

Toxicity Studies on Intrathecal Injection of Low Dose of DMSO Used for Cryopreservation of Human Astrocytes in Mice

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Supplementary Table 1: Study design.

Group No. and Sex	Individual Animal No.	T R E A T M E N T				Scheduled Sacrifice Post Dosing
		Test Material	Dose Level (Cells/ animal)	Dose Volume (µl/an.)	Route and Frequency	
1M	41, 42, 43, 44, 45	Untreated Control	0	0	NA	28 days
2M	1, 58, 3, 4, 5	Vehicle (PlasmaLyte, for fresh AstroRx) (Vehicle Control I)		10	Single CM Injection	28 days
	50 , 51 - Satellite					1 day
	6, 7, 8, 9, 10					28 days
3M	11, 12, 13, 14, 15	Vehicle (Diluted SFM, for cryopreserve d AstroRx) (Vehicle Control II)				1 day
	52 , 53 - Satellite					28 days
	16, 17, 18, 19, 20					1 day
4M	59, 22, 23, 24, 25	Fresh AstroRx (Test Item I)	0.4×10 ⁶ /10 µl			
	54 , 55 - Satellite			1 day		
	63, 66, 28, 29, 30			28 days		
5M	31, 32, 33, 34 35	Cryopreserve d F-AstroRx (Test Item II)		1 day		
	56 , 57 - Satellite			28 days		
	36, 37, 38, 39 40			1 day		

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1F	141, 142, 143, 144 145	Untreated Control	0	0	NA	28 days				
2F	101, 102, 103, 104, 105	Vehicle (PlasmaLyte, for fresh AstroRx) (Vehicle Control I)		10	Single CM Injection	28 days				
	150 , 151 - Satellite					1 day				
3F	166, 167, 108, 109, 110	Vehicle (Diluted SFM, for cryopreserve d AstroRx) (Vehicle Control II)				28 days				
	111, 112, 113, 114 115					1 day				
	152 , 153 - Satellite					28 days				
4F	116, 117, 118, 119 120	Fresh AstroRx (Test Item I)				0.4×10 ⁶ /1 0 µl		1 day		
	121, 122, 123, 124 125							28 days		
	154 , 155 - Satellite							1 day		
5F	126, 127, 169, 129 130	Cryopreserve d F-AstroRx (Test Item II)								28 days
	131, 132, 133, 134									1 day
	135									28 days
	156 , 157 – Satellite				1 day					
	136, 137, 165, 139 168				28 days					
					1 day					

Supplementary Table 2: Clinical pathology parameters.

Hematology	
Parameter	System / Method
WBC	Sysmex XS-1000i
RBC	
HGB	
HCT	
MCV	
MCH	
MCHC	
Platelets	
Differential Count (relative and absolute)	Manual (if applicable)
Biochemistry	
Parameter	System / Method
Creatinine	ROCHE-COBAS 6000 C501 Analyzer
Calcium	
Glucose	
Cholesterol	
Total Protein	
Globulin	
LDH	
Aspartate Aminotransferase (AST)	
Potassium	
CPK	
Phosphorus	
Urea	
Albumin	
Albumin/Globulin Ratio	
Total Bilirubin	
Alanine Aminotransferase (ALT)	
Sodium	

γ -Glutamyl Transpeptidase (GGT)	
Chloride	
Triglycerides	
Alkaline Phosphatase (ALP)	

Supplementary Table 3: Neurological Assessment.

Behavioral step	Parameter	Group 1M (Untreated control)			
		On study day			
		Number Affected/Total Number of Animals			
		(days post dosing)			
		Pre-dosing (acclimation)	3	7	24
Observation in the home cage	Body position-Normal	5/5	5/5	5/5	5/5
	No motor activity although animal awake - Not observed	5/5	5/5	5/5	5/5
	Animal moving around the cage - Observed	5/5	5/5	5/5	5/5
	Rearing-Observed	5/5	5/5	4/5	5/5
	<i>Rearing-not Observed</i>			1/5 (43)	
	Grooming-Not observed	5/5	5/5	5/5	5/5
	Animal darting around cage- not observed	5/5	5/5	5/5	5/5
	Aggressiveness towards cage mates - Not observed	5/5	5/5	5/5	5/5
	Animal eats -Not observed	5/5	5/5	5/5	5/5
	Animal drinks - Not observed	5/5	5/5	5/5	5/5
	Animal sleeps -Not observed	5/5	5/5	5/5	5/5
	Sedation - Not observed	5/5	5/5	5/5	5/5
	Excitation - Not observed	5/5	5/5	5/5	5/5
	Piloerection - Absence	5/5	5/5	5/5	5/5
Behavioral symptoms (Observation in the home cage)	Ptosis [Palpebral (eyelid) closure] - Absence	5/5	5/5	5/5	5/5
	Exophthalmos (protrusion of the eyeball) - Not observed	5/5	5/5	5/5	5/5
	Bizarre behavior - Not observed	5/5	5/5	5/5	5/5
	Writhing (Abdominal stretching) - Absence	5/5	5/5	5/5	5/5
	Respiration - Normal	5/5	5/5	5/5	5/5
	Head twitches (Twitch or flick only of head) - Not observed	5/5	5/5	5/5	5/5
	Jumping - Not observed	5/5	5/5	5/5	5/5

Behavior during Handling	Tremors - No tremors	5/5	5/5	5/5	5/5
	Twitch (More than head flicks, often prelude to convulsive behavior) - Absence	5/5	5/5	5/5	5/5
	Convulsions - Not observed	5/5	5/5	5/5	5/5
	Arousal - Normal	5/5	5/5	5/5	5/5
	Startle response - prayer reflex, without jump - Normal	5/5	5/5	5/5	5/5
	Reactivity to touch - Irritable	3/5	3/5	5/5	5/5
	<i>vocalizing when handled</i>	2/5 (41, 45)	2/5 (41, 45)		
	Abdominal tone - Normal	5/5	5/5	5/5	5/5
	Limb tone - Slight	5/5	5/5	5/5	5/5
	Aggressiveness towards handler - Passive (Normal)	5/5	4/5	5/5	5/5
	<i>Irritated</i>		1/5 (44)		

Behavioral step	Parameter	Group 1M (Untreated control)			
		On Study Day			
		Number Affected / Total Number of Animals (days post dosing)			
		Pre -dosing (acclimation)	3	7	24
Behavior during Handling	Pupil size – Normal size	5/5	5/5	5/5	5/5
	Visual placing - Normal	5/5	5/5	5/5	5/5
	Tail suspension - Normal	5/5	5/5	5/5	5/5
	Corneal reflex - Normal	5/5	5/5	5/5	5/5
	Grip strength – Normal	5/5	5/5	5/5	5/5
	Hind limb reflex - Normal	5/5	5/5	5/5	5/5
	Righting reflex - Normal	5/5	5/5	5/5	5/5
	Lacrimation - Normal	5/5	5/5	5/5	5/5
	Salivation - Normal	5/5	5/5	5/5	5/5
	Diarrhea - Not observed	5/5	5/5	5/5	5/5
	Urination – no urine puddle on the arena floor	3/5		5/5	4/5
	One urine puddle	2/5 (43, 44)	1/5 (43)		1/5 (42)
	Two or three urine puddles		4/5 (41, 42, 44, 45)		
	Defecation – No defecation on the arena floor	3/5	3/5	4/5	5/5
	One fecal pellet		2/5 (41, 45)		
	Two or three fecal pellets	2/5 (43, 44)		1/5 (44)	
	Feces consistency - Not evaluated because no defecation occurring during observation	3/5	3/5	4/5	5/5
	Well-formed stools	2/5 (43, 44)	2/5 (41, 45)	1/5 (44)	
	Abnormal vocalization during handling – No abnormal	5/5	5/5	5/5	5/5
sy mp to ms (Obs)	Transfer arousal - Normal	5/5	5/5	5/5	5/5

Locomotor activity - Normal	5/5	5/5	5/5	5/5
Ataxic Gait - Normal	5/5	5/5	5/5	5/5
Hypotonic gait - Normal	5/5	5/5	5/5	5/5
Tail position - Tail horizontal and rigid	5/5	5/5	5/5	5/5
Tail pinch response - No attention to pinch	0/5 ¹	5/5	5/5	5/5
Mild escape attention	5/5			

¹ During the performance of the FOB tests it was decided that both these observations regarding the tail pinch are considered normal but the first one (no attention) represents a more accurate reaction

Supplementary Table 3 Continues

Behavioral step	Parameter	Group 2M (Vehicle Control I)			
		On Study Day			
		Number Affected / Total Number of Animals (days post dosing)			
		Pre -dosing (acclimation)	3	7	24
Observation in the home cage	Body position - Normal	5/5	5/5	5/5	5/5
	No motor activity although animal awake - Not observed	5/5	5/5	5/5	5/5
	Animal moving around the cage - Observed	5/5	5/5	5/5	5/5
	Rearing - Observed	5/5	5/5	5/5	5/5
	Grooming - Not observed	5/5	4/5	5/5	5/5
	Grooming - Observed		1/5 (3)		
	Animal darting around cage- not observed	5/5	5/5	5/5	5/5
	Aggressiveness towards cage mates - Not observed	5/5	5/5	5/5	5/5
	Animal eats - Not observed	5/5	5/5	5/5	5/5
	Animal drinks - Not observed	5/5	5/5	5/5	5/5
	Animal sleeps - Not observed	5/5	5/5	5/5	5/5
	Sedation - Not observed	5/5	5/5	5/5	5/5
	Excitation - Not observed	5/5	5/5	5/5	5/5
	Piloerection - Absence	5/5	5/5	5/5	5/5
Behavioral symptoms (Observation in the home cage)	Ptosis [Palpebral (eyelid) closure] - Absence	5/5	5/5	5/5	5/5
	Exophthalmos (protrusion of the eyeball) - Not observed	5/5	5/5	5/5	5/5
	Bizarre behavior - Not observed	5/5	5/5	5/5	5/5
	Writhing (Abdominal stretching) - Absence	5/5	5/5	5/5	5/5
	Respiration - Normal	5/5	5/5	5/5	5/5
	Head twitches (Twitch or flick only of head) - Not observed	5/5	5/5	5/5	5/5
	Jumping - Not observed	5/5	5/5	5/5	5/5

Behavior during Handling	Tremors - No tremors	5/5	5/5	5/5	5/5
	Twitch (More than head flicks, often prelude to convulsive behavior) - Absence	5/5	5/5	5/5	5/5
	Convulsions - Not observed	5/5	5/5	5/5	5/5
	Arousal - Normal	5/5	5/5	5/5	5/5
	Startle response - prayer reflex, without jump - Normal	5/5	5/5	5/5	5/5
	Reactivity to touch - Irritable	5/5	4/5	4/5	5/5
	<i>vocalizing when handled</i>		1/5 (5)	1/5 (58)	
	Abdominal tone - Normal	5/5	5/5	5/5	5/5
	Limb tone - Slight	5/5	5/5	5/5	5/5
	Aggressiveness towards handler - Passive (Normal)	5/5	5/5	5/5	5/5

Supplementary Table 3 Continues

Behavioral step	Parameter	Group 2M (Vehicle Control I)			
		On Study Day			
		Number Affected / Total Number of Animals (days post dosing)			
		Pre -dosing (acclimation)	3	7	24
Behavior during Handling	Pupil size – Normal size	5/5	5/5	5/5	5/5
	Visual placing - Normal	5/5	5/5	5/5	5/5
	Tail suspension - Normal	5/5	5/5	5/5	5/5
	Corneal reflex - Normal	5/5	5/5	5/5	5/5
	Grip strength – Normal	5/5	5/5	5/5	5/5
	Hind limb reflex - Normal	5/5	5/5	5/5	5/5
	Righting reflex - Normal	5/5	5/5	5/5	5/5
	Lacrimation - Normal	5/5	5/5	5/5	5/5
	Salivation - Normal	5/5	5/5	5/5	5/5
	Diarrhea - Not observed	5/5	5/5	5/5	5/5
	Urination – no urine puddle on the arena floor	3/5		5/5	5/5
	One urine puddle	2/5 (4,5)			
	Two or three urine puddles		5/5		
	Defecation – No defecation on the arena floor	3/5	4/5	1/5	4/5
	One fecal pellet	1/5 (4)			1/5 (58)
	Two or three fecal pellets	1/5 (5)	1/5 (1)	4/5 (1,58,3,4)	
	Feces consistency - Not evaluated because no defecation occurring during observation	3/5	4/5	1/5	4/5
	Well-formed stools	2/5 (4,5)	1/5 (1)	4/5 (1,58,3,4)	1/5 (58)
	Abnormal vocalization during handling – No abnormal	5/5	5/5	5/5	5/5

Behavioral symptoms (Observation in the open area))	Transfer arousal - Normal	5/5	5/5	5/5	5/5
	Locomotor activity - Normal	5/5	5/5	5/5	5/5
	Ataxic Gait – Normal	5/5	5/5	5/5	5/5
	Hypotonic gait - Normal	5/5	5/5	5/5	5/5
	Tail position – Tail horizontal and rigid	5/5	5/5	5/5	5/5
	Tail pinch response – No attention to pinch	0/5 ²	5/5	5/5	5/5
	Mild escape attention	5/5			

Supplementary Table 3 Continues

Behavioral step	Parameter	Group 3M (Vehicle Control II)			
		On Study Day			
		Number Affected / Total Number of Animals (days post dosing)			
		Pre -dosing (acclimation)	3	7	24
Observation in the home cage	Body position - Normal	5/5	5/5	5/5	5/5
	No motor activity although animal awake - Not observed	5/5	5/5	5/5	5/5
	Animal moving around the cage - Observed	5/5	5/5	5/5	5/5
	Rearing - Observed	5/5	5/5	5/5	5/5
	Grooming - Not observed	5/5	5/5	5/5	5/5
	Animal darting around cage- not observed	5/5	5/5	5/5	5/5
	Aggressiveness towards cage mates - Not observed	5/5	5/5	5/5	5/5
	Animal eats - Not observed	5/5	5/5	5/5	5/5
	Animal drinks - Not observed	5/5	5/5	5/5	5/5
	Animal sleeps - Not observed	5/5	5/5	5/5	5/5
	Sedation - Not observed	5/5	5/5	5/5	5/5
	Excitation - Not observed	5/5	5/5	5/5	5/5
	Piloerection - Absence	5/5	5/5	5/5	5/5
Behavioral symptoms (Observation in the home cage)	Ptosis [Palpebral (eyelid) closure] - Absence	5/5	5/5	5/5	5/5
	Exophthalmos (protrusion of the eyeball) - Not observed	5/5	5/5	5/5	5/5
	Bizarre behavior - Not observed	5/5	5/5	5/5	5/5
	Writhing (Abdominal stretching) - Absence	5/5	5/5	5/5	5/5
	Respiration - Normal	5/5	5/5	5/5	5/5
	Head twitches (Twitch or flick only of head) - Not observed	5/5	5/5	5/5	5/5
	Jumping - Not observed	5/5	5/5	5/5	5/5
	Tremors - No tremors	5/5	5/5	5/5	5/5
	Twitch (More than head flicks, often	5/5	5/5	5/5	5/5

Behavior during Handling	prelude to convulsive behavior) - Absence				
	Convulsions - Not observed	5/5	5/5	5/5	5/5
	Arousal - Normal	5/5	5/5	5/5	5/5
	Startle response – prayer reflex , without jump - Normal	5/5	5/5	5/5	5/5
	Reactivity to touch – Irritable	5/5	3/5	4/5	5/5
	<i>vocalizing when handled</i>		2/5 (11,15)	1/5 (11)	
	Abdominal tone - Normal	5/5	5/5	5/5	5/5
	Limb tone - Slight	5/5	5/5	5/5	5/5
	Aggressiveness towards handler – Passive (Normal)	0/5	5/5	5/5	5/5
	<i>Irritated</i>	4/5 (11, 12, 14, 15)			
	<i>Aggressive</i>	1/5 (13)			

Supplementary Table 3 Continues

Behavioral step	Parameter	Group 3M (Vehicle Control II)			
		On Study Day			
		Number Affected / Total Number of Animals (days post dosing)			
		Pre -dosing (acclimation)	3	7	24
Behavior during Handling	Pupil size - Normal size	5/5	5/5	5/5	5/5
	Visual placing - Normal	5/5	5/5	5/5	5/5
	Tail suspension - Normal	5/5	5/5	5/5	5/5
	Corneal reflex - Normal	5/5	5/5	5/5	5/5
	Grip strength - Normal	5/5	5/5	5/5	5/5
	Hind limb reflex - Normal	5/5	5/5	5/5	5/5
	Righting reflex - Normal	5/5	5/5	5/5	5/5
	Lacrimation - Normal	5/5	5/5	5/5	5/5
	Salivation - Normal	5/5	5/5	5/5	5/5
	Diarrhea - Not observed	5/5	5/5	5/5	5/5
	Urination - no urine puddle on the arena floor	4/5	4/5	5/5	5/5
	Two or three urine puddles	1/5 (13)	1/5 (11)		
	Defecation - No defecation on the arena floor	4/5	3/5	4/5	4/5
	One fecal pellet	1/5 (14)	1/5 (12)	1/5 (13)	1/5 (14)
	Two or three fecal pellets		1/5 (11)		
	Feces consistency - Not evaluated because no defecation occurring during observation	4/5	3/5	4/5	4/5
	Well-formed stools	1/5 (14)	2/5 (11,12)	1/5 (13)	1/5 (14)
	Abnormal vocalization during handling - No abnormal	5/5	5/5	5/5	5/5
symp to ms (Obs)	Transfer arousal - Normal	5/5	5/5	5/5	5/5

Locomotor activity - Normal	5/5	5/5	5/5	5/5
Ataxic Gait – Normal	5/5	5/5	5/5	5/5
Hypotonic gait - Normal	5/5	5/5	5/5	5/5
Tail position – Tail horizontal and rigid	5/5	5/5	5/5	5/5
Tail pinch response – No attention to pinch	0/5 ³	5/5	5/5	5/5
<i>Mild escape attention</i>	5/5			

Supplementary Table 3 Continues

Behavioral step	Parameter	Group 4M (Test Item I)			
		On Study Day			
		Number Affected / Total Number of Animals (days post dosing)			
		Pre -dosing (acclimation)	3	7	24
Observation in the home cage	Body position - Normal	5/5	5/5	5/5	5/5
	No motor activity although animal awake - Not observed	5/5	5/5	5/5	5/5
	Animal moving around the cage - Observed	5/5	5/5	5/5	5/5
	Rearing - Observed	5/5	5/5	5/5	5/5
	Grooming - Not observed	5/5	5/5	5/5	5/5
	Animal darting around cage- not observed	5/5	5/5	5/5	5/5
	Aggressiveness towards cage mates - Not observed	5/5	5/5	5/5	5/5
	Animal eats - Not observed	5/5	5/5	5/5	5/5
	Animal drinks - Not observed	5/5	5/5	5/5	5/5
	Animal sleeps - Not observed	5/5	5/5	5/5	5/5
	Sedation - Not observed	5/5	5/5	5/5	5/5
	Excitation - Not observed	5/5	5/5	5/5	5/5
	Piloerection - Absence	5/5	5/5	5/5	5/5
Behavioral symptoms (Observation in the home cage)	Ptosis [Palpebral (eyelid) closure] - Absence	5/5	5/5	5/5	5/5
	Exophthalmos (protrusion of the eyeball) - Not observed	5/5	5/5	5/5	5/5
	Bizarre behavior - Not observed	5/5	5/5	5/5	5/5
	Writhing (Abdominal stretching) - Absence	5/5	5/5	5/5	5/5
	Respiration - Normal	5/5	5/5	5/5	5/5
	Head twitches (Twitch or flick only of head) - Not observed	5/5	5/5	5/5	5/5
	Jumping - Not observed	5/5	5/5	5/5	5/5
	Tremors - No tremors	5/5	5/5	5/5	5/5
	Twitch (More than head flicks, often	5/5	5/5	5/5	5/5

	prelude to convulsive behavior) - Absence				
	Convulsions - Not observed	5/5	5/5	5/5	5/5
	Arousal - Normal	5/5	5/5	5/5	5/5
	Startle response – prayer reflex , without jump - Normal	5/5	5/5	5/5	5/5
Behavior during Handling	Reactivity to touch – Irritable	4/5	5/5	5/5	5/5
	<i>vocalizing when handled</i>	1/5 (25)			
	Abdominal tone - Normal	5/5	5/5	5/5	5/5
	Limb tone - Slight	5/5	5/5	5/5	5/5
	Aggressiveness towards handler – Passive (Normal)	5/5	5/5	5/5	5/5

Supplementary Table 3 Continues

Behavioral step	Parameter	Group 4M (Test Item I)			
		On Study Day			
		Number Affected / Total Number of Animals (days post dosing)			
		Pre -dosing (acclimation)	3	7	24
Behavior during Handling	Pupil size - Normal size	5/5	5/5	5/5	5/5
	Visual placing - Normal	5/5	5/5	5/5	5/5
	Tail suspension - Normal	5/5	5/5	5/5	5/5
	Corneal reflex - Normal	5/5	5/5	5/5	5/5
	Grip strength - Normal	5/5	5/5	5/5	5/5
	Hind limb reflex - Normal	5/5	5/5	5/5	5/5
	Righting reflex - Normal	5/5	5/5	5/5	5/5
	Lacrimation - Normal	5/5	5/5	5/5	5/5
	Salivation - Normal	5/5	5/5	5/5	5/5
	Diarrhea - Not observed	5/5	5/5	5/5	5/5
	Urination - no urine puddle on the arena floor	4/5		5/5	5/5
	One urine puddle	1/5 (24)			
	Two or three urine puddles		5/5		
	Defecation - No defecation on the arena floor	3/5	4/5	5/5	5/5
	One fecal pellet	2/5 (21,25)	1/5 (22)		
	Feces consistency - Not evaluated because no defecation occurring during observation	3/5	4/5	5/5	4/5
	Well-formed stools	2/5 (21,25)	1/5 (22)		1/5 (22)
	Abnormal vocalization during handling - No abnormal	5/5	5/5	5/5	5/5
ral sympto ms (Observati n in the	Transfer arousal - Normal	5/5	5/5	5/5	5/5
	Locomotor activity - Normal	5/5	5/5	5/5	5/5

Ataxic Gait – Normal	5/5	5/5	5/5	5/5
Hypotonic gait - Normal	5/5	5/5	5/5	5/5
Tail position – Tail horizontal and rigid	5/5	5/5	5/5	5/5
Tail pinch response – No attention to pinch	0/5 ⁴	5/5	5/5	5/5
<i>Mild escape attention</i>	5/5			

Supplementary Table 3 Continues

Behavioral step	Parameter	Group 5M (Test Item II)			
		On Study Day			
		Number Affected / Total Number of Animals (days post dosing)			
		Pre -dosing (acclimation)	3	7	24
Observation in the home cage	Body position - Normal	5/5	5/5	5/5	5/5
	No motor activity although animal awake - Not observed	5/5	5/5	5/5	5/5
	Animal moving around the cage - Observed	5/5	5/5	5/5	5/5
	Rearing - Observed	5/5	5/5	5/5	5/5
	Grooming - Not observed	5/5	5/5	5/5	5/5
	Animal darting around cage- not observed	5/5	5/5	5/5	5/5
	Aggressiveness towards cage mates - Not observed	5/5	5/5	5/5	5/5
	Animal eats - Not observed	5/5	5/5	5/5	5/5
	Animal drinks - Not observed	5/5	5/5	5/5	5/5
	Animal sleeps - Not observed	5/5	5/5	5/5	5/5
	Sedation - Not observed	5/5	5/5	5/5	5/5
	Excitation - Not observed	5/5	5/5	5/5	5/5
	Piloerection - Absence	5/5	5/5	5/5	5/5
Behavioral symptoms (Observation in the home cage)	Ptosis [Palpebral (eyelid) closure] - Absence	5/5	5/5	5/5	5/5
	Exophthalmos (protrusion of the eyebal - Not observed	5/5	5/5	5/5	5/5
	Bizarre behavior - Not observed	5/5	5/5	5/5	5/5
	Writhing (Abdominal stretching) - Absence	5/5	5/5	5/5	5/5
	Respiration - Normal	5/5	5/5	5/5	5/5
	Head twitches (Twitch or flick only of head) - Not observed	5/5	5/5	5/5	5/5
	Jumping - Not observed	5/5	5/5	5/5	5/5
	Tremors - No tremors	5/5	5/5	5/5	5/5
	Twitch (More than head flicks, often	5/5	5/5	5/5	5/5

	prelude to convulsive behavior) - Absence				
	Convulsions - Not observed	5/5	5/5	5/5	5/5
	Arousal - Normal	5/5	5/5	5/5	5/5
	Startle response – prayer reflex , without jump - Normal	5/5	5/5	5/5	5/5
Behavior during Handling	Reactivity to touch – Irritable	3/5	5/5	5/5	4/5
	<i>vocalizing when handled</i>	2/5			1/5
		)33,34)			(32)
	Abdominal tone - Normal	5/5	5/5	5/5	5/5
	Limb tone - Slight	5/5	5/5	5/5	5/5
	Aggressiveness towards handler – Passiv (Normal)	5/5	5/5	5/5	5/5

Supplementary Table 3 Continues

Behavioral step	Parameter	Group 5M (Test Item II)			
		On Study Day			
		Number Affected / Total Number of Animals (days post dosing)			
		Pre -dosing (acclimation)	3	7	24
Behavior during Handling	Pupil size – Normal size	5/5	5/5	5/5	5/5
	Visual placing - Normal	5/5	5/5	5/5	5/5
	Tail suspension - Normal	5/5	5/5	5/5	5/5
	Corneal reflex - Normal	5/5	5/5	5/5	5/5
	Grip strength – Normal	5/5	5/5	5/5	5/5
	Hind limb reflex - Normal	5/5	5/5	5/5	5/5
	Righting reflex - Normal	5/5	5/5	5/5	5/5
	Lacrimation - Normal	5/5	5/5	5/5	5/5
	Salivation - Normal	5/5	5/5	5/5	5/5
	Diarrhea - Not observed	5/5	5/5	5/5	5/5
	Urination – no urine puddle on the arena floor	3/5		5/5	4/5
	One urine puddle	2/5 (32,34)			1/5 (34)
	Two or three urine puddles		5/5		
	Defecation – No defecation on the arena floor	3/5	5/5	4/5	4/5
	One fecal pellet	1/5 (31)			1/5 (34)
	Two or three fecal pellets	1/5 (35)		1/5 (35)	
	Feces consistency - Not evaluated because no defecation occurring during observation	3/5	5/5	4/5	4/5
	Well-formed stools	2/5 (31,35)		1/5 (35)	1/5 (34)
	Abnormal vocalization during handling – No abnormal	5/5	5/5	5/5	5/5

Behavioral symptoms (Observation in the open area))	Transfer arousal - Normal	5/5	5/5	5/5	5/5
	Locomotor activity - Normal	5/5/	5/5	5/5	5/5
	Ataxic Gait – Normal	5/5	5/5	5/5	5/5
	Hypotonic gait - Normal	5/5	5/5	5/5	5/5
	Tail position – Tail horizontal and rigid	5/5	5/5	5/5	5/5
	Tail pinch response – No attention to pinch	0/5 ⁵	5/5	5/5	5/5
	Mild escape attention	5/5			

Supplementary Table 3 Neurological Assessment - Females

Behavioral step	Parameter	Group 1F (Untreated control)			
		On Study Day			
		Number Affected / Total Number of Animals			
		(days post dosing)			
		Pre -dosing (acclimation)	3	7	24
Observation in the home cage	Body position - Normal	5/5	5/5	5/5	5/5
	No motor activity although animal awake - Not observed	5/5	5/5	5/5	5/5
	Animal moving around the cage - Observed	5/5	5/5	5/5	5/5
	Rearing - Observed	5/5	5/5	5/5	5/5
	Grooming - Not observed	5/5	5/5	5/5	5/5
	Animal darting around cage- not observed	5/5	5/5	5/5	5/5
	Aggressiveness towards cage mates - Not observed	5/5	5/5	5/5	5/5
	Animal eats - Not observed	5/5	5/5	5/5	5/5
	Animal drinks - Not observed	5/5	5/5	5/5	5/5
	Animal sleeps - Not observed	5/5	5/5	5/5	5/5
	Sedation - Not observed	5/5	5/5	5/5	5/5
	Excitation - Not observed	5/5	5/5	5/5	5/5
	Piloerection - Absence	5/5	5/5	5/5	5/5
Behavioral symptoms (Observation in the home cage)	Ptosis [Palpebral (eyelid) closure] - Absence	5/5	5/5	5/5	5/5
	Exophthalmos (protrusion of the eyeball) - Not observed	5/5	5/5	5/5	5/5
	Bizarre behavior - Not observed	5/5	5/5	5/5	5/5
	Writhing (Abdominal stretching) - Absence	5/5	5/5	5/5	5/5
	Respiration - Normal	5/5	5/5	5/5	5/5
	Head twitches (Twitch or flick only of head) - Not observed	5/5	5/5	5/5	5/5
	Jumping - Not observed	5/5	5/5	5/5	5/5
	Tremors - No tremors	5/5	5/5	5/5	5/5
	Twitch (More than head flicks, often	5/5	5/5	5/5	5/5

Behavior during Handling	prelude to convulsive behavior) - Absence				
	Convulsions - Not observed	5/5	5/5	5/5	5/5
	Arousal - Normal	5/5	5/5	5/5	5/5
	Startle response – prayer reflex , without jump - Normal	5/5	5/5	5/5	5/5
	Reactivity to touch – Irritable	5/5	4/5	5/5	5/5
	<i>vocalizing when handled</i>		1/5 (141)		
	Abdominal tone - Normal	5/5	5/5	5/5	5/5
	Limb tone - Slight	5/5	5/5	5/5	5/5
	Aggressiveness towards handler – Passive (Normal)	5/5	5/5	5/5	5/5

Supplementary Table 3 Continues

Behavioral step	Parameter	Group 1F (Untreated control)			
		On Study Day			
		Number Affected / Total Number of Animals			
		(days post dosing)			
		Pre -dosing (acclimation)	3	7	24
Behavior during Handling	Pupil size – Normal size	5/5	5/5	5/5	5/5
	Visual placing - Normal	5/5	5/5	5/5	5/5
	Tail suspension - Normal	5/5	5/5	5/5	5/5
	Corneal reflex - Normal	5/5	5/5	5/5	5/5
	Grip strength – Normal	5/5	5/5	5/5	5/5
	Hind limb reflex - Normal	5/5	5/5	5/5	5/5
	Righting reflex - Normal	5/5	5/5	5/5	5/5
	Lacrimation - Normal	5/5	5/5	5/5	5/5
	Salivation - Normal	5/5	5/5	5/5	5/5
	Diarrhea - Not observed	5/5	5/5	5/5	5/5
	Urination – no urine puddle on the aren floor	5/5	5/5	5/5	5/5
	Defecation – No defecation on the arena floor	4/5	4/5	4/5	5/5
	<i>one fecal pellet</i>	1/5 (142)	1/5 (145)	1/5 (144)	
	Feces consistency - Not evaluated because no defecation occurring during observation	4/5	4/5	4/5	5/5
	<i>Well-formed stools</i>	1/5 (142)	1/5 (145)	1/5 (144)	
	Abnormal vocalization during handling – No abnormal	5/5	5/5	5/5	5/5
Behavioral symptoms (Observation in the open area)	Transfer arousal - Normal	5/5	5/5	5/5	5/5
	Locomotor activity - Normal	5/5	5/5	5/5	5/5
	Ataxic Gait – Normal	5/5	5/5	5/5	5/5
	Hypotonic gait - Normal	5/5	5/5	5/5	5/5
	Tail position – Tail horizontal and rigid	5/5	5/5	5/5	5/5

Tail pinch response – No attention to pinch	5/5	5/5	5/5	5/5
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Supplementary Table 3 Continues

Behavioral step	Parameter	Group 2F (Vehicle Control I)			
		On Study Day			
		Number Affected / Total Number of Animals (days post dosing)			
		Pre -dosing (acclimation)	3	7	24
Observation in the home cage	Body position - Normal	5/5	5/5	5/5	5/5
	No motor activity although animal awake - Not observed	5/5	5/5	5/5	5/5
	Animal moving around the cage - Observed	5/5	5/5	5/5	5/5
	Rearing - Observed	5/5	5/5	5/5	5/5
	Grooming - Not observed	5/5	5/5	5/5	5/5
	Animal darting around cage- not observed	5/5	5/5	5/5	5/5
	Aggressiveness towards cage mates - Not observed	5/5	5/5	5/5	5/5
	Animal eats - Not observed	5/5	5/5	5/5	5/5
	Animal drinks - Not observed	5/5	5/5	5/5	5/5
	Animal sleeps - Not observed	5/5	5/5	5/5	5/5
	Sedation - Not observed	5/5	5/5	5/5	5/5
	Excitation - Not observed	5/5	5/5	5/5	5/5
	Piloerection - Absence	5/5	5/5	5/5	5/5
Behavioral symptoms (Observation in the home cage)	Ptosis [Palpebral (eyelid) closure] - Absence	5/5	5/5	5/5	5/5
	Exophthalmos (protrusion of the eyebal - Not observed	5/5	5/5	5/5	5/5
	Bizarre behavior - Not observed	5/5	5/5	5/5	5/5
	Writhing (Abdominal stretching) - Absence	5/5	5/5	5/5	5/5
	Respiration - Normal	5/5	5/5	5/5	5/5
	Head twitches (Twitch or flick only of head) - Not observed	5/5	5/5	5/5	5/5
	Jumping - Not observed	5/5	5/5	5/5	5/5
	Tremors - No tremors	5/5	5/5	5/5	5/5
	Twitch (More than head flicks, often	5/5	5/5	5/5	5/5

	prelude to convulsive behavior) - Absence				
	Convulsions - Not observed	5/5	5/5	5/5	5/5
	Arousal - Normal	5/5	5/5	5/5	5/5
	Startle response – prayer reflex , without jump - Normal	5/5	5/5	5/5	5/5
Behavior during Handling	Reactivity to touch – Irritable	4/5	5/5	5/5	5/5
	<i>vocalizing when handled</i>	1/5 (104)			
	Abdominal tone - Normal	5/5	5/5	5/5	5/5
	Limb tone - Slight	5/5	5/5	5/5	5/5
	Aggressiveness towards handler – Passive (Normal)	5/5	5/5	5/5	5/5

Supplementary Table 3 Continues

Behavioral step	Parameter	Group 2F (Vehicle Control I)			
		On Study Day			
		Number Affected / Total Number of Animals			
		(days post dosing)			
		Pre -dosing (acclimation)	3	7	24
Behavior during Handling	Pupil size - Normal size	5/5	5/5	5/5	5/5
	Visual placing - Normal	5/5	5/5	5/5	5/5
	Tail suspension - Normal	5/5	5/5	5/5	5/5
	Corneal reflex - Normal	5/5	5/5	5/5	5/5
	Grip strength - Normal	5/5	5/5	5/5	5/5
	Hind limb reflex - Normal	5/5	5/5	5/5	5/5
	Righting reflex - Normal	5/5	5/5	5/5	5/5
	Lacrimation - Normal	5/5	5/5	5/5	5/5
	Salivation - Normal	5/5	5/5	5/5	5/5
	Diarrhea - Not observed	5/5	5/5	5/5	5/5
	Urination - no urine puddle on the arena floor	5/5	5/5	5/5	5/5
	Defecation - No defecation on the arena floor	5/5	3/5	1/5	5/5
	One fecal pellet		2/5 (103,104)		
	Two or three fecal pellets			4/5 (101,102,103, 104)	
	Feces consistency - Not evaluated because no defecation occurring during observation	5/5	3/5	1/5	5/5
Behavioral symptoms (Observation in the open area)	Well-formed stools		2/5 (103,104)	4/5 (101,102,103, 104)	
	Abnormal vocalization during handling - No abnormal	5/5	5/5	5/5	5/5
	Transfer arousal - Normal	5/5	5/5	5/5	5/5
	Locomotor activity - Normal	5/5	5/5	5/5	5/5
	Ataxic Gait - Normal	5/5	5/5	5/5	5/5

Hypotonic gait - Normal	5/5	5/5	4/5	5/5
<i>Hypotonic gait - slight</i>			1/5 (101)	
Tail position – Tail horizontal and rigid	5/5	5/5	5/5	5/5
Tail pinch response – No attention to pinch	5/5	5/5	5/5	5/5

Supplementary Table 3 Continues

Behavioral step	Parameter	Group 3F (Vehicle Control II)			
		On Study Day			
		Number Affected / Total Number of Animals			
		(days post dosing)			
		Pre -dosing (acclimation)	3	7	24
Observation in the home cage	Body position - Normal	5/5	5/5	5/5	5/5
	No motor activity although animal awake - Not observed	5/5	5/5	5/5	5/5
	Animal moving around the cage - Observed	5/5	5/5	5/5	5/5
	Rearing - Observed	5/5	5/5	5/5	5/5
	Grooming - Not observed	5/5	5/5	5/5	5/5
	Animal darting around cage- not observed	5/5	4/5	5/5	5/5
	Animal darting around cage - observed		1/5 (114)		
	Aggressiveness towards cage mates - Not observed	5/5	5/5	5/5	5/5
	Animal eats - Not observed	5/5	5/5	5/5	5/5
	Animal drinks - Not observed	5/5	5/5	5/5	5/5
	Animal sleeps - Not observed	5/5	5/5	5/5	5/5
	Sedation - Not observed	5/5	5/5	5/5	5/5
	Excitation - Not observed	5/5	5/5	5/5	5/5
	Piloerection - Absence	5/5	5/5	5/5	5/5
Behavioral symptoms (Observation in the home cage)	Ptosis [Palpebral (eyelid) closure] - Absence	5/5	5/5	5/5	5/5
	Exophthalmos (protrusion of the eyeball) - Not observed	5/5	5/5	5/5	5/5
	Bizarre behavior - Not observed	5/5	4/5	5/5	5/5
	Bizarre behavior - observed		1/5 (114)		
	Writhing (Abdominal stretching) - Absence	5/5	5/5	5/5	5/5
	Respiration - Normal	5/5	5/5	5/5	5/5

Behavior during Handling	Head twitches (Twitch or flick only of head) - Not observed	5/5	5/5	5/5	5/5
	Jumping - Not observed	5/5	5/5	5/5	5/5
	Tremors - No tremors	5/5	5/5	5/5	5/5
	Twitch (More than head flicks, often prelude to convulsive behavior) - Absence	5/5	5/5	5/5	5/5
	Convulsions - Not observed	5/5	5/5	5/5	5/5
	Arousal - Normal	5/5	5/5	5/5	5/5
	Startle response – prayer reflex , without jump - Normal	5/5	5/5	5/5	5/5
	Reactivity to touch – Irritable	5/5	5/5	5/5	5/5
	Abdominal tone - Normal	5/5	5/5	5/5	5/5
	Limb tone - Slight	5/5	5/5	5/5	5/5
	Aggressiveness towards handler – Passive (Normal)	5/5	5/5	5/5	5/5

Supplementary Table 3 Continues

Behavioral step	Parameter	Group 3F (Vehicle Control II)			
		On Study Day			
		Number Affected / Total Number of Animals			
		(days post dosing)			
		Pre -dosing (acclimation)	3	7	24
Behavior during Handling	Pupil size - Normal size	5/5	5/5	5/5	5/5
	Visual placing - Normal	5/5	5/5	5/5	5/5
	Tail suspension - Normal	5/5	5/5	5/5	5/5
	Corneal reflex - Normal	5/5	5/5	5/5	5/5
	Grip strength - Normal	5/5	5/5	5/5	5/5
	Hind limb reflex - Normal	5/5	5/5	5/5	5/5
	Righting reflex - Normal	5/5	5/5	5/5	5/5
	Lacrimation - Normal	5/5	5/5	5/5	5/5
	Salivation - Normal	5/5	5/5	5/5	5/5
	Diarrhea - Not observed	5/5	5/5	5/5	5/5
	Urination - no urine puddle on the arena floor	5/5	5/5	5/5	5/5
	Defecation - No defecation on the arena floor	4/5	5/5	4/5	5/5
	One fecal pellet	1/5 (111)		1/5 (113)	
	Feces consistency - Not evaluated because no defecation occurring during observation	4/5	5/5	4/5	5/5
	Well-formed stools	1/5 (111)		1/5 (113)	
	Abnormal vocalization during handling - No abnormal	5/5	5/5	5/5	5/5
Behavioral symptoms (Observation in the open area)	Transfer arousal - Normal	5/5	5/5	5/5	5/5
	Locomotor activity - Normal	5/5	5/5	5/5	5/5
	Ataxic Gait - Normal	5/5	5/5	5/5	5/5
	Hypotonic gait - Normal	5/5	5/5	5/5	5/5
	Tail position - Tail horizontal and rigid	5/5	5/5	5/5	5/5

Tail pinch response – No attention to pinch	5/5	5/5	5/5	5/5
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Supplementary Table 3 Continues

Behavioral step	Parameter	Group 4F (Test Item I)			
		On Study Day			
		Number Affected / Total Number of Animals (days post dosing)			
		Pre -dosing (acclimation)	3	7	24
Observation in the home cage	Body position - Normal	5/5	5/5	5/5	5/5
	No motor activity although animal awake - Not observed	5/5	5/5	5/5	5/5
	Animal moving around the cage - Observed	5/5	5/5	5/5	5/5
	Rearing - Observed	5/5	5/5	5/5	5/5
	Grooming - Not observed	5/5	5/5	5/5	5/5
	Animal darting around cage- not observed	5/5	5/5	5/5	5/5
	Aggressiveness towards cage mates - Not observed	5/5	5/5	5/5	5/5
	Animal eats - Not observed	5/5	5/5	5/5	5/5
	Animal drinks - Not observed	5/5	5/5	5/5	5/5
	Animal sleeps - Not observed	5/5	5/5	5/5	5/5
	Sedation - Not observed	5/5	5/5	5/5	5/5
	Excitation - Not observed	5/5	5/5	5/5	5/5
	Piloerection - Absence	5/5	5/5	5/5	5/5
Behavioral symptoms (Observation in the home cage)	Ptosis [Palpebral (eyelid) closure] - Absence	5/5	5/5	5/5	5/5
	Exophthalmos (protrusion of the eyeball) - Not observed	5/5	5/5	5/5	5/5
	Bizarre behavior - Not observed	5/5	5/5	5/5	5/5
	Writhing (Abdominal stretching) - Absence	5/5	5/5	5/5	5/5
	Respiration - Normal	5/5	5/5	5/5	5/5
	Head twitches (Twitch or flick only of head) - Not observed	5/5	5/5	5/5	5/5
	Jumping - Not observed	5/5	5/5	5/5	5/5
	Tremors - No tremors	5/5	5/5	5/5	5/5
	Twitch (More than head flicks, often	5/5	5/5	5/5	5/5

Behavior during Handling	prelude to convulsive behavior) - Absence				
	Convulsions - Not observed	5/5	5/5	5/5	5/5
	Arousal - Normal	5/5	5/5	5/5	5/5
	Startle response – prayer reflex , without jump - Normal	5/5	5/5	5/5	5/5
	Reactivity to touch – Irritable	5/5	3/5	5/5	5/5
	<i>vocalizing when handled</i>		2/5 (122,123)		
	Abdominal tone - Normal	5/5	5/5	4/5	5/5
	Abdominal tone – Flaccid but slow return			1/5 (123)	
	Limb tone - Slight	5/5	5/5	5/5	5/5
	Aggressiveness towards handler – Passive (Normal)	5/5	5/5	5/5	5/5

Supplementary Table 3 Continues

Behavioral step	Parameter	Group 4F (Test Item I)			
		On Study Day			
		Number Affected / Total Number of Animals			
		(days post dosing)			
		Pre -dosing (acclimation)	3	7	24
Behavior during Handling	Pupil size – Normal size	5/5	5/5	5/5	5/5
	Visual placing - Normal	5/5	5/5	5/5	5/5
	Tail suspension - Normal	5/5	5/5	5/5	5/5
	Corneal reflex - Normal	5/5	5/5	5/5	5/5
	Grip strength – Normal	5/5	5/5	5/5	5/5
	Hind limb reflex - Normal	5/5	5/5	4/5	5/5
	<i>Hind limb reflex -Moderate</i>			1/5 (123)	
	Righting reflex - Normal	5/5	5/5	5/5	5/5
	Lacrimation - Normal	5/5	5/5	5/5	5/5
	Salivation - Normal	5/5	5/5	5/5	5/5
	Diarrhea - Not observed	5/5	5/5	5/5	5/5
	Urination – no urine puddle on the arena floor	5/5	5/5	5/5	5/5
	Defecation – No defecation on the arena floor	5/5	5/5	5/5	5/5
	Feces consistency - Not evaluated because no defecation occurring during observation	5/5	5/5	5/5	5/5
	Abnormal vocalization during handling – No abnormal	5/5	4/5	5/5	5/5
	<i>Abnormal vocalization during handling – Abnormal when handled</i>		1/5 (123)		
Behavioral symptoms (Observation in the open area)	Transfer arousal - Normal	5/5	5/5	5/5	5/5
	Locomotor activity - Normal	5/5	5/5	5/5	5/5
	Ataxic Gait – Normal	5/5	5/5	5/5	5/5
	Hypotonic gait - Normal	5/5	5/5	4/5	5/5
	<i>Hypotonic gait – Slight hypotonic gait</i>			1/5	

			(123)	
Tail position – Tail horizontal and rigid	5/5	5/5	5/5	5/5
Tail pinch response – No attention to pinch	5/5	5/5	5/5	5/5

Supplementary Table 3 Continues

Behavioral step	Parameter	Group 5F (Test Item II)			
		On Study Day			
		Number Affected / Total Number of Animals (days post dosing)			
		Pre -dosing (acclimation)	3	7	24
Observation in the home cage	Body position - Normal	5/5	5/5	5/5	5/5
	No motor activity although animal awake - Not observed	5/5	5/5	5/5	5/5
	Animal moving around the cage - Observed	5/5	5/5	5/5	5/5
	Rearing - Observed	5/5	5/5	5/5	5/5
	Grooming - Not observed	5/5	5/5	5/5	5/5
	Animal darting around cage- not observed	5/5	5/5	5/5	5/5
	Aggressiveness towards cage mates - Not observed	5/5	5/5	5/5	5/5
	Animal eats - Not observed	5/5	5/5	5/5	5/5
	Animal drinks - Not observed	5/5	5/5	5/5	5/5
	Animal sleeps - Not observed	5/5	5/5	5/5	5/5
	Sedation - Not observed	5/5	5/5	5/5	5/5
	Excitation - Not observed	5/5	5/5	5/5	5/5
	Piloerection - Absence	5/5	5/5	5/5	5/5
Behavioral symptoms (Observation in the home cage)	Ptosis [Palpebral (eyelid) closure] - Absence	5/5	5/5	5/5	5/5
	Exophthalmos (protrusion of the eyebal - Not observed	5/5	5/5	5/5	5/5
	Bizarre behavior - Not observed	5/5	5/5	5/5	5/5
	Writhing (Abdominal stretching) - Absence	5/5	5/5	5/5	5/5
	Respiration - Normal	5/5	5/5	5/5	5/5
	Head twitches (Twitch or flick only of head) - Not observed	5/5	5/5	5/5	5/5
	Jumping - Not observed	5/5	5/5	5/5	5/5
	Tremors - No tremors	5/5	5/5	5/5	5/5
	Twitch (More than head flicks, often	5/5	5/5	5/5	5/5

	prelude to convulsive behavior) - Absence				
	Convulsions - Not observed	5/5	5/5	5/5	5/5
	Arousal - Normal	5/5	5/5	5/5	5/5
	Startle response – prayer reflex , without jump - Normal	5/5	5/5	5/5	5/5
Behavior during Handling	Reactivity to touch – Irritable	3/5	5/5	5/5	5/5
	<i>vocalizing when handled</i>	2/5 (131,134)			
	Abdominal tone - Normal	5/5	5/5	5/5	5/5
	Limb tone - Slight	5/5	5/5	5/5	5/5
	Aggressiveness towards handler – Passiv (Normal)	5/5	5/5	5/5	5/5

Supplementary Table 3 Continues

Behavioral step	Parameter	Group 5F (Test Item II)			
		On Study Day			
		Number Affected / Total Number of Animals (days post dosing)			
		Pre -dosing (acclimation)	3	7	24
Behavior during Handling	Pupil size – Normal size	5/5	5/5	5/5	5/5
	Visual placing - Normal	5/5	5/5	5/5	5/5
	Tail suspension - Normal	5/5	5/5	5/5	5/5
	Corneal reflex - Normal	5/5	5/5	5/5	5/5
	Grip strength – Normal	5/5	5/5	5/5	5/5
	Hind limb reflex - Normal	5/5	3/5	5/5	5/5
	<i>Hind limb reflex- Absence</i>		1/5 (131)		
	<i>Hind limb reflex -moderate impairment</i>		1/5 (134)		
	Righting reflex - Normal	5/5	5/5	5/5	5/5
	Lacrimation - Normal	5/5	5/5	5/5	5/5
	Salivation - Normal	5/5	5/5	5/5	5/5
	Diarrhea - Not observed	5/5	5/5	5/5	5/5
	Urination – no urine puddle on the arena floor	5/5	5/5	5/5	5/5
	Defecation – No defecation on the arena floor	4/5	5/5	3/5	5/5
	<i>One fecal pellet</i>	1/5 (134)		1/5 (133)	
	<i>Two or three fecal pellets</i>			1/5 (134)	
	Feces consistency - Not evaluated because no defecation occurring during observation	4/5	5/5	3/5	5/5
	<i>Well-formed stools</i>	1/5 (134)		2/5 (133,134)	
	Abnormal vocalization during handling –	3/5	5/5	5/5	5/5

Behavioral symptoms (Observation in the open area)	No abnormal				
	Abnormal vocalization during handling – Abnormal when handled	2/5 (131,134)			
	Transfer arousal - Normal	5/5	5/5	5/5	5/5
	Locomotor activity - Normal	5/5	5/5	5/5	5/5
	Ataxic Gait – Normal	5/5	5/5	5/5	5/5
	Hypotonic gait - Normal	5/5	3/5	3/5	5/5
	Hypotonic gait- Slight hypotonic gait		1/5 (131)	2/5 (131,134)	
	Hypotonic gait -marked hypotonic		1/5 (134)		
	Tail position – Tail horizontal and rigid	5/5	5/5	5/5	5/5
	Tail pinch response – No attention to pinch	5/5	5/5	5/5	5/5

Supplementary Table 4: Mean Body weight (Males and Females).

Mean Body

Weight - Male

Group No. and Sex		Body Weights (g) (Days Post Dosing)					
		0	1	7	15	21	28
1M	Mean	26.1		26.8	29.2	29.6	30.1
	SD	1.77		1.90	2.21	2.32	2.51
	n	5		5	5	5	5
2M	Mean	25.2	25.4	25.4	27.3	27.5	27.7
	SD	1.40	0.77	2.00	2.02	2.13	2.14
	n	10	5	5	5	5	5
3M	Mean	25.6	25.6	25.5	26.8	27.5	28.5
	SD	1.23	0.89	1.89	2.22	2.31	2.46
	n	10	5	5	5	5	5
4M	Mean	26.4	25.5	27.2	29.3	29.8	30.0
	SD	1.62	1.73	1.38	1.48	1.22	1.27
	n	10	5	5	5	5	5
5M	Mean	24.3	24.4	24.1	25.9&↓	26.9	27.2
	SD	1.08	1.17	1.31	1.47	1.78	1.73
	n	10	5	5	5	5	5

Note: &p<0.05 Vs. Control(1M) (multiple comparisons test); ↓: Decrease.

Supplementary Table 4: Mean Body Weight-Female.

Group No. and Sex		Body Weights (g) (Days Post Dosing)					
		0	1	7	15	21	28
1F	Mean	20.6		21.1	21.9	22.1	22.2
	SD	1.53		1.31	1.11	1.08	1.16
	n	5		5	5	5	5
2F	Mean	20.5	19.4	20.6	21.1	22.0	22.1
	SD	0.86	1.02	1.22	1.12	1.01	1.15
	n	10	5	5	5	5	5
3F	Mean	20.3	18.5	20.4	21.1	21.5	21.7
	SD	1.30	1.09	1.65	1.63	1.46	1.52
	n	10	5	5	5	5	5
4F	Mean	20.7	19.5	20.6	22.0	22.6	23.2
	SD	0.84	0.39	1.10	1.05	0.60	0.97
	n	10	5	5	5	5	5
5F	Mean	21.3	19.2	21.7	22.5	23.6#↑	23.9
	SD	1.49	0.95	1.80	2.08	1.61	1.67
	n	10	5	5	5	5	5

Note: #p<0.05 Vs. Vehicle Control II (3F) (multiple comparisons test); ↑: Increase; Shaded area-Not Applicable.

Supplementary Table 5: Mean Group Hematology Values (1-day post dosing)-Males.

Parameter	Group 2M			Group 3M			Group 4M			Group 5M		
	Mean	$\pm$ SD	n	Mean	$\pm$ SD	n	Mean	$\pm$ SD	n	Mean	$\pm$ SD	n
WBC (10 ³ /CMM)	2.59	0.614	5	2.83	0.849	5	1.97	0.423	5	1.76*#↓	0.489	5
RBC (10 ⁶ /CMM)	8.92	0.419	5	8.69	0.224	5	9.11##↑	0.370	5	8.96	0.157	5
HGB (g/dl)	13.9	0.68	5	13.5	0.32	5	14.0	0.61	5	13.9	0.22	5
HCT (%)	42.7	1.58	5	41.7	0.73	5	43.5##↑	1.41	5	42.5	0.81	5
MCV (U3)	47.9	0.72	5	48.0	0.43	5	47.7	0.72	5	47.4	0.47	5
MCH (PG)	15.6	0.09	5	15.5	0.12	5	15.4*↓	0.12	5	15.5	0.04	5
MCHC (%)	32.5	0.43	5	32.3	0.24	5	32.3	0.52	5	32.7	0.31	5
Neutrophils (%)	89	5.8	5	93	3.9	5	86#↓	4.0	5	89	4.1	5
Stab (%)	0	0.0	5	0	0.0	5	0	0.0	5	0	0.0	5
Lymphocytes (%)	9	6.8	5	5	2.6	5	12###↑	3.9	5	8	2.7	5
Monocytes (%)	1	0.8	5	1	1.2	5	1	1.8	5	2	1.1	5
Eosinophils (%)	1	1.3	5	1	0.8	5	1	0.5	5	1	1.1	5
Basophils (%)	0	0.0	5	0	0.0	5	0	0.0	5	0	0.0	5
Platelets (10 ³ /CMM)	1295	71.8	5	1307	90.9	5	1346	140.2	5	1288	97.8	5
Neutrophils Abs (10 ³ /μl)	2.31	0.618	5	2.66	0.854	5	1.70#↓	0.399	5	1.57#↓	0.457	5
Bands Abs (10 ³ /μl)	0	0.0	5	0	0.0	5	0	0.0	5	0	0.0	5
Lymphocytes Abs (10 ³ /μl)	0.23	0.168	5	0.13	0.079	5	0.23	0.102	5	0.15	0.045	5
Monocytes Abs (10 ³ /μl)	0.03	0.025	5	0.02	0.023	5	0.02	0.031	5	0.03	0.022	5
Eosinophils Abs (10 ³ /μl)	0.02	0.031	5	0.02	0.016	5	0.01	0.011	5	0.02	0.015	5
Basophils Abs (10 ³ /μl)	0	0.0	5	0	0.0	5	0	0.0	5	0	0.0	5

Note: *p<0.05 Vs. Vehicle Control I (2M), #p<0.05 or ##p<0.01 Vs. Vehicle Control II (3M) (multiple comparisons test); ↑: Increase, ↓: Decrease

Supplementary Table 6: Mean Group Hematology Values (1-day post dosing)-Females.

Parameter	Group 2F			Group 3F			Group 4F			Group 5F		
	Mean	$\pm$ SD	n	Mean	$\pm$ SD	n	Mean	$\pm$ SD	n	Mean	$\pm$ SD	n
WBC (10^3 /CMM)	2.24	0.472	5	0.76	0.642	5	2.44## $\uparrow$	1.096	5	1.63	0.384	5
RBC (10^6 /CMM)	8.63	0.233	5	8.65	0.127	5	8.86	0.503	5	8.80	0.245	5
HGB (g/dl)	13.5	0.42	5	13.6	0.34	5	13.9	0.81	5	13.8	0.37	5
HCT (%)	41.5	0.88	5	40.6	0.38	5	42.9## $\uparrow$	1.86	5	42.1	0.98	5
MCV (U3)	48.1	0.65	5	46.9	0.35	5	48.4## $\uparrow$	0.88	5	47.8	0.24	5
MCH (PG)	15.7	0.14	5	15.7	0.17	5	15.71	0.10	5	15.7	0.04	5
MCHC (%)	32.6	0.45	5	33.4	0.56	5	32.5## $\downarrow$	0.59	5	32.9	0.12	5
Neutrophils (%)	84	4.6	5	82	NA	1	84	5.0	4	90	5.9	4
Stab (%)	0	0.0	5	0	NA	1	0	0.0	4	0	0.0	4
Lymphocytes (%)	10	5.3	5	16	NA	1	10	7.4	4	8	6.2	4
Monocytes (%)	6	3.3	5	2	NA	1	6	2.8	4	2	2.8	4
Eosinophils (%)	0	0.0	5	0	NA	1	0	0.0	4	0	1.0	4
Basophils (%)	0	0.0	5	0	NA	1	0	0.0	4	0	0.0	4
Platelets (10^3 /CMM)	1078	60.0	5	1182	89.9	5	1088	21.2	5	1139	58.0	5
Neutrophils Abs ($10^3/\mu$ l)	1.89	0.412	5	1.53	NA	1	2.31	0.830	4	1.60	0.325	4
Bands Abs ($10^3/\mu$ l)	0	0.0	5	0	NA	1	0	0.0	4	0	0.0	4
Lymphocytes Abs ($10^3/\mu$ l)	0.23	0.148	5	0.29	0.014	2	0.29	0.276	4	0.12	0.083	4
Monocytes Abs ($10^3/\mu$ l)	0.12	0.076	5	0.04	0.000	2	0.16	0.100	4	0.04	0.052	4
Eosinophils Abs ($10^3/\mu$ l)	0.00	0.000	5	0.00	0.007	2	0.00	0.000	4	0.01	0.015	4
Basophils Abs ($10^3/\mu$ l)	0.00	0.000	5	0.22	0.304	2	0.00	0.000	4	0.00	0.000	4

Note: #p<0.05 or ##p<0.01 Vs. Vehicle Control II (3F) (multiple comparisons test); $\uparrow$: Increase, $\downarrow$: Decrease; NA-Not Applicable.

Supplementary Table 7: Mean Group Hematology Values (28-day post dosing)-Males.

Parameter	Group 1M			Group 2M			Group 3M			Group 4M			Group 5M		
	Mean	$\pm$ SD	n	Mean	$\pm$ SD	n	Mean	$\pm$ SD	n	Mean	$\pm$ SD	n	Mean	$\pm$ SD	n
WBC (10 ³ /CMM)	1.26	0.230	5	0.97	0.416	5	1.38	0.273	5	1.15	0.415	5	1.58* [↑]	0.162	5
RBC (10 ⁶ /CMM)	8.73	0.199	5	8.59	0.225	5	8.56	0.200	5	8.62	0.175	5	8.76	0.165	5
HGB (g/dl)	13.5	0.34	5	13.3	0.31	5	13.1	0.31	5	13.3	0.26	5	13.4	0.34	5
HCT (%)	41.9	0.90	5	40.9	1.02	5	41.0	0.86	5	41.5	0.83	5	42.4* [#] [↑]	0.94	5
MCV (U3)	48.1	0.80	5	47.6	0.27	5	47.9	0.21	5	48.1* [↑]	0.32	5	48.5* [#] [↑]	0.35	5
MCH (PG)	15.5	0.24	5	15.4	0.15	5	15.3	0.11	5	15.4	0.08	5	15.3	0.18	5
MCHC (%)	32.3	0.23	5	32.5	0.39	5	32.0	0.30	5	32.0* [↓]	0.18	5	31.7& ^{**} [↓]	0.25	5
Neutrophils (%)	67	1.4	2	70	NA	1	62	14.0	3	63	7.1	2	68	6.3	5
Stab (%)	0	0.0	2	0	NA	1	0	0.0	3	0	0.0	2	0	0.0	5
Lymphocytes (%)	16	2.8	2	28	NA	1	25	11.7	3	20	2.8	2	25	2.6	5
Monocytes (%)	17	4.2	2	2	NA	1	11	8.1	3	13	7.1	2	5	6.5	5
Eosinophils (%)	0	0.0	2	0	NA	1	1	1.2	3	4	2.8	2	2	1.5	5
Basophils (%)	0	0.0	2	0	NA	1	0	0.0	3	0	0.0	2	0	0.0	5
Platelets (10 ³ /CMM)	1380	33.3	5	1446	140.0	5	1434	64.6	5	1433	80.0	5	1410	45.2	5
Neutrophils Abs (10*3/μl)	1.01	0.042	2	0.95	NA	1	0.73	0.529	4	0.97	0.127	2	1.09	0.191	5
Bands Abs (10*3/μl)	0	0.0	2	0	NA	1	0	0.0	4	0	0.0	2	0	0.0	5
Lymphocytes Abs (10*3/μl)	0.24	0.049	2	0.38	NA	1	0.30	0.240	4	0.31	0.028	2	0.40	0.074	5
Monocytes Abs (10*3/μl)	0.26	0.064	2	0.03	NA	1	0.14	0.141	4	0.22	0.163	2	0.06	0.084	5

Eosinophils Abs (10*3/μl)	0.00	0.000	2	0.00	NA	1	0.02	0.017	4	0.07#↑	0.057	2	0.02	0.018	5
Basophils Abs (10*3/μl)	0	0.0	2	0	NA	1	0	0.0	4	0	0.0	2	0	0.0	5

Note: &p<0.05 Vs. Control (1M), *p<0.05 or **p<001 Vs. Vehicle Control I (2M), #p<0.05 Vs. Vehicle Control II (3M) (multiple comparisons test); ↑: Increase, ↓: Decrease; NA - Not Applicable.

Supplementary Table 8: Mean Group Hematology Values (28-day post dosing) – Females.

Parameter	Group 1F			Group 2F			Group 3F			Group 4F			Group 5F		
	Mean	$\pm SD$	<i>n</i>	Mean	$\pm SD$	<i>n</i>	Mean	$\pm SD$	<i>n</i>	Mean	$\pm SD$	<i>n</i>	Mean	$\pm SD$	<i>n</i>
WBC (10 ³ /CMM)	0.91	0.309	5	0.78	0.355	5	1.00	0.203	5	1.12	0.126	5	0.89	0.202	5
RBC (10 ⁶ /CMM)	8.67	0.474	5	8.75	0.212	5	8.93	0.372	5	8.77	0.125	5	8.74	0.213	5
HGB (g/dl)	13.5	0.67	5	13.7	0.43	5	14.1	0.50	5	13.8	0.26	5	13.7	0.26	5
HCT (%)	40.9	1.99	5	41.0	1.11	5	42.1	1.24	5	41.8	0.73	5	41.5	0.81	5
MCV (U3)	47.2	0.46	5	46.8	0.44	5	47.2	1.36	5	47.7*↑	0.29	5	47.6*↑	0.44	5
MCH (PG)	15.6	0.09	5	15.6	0.15	5	15.7	0.11	5	15.7	0.08	5	15.7	0.09	5
MCHC (%)	33.1	0.13	5	33.3	0.27	5	33.4	0.79	5	32.9	0.23	5	32.9	0.36	5
Neutrophils (%)	NA	NA	0	88	NA	1	NA	NA	0	NA	NA	0	NA	NA	0
Stab (%)	NA	NA	0	0	NA	1	NA	NA	0	NA	NA	0	NA	NA	0
Lymphocytes (%)	NA	NA	0	12	NA	1	NA	NA	0	NA	NA	0	NA	NA	0
Monocytes (%)	NA	NA	0	0	NA	1	NA	NA	0	NA	NA	0	NA	NA	0
Eosinophils (%)	NA	NA	0	0	NA	1	NA	NA	0	NA	NA	0	NA	NA	0
Basophils (%)	NA	NA	0	0	NA	1	NA	NA	0	NA	NA	0	NA	NA	0
Platelets (10 ³ /CMM)	1169	124.0	5	1155	47.3	5	1171	126.7	5	1225	105.5	5	1173	42.8	5
Neutrophils Abs (10*3/μl)	NA	NA	0	1.17	NA	1	NA	NA	0	NA	NA	0	NA	NA	0
Bands Abs (10*3/μl)	NA	NA	0	0	NA	1	NA	NA	0	NA	NA	0	NA	NA	0
Lymphocytes Abs (10*3/μl)	NA	NA	0	0.16	NA	1	NA	NA	0	NA	NA	0	NA	NA	0
Monocytes Abs (10*3/μl)	NA	NA	0	0	NA	1	NA	NA	0	NA	NA	0	NA	NA	0

Eosinophils Abs (10*3/ μ l)	NA	NA	0	0	NA	1	NA	NA	0	NA	NA	0	NA	NA	0
Basophils Abs (10*3/ μ l)	NA	NA	0	0	NA	1	NA	NA	0	NA	NA	0	NA	NA	0

Note: *p<0.05 Vs. Vehicle Control I (2F) (multiple comparisons test); ↑: Increase; NA -Not Applicable.

Supplementary Table 9: Mean Group Blood Biochemistry Values (1-day post dosing)-Males.

Parameter	Group 2M			Group 3M			Group 4M			Group 5M		
	Mean	$\pm$ SD	n	Mean	$\pm$ SD	n	Mean	$\pm$ SD	n	Mean	$\pm$ SD	n
Creatinine (mg/dl)	0.12	0.024	5	0.13	0.029	5	0.12	0.030	5	0.08*#↓	0.020	5
Calcium (mg/dl)	9.77	0.231	5	9.86	0.101	5	9.87	0.229	5	9.81	0.288	5
Phosphorus (mg/dl)	7.2	0.80	5	7.9	0.95	5	8.2	1.01	5	9.0*↑	0.84	5
Glucose (mg/dl)	215	28.5	5	221	39.7	5	250	60.8	5	202	74.5	5
Urea (mg/dl)	33.3	2.01	5	33.5	2.24	5	37.3	1.30	5	38.2	4.94	5
Cholesterol (mg/dl)	112	9.6	5	107	3.7	5	115	10.8	5	108	8.2	5
Total Protein (g/dl)	4.54	0.214	5	4.56	0.134	5	4.69	0.308	5	4.59	0.217	5
Albumin (g/dl)	3.2	0.15	5	3.2	0.15	5	3.3	0.24	5	3.3	0.17	5
Globulin (g/dl)	1.30	0.116	5	1.32	0.132	5	1.37	0.085	5	1.25	0.070	5
Alb/Glob (Ratio)	2.50	0.230	5	2.49	0.324	5	2.43	0.118	5	2.68	0.129	5
Total Bilirubin (mg/dl)	0.24	0.042	5	0.20	0.017	5	0.20	0.021	5	0.22	0.043	5
Alkaline Phosphatase (IU/L)	102	11.9	5	99	9.3	5	103	12.7	5	105	10.2	5
LDH (IU/L)	1182	106.8	5	1100	67.9	5	1112	233.8	5	837**#↓	87.8	5
SGOT (IU/L)	89	9.8	5	91	17.8	5	80	12.0	5	92	13.5	5
SGPT (IU/L)	32	5.7	5	28	4.4	5	24	2.6	5	29	3.5	5
Triglycerides (mg/dl)	63	10.1	5	48	10.3	5	48*↓	6.7	5	42**↓	3.9	5
CPK (IU/L)	327	4.3	5	384	95.8	5	329	99.1	5	270*↓	41.6	5
Na (mmol/L)	153	2.3	5	153	1.3	5	153	1.5	5	154	0.9	5
K (mmol/L)	5.1	0.40	5	5.2	0.60	5	5.1	0.66	5	4.7	0.32	5

Chloride (mmol/L)	112	2.4	5	112	0.9	5	112	1.3	5	114	0.4	5
GGT (IU/L)	0	0.4	5	0	0.0	5	0	0.4	5	0	0.0	5

Note: *p<0.05 or **p<001 Vs. Vehicle Control I (2M), #p<0.05 Vs. Vehicle Control II (3M) (multiple comparisons test); ↑: Increase, ↓: Decrease.

Supplementary Table 10: Mean Group Blood Biochemistry Values (1-day post dosing)-Females.

Parameter	Group 2F			Group 3F			Group 4F			Group 5F		
	Mean	$\pm SD$	<i>n</i>	Mean	$\pm SD$	<i>n</i>	Mean	$\pm SD$	<i>n</i>	Mean	$\pm SD$	<i>n</i>
Creatinine (mg/dl)	0.13	0.034	5	0.12	0.025	5	0.12	0.043	5	0.14	0.055	5
Calcium (mg/dl)	9.85	0.155	5	10.09	0.240	5	10.11	0.224	5	10.18	0.250	5
Phosphorus (mg/dl)	8.4	2.25	5	9.9	0.78	5	8.2*↓	0.60	5	9.9	1.42	5
Glucose (mg/dl)	220	44.0	5	206	32.2	5	261	43.2	5	200	43.5	5
Urea (mg/dl)	35.1	6.58	5	37.5	4.41	5	30.5	3.36	5	37.1	7.18	5
Cholesterol (mg/dl)	88	9.2	5	91	10.0	5	96	6.6	5	97	8.1	5
Total Protein (g/dl)	4.86	0.257	5	5.23	0.398	5	4.86	0.282	5	5.28*↑	0.183	5
Albumin (g/dl)	3.8	0.11	5	4.0	0.49	5	3.7	0.30	5	4.0	0.27	5
Globulin (g/dl)	1.02	0.242	5	1.23	0.281	5	1.18	0.156	5	1.24	0.172	5
Alb/Glob (Ratio)	3.92	0.907	5	3.47	1.262	5	3.17	0.624	5	3.32	0.682	5
Total Bilirubin (mg/dl)	0.11	0.028	5	0.09	0.029	5	0.11	0.011	5	0.10	0.013	5
Alkaline Phosphatase (IU/L)	133	9.4	5	163	17.3	5	132#↓	11.5	5	133#↓	20.9	5
LDH (IU/L)	975	177.2	5	1020	116.9	5	942	205.0	5	767#↓	120.9	5
SGOT (IU/L)	126	51.9	5	138	18.1	5	119	41.5	5	122	12.3	5
SGPT (IU/L)	34	16.6	5	35	4.1	5	28	6.8	5	28	2.9	5
Triglycerides (mg/dl)	54	9.6	5	56	6.5	5	52	6.8	5	41*##↓	5.2	5
CPK (IU/L)	502	260.1	5	438	106.2	5	508	393.3	5	417	108.9	5
Na (mmol/L)	149	3.1	5	148	1.3	5	149	0.9	5	150	2.3	5

K (mmol/L)	4.8	0.52	5	4.6	0.33	5	3.9	0.71	5	4.1	0.39	5
Chloride (mmol/L)	110	2.3	5	109	3.8	5	111	0.7	5	112	1.6	5
GGT (IU/L)	0	0.0	5	0	0.0	5	0	0.0	5	0	0.0	5

Note: *p<0.05 or **p<0.01 Vs. Vehicle Control I (2F), #p<0.05 Vs. Vehicle Control II (3F) (multiple comparisons test); ↑: Increase, ↓: Decrease.

Supplementary Table 11: Mean Group Blood Biochemistry Values (28-day post dosing)-Males.

Parameter	Group 1M			Group 2M			Group 3M			Group 4M			Group 5M		
	Mean	$\pm SD$	<i>n</i>	Mean	$\pm SD$	<i>n</i>	Mean	$\pm SD$	<i>n</i>	Mean	$\pm SD$	<i>n</i>	Mean	$\pm SD$	<i>n</i>
Creatinine (mg/dl)	0.12	0.033	5	0.16	0.036	5	0.15	0.033	5	0.13	0.026	5	0.14	0.038	5
Calcium (mg/dl)	9.80	0.196	5	9.95	0.171	5	10.05	0.145	5	9.85	0.217	5	10.20&↑	0.271	5
Phosphorus (mg/dl)	8.0	1.51	5	7.9	1.56	5	8.2	0.58	5	8.4	0.97	5	8.1	0.25	5
Glucose (mg/dl)	212	26.2	5	230	59.2	5	253	49.1	5	237	37.8	5	232	39.5	5
Urea (mg/dl)	53.5	2.52	5	52.9	8.08	5	55.1	3.04	5	52.8	5.28	5	45.9#↓	5.48	5
Cholesterol (mg/dl)	112	4.6	5	112	9.6	5	102	3.4	5	109	3.6	5	111	13.6	5
Total Protein (g/dl)	4.58	0.118	5	4.60	0.267	5	4.42	0.053	5	4.54	0.073	5	4.57	0.168	5
Albumin (g/dl)	3.6	0.09	5	3.6	0.23	5	3.4	0.07	5	3.6#↑	0.17	5	3.5	0.11	5
Globulin (g/dl)	1.02	0.068	5	1.04	0.068	5	1.02	0.113	5	0.94	0.130	5	1.09	0.126	5
Alb/Glob (Ratio)	3.49	0.237	5	3.42	0.241	5	3.37	0.483	5	3.92	0.823	5	3.24	0.448	5
Total Bilirubin (mg/dl)	0.13	0.023	5	0.14	0.034	5	0.16	0.019	5	0.17&↑	0.021	5	0.14	0.013	5
Alkaline Phosphatase (IU/L)	90	7.4	5	83	8.0	5	83	5.5	5	77&↓	4.1	5	86	12.0	5
LDH (IU/L)	1186	170.3	5	1069	49.9	5	868&↓	215.7	5	972	200.2	5	927	205.8	5
SGOT (IU/L)	83	35.6	5	83	14.3	5	69	15.2	5	70	12.2	5	86	43.7	5
SGPT (IU/L)	28	4.4	5	31	2.7	5	25	1.5	5	27*↓	1.9	5	31	13.5	5
Triglycerides (mg/dl)	76	23.2	5	67	17.3	5	62	12.4	5	60	14.4	5	114*##↑	36.6	5
CPK (IU/L)	548	424.6	5	455	197.8	5	348	151.9	5	388	144.8	5	526	393.1	5
Na (mmol/L)	149	1.1	5	148	1.3	5	148	1.6	5	147	1.3	5	148	2.3	5

K (mmol/L)	4.9	0.59	5	4.9	0.32	5	5.1	0.32	5	5.0	0.25	5	5.2	0.80	5
Chloride (mmol/L)	109	0.8	5	108	0.8	5	109	1.6	5	108	1.9	5	109	1.7	5
GGT (IU/L)	0	0.0	5	0	0.0	5	0	0.0	5	0	0.0	5	0	0.0	5

Note: &p<0.05 Vs. Control (1M), *p<0.05 Vs. Vehicle Control I (2M), #p<0.05 Vs. Vehicle Control II (3M) (multiple comparisons test); ↑: Increase, ↓: Decrease.

Supplementary Table 12: Mean Group Blood Biochemistry Values (28-day post dosing)-Females.

Parameter	Group 1F			Group 2F			Group 3F			Group 4F			Group 5F		
	Mean	$\pm SD$	<i>n</i>	Mean	$\pm SD$	<i>n</i>	Mean	$\pm SD$	<i>n</i>	Mean	$\pm SD$	<i>n</i>	Mean	$\pm SD$	<i>n</i>
Creatinine (mg/dl)	0.12	0.032	5	0.09	0.027	5	0.12	0.046	5	0.10	0.015	5	0.11	0.023	5
Calcium (mg/dl)	9.62	0.089	5	9.46	0.106	5	9.79	0.394	5	9.51	0.143	5	9.48	0.147	5
Phosphorus (mg/dl)	7.1	0.60	5	8.1	1.32	5	6.7	0.88	5	7.5	0.78	5	7.4	1.41	5
Glucose (mg/dl)	191	51.6	5	161	43.9	5	174	70.1	5	258** $\uparrow$	28.2	5	236* $\uparrow$	33.5	5
Urea (mg/dl)	46.0	5.36	5	42.7	3.34	5	48.2	4.96	5	45.9	3.82	5	45.4	5.44	5
Cholesterol (mg/dl)	70	6.6	5	70	7.5	5	74	9.5	5	70	5.2	5	70	3.3	5
Total Protein (g/dl)	4.59	0.061	5	4.55	0.173	5	4.66	0.256	5	4.50	0.070	5	4.44	0.064	5
Albumin (g/dl)	3.6	0.05	5	3.6	0.16	5	3.7	0.20	5	3.5	0.11	5	3.5	0.04	5
Globulin (g/dl)	1.03	0.064	5	0.97	0.076	5	0.98	0.059	5	0.98	0.065	5	0.92& $\downarrow$	0.046	5
Alb/Glob (Ratio)	3.46	0.246	5	3.71	0.349	5	3.78	0.143	5	3.63	0.331	5	3.83	0.202	5
Total Bilirubin (mg/dl)	0.12	0.016	5	0.11	0.013	5	0.14	0.020	5	0.11	0.011	5	0.12	0.025	5
Alkaline Phosphatase (IU/L)	111	11.1	5	117	15.8	5	110	6.1	5	108	10.4	5	102	9.7	5
LDH (IU/L)	1058	90.1	5	818	260.4	5	972	178.0	5	693&& $\downarrow$	92.0	5	687&& $\downarrow$	127.7	5
SGOT (IU/L)	121	48.0	5	83	14.9	5	102	19.3	5	70&## $\downarrow$	11.6	5	79	12.7	5
SGPT (IU/L)	44	38.3	5	27	3.4	5	29	4.6	5	23& $\downarrow$	1.9	5	26	4.8	5
Triglycerides (mg/dl)	60	10.2	5	56	14.8	5	92	31.1	5	56# $\downarrow$	3.7	5	55# $\downarrow$	7.2	5
CPK (IU/L)	593	198.7	5	411	237.8	5	581	207.8	5	298# $\downarrow$	113.6	5	381	52.9	5

Na (mmol/L)	149	1.0	5	148	2.2	5	150	1.3	5	147#↓	0.8	5	148#↓	0.9	5
K (mmol/L)	5.2	0.35	5	4.9	0.51	5	4.9	0.85	5	4.7	0.41	5	4.6	0.15	5
Chloride (mmol/L)	111	0.5	5	111	2.0	5	110	1.9	5	110	1.1	5	112	1.1	5
GGT (IU/L)	0	0.0	5	0	0.0	5	0	0.0	5	0	0.0	5	0	0.0	5

Note: &p<0.05 Vs. Control (1F), *p<0.05 or **p<0.01 Vs. Vehicle Control I (2F), #p<0.05 or ##p<0.01 Vs. Vehicle Control II (3F) (multiple comparisons test); ↑: Increase, ↓: Decrease.

Supplementary Table 13: Gross necropsy findings.

Group No. and Sex	Group Size	OBSERVATIONS Number affected/Total number of animals
1M	n=5	No gross lesions observed (5/5)
2M	n=10	No gross lesions observed (10/10)
3M	n=10	No gross lesions observed (10/10)
4M	n=10	No gross lesions observed (10/10)
5M	n=10	No gross lesions observed (10/10)
1F	n=5	No gross lesions observed (5/5)
2F	n=10	No gross lesions observed (10/10)
3F	n=10	No gross lesions observed (10/10)
4F	n=10	No gross lesions observed (10/10)
5F	n=10	No gross lesions observed (10/10)