Appendix

	Atropine			Saline		
	n	(%)	Number of Events	n	(%)	Number of Events
Subjects in population	12			12		
with one or more non-serious adverse events that met the incidence cutoff	5	41.7	10	6	50.0	10
with no non-serious adverse events that met the incidence cutoff	7	58.3		6	50.0	
Blood and lymphatic system disorders						
Neutropenia	0	0.0	0	1	8.3	1
Cardiac disorders						
Palpitations	2	16.7	2	0	0.0	0
Gastrointestinal disorders						
Abdominal pain	0	0.0	0	1	8.3	1
Dry mouth	2	16.7	2	0	0.0	0
General disorders and administration site conditions						
Vessel puncture site haematoma	0	0.0	0	1	8.3	1
Infections and infestations						
Nasopharyngitis	0	0.0	0	1	8.3	1
Injury, poisoning and procedural complications						
Arthropod bite	1	8.3	1	0	0.0	0
Musculoskeletal and connective tissue disorders						
Muscle spasms	0	0.0	0	1	8.3	1
Nervous system disorders						
Dizziness postural	0	0.0	0	1	8.3	1
Dysgeusia	1	8.3	1	0	0.0	0
Paraesthesia	0	0.0	0	1	8.3	2
Somnolence	1	8.3	1	0	0.0	0
Respiratory, thoracic and mediastinal disorders						
Hypopnoea	1	8.3	1	0	0	0
Skin and subcutaneous tissue disorders						
Dry skin	0	0.0	0	1	8.3	1
Psoriasis	1	8.3	1	0	0.0	0
Skin irritation	0	0.0	0	1	8.3	1
Vascular disorders						
Hot flush	1	8.3	1	0	0.0	0
Every subject is counted a single time for each applicable non-serious adverse event. Serious adverse events are not counted in this report						
A specific non-serious adverse event appears on this report only if its incidence in one or more of the columns is greater than the percent incidence specified in the report title, prior to rounding.						
Subjects were given Saline twice in replicate periods; therefore, adverse events reported in the Saline group reflects incidences of adverse events reported in either period.						
Adverse event terms are from MedDRA Version 22.0						

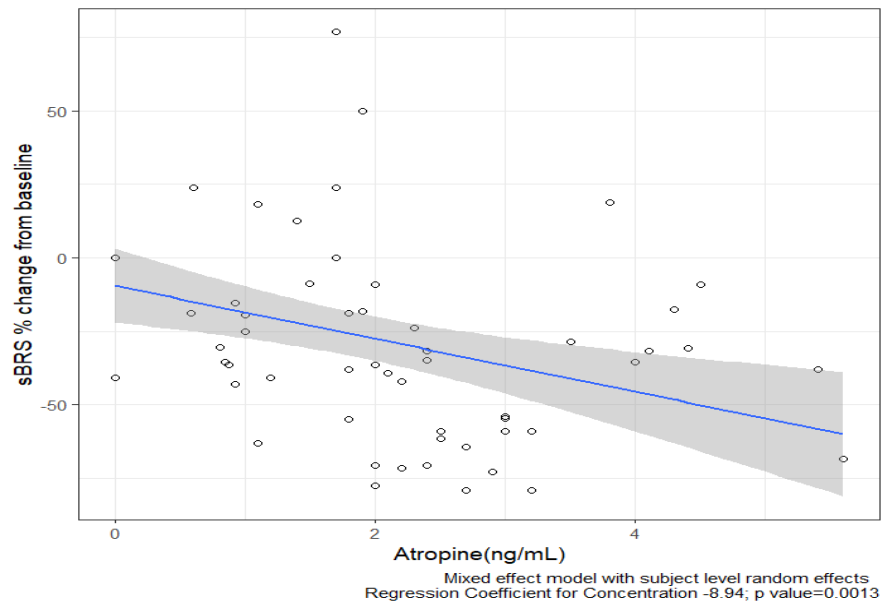
Supplemental Table 1: Adverse events following atropine or saline administration.

Study Period	N per period	GM (90% CI)
Period 1	8	18.49 (15.52, 22.03)
Period 2	8	18.79 (15.77, 22.38)
Period 3	8	18.51 (15.54, 22.05)
CI=confidence interval; GM=geometric mean; N=number of Subjects; TWA=time-weighted average.		
sBRS expressed in msec/mmHg		
Subjects were given Saline twice in replicate study periods.		
CI obtained from a linear mixed effects model with fixed effect of study period and a random effect of subject. The response vector consists of TWA of sBRS on the natural log scale (TWA0-3hours)		

Supplemental Table 2: Geometric Mean of Time Weighted Average of Spontaneous Baroreceptor Sensitivity (sBRS) Following Saline Administration to Healthy Male Subjects (N=12) by Period (Morning Session).

Session	F-Statistic	p-value
Morning	0.073	0.930
Afternoon	1.048	0.394

Supplemental Table 3: Bradley Blackwood procedure: Test for Equality of the Means and Variances of Spontaneous Baroreceptor Sensitivity (sBRS) Administration of Saline 1 and Saline 2 to Healthy Male Subjects (N=12).



Supplemental Figure 1: Atropine concentration vs. percent change from baseline in sBRS.

Linear regression of exploratory PKPD relationship of sBRS percent change from baseline and atropine plasma concentrations following IV bolus administration of atropine (10 µg/kg) to healthy male subjects (n=11 [One subject had only one quantifiable concentration and was excluded from all summary statistics]).