Appendix A. Summary of Alanine Aminotransferase and Aspartate Aminotransferase Elevations by Sex, Race, and Treatment Cohort

Cohort	Sex	Asian n/N (%)	Black or African American n/N (%)	White n/N (%)	Multiracial n/N (%)
All Subjects	Male	3/3 (100)	7/17 (41)	2/4 (50)	-
	Female	2/4 (50)	3/12 (25)	2/6 (33)	0/2 (0)
Cohort 1	Male	-	0/2 (0)	1/2 (50)	-
	Female	-	0/4 (0)	-	-
Cohort 2	Male	-	1/5 (20)	0/1 (0)	-
	Female	-	-	0/1 (0)	0/1 (0)
Cohort 3	Male	-	1/2 (50)	1/1 (100)	-
	Female	2/3 (67)	1/1 (100)	0/1 (0)	-
Cohort 4	Male	-	2/3 (67)	-	-
	Female	-	0/4 (0)	1/1 (100)	-
Cohort 5	Male	1/1 (100)	2/3 (67)	-	-
	Female	0/1 (0)	1/1 (100)	0/1 (0)	0/1 (0)
Cohort 6	Male	2/2 (100)	1/2 (50)	-	-
	Female	-	1/2 (50)	1/2 (50)	-

Appendix B. Toxicity Grading Tables

Clinical Adverse Events

CARDIOVASCULAR TOXICITY	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Arrhythmia		Asymptomatic; transient signs; no medical intervention required	Recurrent/persistent; symptomatic medical intervention required
Hemorrhage, Blood Loss	Estimated blood loss <100 mL	Estimated blood loss ≥100 mL, no transfusion required	Transfusion required
QTc (Fridericia's correction)[1] or QTcb (Bazett's)[1]	Asymptomatic, QTc interval 450-479 msec OR Increase in interval 20-30 msec above baseline	Asymptomatic, QTc interval 480-499 msec OR Increase in interval 31-50 msec above baseline	Asymptomatic, QTc interval ≥ 500 msec OR Increase in interval ≥ 51 msec above baseline
PR Interval (prolonged)[1]	PR interval 0.21-0.25 sec	PR interval >0.25	Type II 2nd degree AV block OR Ventricular pause >3.0 sec
RESPIRATORY TOXICITY	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Cough	Transient; no treatment	Persistent cough	Interferes with daily activities
Bronchospasm, Acute	Transient; no treatment; 71% - 80% FEV1 of predicted peak flow	Requires medical intervention; normalizes with bronchodilator; FEV1 60% - 70% (of predicted peak flow)	No normalization with bronchodilator; FEV1 < 60% of predicted peak flow
Dyspnea	Does not interfere with usual and social activities	Interferes with usual and social activities; no treatment	Prevents daily and usual social activity OR requires treatment
GASTROINTESTINAL TOXICITY	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Nausea	No interference with activity	Some interference with activity	Prevents daily activities
Vomiting	No interference with activity OR 1 - 2 episodes/24 hours	Some interference with activity OR >2 episodes/24 hours	Prevents daily activity OR requires IV hydration OR requires medical intervention
Diarrhea	2 - 3 loose or watery stools or <400 g24 hours	4 - 5 loose or watery stools or 400 - 800 g/24 hours	6 or more loose or watery stools or >800g24 hours OR requires IV hydration OR requires medical intervention

[1] Inclusion dependent upon protocol requirements.

LOCAL REACTIONS	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours OR interferes with activity	Any use of narcotic pain reliever OR prevents daily activity
Tenderness	Discomfort only to touch	Discomfort with movement	Significant discomfort at rest
Erythema/Redness[2]	2.5 - 5 cm	5.1 - 10 cm	>10 cm
Induration/Swelling[3]	2.5 - 5 cm and does not interfere with activity	5.1 - 10 cm OR interferes with activity	>10 cm OR prevents daily activity
SYSTEMIC REACTIONS	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Allergic Reaction	Pruritus without rash	Localized urticaria OR requires oral therapy	Generalized urticaria; angioedema OR anaphylaxis OR requires epinephrine
Headache	No interference with activity	Repeated use of non-narcotic pain reliever >24 hours OR some interference with activity	Significant; any use of narcotic pain reliever OR prevents daily activity OR requires triptans
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity
All Other conditions	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention

[2] In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

[3] Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Laboratory and Vital Signs Reference Ranges, Eligibility Ranges, and Toxicity Grading

Blood, Serum, or Plasma Chemistries[1]	Reference Range[2]	Eligibility Range[3]	LO/HI/N[4]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Sodium (mEq/L)	135 - 145	135 - 145	LO	132 - <LLN	130 - 131	<130
			HI	>ULN - 148	149 - 150	>150
Potassium (mEq/L)	3.5 – 5.0	3.5 – 5.0	HI	>ULN - 5.2	5.3 - 5.4	>5.4
			LO	>LLN - 3.1	<3.1 - 3.0	<3.0
Blood Urea Nitrogen (BUN, mg/dL)	7 - 20	7 - 20	HI	21 - 26	27 - 31	>31
Creatinine (mg/dL)	0.5 - 1.2	0.5 – 1.2	HI	>ULN - 1.7	1.8 - 2.0	>2.0
Glucose (mg/dL)	<70	<70	LO	65 - 69	55 - 64	<55
	70 - 99	70 - 99	HI[5]	>ULN - 120	121 - 130	>130
	70 - 140	70 - 140	HI[6]	141 - 159	160 - 200	>200
Total Protein (g/dL)	5.8 - 7.8	5.8 - 7.8	LO	5.2 - <LLN	4.8 - 5.1	<4.8
Bilirubin, serum total (mg/dL)	0.4 - 1.5	0.4 - 1.5	HI	1.6 - 2.0	2.1 - 2.5	>2.5
ALT (U/L)	Female: 14-54	Female: 14-54	HI	>ULN - 105	106 - 175	>175
	Male: 17-63	Male: 17-63				
AST (U/L)	15 - 41	15 - 41	HI	42 - 105	106 - 175	>175
Alkaline phosphatase (U/L)	24 - 110	24 - 110	HI	111 - 240	241 - 360	>360

Hematology	Reference Range[7]	Eligibility Range[8]	LO/HI/N[9]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Hemoglobin (Females) (g/dL)	12.0-15.5	12.0-15.5	LO	11.0 - 11.9	9.5 - 10.9	<9.5
Hemoglobin (Males) (g/dL)	13.7-17.3	13.7-17.3	LO	12.0 – 13.6	10.0 - 11.9	<10.0

[1] Depending upon the lab used, references ranges, eligibility ranges and grading may be split out by sex and/or age.
[2] Reference range of site laboratory
[3] Laboratory values acceptable for eligibility for enrollment
[4] High, Low, Not Graded
[5] Fasting
[6] Non-fasting
[7] Reference range of site laboratory
[8] Laboratory values acceptable for eligibility for enrollment
[9] High, Low, Not Graded

Hematology	Reference Range[7]	Eligibility Range[8]	LO/HI/N[9]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
White Blood Cell Count (WBC, K/CUMM)	3.2-9.8	3.2-9.8	HI	9.9 – 14.99	15.00 - 20.00	>20.00
			LO	2.50 - 3.19	1.50 - 2.49	<1.50
Lymphocytes (K/CUMM)	0.6-4.2	0.6-4.2	LO	0.50 – 0.59	0.40 - 0.49	<0.4
Neutrophils (K/CUMM)	2.0-8.6	2.0-8.6	LO	1.50 – 1.99	1.00 - 1.49	<1.00
Eosinophils (K/CUMM)	0.0-0.7	0.0-0.7	HI	>ULN - 0.74	0.75 - 1.50	>1.50
Platelets (K/CUMM)	150-450	150-450	LO	120 - 149	100 - 119	<100
Coagulation						
Prothrombin time (PT, seconds)	9.5-13.1	9.5-13.1	HI	>ULN - 14.4	14.5 - 15.7	>15.7
Partial thromboplastin time (PTT or aPTT, seconds)	26.8-37.1	26.8-37.1	HI	>ULN - 42.1	42.2 - 50.0	>50.0
Urine*						
Protein (dipstick)	0	0	HI	1+	2+	>2+
Glucose (dipstick)	0	0	HI	1+	2+	>2+

Vital Signs	Mild (Grade 1)[10]	Moderate (Grade 2)	Severe (Grade 3)
Fever (°F)	100.4 - 101.1	101.2 - 102.0	≥102.1
Tachycardia - beats per minute[11]	101 - 115	116 - 130	>130 or ventricular dysrhythmias
Bradycardia - beats per minute[12]	50 – 54 or 45 – 49 if baseline 50-59 bpm	45 – 49 or 40 - 44 if baseline 50-59 bpm	< 45 or <40 if baseline 50-59 bpm
Hypertension (systolic) - mm Hg[13]	141 - 150	151 - 160	>160
Hypertension (diastolic) - mm Hg	91 - 95	96 - 100	>100

[10] If initial bound of Grade 1 has gap from reference range or eligibility range, calculations based on NEJM reference ranges
[11] Expanded heart rate limits can be considered with normal ECGs.
[12] Expanded heart rate limits can be considered with normal ECGs.
[13] Assuming subject is awake, resting, and supine; for AE, 3 measurements on the same arm with concordant results.

Vital Signs	**Mild (Grade 1)[10]**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Hypotension (systolic) - mm Hg	85 - 89	80 - 84	<80
Tachypnea - breaths per minute	23 - 25	26 - 30	>30