

<b>Title of the Protocol:</b> Arginine Supplementation in Sickle Cell Anemia: Physiological and Prophylactic Effects
<b>CSCC Protocol Number:</b> November 28, 2005, Version 4.0
<b>Overview:</b> Nitric oxide is an important inflammatory mediator produced from arginine by nitric oxide synthase. Nitric oxide has a multitude of functions which could impact favorably on vaso-occlusion in sickle cell disease. Oral arginine has been shown to raise levels of nitric oxide. This study will test whether daily oral arginine results in an increase in nitric oxide and other beneficial effects in patients with sickle cell disease. The results of this study will serve as the basis for further clinical trials to determine if daily arginine is a beneficial therapy for patients with sickle cell disease.
<b>CSCC Protocol Chair:</b> Lori Styles, MD
<b>Intervention:</b> Patients will be treated with one of two doses of oral arginine (0.05 or 0.1 g/kg/day) or placebo for 12 weeks.
<b>IND Holder:</b> Lori Styles, MD
<b>IND Number:</b> 59,995
<b>Objectives:</b> <u>Primary Objective(s):</u> To assess the physiological effects (both beneficial and deleterious) of the administration of oral arginine in patients with SCD. <u>Secondary Objective(s):</u> To evaluate the effect of daily oral arginine on clinical vaso-occlusive events in SCD patients.
<b>Hypotheses/Estimates:</b> The hypothesis of this study is that oral arginine, given daily, will increase nitric oxide production which will, in turn, produce beneficial effects on vascular homeostasis in sickle cell disease.
<b>Criteria for Evaluation:</b> <u>Efficacy:</u> Primary Endpoint: Efficacy will be determined by changes in three laboratory parameters which will serve as surrogates for potential clinical benefit: nitric oxide, Gardos channel activity, and RBC density (Table 1). Secondary Endpoint: sVCAM, Nitrotyrosine, 8-iso-PGF2a, Ektacytometry, endothelin-1, fetal hemoglobin (Hb F) and echocardiogram results (Table 2) as well as clinical outcomes including hospitalizations, ER visits, and pain medication use. <u>Safety:</u> <b>SAFETY VARIABLES TO BE COLLECTED IN ADDITION TO ADVERSE EVENTS</b>
<b>Study Design:</b> Double-blinded, placebo-controlled, phase II trial in which 96 patients will be randomized to receive one of two doses of arginine or placebo for 12 weeks.
<b>Study Population:</b> Male or female Hb SS patients age 5 or more years <b>Major Inclusion Criteria:</b> History of at least one pain event in last 12 months <b>Major Exclusion Criteria:</b> Major organ dysfunction, treatment with hydroxyurea or transfusion within 3 months, history of recent priapism or retinopathy, pregnancy.
<b>Sample Size:</b> 96 (grouped into 48 children and 48 adults)
<b>Randomization:</b> Two doses of arginine hydrochloride will be evaluated in this trial. Patients in each age group (children and adult) will be treated with one of two doses of arginine (0.05 g/kg/day or 0.10 g/kg/day) or placebo divided for BID dosing. Sixteen patients will be randomized to each dose level and placebo (Fig. 1). Randomization will be stratified by center to preserve balance across treatment groups.
<b>Data Analyses:</b> Within each age group, we will evaluate differences in laboratory measures among the 3 groups (2 arginine groups and one placebo group) using random effects analysis of covariance techniques. Here the change in laboratory measures over each measurement time will act as the dependent variable of interest and the treatment status as the grouping factor. The baseline value of the laboratory measure and the time of the measurement visit will act as the fixed effect covariates and each patient will have a random intercept. Additionally, each laboratory measurement will be summarized by age group (pediatric and adult), treatment arm, and measurement time. No interim analyses are planned for this study. The SDCC will be responsible for data management and analysis.

**Figure 1. SUBJECT FLOW DIAGRAM**



**Table 1.** Schedule for assessing Primary and Secondary research lab outcomes\*

Test	Wk -4	Wk -2	Study Entry	Wk 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 14	Wk 16
<u>Free Radical Biology</u>										
<i>Nitrotyrosine</i>	X	X	X	X	X	X	X	X		X
<i>8-iso-PGF<sub>2α</sub></i>	X	X	X	X	X	X	X	X		X
<u>Endothelial Function</u>										
ET-1	X	X	X	X		X	X	X		X
sVCAM-1	X	X	X	X		X	X	X		X
<u>Erythrocyte Characterization</u>										
Advia	X	X	X	X	X	X	X	X	X	X
Ektacytometry	X	X	X	X	X	X	X	X	X	X
Gardos Channel	X	X	X	X	X	X	X	X	X	X
Fetal Hemoglobin	X	X	X			X	X	X		X

\* Whenever possible, outcome assessments will be made when the patient is in the steady state and not in the midst of a complication due to sickle cell disease.

**Table 2.** Laboratory monitoring of patients enrolled in the trial will occur as outlined in the table below:

Test	Week -4	Week -2	Study Entry	Week 1	Week 2	Week 4	Week 8	Week 12	Week 14	Week 16
NO—serum	X	X	X	X	X	X	X	X	X	X
Arginine	X	X	X	X	X	X	X	X	X	X
Arginase	X	X	X	X	X	X	X	X	X	X
CBC/retic	X		X	X	X	X	X	X	X	X
Chem panel	X		X	X	X	X	X	X		X
Urinalysis	X		X	X		X		X		X
Met Hb	X		X	X		X	X	X		
βHCG	X	X	X	X	X	X	X	X	X	
Echocardiogram*			X					X		

**\*The second echocardiogram will be performed at Week 12 only if the first echocardiogram is abnormal at Study Entry.**

**Table 3. Summary of Patient Demographic Data (Unredacted)**

	Age < 18 Years				Age ≥ 18 Years			
	Placebo	Low Dose	High Dose	Total	Placebo	Low Dose	High Dose	Total
	(N=18)	(N=14)	(N=18)	(N=50)	(N=20)	(N=21)	(N=16)	(N=57)
Age (years)								
N	18	14	18	50	20	21	16	57
Mean	11.6	11.9	12.5	12.0	29.4	31.4	28.2	29.8
SD	4.19	3.91	3.43	3.79	9.08	8.50	8.54	8.67
Median	10.9	12.3	13.1	12.5	27.5	31.4	24.2	29.5
(Min, Max)	( 6, 17)	( 5, 17)	( 6, 17)	( 5, 17)	(18, 49)	(20, 50)	(18, 45)	(18, 50)
Gender N (%)								
Male	10 ( 56%)	8 ( 57%)	12 ( 67%)	30 ( 60%)	8 ( 40%)	6 ( 29%)	3 ( 19%)	17 ( 30%)
Female	8 ( 44%)	6 ( 43%)	6 ( 33%)	20 ( 40%)	12 ( 60%)	15 ( 71%)	13 ( 81%)	40 ( 70%)
Diagnosis N (%)								
SB <sup>0</sup>	2 ( 11%)	0	2 ( 11%)	4 ( 8%)	0	2 ( 10%)	1 ( 6%)	3 ( 5%)
SS	16 ( 89%)	14 (100%)	16 ( 89%)	46 ( 92%)	20 (100%)	19 ( 90%)	15 ( 94%)	54 ( 95%)

**Table 4. Summary of Patient Demographic Data (Redacted)**

	Age < 18 Years				Age ≥ 18 Years			
	Placebo	Low Dose	High Dose	Total	Placebo	Low Dose	High Dose	Total
	(N=18)	(N=14)	(N=18)	(N=50)	(N=20)	(N=21)	(N=16)	(N=57)
Age (years)								
N	18	14	18	50	20	21	16	57
Mean	11.6	11.9	12.5	12.0	29.2	31.2	28.2	29.7
SD	4.19	3.91	3.43	3.79	8.68	8.03	8.49	8.34
Median	10.9	12.3	13.1	12.5	27.5	31.4	24.2	29.5
(Min, Max)	( 6, 17)	( 5, 17)	( 6, 17)	( 5, 17)	(18, 45)	(20, 45)	(18, 45)	(18, 45)
Gender N (%)								
Male	10 ( 56%)	8 ( 57%)	12 ( 67%)	30 ( 60%)	8 ( 40%)	6 ( 29%)	3 ( 19%)	17 ( 30%)
Female	8 ( 44%)	6 ( 43%)	6 ( 33%)	20 ( 40%)	12 ( 60%)	15 ( 71%)	13 ( 81%)	40 ( 70%)
Diagnosis N (%)								
SB <sup>0</sup>	2 ( 11%)	0	2 ( 11%)	4 ( 8%)	0	2 ( 10%)	1 ( 6%)	3 ( 5%)
SS	16 ( 89%)	14 (100%)	16 ( 89%)	46 ( 92%)	20 (100%)	19 ( 90%)	15 ( 94%)	54 ( 95%)

**Table 5. Weekly Summaries of Nitric Oxide Values in Patients <18 Years Old**

Nitric Oxide (NOx) (uM)	Placebo (N=18)	Low Dose (N=14)	High Dose (N=18)	All Subjects (N=50)	P-value [1]
<b>Visit 1</b>					
N	17	14	18	49	[P-L-H] 0.915[A]
Mean	20.81	22.58	21.11	21.42	[P-L] 0.687[A]
(SD)	(6.390)	(11.478)	(6.652)	(8.095)	[P-H] 0.927[A]
Min	10.5	5.9	11.5	5.9	[L-H] 0.749[A]
Median	21.20	21.50	19.25	20.50	
Max	38.0	51.9	30.7	51.9	
<b>Visit 2</b>					
N	15	14	18	47	[P-L-H] 0.159[A]
Mean	23.59	28.66	19.88	23.68	[P-L] 0.273[A]
(SD)	(9.489)	(28.575)	(4.786)	(16.728)	[P-H] 0.428[A]
Min	11.0	10.0	12.2	10.0	[L-H] 0.056[A]
Median	22.50	22.00	18.75	20.00	
Max	44.5	125.0	28.5	125.0	
<b>Visit 3</b>					
N	14	14	14	42	[P-L-H] 0.273[A]
Mean	23.79	30.73	24.41	26.31	[P-L] 0.151[A]
(SD)	(6.480)	(16.574)	(8.735)	(11.605)	[P-H] 0.940[A]
Min	11.6	9.1	12.1	9.1	[L-H] 0.177[A]
Median	23.65	24.90	22.75	23.75	
Max	32.0	66.5	39.5	66.5	
<b>Baseline [2]</b>					
N	18	14	18	50	
Mean	22.34	27.32	21.49	23.43	
(SD)	(5.228)	(11.055)	(5.090)	(7.553)	
Min	13.9	10.5	13.1	10.5	
Median	21.30	24.37	22.29	23.38	
Max	33.8	55.3	29.7	55.3	
<b>Visit 4</b>					
N	17	12	13	42	[P-L-H] 0.435[B]
Mean	23.90	21.09	20.92	22.17	[P-L] 0.213[B]
(SD)	(11.000)	(6.506)	(7.189)	(8.705)	[P-H] 0.408[B]
Min	7.0	10.5	10.9	7.0	[L-H] 0.675[B]
Median	24.00	22.60	18.70	22.00	
Max	49.0	29.0	37.5	49.0	
<b>Change from Base</b>					
N	17	12	13	42	
Mean	1.49	-6.83	-0.44	-1.49	
(SD)	(9.909)	(11.480)	(6.904)	(10.001)	
Min	-20.5	-31.6	-12.4	-31.6	
Median	1.95	-4.38	-0.75	-1.04	
Max	15.9	4.1	12.1	15.9	
<b>%Change from Base</b>					
N	17	12	13	42	[P-L-H] 0.695[B]
Mean	7.89	-16.05	0.11	-1.36	[P-L] 0.466[B]
(SD)	(42.482)	(32.731)	(30.200)	(36.851)	[P-H] 0.480[B]
Min	-74.5	-57.2	-53.1	-74.5	[L-H] 0.968[B]
Median	11.85	-13.34	-3.16	-4.06	
Max	70.6	38.6	48.5	70.6	

Nitric Oxide (NOx) (uM)	Placebo (N=18)	Low Dose (N=14)	High Dose (N=18)	All Subjects (N=50)	P-value [1]
<b>Visit 5</b>					
N	16	14	15	45	[P-L-H] 0.111[B]
Mean	26.94	21.41	22.14	23.62	[P-L] 0.042[B]
(SD)	(17.746)	(6.712)	(9.101)	(12.383)	[P-H] 0.160[B]
Min	12.9	11.1	10.5	10.5	[L-H] 0.511[B]
Median	22.00	20.85	21.50	22.00	
Max	74.0	33.5	39.5	74.0	
<b>Change from Base</b>					
N	16	14	15	45	
Mean	4.47	-5.91	0.56	-0.06	
(SD)	(14.727)	(9.247)	(7.474)	(11.639)	
Min	-14.5	-31.8	-10.8	-31.8	
Median	-0.88	-6.02	-1.90	-2.57	
Max	40.2	9.2	16.0	40.2	
<b>%Change from Base</b>					
N	16	14	15	45	[P-L-H] 0.357[B]
Mean	16.47	-16.83	3.50	1.79	[P-L] 0.167[B]
(SD)	(51.139)	(23.795)	(37.223)	(41.102)	[P-H] 0.323[B]
Min	-52.7	-57.5	-50.8	-57.5	[L-H] 0.681[B]
Median	-4.23	-21.66	-7.63	-10.45	
Max	124.2	37.7	79.8	124.2	
<b>Visit 6</b>					
N	17	14	17	48	[P-L-H] 0.713[B]
Mean	24.16	22.96	22.93	23.38	[P-L] 0.413[B]
(SD)	(6.864)	(7.015)	(8.026)	(7.206)	[P-H] 0.754[B]
Min	15.4	9.1	10.6	9.1	[L-H] 0.603[B]
Median	22.60	21.60	23.00	22.55	
Max	42.0	33.0	43.0	43.0	
<b>Change from Base</b>					
N	17	14	17	48	
Mean	1.75	-4.36	1.65	-0.07	
(SD)	(8.234)	(11.959)	(8.302)	(9.687)	
Min	-8.4	-34.8	-7.3	-34.8	
Median	-1.07	-2.27	-0.50	-1.25	
Max	23.2	10.8	23.6	23.6	
<b>%Change from Base</b>					
N	17	14	17	48	[P-L-H] 0.809[B]
Mean	13.02	-8.12	11.30	6.25	[P-L] 0.516[B]
(SD)	(41.318)	(33.973)	(44.147)	(40.636)	[P-H] 0.737[B]
Min	-34.1	-63.0	-33.7	-63.0	[L-H] 0.740[B]
Median	-6.07	-11.31	-2.13	-6.69	
Max	123.0	56.5	122.0	123.0	



Nitric Oxide (NOx) (uM)	Placebo (N=18)	Low Dose (N=14)	High Dose (N=18)	All Subjects (N=50)	P-value [1]
<b>Visit 7</b>					
N	16	13	14	43	[P-L-H] 0.802[B]
Mean	23.76	23.29	24.01	23.70	[P-L] 0.563[B]
(SD)	(13.935)	(10.713)	(7.578)	(10.955)	[P-H] 0.975[B]
Min	8.0	10.0	13.8	8.0	[L-H] 0.557[B]
Median	18.90	19.70	26.50	20.00	
Max	64.0	46.0	38.5	64.0	
<b>Change from Base</b>					
N	16	13	14	43	
Mean	1.29	-4.26	2.73	0.08	
(SD)	(10.620)	(12.586)	(7.420)	(10.550)	
Min	-12.0	-25.3	-13.9	-25.3	
Median	-0.59	-4.60	3.69	-1.30	
Max	30.2	27.7	13.6	30.2	
<b>%Change from Base</b>					
N	16	13	14	43	[P-L-H] 0.795[B]
Mean	1.98	-7.79	17.15	3.97	[P-L] 0.929[B]
(SD)	(37.693)	(52.892)	(37.767)	(43.017)	[P-H] 0.523[B]
Min	-43.6	-58.9	-48.9	-58.9	[L-H] 0.607[B]
Median	-3.08	-18.39	18.14	-4.59	
Max	89.2	150.9	94.0	150.9	
<b>Visit 8</b>					
N	16	12	13	41	[P-L-H] 0.078[B]
Mean	22.59	16.89	22.23	20.81	[P-L] 0.037[B]
(SD)	(9.953)	(8.451)	(8.377)	(9.185)	[P-H] 0.908[B]
Min	9.6	3.0	8.6	3.0	[L-H] 0.060[B]
Median	20.25	18.50	22.00	20.00	
Max	48.0	35.0	40.5	48.0	
<b>Change from Base</b>					
N	16	12	13	41	
Mean	0.11	-11.02	0.87	-2.91	
(SD)	(11.696)	(12.847)	(8.362)	(12.070)	
Min	-17.9	-35.3	-19.7	-35.3	
Median	-1.95	-10.57	2.60	-1.83	
Max	34.1	11.0	10.8	34.1	
<b>%Change from Base</b>					
N	16	12	13	41	[P-L-H] 0.175[B]
Mean	8.45	-33.36	7.20	-4.18	[P-L] 0.074[B]
(SD)	(70.353)	(36.628)	(35.278)	(54.403)	[P-H] 0.775[B]
Min	-65.1	-88.8	-69.6	-88.8	[L-H] 0.151[B]
Median	-9.23	-38.17	10.64	-8.00	
Max	246.2	46.0	52.4	246.2	

Nitric Oxide (NOx) (uM)	Placebo (N=18)	Low Dose (N=14)	High Dose (N=18)	All Subjects (N=50)	P-value [1]
Visit 9					
N	15	13	13	41	[P-L-H] 0.239[B]
Mean	26.61	25.94	21.42	24.75	[P-L] 0.389[B]
(SD)	(6.492)	(16.318)	(8.278)	(10.980)	[P-H] 0.092[B]
Min	13.2	8.4	8.0	8.0	[L-H] 0.436[B]
Median	26.00	22.50	21.00	25.00	
Max	36.0	71.2	37.5	71.2	
Change from Base					
N	15	13	13	41	
Mean	4.89	-1.61	0.05	1.29	
(SD)	(5.925)	(16.957)	(9.492)	(11.561)	
Min	-8.5	-21.2	-20.3	-21.2	
Median	5.00	-2.13	-0.10	1.43	
Max	13.7	47.0	21.8	47.0	
%Change from Base					
N	15	13	13	41	[P-L-H] 0.397[B]
Mean	24.86	-0.07	5.07	10.68	[P-L] 0.440[B]
(SD)	(29.319)	(64.270)	(48.652)	(48.718)	[P-H] 0.178[B]
Min	-30.9	-62.0	-71.7	-71.7	[L-H] 0.586[B]
Median	21.35	-15.09	-0.55	5.83	
Max	78.2	193.8	138.9	193.8	
Visit 10					
N	16	12	15	43	[P-L-H] 0.143[B]
Mean	27.44	23.54	21.13	24.15	[P-L] 0.127[B]
(SD)	(10.500)	(9.326)	(6.830)	(9.231)	[P-H] 0.072[B]
Min	9.6	12.8	10.5	9.6	[L-H] 0.878[B]
Median	29.80	21.90	21.00	23.50	
Max	50.5	38.5	34.5	50.5	
Change from Base					
N	16	12	15	43	
Mean	4.97	-4.22	-0.15	0.62	
(SD)	(12.866)	(14.432)	(9.418)	(12.544)	
Min	-17.9	-24.3	-17.8	-24.3	
Median	6.87	-6.50	-0.43	-0.40	
Max	29.4	28.0	18.8	29.4	
%Change from Base					
N	16	12	15	43	[P-L-H] 0.215[B]
Mean	31.61	3.43	7.28	15.26	[P-L] 0.334[B]
(SD)	(63.007)	(87.593)	(48.536)	(66.159)	[P-H] 0.082[B]
Min	-65.1	-52.0	-62.9	-65.1	[L-H] 0.515[B]
Median	34.45	-28.73	-3.00	-1.57	
Max	143.2	265.5	119.7	265.5	

**Table 6. Weekly Summaries of Nitric Oxide Values in Patients ≥ 18 years old**

Nitric Oxide (NOx) (uM)	Placebo (N=20)	Low Dose (N=21)	High Dose (N=16)	All Subjects (N=57)	P-value [1]
<b>Visit 1</b>					
N	11	9	10	30	[P-L-H] 0.222[A]
Mean	25.75	30.52	19.23	25.01	[P-L] 0.313[A]
(SD)	(6.266)	(24.666)	(11.769)	(15.669)	[P-H] 0.426[A]
Min	17.4	10.5	7.5	7.5	[L-H] 0.085[A]
Median	24.50	19.90	14.30	22.25	
Max	39.0	87.0	41.0	87.0	
<b>Visit 2</b>					
N	10	9	10	29	[P-L-H] 0.043[A]
Mean	32.85	23.10	16.50	24.19	[P-L] 0.110[A]
(SD)	(14.526)	(9.609)	(4.674)	(12.227)	[P-H] 0.014[A]
Min	12.6	8.0	8.9	8.0	[L-H] 0.377[A]
Median	34.55	24.20	17.85	21.50	
Max	52.5	39.1	22.5	52.5	
<b>Visit 3</b>					
N	10	10	10	30	[P-L-H] 0.904[A]
Mean	25.99	22.99	23.48	24.15	[P-L] 0.713[A]
(SD)	(12.708)	(4.564)	(8.044)	(8.857)	[P-H] 0.972[A]
Min	8.8	17.3	15.0	8.8	[L-H] 0.688[A]
Median	24.50	22.75	22.30	22.80	
Max	50.0	28.5	44.0	50.0	
<b>Baseline [2]</b>					
N	11	10	10	31	
Mean	27.47	25.63	19.74	24.38	
(SD)	(7.720)	(10.363)	(6.600)	(8.738)	
Min	17.4	13.5	13.2	13.2	
Median	27.33	24.05	18.60	21.23	
Max	39.7	46.5	35.8	46.5	
<b>Visit 4</b>					
N	9	7	8	24	[P-L-H] 0.804[B]
Mean	26.30	26.57	22.88	25.24	[P-L] 0.552[B]
(SD)	(14.555)	(9.410)	(7.675)	(10.846)	[P-H] 0.606[B]
Min	9.4	12.8	14.5	9.4	[L-H] 0.928[B]
Median	26.00	28.20	21.00	22.75	
Max	48.5	37.0	39.0	48.5	
<b>Change from Base</b>					
N	9	7	8	24	
Mean	-1.52	-1.05	2.85	0.07	
(SD)	(15.409)	(10.153)	(4.515)	(10.942)	
Min	-25.3	-12.0	-1.8	-25.3	
Median	-1.83	-0.70	1.57	0.07	
Max	28.0	13.9	10.4	28.0	
<b>%Change from Base</b>					
N	9	7	8	24	[P-L-H] 0.809[B]
Mean	-1.24	2.63	16.66	5.85	[P-L] 0.546[B]
(SD)	(61.483)	(37.434)	(29.194)	(44.757)	[P-H] 0.631[B]
Min	-71.7	-35.8	-8.4	-71.7	[L-H] 0.896[B]
Median	-8.63	-5.19	7.81	-0.30	
Max	136.6	67.5	73.3	136.6	

Nitric Oxide (NOx) (uM)	Placebo (N=20)	Low Dose (N=21)	High Dose (N=16)	All Subjects (N=57)	P-value [1]
<b>Visit 5</b>					
N	7	7	7	21	[P-L-H] 0.709[B]
Mean	22.24	23.96	20.34	22.18	[P-L] 0.416[B]
(SD)	(14.528)	(15.981)	(11.938)	(13.601)	[P-H] 0.774[B]
Min	10.1	7.1	9.5	7.1	[L-H] 0.595[B]
Median	14.90	20.50	15.50	15.50	
Max	52.0	48.0	43.0	52.0	
<b>Change from Base</b>					
N	7	7	7	21	
Mean	-0.47	0.66	-0.33	-0.05	
(SD)	(12.658)	(13.990)	(6.952)	(11.025)	
Min	-14.7	-15.9	-9.7	-15.9	
Median	-4.90	-3.80	-0.90	-3.80	
Max	24.7	27.4	7.3	27.4	
<b>%Change from Base</b>					
N	7	7	7	21	[P-L-H] 0.664[B]
Mean	-4.99	3.58	-2.91	-1.44	[P-L] 0.374[B]
(SD)	(48.932)	(64.944)	(37.454)	(49.178)	[P-H] 0.759[B]
Min	-49.6	-57.8	-50.5	-57.8	[L-H] 0.557[B]
Median	-28.16	-19.69	-6.04	-19.69	
Max	90.2	133.0	55.7	133.0	
<b>Visit 6</b>					
N	5	8	8	21	[P-L-H] 0.793[B]
Mean	29.18	24.08	22.95	24.86	[P-L] 0.498[B]
(SD)	(21.198)	(11.819)	(7.240)	(12.786)	[P-H] 0.712[B]
Min	8.6	12.5	14.1	8.6	[L-H] 0.728[B]
Median	23.30	21.00	23.50	23.30	
Max	65.0	49.6	37.0	65.0	
<b>Change from Base</b>					
N	5	8	8	21	
Mean	5.73	-2.12	2.30	1.43	
(SD)	(22.019)	(6.579)	(6.309)	(11.663)	
Min	-8.9	-15.0	-9.9	-15.0	
Median	-5.33	-1.00	3.88	1.17	
Max	43.8	4.0	9.8	43.8	
<b>%Change from Base</b>					
N	5	8	8	21	[P-L-H] 0.688[B]
Mean	29.93	-5.20	16.67	11.50	[P-L] 0.399[B]
(SD)	(103.102)	(25.989)	(35.619)	(54.896)	[P-H] 0.712[B]
Min	-50.8	-54.5	-41.2	-54.5	[L-H] 0.592[B]
Median	-19.51	-5.03	20.56	3.26	
Max	206.1	29.6	74.7	206.1	

Nitric Oxide (NOx) (uM)	Placebo (N=20)	Low Dose (N=21)	High Dose (N=16)	All Subjects (N=57)	P-value [1]
Visit 7					
N	6	7	5	18	[P-L-H] 0.530[B]
Mean	26.53	17.23	23.10	21.96	[P-L] 0.298[B]
(SD)	(10.679)	(3.355)	(9.263)	(8.642)	[P-H] 0.886[B]
Min	14.3	12.5	9.0	9.0	[L-H] 0.402[B]
Median	26.00	18.50	25.00	19.90	
Max	45.6	22.5	34.0	45.6	
Change from Base					
N	6	7	5	18	
Mean	2.75	-6.07	1.67	-0.98	
(SD)	(9.247)	(6.301)	(8.256)	(8.534)	
Min	-8.8	-15.4	-8.8	-15.4	
Median	1.72	-1.70	3.83	-1.25	
Max	18.3	-0.8	12.2	18.3	
%Change from Base					
N	6	7	5	18	[P-L-H] 0.565[B]
Mean	11.91	-21.28	9.91	-1.55	[P-L] 0.336[B]
(SD)	(34.036)	(17.998)	(37.040)	(32.261)	[P-H] 0.942[B]
Min	-26.0	-46.5	-31.6	-46.5	[L-H] 0.404[B]
Median	8.47	-9.26	23.00	-7.83	
Max	66.8	-4.1	55.7	66.8	
Visit 8					
N	6	6	6	18	[P-L-H] 0.368[B]
Mean	29.32	31.03	20.20	26.85	[P-L] 0.637[B]
(SD)	(10.991)	(20.581)	(11.237)	(14.872)	[P-H] 0.353[B]
Min	15.4	18.0	13.0	13.0	[L-H] 0.166[B]
Median	28.50	25.25	16.50	23.80	
Max	48.0	72.5	42.7	72.5	
Change from Base					
N	6	6	6	18	
Mean	5.53	4.12	-0.14	3.17	
(SD)	(10.123)	(13.415)	(4.017)	(9.695)	
Min	-4.3	-12.9	-3.8	-12.9	
Median	1.70	1.00	-1.03	0.78	
Max	20.7	26.0	6.9	26.0	
%Change from Base					
N	6	6	6	18	[P-L-H] 0.296[B]
Mean	25.76	19.22	-3.07	13.97	[P-L] 0.722[B]
(SD)	(44.895)	(45.708)	(16.543)	(38.067)	[P-H] 0.250[B]
Min	-12.7	-34.1	-22.0	-34.1	[L-H] 0.136[B]
Median	7.21	6.07	-5.99	3.74	
Max	89.1	90.4	19.2	90.4	

Nitric Oxide (NOx) (uM)	Placebo (N=20)	Low Dose (N=21)	High Dose (N=16)	All Subjects (N=57)	P-value [1]
Visit 9					
N	5	5	4	14	[P-L-H] 0.798[B]
Mean	31.70	25.34	28.15	28.41	[P-L] 0.580[B]
(SD)	(5.869)	(7.792)	(11.518)	(8.228)	[P-H] 0.946[B]
Min	24.0	18.5	18.0	18.0	[L-H] 0.553[B]
Median	32.00	24.10	25.05	26.80	
Max	38.5	38.0	44.5	44.5	
Change from Base					
N	5	5	4	14	
Mean	6.64	-0.16	5.31	3.83	
(SD)	(7.767)	(14.039)	(14.336)	(11.682)	
Min	-5.8	-19.4	-8.7	-19.4	
Median	6.53	-1.53	2.33	4.72	
Max	14.8	18.7	25.3	25.3	
%Change from Base					
N	5	5	4	14	[P-L-H] 0.889[B]
Mean	31.26	13.84	33.09	25.56	[P-L] 0.827[B]
(SD)	(31.510)	(57.853)	(68.142)	(49.896)	[P-H] 0.783[B]
Min	-17.2	-51.2	-24.4	-51.2	[L-H] 0.628[B]
Median	37.40	-5.47	12.47	21.30	
Max	69.5	96.9	131.8	131.8	
Visit 10					
N	6	6	6	18	[P-L-H] 0.312[B]
Mean	31.33	25.18	17.13	24.55	[P-L] 0.319[B]
(SD)	(12.164)	(9.208)	(7.009)	(10.895)	[P-H] 0.135[B]
Min	19.5	16.0	10.5	10.5	[L-H] 0.614[B]
Median	29.00	23.95	15.25	22.45	
Max	52.0	37.7	26.5	52.0	
Change from Base					
N	6	6	6	18	
Mean	7.03	-4.27	-4.28	-0.51	
(SD)	(9.151)	(11.514)	(7.090)	(10.416)	
Min	-0.7	-21.9	-11.5	-21.9	
Median	3.87	-0.08	-4.22	-0.04	
Max	24.7	9.7	7.3	24.7	
%Change from Base					
N	6	6	6	18	[P-L-H] 0.345[B]
Mean	27.70	-8.40	-17.40	0.63	[P-L] 0.549[B]
(SD)	(33.924)	(31.819)	(30.570)	(36.239)	[P-H] 0.148[B]
Min	-3.5	-57.8	-47.8	-57.8	[L-H] 0.393[B]
Median	13.15	-0.94	-24.56	-0.60	
Max	90.2	34.5	38.0	90.2	

**Table 7. Weekly Summaries of Gardos Channel Values in Patients <18 Years Old**

Gardos Channel Activity (mmol/10 13 cells x min)	Placebo (N=18)	Low Dose (N=14)	High Dose (N=18)	All Subjects (N=50)	P-value [1]
<b>Visit 1</b>					
N	17	14	18	49	[P-L-H] 0.821[A]
Mean	0.7237	0.7261	0.7579	0.7370	[P-L] 0.977[A]
(SD)	(0.17808)	(0.18306)	(0.20399)	(0.18613)	[P-H] 0.573[A]
Min	0.432	0.405	0.474	0.405	[L-H] 0.613[A]
Median	0.7130	0.7235	0.7110	0.7130	
Max	1.061	1.190	1.249	1.249	
<b>Visit 2</b>					
N	15	14	16	45	[P-L-H] 0.523[A]
Mean	0.7199	0.6488	0.6782	0.6829	[P-L] 0.261[A]
(SD)	(0.18815)	(0.16816)	(0.13469)	(0.16324)	[P-H] 0.480[A]
Min	0.461	0.517	0.430	0.430	[L-H] 0.654[A]
Median	0.7070	0.6155	0.6840	0.6660	
Max	1.172	1.031	0.999	1.172	
<b>Visit 3</b>					
N	14	14	13	41	[P-L-H] 0.605[A]
Mean	0.7404	0.6752	0.7165	0.7105	[P-L] 0.323[A]
(SD)	(0.10852)	(0.10825)	(0.22403)	(0.15314)	[P-H] 0.732[A]
Min	0.585	0.517	0.257	0.257	[L-H] 0.534[A]
Median	0.7195	0.6590	0.6450	0.6750	
Max	0.906	0.866	1.091	1.091	
<b>Baseline [2]</b>					
N	18	14	18	50	
Mean	0.7332	0.6834	0.7191	0.7142	
(SD)	(0.09553)	(0.08075)	(0.12909)	(0.10531)	
Min	0.616	0.558	0.472	0.472	
Median	0.7293	0.6890	0.7068	0.7045	
Max	0.914	0.799	0.998	0.998	
<b>Visit 4</b>					
N	16	12	13	41	[P-L-H] 0.589[B]
Mean	0.7048	0.7626	0.7763	0.7444	[P-L] 0.395[B]
(SD)	(0.23849)	(0.15272)	(0.24364)	(0.21589)	[P-H] 0.371[B]
Min	0.432	0.535	0.488	0.432	[L-H] 0.985[B]
Median	0.6320	0.8015	0.7250	0.6930	
Max	1.374	0.968	1.181	1.374	
<b>Change from Base</b>					
N	16	12	13	41	
Mean	-0.0284	0.0807	0.0740	0.0360	
(SD)	(0.24021)	(0.14349)	(0.18145)	(0.19977)	
Min	-0.208	-0.163	-0.198	-0.208	
Median	-0.1140	0.0978	0.0160	0.0100	
Max	0.758	0.257	0.396	0.758	
<b>%Change from Base</b>					
N	16	12	13	41	[P-L-H] 0.703[B]
Mean	-2.8425	12.3331	10.1119	5.7066	[P-L] 0.451[B]
(SD)	(37.10639)	(21.26766)	(23.84838)	(29.32672)	[P-H] 0.505[B]
Min	-30.472	-23.389	-22.601	-30.472	[L-H] 0.919[B]
Median	-12.9691	13.0804	3.3898	1.6835	
Max	123.173	41.006	50.510	123.173	

Gardos Channel					
Activity (mmol/10 13 cells x min)	Placebo (N=18)	Low Dose (N=14)	High Dose (N=18)	All Subjects (N=50)	P-value [1]
Visit 5					
N	16	14	15	45	[P-L-H] 0.287[B]
Mean	0.7238	0.8049	0.6769	0.7334	[P-L] 0.305[B]
(SD)	(0.27989)	(0.20810)	(0.21942)	(0.23993)	[P-H] 0.567[B]
Min	0.299	0.475	0.443	0.299	[L-H] 0.118[B]
Median	0.6595	0.8295	0.6420	0.6800	
Max	1.483	1.154	1.372	1.483	
Change from Base					
N	16	14	15	45	
Mean	0.0010	0.1215	-0.0411	0.0245	
(SD)	(0.26583)	(0.22988)	(0.22594)	(0.24618)	
Min	-0.363	-0.256	-0.187	-0.363	
Median	-0.0300	0.1077	-0.1183	-0.0297	
Max	0.667	0.531	0.722	0.722	
%Change from Base					
N	16	14	15	45	[P-L-H] 0.300[B]
Mean	0.3275	19.5350	-4.0668	4.8384	[P-L] 0.268[B]
(SD)	(36.57650)	(34.85009)	(33.72629)	(35.77706)	[P-H] 0.666[B]
Min	-54.176	-32.012	-26.451	-54.176	[L-H] 0.132[B]
Median	-4.5708	14.9064	-16.4034	-4.8276	
Max	81.629	85.332	111.185	111.185	
Visit 6					
N	16	14	17	47	[P-L-H] 0.902[B]
Mean	0.6471	0.6704	0.6722	0.6631	[P-L] 0.679[B]
(SD)	(0.23808)	(0.20734)	(0.20508)	(0.21306)	[P-H] 0.715[B]
Min	0.399	0.375	0.450	0.375	[L-H] 0.945[B]
Median	0.5920	0.6055	0.6510	0.6040	
Max	1.440	1.270	1.155	1.440	
Change from Base					
N	16	14	17	47	
Mean	-0.0854	-0.0129	-0.0418	-0.0481	
(SD)	(0.26325)	(0.18307)	(0.25771)	(0.23674)	
Min	-0.382	-0.238	-0.413	-0.413	
Median	-0.1262	-0.0318	-0.0293	-0.0800	
Max	0.752	0.519	0.620	0.752	
%Change from Base					
N	16	14	17	47	[P-L-H] 0.893[B]
Mean	-9.9697	-2.2143	-2.1536	-4.8325	[P-L] 0.864[B]
(SD)	(36.69353)	(25.29062)	(38.97108)	(34.08792)	[P-H] 0.638[B]
Min	-48.879	-38.792	-47.856	-48.879	[L-H] 0.780[B]
Median	-18.3311	-4.9139	-4.0497	-10.2273	
Max	109.404	69.183	115.888	115.888	



Gardos Channel					
Activity (mmol/10 13 cells x min)	Placebo (N=18)	Low Dose (N=14)	High Dose (N=18)	All Subjects (N=50)	P-value [1]
Visit 7					
N	15	13	14	42	[P-L-H] 0.693[B]
Mean	0.7229	0.6976	0.6591	0.6938	[P-L] 0.814[B]
(SD)	(0.23948)	(0.18988)	(0.18882)	(0.20534)	[P-H] 0.403[B]
Min	0.390	0.356	0.428	0.356	[L-H] 0.567[B]
Median	0.6740	0.6810	0.6330	0.6660	
Max	1.357	0.996	1.091	1.357	
Change from Base					
N	15	13	14	42	
Mean	0.0025	0.0148	-0.0555	-0.0130	
(SD)	(0.26822)	(0.18699)	(0.21691)	(0.22509)	
Min	-0.345	-0.331	-0.350	-0.350	
Median	-0.0647	0.0193	-0.0563	-0.0343	
Max	0.669	0.373	0.445	0.669	
%Change from Base					
N	15	13	14	42	[P-L-H] 0.744[B]
Mean	2.2947	2.7174	-5.5290	-0.1823	[P-L] 0.734[B]
(SD)	(38.42466)	(27.54131)	(29.69438)	(31.94394)	[P-H] 0.443[B]
Min	-40.230	-48.180	-40.242	-48.180	[L-H] 0.686[B]
Median	-7.5930	2.9219	-7.8698	-5.2316	
Max	97.334	59.957	68.885	97.334	
Visit 8					
N	15	11	13	39	[P-L-H] 0.468[B]
Mean	0.7665	0.6637	0.7001	0.7154	[P-L] 0.249[B]
(SD)	(0.23514)	(0.17791)	(0.29809)	(0.24217)	[P-H] 0.367[B]
Min	0.543	0.405	0.423	0.405	[L-H] 0.775[B]
Median	0.6830	0.6530	0.5830	0.6780	
Max	1.502	1.056	1.507	1.507	
Change from Base					
N	15	11	13	39	
Mean	0.0461	-0.0105	-0.0245	0.0066	
(SD)	(0.27260)	(0.18322)	(0.35768)	(0.27865)	
Min	-0.274	-0.283	-0.301	-0.301	
Median	0.0043	-0.0270	-0.1790	-0.0270	
Max	0.886	0.305	0.972	0.972	
%Change from Base					
N	15	11	13	39	[P-L-H] 0.468[B]
Mean	9.0396	-0.6891	2.8994	4.2489	[P-L] 0.218[B]
(SD)	(41.98285)	(26.64643)	(61.81302)	(45.38215)	[P-H] 0.575[B]
Min	-33.497	-35.392	-41.601	-41.601	[L-H] 0.496[B]
Median	0.6098	-4.8387	-26.5579	-4.8387	
Max	143.963	45.853	181.682	181.682	

Gardos Channel					
Activity (mmol/10 13 cells x min)	Placebo (N=18)	Low Dose (N=14)	High Dose (N=18)	All Subjects (N=50)	P-value [1]
Visit 9					
N	13	13	13	39	[P-L-H] 0.712[B]
Mean	0.7078	0.6922	0.7797	0.7266	[P-L] 0.809[B]
(SD)	(0.20633)	(0.22587)	(0.22102)	(0.21557)	[P-H] 0.572[B]
Min	0.424	0.413	0.533	0.413	[L-H] 0.423[B]
Median	0.6900	0.6620	0.7920	0.6900	
Max	1.076	1.271	1.361	1.361	
Change from Base					
N	13	13	13	39	
Mean	-0.0118	0.0094	0.0552	0.0176	
(SD)	(0.26032)	(0.21354)	(0.28730)	(0.25033)	
Min	-0.416	-0.274	-0.312	-0.416	
Median	-0.0345	-0.0310	-1.0090	-0.0310	
Max	0.455	0.520	0.826	0.826	
%Change from Base					
N	13	13	13	39	[P-L-H] 0.506[B]
Mean	1.2529	1.6001	13.4588	5.4373	[P-L] 0.666[B]
(SD)	(36.02933)	(30.26069)	(50.55453)	(39.23294)	[P-H] 0.467[B]
Min	-45.684	-39.884	-35.866	-45.684	[L-H] 0.249[B]
Median	-4.4202	-5.5556	-1.0936	-4.4202	
Max	73.176	69.316	154.393	154.393	
Visit 10					
N	15	12	15	42	[P-L-H] 0.986[B]
Mean	0.7631	0.7666	0.7819	0.7708	[P-L] 0.963[B]
(SD)	(0.27255)	(0.21179)	(0.26489)	(0.24785)	[P-H] 0.868[B]
Min	0.338	0.442	0.410	0.338	[L-H] 0.912[B]
Median	0.7460	0.7560	0.7540	0.7500	
Max	1.268	1.192	1.268	1.268	
Change from Base					
N	15	12	15	42	
Mean	0.0427	0.0935	0.0698	0.0669	
(SD)	(0.25810)	(0.25325)	(0.30204)	(0.26745)	
Min	-0.310	-0.245	-0.318	-0.318	
Median	0.0247	0.0207	0.0400	0.0323	
Max	0.528	0.594	0.733	0.733	
%Change from Base					
N	15	12	15	42	[P-L-H] 0.893[B]
Mean	6.0336	16.8045	13.8549	11.9043	[P-L] 0.766[B]
(SD)	(35.68018)	(41.12799)	(47.51258)	(40.99259)	[P-H] 0.640[B]
Min	-47.813	-35.662	-39.169	-47.813	[L-H] 0.887[B]
Median	3.9383	2.8422	4.8603	4.3993	
Max	71.429	99.331	137.009	137.009	

**Table 8. Weekly Summaries of Gardos Channel Values in Patients ≥ 18 Years Old**

Gardos Channel Activity (mmol/10 13 cells x min)	Placebo (N=20)	Low Dose (N=21)	High Dose (N=16)	All Subjects (N=57)	P-value [1]
<b>Visit 1</b>					
N	17	16	15	48	[P-L-H] 0.504[A]
Mean	0.78076	0.78338	0.72480	0.76415	[P-L] 0.500[A]
(SD)	(0.249762)	(0.177668)	(0.260654)	(0.228622)	[P-H] 0.603[A]
Min	0.3740	0.4820	0.4330	0.3740	[L-H] 0.246[A]
Median	0.78800	0.79500	0.61400	0.78450	
Max	1.3780	1.1180	1.2560	1.3780	
<b>Visit 2</b>					
N	17	17	16	50	[P-L-H] 0.771[A]
Mean	0.79612	0.81371	0.75713	0.78962	[P-L] 0.763[A]
(SD)	(0.199970)	(0.267528)	(0.204927)	(0.223257)	[P-H] 0.675[A]
Min	0.5400	0.5240	0.4000	0.4000	[L-H] 0.473[A]
Median	0.74800	0.74800	0.76250	0.74900	
Max	1.1970	1.5850	1.1030	1.5850	
<b>Visit 3</b>					
N	16	20	14	50	[P-L-H] 0.157[A]
Mean	0.73619	0.89760	0.78979	0.81576	[P-L] 0.061[A]
(SD)	(0.185676)	(0.245195)	(0.223519)	(0.228287)	[P-H] 0.544[A]
Min	0.2700	0.5360	0.4690	0.2700	[L-H] 0.243[A]
Median	0.74100	0.84050	0.80200	0.80850	
Max	1.1320	1.4960	1.3010	1.4960	
<b>Baseline [2]</b>					
N	18	21	16	55	
Mean	0.77398	0.85890	0.76857	0.80483	
(SD)	(0.151251)	(0.239481)	(0.185110)	(0.199513)	
Min	0.6137	0.5840	0.4910	0.4910	
Median	0.77017	0.79767	0.74400	0.77900	
Max	1.2495	1.4150	1.1463	1.4150	
<b>Visit 4</b>					
N	16	12	11	39	[P-L-H] 0.292[B]
Mean	0.76294	0.68892	0.86255	0.76826	[P-L] 0.603[B]
(SD)	(0.244822)	(0.211817)	(0.309520)	(0.257744)	[P-H] 0.257[B]
Min	0.1270	0.2120	0.5240	0.1270	[L-H] 0.126[B]
Median	0.78300	0.72650	0.81600	0.77900	
Max	1.0900	0.9250	1.4240	1.4240	
<b>Change from Base</b>					
N	16	12	11	39	
Mean	-0.01923	-0.14639	0.08586	-0.02871	
(SD)	(0.213865)	(0.228571)	(0.254075)	(0.241613)	
Min	-0.4867	-0.5957	-0.1783	-0.5957	
Median	-0.03633	-0.13067	-0.04833	-0.04467	
Max	0.3097	0.1160	0.5295	0.5295	
<b>%Change from Base</b>					
N	16	12	11	39	[P-L-H] 0.370[B]
Mean	-2.39487	-16.12829	11.75990	-2.62817	[P-L] 0.813[B]
(SD)	(29.519744)	(25.200575)	(32.567938)	(30.404633)	[P-H] 0.244[B]
Min	-79.3047	-73.7515	-25.3916	-79.3047	[L-H] 0.191[B]
Median	-4.49969	-19.40307	-6.07712	-5.69715	
Max	39.6839	14.3387	60.6804	60.6804	

Gardos Channel					
Activity (mmol/10 13 cells x min)	Placebo (N=20)	Low Dose (N=21)	High Dose (N=16)	All Subjects (N=57)	P-value [1]
Visit 5					
N	14	15	10	39	[P-L-H] 0.226[B]
Mean	0.89193	0.95227	0.79810	0.89108	[P-L] 0.614[B]
(SD)	(0.312910)	(0.327693)	(0.284342)	(0.309775)	[P-H] 0.218[B]
Min	0.4610	0.4110	0.4210	0.4110	[L-H] 0.090[B]
Median	0.85800	0.90600	0.72000	0.85700	
Max	1.7300	1.6610	1.3790	1.7300	
Change from Base					
N	14	15	10	39	
Mean	0.12431	0.10129	-0.00335	0.08272	
(SD)	(0.335464)	(0.351500)	(0.181062)	(0.307418)	
Min	-0.2195	-0.4400	-0.2813	-0.4400	
Median	0.08217	0.16100	-0.04800	0.08000	
Max	1.1125	0.7787	0.2845	1.1125	
%Change from Base					
N	14	15	10	39	[P-L-H] 0.198[B]
Mean	19.61971	15.19308	-1.10372	12.60346	[P-L] 0.794[B]
(SD)	(51.652494)	(39.742203)	(22.012825)	(40.983202)	[P-H] 0.144[B]
Min	-24.8778	-32.6895	-40.0570	-40.0570	[L-H] 0.088[B]
Median	10.59208	21.26082	-6.07720	10.26958	
Max	180.1619	88.2509	31.8055	180.1619	
Visit 6					
N	9	14	11	34	[P-L-H] 0.311[B]
Mean	0.89033	0.80657	0.73409	0.80529	[P-L] 0.366[B]
(SD)	(0.285369)	(0.264437)	(0.222398)	(0.256788)	[P-H] 0.127[B]
Min	0.4640	0.1740	0.3600	0.1740	[L-H] 0.464[B]
Median	0.88700	0.91500	0.67700	0.86300	
Max	1.3400	1.2310	1.0400	1.3400	
Change from Base					
N	9	14	11	34	
Mean	0.15676	0.00129	0.00656	0.04415	
(SD)	(0.256062)	(0.244108)	(0.211352)	(0.240031)	
Min	-0.1737	-0.6233	-0.2317	-0.6233	
Median	0.11467	0.08783	-0.02533	0.08783	
Max	0.5723	0.3110	0.4060	0.5723	
%Change from Base					
N	9	14	11	34	[P-L-H] 0.360[B]
Mean	21.17035	1.98255	3.88178	7.67613	[P-L] 0.393[B]
(SD)	(34.371645)	(31.444105)	(35.420160)	(33.530501)	[P-H] 0.154[B]
Min	-24.3889	-78.1773	-39.1549	-78.1773	[L-H] 0.503[B]
Median	13.86393	11.94117	-3.60702	11.52639	
Max	74.5549	49.2868	82.6884	82.6884	

Gardos Channel					
Activity (mmol/10 13 cells x min)	Placebo (N=20)	Low Dose (N=21)	High Dose (N=16)	All Subjects (N=57)	P-value [1]
Visit 7					
N	11	13	9	33	[P-L-H] 0.528[B]
Mean	0.81491	0.80162	0.92400	0.83942	[P-L] 0.724[B]
(SD)	(0.293304)	(0.170847)	(0.174923)	(0.219722)	[P-H] 0.441[B]
Min	0.1750	0.4380	0.7560	0.1750	[L-H] 0.264[B]
Median	0.81500	0.81300	0.88100	0.82300	
Max	1.2750	1.0580	1.2200	1.2750	
Change from Base					
N	11	13	9	33	
Mean	0.03279	-0.07197	0.15780	0.02561	
(SD)	(0.257024)	(0.261689)	(0.113306)	(0.241526)	
Min	-0.4387	-0.6050	-0.0197	-0.6050	
Median	-0.03400	-0.07100	0.16367	0.05433	
Max	0.5073	0.2877	0.3255	0.5073	
%Change from Base					
N	11	13	9	33	[P-L-H] 0.596[B]
Mean	4.49226	-3.86430	23.58132	6.40639	[P-L] 0.925[B]
(SD)	(36.508423)	(27.545497)	(19.200460)	(30.336344)	[P-H] 0.399[B]
Min	-71.4829	-42.9078	-2.3339	-71.4829	[L-H] 0.343[B]
Median	-4.41751	-9.64674	20.57837	6.61258	
Max	66.0877	38.5957	53.9715	66.0877	
Visit 8					
N	10	11	8	29	[P-L-H] 0.301[B]
Mean	0.93630	0.75666	0.79650	0.82960	[P-L] 0.175[B]
(SD)	(0.263990)	(0.172521)	(0.228753)	(0.229306)	[P-H] 0.193[B]
Min	0.6250	0.5200	0.4740	0.4740	[L-H] 0.966[B]
Median	0.87950	0.80300	0.81000	0.80700	
Max	1.3820	1.0333	1.2080	1.3820	
Change from Base					
N	10	11	8	29	
Mean	0.19992	-0.05791	0.05102	0.06104	
(SD)	(0.284557)	(0.283368)	(0.196592)	(0.277204)	
Min	-0.2277	-0.6070	-0.1887	-0.6070	
Median	0.18600	-0.06400	0.02783	0.06167	
Max	0.7075	0.3340	0.3135	0.7075	
%Change from Base					
N	10	11	8	29	[P-L-H] 0.335[B]
Mean	29.20004	-2.02551	9.54802	11.93462	[P-L] 0.256[B]
(SD)	(41.075271)	(31.295147)	(30.869250)	(36.262481)	[P-H] 0.170[B]
Min	-26.7005	-43.0496	-28.4708	-43.0496	[L-H] 0.748[B]
Median	25.17610	-10.95890	3.51968	8.27370	
Max	114.5749	52.5984	59.6741	114.5749	

Gardos Channel					
Activity (mmol/10 13 cells x min)	Placebo (N=20)	Low Dose (N=21)	High Dose (N=16)	All Subjects (N=57)	P-value [1]
Visit 9					
N	9	9	5	23	[P-L-H] 0.446[B]
Mean	0.70111	0.87733	0.82480	0.79696	[P-L] 0.213[B]
(SD)	(0.297565)	(0.326104)	(0.213707)	(0.292830)	[P-H] 0.756[B]
Min	0.2700	0.4270	0.5600	0.2700	[L-H] 0.449[B]
Median	0.75600	0.87900	0.81100	0.84700	
Max	1.1110	1.5210	1.1440	1.5210	
Change from Base					
N	9	9	5	23	
Mean	-0.02417	0.00330	0.06183	0.00528	
(SD)	(0.305311)	(0.246482)	(0.405860)	(0.294994)	
Min	-0.4897	-0.5067	-0.3353	-0.5067	
Median	0.01900	0.10167	0.04367	0.04333	
Max	0.3433	0.2650	0.5523	0.5523	
%Change from Base					
N	9	9	5	23	[P-L-H] 0.482[B]
Mean	-2.10931	0.64998	22.20492	4.25612	[P-L] 0.277[B]
(SD)	(43.527379)	(28.972904)	(60.473085)	(41.883483)	[P-H] 0.349[B]
Min	-59.5943	-52.5770	-37.3952	-59.5943	[L-H] 0.998[B]
Median	2.84858	7.87234	6.31630	5.08210	
Max	50.4009	35.0529	93.3521	93.3521	
Visit 10					
N	11	9	11	31	[P-L-H] 0.116[B]
Mean	0.76855	0.88556	0.67300	0.76861	[P-L] 0.377[B]
(SD)	(0.231453)	(0.163290)	(0.177740)	(0.207249)	[P-H] 0.214[B]
Min	0.1820	0.7120	0.2710	0.1820	[L-H] 0.040[B]
Median	0.80200	0.85300	0.68100	0.79200	
Max	1.0550	1.1600	0.9130	1.1600	
Change from Base					
N	11	9	11	31	
Mean	0.03408	-0.03581	-0.11314	-0.03845	
(SD)	(0.218223)	(0.251100)	(0.207825)	(0.225966)	
Min	-0.4317	-0.4930	-0.5907	-0.5907	
Median	-0.00567	-0.01733	-0.06733	-0.03650	
Max	0.3213	0.3100	0.0820	0.3213	
%Change from Base					
N	11	9	11	31	[P-L-H] 0.115[B]
Mean	4.84517	1.19950	-11.44500	-1.99363	[P-L] 0.310[B]
(SD)	(33.344382)	(25.397673)	(23.437042)	(27.904958)	[P-H] 0.259[B]
Min	-70.3422	-36.6270	-68.5493	-70.3422	[L-H] 0.038[B]
Median	-0.68966	-2.32558	-9.73963	-4.08049	
Max	51.5232	41.0053	16.7006	51.5232	

**Table 9. Weekly Summaries of RBC Values in Patients < 18 Years Old**

Red Blood Cell Count (RBC) (x10 <sup>6</sup> cells/uL)	Placebo (N=18)	Low Dose (N=14)	High Dose (N=18)	All Subjects (N=50)	P-value [1]
<b>Visit 1</b>					
N	17	14	18	49	[P-L-H] 0.837[A]
Mean	2.812	2.771	2.893	2.830	[P-L] 0.920[A]
(SD)	(0.4905)	(0.5498)	(0.8194)	(0.6344)	[P-H] 0.639[A]
Min	2.21	2.17	1.84	1.84	[L-H] 0.587[A]
Median	2.650	2.640	2.695	2.690	
Max	4.00	3.84	5.37	5.37	
<b>Visit 2</b>					
N	14	13	16	43	[P-L-H] 0.376[A]
Mean	3.036	2.963	2.718	2.895	[P-L] 0.938[A]
(SD)	(0.8021)	(0.6595)	(0.7868)	(0.7514)	[P-H] 0.209[A]
Min	2.03	2.16	2.00	2.00	[L-H] 0.259[A]
Median	2.630	2.690	2.430	2.670	
Max	4.72	4.31	4.55	4.72	
<b>Visit 3</b>					
N	13	14	12	39	[P-L-H] 0.602[A]
Mean	2.868	2.750	2.688	2.770	[P-L] 0.358[A]
(SD)	(0.5249)	(0.4353)	(0.7454)	(0.5642)	[P-H] 0.425[A]
Min	2.27	2.19	1.88	1.88	[L-H] 0.892[A]
Median	2.690	2.675	2.510	2.630	
Max	3.81	3.74	4.68	4.68	
<b>Baseline [2]</b>					
N	18	14	18	50	
Mean	2.903	2.826	2.792	2.842	
(SD)	(0.5500)	(0.4944)	(0.7245)	(0.5952)	
Min	2.17	2.26	2.08	2.08	
Median	2.715	2.718	2.653	2.673	
Max	4.20	3.82	4.87	4.87	
<b>Visit 4</b>					
N	16	12	12	40	[P-L-H] 0.286[B]
Mean	2.919	2.928	2.806	2.888	[P-L] 0.492[B]
(SD)	(0.4904)	(0.8714)	(0.6764)	(0.6623)	[P-H] 0.324[B]
Min	2.26	1.89	1.97	1.89	[L-H] 0.116[B]
Median	2.815	2.675	2.655	2.770	
Max	4.00	4.75	4.39	4.75	
<b>Change from Base</b>					
N	16	12	12	40	
Mean	0.014	0.131	-0.165	-0.005	
(SD)	(0.4990)	(0.6582)	(0.3708)	(0.5200)	
Min	-0.74	-0.74	-0.91	-0.91	
Median	-0.047	-0.010	-0.134	-0.090	
Max	1.43	1.64	0.60	1.64	
<b>%Change from Base</b>					
N	16	12	12	40	[P-L-H] 0.481[B]
Mean	2.011	4.051	-4.518	0.664	[P-L] 0.753[B]
(SD)	(17.8165)	(22.4085)	(11.5023)	(17.7079)	[P-H] 0.360[B]
Min	-17.62	-22.56	-22.71	-22.71	[L-H] 0.248[B]
Median	-1.422	-0.444	-5.646	-3.027	
Max	55.44	56.75	21.83	56.75	

Red Blood Cell Count (RBC) (x10 <sup>6</sup> cells/uL)	Placebo (N=18)	Low Dose (N=14)	High Dose (N=18)	All Subjects (N=50)	P-value [1]
<b>Visit 5</b>					
N	14	14	15	43	[P-L-H] 0.121[B]
Mean	2.941	2.616	2.863	2.808	[P-L] 0.055[B]
(SD)	(0.4136)	(0.8224)	(0.7034)	(0.6682)	[P-H] 0.730[B]
Min	2.40	0.40	2.11	0.40	[L-H] 0.108[B]
Median	2.735	2.645	2.680	2.710	
Max	3.67	3.73	4.25	4.25	
<b>Change from Base</b>					
N	14	14	15	43	
Mean	0.101	-0.209	0.049	-0.018	
(SD)	(0.3328)	(0.7480)	(0.7492)	(0.6427)	
Min	-0.50	-2.43	-0.71	-2.43	
Median	0.079	-0.142	-0.120	-0.025	
Max	0.80	1.12	1.99	1.99	
<b>%Change from Base</b>					
N	14	14	15	43	[P-L-H] 0.079[B]
Mean	4.544	-6.749	5.620	1.242	[P-L] 0.065[B]
(SD)	(11.8171)	(26.9488)	(32.5001)	(25.5316)	[P-H] 0.854[B]
Min	-13.16	-85.85	-23.62	-85.85	[L-H] 0.040[B]
Median	3.077	-4.820	-3.763	-0.677	
Max	32.39	42.91	93.13	93.13	
<b>Visit 6</b>					
N	14	14	16	44	[P-L-H] 0.843[B]
Mean	2.801	2.784	2.751	2.778	[P-L] 0.559[B]
(SD)	(0.4203)	(0.4589)	(0.5894)	(0.4886)	[P-H] 0.742[B]
Min	2.32	2.23	2.14	2.14	[L-H] 0.785[B]
Median	2.705	2.630	2.610	2.640	
Max	3.52	3.91	4.35	4.35	
<b>Change from Base</b>					
N	14	14	16	44	
Mean	-0.180	-0.041	-0.065	-0.094	
(SD)	(0.3241)	(0.3179)	(0.3066)	(0.3142)	
Min	-0.70	-0.46	-0.60	-0.70	
Median	-0.170	-0.082	0.073	-0.078	
Max	0.29	0.78	0.36	0.78	
<b>%Change from Base</b>					
N	14	14	16	44	[P-L-H] 0.880[B]
Mean	-5.104	-0.682	-0.743	-2.111	[P-L] 0.628[B]
(SD)	(10.2559)	(12.2664)	(10.1274)	(10.8325)	[P-H] 0.709[B]
Min	-22.52	-12.50	-17.16	-22.52	[L-H] 0.898[B]
Median	-5.464	-2.960	2.740	-2.862	
Max	11.74	34.71	15.58	34.71	



Red Blood Cell Count (RBC) (x10 <sup>6</sup> cells/uL)	Placebo (N=18)	Low Dose (N=14)	High Dose (N=18)	All Subjects (N=50)	P-value [1]
Visit 7					
N	15	13	12	40	[P-L-H] 0.784[B]
Mean	2.809	2.744	2.464	2.685	[P-L] 0.683[B]
(SD)	(0.4061)	(0.4487)	(0.4117)	(0.4371)	[P-H] 0.492[B]
Min	2.10	2.24	1.90	1.90	[L-H] 0.781[B]
Median	2.830	2.600	2.425	2.610	
Max	3.56	3.82	3.35	3.82	
Change from Base					
N	15	13	12	40	
Mean	-0.062	-0.112	-0.069	-0.080	
(SD)	(0.3545)	(0.2417)	(0.4062)	(0.3318)	
Min	-0.56	-0.68	-0.77	-0.77	
Median	-0.093	-0.060	-0.143	-0.078	
Max	0.83	0.11	0.78	0.83	
%Change from Base					
N	15	13	12	40	[P-L-H] 0.834[B]
Mean	-1.266	-3.446	-1.507	-2.047	[P-L] 0.642[B]
(SD)	(12.7613)	(7.2537)	(17.1113)	(12.5781)	[P-H] 0.581[B]
Min	-14.73	-20.73	-25.63	-25.63	[L-H] 0.926[B]
Median	-3.226	-2.299	-4.759	-3.119	
Max	33.24	5.02	37.14	37.14	
Visit 8					
N	15	12	13	40	[P-L-H] 0.426[B]
Mean	3.006	2.867	2.629	2.842	[P-L] 0.684[B]
(SD)	(0.5355)	(0.6080)	(0.5078)	(0.5587)	[P-H] 0.198[B]
Min	2.55	1.92	1.88	1.88	[L-H] 0.407[B]
Median	2.770	2.635	2.590	2.695	
Max	4.30	3.90	3.84	4.30	
Change from Base					
N	15	12	13	40	
Mean	0.134	0.084	-0.027	0.067	
(SD)	(0.4637)	(0.4182)	(0.4748)	(0.4480)	
Min	-0.41	-0.62	-0.96	-0.96	
Median	0.065	0.102	0.043	0.067	
Max	1.54	1.01	0.82	1.54	
%Change from Base					
N	15	12	13	40	[P-L-H] 0.577[B]
Mean	5.586	3.058	0.531	3.185	[P-L] 0.595[B]
(SD)	(16.5198)	(14.6058)	(17.9138)	(16.1692)	[P-H] 0.296[B]
Min	-12.04	-23.20	-23.96	-23.96	[L-H] 0.633[B]
Median	2.439	3.424	1.831	2.356	
Max	55.52	34.95	39.42	55.52	

Red Blood Cell Count (RBC) (x10 <sup>6</sup> cells/uL)	Placebo (N=18)	Low Dose (N=14)	High Dose (N=18)	All Subjects (N=50)	P-value [1]
Visit 9					
N	13	13	13	39	[P-L-H] 0.043[B]
Mean	2.691	3.092	2.619	2.801	[P-L] 0.016[B]
(SD)	(0.4055)	(0.8050)	(0.5754)	(0.6368)	[P-H] 0.522[B]
Min	1.95	2.26	1.65	1.65	[L-H] 0.074[B]
Median	2.730	2.760	2.520	2.690	
Max	3.40	4.75	3.82	4.75	
Change from Base					
N	13	13	13	39	
Mean	-0.194	0.236	-0.037	0.002	
(SD)	(0.5415)	(0.4790)	(0.6480)	(0.5746)	
Min	-1.43	-0.52	-1.23	-1.43	
Median	-0.095	0.080	-0.143	-0.070	
Max	0.75	1.03	1.13	1.13	
%Change from Base					
N	13	13	13	39	[P-L-H] 0.172[B]
Mean	-4.916	7.703	0.716	1.168	[P-L] 0.064[B]
(SD)	(17.6260)	(15.5139)	(24.3532)	(19.7165)	[P-H] 0.508[B]
Min	-42.25	-15.85	-30.74	-42.25	[L-H] 0.234[B]
Median	-3.565	3.065	-4.045	-2.869	
Max	30.36	33.85	54.33	54.33	
Visit 10					
N	15	12	15	42	[P-L-H] 0.131[B]
Mean	2.729	3.095	2.651	2.806	[P-L] 0.050[B]
(SD)	(0.4503)	(0.5046)	(0.4861)	(0.5036)	[P-H] 0.612[B]
Min	1.77	2.43	2.01	1.77	[L-H] 0.140[B]
Median	2.680	3.005	2.610	2.695	
Max	3.65	3.93	3.38	3.93	
Change from Base					
N	15	12	15	42	
Mean	-0.142	0.210	0.024	0.018	
(SD)	(0.4105)	(0.3650)	(0.4946)	(0.4439)	
Min	-0.82	-0.40	-0.66	-0.82	
Median	-0.145	0.165	-0.007	-0.030	
Max	0.85	0.92	1.28	1.28	
%Change from Base					
N	15	12	15	42	[P-L-H] 0.200[B]
Mean	-4.062	8.274	2.720	1.885	[P-L] 0.075[B]
(SD)	(14.8568)	(14.0745)	(20.5423)	(17.2555)	[P-H] 0.505[B]
Min	-31.22	-14.03	-21.94	-31.22	[L-H] 0.250[B]
Median	-5.441	6.002	-0.254	-0.992	
Max	34.41	37.70	61.54	61.54	

**Table 10. Weekly Summaries of RBC Values in Patients ≥ 18 Years Old**

Red Blood Cell Count (RBC) (x10 <sup>6</sup> cells/uL)	Placebo (N=20)	Low Dose (N=21)	High Dose (N=16)	All Subjects (N=57)	P-value [1]
<b>Visit 1</b>					
N	17	18	13	48	[P-L-H] 0.434[A]
Mean	2.8318	2.8033	2.9523	2.8538	[P-L] 0.891[A]
(SD)	(0.75461)	(0.48909)	(0.91136)	(0.70446)	[P-H] 0.289[A]
Min	1.890	2.240	1.970	1.890	[L-H] 0.225[A]
Median	2.7000	2.6550	3.0800	2.6800	
Max	5.220	4.040	4.650	5.220	
<b>Visit 2</b>					
N	16	17	14	47	[P-L-H] 0.154[A]
Mean	2.5144	2.9271	2.9621	2.7970	[P-L] 0.287[A]
(SD)	(0.43985)	(0.51114)	(0.97796)	(0.68307)	[P-H] 0.054[A]
Min	1.520	2.260	1.970	1.520	[L-H] 0.322[A]
Median	2.5300	2.7500	2.4550	2.6400	
Max	3.430	4.000	4.820	4.820	
<b>Visit 3</b>					
N	15	19	14	48	[P-L-H] 0.344[A]
Mean	2.6980	2.9263	3.0286	2.8848	[P-L] 0.385[A]
(SD)	(0.58832)	(0.58295)	(0.88806)	(0.68511)	[P-H] 0.148[A]
Min	2.000	2.270	2.130	2.000	[L-H] 0.492[A]
Median	2.3900	2.7500	2.7700	2.6700	
Max	4.260	4.460	4.800	4.800	
<b>Baseline [2]</b>					
N	18	21	15	54	
Mean	2.7510	2.8609	2.9907	2.8603	
(SD)	(0.63663)	(0.47250)	(0.88619)	(0.65617)	
Min	1.803	2.290	1.985	1.803	
Median	2.5633	2.6633	2.6167	2.6550	
Max	4.740	3.937	4.693	4.740	
<b>Visit 4</b>					
N	16	12	10	38	[P-L-H] 0.071[B]
Mean	2.4969	2.7233	3.1040	2.7282	[P-L] 0.349[B]
(SD)	(0.54620)	(0.50137)	(1.17638)	(0.77046)	[P-H] 0.022[B]
Min	1.550	2.270	1.980	1.550	[L-H] 0.170[B]
Median	2.4950	2.5600	2.5600	2.5450	
Max	3.700	3.880	5.030	5.030	
<b>Change from Base</b>					
N	16	12	10	38	
Mean	-0.2330	-0.0775	0.1543	-0.0820	
(SD)	(0.36674)	(0.19809)	(0.61695)	(0.42865)	
Min	-1.040	-0.377	-0.590	-1.040	
Median	-0.1117	-0.0383	0.0092	-0.0417	
Max	0.217	0.260	1.787	1.787	
<b>%Change from Base</b>					
N	16	12	10	38	[P-L-H] 0.084[B]
Mean	-7.7003	-2.2518	5.1960	-2.5859	[P-L] 0.347[B]
(SD)	(12.57996)	(7.10468)	(19.36787)	(14.07560)	[P-H] 0.026[B]
Min	-33.855	-13.469	-19.344	-33.855	[L-H] 0.196[B]
Median	-4.2301	-1.5902	0.1251	-1.4974	
Max	12.015	11.354	55.087	55.087	

Red Blood Cell Count (RBC) (x10 <sup>6</sup> cells/uL)	Placebo (N=20)	Low Dose (N=21)	High Dose (N=16)	All Subjects (N=57)	P-value [1]
Visit 5					
N	13	15	10	38	[P-L-H] 0.317[B]
Mean	2.6338	2.7366	3.2150	2.8273	[P-L] 0.665[B]
(SD)	(0.47391)	(0.46851)	(0.95325)	(0.65882)	[P-H] 0.138[B]
Min	1.850	2.299	2.100	1.850	[L-H] 0.262[B]
Median	2.6600	2.5900	2.9850	2.6600	
Max	3.440	3.810	4.710	4.710	
Change from Base					
N	13	15	10	38	
Mean	-0.1173	0.0002	0.1257	-0.0070	
(SD)	(0.51961)	(0.28594)	(0.32758)	(0.39199)	
Min	-1.300	-0.450	-0.370	-1.300	
Median	-0.0550	0.0067	0.1375	0.0017	
Max	0.917	0.510	0.725	0.917	
%Change from Base					
N	13	15	10	38	[P-L-H] 0.365[B]
Mean	-1.9026	0.1978	5.2663	0.8131	[P-L] 0.853[B]
(SD)	(17.02925)	(9.86994)	(11.26068)	(13.03307)	[P-H] 0.185[B]
Min	-27.426	-14.730	-12.131	-27.426	[L-H] 0.235[B]
Median	-2.0110	0.2601	4.9533	0.0554	
Max	38.787	21.250	28.265	38.787	
Visit 6					
N	9	15	10	34	[P-L-H] 0.267[B]
Mean	2.8167	2.6353	2.8220	2.7382	[P-L] 0.106[B]
(SD)	(0.59900)	(0.61318)	(0.96790)	(0.71457)	[P-H] 0.311[B]
Min	1.900	1.520	2.000	1.520	[L-H] 0.621[B]
Median	2.8100	2.6600	2.3200	2.5350	
Max	3.720	3.710	4.760	4.760	
Change from Base					
N	9	15	10	34	
Mean	-0.0006	-0.2691	-0.1983	-0.1772	
(SD)	(0.53666)	(0.50443)	(0.45629)	(0.49702)	
Min	-1.020	-1.350	-0.963	-1.350	
Median	0.0967	-0.1767	-0.0742	-0.0775	
Max	0.695	0.457	0.467	0.695	
%Change from Base					
N	9	15	10	34	[P-L-H] 0.156[B]
Mean	2.3009	-8.5612	-5.7637	-4.8631	[P-L] 0.056[B]
(SD)	(16.87137)	(16.95057)	(13.62352)	(16.18568)	[P-H] 0.209[B]
Min	-21.519	-47.038	-28.987	-47.038	[L-H] 0.601[B]
Median	4.0741	-6.0990	-2.9622	-2.9622	
Max	25.411	19.323	14.388	25.411	

Red Blood Cell Count (RBC) (x10 <sup>6</sup> cells/uL)	Placebo (N=20)	Low Dose (N=21)	High Dose (N=16)	All Subjects (N=57)	P-value [1]
<b>Visit 7</b>					
N	10	12	9	31	[P-L-H] 0.491[B]
Mean	2.8900	2.6925	2.8478	2.8013	[P-L] 0.583[B]
(SD)	(0.64434)	(0.59565)	(1.02296)	(0.73601)	[P-H] 0.234[B]
Min	2.030	2.160	2.010	2.010	[L-H] 0.480[B]
Median	2.7000	2.4550	2.4300	2.5300	
Max	4.150	4.000	5.060	5.060	
<b>Change from Base</b>					
N	10	12	9	31	
Mean	-0.0942	-0.0850	-0.3244	-0.1575	
(SD)	(0.47034)	(0.26807)	(0.52427)	(0.42168)	
Min	-0.930	-0.867	-1.083	-1.083	
Median	-0.0875	-0.0367	-0.1233	-0.0700	
Max	0.767	0.120	0.413	0.767	
<b>%Change from Base</b>					
N	10	12	9	31	[P-L-H] 0.483[B]
Mean	-1.5103	-2.8436	-9.4090	-4.3196	[P-L] 0.470[B]
(SD)	(13.43620)	(9.01270)	(14.90784)	(12.42904)	[P-H] 0.233[B]
Min	-19.620	-28.634	-33.402	-33.402	[L-H] 0.586[B]
Median	-3.0167	-1.5418	-5.3314	-2.1944	
Max	22.660	4.803	8.895	22.660	
<b>Visit 8</b>					
N	11	10	7	28	[P-L-H] 0.510[B]
Mean	2.8327	2.8680	3.2214	2.9425	[P-L] 0.731[B]
(SD)	(0.64841)	(0.54501)	(1.13530)	(0.75385)	[P-H] 0.394[B]
Min	1.890	2.270	1.960	1.890	[L-H] 0.254[B]
Median	2.6500	2.6900	3.4200	2.6600	
Max	3.960	3.820	4.680	4.680	
<b>Change from Base</b>					
N	11	10	7	28	
Mean	-0.0944	-0.0247	0.1917	0.0020	
(SD)	(0.44080)	(0.19899)	(0.79626)	(0.48932)	
Min	-0.790	-0.323	-1.243	-1.243	
Median	-0.0600	-0.0150	0.0600	-0.0150	
Max	0.745	0.330	1.107	1.107	
<b>%Change from Base</b>					
N	11	10	7	28	[P-L-H] 0.444[B]
Mean	-1.8797	-0.3818	7.8995	1.1000	[P-L] 0.682[B]
(SD)	(13.58219)	(7.16111)	(27.28540)	(16.34864)	[P-H] 0.360[B]
Min	-22.832	-12.325	-37.412	-37.412	[L-H] 0.209[B]
Median	-1.8809	-0.4872	2.7907	-0.4872	
Max	27.239	12.791	47.839	47.839	

Red Blood Cell Count (RBC) (x10 <sup>6</sup> cells/uL)	Placebo (N=20)	Low Dose (N=21)	High Dose (N=16)	All Subjects (N=57)	P-value [1]
Visit 9					
N	9	9	6	24	[P-L-H] 0.607[B]
Mean	2.8411	3.0167	3.3333	3.0300	[P-L] 0.930[B]
(SD)	(0.80865)	(0.66098)	(0.74500)	(0.73356)	[P-H] 0.353[B]
Min	1.850	2.230	2.140	1.850	[L-H] 0.394[B]
Median	2.7300	2.7900	3.7450	2.8100	
Max	4.180	4.300	3.940	4.300	
Change from Base					
N	9	9	6	24	
Mean	-0.0706	0.0552	-0.0308	-0.0135	
(SD)	(0.54124)	(0.21619)	(0.49163)	(0.41700)	
Min	-0.970	-0.277	-0.753	-0.970	
Median	0.0300	0.0000	0.0075	0.0233	
Max	0.990	0.420	0.527	0.990	
%Change from Base					
N	9	9	6	24	[P-L-H] 0.568[B]
Mean	-1.6122	1.8882	0.6913	0.2763	[P-L] 0.960[B]
(SD)	(16.07037)	(6.75993)	(13.51356)	(12.16057)	[P-H] 0.331[B]
Min	-23.506	-7.028	-16.051	-23.506	[L-H] 0.353[B]
Median	1.1111	0.0000	2.1048	0.9112	
Max	31.034	10.825	16.238	31.034	
Visit 10					
N	12	9	8	29	[P-L-H] 0.518[B]
Mean	2.8792	2.9222	2.7313	2.8517	[P-L] 0.469[B]
(SD)	(0.69217)	(0.67232)	(1.14377)	(0.80653)	[P-H] 0.622[B]
Min	1.890	2.120	1.980	1.890	[L-H] 0.258[B]
Median	2.7200	3.1200	2.3250	2.5900	
Max	4.180	3.990	5.470	5.470	
Change from Base					
N	12	9	8	29	
Mean	0.0582	-0.0456	0.1058	0.0391	
(SD)	(0.61423)	(0.26962)	(0.95292)	(0.63224)	
Min	-1.010	-0.433	-0.993	-1.010	
Median	0.0433	-0.0833	-0.0792	-0.0433	
Max	1.587	0.457	2.227	2.227	
%Change from Base					
N	12	9	8	29	[P-L-H] 0.481[B]
Mean	3.7616	-1.6912	3.3368	1.9522	[P-L] 0.313[B]
(SD)	(21.34058)	(9.85296)	(29.83487)	(20.86624)	[P-H] 0.864[B]
Min	-21.308	-16.518	-29.890	-29.890	[L-H] 0.280[B]
Median	1.6352	-3.2510	-3.5588	-1.8492	
Max	61.183	17.146	68.654	68.654	