVDD, cm	5.1 (4.9-5.9)	5.4 (4.8-6.2)	5.1 (4.9-5.7)	0.739
LVSD, cm	4 (3.7-4.9)	4.2 (4-5)	3.8 (3.5-4.5)	0.232
LA dimension, cm	3.7 (3-4.3)	3.7 (3.5-4.6)	3.7(2.8-4.1)	0.412
LA volume, ml	61.2 (52.7-79.6)	59.8 (52.7-71.4)	67.9 (41.4-85)	0.405
RA volume, ml	37.0 (29.2-61.6)	45.4 (36.7-58)	35.7 (20.9-63.0)	0.244
LA volume indexed for BSA, ml/m ²	32.1 (25.6-40.1)	32.0 (25.6-35.0)	32.1 (19.8-45.9)	0.657
RA volume indexed for BSA, ml/m ²	19.1 (14.6-29.4)	22.9 (17.9-26.6)	16.6 (11.2-30.4)	0.202
LVEF, %	39 (33-44)	39 (33-46)	42 (29-44)	0.979
Heart rate, beats/min	63 (54-69)	59 (49-63)	64 (60-74)	0.085
PR interval, msec	176 (164-200)	172 (160-188)	176 (164-200)	0.823
QRS Duration, msec	106 (88-136)	106 (98-136)	94 (82-150)	0.505
QT, msec	424 (412 – 464)	456 (416 – 464)	416 (400-468)	0.211
QTc, msec	453 (415-476)	444 (412-470)	453 (430-498)	0.471
Max P-wave duration, msec	118 (112 -127)	115 (112 – 122)	118 (116-129)	0.346
Min P-wave duration, msec	84 (74 – 90)	84 (79-99)	84 (73-88)	0.375
P-wave Dispersion, msec	45.2 (35.6-51.9)	44.8 (35.6-50.65)	45.85 (29.7-53.8)	0.868

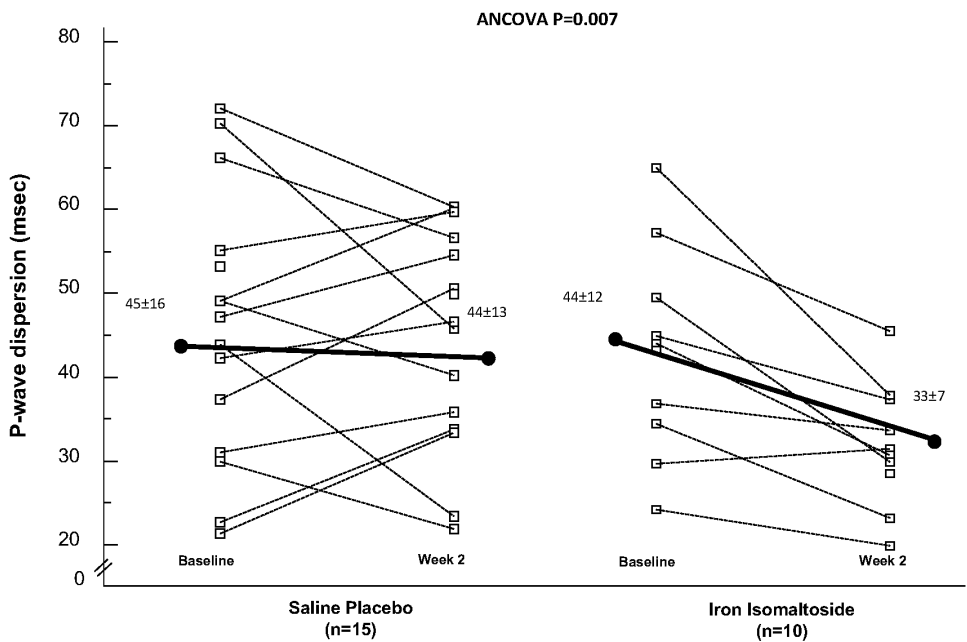
Data are mean±SD, median (interquartile range), or numbers (%)

P-value for comparison between iron and saline placebo group. Student's t-test used except for * Fisher Exact test

FIGURE 4

Endpoints	Difference (95% CI)	ANCOVA P-value
P-wave dispersion, msec	-10.2 (-17.3,-3.2)	0.007
QRS duration, msec	-2.4 (-8.8,4.0)	0.45
QTc, msec	-0.2 (-25.6,25.3)	0.99
PR interval, msec	4.9 (-7.5,17.4)	0.42
Heart rate, beats/min	-5.0 (-13.8,3.8)	0.25
LA dimension, cm	0 (-0.4,0.3)	0.96
LA volume, ml	3.9 (-5.6,13.3)	0.41
LA volume indexed to BSA, ml/m ²	2.3 (-2.7,7.4)	0.35
RA volume, ml	-4.1 (-17.5,9.4)	0.54
RA volume indexed to BSA, ml/m ²	-1.1 (-8.3,6.1)	0.76
LVSD, cm	0.3 (-0.2,0.8)	0.21
LVDD, cm	0.2 (-0.2,0.6)	0.34
LVEF, %	-1.2 (-5.2,2.7)	0.52

FIGURE 5



	CKD-04					IDA-03					CKD-04/IDA-03				
	Iron isomaltoside		Iron sucrose			Iron isomaltoside		Iron sucrose			Iron isomaltoside		Iron sucrose		
	N	%	N	%	p-value	N	%	N	%	p-value	N	%	N	%	p-value
Safety Analysis Set	1019		505			589		494			2008		1006		
Any composite cardiovascular event	42	4.12	35	6.92	0.0248	8	0.81	8	1.21	0.5695	50	2.49	41	4.10	0.0176
- Cardiac failure congestive	7	0.69	11	2.17	0.0002						7	0.35	11	1.10	0.0007
- Hypertension	11	1.08	10	1.98	0.1869	3	0.20	4	0.81	0.0595	13	0.65	14	1.40	0.0621
- Atrial fibrillation	3	0.29	6	1.19	0.0673	1	0.10	0		1.0000	4	0.20	6	0.60	0.0828
- Hypotension	2	0.20	3	0.40	0.6039	3	0.30	2	0.40	1.0000	5	0.25	4	0.40	0.4913
- Cardiac arrest	1	0.10	2	0.40	0.2571						1	0.05	2	0.20	0.2580

N: Number of patients
(%): Percentage of patients

Figure 6

		CKD-04					IDA-03					CKD-04/IDA-03				
		Iron isomaltonide		Iron sucrose		p-value	Iron isomaltonide		Iron sucrose		p-value	Iron isomaltonide		Iron sucrose		p-value
		N	%	N	%		N	%	N	%		N	%	N	%	
All patients	Safety Analysis Set	1018		506			989		494			2008		1000		
	Total	8	0.8	11	2.2	0.0273	0		1	0.2	0.3351	8	0.4	12	1.2	0.0157
	Worsening/exacerbation of heart failure	8	0.8	6	1.2	0.2292	0		1	0.2	0.3351	8	0.4	7	0.7	0.1406
All patients with CHF	Safety Analysis Set	159		86			10		6			160		82		
	Total	3	1.8	5	5.8	0.1342	0		1	16.7	0.3750	3	1.8	6	6.5	0.0714
	Worsening/exacerbation of heart failure	3	1.8	4	4.7	0.2453	0		1	16.7	0.3750	3	1.8	5	5.4	0.1857
All patients without CHF	Safety Analysis Set	861		420			979		488			1848		918		
	Total	5	0.6	6	1.4	0.1927	0		0			5	0.3	6	0.7	0.1948
	Worsening/exacerbation of heart failure	3	0.2	2	0.5	0.6552	0		0			3	0.2	2	0.2	0.5678
Patients with CV risk	Safety Analysis Set	219		160			36		15			345		173		
	Total	4	1.8	5	3.1	0.1588	0		1	7.7	0.3333	4	1.2	6	3.5	0.0917
	Worsening/exacerbation of heart failure	4	1.8	2	1.3	1.0000	0		1	7.7	0.3333	4	1.2	3	1.7	0.6512
CHF: Patients with congestive heart failure in medical history																
Preferred term: Cardio failure congestive																
Worsening/exacerbation: Verbatim contains 'worse', 'exacerbation' or 'exacerbation'																

Figure 7

			CKD-04				CKD-04/BA-03			
			95% CI				95% CI			
			Lower		Upper	p-value	Lower		Upper	p-value
Effect			OR	CI	CI		OR	CI	CI	
All patients	Total	Treatment: Iron isosulfosime vs Iron sucrose	0.86	0.15	0.01	0.0913	0.34	0.14	0.83	0.0186
		CNF in medical history y/n	0.98	1.80	0.00	0.0044	0.70	0.50	01.40	<.0001
	Worsening/exacerbation of heart failure	Treatment: Iron isosulfosime vs Iron sucrose	0.51	0.10	1.01	0.0006	0.44	0.15	1.84	0.1481
		CNF in medical history y/n	7.48	2.84	20.02	0.0007	17.15	5.66	52.87	<.0001
Patients with CV risk	Total	Treatment: Iron isosulfosime vs Iron sucrose	0.40	0.13	1.80	0.1788	0.34	0.09	1.32	0.0960
		CNF in medical history y/n	1.48	0.39	5.82	0.5610	1.80	0.51	6.89	0.3449
	Worsening/exacerbation of heart failure	Treatment: Iron isosulfosime vs Iron sucrose	1.05	0.10	5.80	0.0076	0.71	0.10	5.21	0.0006
		CNF in medical history y/n	3.49	0.48	18.74	0.0087	0.30	0.02	10.70	0.1950
Odds ratios estimated from logistic regression with treatment and CNF in medical history. Only estimates from converged models										
Preferred term: Cardiac failure congestive										
Worsening/exacerbation: Verbatim contains 'worse', 'exacerbation' or 'exacerbation'										

Figure 8

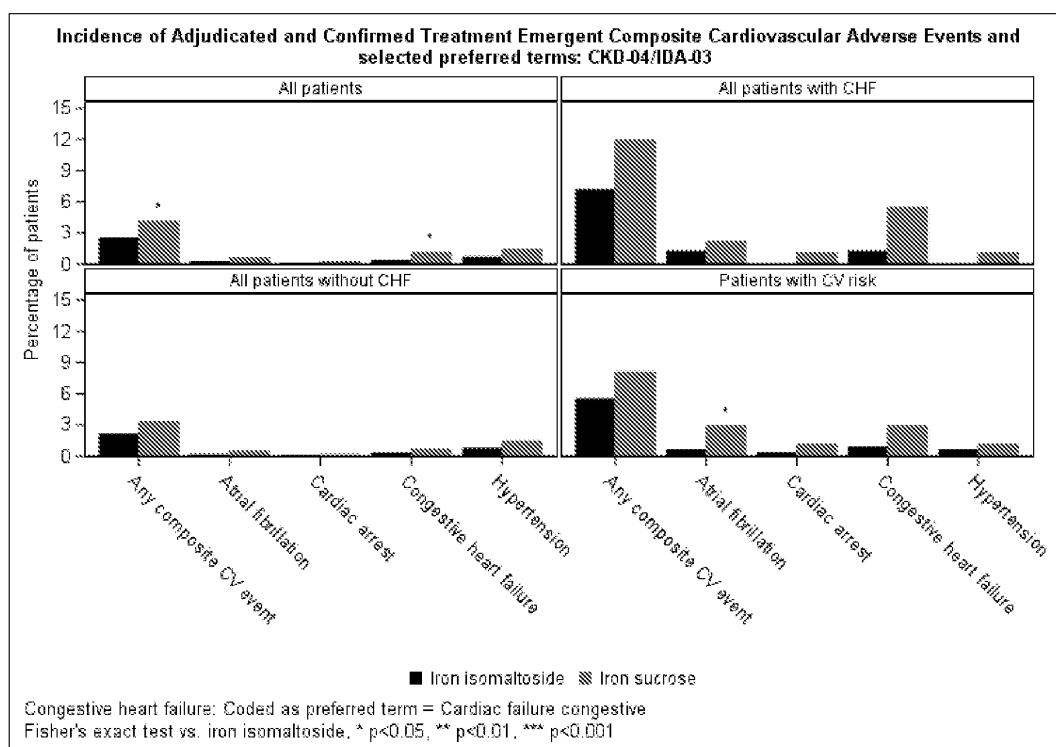


Figure 9

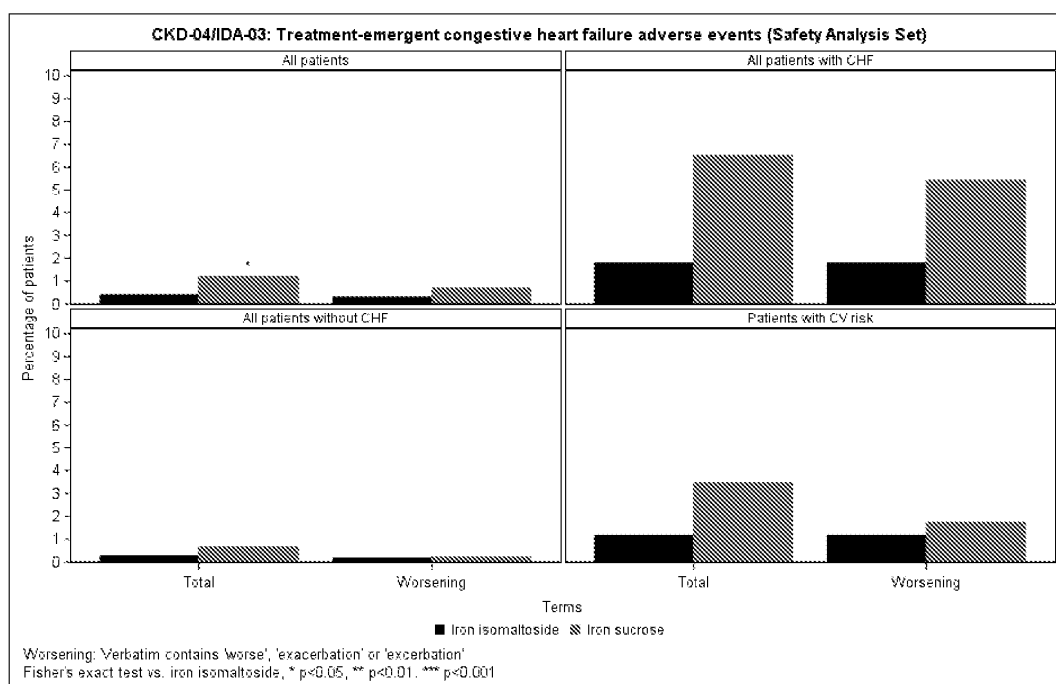
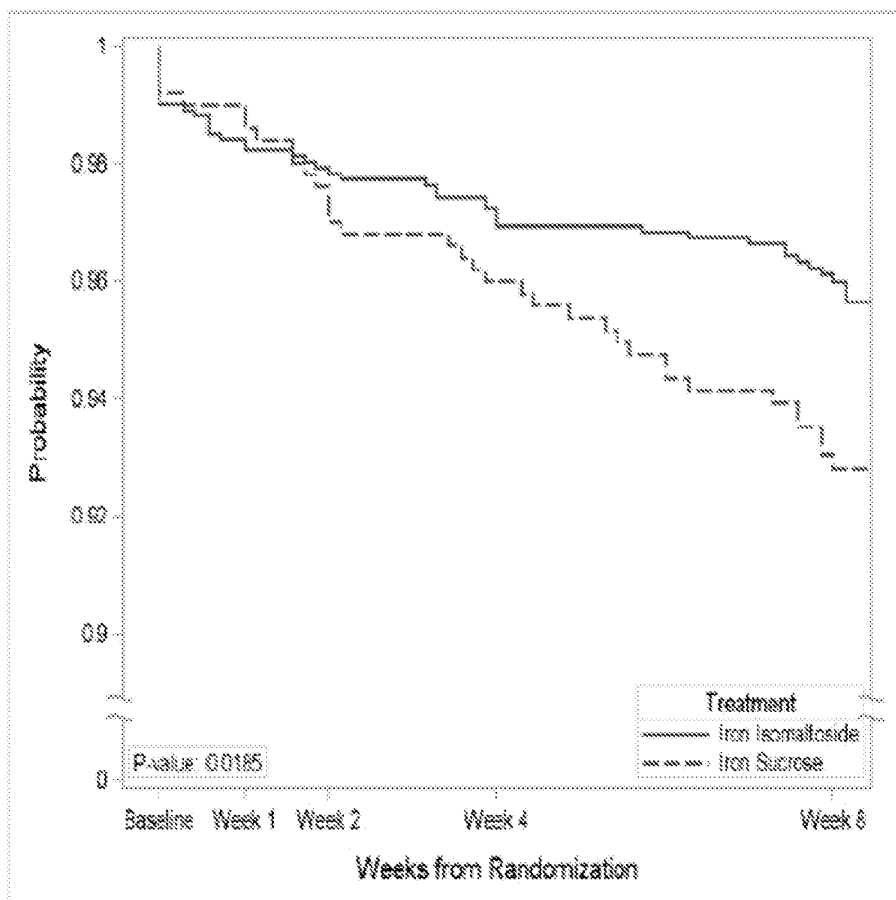


Figure 10

**Figure 11**

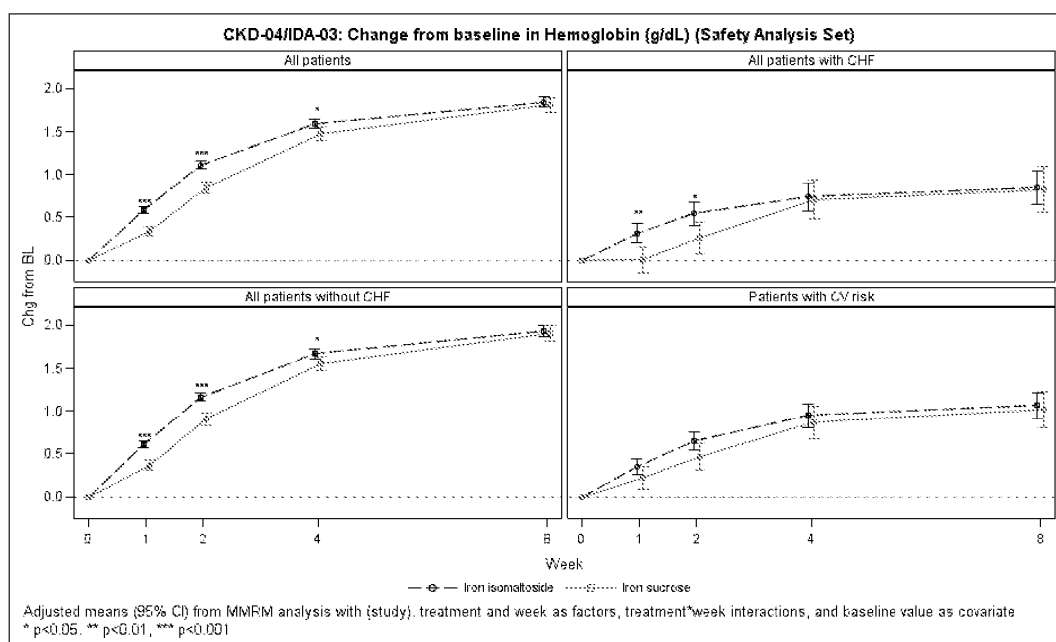


Figure 12

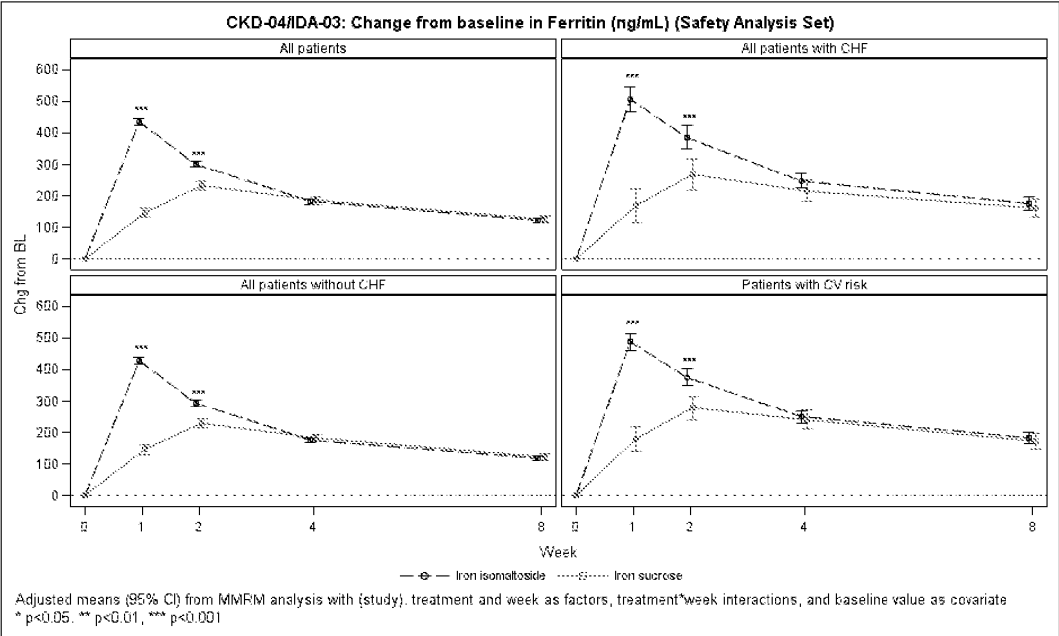


Figure 13

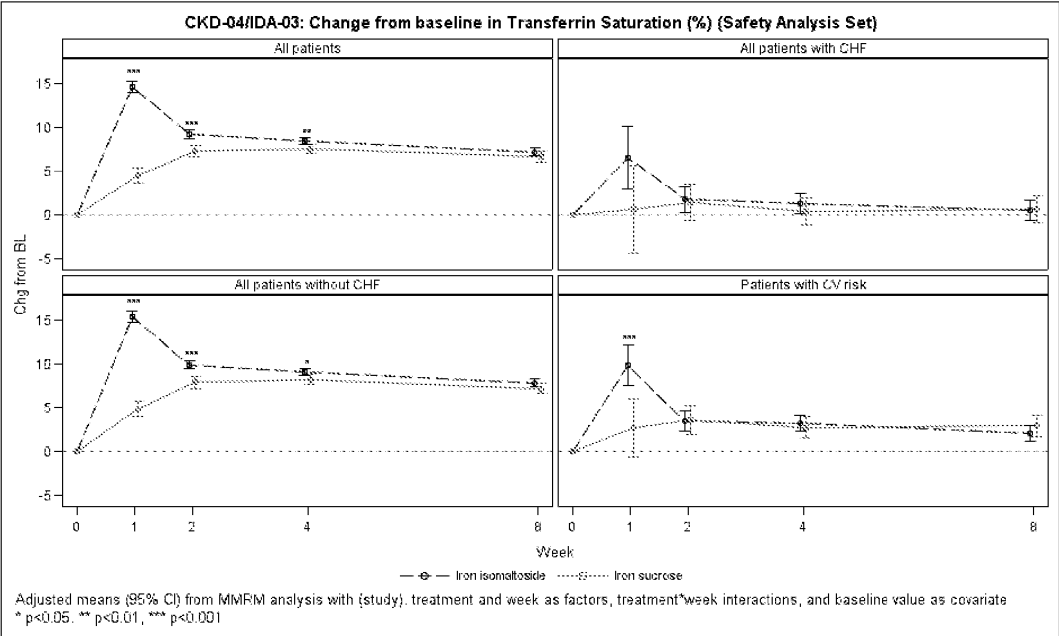


Figure 14

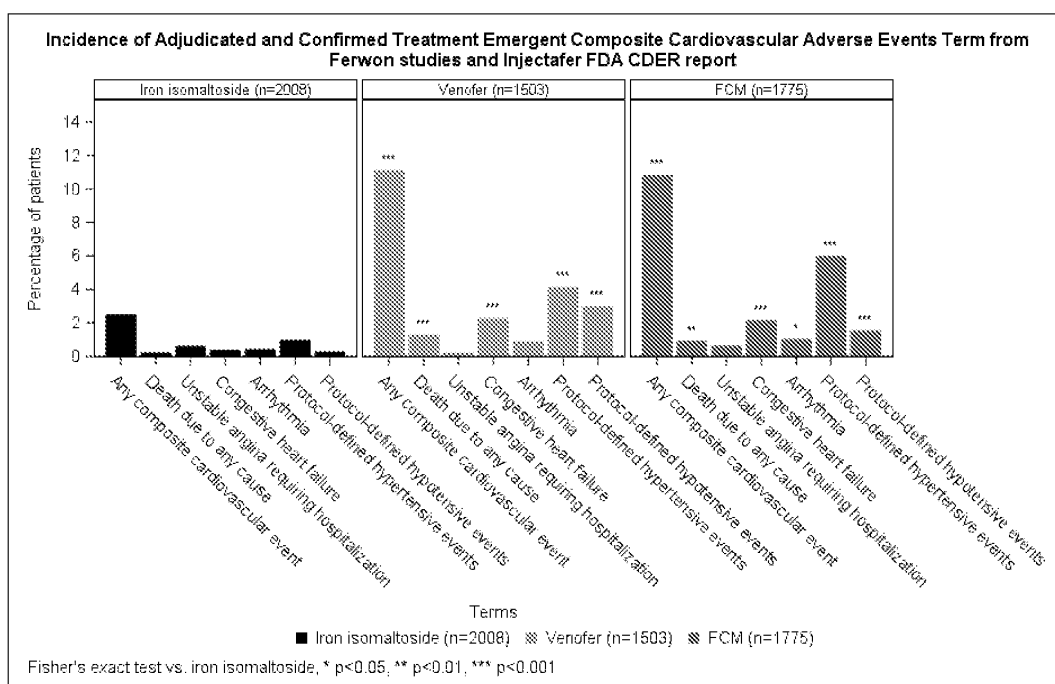


Figure 15

	Fervent studies performed with iron biomarkers												Injectate FDA CDER report July 2013			
	CKD-04				IDA-03				CKD-04/IDA-03				Venofor		FCM	
	N	%	Fisher's exact test Venofor	FCM	N	%	Fisher's exact test Venofor	FCM	N	%	Fisher's exact test Venofor	FCM	N	%	N	%
Safety Analysis Set	1610				889				2806				1503		1773	
Any composite cardiovascular event	40	4.1	<.0001	<.0001	8	0.9	<.0001	<.0001	50	0.5	<.0001	<.0001	167	11.1	136	10.0
Death due to any cause	3	0.3	0.0007	0.0001	1	0.1	0.0008	0.0002	4	0.2	0.0002	0.0001	19	1.3	16	0.9
Nonfatal myocardial infarction													14	0.9	9	0.8
Nonfatal stroke													3	0.2	3	0.2
Unstable angina requiring hospitalization	12	1.2	0.0005	0.1901					12	0.2	0.1140	0.0005	3	0.2	11	0.8
Congestive heart failure	7	0.7	0.0000	0.0007					7	0.3	<.0001	<.0001	34	2.3	53	2.1
Arrhythmias	7	0.7	0.0107	0.4154	1	0.1	0.0100	0.0032	8	0.4	0.0015	0.0007	13	0.9	19	1.0
Protocol-defined hypertensive events	17	1.7	0.0004	<.0001	0	0.2	<.0001	<.0001	10	0.9	<.0001	<.0001	60	4.1	106	8.0
Protocol-defined hypotensive events	2	0.2	<.0001	0.0004	2	0.3	<.0001	0.0012	0	0.3	<.0001	<.0001	45	3.0	57	1.5
Composite endpoint, excluding protocol-defined hypotensive and hypertensive events													70	4.7	70	4.4
Death, myocardial infarction, or stroke													36	2.4	26	1.2
N: Number of patients																
(%): Percentage of patients																
Injectate FDA CDER report July 2013, Table 35																
- Venofor: Primary maximum 750 mg FCM infusion trials																
- FCM: Primary maximum 750 mg FCM infusion trials																

Figure 16