

**REVISED DRAFT REPORT**

**Testing Facility Study No.** [REDACTED]

**Sponsor Reference No.** [REDACTED]

**Sponsor Report No.** [REDACTED]

**Cardiovascular Safety Evaluation of Orally Administered [REDACTED]  
[REDACTED] in Beagle Dogs**

**SPONSOR:**  
[REDACTED]

**TESTING FACILITY:**  
[REDACTED]

**TABLE OF CONTENTS**

	Page
TABLE OF CONTENTS	2
REPORT TEXT	5
COMPLIANCE STATEMENT AND REPORT APPROVAL	5
QUALITY ASSURANCE STATEMENT	6
1. RESPONSIBLE PERSONNEL	7
1.1. Testing Facility	7
1.2. Individual Scientists (IS) at Testing Facility	7
1.3. Principal Investigators (PI)	7
2. SUMMARY	8
3. INTRODUCTION	8
3.1. Study Schedule	8
4. MATERIALS AND METHODS	9
4.1. Test Item and Vehicle Information	9
4.2. Test Item and Vehicle Characterization	10
4.3. Reserve Samples	10
4.4. Test Item Inventory and Disposition	10
4.5. Dose Formulation and Analysis	10
4.6. Test System	11
4.7. Experimental Design	14
4.8. In-life Procedures, Observations, and Measurements	15
4.9. Laboratory Evaluations	16
5. STATISTICS	16
5.1. Paired Sample T-Test Comparison	17
6. COMPUTER SYSTEMS	17
7. RETENTION OF RECORDS, SAMPLES, AND SPECIMENS	18
8. RESULTS	19
8.1. Dose Formulation Analyses	19
8.2. Mortality	19
8.3. Detailed Clinical Observations	19
8.4. Body Weight	19
8.5. Telemetry Data	19
8.6. Bioanalysis Evaluation	21
9. CONCLUSION	22
10. REFERENCES	23
FIGURE	24

**TABLE OF CONTENTS**

	Page
1. Mean Body Temperature	24
2. Mean Systolic Blood Pressure	26
3. Mean Diastolic Blood Pressure	28
4. Mean Arterial Blood Pressure	30
5. Mean Heart Rate	32
6. Mean RR Interval	34
7. Mean PR Interval	36
8. Mean QRS Duration	38
9. Mean QT Interval	40
10. Mean Corrected QT Interval	42
<b>TABLE</b>	<b>44</b>
1. Summary of Detailed Clinical Observations	44
2. Summary of Body Temperature	49
3. Summary of Systolic Blood Pressure	51
4. Summary of Diastolic Blood Pressure	53
5. Summary of Mean Arterial Blood Pressure	55
6. Summary of Heart Rate	57
7. Summary of RR Interval	59
8. Summary of PR Interval	61
9. Summary of QRS Duration	63
10. Summary of QT Interval	65
11. Summary of Corrected QT Interval	67
<b>APPENDIX</b>	<b>69</b>
1. Amended Protocol, Protocol, and Deviations	69
2. Test Item Characterization	130
3. Dose Formulation Analysis Report	134
4. Individual Detailed Clinical Observations	149
5. Individual Body Weight Values	166
6. Individual Body Temperature	168
7. Individual Systolic Blood Pressure	178
8. Individual Diastolic Blood Pressure	188
9. Individual Mean Arterial Blood Pressure	198
10. Individual Heart Rate	208
11. Individual RR Interval	218
12. Individual PR Interval	228

**TABLE OF CONTENTS**

	Page
13. Individual QRS Duration	238
14. Individual QT Interval	248
15. Individual Corrected QT Interval	258
16. Bioanalysis Report	268

**COMPLIANCE STATEMENT AND REPORT APPROVAL**

The study was conducted in accordance with the United States (US) Department of Health and Human Services, Food and Drug Administration (FDA), United States Code of Federal Regulations (CFR), Title 21, Part 58: Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies, and as accepted by Regulatory Authorities throughout the European Union (Organization for Economic Co-operation and Development [OECD] Principles of GLP), Japan (Ministry of Health, Labor and Welfare [MHLW]), and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement. There were no deviations from the above regulations that affected the overall integrity of the study or the interpretation of the study results and conclusions. Exceptions from the above regulations are listed below.

- The bulk test item characterization was conducted using validated methods in a Good Manufacturing Practices (GMP) based quality system. This does not impact the quality of this study as GMP procedures are an acceptable quality-based system.
- The Final Formulation Analysis Report and Bioanalysis Report are not yet available from [REDACTED] for inclusion in this report; draft reports are currently included.

This study was conducted in accordance with the procedures described herein. The report represents an accurate and complete record of the results obtained.



## 2. SUMMARY

The objective of this study was to evaluate the potential cardiovascular effects of the test item, [REDACTED] in conscious freely moving beagle dogs. Six male dogs were administered the vehicle (0 mg [REDACTED] kg; 0.5% hydroxypropylmethylcellulose [HPMC; low viscosity], 0.1% Tween 80 in NANOPure Diamond Ultrapure water [w/v]) or [REDACTED] in vehicle at doses of 20, 50, and 150 mg [REDACTED] kg via oral gavage at a dose volume of 5 mL/kg. All doses were administered according to a Latin-square design with at least a 10-day washout period between treatments.

Assessments of cardiovascular effects and general toxicity were based on mortality, clinical observations, body weight, body temperature, blood pressure (systolic, diastolic, and mean arterial), heart rate, and the electrocardiogram (QRS duration and the RR, PR, and QT intervals). Plasma concentrations of the test item were also determined.

[REDACTED] administered orally to male beagle dogs at doses of 20, 50, and 150 mg [REDACTED] kg did not result in mortality, nor were there any effects on body weight or the PR interval. Vomitus was observed for 2/6 animals following the 150 mg [REDACTED] kg treatment. Increases in heart rate were observed following all [REDACTED] treatments. Increases in the uncorrected QT interval and the corrected QT interval (i.e., QTc) were noted following both the 50 and 150 mg [REDACTED] kg treatments. Decreases in blood pressure and increases in body temperature and the QRS duration were only observed following the 150 mg [REDACTED] kg treatment. Therefore, based on the slight increases in heart rate observed at 20 mg [REDACTED] kg, oral administration of [REDACTED] produced cardiovascular effects in dogs at all doses tested.

## 3. INTRODUCTION

The objective of this study was to evaluate the potential cardiovascular effects of [REDACTED] in conscious freely moving beagle dogs.

The design of this study was based on the current International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines and generally accepted procedures for the testing of pharmaceutical compounds,<sup>1,2,3</sup> and in accordance with all applicable sections of the Final Rules of the Animal Welfare Act regulations (Code of Federal Regulations, Title 9), the *Public Health Service Policy on Humane Care and Use of Laboratory Animals* from the Office of Laboratory Animal Welfare, and the *Guide for the Care and Use of Laboratory Animals* from the National Research Council.<sup>4,5</sup> The study protocol, the last amended study protocol, and deviations are presented in [Appendix 1](#). No protocol deviations occurred during this study.

### 3.1. Study Schedule

#### Study Initiation Date

(Protocol Signed by Study Director) 02 Jul 2019

#### Experimental Starting Date

(Transfer of Test System) 08 Jul 2019

#### Experimental Start Date

(First Day of Dose Administration; Day 1) 15 Jul 2019

#### Experimental Termination Date

(Last Animal Removed from Study) 27 Aug 2019

Sponsor Reference No.

Testing Facility Study No.

Experimental Completion Date  
(Final Data Collection) 29 Aug 2019  
Draft Report Mail Date 01 Oct 2019

#### 4. MATERIALS AND METHODS

##### 4.1. Test Item and Vehicle Information

###### 4.1.1. Test Item

Identification: [REDACTED] (also known as [REDACTED] or [REDACTED])

Batch (Lot) No.: [REDACTED]  
[REDACTED]

Receipt Date: 19 Jun 2019

Retest Date: 31 May 2020

Physical Description: Light, white powder

Chemical Potency: 995 µg [REDACTED] mg

Correction Factor: 1.01

Storage Conditions: Controlled room temperature, protected from light

Supplier: [REDACTED]

###### 4.1.2. Vehicle

Identification: 0.5% hydroxypropylmethylcellulose (HPMC; low viscosity),  
0.1% Tween 80 in NANOPure Diamond Ultrapure water (w/v)

###### 4.1.2.1. Vehicle Components

Identification: Methocel E5 Premium LV

Batch (Lot) No.: D011H8RL01

Receipt Date: 09 Feb 2018

Retest Date: 26 Aug 2022

Physical Description: Neutral, white powder

Storage Conditions: Controlled room temperature

Supplier: Peoples Services Inc

Identification: Polysorbate 80, N.F.

Batch (Lot) No.: 2HA0337

Receipt Date: 30 Aug 2018

Expiration Date: 20 Dec 2019

Physical Description: Clear, yellow liquid

Storage Conditions: Controlled room temperature, protected from light

Supplier: Spectrum Chemical Mfg Corp

Identification: NANOpure Diamond Ultrapure water

Supplier: Testing Facility

#### **4.2. Test Item and Vehicle Characterization**

The Sponsor provided to the Testing Facility documentation of the identity, purity, composition, and stability for the test item in the form of a Certificate of Analysis as presented in [Appendix 2](#).

Documentation of the strength, purity, composition, stability, and other pertinent information for the vehicle components used on study was limited to that information listed on the label and accompanying documentation of these commercially available products.

The production, testing, and documentation of the bulk test item were performed according to Good Manufacturing Practices (GMP).

#### **4.3. Reserve Samples**

A reserve sample from the batch (lot) of test item used in this study was neither required nor retained.

#### **4.4. Test Item Inventory and Disposition**

Records of the receipt, distribution, and storage of the vehicle and test item were maintained. All unused test item was returned to the Sponsor.

#### **4.5. Dose Formulation and Analysis**

##### **4.5.1. Preparation of Vehicle**

Fresh vehicle, 0.5% HPMC (low viscosity), 0.1% Tween 80 in NANOPure Diamond Ultrapure water (w/v), was prepared 4 times for use on study, up to 6 days prior to dosing, and was stored refrigerated at 2°C to 8°C. To prepare the 0 mg/kg dosing formulation, prior to handling the test item, the vehicle was mixed for at least 5 minutes using a magnetic stir bar and stir plate and until uniform in appearance, and the pH was measured and adjusted as needed to  $8.2 \pm 0.1$  using either 0.1N NaOH or 1N NaOH (provided by the Testing Facility), while stirring. The vehicle dosing formulation was dispensed into an amber glass container up to 4 days prior to dosing and was stored refrigerated at 2°C to 8°C until acquired for dosing.

##### **4.5.2. Preparation of Test Item**

The test item, [REDACTED] was used as received from the Sponsor. A correction factor of 1.01 was used to adjust for potency when preparing the test item formulations. Formulations of the test item were prepared by mixing the appropriate amount of vehicle with the appropriate amount of test item to achieve nominal concentrations of 4, 10, and 30 mg [REDACTED] mL. The required volume of 5N NaOH (provided by the Testing Facility) was added to achieve solubility and the formulations were stirred and homogenized as needed. The pH was measured and adjusted as needed to  $8.2 \pm 0.1$  using 0.1N NaOH, 1N NaOH, 0.1N HCl, and/or 1N HCl (provided by the Testing Facility). Formulations were prepared up to 4 days prior to dosing, dispensed into amber glass containers, and were stored refrigerated at 2°C to 8°C until acquired for dosing.

### 4.5.3. Sample Collection and Analysis

Dosing formulations prepared for the study were evaluated for homogeneity and concentration. Appropriate samples (see Text Table 1) were collected using a syringe, while stirring, and placed into 15 mL amber glass bottles. Any remaining formulation samples will be discarded after acceptance of the analytical results by the Study Director or upon receipt of authorization to finalize the report.

Text Table 1  
Dosing Formulation Analysis Sample Collection

Sample Type	Dose Concentration Sampled (mg [REDACTED] mL)	Stratum	No. of Samples per Concentration			Sample Volume (mL)	Intervals
			Collected	Analyzed	Backup		
Concentration/ Homogeneity Analyses <sup>a,b</sup>	4, 10, 30	Top	2	1	1	2	First Preparation
		Middle	2	1	1	2	
		Bottom	2	1	1	2	
Concentration Analyses <sup>b</sup>	0	Middle	2	1	1	5	Each Preparation
Concentration Analyses <sup>b</sup>	4, 10, 30	Middle	2	1	1	2	Each Preparation

<sup>a</sup> The averaged result from homogeneity analysis served as concentration verification for the first preparation.

<sup>b</sup> The samples, including backup samples, were stored frozen at -60°C to -90°C pending analyses or final disposition.

Stability of the dosing formulations at the concentrations used on study was previously established for at least 7 days under refrigerated (2°C to 8°C) or frozen (-70°C) conditions by the Sponsor; therefore, stability analysis was not performed. The documentation for the stability is included in [Appendix 3](#).

#### 4.5.3.1. Analytical Method

Samples were shipped on dry ice to the Sponsor for analysis. All analytical work was conducted by the Sponsor using an analytical method developed and validated by that laboratory [REDACTED]. For control preparations, samples were analyzed to confirm the absence of test item.

### 4.6. Test System

#### 4.6.1. Transfer

On 08 Jul 2019, non-naïve beagle dogs (7 males) were transferred from the telemetry stock colony. The animals were originally received from [REDACTED]

[REDACTED] At the initiation of dosing, the animals assigned to study were 10 months to 1 year and 3 months old and weighed between 7.85 kg and 10.65 kg. While housed in the stock colony, the animals were weighed periodically and observed with respect to general health and any signs of disease. The source, health, and housing records of the animals are maintained in the stock colony study file.

#### 4.6.2. Justification for Test System and Number of Animals

The beagle is the usual non-rodent model used for evaluating the cardiovascular safety of various test articles and for which there is a large historical database.<sup>6</sup> There were no known or expected

differences between male and female animals relative to exposure levels or the effects of the test item on cardiovascular function; therefore, only males were used to conserve animals.

The total number of animals used in this study was considered to be the minimum required to properly characterize the effects of the test item and the study was designed such as to not require an unnecessary number of animals to accomplish the study objectives.

#### **4.6.3. Animal Identification**

Each animal was identified using a subcutaneously implanted electronic identification chip. Each animal was also identified by a permanent tattoo with the vendor animal number.

#### **4.6.4. Environmental Acclimation**

During the 7-day acclimation period, the animals were observed daily with respect to general health and any signs of disease. All animals were given a detailed clinical examination upon transfer to study. All animals were given a physical examination by a staff veterinarian prior to selection for study. Representative electrocardiographic (ECG) tracings from the 24-hour baseline telemetry monitoring sessions were evaluated for all animals to rule out electrophysiological abnormalities of the heart and determine suitability for placement on study. All animals had blood samples collected prior to selection for study to evaluate clinical chemistry and hematology parameters. These detailed clinical observations, physical, ECG, and clinical pathology examinations conducted prior to selection for study are not reported but are maintained in the study file.

The animals were acclimated to the oral gavage dosing procedure on 3 occasions prior to test item administration. A fixed dose volume of 10 mL of tap water was administered on each occasion.

#### **4.6.5. Selection, Assignment, and Disposition of Animals**

Animals were assigned to study groups by a simple randomization procedure.

The disposition of all animals was documented in the study records.

#### **4.6.6. Husbandry**

##### **4.6.6.1. Housing**

The dogs were pair-housed (single sex) in double-sized stainless-steel mobile cages. Due to the design of the study (i.e., Latin square), in order to prevent cross contamination on dosing days, the animals were housed individually overnight prior to each planned dose and remained individually housed until each telemetry monitoring session was completed. This type of housing was considered adequate for exercise. The housing was equipped with an automatic watering valve as specified in the *USDA Animal Welfare Act* (9 CFR, Parts 1, 2 and 3) and as described in the *Guide for the Care and Use of Laboratory Animals*.<sup>5</sup>

One companion animal (male beagle dog) was transferred from the stock colony on 08 Jul 2019 for the purpose of social housing of all study animals and was not considered part of the test system. The companion animal was maintained according to SOP. The data collected from the companion animal are not reported but are maintained in the study file.

Each cage was clearly labeled with study, group, animal number, and sex.

#### **4.6.6.2. Environmental Conditions**

Target temperatures of 64°F to 84°F with a target relative humidity of 30% to 70% were maintained. A 12-hour light/12-hour dark cycle was maintained, except when interrupted for designated procedures. Ten or greater air changes per hour with 100% fresh air (no air recirculation) were maintained in the animal rooms.

#### **4.6.6.3. Food**

[REDACTED] [REDACTED] was provided as a daily ration throughout the study. An 800 mL (approximately 300 g) ration of feed was provided once daily. The food ration was offered for at least 4 hours to all animals.

Supplemental diet was provided to the animals as warranted by clinical signs or other changes. Any food supplementation was approved by the Study Director and Clinical Veterinarian and documented accordingly.

The feed was analyzed by the supplier for nutritional components and environmental contaminants. Results of the analysis are provided by the supplier and are on file at the Testing Facility. It is considered that there are no known contaminants in the feed that would interfere with the objectives of the study.

#### **4.6.6.4. Water**

Tap water was available ad libitum to each animal via an automatic watering system.

Periodic analysis of the water is performed, and results of these analyses are on file at the Testing Facility. It is considered that there are no known contaminants in the water that could interfere with the outcome of the study.

#### **4.6.6.5. Animal Enrichment**

Psychological/environmental enrichment was provided according to SOP.

#### **4.6.6.6. Veterinary Care**

Veterinary care was available throughout the course of the study, and animals were examined by the veterinary staff as warranted by clinical signs or other changes. All veterinary examinations and recommended therapeutic treatments, if any, were documented in the study records and reviewed by the Study Director. The medical treatments and observations recorded are not reported but maintained in the study file.

#### **4.6.7. Animal Preparation**

All animals transferred to study were previously surgically instrumented with telemetry transmitters for physiological monitoring.

Within 2 weeks of transfer to study, baseline telemetry monitoring (body temperature, blood pressure, heart rate, the electrocardiogram, and activity) was conducted while animals were housed in the stock colony.

## 4.7. Experimental Design

Text Table 2  
Experimental Design

Treatment No.	Dose Level (mg [REDACTED] kg)	Dose Concentration (mg [REDACTED] mL)	Dose Volume (mL/kg)	Male Animal No. <sup>a,b</sup>
1	0	0	5	1001 - 1006
2	20	4	5	1001 - 1006
3	50	10	5	1001 - 1006
4	150	30	5	1001 - 1006

<sup>a</sup> The same 6 animals received all 4 treatments according to a Latin square design with at least a 10-day washout between treatments.

<sup>b</sup> Body temperature, blood pressure, heart rate, and the electrocardiogram (ECG) were monitored continuously for at least 2 hours prior to dosing and for at least 24 hours postdose.

### 4.7.1. Administration of Test Materials

The same 6 male dogs were administered the vehicle (0 mg [REDACTED] kg) and test item at dose levels of 20, 50, and 150 mg [REDACTED] kg, via oral gavage at a dose volume of 5 mL/kg. All doses were administered to all animals according to a Latin square design, as indicated in Text Table 3. with at least a 10-day washout period between administrations until each animal received all treatments.

After each dose and prior to removal of the gavage tube, the tube was flushed with 10 mL of tap water provided by the Testing Facility. All reported postdose telemetry data are based on the tap water flush time. Dosing formulations were stirred continuously at ambient temperature for at least 1 hour prior to and throughout the administration period. Individual doses were based on the most recent body weights.

Text Table 3  
Dosing Schedule

Animal No.	Dose level (mg [REDACTED] kg)			
	0	20	50	150
1001	Day 1	Day 11	Day 22	Day 36
1002	Day 36	Day 22	Day 11	Day 1
1003	Day 1	Day 22	Day 11	Day 36
1004	Day 36	Day 11	Day 22	Day 1
1005	Day 11	Day 1	Day 36	Day 22
1006	Day 22	Day 36	Day 1	Day 11

### 4.7.2. Justification of Route and Dose Levels

The oral route is the intended route of administration of this test item in humans.

In a previous repeat dose range finding toxicity study in dogs, [REDACTED] was tolerated up to 150 mg/kg/day. Test-item-related findings were noted in heart, kidney, gall bladder, and stomach. Based upon the results of that study, it was expected that the highest dose might have produced some toxic effects, but not lethality or excessive toxicity that would prevent meaningful evaluation. The mid-dose level was expected to produce minimal to moderate effects. The low-dose level was expected to produce no observable effects.

## **4.8. In-life Procedures, Observations, and Measurements**

### **4.8.1. Cage Side Observations**

All animals were observed for morbidity, mortality, injury, and the availability of food and water at least twice daily. Animals were not removed from the cage during observation, unless necessary for identification or confirmation of possible findings.

### **4.8.2. Detailed Clinical Observations**

A detailed clinical examination of each animal was performed prior to dosing, at approximately 1 hours postdose ( $\pm 15$  minutes), and following completion of the telemetry monitoring periods. On occasion, clinical observations were recorded at unscheduled intervals. Unscheduled observations conducted prior to Day 1 are not reported but are maintained in the study file.

The observations included, but were not limited to, evaluation of the skin, fur, eyes, ears, nose, oral cavity, thorax, abdomen, external genitalia, limbs and feet, respiratory and circulatory effects, autonomic effects such as salivation, nervous system effects including tremors, convulsions, reactivity to handling, and unusual behavior. The 1-hour postdose observations conducted during the cardiovascular monitoring period were conducted via remote camera and were limited to those which could be conducted without handling the animals.

### **4.8.3. Body Weights**

Body weights for all animals were measured and recorded at transfer to study, prior to randomization, on the day prior to each dose during the study, and at termination of the study (prior to returning to stock colony). The body weights recorded at transfer and prior to randomization are not reported but are maintained in the study file.

### **4.8.4. Telemetry Monitoring**

Five days prior to transfer to study, animals were continuously monitored via telemetry for at least 24 hours for body temperature and cardiovascular endpoints while on the stock colony (12 days prior to the first administration). These data were collected in 1-minute intervals. The first 24 hours of the data were used in the calculation of the corrected QT (QTc) interval. The individual baseline data are not reported but are maintained in the study data.

The animals were unrestrained and monitored for selected physiological parameters via telemetry. Body temperature, blood pressure, heart rate (derived from blood pressure and ECG), and the ECG parameters were monitored continuously from at least 2 hours predose until at least 24 hours postdose. On occasion, animals experienced minor temporary intermittent signal disruptions. Data were collected and analyzed in 1-minute intervals and are reported in approximately 60-minute intervals. Only 2 hours of predose data are reported. The negative time intervals on the figures and tables in the report represent the duration of predose data reported for each animal, but do not necessarily reflect the immediate 120-minute period prior to the time of dose administration.

Blood pressure parameters reported include systolic, diastolic, and mean arterial pressures. ECG parameters reported include RR interval, PR interval, QRS duration, QT interval, and QTc interval. Temporally correlated blood pressure-derived heart rate data are reported and were utilized with QT interval measurements for determining QTc interval throughout the study. The QTc interval was calculated using a procedure based on the method described by Spence, et al.<sup>7</sup> and modified by Miyazaki and Tagawa.<sup>8</sup>

Values judged by the Study Director as physiologically improbable were excluded from the report. Excluded values are maintained in the study file.

Total activity (movements within the cage) was also measured continuously by the DSI Telemetry System and collected in the same intervals as the cardiovascular data to help to clarify results obtained from the cardiovascular and/or body temperature data if needed. However, these data from the activity measurement were not necessary to aid in data interpretation, and therefore are not reported but are maintained in the study file.

On Day 36 upon initiation of telemetry monitoring of Animal No. 1006 at the 20 mg [REDACTED] kg dose, there was an unreliable ECG signal that produced physiologically improbable data; however the blood pressure and temperature data appeared normal. As such, no ECG telemetry data are reported for Animal No. 1006 at 20 mg [REDACTED] kg.

#### **4.9.      Laboratory Evaluations**

##### **4.9.1.    Bioanalysis Evaluation**

###### **4.9.1.1.   Bioanalytical Sample Collection**

Blood samples (approximately 1 mL) were collected from all animals via the jugular vein for determination of the plasma concentrations of the test item at 6 hours ( $\pm$ 15 minutes) postdose. The animals were not fasted prior to blood collection.

###### **4.9.1.2.   Bioanalytical Sample Processing**

Blood samples were collected in tubes containing K<sub>2</sub>EDTA, placed on wet ice, and centrifuged at 1300 g for 10 minutes under refrigerated conditions within 60 minutes of collection. The resulting plasma was placed in pre-labeled 2 mL polypropylene Greiner cryovial tubes. All samples were stored frozen at -60°C to -90°C.

###### **4.9.1.3.   Bioanalytical Sample Analysis**

Samples were shipped on dry ice to the Sponsor for analysis. All analytical work was conducted by the Sponsor using an analytical method developed and validated by that laboratory (Bioanalytical Method for the Determination of [REDACTED] and [REDACTED] in Dog Plasma K<sub>2</sub>EDTA using Liquid-Liquid Extraction Followed by LC-MS/MS Detection).

### **5.       STATISTICS**

Text Table 4 defines the set of comparisons used in the statistical analyses described in this section.

Text Table 4  
Statistical Comparisons

Control Treatment	Comparison Treatments
1	2, 3, 4

The raw data were tabulated within each time interval, and the mean and standard deviation were calculated for each endpoint by group. For each endpoint, treatment groups were compared to the control group using the analysis outlined in [Text Table 5](#).

Text Table 5  
Statistical Analysis

Endpoints	Type of Analysis
Body Temperature Cardiovascular Endpoints Systolic Blood Pressure Diastolic Blood Pressure Mean Arterial Blood Pressure Heart Rate ECG (RR, PR, QRS, QT, and QTc)	Descriptive Statistics and Paired Sample T-test

### 5.1. Paired Sample T-Test Comparison

For each specified endpoint, and for each time interval, a Paired Sample t-test<sup>9</sup> was used to test for no treatment effect. For each treatment, each subject served as its own control to generate a calculated difference between treatment and control. The mean of this difference was tested against a mean of 0, for no change. A Bonferroni correction was applied. Results of the comparison are reported at the 0.05 and 0.01 significance levels. The step-down Sidak method was applied to previously obtained p-values to adjust for multiple testing.<sup>10</sup> All endpoints were analyzed using 2-tailed tests.

### 6. COMPUTER SYSTEMS

Critical computerized systems used in the study are listed in [Text Table 6](#). All computerized systems used in the conduct of this study have been validated; when a particular system has not satisfied all requirements, appropriate administrative and procedural controls were implemented to assure the quality and integrity of data.

Text Table 6  
Critical Computerized Systems

<b>System Name</b>	<b>Version No.</b>	<b>Description of Data Collected and/or Analyzed</b>
DocuSign®	19	Collection of Part 11 compliant signature.
Logbook	5.3	Electronic notebook and data collection system for veterinary communications, observations, and treatments.
ExyLIMS	3.0	A comprehensive laboratory information management system used to manage data, including but not limited to: instrumentation, test articles, standards, and samples.
NextDocs®	6.1	Electronic documentation management of Deviation Events and Corrective and Preventative Actions (CAPA).
Provantis™	9.4	Client-server, Oracle-based system used for electronic documentation and data management from compound receipt through reporting.
SAS®	9.4	The SAS® System is an integrated system of software products that enables a user to perform data entry, retrieval, data management, reporting, graphics, statistical analysis, and applications development.
SAS/STAT®	14.1	Software used for statistical procedures.
Siemens Environmental Monitoring	3.11	Environmental monitoring, alarming, and reporting applications.
Niagara Framework® Software System	2.3	
Cardiopulmonary Automated Reporting System (CARS)	3.1	In-house developed reporting system for cardiopulmonary data.
Ponemah Physiology Platform™	5.2	Telemetry system designed to collect and analyze cardiovascular and pulmonary data.

## 7. RETENTION OF RECORDS, SAMPLES, AND SPECIMENS

All study-specific raw data, documentation, protocol, samples, specimens, and final reports from this study were archived at the Testing Facility, or an approved archive facility contracted by the Testing Facility. At least 1 year after issue of the draft report, the Sponsor will be contacted.

All records, retained samples, and reports generated from phases or segments performed by the Sponsor for dose formulation analysis or bioanalysis were maintained by [REDACTED] Archival location is detailed in the applicable PI report.

## 8. RESULTS

### 8.1. Dose Formulation Analyses

The Dose Formulation Analysis Report is presented in [Appendix 3](#).

The results indicate that the [REDACTED] dosing formulations were homogeneous ( $\leq 5.1\%$  relative standard deviation [RSD]) and were prepared at the correct concentrations (94% to 106% of the theoretical values). No peaks corresponding to [REDACTED] were detected in the control sample.

### 8.2. Mortality

All animals survived to study termination.

### 8.3. Detailed Clinical Observations

Detailed clinical observations are summarized in [Table 1](#). Individual detailed clinical observations are presented in [Appendix 4](#).

Vomitus was observed at the end of the 24-hour monitoring period for 2/6 animals following the 150 mg [REDACTED] kg treatment.

Inappetence, salivation, lacrimation, discolored/soft/mucoid feces, scabbed areas, emesis following dosing, vomitus (noted several days following the vehicle treatment), thin appearance, and dental observations (calculus and discolored teeth/gums) were noted over the course of the study; however, these findings were present prior to dosing, occurred sporadically, and/or were not dose dependent, and were therefore considered not test item-related.

### 8.4. Body Weight

Individual body weight values are presented in [Appendix 5](#).

Body weights were collected on the day prior to each dose to calculate the appropriate dose volume for each animal.

There were no notable changes in body weight over the course of the study.

### 8.5. Telemetry Data

#### 8.5.1. Body Temperature

Summarized body temperature data are presented in [Table 2](#) and the mean values are illustrated in [Figure 1](#). Individual body temperature data are presented in [Appendix 6](#).

No test item-related changes in body temperature were noted following the 20 or 50 mg [REDACTED] kg treatments.

Following the 150 mg [REDACTED] kg treatment, slight increases in mean body temperature were observed ( $<0.5^{\circ}\text{C}$ ) from 3 to 16 hours postdose. Although the increases were small in magnitude and did not reach statistical significance, they were present in 5 of the 6 animals on study and, therefore, these changes are considered to be test item-related.

#### 8.5.2. Systolic, Diastolic, and Mean Arterial Blood Pressures

Summarized systolic, diastolic, and mean arterial blood pressure data are presented in [Tables 3](#), [4](#), and [5](#) and the mean values are illustrated in [Figures 2](#), [3](#), and [4](#), respectively. Individual systolic, diastolic, and mean arterial blood pressure data are presented in [Appendices 7](#), [8](#), and [9](#), respectively.

No test item-related changes in blood pressure were noted following the 20 or 50 mg [REDACTED] kg treatments.

Following the 150 mg [REDACTED] kg treatment, decreases in blood pressure were observed from 10 to 24 hours postdose. The decreases were small in magnitude (<11% below control for systolic, diastolic, and mean arterial pressures), did not reach statistical significance, and were not clearly dose-dependent within each individual animal; however, all animals exhibited some degree of decrease in blood pressure following the 150 mg [REDACTED] kg treatment during this period and, therefore, these changes are considered to be test item-related.

### 8.5.3. Heart Rate

Summarized heart rate data are presented in [Table 6](#) and the mean values are illustrated in [Figure 5](#). Individual heart rate data are presented in [Appendix 10](#).

Increases in heart rate were observed following all [REDACTED] treatments from 10 to 24 hours postdose. The increases were relatively small in magnitude (<30% above control), did not reach statistical significance, and were not clearly dose-dependent; however, all animals exhibited some degree of increase in heart rate following the [REDACTED] treatments during this period and, therefore, these changes are considered to be test item-related.

Slight decreases in heart rate were observed from 1 to 3 hours postdose following the 50 and 150 mg [REDACTED] kg treatments; however, there were no consistent trends observed among the individual animals to indicate a [REDACTED] related effect during this time.

### 8.5.4. RR Interval, PR Interval, QRS Duration, QT Interval, and Corrected QT (QTc) Interval

Summarized RR interval, PR interval, QRS duration, QT interval, and QTc interval data are presented in [Tables 7, 8, 9, 10](#), and [11](#) and the mean values are illustrated in [Figures 6, 7, 8, 9](#), and [10](#), respectively. Individual RR interval, PR interval, QRS duration, QT interval, and QTc interval data are presented in [Appendices 11, 12, 13, 14](#), and [15](#), respectively.

In general, variations in RR interval were inversely-related to those observed in heart rate, as expected.

Slight increases in the mean PR interval values were observed from 1 to 3 hours postdose following all [REDACTED] treatments and slight decreases in the mean PR interval values were observed following the 150 mg [REDACTED] kg treatment from 8 to 17 hours postdose; however, there were no consistent trends observed among the individual animals to indicate that these changes were related to [REDACTED] administration.

Following the 150 mg [REDACTED] kg treatment, increases in QRS duration were observed from 2 to 24 hours postdose. The mean increases were small in magnitude (<5% above control) and did not reach statistical significance; however, 3 of the 6 animals exhibited increases over a similar time course following this treatment, with the increases for Animal No. 1002 reaching up to 16% above the control treatment. Therefore, these changes are considered to be test item-related.

[REDACTED] related, dose-dependent, and statistically significant increases in the uncorrected QT interval and the corrected QT interval (i.e., QTc) were noted following the 50 and 150 mg [REDACTED] kg treatments. The values remained relatively unchanged following heart rate correction, therefore only QTc changes are discussed below. The increases in QTc began at

1 hour postdose for both treatments. The increases at 50 mg [REDACTED] kg resolved by 18 hours postdose, while the increases at 150 mg [REDACTED] kg lasted throughout the 24-hour postdose monitoring period. The mean increases in QTc reached up to 8% and 18% above controls following the 50 and 150 [REDACTED] kg treatments, respectively.

#### **8.6. Bioanalysis Evaluation**

The Bioanalysis Report is presented in [Appendix 16](#).

Oral administration of [REDACTED] at 20, 50, and 150 mg [REDACTED] kg produced respective mean  $\pm$  SEM plasma [REDACTED] concentrations of  $31.2 \pm 3.97$ ,  $113 \pm 12.7$ , and  $392 \pm 38.8$   $\mu\text{g}/\text{mL}$  at approximately 6 hours following dosing. [REDACTED] plasma concentrations were below the lower limit of quantification (BQL; <249 ng/mL) in all samples from the vehicle treated animals.

**9. CONCLUSION**

[REDACTED] administered orally to male beagle dogs at doses of 20, 50, and 150 mg [REDACTED] kg did not result in mortality, nor were there any effects on body weight or the PR interval. Vomitus was observed for 2/6 animals following the 150 mg [REDACTED] kg treatment. Increases in heart rate were observed following all [REDACTED] treatments. Increases in the uncorrected QT interval and the corrected QT interval (i.e., QTc) were noted following both the 50 and 150 mg [REDACTED] kg treatments. Decreases in blood pressure and increases in body temperature and the QRS duration were only observed following the 150 mg [REDACTED] kg treatment. Therefore, based on the slight increases in heart rate observed at 20 mg [REDACTED] kg, oral administration of [REDACTED] produced cardiovascular effects in dogs at all doses tested.

**10. REFERENCES**

1. ICH Harmonised Tripartite Guideline M3(R2). *Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*.
2. ICH Harmonised Tripartite Guideline S7A. *Safety Pharmacology Studies for Human Pharmaceuticals*.
3. ICH Harmonised Tripartite Guideline S7B. *The Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals*.
4. Office of Laboratory Animal Welfare. *Public Health Services Policy on Humane Care and Use of Laboratory Animals*. Bethesda, MD: National Institutes of Health. Current edition.
5. National Research Council. *Guide for the Care and Use of Laboratory Animals*. 8th ed. Washington, DC: National Academies Press; 2011.
6. Guidance for industry, investigators, and reviewers: exploratory IND studies. U.S. F.D.A. Center for Drug Evaluation and Research (CDER). 2006 Jan.
7. Spence S, Soper K, Hoe CM, Coleman J. The heart rate-corrected QT interval of conscious beagle dogs: a formula based on analysis of covariance. *Toxicol Sci*. 1998;45:247-258.
8. Miyazaki H, Tagawa M. Rate-correction technique for QT interval in long-term telemetry ECG recording in beagle dogs. *Exp Anim*. 2002;51:465-475.
9. Zar JH. *Biostatistical Analysis*. 4th ed. New Jersey: Prentice Hall; 1999: 161-164.
10. Westfall PH, Tobias RD, Wolfinger RD. *Multiple Comparisons and Multiple Tests Using SAS®*. 2nd ed. Cary, NC: SAS Institute; 2011.

Figure 1  
Mean Body Temperature

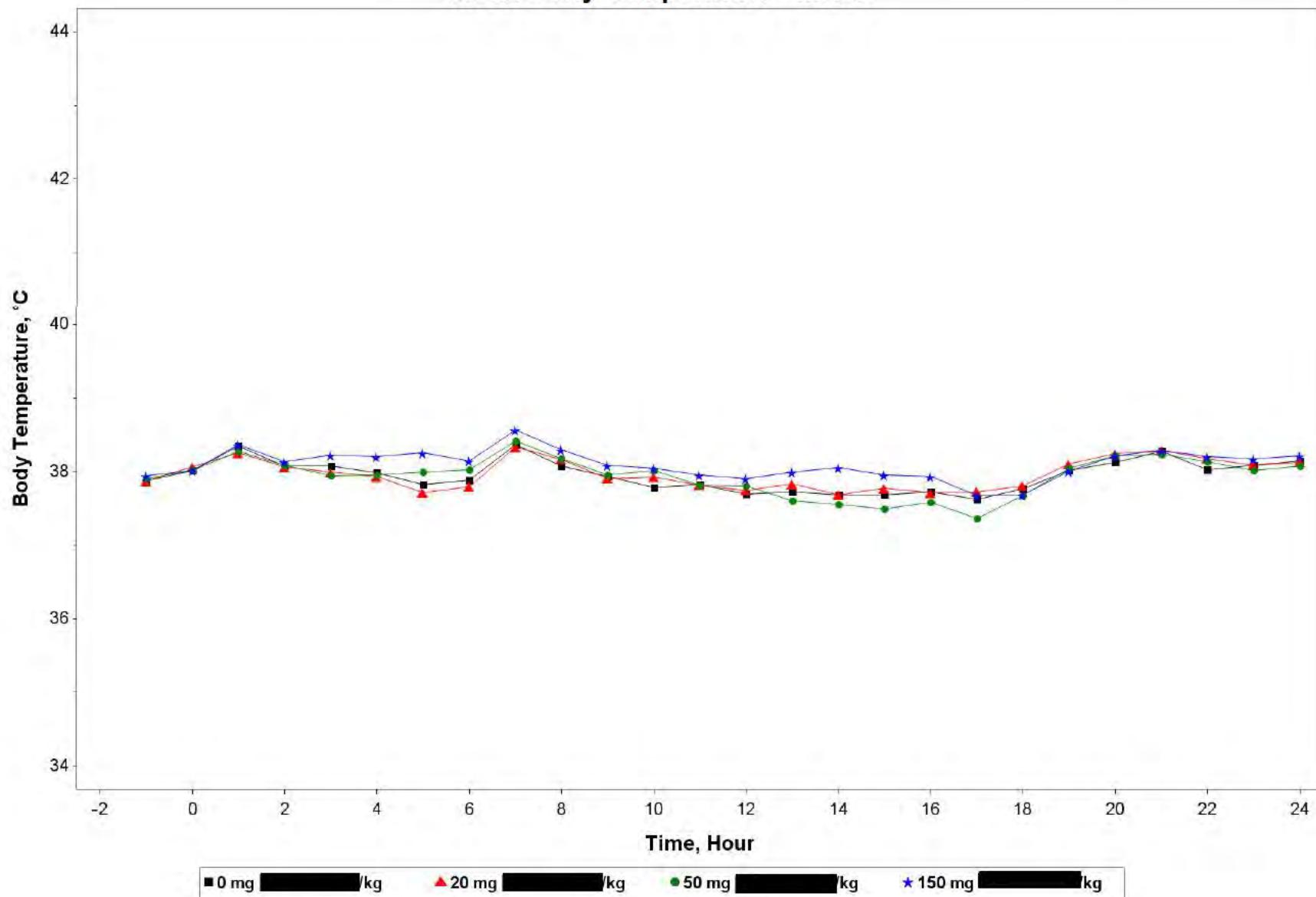
**Mean Body Temperature - MALE**

Figure 2  
Mean Systolic Blood Pressure

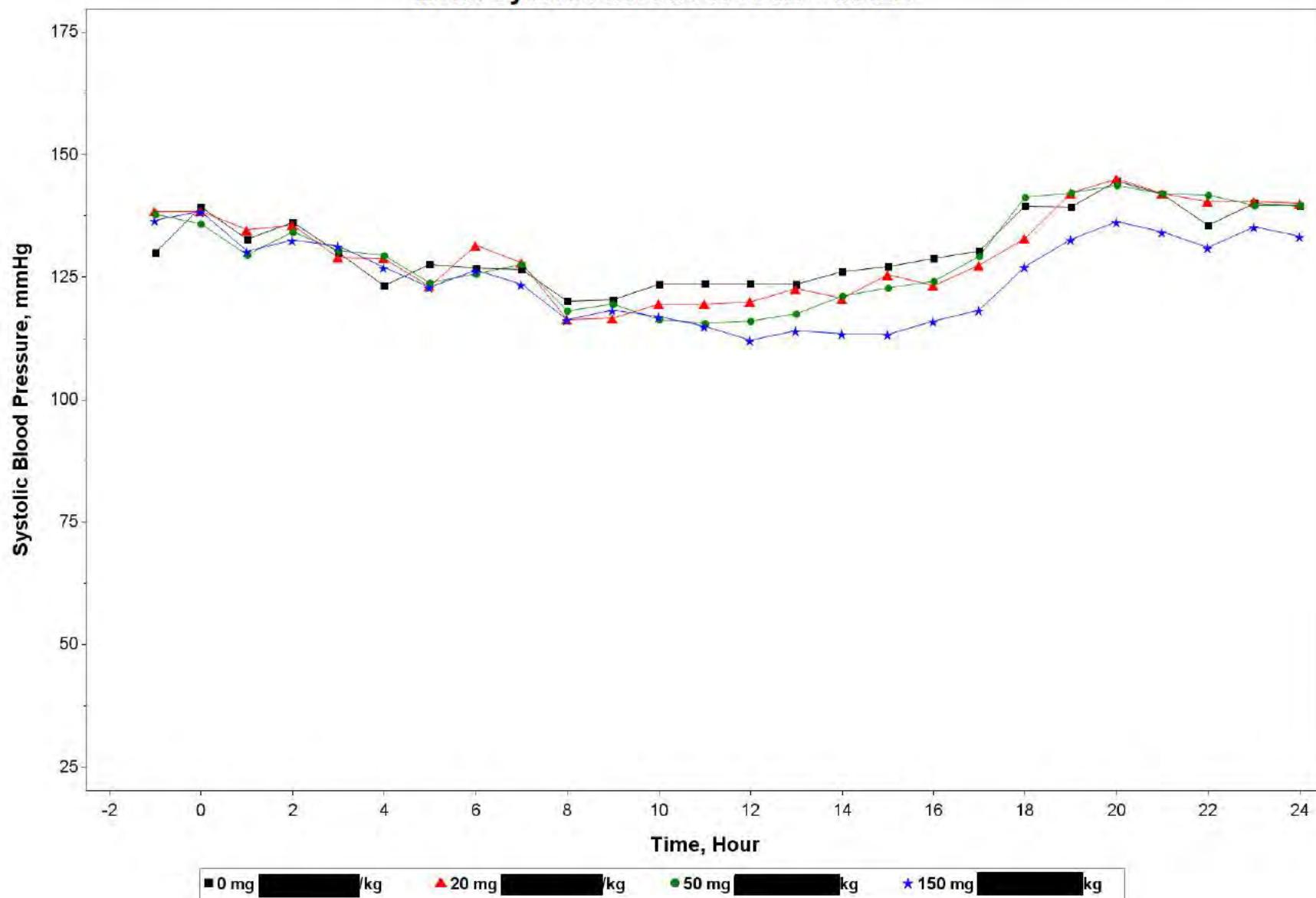
**Mean Systolic Blood Pressure - MALE**

Figure 3  
Mean Diastolic Blood Pressure

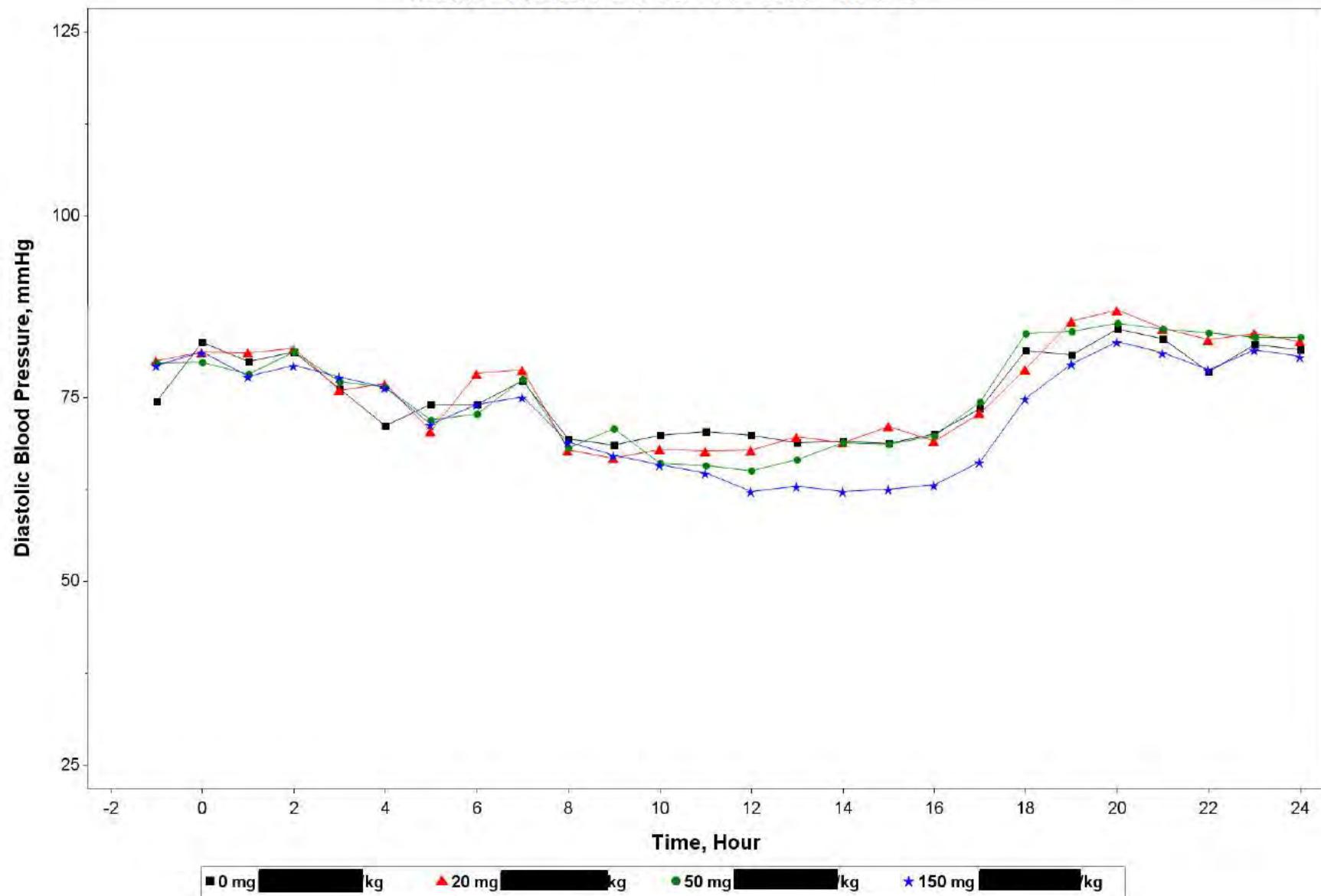
**Mean Diastolic Blood Pressure - MALE**

Figure 4  
Mean Arterial Blood Pressure

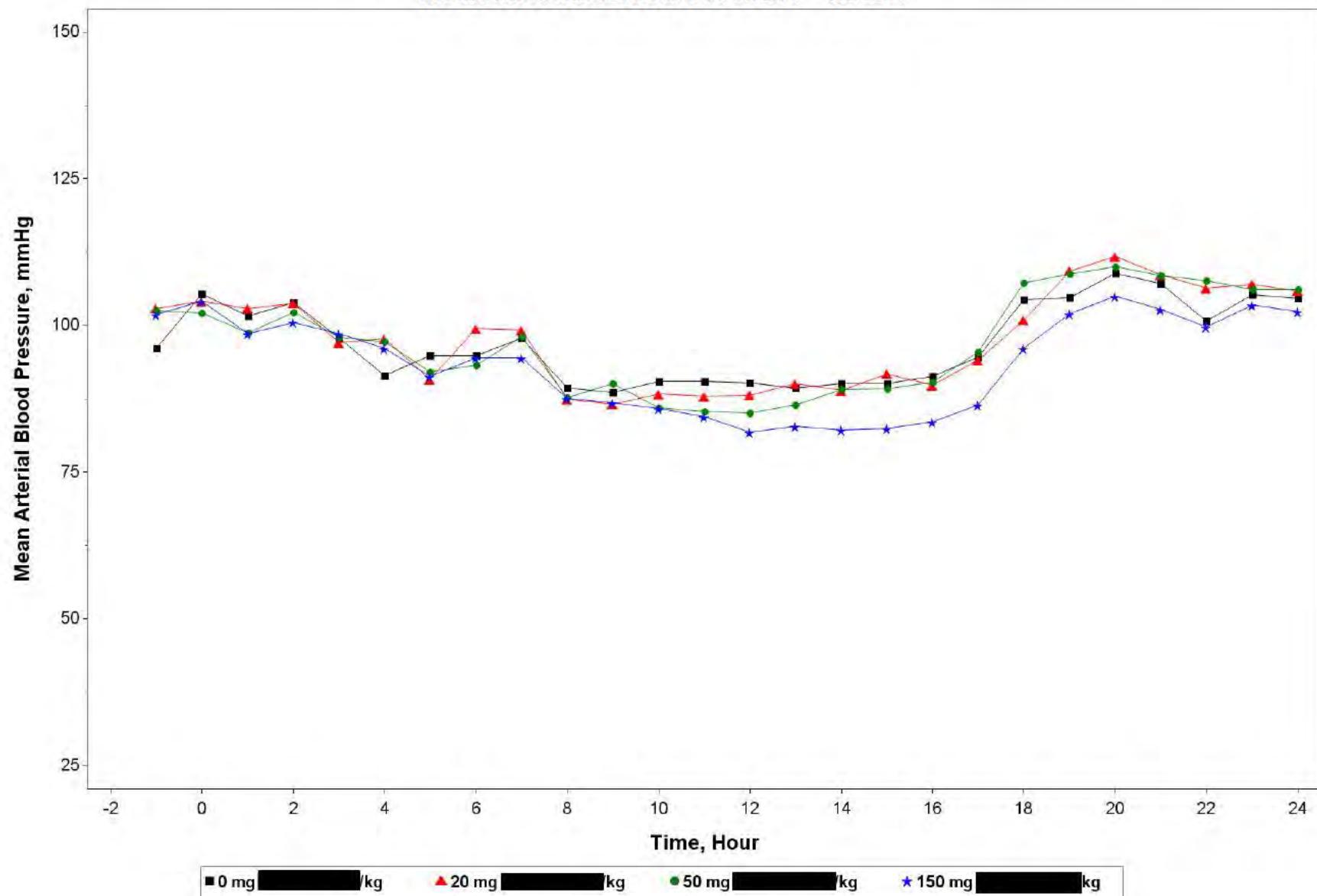
**Mean Arterial Blood Pressure - MALE**

Figure 5  
Mean Heart Rate

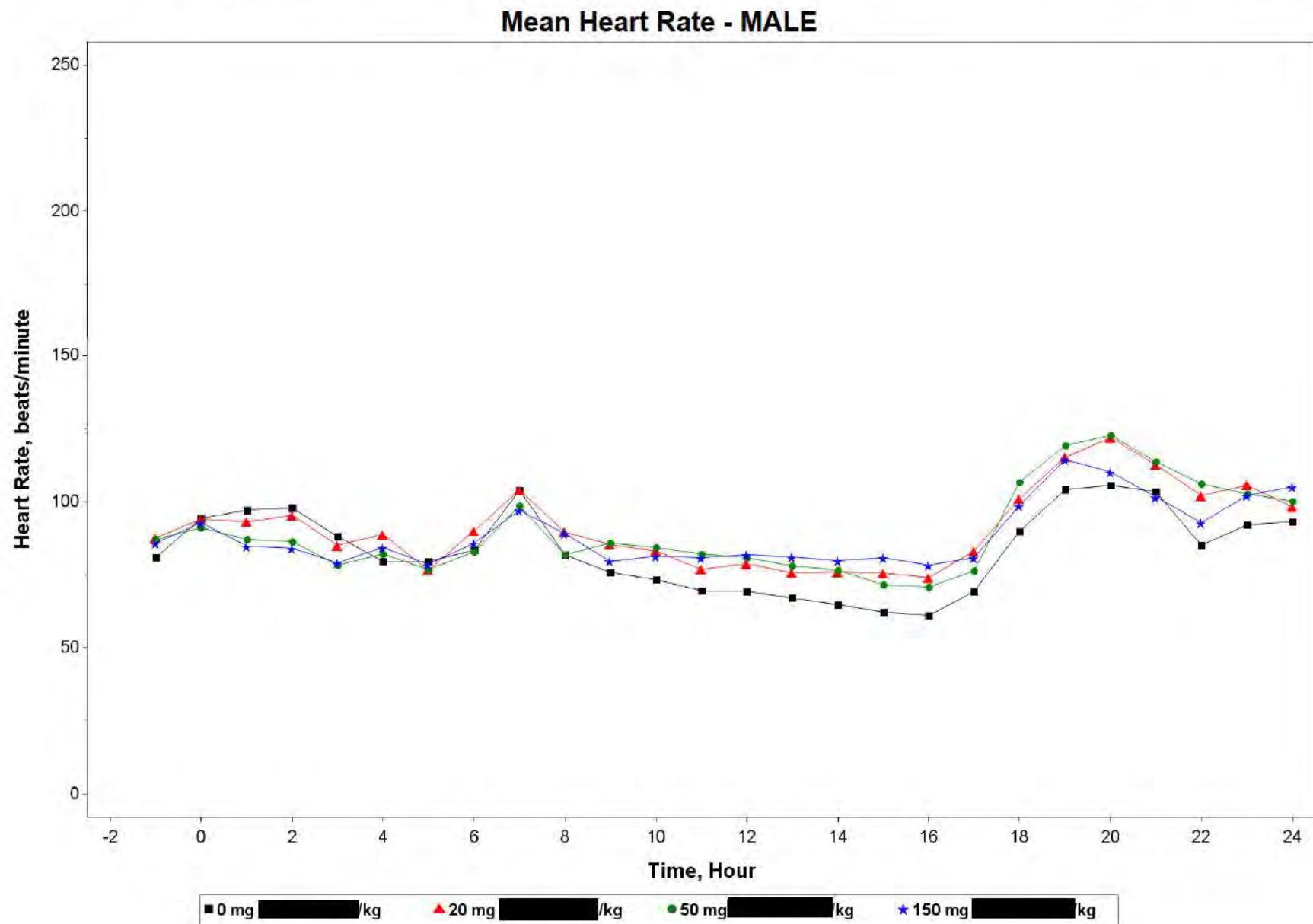


Figure 6  
Mean RR Interval

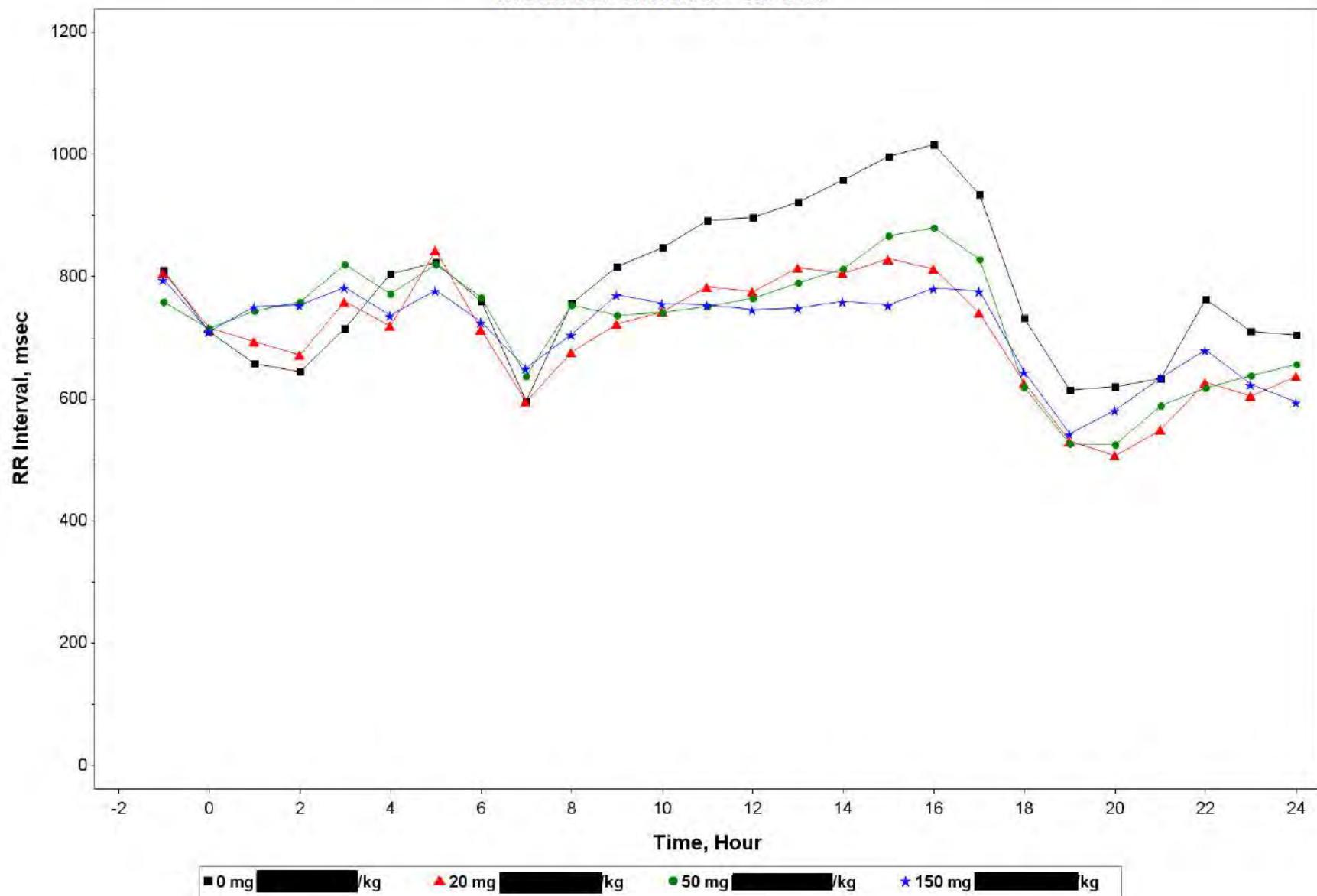
**Mean RR Interval - MALE**

Figure 7  
Mean PR Interval

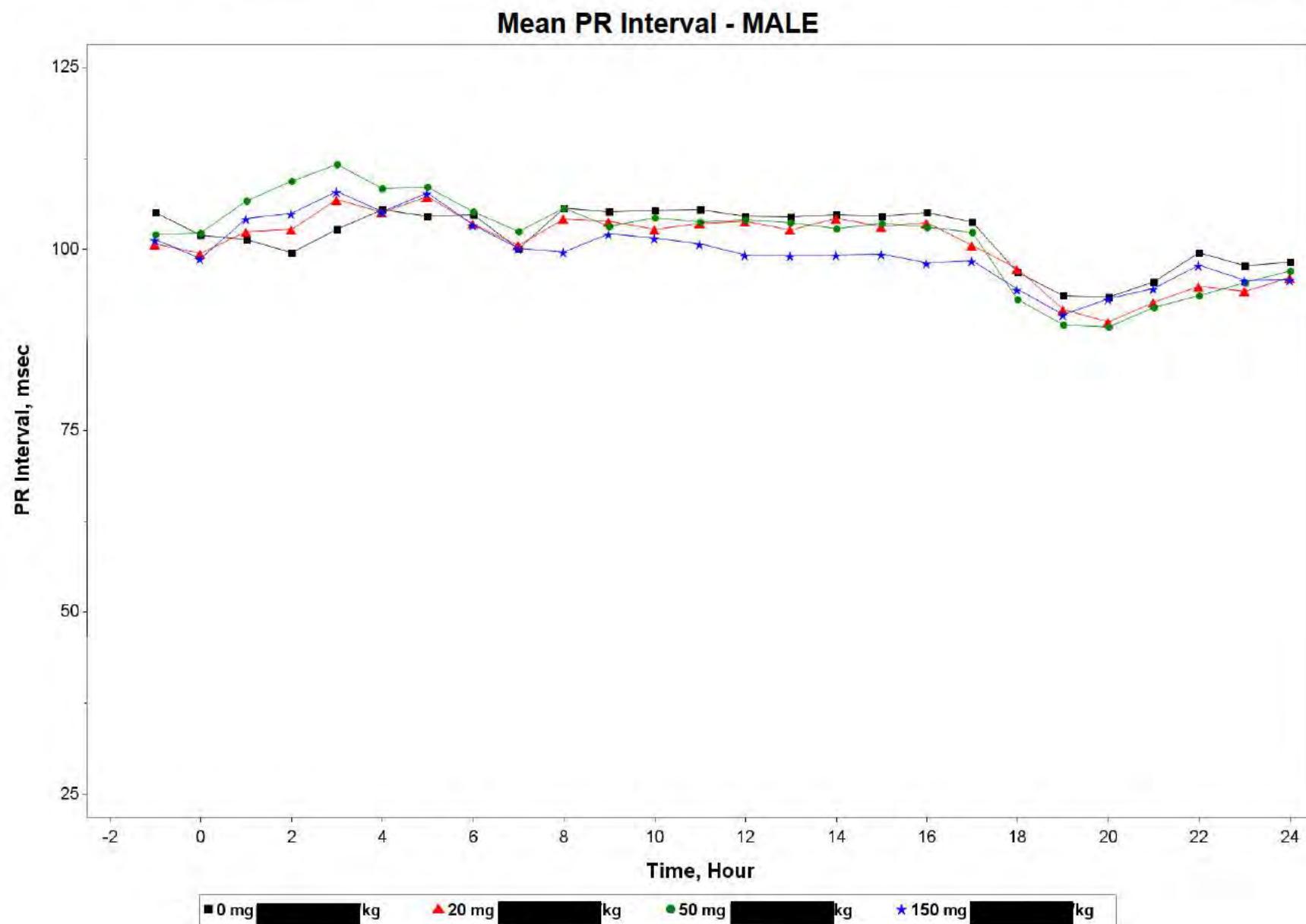


Figure 8  
Mean QRS Duration

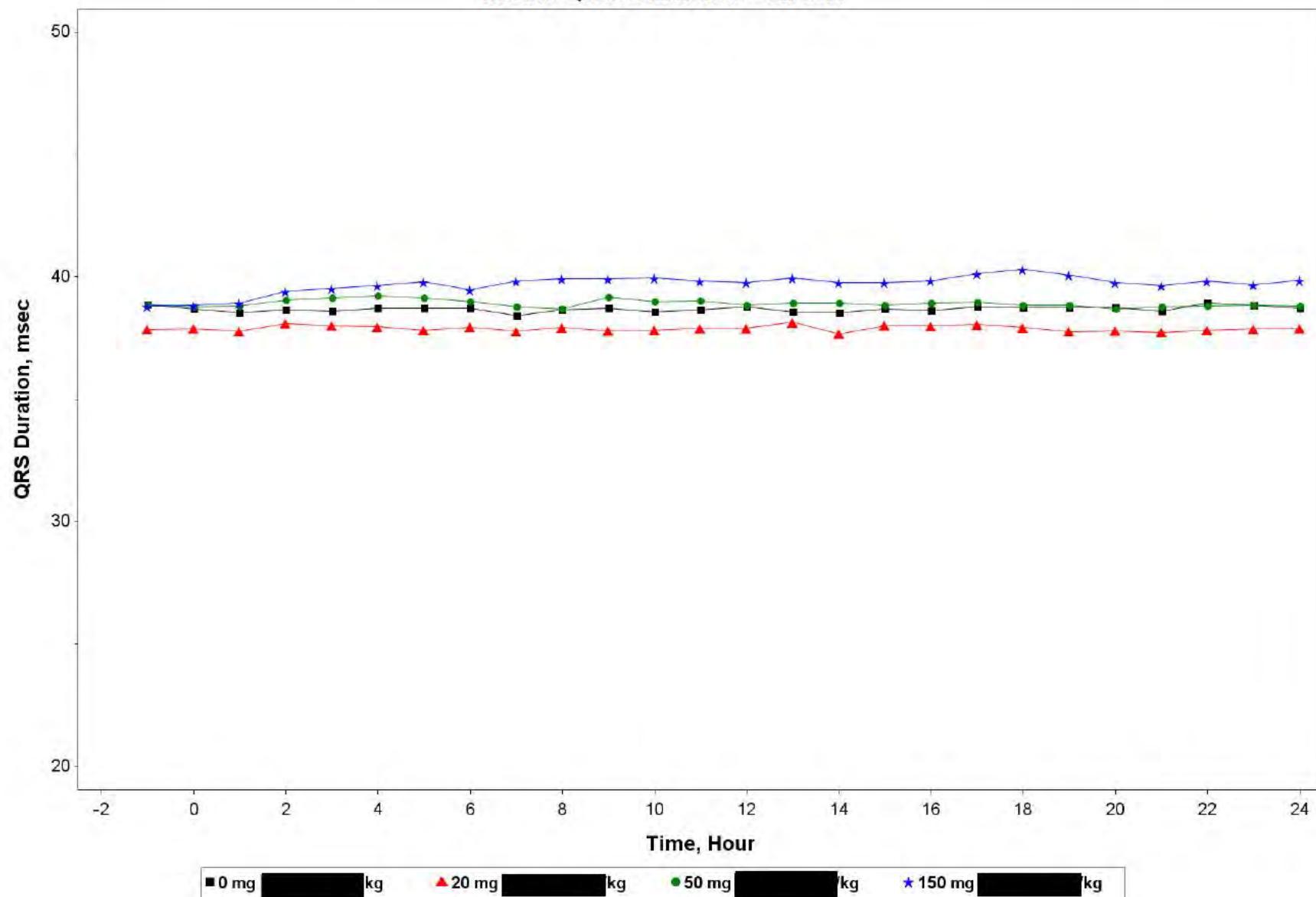
**Mean QRS Duration - MALE**

Figure 9  
Mean QT Interval

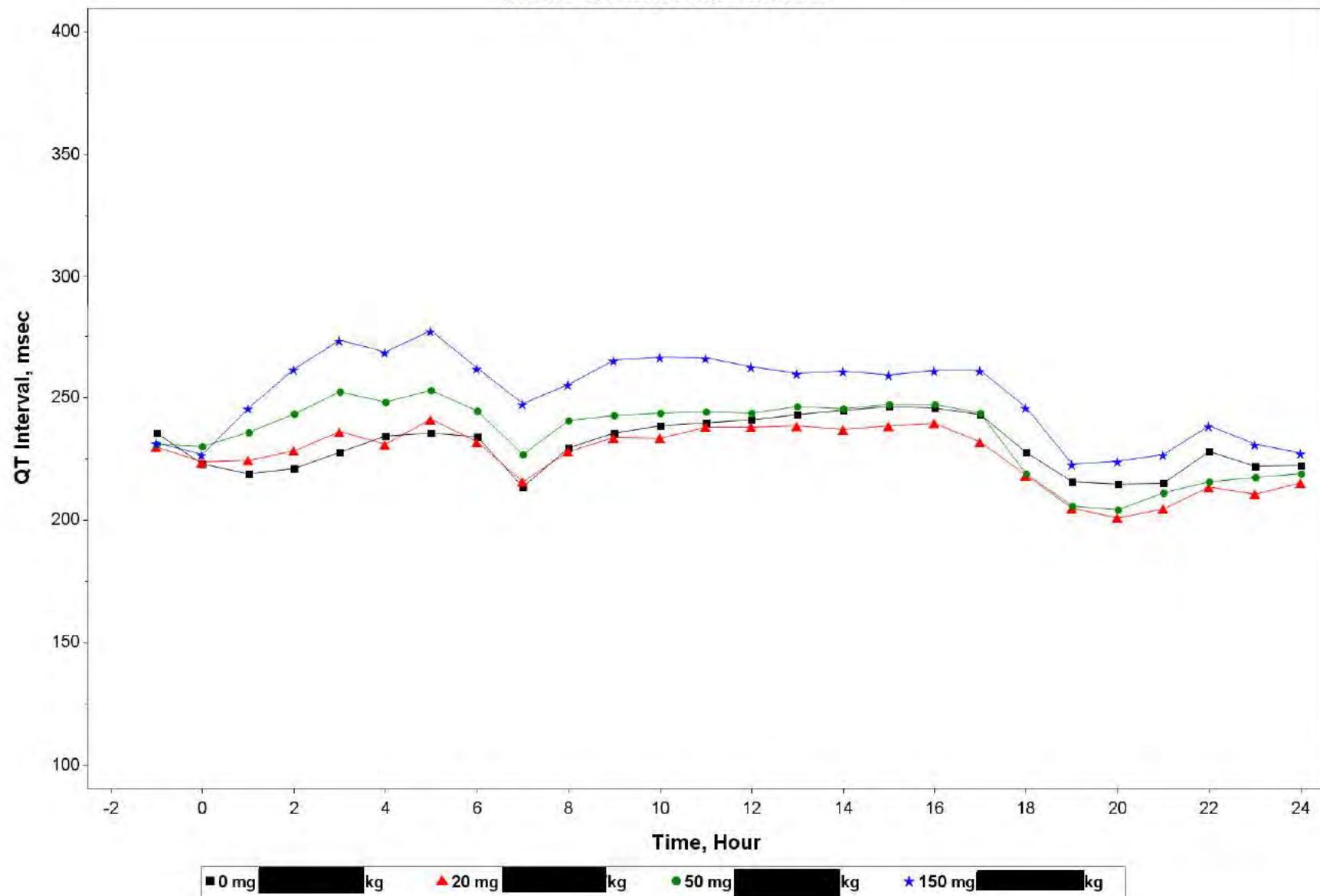
**Mean QT Interval - MALE**

Figure 10  
Mean Corrected QT Interval

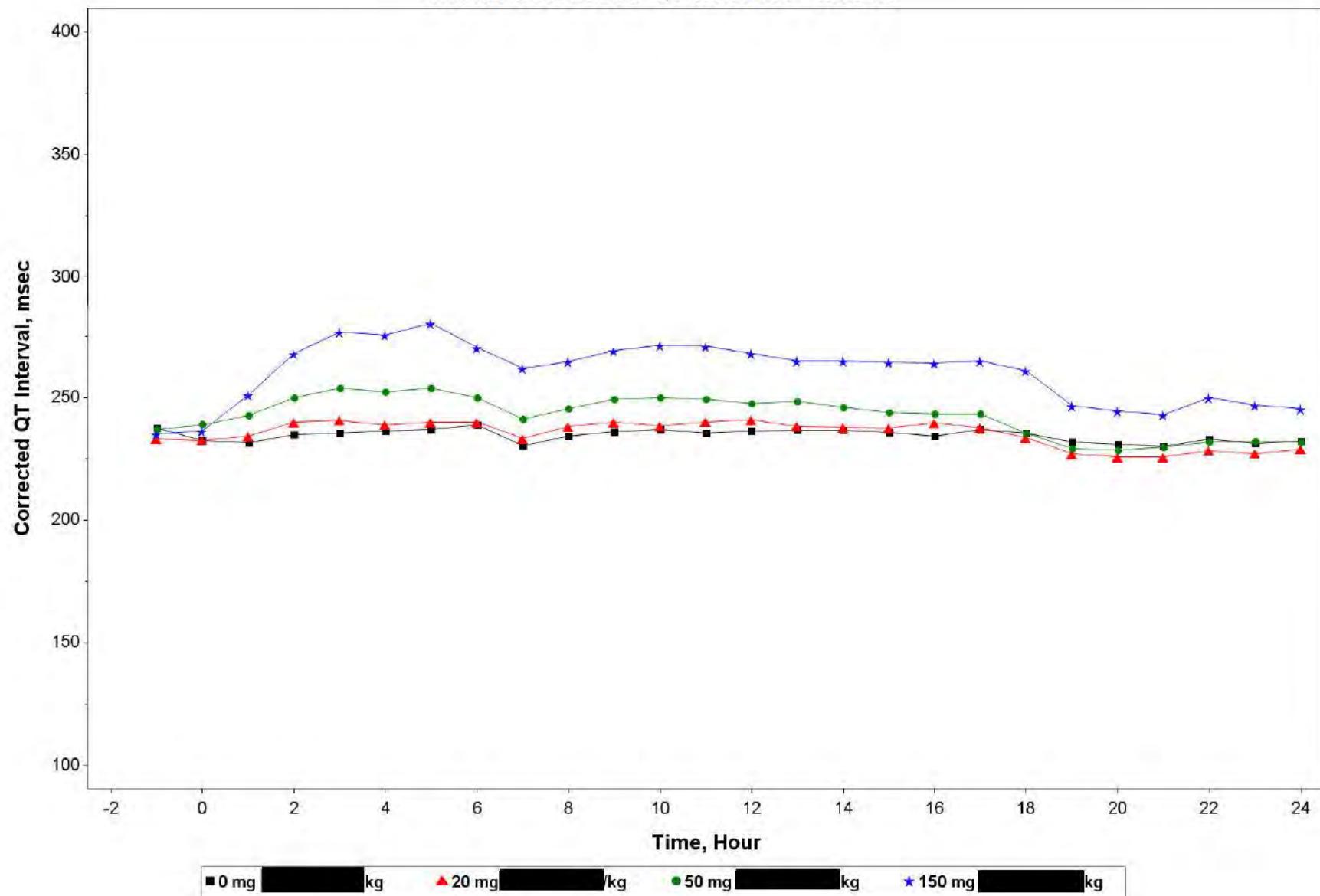
**Mean Corrected QT Interval - MALE**

Table 1  
Summary of Detailed Clinical Observations

**Abbreviations**

- PRDO – Predose  
1HPD – 1 hour postdose  
EndM – End of monitoring  
NAD – No abnormalities detected  
UNSCH – Unscheduled

## Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs

Summary of Detailed Clinical Observations<sup>+</sup>

Sex: Male Observation Type: Combined

		Timeslot(s)				
0 mg [REDACTED] kg		PRDO	1HPD	EndM	UN SCH	Total <sup>z</sup>
Number of Animals Examined		6	6	6	3	
Normal	NAD	1	6	2	0	9/6
Behavior/Activity	Inappetence	0	0	0	0	0/0
Clinical Medicine	Calculus	5	0	1	0	6/6
Excretion	Emesis, Tan	0	0	0	0	0/0
	Feces discolored, Yellow	0	0	0	1	1/1
	Feces mucoid	0	0	0	1	1/1
	Feces soft	0	0	0	1	2/1
	Vomitus, Tan	0	0	0	1	1/1
External Appearance	Gums discolored, Red	3	0	2	0	5/3
	Lacration	0	0	1	0	1/1
	Teeth discolored, Brown	1	0	0	0	1/1
	Teeth discolored, Yellow	2	0	1	0	3/3
	Thin	0	0	0	0	0/0
Pelage/Skin	Scabbed area	0	0	0	0	0/0

<sup>+</sup>Number of animals affected<sup>z</sup>Number of times observed/Total number of animals affected

## Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs

Summary of Detailed Clinical Observations<sup>+</sup>

Sex: Male      Observation Type: Combined

		Timeslot(s)				
20 mg [REDACTED] kg		PRDO	1HPD	EndM	UN SCH	Total <sup>z</sup>
Number of Animals Examined		6	6	6	3	
Normal	NAD	1	6	3	0	10/6
Behavior/Activity	Inappetence	0	0	0	1	1/1
Clinical Medicine	Calculus	3	0	1	0	4/4
Excretion	Emesis, Tan	0	0	0	0	0/0
	Feces discolored, Yellow	0	0	0	0	0/0
	Feces mucoid	0	0	0	1	1/1
	Feces soft	0	0	0	2	3/2
	Vomitus, Tan	0	0	0	0	0/0
External Appearance	Gums discolored, Red	3	0	1	0	4/3
	Lacration	0	0	1	0	1/1
	Teeth discolored, Brown	1	0	1	0	2/2
	Teeth discolored, Yellow	1	0	1	0	2/2
	Thin	0	0	0	0	0/0
Pelage/Skin	Scabbed area	0	0	0	0	0/0

<sup>+</sup>Number of animals affected<sup>z</sup>Number of times observed/Total number of animals affected

## Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs

Summary of Detailed Clinical Observations<sup>+</sup>

Sex: Male Observation Type: Combined

		Timeslot(s)				
50 mg [REDACTED] kg		PRDO	1HPD	EndM	UN SCH	Total <sup>z</sup>
Number of Animals Examined		6	6	6	3	
Normal	NAD	3	6	2	0	11/6
Behavior/Activity	Inappetence	0	0	0	0	0/0
Clinical Medicine	Calculus	3	0	2	0	5/4
Excretion	Emesis, Tan	0	0	0	1	1/1
	Feces discolored, Yellow	0	0	0	2	2/2
	Feces mucoid	0	0	0	2	2/2
	Feces soft	0	0	0	1	2/1
	Vomitus, Tan	0	0	0	0	0/0
External Appearance	Gums discolored, Red	2	0	1	0	3/3
	Lacration	0	0	1	0	1/1
	Teeth discolored, Brown	0	0	1	0	1/1
	Teeth discolored, Yellow	2	0	1	0	3/3
	Thin	1	0	0	0	1/1
Pelage/Skin	Scabbed area	0	0	1	0	1/1

<sup>+</sup>Number of animals affected<sup>z</sup>Number of times observed/Total number of animals affected

## Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs

Summary of Detailed Clinical Observations<sup>+</sup>

Sex: Male      Observation Type: Combined

		Timeslot(s)				
150 mg [REDACTED] kg		PRDO	1HPD	EndM	UN SCH	Total <sup>z</sup>
Number of Animals Examined		6	6	6	1	
Normal	NAD	1	6	2	0	9/6
Behavior/Activity	Inappetence	0	0	0	0	0/0
Clinical Medicine	Calculus	4	0	0	0	4/4
Excretion	Emesis, Tan	0	0	0	0	0/0
	Feces discolored, Yellow	0	0	0	0	0/0
	Feces mucoid	0	0	0	0	0/0
	Feces soft	0	0	1	1	2/2
	Vomitus, Tan	0	0	2	0	2/2
External Appearance	Gums discolored, Red	1	0	2	0	3/3
	Lacrimation	1	0	0	0	1/1
	Teeth discolored, Brown	0	0	2	0	2/2
	Teeth discolored, Yellow	2	0	1	0	3/2
	Thin	0	0	0	0	0/0
Pelage/Skin	Scabbed area	0	0	0	0	0/0

<sup>+</sup>Number of animals affected<sup>z</sup>Number of times observed/Total number of animals affected

**Table 2**  
**Summary of Body Temperature**

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Summary of Body Temperature - MALE**

Endpoint	Study Interval (hour:minute)	0 mg [REDACTED] kg			20 mg [REDACTED] kg			50 mg [REDACTED] kg			150 mg [REDACTED] kg		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
<b>Body Temperature °C</b>													
	-1:00	37.88	0.233	6	37.87	0.136	6	37.91	0.283	6	37.94	0.348	6
	0:00	38.01	0.213	6	38.06	0.275	6	38.01	0.218	6	38.01	0.333	6
	1:00	38.34	0.165	6	38.25	0.172	6	38.27	0.146	6	38.36	0.174	6
	2:00	38.08	0.197	6	38.06	0.370	6	38.08	0.181	6	38.13	0.349	6
	3:00	38.07	0.296	6	37.99	0.283	6	37.95	0.294	6	38.22	0.359	6
	4:00	37.98	0.152	6	37.93	0.291	6	37.96	0.292	6	38.21	0.334	6
	5:00	37.82	0.211	6	37.71	0.250	6	37.99	0.311	6	38.26	0.396	6
	6:00	37.88	0.305	6	37.80	0.145	6	38.02	0.331	6	38.14	0.436	6
	7:00	38.36	0.234	6	38.33	0.279	6	38.41	0.205	6	38.57	0.277	6
	8:00	38.08	0.193	6	38.16	0.247	6	38.18	0.279	6	38.29	0.694	6
	9:00	37.93	0.235	6	37.91	0.338	6	37.96	0.237	6	38.09	0.558	6
	10:00	37.79	0.386	6	37.93	0.215	6	38.02	0.230	6	38.04	0.303	6
	11:00	37.82	0.303	6	37.82	0.170	6	37.82	0.393	6	37.96	0.288	6
	12:00	37.69	0.283	6	37.75	0.138	6	37.80	0.212	6	37.91	0.316	6
	13:00	37.72	0.238	6	37.83	0.101	6	37.60	0.411	6	38.00	0.554	6
	14:00	37.68	0.299	6	37.69	0.282	6	37.55	0.365	6	38.05	0.550	6
	15:00	37.68	0.305	6	37.77	0.271	6	37.49	0.528	6	37.95	0.318	6
	16:00	37.73	0.125	6	37.71	0.119	6	37.58	0.368	6	37.93	0.241	6
	17:00	37.63	0.107	6	37.72	0.243	6	37.36	0.383	6	37.68	0.230	6
	18:00	37.76	0.216	6	37.80	0.242	6	37.67	0.412	6	37.68	0.241	6
	19:00	38.01	0.340	6	38.10	0.332	6	38.05	0.374	6	38.00	0.312	6
	20:00	38.12	0.344	6	38.24	0.410	6	38.21	0.399	6	38.21	0.368	6
	21:00	38.28	0.152	6	38.29	0.392	6	38.23	0.462	6	38.29	0.596	6
	22:00	38.02	0.303	6	38.18	0.360	6	38.14	0.375	6	38.21	0.587	6
	23:00	38.08	0.249	6	38.09	0.346	6	38.01	0.271	6	38.18	0.440	6
	24:00	38.14	0.216	6	38.13	0.257	6	38.07	0.261	6	38.21	0.413	6

N - Number of measures used to calculate mean

SD - Standard Deviation

**Table 3**  
**Summary of Systolic Blood Pressure**

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Summary of Systolic Blood Pressure - MALE**

Endpoint	Study Interval (hour:minute)	0 mg [REDACTED] kg			20 mg [REDACTED] kg			50 mg [REDACTED] kg			150 mg [REDACTED] kg			
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	
<b>Systolic Blood Pressure</b>														
<b>mmHg</b>														
-1:00		130.1	8.59	6	138.5	9.05	6	137.9	12.90	6	136.6	12.61	6	
0:00		139.3	11.49	6	138.5	11.79	6	135.9	10.49	6	138.5	11.28	6	
1:00		132.7	10.32	6	134.6	9.49	6	129.5	9.29	6	130.4	6.06	6	
2:00		136.1	12.27	6	135.7	12.98	6	134.2	11.28	6	132.6	9.49	6	
3:00		130.0	13.53	6	129.0	9.27	6	130.4	10.33	6	131.3	4.62	6	
4:00		123.3	9.11	6	128.9	9.43	6	129.5	10.51	6	127.0	6.56	6	
5:00		127.7	9.06	6	123.2	9.19	6	123.9	12.32	6	122.9	5.94	6	
6:00		126.9	4.66	6	131.5	10.54	6	125.6	9.02	6	126.4	4.51	6	
7:00		126.5	3.87	6	128.0	5.79	6	127.7	4.41	6	123.6	4.62	6	
8:00		120.0	6.68	6	116.4	5.70	6	118.1	6.90	6	116.4	2.90	6	
9:00		120.4	6.76	6	116.6	6.16	6	119.6	5.29	6	118.3	1.58	6	
10:00		123.5	8.13	6	119.5	8.28	6	116.3	5.83	6	116.9	6.56	6	
11:00		123.7	6.97	6	119.5	9.15	6	115.6	4.70	6	114.9	7.59	6	
12:00		123.7	8.54	6	120.0	8.09	6	116.0	4.03	6	112.1	7.02	6	
13:00		123.6	7.40	6	122.6	11.58	6	117.5	3.79	6	114.1	7.90	6	
14:00		126.1	7.07	6	120.7	11.04	6	121.2	5.40	6	113.6	6.51	6	
15:00		127.1	6.99	6	125.4	12.58	6	122.9	3.22	6	113.4	4.94	6	
16:00		128.8	3.34	6	123.3	11.34	6	124.1	2.45	6	116.1	8.55	6	
17:00		130.3	3.83	6	127.4	9.94	6	129.3	3.68	6	118.3	6.13	6	
18:00		139.5	11.93	6	132.9	7.52	6	141.3	11.57	6	127.2	8.58	6	
19:00		139.3	12.74	6	142.2	11.94	6	142.3	11.87	6	132.8	11.59	6	
20:00		144.6	12.50	6	145.1	12.97	6	143.7	10.69	6	136.3	5.18	6	
21:00		141.8	9.87	6	142.1	10.35	6	142.1	14.34	6	134.2	9.06	6	
22:00		135.6	7.90	6	140.4	8.03	6	141.7	10.62	6	131.1	7.93	6	
23:00		140.1	10.08	6	140.4	10.45	6	139.6	11.36	6	135.3	5.28	6	
24:00		139.5	10.52	6	140.1	8.49	6	139.6	11.53	6	133.4	4.12	6	

N - Number of measures used to calculate mean

SD - Standard Deviation

**Table 4**  
**Summary of Diastolic Blood Pressure**

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Summary of Diastolic Blood Pressure - MALE**

Endpoint	Study Interval (hour:minute)	0 mg [REDACTED] kg			20 mg [REDACTED] kg			50 mg [REDACTED] kg			150 mg [REDACTED] kg		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
<b>Diastolic Blood Pressure</b>													
mmHg													
-1:00	74.5	7.86	6	80.0	9.04	6	79.7	9.65	6	79.4	9.61	6	
0:00	82.5	9.25	6	81.1	8.63	6	79.8	9.86	6	81.2	5.80	6	
1:00	79.9	5.95	6	81.1	6.07	6	78.2	7.45	6	77.9	3.05	6	
2:00	81.2	7.03	6	81.7	6.51	6	81.2	11.12	6	79.4	5.99	6	
3:00	76.2	8.01	6	76.0	4.00	6	77.2	10.07	6	77.8	3.05	6	
4:00	71.1	9.27	6	76.8	5.27	6	76.3	9.04	6	76.4	3.50	6	
5:00	74.1	7.94	6	70.4	5.50	6	71.9	10.04	6	71.4	5.22	6	
6:00	74.1	7.05	6	78.2	9.24	6	72.7	7.36	6	74.1	4.04	6	
7:00	77.3	3.89	6	78.7	4.28	6	77.4	4.46	6	75.1	6.56	6	
8:00	69.4	4.34	6	67.8	1.65	6	68.1	6.06	6	68.9	7.59	6	
9:00	68.5	6.85	6	66.8	4.91	6	70.7	6.95	6	67.1	5.43	6	
10:00	69.9	8.13	6	68.0	5.64	6	66.0	5.39	6	65.9	5.63	6	
11:00	70.3	8.60	6	67.7	7.99	6	65.7	3.31	6	64.8	5.56	6	
12:00	69.9	9.71	6	67.8	6.83	6	65.1	5.62	6	62.2	6.06	6	
13:00	68.8	7.11	6	69.6	9.13	6	66.5	3.78	6	62.9	6.36	6	
14:00	69.0	7.33	6	68.9	8.91	6	68.8	5.27	6	62.2	4.65	6	
15:00	68.7	6.00	6	71.1	9.62	6	68.6	3.80	6	62.6	4.02	6	
16:00	70.1	3.58	6	69.1	8.29	6	69.8	4.71	6	63.1	6.51	6	
17:00	73.4	2.59	6	72.9	8.71	6	74.3	2.73	6	66.2	6.50	6	
18:00	81.4	7.50	6	78.8	4.95	6	83.7	4.52	6	74.8	5.85	6	
19:00	80.7	7.43	6	85.4	7.23	6	84.0	6.54	6	79.6	8.08	6	
20:00	84.3	8.29	6	86.9	9.06	6	85.1	8.66	6	82.6	7.94	6	
21:00	83.0	5.55	6	84.4	8.08	6	84.3	12.21	6	81.0	8.97	6	
22:00	78.4	6.11	6	82.8	7.07	6	83.8	9.16	6	78.7	8.09	6	
23:00	82.2	7.08	6	83.7	6.99	6	83.2	9.51	6	81.5	6.73	6	
24:00	81.4	7.63	6	82.6	4.74	6	83.2	8.76	6	80.5	6.29	6	

N - Number of measures used to calculate mean

SD - Standard Deviation

**Table 5**  
**Summary of Mean Arterial Blood Pressure**

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Summary of Mean Arterial Blood Pressure - MALE**

Endpoint	Study Interval (hour:minute)	0 mg [REDACTED] kg			20 mg [REDACTED] kg			50 mg [REDACTED] kg			150 mg [REDACTED] kg		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
<b>Mean Arterial Blood Pressure</b>													
<b>mmHg</b>													
-1:00	96.0	7.86	6	102.9	9.45	6	102.5	10.57	6	101.8	11.06	6	
0:00	105.4	9.93	6	104.1	9.83	6	102.2	10.21	6	104.2	7.59	6	
1:00	101.6	6.32	6	102.9	6.09	6	98.8	7.13	6	98.6	2.57	6	
2:00	103.9	7.99	6	103.7	8.40	6	102.2	10.91	6	100.6	7.30	6	
3:00	97.8	8.69	6	97.0	4.45	6	98.0	9.89	6	98.6	3.46	6	
4:00	91.5	8.83	6	97.7	5.22	6	97.3	8.99	6	96.2	3.76	6	
5:00	94.9	7.38	6	90.8	5.26	6	92.1	9.66	6	91.3	4.87	6	
6:00	94.8	6.08	6	99.5	9.07	6	93.2	6.75	6	94.5	3.90	6	
7:00	97.8	2.95	6	99.2	4.57	6	98.1	3.82	6	94.5	5.66	6	
8:00	89.3	3.93	6	87.4	1.30	6	87.7	4.95	6	87.6	5.59	6	
9:00	88.6	6.24	6	86.6	4.99	6	90.0	6.16	6	86.8	4.24	6	
10:00	90.5	7.68	6	88.3	6.02	6	85.9	4.80	6	85.8	5.56	6	
11:00	90.5	7.53	6	88.0	8.31	6	85.4	2.98	6	84.4	5.56	6	
12:00	90.2	8.82	6	88.1	7.14	6	85.1	5.36	6	81.8	6.07	6	
13:00	89.3	6.33	6	90.1	9.17	6	86.5	3.40	6	82.8	7.02	6	
14:00	90.1	7.18	6	88.9	8.89	6	89.1	5.00	6	82.2	4.90	6	
15:00	90.1	6.40	6	91.8	10.02	6	89.2	3.05	6	82.5	3.65	6	
16:00	91.4	3.58	6	89.8	8.89	6	90.4	4.02	6	83.6	6.63	6	
17:00	94.6	2.50	6	94.0	9.09	6	95.5	1.75	6	86.4	5.78	6	
18:00	104.4	8.88	6	100.9	5.44	6	107.3	7.23	6	96.2	5.50	6	
19:00	104.8	9.29	6	109.3	8.62	6	108.7	8.19	6	102.0	8.68	6	
20:00	108.9	10.13	6	111.7	10.85	6	110.0	9.75	6	105.0	6.15	6	
21:00	107.1	5.95	6	108.6	8.91	6	108.5	13.61	6	102.7	9.59	6	
22:00	100.8	6.71	6	106.3	7.30	6	107.6	9.50	6	99.7	7.27	6	
23:00	105.3	7.55	6	107.0	7.89	6	106.2	10.26	6	103.5	5.58	6	
24:00	104.7	8.47	6	105.9	5.34	6	106.1	9.78	6	102.3	4.88	6	

N - Number of measures used to calculate mean

SD - Standard Deviation

**Table 6**  
**Summary of Heart Rate**

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Summary of Heart Rate - MALE**

Endpoint	Study Interval (hour:minute)	0 mg [REDACTED] kg			20 mg [REDACTED] kg			50 mg [REDACTED] kg			150 mg [REDACTED] kg		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Heart Rate beats/minute	-1:00	80.8	20.24	6	87.6	17.95	6	87.1	15.32	6	85.7	24.38	6
	0:00	94.3	22.58	6	94.0	17.54	6	91.1	19.52	6	92.9	17.66	6
	1:00	97.1	4.89	6	93.1	6.92	6	87.1	18.20	6	84.9	11.13	6
	2:00	97.9	6.38	6	95.3	11.64	6	86.2	19.37	6	84.1	13.84	6
	3:00	87.9	7.62	6	85.0	13.91	6	78.3	19.01	6	79.0	8.56	6
	4:00	79.6	14.26	6	88.7	15.05	6	82.0	14.36	6	84.3	11.11	6
	5:00	79.5	17.27	6	76.6	15.03	6	76.7	11.75	6	78.6	4.91	6
	6:00	83.3	14.27	6	90.0	16.49	6	82.7	8.48	6	85.7	6.31	6
	7:00	103.9	13.52	6	103.9	14.53	6	98.6	13.54	6	97.2	16.79	6
	8:00	81.8	10.89	6	89.6	7.04	6	81.8	9.71	6	89.0	18.03	6
	9:00	75.9	11.13	6	85.4	7.13	6	85.8	18.27	6	79.7	8.46	6
	10:00	73.3	10.56	6	83.1	7.50	6	84.3	16.12	6	81.3	9.89	6
	11:00	69.6	9.89	6	76.8	6.60	6	82.0	10.88	6	80.7	5.30	6
	12:00	69.4	9.12	6	78.7	9.86	6	80.8	11.10	6	81.7	4.47	6
	13:00	66.9	8.39	6	75.5	7.73	6	78.1	10.91	6	81.0	4.87	6
	14:00	64.8	9.40	6	75.9	10.63	6	76.6	12.68	6	79.8	5.01	6
	15:00	62.2	8.38	6	75.5	7.44	6	71.4	10.34	6	80.7	3.70	6
	16:00	60.9	8.43	6	73.9	7.54	6	70.8	11.46	6	78.2	6.96	6
	17:00	69.3	12.30	6	83.0	12.49	6	76.2	8.35	6	80.7	12.53	6
	18:00	89.8	7.72	6	101.0	20.34	6	106.5	13.93	6	98.6	10.78	6
	19:00	104.0	12.60	6	115.2	13.55	6	119.1	11.82	6	114.5	14.60	6
	20:00	105.6	22.02	6	121.8	20.78	6	122.7	21.72	6	110.1	16.24	6
	21:00	103.4	15.63	6	112.6	20.31	6	113.5	27.10	6	101.7	24.21	6
	22:00	85.0	14.54	6	102.1	19.54	6	106.0	19.11	6	92.8	8.94	6
	23:00	92.1	15.09	6	105.6	17.02	6	102.5	18.67	6	102.0	8.12	6
	24:00	93.1	19.45	6	98.1	9.18	6	100.0	23.28	6	105.2	9.91	6

N - Number of measures used to calculate mean

SD - Standard Deviation

**Table 7**  
**Summary of RR Interval**

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Summary of RR Interval - MALE**

Endpoint	Study Interval (hour:minute)	0 mg [REDACTED] kg			20 mg [REDACTED] kg			50 mg [REDACTED] kg			150 mg [REDACTED] kg		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
RR Interval msec	-1:00	810.7	202.79	6	806.0	147.30	5	758.1	141.79	6	795.7	209.63	6
	0:00	710.6	190.56	6	715.8	144.18	5	714.7	137.51	6	709.7	155.89	6
	1:00	657.1	36.90	6	693.9	68.28	5	744.3	167.05	6	751.3	95.46	6
	2:00	644.3	38.54	6	672.0	101.72	5	758.0	174.46	6	753.9	118.72	6
	3:00	714.9	53.42	6	759.4	129.77	5	819.9	179.45	6	782.5	83.34	6
	4:00	803.7	165.55	6	719.0	131.86	5	772.1	132.71	6	736.9	85.68	6
	5:00	823.8	212.72	6	842.9	187.82	5	819.5	128.19	6	777.1	50.14	6
	6:00	759.6	133.64	6	712.8	133.69	5	766.1	92.61	6	726.0	59.63	6
	7:00	596.1	79.65	6	595.1	88.93	5	636.5	84.12	6	649.9	111.66	6
	8:00	756.4	106.04	6	676.0	56.73	5	753.4	94.43	6	705.5	122.14	6
	9:00	816.1	123.42	6	722.5	59.33	5	736.2	149.18	6	770.3	77.85	6
	10:00	847.4	134.50	6	743.2	69.17	5	741.3	129.98	6	756.4	87.79	6
	11:00	892.5	136.51	6	783.1	70.18	5	751.1	102.57	6	753.7	47.07	6
	12:00	896.9	139.78	6	775.4	110.26	5	764.8	109.17	6	746.5	38.28	6
	13:00	922.5	135.77	6	814.8	104.85	5	790.0	121.82	6	749.0	41.29	6
	14:00	957.7	153.97	6	805.4	136.60	5	812.5	132.46	6	759.9	47.19	6
	15:00	996.1	146.83	6	829.1	108.07	5	867.3	138.84	6	753.5	35.52	6
	16:00	1015.7	147.70	6	812.6	75.46	5	879.6	146.42	6	781.6	68.00	6
	17:00	934.2	173.79	6	740.6	90.19	5	827.9	104.37	6	776.5	104.28	6
	18:00	732.0	55.42	6	625.5	120.22	5	618.6	79.80	6	643.6	69.48	6
	19:00	614.3	77.74	6	530.9	58.14	5	526.5	51.50	6	543.6	77.97	6
	20:00	620.5	141.71	6	506.9	106.05	5	525.3	104.21	6	582.0	109.89	6
	21:00	633.7	92.97	6	549.3	97.52	5	588.7	180.47	6	634.7	158.88	6
	22:00	762.8	148.60	6	626.9	133.99	5	617.6	126.95	6	680.1	72.40	6
	23:00	710.7	136.48	6	604.9	114.35	5	637.5	128.13	6	623.9	53.06	6
	24:00	704.5	130.61	6	637.0	68.63	5	656.5	137.49	6	594.4	65.21	6

N - Number of measures used to calculate mean

SD - Standard Deviation

**Table 8**  
**Summary of PR Interval**

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Summary of PR Interval - MALE**

Endpoint	Study Interval (hour:minute)	0 mg [REDACTED] kg			20 mg [REDACTED] kg			50 mg [REDACTED] kg			150 mg [REDACTED] kg		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
PR Interval msec	-1:00	105.0	9.20	6	100.7	7.56	5	102.0	5.63	6	101.4	9.36	6
	0:00	101.9	9.09	6	99.4	5.04	5	102.2	8.76	6	98.7	6.13	6
	1:00	101.3	5.96	6	102.4	4.57	5	106.7	8.16	6	104.2	7.69	6
	2:00	99.6	5.67	6	102.7	5.56	5	109.3	8.89	6	105.0	11.17	6
	3:00	102.8	4.72	6	106.8	4.91	5	111.6	9.57	6	108.0	11.30	6
	4:00	105.5	8.98	6	105.1	6.07	5	108.4	7.97	6	105.1	13.11	6
	5:00	104.6	8.47	6	107.2	6.48	5	108.6	7.28	6	107.7	10.57	6
	6:00	104.7	7.87	6	103.4	8.93	5	105.1	7.08	6	103.4	9.25	6
	7:00	100.0	7.77	6	100.6	8.24	5	102.4	10.17	6	100.1	8.68	6
	8:00	105.7	7.17	6	104.2	6.48	5	105.6	6.34	6	99.6	9.62	6
	9:00	105.2	7.48	6	103.8	6.88	5	103.2	7.83	6	102.2	10.83	6
	10:00	105.4	7.71	6	102.7	5.84	5	104.3	8.75	6	101.5	11.36	6
	11:00	105.4	7.10	6	103.5	5.53	5	103.7	7.62	6	100.8	10.71	6
	12:00	104.5	7.04	6	103.8	7.99	5	104.1	6.76	6	99.2	8.03	6
	13:00	104.5	7.94	6	102.7	7.55	5	103.7	7.60	6	99.1	10.92	6
	14:00	104.7	9.64	6	104.2	6.90	5	102.9	6.12	6	99.2	9.44	6
	15:00	104.5	9.40	6	103.1	8.02	5	103.6	7.48	6	99.4	9.25	6
	16:00	105.1	9.16	6	103.6	6.37	5	103.1	8.00	6	98.1	9.25	6
	17:00	103.7	8.84	6	100.5	8.93	5	102.4	7.30	6	98.4	11.01	6
	18:00	96.8	5.71	6	97.3	6.64	5	93.1	6.33	6	94.5	12.29	6
	19:00	93.6	7.24	6	91.7	4.84	5	89.6	7.63	6	91.0	10.22	6
	20:00	93.5	7.92	6	90.0	7.26	5	89.3	9.40	6	93.2	14.23	6
	21:00	95.5	4.14	6	92.7	6.98	5	92.0	10.08	6	94.6	14.56	6
	22:00	99.5	6.63	6	94.9	7.98	5	93.6	8.87	6	97.9	8.38	6
	23:00	97.7	5.74	6	94.3	7.08	5	95.4	8.99	6	95.7	8.80	6
	24:00	98.2	5.79	6	96.1	5.22	5	97.0	9.74	6	95.8	9.11	6

N - Number of measures used to calculate mean

SD - Standard Deviation

**Table 9**  
**Summary of QRS Duration**

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Summary of QRS Duration - MALE**

Endpoint	Study Interval (hour:minute)	0 mg [REDACTED] kg			20 mg [REDACTED] kg			50 mg [REDACTED] kg			150 mg [REDACTED] kg		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
QRS Duration msec	-1:00	38.9	2.38	6	37.9	0.95	5	38.9	2.18	6	38.8	1.96	6
	0:00	38.7	2.25	6	37.9	0.92	5	38.8	2.11	6	38.9	2.07	6
	1:00	38.5	2.22	6	37.8	0.84	5	38.8	1.83	6	38.9	1.92	6
	2:00	38.7	2.25	6	38.1	1.10	5	39.0	2.06	6	39.4	2.01	6
	3:00	38.6	2.35	6	38.0	1.27	5	39.1	2.08	6	39.5	2.10	6
	4:00	38.7	2.25	6	38.0	1.29	5	39.2	1.99	6	39.6	1.69	6
	5:00	38.7	2.35	6	37.8	1.47	5	39.1	2.16	6	39.8	2.15	6
	6:00	38.7	2.37	6	37.9	1.17	5	39.0	2.07	6	39.5	1.79	6
	7:00	38.4	1.99	6	37.8	1.07	5	38.8	1.94	6	39.8	1.90	6
	8:00	38.7	2.07	6	37.9	0.90	5	38.7	1.96	6	39.9	1.64	6
	9:00	38.7	2.22	6	37.8	1.16	5	39.2	2.07	6	39.9	1.87	6
	10:00	38.6	2.14	6	37.8	1.16	5	39.0	2.26	6	39.9	1.48	6
	11:00	38.7	2.03	6	37.9	1.37	5	39.0	2.18	6	39.8	1.94	6
	12:00	38.8	2.16	6	37.9	1.18	5	38.8	2.41	6	39.8	1.66	6
	13:00	38.6	2.71	6	38.1	0.95	5	38.9	2.03	6	40.0	2.12	6
	14:00	38.5	2.39	6	37.7	1.41	5	38.9	1.85	6	39.8	1.80	6
	15:00	38.7	2.38	6	38.0	1.08	5	38.8	2.33	6	39.8	2.03	6
	16:00	38.6	2.12	6	38.0	1.23	5	38.9	2.20	6	39.8	2.19	6
	17:00	38.8	2.17	6	38.1	1.00	5	39.0	2.09	6	40.1	2.02	6
	18:00	38.7	2.32	6	37.9	0.71	5	38.8	2.14	6	40.3	1.88	6
	19:00	38.7	2.43	6	37.8	0.87	5	38.8	2.07	6	40.1	1.82	6
	20:00	38.7	2.31	6	37.8	0.97	5	38.7	2.12	6	39.8	1.83	6
	21:00	38.6	2.24	6	37.7	0.81	5	38.8	1.98	6	39.6	1.78	6
	22:00	38.9	2.33	6	37.8	0.69	5	38.8	2.12	6	39.8	2.15	6
	23:00	38.8	2.22	6	37.9	0.79	5	38.9	1.96	6	39.7	2.14	6
	24:00	38.7	2.10	6	37.9	0.96	5	38.8	2.00	6	39.9	2.21	6

N - Number of measures used to calculate mean

SD - Standard Deviation

Table 10  
Summary of QT Interval

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Summary of QT Interval - MALE**

Endpoint	Study Interval (hour:minute)	0 mg [REDACTED] kg			20 mg [REDACTED] kg			50 mg [REDACTED] kg			150 mg [REDACTED] kg		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
QT Interval msec	-1:00	235.4	14.69	6	229.8	13.84	5	230.8	15.11	6	231.5	21.24	6
	0:00	222.9	16.69	6	223.6	11.66	5	229.9	16.51	6	226.8	16.35	6
	1:00	218.9	3.50	6	224.4	5.65	5	235.8	9.86	6	245.5	9.47	6
	2:00	221.2	5.26	6	228.3	14.95	5	243.3	13.21	6	261.7	13.86	6
	3:00	227.8	4.86	6	236.0	8.18	5	252.3	17.49	6	273.4 <sup>a</sup>	9.38	6
	4:00	234.2	11.32	6	230.9	9.89	5	247.9	14.12	6	268.6	22.41	6
	5:00	235.4	12.29	6	241.1	12.02	5	253.0	10.84	6	277.2	16.75	6
	6:00	233.9	14.82	6	231.8	14.64	5	244.5	8.62	6	261.9	16.02	6
	7:00	213.6	8.96	6	215.7	13.46	5	226.8	11.03	6	247.5	17.45	6
	8:00	229.5	7.30	6	228.1	6.42	5	240.5	8.34	6	255.3	17.41	6
	9:00	235.4	5.32	6	233.6	6.16	5	242.6	13.02	6	265.3	15.14	6
	10:00	238.4	6.48	6	233.4	6.58	5	243.7	11.48	6	266.6	21.63	6
	11:00	239.7	4.75	6	238.0	6.38	5	244.1	8.49	6	266.2	16.51	6
	12:00	240.9	4.98	6	238.0	6.53	5	243.6	8.00	6	262.5	13.30	6
	13:00	243.0	3.94	6	238.3	5.73	5	246.1	9.92	6	259.9	17.00	6
	14:00	244.8	5.11	6	236.9	6.56	5	245.3	9.33	6	260.6	13.51	6
	15:00	246.2	5.09	6	238.4	6.16	5	247.1	10.44	6	259.3	12.33	6
	16:00	245.7	5.61	6	239.4	5.32	5	247.2	10.41	6	261.0	11.54	6
	17:00	243.0	9.54	6	231.7	7.27	5	243.5	10.71	6	261.0	12.62	6
	18:00	227.5	7.44	6	218.3	11.87	5	218.8	9.03	6	245.9	10.53	6
	19:00	215.7	9.58	6	204.6	8.97	5	205.7	8.75	6	222.8	18.87	6
	20:00	214.6	16.83	6	201.0	14.73	5	204.3	14.07	6	224.0	14.61	6
	21:00	215.1	10.64	6	204.6	9.60	5	211.0	20.75	6	226.9	15.07	6
	22:00	228.0	13.97	6	213.4	13.09	5	215.5	15.14	6	238.4	6.89	6
	23:00	222.0	12.98	6	210.5	9.59	5	217.3	14.83	6	231.1	10.52	6
	24:00	222.3	14.19	6	215.2	4.18	5	218.8	14.75	6	227.4	11.70	6

N - Number of measures used to calculate mean

SD - Standard Deviation

a = different from 0 mg 1760001.0/kg, p&lt;0.05

**Table 11**  
**Summary of Corrected QT Interval**

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Summary of Corrected QT Interval - MALE**

Endpoint	Study Interval (hour:minute)	0 mg [REDACTED] kg			20 mg [REDACTED] kg			50 mg [REDACTED] kg			150 mg [REDACTED] kg		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
<b>Corrected QT Interval msec</b>													
-1:00	237.4	9.12	6	233.1	10.57	5	237.0	10.91	6	235.0	9.93	6	
0:00	232.5	8.73	6	232.5	9.83	5	238.9	14.43	6	236.2	10.28	6	
1:00	231.4	8.33	6	234.1	9.65	5	242.5	10.41	6	251.1	8.75	6	
2:00	234.8	7.63	6	239.8	9.34	5	249.8	10.47	6	268.0 <sup>a</sup>	9.45	6	
3:00	235.4	6.14	6	240.6	6.65	5	253.7	12.01	6	276.8 <sup>a</sup>	10.52	6	
4:00	236.4	4.55	6	238.8	7.58	5	252.3	12.10	6	275.4	17.40	6	
5:00	236.9	5.44	6	239.9	8.19	5	253.9	10.34	6	280.3	12.65	6	
6:00	238.9	8.68	6	239.8	10.63	5	249.9	6.24	6	270.3	11.22	6	
7:00	230.3	8.34	6	233.2	10.46	5	241.2	9.51	6	261.9	13.30	6	
8:00	234.2	6.95	6	238.1	8.73	5	245.5	7.87	6	264.8	12.51	6	
9:00	236.0	6.04	6	239.9	5.96	5	249.3	7.31	6	269.2	14.08	6	
10:00	236.9	6.69	6	238.4	7.81	5	249.8	6.98	6	271.2	15.10	6	
11:00	235.4	6.15	6	240.0	9.92	5	249.2	6.10	6	271.0	14.07	6	
12:00	236.4	6.59	6	240.8	9.31	5	247.6	4.48	6	267.9	12.09	6	
13:00	236.8	5.32	6	238.3	11.20	5	248.3	6.28	6	265.0	15.87	6	
14:00	236.5	6.40	6	237.7	9.62	5	245.9	5.66	6	264.9	12.89	6	
15:00	235.8	6.03	6	237.5	9.67	5	244.0	5.62	6	264.3	13.52	6	
16:00	234.2	6.50	6	239.6	9.07	5	243.4	6.33	6	263.9	13.33	6	
17:00	237.1	5.73	6	237.7	9.64	5	243.4	6.63	6	265.0	16.07	6	
18:00	235.3	7.58	6	233.6	7.84	5	235.3	4.80	6	261.0	16.19	6	
19:00	232.0	7.85	6	226.9	5.42	5	229.0	8.48	6	246.5	20.47	6	
20:00	230.9	9.71	6	225.7	8.28	5	228.4	9.76	6	244.4	16.26	6	
21:00	230.1	10.37	6	225.7	9.00	5	229.6	10.55	6	242.8	9.65	6	
22:00	233.1	10.07	6	228.3	9.12	5	232.0	9.32	6	249.8	12.88	6	
23:00	231.4	9.61	6	227.1	8.25	5	232.2	9.67	6	246.8	15.08	6	
24:00	232.1	10.83	6	228.8	5.68	5	231.7	10.00	6	245.3	15.13	6	

N - Number of measures used to calculate mean

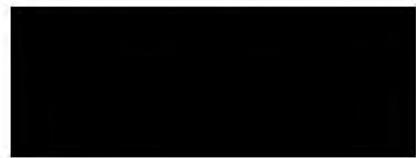
SD - Standard Deviation

a = different from 0 mg 1760001.0/kg, p&lt;0.05

Appendix 1  
Amended Protocol, Protocol, and Deviations

Sponsor Reference No.

Page 70  
Testing Facility Study No. [REDACTED]



**PROTOCOL AMENDMENT NO. 1**

Testing Facility Study No. [REDACTED]

Sponsor Reference No. [REDACTED]

**Cardiovascular Safety Evaluation of Orally Administered [REDACTED]  
[REDACTED] in Beagle Dogs**

**SPONSOR:**



**TESTING FACILITY:**



**SUMMARY OF CHANGES AND JUSTIFICATIONS**

Note: When applicable, additions are indicated in bold underlined text and deletions are indicated in bold strikethrough text in the affected sections of the document.

Item or Section(s)	Justification
<b>Amendment 1</b>	<b>Effective Date of Change: 08 Aug 2019</b>
12.3 Bioanalytical Sample Analysis	Addition of bioanalytical method name

**TABLE OF CONTENTS**

1. OBJECTIVE(S).....	4
2. PROPOSED STUDY SCHEDULE .....	4
3. SPONSOR .....	4
4. RESPONSIBLE PERSONNEL.....	4
5. TEST MATERIALS.....	7
6. DOSE FORMULATION AND ANALYSIS .....	8
7. TEST SYSTEM.....	10
8. HUSBANDRY .....	12
9. EXPERIMENTAL DESIGN.....	14
10. IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS .....	15
11. TELEMETRY MONITORING.....	17
12. BIOANALYSIS .....	19
13. TERMINAL PROCEDURES .....	21
14. HISTOLOGY AND MICROSCOPIC EVALUATION .....	22
15. STATISTICAL ANALYSIS .....	22
16. COMPUTER SYSTEMS .....	23
17. REGULATORY COMPLIANCE .....	23
18. QUALITY ASSURANCE.....	24
19. AMENDMENTS AND DEVIATIONS .....	24
20. RETENTION AND DISPOSITION OF RECORDS, SAMPLES, AND SPECIMENS .....	24
21. STUDY CLASSIFICATION .....	25
22. REPORTING.....	25
23. JUSTIFICATIONS AND GUIDELINES .....	25
24. ANIMAL WELFARE .....	26
25. REFERENCES .....	27
TESTING FACILITY APPROVAL.....	28
SPONSOR APPROVAL .....	29
ATTACHMENT A .....	30

**1. OBJECTIVE(S)**

[REDACTED] The purpose of this study is to evaluate the potential cardiovascular effects of [REDACTED] in conscious freely moving beagle dogs.

**2. PROPOSED STUDY SCHEDULE**

Proposed study dates are listed below. Actual dates will be included in the Final Report.

Experimental Starting Date: 08 Jul 2019

Experimental Completion Date: 03 Sep 2019

Animal Transfer: 08 Jul 2019

Initiation of Dosing: 15 Jul 2019

Completion of In-life: 20 Aug 2019

Draft Report: 15 Oct 2019

Final Report: The date on which the Study Director signs the final report.



- A listing of critical computerized systems used in the conduct and/or interpretation of the assigned study phase

## 5. TEST MATERIALS

### 5.1. Test Item Characterization

The Sponsor will provide to the Testing Facility documentation of the identity, strength, purity, composition, and stability for the test item. A Certificate of Analysis or equivalent documentation will be provided for inclusion in the Final Report.

### 5.2. Test Item Identification

	Test Item
<b>Identification:</b>	[REDACTED]
<b>Alternate Identification:</b>	[REDACTED]
<b>Batch/Lot No.:</b>	2560760
<b>Expiration/Retest Date:</b>	31 May 2020
<b>Physical Description:</b>	Off-white powder
<b>Assigned Chemical Potency:</b>	995 µg [REDACTED] mg
<b>Correction Factor:</b>	1.01
<b>Storage Conditions:</b>	Room Temperature; Protected from light
<b>Provided by:</b>	Sponsor

### 5.3. Control Item/Vehicle Information

	Control Item/Vehicle
<b>Identification:</b>	0.5% hydroxypropylmethylcellulose (HPMC; low viscosity), 0.1% Tween 80 in NANOPure Diamond Ultrapure water (w/v)
<b>Alternate Identification:</b>	No alternate ID
<b>Storage Conditions:</b>	Refrigerated (2 to 8°C); Protected from light
<b>Characterization:</b>	Documentation of the strength, purity, composition, stability, physical properties, and other pertinent information on each of the individual components for the lot/batch of vehicle or the commercially available vehicle, will be limited to that information listed on the label unless otherwise noted or provided by the Sponsor.

### 5.4. Reserve Samples

A reserve sample from each lot of test item used in this study is not required. However, if multiple studies are conducted with the same test item, a common reserve sample may be collected and labeled and stored appropriately.

### 5.5. Test Item Inventory and Disposition

Records of the receipt, distribution, storage, and disposition of test materials (including empty containers of Sponsor-provided materials) will be maintained until study finalization.

All unused Sponsor-supplied bulk test materials, with the exception of reserve samples, will be returned to the Sponsor following issuance of the Draft Report unless otherwise requested

(documentation will be retained in the study record). An earlier shipment of these materials may also be requested and authorized by the Study Director and Sponsor. See [Attachment A](#) for shipping details.

Upon receipt of the finalized formulation report, any remaining formulation samples will be discarded.

### **5.6. Safety**

A Safety Data Sheet (SDS), or equivalent documentation, will be provided by the Sponsor (if available). It is the responsibility of the Sponsor to notify the Testing Facility of any special handling requirements of the test item. Otherwise routine safety precautions will be followed. Appropriate gloves, safety glasses and arm covers will be worn by individuals working with neat test material or formulations.

## **6. DOSE FORMULATION AND ANALYSIS**

### **6.1. Preparation of Formulations**

Dose formulations will be divided into aliquots where required to allow to be dispensed on each dosing occasion.

<b>Dose Formulation</b>	<b>Administration Dose Form</b>	<b>Frequency of Preparation</b>	<b>Storage Conditions</b>
Control Item	Suspension	Once for each dosing day (or as needed), no more than 7 days prior to use	Refrigerated (2 to 8°C); Protected from light
Test Item	Suspension	Once for each dosing day (or as needed), no more than 7 days prior to use	Refrigerated (2 to 8°C); Protected from light

Formulations will be stirred at room temperature for at least one hour prior to dose administration. Formulations prepared and used on the same day of dosing will be stored at room temperature and protected from light.

Any residual volumes from each dosing occasion will be discarded unless otherwise requested by the Study Director.

### **6.2. Preparation Details**

The test item will be mixed with an appropriate volume of vehicle and subsequently brought to final volume with vehicle to achieve the final concentrations for treatments 2, 3, and 4.

[REDACTED] dosing formulations (Treatments 2, 3, and 4) require 1 molar equivalent of sodium hydroxide (NaOH) to achieve solubility. The final pH value of formulations will be measured and should be adjusted to  $8.2 \pm 0.1$  with the appropriate amount of NaOH or HCl. The test item concentration will be adjusted to reflect lot specific analysis of test item content. Formulation instructions will be retained with the raw data. Formulations for Treatment 1 (vehicle control) will also be adjusted to a final pH of  $8.2 \pm 0.1$  with the appropriate amount of NaOH or HCl.

### 6.3. Sample Collection and Analysis

Dose formulation samples will be collected for analysis as indicated in the following table. Additional samples may be collected and analyzed at the discretion of the Study Director.

**Dose Formulation Sample Collection Schedule**

Sample Type <sup>a</sup>	Concentrations	Stratum	Number of Samples per Concentration			Sample Volume (mL) <sup>b</sup>	Intervals
			Collected	Analyzed	Backup		
Concentration/ Homogeneity Analyses	Low, Mid, and High	Top	2	1	1	2.0	First Preparation
		Middle	2	1	1	2.0	
		Bottom	2	1	1	2.0	
Concentration Analyses	Control	Middle	2	1	1	5.0	Each Preparation
Concentration Analyses	Low, Mid, and High	Middle	2	1	1	2.0	Each Preparation

<sup>a</sup>The averaged result from the homogeneity analysis will serve as concentration verification, when applicable.  
<sup>b</sup>5.0 mL sample volume for concentrations < 1.0 mg/mL; 2.0 mL sample volume for concentrations ≥ 1.0 mg/mL.

Special Instructions: Appropriate samples (see previous table) will be collected while the preparations are being stirred.

Samples Analyzed By: All samples to be analyzed will be shipped to the Sponsor for analysis. See Attachment A for shipping details.

The analytical laboratory will be notified before shipment of the samples. Upon receipt at the analytical laboratory, the samples will be stored under the conditions listed below

Sample Transfer and Storage Conditions: Frozen (-60 to -90°C)

Formulation Sample Disposition: Any remaining formulation samples will be discarded after acceptance of the analytical results by the Study Director or upon receipt of authorization to finalize the report.

#### 6.3.1. Analytical Method

All analytical work will be conducted by the Sponsor using an analytical method developed and validated by that laboratory (GLP19-FA-ARM00612).

##### 6.3.1.1. Concentration and Homogeneity Analysis

Sample Allocation: 1 for analysis, 1 for backup

Storage Conditions: Frozen (-60 to -90°C)

Acceptance Criteria: For concentration: mean sample concentration results within or equal to  $\pm 10\%$  of theoretical concentration.  
For homogeneity, relative standard deviation (RSD) of concentrations of  $\leq 10\%$  for each group.  
Assay values that deviate from the intended concentration by more than 10% or RSD values that are greater than 10% will be referred immediately to the Study Director.

#### 6.3.1.2. Stability Analysis

The [REDACTED] formulations at concentrations that bracket those used in this study, were shown to be stable for at least seven days at 2-8°C and -70°C. Stability data provided by the Sponsor are retained in the study records.

### 7. TEST SYSTEM

Species: Dog  
Strain: Beagle  
Condition: Purpose-bred, non-naïve  
Source: Testing Facility Study Number 999-945 (non-naïve telemetry colony)  
Original Source: Based on availability, any of the following sources may be used:

- Marshall BioResources, North Rose, NY
- Covance Research Products, Cumberland, VA
- Ridglan Farms, Inc., Mt. Horeb, WI

The source for each animal will be documented in the raw data.

Number Transferred:

Male: 7

Number on Study:

Male: 6

Companion Animal Number on Study:

Male: 1

Expected Age at Transfer: At least 5 months of age

Expected Weight at Transfer: Commensurate with age; males will generally weigh 5.5 to 12.0 kg, as measured within 3 days of transfer. The actual range may vary but will be documented in the data.

The actual age and weight of animals on study will be listed in the Final Report.

### **7.1. Companion Animal Details**

Species:	Dog
Breed:	Beagle
Source:	Testing Facility Study Number 999-945 (non-naïve telemetry colony) or 999-885 (non-naïve general colony)
Original Source:	Based on availability, any of the following sources may be used: <ul style="list-style-type: none"><li>• Marshall BioResources, North Rose, NY</li><li>• Covance Research Products, Cumberland, VA</li><li>• Ridgian Farms, Inc., Mt. Horeb, WI</li></ul>
Details:	Companion animals will be assigned for the purpose of social housing of all study animals (not considered part of the test system). As such, they will only be subject to the observations/measurements as listed specifically for companion animals. Companion animals will be maintained using the same husbandry procedures as the main study animals (including following the same feeding and fasting procedures). All other functions and monitoring will be performed per Testing Facility SOP.

### **7.2. Animal Identification**

Method:	Each animal will be assigned an animal number to be used in Provantis™ and will be implanted with a microchip bearing a unique identification number. Each animal will have a permanent vendor animal number (e.g., tattoo, ear tag, etc.). The individual animal number, implant number, and the Testing Facility study number will comprise a unique identification for each animal. The animal cage will be identified by the study number, animal number, group number, and sex.
---------	--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

### **7.3. Environmental Acclimation**

Duration:	At least 1 week
Details:	As part of normal Testing Facility standard operating procedures, on arrival at the laboratory, the dogs were weighed and acclimated for a period of at least week. During this period, the animals were weighed monthly and observed with respect to general health and any signs of disease. If the appropriate vaccinations were not administered by the supplier, the animals were immunized at Testing Facility.

Prior to dose initiation, animals will be acclimated to the dosing procedure at least 3 times. A fixed dose volume of 10 mL of tap water will be administered on each occasion.

#### **7.4. Selection, Assignment, Replacement and Disposition of Animals**

**Selection for Study:** A sufficient washout period will occur prior to assignment of animals to the current study. Qualitative electrocardiographic (ECG) examinations, clinical pathology evaluations, and complete physical examinations conducted by a veterinarian will be performed prior to animals being assigned to study. These and other criteria may be used to select animals for study, as determined appropriate by the Study Director. The reason for excluding any animal will be documented in the raw data. These data will be maintained in the study file but will not be presented in the report. Animals considered suitable for study will be selected from the available animals by using a simple randomization procedure.

**Assignment and Randomization:** Animals will be assigned using a simple randomization procedure.

**Replacement:** Before the initiation of dosing, any assigned animals considered unsuitable for use in the study may be replaced by alternate animals maintained under the same environmental conditions.

After initiation of dosing, study animals may be replaced during the replacement period with alternate animals in the event of transmitter failure, accidental injury, non-test article-related health issues, or similar circumstances.

Alternate animals may be used as replacements per Testing Facility SOP.

**Disposition:** The disposition of all animals will be documented in the study records.

### **8. HUSBANDRY**

#### **8.1. Housing**

**Housing:** All animals will be pair-housed (single sex) in double-sized cages when possible. Any animals determined to not be suitable for pair housing, based on veterinary recommendation, will be housed individually.

Due to the design of the study (i.e., Latin square), in order to prevent cross contamination on dosing days, the animals will be housed individually overnight prior to each planned dose and will remain individually housed until each monitoring session has completed. If needed, the dogs will be provided the opportunity for exercise according to Testing Facility SOP.

Housing set-up is as specified in the USDA Animal Welfare Act (9 CFR, Parts 1, 2 and 3) and as described in the *Guide for the Care and Use of Laboratory Animals*. Animals will be separated during designated procedures/activities or will be separated as required for monitoring and/or health purposes, as deemed appropriate by Study Director and/or Clinical Veterinarian.

Caging: Stainless steel cages with stainless steel or plastic coated flooring or runs.

#### **8.2. Animal Enrichment**

Supplemental Enrichment: Animal enrichment will be provided according to Testing Facility SOP.

#### **8.3. Environmental Conditions**

Temperature and Humidity: Temperature and humidity will be maintained according to Testing Facility SOP.

Lighting: Fluorescent lighting will be provided via an automatic timer for approximately 12 hours per day. On occasion, the dark cycle may be interrupted intermittently due to study-related activities.

#### **8.4. Food**

Diet: Lab Diet® Certified Canine Diet #5007, PMI Nutrition International, Inc. It may be necessary during the course of the study to offer supplemental food as part of standard veterinary care. This will not be certified diet but will be commercially available food that has been analyzed for nutritional value.

Frequency: Diet will be provided as a rationed feeding regimen according to Testing Facility SOP for at least 4 hours to all animals, except during fasting periods or select husbandry functions (e.g., room cleaning).

Analysis: Results of analysis for nutritional components and environmental contaminants are provided by the supplier and are on file at the Testing Facility.

There are no known contaminants in the food that would interfere with this study.

#### **8.5. Water**

Type: Tap water

Frequency: Tap water will be supplied ad libitum to all animals via an automatic water system unless otherwise indicated.

**Analysis:** There are no known contaminants in the water that would interfere with this study. The drinking water used will be monitored for specified contaminants at periodic intervals according to Testing Facility SOP.

### 8.6. Veterinary Care

Veterinary care will be available throughout the course of the study and animals will be examined by the veterinary staff as warranted by clinical signs or other changes. In the event that animals show signs of illness or distress, the responsible veterinarian may make initial recommendations about treatment of the animal(s) and/or alteration of study procedures, which must be approved by the Study Director (or scientific designee). Treatment of the animal(s) for minor injuries or ailments may be approved without prior consultation with the Sponsor representative when such treatment does not impact fulfillment of the study objectives. If the condition of the animal(s) warrants significant therapeutic intervention or alterations in study procedures, the Sponsor representative will be contacted, when possible, to discuss appropriate action. If the condition of the animal(s) is such that emergency measures must be taken, the Study Director (or scientific designee) and/or attending veterinarian will attempt to consult with the Sponsor representative prior to responding to the medical crisis, but the Study Director (or scientific designee) and/or veterinarian has authority to act immediately at his/her discretion to alleviate suffering. The Sponsor representative will be fully informed of any such events.

## 9. EXPERIMENTAL DESIGN

Treatment	Dose Level (mg 1760001.0/kg)	Dose Volume (mL/kg)	Concentration (mg 1760001.0/mL) <sup>a</sup>	Concentration (mg bulk/mL) <sup>a</sup>	Number of Animals
1	0	5	0	0	6
2	20	5	4	4.04	6
3	50	5	10	10.1	6
4	150	5	30	30.3	6
<b>Total Number of Animals:</b>					6

a. [REDACTED] doses and concentrations will be adjusted for assigned chemical potency (995 µg/mg substance).

The following dosing regimen will be utilized:

Animal ID	Dosing Day 1	Dosing Day 2	Dosing Day 3	Dosing Day 4
1001	Treatment 1	Treatment 2	Treatment 3	Treatment 4
1002	Treatment 4	Treatment 3	Treatment 2	Treatment 1
1003	Treatment 1	Treatment 3	Treatment 2	Treatment 4
1004	Treatment 4	Treatment 2	Treatment 3	Treatment 1
1005	Treatment 2	Treatment 1	Treatment 4	Treatment 3
1006	Treatment 3	Treatment 4	Treatment 1	Treatment 2

**9.1. Administration of Test and Control Materials**

Route: Oral Gavage

Frequency: The test item and vehicle will be administered to the same 6 animals with at least a 10-day washout between each administration, using a Latin square design, until all doses have been administered to each animal.

Administration Details: For administration, the test article and vehicle will be withdrawn from stirred formulations and dosed via oral gavage. The control animals will receive the vehicle at the same volume as the test article. Individual doses will be based on the most recent body weights. After each dose, and prior to removal of the gavage tube, the tube will be flushed with 5 to 10 mL of tap water.

**10. IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS**

The in-life procedures, observations, and measurements listed below will be performed for all study animals.

**Standard In-life Assessments**

<b>Parameter</b>	<b>Population(s)</b>	<b>Frequency (minimum required)</b>	<b>Comments</b>
Prestudy Clinical Pathology Sample Collection	All animals transferred to study	Pretest	See section below for further details.  These data will be maintained in the study file but will not be presented in the report.
Prestudy Physical Examinations	All animals transferred to study	Pretest	A complete physical examination will be conducted on all animals by a staff veterinarian.  These data will be maintained in the study file but will not be presented in the report.
Prestudy Electrocardiogram	All animals transferred to study	Pretest	Representative ECG tracings and blood pressure signals from the 24-hour baseline telemetry monitoring session will be evaluated.  These data will be maintained in the study file but will not be presented in the report.
Mortality/Cageside Observations	All animals transferred to study (including companion animals)	At least twice daily <sup>a, b</sup> (morning and afternoon) beginning upon arrival through termination/release.	Animals will be observed within their cage unless necessary for identification or confirmation of possible findings.

Parameter	Population(s)	Frequency (minimum required)	Comments
Detailed Clinical Observations	All animals transferred to study	Study Animals: Prior to each dose, 1 hour postdose ( $\pm$ 15 minutes) and at the end of each telemetry monitoring period  Alternate and companion animals: At least monthly	Animals are removed from the cage, except examinations will be limited to that which can be assessed via remote camera if conducted during cardiovascular recording sessions.  Data collected from companion animals will be maintained in the study file and will not be reported as they are for health monitoring purposes only.
Individual Body Weights	All animals transferred to study <sup>c</sup>	Study Animals: Within 3 days of transfer, at least once prior to randomization, the day of or the day prior to each dose, and at termination of the study (i.e., prior to returning to stock colony).  Alternate and companion animals: At least monthly	Body weight data collected at transfer and prior to randomization will be maintained in the study file but will not be presented in the report.  Data collected from companion animals will be maintained in the study file and will not be reported as they are for health monitoring purposes only.

<sup>a</sup> To include alternate animals until released from study.

<sup>b</sup> Except on days of transfer to and from study, where frequency will be at least once daily. Cageside observations should be performed 4 hours apart. Due to the nature of this study, and in order to avoid causing undue excitement of the animals during cardiovascular monitoring and consequent data artifact during this critical recording period, the cageside observations may be performed at the time of other scheduled study functions or following completion of the cardiovascular monitoring period, and therefore may not be conducted at least four hours apart.

<sup>c</sup> To include alternate animals at transfer and prior to randomization.

### 10.1. Animal Preparation

All animals transferred to study were previously instrumented with DSI telemetry transmitters for physiological monitoring. Surgical placement of the transmitter and postoperative care were conducted in accordance with Testing Facility SOP, using IACUC and veterinary approved procedures. Documentation of all surgical procedures will be maintained at the Testing Facility.

## 10.2. Pretest Clinical Pathology Sample Collection and Analysis

### Clinical Pathology Sample Collection

Group Nos.	Hematology	Clinical Chemistry
All animals	X	X
Volume (mL) <sup>a</sup> :	1 mL	1.8 mL
Fasting Required <sup>b</sup> :	The animals will have free access to drinking water but will be fasted overnight (at least 8 hours) prior to blood sample collection.	
Anticoagulant:	K <sub>2</sub> EDTA	Serum Gel Separator
Processing:	None	Serum

X = Sample to be collected; NA = Not applicable.

<sup>a</sup> Additional blood samples may be obtained (e.g. due to sample quality) if permissible sampling frequency and blood volume are not exceeded.

<sup>b</sup> If samples need to be recollected for hematology or coagulation parameters for sample quality purposes (e.g., clotted sample), animals do not need to be fasted.

Analysis: Samples will be collected and analyzed from all animals transferred to study pretest to determine suitability of the animals for study.

Collection Method: Jugular or another suitable vessel

## 10.3. Pretest Hematology

### Hematology Parameters

Leukocyte count (total and absolute differential) Erythrocyte count Hemoglobin Hematocrit Mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration (calculated)	Absolute reticulocytes Platelet count RDW Blood smear preserve and stain (Blood smear review may be performed on select animals per Testing Facility SOP.)
--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	---------------------------------------------------------------------------------------------------------------------------------------------------------------------

## 10.4. Pretest Clinical Chemistry

### Clinical Chemistry Parameters

Alanine aminotransferase Urea nitrogen Creatinine	Total protein Glucose Electrolytes (sodium, potassium, chloride)
---------------------------------------------------------	------------------------------------------------------------------------

## 11. TELEMETRY MONITORING

Body temperature, blood pressure, and electrocardiogram (ECG) signals will be collected continuously using the DSI telemetry transmitters and the Ponemah Physiology Platform<sup>TM</sup>. All animals will be unrestrained for monitoring.

The following parameters will be derived from the telemetry signals:

Signal	Derived Parameters
Body Temperature	<ul style="list-style-type: none"> <li>• Body temperature</li> </ul>
Blood Pressure	<ul style="list-style-type: none"> <li>• Systolic pressure</li> <li>• Diastolic pressure</li> <li>• Mean arterial pressure</li> <li>• Heart rate</li> </ul>
ECG	<ul style="list-style-type: none"> <li>• Heart rate</li> <li>• RR interval</li> <li>• PR interval</li> <li>• QRS duration</li> <li>• QT interval</li> </ul>
Activity	<ul style="list-style-type: none"> <li>• Total activity (may not be reported; see below)</li> </ul>

**Baseline Data:**

All animals will be monitored for at least 24 hours within 2 weeks of transfer to study, while housed on the Testing Facility stock colony.

The heart rate data (derived from the blood pressure, unless otherwise specified) will be summarized in 1-minute intervals and used in the calculation of the heart rate-corrected QT interval for the Main Study data.

The baseline data will not be reported but will be maintained in the study file. The Study Director may determine suitability of the animals for study based on these data. The reason for excluding any animal will be documented in the raw data.

**Main Study Data:**

All animals will be monitored for at least 2 hours predose and for at least 24 hours postdose for each dose administration. All data will be collected and summarized in 1-minute intervals and reported in approximately 60-minute intervals. Other data summary intervals may be used at the discretion of the Study Director to optimize the telemetry evaluations based on the results of the study. Two hours of predose data will be reported but may not reflect the exact 120-minute interval prior to vehicle or test article administration.

**Additional Information:**

The heart rate-corrected QT intervals will be calculated using a method based on Spence and modified by Miyazaki & Tagawa and reported.<sup>1,2</sup>

An individual animal may be retested with one or more of the scheduled doses of test article or vehicle if the Study Director has determined; 1) that the animal did not receive an adequate dose (i.e., due to vomiting); 2) an equipment malfunction that limited or failed to provide sufficient or reliable raw data to analyze; or 3) other unforeseen circumstances. In the case of such retesting the requisite washout periods between doses will be initiated prior to retesting in each animal, unless indicated otherwise by the Study Director, and the retest session(s) will be documented in the

study file. The data from the initial monitoring period may not be reported but will be retained in the study file.

Total activity (movements within the cage) will be measured continuously by the DSI Telemetry System and collected in the same intervals as the cardiovascular data. Although collected, data from the activity measurement will not be summarized or reported unless it is determined by the Study Director, in consultation with the Sponsor, that they may help to clarify results obtained from the cardiovascular and/or body temperature data. All raw activity data collected will be maintained in the study file.

## 12. BIOANALYSIS

### 12.1. Sample Collection

#### Bioanalytical Sample Collection

Treatment Nos.	Postdose Collection Intervals – Each Day of Dosing
	6 hours
1-4	X

X = Sample to be collected

Method/Comments: Jugular, or other suitable vein

The blood samples will be collected within  $\pm 15$  minutes of the stated collection time. Samples collected outside of this time range will be documented as a collection time deviation and the actual collection times may be used. Any sample collection time deviations will be communicated to the Study Director and the Principal Investigator for Bioanalysis in a timely manner.

Volume (mL): 1 mL

Additional blood samples may be obtained (e.g. due to sample quality) if permissible sampling frequency and blood volume are not exceeded.

Anticoagulant: K<sub>2</sub>EDTA

Fasting: The animals will not be fasted before blood collection.

Whole Blood Storage: Wet ice or ice block until centrifuged.

Processing: Plasma

Final Storage Temperature: Frozen (-60 to -90°C)

## 12.2. Bioanalytical Sample Processing

Additional Container: Blood collection and 2D barcoded (2 mL Greiner cryovial #122263-2DG) storage tubes and their labels will be provided by Testing Facility. The labels for the plasma storage tubes will contain the Testing Facility study number, Sponsor's study number, animal number, species, test item number, matrix of sample, interval and timepoint relative to dosing, and analysis type, aliquot number. The 2D barcodes will be included on the sample manifest.

Processing Details: Within 60 minutes of collection, blood samples will be centrifuged (1100 to 1600 g for separation of plasma). The temperature of the centrifuge will be within operating range of 2 to 8°C.

The resultant plasma will be transferred to a labeled 2 mL polypropylene Greiner tube and stored frozen (-60°C to -90°C) until shipped to the Sponsor for analysis. The time and date that the samples are placed in the freezer will be recorded.

Bioanalytical Sample: All samples to be analyzed will be shipped to the Sponsor for analysis.  
Shipping: See [Attachment A](#) for shipping details.

Contact/Details:

Plasma samples will be shipped Monday through Wednesday for next day delivery. [REDACTED] Sample Receiving will be notified prior to shipment and will provide authorization for shipment. The Principal Investigator for Bioanalysis will also be notified. The inventory documentation accompanying the samples will specify the type and number of samples, the date on which each sample was collected, the barcode for each sample, and the storage conditions. Any deviations from the protocol during the study with regard to sample collection, processing, and storage will be included in the inventory documentation and communicated to the Principal Investigator for Bioanalysis in a timely manner.

Upon receipt at the Test Site, the samples will be stored in a freezer set to maintain -70°C.

## 12.3. Bioanalytical Sample Analysis

Analysis Performed By: The plasma will be analyzed for [REDACTED] concentration. All analytical work will be conducted by the Sponsor, using an analytical method developed and validated by that laboratory (**Bioanalytical Method for the Determination of [REDACTED] and [REDACTED] in Dog Plasma K2EDTA using Liquid-Liquid Extraction Followed by LC-MS/MS Detection to be added by amendment**).

Analysis Details:	Concentration levels will be combined and averaged by treatment (rather than by study day). Drug analysis data will be reported as mean $\pm$ SEM. Mean $\pm$ SEM plasma concentrations for each of the three test item treatments (Treatments 2, 3, and 4) will be plotted on a single graph. Data presentation can be adjusted as deemed appropriate by the Principal Investigator after consultation with the Sponsor Representative, or designee. The Study Director will be informed of any adjustments to the data presentation.
Regulatory Requirements:	The work performed in conjunction with this study will be conducted in compliance with GLPs and subject to review by the Quality Assurance Unit (QAU) of that laboratory. The findings of their QAU will be submitted to the Principal Investigator and the Principal Investigator's management as well as to the Testing Facility Study Director and Testing Facility Management. A Final Report, including a Quality Assurance Statement and Statement of Compliance, will be prepared and submitted to Testing Facility for inclusion as an appendix in the main study Final Report.

### **13. TERMINAL PROCEDURES**

No terminal procedures are scheduled.

#### **13.1. Animal Disposition**

At termination of the study, all surviving animals and all extra animals transferred to this study, but not placed on study, will be transferred to a Testing Facility stock colony, unless otherwise directed. The final disposition of each animal will be documented in the study records.

Companion animals will be returned to a Testing Facility stock or training colony when no longer needed.

#### **13.2. Unscheduled Euthanasia**

Any moribund animals will be euthanized for humane reasons. All animals euthanized in extremis or found dead will be subjected to a routine necropsy to determine a cause of death and for removal of the telemetry transmitters. No tissues will be saved and carcasses will be discarded.

#### **13.3. Method of Euthanasia**

Euthanasia will be by euthanasia solution administration, under sedation if necessary (e.g. acepromazine and/or Telazol<sup>®</sup>), followed by a Testing Facility SOP approved method to ensure death, e.g. exsanguination.

## 14. HISTOLOGY AND MICROSCOPIC EVALUATION

No postmortem evaluations are scheduled; however, in the event of unexpected death or euthanasia, a routine necropsy will be performed, and the telemetry transmitters will be removed. No tissues will be saved.

## 15. STATISTICAL ANALYSIS

The following presents a proposed statistical analysis plan. Statistical plans are data dependent, and this analysis plan may require modification if standard data assumptions are not met. Other conceptually equivalent statistical testing routines may also be employed at the discretion of the statistician. The actual analysis plan will be documented in the Final Report.

### 15.1. Statistical Comparisons

Control Treatment	Comparison Treatments
1	2, 3, 4

### 15.2. Statistical Analysis

#### 15.2.1. Descriptive Statistics

Endpoints: Body Temperature

Cardiovascular Endpoints  
Systolic, Diastolic, and Mean Blood Pressures  
Heart Rate  
ECG (RR, PR, QRS, QT, and QTc)

Description: Descriptive statistics will consist of means, standard deviations, and group size for each time period.

#### 15.2.2. Paired Sample T-Test Comparison

Endpoints: Body Temperature

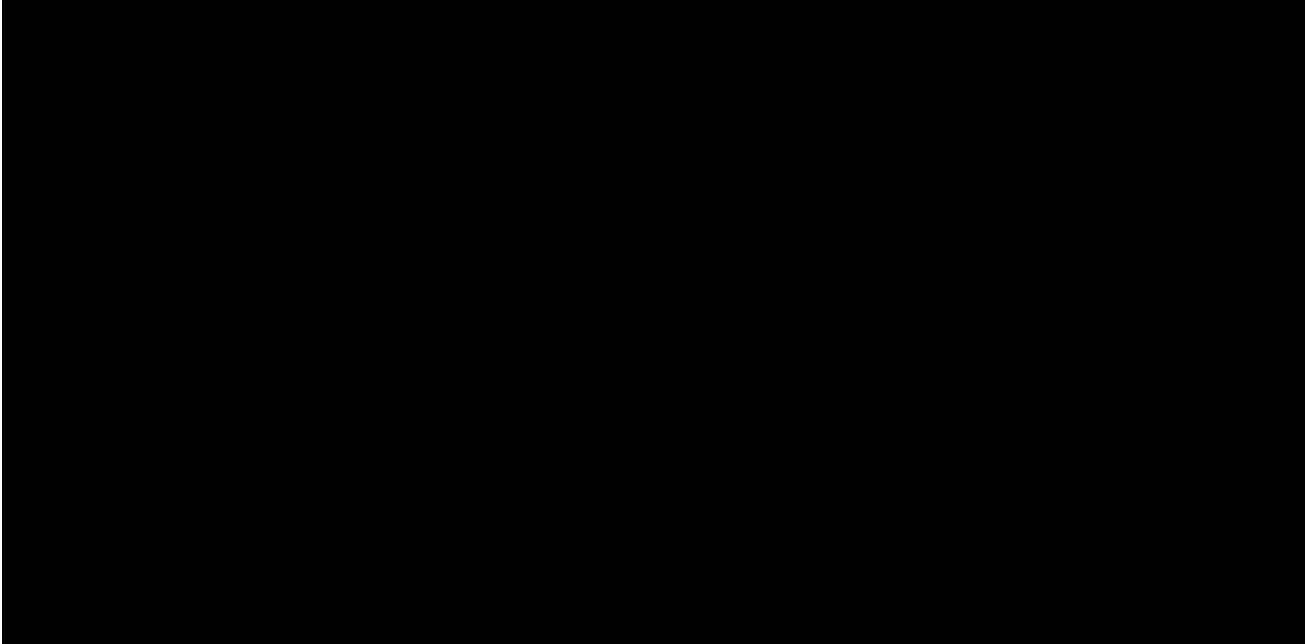
Cardiovascular Endpoints  
Systolic, Diastolic, and Mean Blood Pressures  
Heart Rate and ECG (RR, PR, QRS, QT, and QTc)

Description: For each specified endpoint and for each time interval a Paired Sample t-test<sup>3</sup> will be used to test for no treatment effect. For each treatment, each subject will serve as its own control to generate a calculated difference between treatment and control. The mean of this difference will be tested against a mean of 0, for no change. A Bonferroni correction will be applied. Results of the comparison will be reported at the 0.05 and 0.01 significance levels. The step-down Sidak method will be applied to previously obtained p-values

to adjust for multiple testing. All endpoints will be analyzed using two-tailed tests unless indicated otherwise.

## **16. COMPUTER SYSTEMS**

The following are the proposed computer systems to be used during the conduct of this study and their primary function. The actual systems and versions used will be documented in the Final Report.



## **17. REGULATORY COMPLIANCE**

The study will be performed in accordance with the U.S. Department of Health and Human Services, Food and Drug Administration, United States Code of Federal Regulations, Title 21, Part 58: Good Laboratory Practice for Nonclinical Laboratory Studies and as accepted by Regulatory Authorities throughout the European Union (OECD Principles of Good Laboratory Practice), Japan (MHLW), and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

Exceptions to GLPs include the following study elements:

The initial bulk test item characterization was conducted by the Sponsor using validated methods in a Good Manufacturing Practices (GMP) based quality system.

## **18. QUALITY ASSURANCE**

### **18.1. Testing Facility**

The Testing Facility Quality Assurance Unit (QAU) will monitor the study to assure the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with Good Laboratory Practice regulations. The QAU will review the protocol, conduct inspections at intervals adequate to assure the integrity of the study, and audit the Final Report to assure that it accurately describes the methods and standard operating procedures and that the reported results accurately reflect the raw data of the study.

### **18.2. Test Site(s)/Subcontractor(s)**

For all study phase(s) inspected by test site/subcontractor QAU(s), copies of each periodic inspection report will be made available to the Study Director, Testing Facility Management, and the Testing Facility QAU.

## **19. AMENDMENTS AND DEVIATIONS**

Changes to the approved protocol shall be made in the form of an amendment, which will be signed and dated by the Study Director. Every reasonable effort will be made to discuss any necessary protocol changes in advance with the Sponsor. The Study Director will notify the Sponsor of deviations that may result in a significant impact on the study as soon as possible.

## **20. RETENTION AND DISPOSITION OF RECORDS, SAMPLES, AND SPECIMENS**

Report will be archived by no later than the date of Final Report issue. All retained materials will be archived at [REDACTED] unless specified by the Sponsor. At least 1 year after issue of the Draft Report, the Sponsor will be contacted.

Samples for clinical pathology evaluations are discarded per Testing Facility SOP unless otherwise indicated in the table below.

Disposition of retained analytical samples will be as described in the table below.

**Disposition of Retained Samples**

Sample Type	Disposition	Schedule
Dose Formulation Samples	Discard	Any remaining formulation samples will be discarded after acceptance of the analytical results by the Study Director or upon receipt of authorization to finalize the report.

Records to be maintained will include, but will not be limited to, documentation and data for the following:

- Protocol, protocol amendments, and deviations
- Study schedule
- Study-related correspondence
- Test system receipt, health, and husbandry
- Statistical analysis results
- Test and control item receipt, identification, preparation, and analysis
- In-life measurements and observations

## 21. STUDY CLASSIFICATION

Study Category:	Safety Pharmacology
Study Type:	Cardiovascular Pharmacology
Study Design:	Latin Square
Primary Treatment CAS Registry Number:	Not Available
Primary Treatment Unique Ingredient ID:	Not Available
Class of Compound:	Small Molecule

## 22. REPORTING

A comprehensive Draft Report will be prepared following completion of the study and will be finalized following consultation with the Sponsor. The report will include all information necessary to provide a complete and accurate description of the experimental methods and results and any circumstances that may have affected the quality or integrity of the study.

The Sponsor will receive an electronic version of the Draft and Final Report provided in Adobe Acrobat PDF format (hyperlinked and searchable at final). The PDF document will be created from native electronic files to the extent possible, including text and tables generated by the Testing Facility. Report components not available in native electronic files and/or original signature pages will be scanned and converted to PDF image files for incorporation.

Reports should be finalized within 6 months of issue of the Draft Report. If the Sponsor has not provided comments to the report within 6 months of draft issue, the report will be finalized by the Testing Facility unless other arrangements are made by the Sponsor.

### 22.1. SEND Datasets

SEND datasets will be generated and provided outside the context of the Final GLP Report. These datasets will not be subject to QA Audit nor will they be used as the basis for the Study Director interpretation of the study results. SEND datasets will be provided following the Final Report.

An electronic version of all data collected in support of this study at a Test Site (i.e., formulation analysis), should be provided to Testing Facility.

## 23. JUSTIFICATIONS AND GUIDELINES

### 23.1. Justification of Test System and Number of Animals

The beagle is the usual non-rodent model used for evaluating the cardiovascular safety of various test articles and for which there is a large historical database.<sup>4</sup> There are no known or expected

differences between male and female animals relative to exposure levels or the effects of the test article on cardiovascular function; therefore, only males will be used to conserve animals.

The total number of animals to be used in this study is considered to be the minimum required to properly characterize the effects of the test article and has been designed such that it does not require an unnecessary number of animals to accomplish its objectives.

### **23.2. Justification of Route and Dose Levels**

The oral route is the intended route of administration of this test article in humans.

In a previous repeat dose range finding toxicity study in dogs, [REDACTED] was tolerated up to 150 mg/kg/day. Test-item-related findings were noted in heart, kidney, gall bladder, and stomach. Based upon the results of that study, the highest dose may produce some toxic effects, but not lethality or excessive toxicity that would prevent meaningful evaluation. The mid-dose level is expected to produce minimal to moderate effects. The low-dose level should produce no observable effects.

### **23.3. Guidelines for Study**

The design of this study was based on the study objective(s), the overall product development strategy for the test article, and the following study design guidelines:

- ICH Harmonised Tripartite Guideline M3 (R2). *Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*.
- ICH Harmonised Tripartite Guideline S7A. *Guideline on Safety Pharmacology Studies for Human Pharmaceuticals*.
- ICH Harmonised Tripartite Guideline S7B. *The Non-Clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals*.

## **24. ANIMAL WELFARE**

This study will comply with all applicable sections of the Final Rules of the Animal Welfare Act regulations (Code of Federal Regulations, Title 9), the *Public Health Service Policy on Humane Care and Use of Laboratory Animals* from the Office of Laboratory Animal Welfare, and the *Guide for the Care and Use of Laboratory Animals* from the National Research Council.<sup>5,6</sup> The protocol and any amendments or procedures involving the care or use of animals in this study will be reviewed and approved by the Testing Facility Institutional Animal Care and Use Committee before the initiation of such procedures.

If an animal is determined to be in overt pain/distress, or appears moribund and is beyond the point where recovery appears reasonable, the animal will be euthanized for humane reasons in accordance with the *American Veterinary Medical Association (AVMA) Guidelines on Euthanasia* and with the procedures outlined in the protocol.<sup>7</sup>

By approving this protocol, the Sponsor affirms that there are no acceptable non-animal alternatives for this study, that this study is required by a relevant government regulatory agency(ies) and that it does not unnecessarily duplicate any previous experiments.

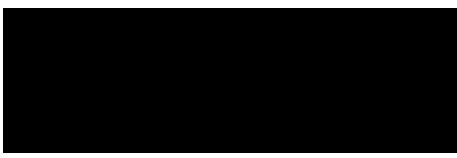
#### **24.1. Institutional Animal Care and Use Committee Approval**

The protocol and any amendment(s) or procedures involving the care and use of animals in this study will be reviewed and approved by CR-MWN Institutional Animal Care and Use Committee (IACUC) before conduct. During the study, the care and use of animals will be conducted with guidance from the guidelines of the USA National Research Council.

#### **25. REFERENCES**

1. Spence S. The Heart Rate-Corrected QT Interval of Conscious Beagle Dogs: A Formula Based on Analysis of Covariance. *Toxicological Sciences*. 1998;45(2):247-258.
2. Miyazaki H, Tagawa M. Rate-Correction Technique for QT Interval in Long-Term Telemetry ECG Recording in Beagle Dogs. *Experimental Animals*. 2002;51(5):465-475.
3. Guidance for industry, investigators, and reviewers: exploratory IND studies. U.S. FDA Center for Drug Evaluation and Research (CDER), 2006 Jan.
4. Office of Laboratory Animal Welfare. *Public Health Services Policy on Humane Care and Use of Laboratory Animals*. Bethesda, MD: National Institutes of Health. Current edition.
5. National Research Council. *Guide for the Care and Use of Laboratory Animals*. Washington, DC: National Academy Press. Current edition.
6. American Veterinary Medical Association. *AVMA Guidelines on Euthanasia*. Current edition.

Sponsor Reference No.

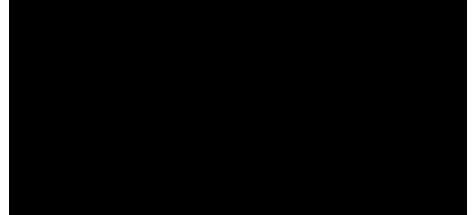
Page 100  
Testing Facility Study No.  


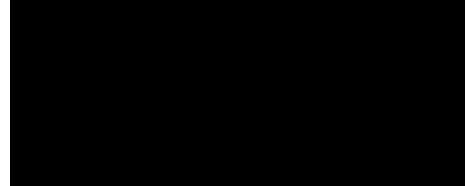
**FINAL PROTOCOL**

Testing Facility Study No. 

Sponsor Reference No. 

**Cardiovascular Safety Evaluation of Orally Administered   
 in Beagle Dogs**

**SPONSOR:**  


**TESTING FACILITY:**  


Sponsor Reference No. 

Testing Facility Study No.   
Page 1

**TABLE OF CONTENTS**

1. OBJECTIVE(S).....	3
2. PROPOSED STUDY SCHEDULE .....	3
3. SPONSOR.....	3
4. RESPONSIBLE PERSONNEL.....	3
5. TEST MATERIALS.....	6
6. DOSE FORMULATION AND ANALYSIS .....	7
7. TEST SYSTEM.....	9
8. HUSBANDRY .....	11
9. EXPERIMENTAL DESIGN.....	13
10. IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS .....	14
11. TELEMETRY MONITORING.....	16
12. BIOANALYSIS .....	18
13. TERMINAL PROCEDURES .....	20
14. HISTOLOGY AND MICROSCOPIC EVALUATION .....	20
15. STATISTICAL ANALYSIS .....	21
16. COMPUTER SYSTEMS .....	22
17. REGULATORY COMPLIANCE .....	22
18. QUALITY ASSURANCE.....	22
19. AMENDMENTS AND DEVIATIONS .....	23
20. RETENTION AND DISPOSITION OF RECORDS, SAMPLES, AND SPECIMENS .....	23
21. STUDY CLASSIFICATION .....	23
22. REPORTING.....	24
23. JUSTIFICATIONS AND GUIDELINES .....	24
24. ANIMAL WELFARE .....	25
25. REFERENCES .....	26
TESTING FACILITY APPROVAL.....	27
SPONSOR APPROVAL .....	28
ATTACHMENT A .....	29

**1. OBJECTIVE(S)**

[REDACTED] The purpose of this study is to evaluate the potential cardiovascular effects of [REDACTED] in conscious freely moving beagle dogs.

**2. PROPOSED STUDY SCHEDULE**

Proposed study dates are listed below. Actual dates will be included in the Final Report.

Experimental Starting Date: 08 Jul 2019

Experimental Completion Date: 03 Sep 2019

Animal Transfer: 08 Jul 2019

Initiation of Dosing: 15 Jul 2019

Completion of In-life: 20 Aug 2019

Draft Report: 15 Oct 2019

Final Report: The date on which the Study Director signs the final report.

[REDACTED]

- A listing of critical computerized systems used in the conduct and/or interpretation of the assigned study phase

## 5. TEST MATERIALS

### 5.1. Test Item Characterization

The Sponsor will provide to the Testing Facility documentation of the identity, strength, purity, composition, and stability for the test item. A Certificate of Analysis or equivalent documentation will be provided for inclusion in the Final Report.

### 5.2. Test Item Identification

	Test Item
Identification:	[REDACTED]
Alternate Identification:	[REDACTED]
Batch/Lot No.:	[REDACTED]
Expiration/Retest Date:	[REDACTED]
Physical Description:	Off-white powder
Assigned Chemical Potency:	995 µg [REDACTED] mg
Correction Factor:	1.01
Storage Conditions:	Room Temperature; Protected from light
Provided by:	Sponsor

### 5.3. Control Item/Vehicle Information

	Control Item/Vehicle
Identification:	0.5% hydroxypropylmethylcellulose (HPMC; low viscosity), 0.1% Tween 80 in NANOPure Diamond Ultrapure water (w/v)
Alternate Identification:	No alternate ID
Storage Conditions:	Refrigerated (2 to 8°C); Protected from light
Characterization:	Documentation of the strength, purity, composition, stability, physical properties, and other pertinent information on each of the individual components for the lot/batch of vehicle or the commercially available vehicle, will be limited to that information listed on the label unless otherwise noted or provided by the Sponsor.

### 5.4. Reserve Samples

A reserve sample from each lot of test item used in this study is not required. However, if multiple studies are conducted with the same test item, a common reserve sample may be collected and labeled and stored appropriately.

### 5.5. Test Item Inventory and Disposition

Records of the receipt, distribution, storage, and disposition of test materials (including empty containers of Sponsor-provided materials) will be maintained until study finalization.

All unused Sponsor-supplied bulk test materials, with the exception of reserve samples, will be returned to the Sponsor following issuance of the Draft Report unless otherwise requested

(documentation will be retained in the study record). An earlier shipment of these materials may also be requested and authorized by the Study Director and Sponsor. See [Attachment A](#) for shipping details.

Upon receipt of the finalized formulation report, any remaining formulation samples will be discarded.

### 5.6. Safety

A Safety Data Sheet (SDS), or equivalent documentation, will be provided by the Sponsor (if available). It is the responsibility of the Sponsor to notify the Testing Facility of any special handling requirements of the test item. Otherwise routine safety precautions will be followed. Appropriate gloves, safety glasses and arm covers will be worn by individuals working with neat test material or formulations.

## 6. DOSE FORMULATION AND ANALYSIS

### 6.1. Preparation of Formulations

Dose formulations will be divided into aliquots where required to allow to be dispensed on each dosing occasion.

Dose Formulation	Administration Dose Form	Frequency of Preparation	Storage Conditions
Control Item	Suspension	Once for each dosing day (or as needed), no more than 7 days prior to use	Refrigerated (2 to 8°C); Protected from light
Test Item	Suspension	Once for each dosing day (or as needed), no more than 7 days prior to use	Refrigerated (2 to 8°C); Protected from light

Formulations will be stirred at room temperature for at least one hour prior to dose administration. Formulations prepared and used on the same day of dosing will be stored at room temperature and protected from light.

Any residual volumes from each dosing occasion will be discarded unless otherwise requested by the Study Director.

### 6.2. Preparation Details

The test item will be mixed with an appropriate volume of vehicle and subsequently brought to final volume with vehicle to achieve the final concentrations for treatments 2, 3, and 4.

[REDACTED] dosing formulations (Treatments 2, 3, and 4) require 1 molar equivalent of sodium hydroxide (NaOH) to achieve solubility. The final pH value of formulations will be measured and should be adjusted to  $8.2 \pm 0.1$  with the appropriate amount of NaOH or HCl. The test item concentration will be adjusted to reflect lot specific analysis of test item content. Formulation instructions will be retained with the raw data. Formulations for Treatment 1 (vehicle control) will also be adjusted to a final pH of  $8.2 \pm 0.1$  with the appropriate amount of NaOH or HCl.

### 6.3. Sample Collection and Analysis

Dose formulation samples will be collected for analysis as indicated in the following table. Additional samples may be collected and analyzed at the discretion of the Study Director.

**Dose Formulation Sample Collection Schedule**

Sample Type <sup>a</sup>	Concentrations	Stratum	Number of Samples per Concentration			Sample Volume (mL) <sup>b</sup>	Intervals
			Collected	Analyzed	Backup		
Concentration/ Homogeneity Analyses	Low, Mid, and High	Top	2	1	1	2.0	First Preparation
		Middle	2	1	1	2.0	
		Bottom	2	1	1	2.0	
Concentration Analyses	Control	Middle	2	1	1	5.0	Each Preparation
Concentration Analyses	Low, Mid, and High	Middle	2	1	1	2.0	Each Preparation

<sup>a</sup>The averaged result from the homogeneity analysis will serve as concentration verification, when applicable.  
<sup>b</sup>5.0 mL sample volume for concentrations < 1.0 mg/mL; 2.0 mL sample volume for concentrations ≥ 1.0 mg/mL.

Special Instructions: Appropriate samples (see previous table) will be collected while the preparations are being stirred.

Samples Analyzed By: All samples to be analyzed will be shipped to the Sponsor for analysis. See Attachment A for shipping details.

The analytical laboratory will be notified before shipment of the samples. Upon receipt at the analytical laboratory, the samples will be stored under the conditions listed below

Sample Transfer and Storage Conditions: Frozen (-60 to -90°C)

Formulation Sample Disposition: Any remaining formulation samples will be discarded after acceptance of the analytical results by the Study Director or upon receipt of authorization to finalize the report.

#### 6.3.1. Analytical Method

All analytical work will be conducted by the Sponsor using an analytical method developed and validated by that laboratory [REDACTED]

##### 6.3.1.1. Concentration and Homogeneity Analysis

Sample Allocation: 1 for analysis, 1 for backup

Storage Conditions: Frozen (-60 to -90°C)

Acceptance Criteria: For concentration: mean sample concentration results within or equal to  $\pm 10\%$  of theoretical concentration.  
For homogeneity, relative standard deviation (RSD) of concentrations of  $\leq 10\%$  for each group.  
Assay values that deviate from the intended concentration by more than 10% or RSD values that are greater than 10% will be referred immediately to the Study Director.

#### 6.3.1.2. Stability Analysis

The [REDACTED] formulations at concentrations that bracket those used in this study, were shown to be stable for at least seven days at 2-8°C and -70°C. Stability data provided by the Sponsor are retained in the study records.

#### 7. TEST SYSTEM

Species: Dog  
Strain: Beagle  
Condition: Purpose-bred, non-naive  
Source: [REDACTED]  
Original Source: [REDACTED]

Number Transferred:

Male: 7

Number on Study:

Male: 6

Companion Animal Number on Study:

Male: 1

Expected Age at Transfer: At least 5 months of age

Expected Weight at Transfer: Commensurate with age; males will generally weigh 5.5 to 12.0 kg, as measured within 3 days of transfer. The actual range may vary but will be documented in the data.

The actual age and weight of animals on study will be listed in the Final Report.

### **7.1. Companion Animal Details**

Species: Dog

Breed: Beagle

Source:

Original Source:

Details: Companion animals will be assigned for the purpose of social housing of all study animals (not considered part of the test system). As such, they will only be subject to the observations/measurements as listed specifically for companion animals. Companion animals will be maintained using the same husbandry procedures as the main study animals (including following the same feeding and fasting procedures). All other functions and monitoring will be performed per Testing Facility SOP.

### **7.2. Animal Identification**

Method: Each animal will be assigned an animal number to be used in [REDACTED] and will be implanted with a microchip bearing a unique identification number. Each animal will have a permanent vendor animal number (e.g., tattoo, ear tag, etc.). The individual animal number, implant number, and the Testing Facility study number will comprise a unique identification for each animal. The animal cage will be identified by the study number, animal number, group number, and sex.

### **7.3. Environmental Acclimation**

Duration: At least 1 week

Details: As part of normal Testing Facility standard operating procedures, on arrival at the laboratory, the dogs were weighed and acclimated for a period of at least week. During this period, the animals were weighed monthly and observed with respect to general health and any signs of disease. If the appropriate vaccinations were not administered by the supplier, the animals were immunized at Testing Facility.

Prior to dose initiation, animals will be acclimated to the dosing procedure at least 3 times. A fixed dose volume of 10 mL of tap water will be administered on each occasion.

#### **7.4. Selection, Assignment, Replacement and Disposition of Animals**

**Selection for Study:** A sufficient washout period will occur prior to assignment of animals to the current study. Qualitative electrocardiographic (ECG) examinations, clinical pathology evaluations, and complete physical examinations conducted by a veterinarian will be performed prior to animals being assigned to study. These and other criteria may be used to select animals for study, as determined appropriate by the Study Director. The reason for excluding any animal will be documented in the raw data. These data will be maintained in the study file but will not be presented in the report. Animals considered suitable for study will be selected from the available animals by using a simple randomization procedure.

**Assignment and Randomization:** Animals will be assigned using a simple randomization procedure.

**Replacement:** Before the initiation of dosing, any assigned animals considered unsuitable for use in the study may be replaced by alternate animals maintained under the same environmental conditions.

After initiation of dosing, study animals may be replaced during the replacement period with alternate animals in the event of transmitter failure, accidental injury, non-test article-related health issues, or similar circumstances.

Alternate animals may be used as replacements per Testing Facility SOP.

**Disposition:** The disposition of all animals will be documented in the study records.

### **8. HUSBANDRY**

#### **8.1. Housing**

**Housing:** All animals will be pair-housed (single sex) in double-sized cages when possible. Any animals determined to not be suitable for pair housing, based on veterinary recommendation, will be housed individually.

Due to the design of the study (i.e., Latin square), in order to prevent cross contamination on dosing days, the animals will be housed individually overnight prior to each planned dose and will remain individually housed until each monitoring session has completed. If needed, the dogs will be provided the opportunity for exercise according to Testing Facility SOP.

Housing set-up is as specified in the USDA Animal Welfare Act (9 CFR, Parts 1, 2 and 3) and as described in the *Guide for the Care and Use of Laboratory Animals*. Animals will be separated during designated procedures/activities or will be separated as required for monitoring and/or health purposes, as deemed appropriate by Study Director and/or Clinical Veterinarian.

Caging: Stainless steel cages with stainless steel or plastic coated flooring or runs.

#### **8.2. Animal Enrichment**

Supplemental Enrichment: Animal enrichment will be provided according to Testing Facility SOP.

#### **8.3. Environmental Conditions**

Temperature and Humidity: Temperature and humidity will be maintained according to Testing Facility SOP.

Lighting: Fluorescent lighting will be provided via an automatic timer for approximately 12 hours per day. On occasion, the dark cycle may be interrupted intermittently due to study-related activities.

#### **8.4. Food**

Diet: Lab Diet® Certified Canine Diet #5007, PMI Nutrition International, Inc. It may be necessary during the course of the study to offer supplemental food as part of standard veterinary care. This will not be certified diet but will be commercially available food that has been analyzed for nutritional value.

Frequency: Diet will be provided as a rationed feeding regimen according to Testing Facility SOP for at least 4 hours to all animals, except during fasting periods or select husbandry functions (e.g., room cleaning).

Analysis: Results of analysis for nutritional components and environmental contaminants are provided by the supplier and are on file at the Testing Facility.

There are no known contaminants in the food that would interfere with this study.

#### **8.5. Water**

Type: Tap water

Frequency: Tap water will be supplied ad libitum to all animals via an automatic water system unless otherwise indicated.

**Analysis:**

There are no known contaminants in the water that would interfere with this study. The drinking water used will be monitored for specified contaminants at periodic intervals according to Testing Facility SOP.

### **8.6. Veterinary Care**

Veterinary care will be available throughout the course of the study and animals will be examined by the veterinary staff as warranted by clinical signs or other changes. In the event that animals show signs of illness or distress, the responsible veterinarian may make initial recommendations about treatment of the animal(s) and/or alteration of study procedures, which must be approved by the Study Director (or scientific designee). Treatment of the animal(s) for minor injuries or ailments may be approved without prior consultation with the Sponsor representative when such treatment does not impact fulfillment of the study objectives. If the condition of the animal(s) warrants significant therapeutic intervention or alterations in study procedures, the Sponsor representative will be contacted, when possible, to discuss appropriate action. If the condition of the animal(s) is such that emergency measures must be taken, the Study Director (or scientific designee) and/or attending veterinarian will attempt to consult with the Sponsor representative prior to responding to the medical crisis, but the Study Director (or scientific designee) and/or veterinarian has authority to act immediately at his/her discretion to alleviate suffering. The Sponsor representative will be fully informed of any such events.

## **9. EXPERIMENTAL DESIGN**

Treatment	Dose Level (mg 1760001.0/kg)	Dose Volume (mL/kg)	Concentration (mg 1760001.0/mL) <sup>a</sup>	Concentration (mg bulk/mL) <sup>a</sup>	Number of Animals
1	0	5	0	0	6
2	20	5	4	4.04	6
3	50	5	10	10.1	6
4	150	5	30	30.3	6
<b>Total Number of Animals:</b>					6

- a. [REDACTED] doses and concentrations will be adjusted for assigned chemical potency (995 µg/mg substance).

The following dosing regimen will be utilized:

Animal ID	Dosing Day 1	Dosing Day 2	Dosing Day 3	Dosing Day 4
1001	Treatment 1	Treatment 2	Treatment 3	Treatment 4
1002	Treatment 4	Treatment 3	Treatment 2	Treatment 1
1003	Treatment 1	Treatment 3	Treatment 2	Treatment 4
1004	Treatment 4	Treatment 2	Treatment 3	Treatment 1
1005	Treatment 2	Treatment 1	Treatment 4	Treatment 3
1006	Treatment 3	Treatment 4	Treatment 1	Treatment 2

**9.1. Administration of Test and Control Materials**

Route: Oral Gavage

Frequency: The test item and vehicle will be administered to the same 6 animals with at least a 10-day washout between each administration, using a Latin square design, until all doses have been administered to each animal.

Administration Details: For administration, the test article and vehicle will be withdrawn from stirred formulations and dosed via oral gavage. The control animals will receive the vehicle at the same volume as the test article. Individual doses will be based on the most recent body weights. After each dose, and prior to removal of the gavage tube, the tube will be flushed with 5 to 10 mL of tap water.

**10. IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS**

The in-life procedures, observations, and measurements listed below will be performed for all study animals.

**Standard In-life Assessments**

<b>Parameter</b>	<b>Population(s)</b>	<b>Frequency (minimum required)</b>	<b>Comments</b>
Prestudy Clinical Pathology Sample Collection	All animals transferred to study	Pretest	See section below for further details.  These data will be maintained in the study file but will not be presented in the report.
Prestudy Physical Examinations	All animals transferred to study	Pretest	A complete physical examination will be conducted on all animals by a staff veterinarian.  These data will be maintained in the study file but will not be presented in the report.
Prestudy Electrocardiogram	All animals transferred to study	Pretest	Representative ECG tracings and blood pressure signals from the 24-hour baseline telemetry monitoring session will be evaluated.  These data will be maintained in the study file but will not be presented in the report.
Mortality/Cageside Observations	All animals transferred to study (including companion animals)	At least twice daily <sup>a, b</sup> (morning and afternoon) beginning upon arrival through termination/release.	Animals will be observed within their cage unless necessary for identification or confirmation of possible findings.

Parameter	Population(s)	Frequency (minimum required)	Comments
Detailed Clinical Observations	All animals transferred to study	Study Animals: Prior to each dose, 1 hour postdose ( $\pm$ 15 minutes) and at the end of each telemetry monitoring period  Alternate and companion animals: At least monthly	Animals are removed from the cage, except examinations will be limited to that which can be assessed via remote camera if conducted during cardiovascular recording sessions.  Data collected from companion animals will be maintained in the study file and will not be reported as they are for health monitoring purposes only.
Individual Body Weights	All animals transferred to study <sup>c</sup>	Study Animals: Within 3 days of transfer, at least once prior to randomization, the day of or the day prior to each dose, and at termination of the study (i.e., prior to returning to stock colony).  Alternate and companion animals: At least monthly	Body weight data collected at transfer and prior to randomization will be maintained in the study file but will not be presented in the report.  Data collected from companion animals will be maintained in the study file and will not be reported as they are for health monitoring purposes only.

<sup>a</sup> To include alternate animals until released from study.

<sup>b</sup> Except on days of transfer to and from study, where frequency will be at least once daily. Cageside observations should be performed 4 hours apart. Due to the nature of this study, and in order to avoid causing undue excitement of the animals during cardiovascular monitoring and consequent data artifact during this critical recording period, the cageside observations may be performed at the time of other scheduled study functions or following completion of the cardiovascular monitoring period, and therefore may not be conducted at least four hours apart.

<sup>c</sup> To include alternate animals at transfer and prior to randomization.

### 10.1. Animal Preparation

All animals transferred to study were previously instrumented with DSI telemetry transmitters for physiological monitoring. Surgical placement of the transmitter and postoperative care were conducted in accordance with Testing Facility SOP, using IACUC and veterinary approved procedures. Documentation of all surgical procedures will be maintained at the Testing Facility.

## 10.2. Pretest Clinical Pathology Sample Collection and Analysis

### Clinical Pathology Sample Collection

Group Nos.	Hematology	Clinical Chemistry
All animals	X	X
Volume (mL) <sup>a</sup> :	1 mL	1.8 mL
Fasting Required <sup>b</sup> :	The animals will have free access to drinking water but will be fasted overnight (at least 8 hours) prior to blood sample collection.	
Anticoagulant:	K <sub>2</sub> EDTA	Serum Gel Separator
Processing:	None	Serum

X = Sample to be collected; NA = Not applicable.

<sup>a</sup> Additional blood samples may be obtained (e.g. due to sample quality) if permissible sampling frequency and blood volume are not exceeded.

<sup>b</sup> If samples need to be recollected for hematology or coagulation parameters for sample quality purposes (e.g., clotted sample), animals do not need to be fasted.

Analysis: Samples will be collected and analyzed from all animals transferred to study pretest to determine suitability of the animals for study.

Collection Method: Jugular or another suitable vessel

## 10.3. Pretest Hematology

### Hematology Parameters

Leukocyte count (total and absolute differential) Erythrocyte count Hemoglobin Hematocrit Mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration (calculated)	Absolute reticulocytes Platelet count RDW Blood smear preserve and stain (Blood smear review may be performed on select animals per Testing Facility SOP.)
--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	---------------------------------------------------------------------------------------------------------------------------------------------------------------------

## 10.4. Pretest Clinical Chemistry

### Clinical Chemistry Parameters

Alanine aminotransferase Urea nitrogen Creatinine	Total protein Glucose Electrolytes (sodium, potassium, chloride)
---------------------------------------------------------	------------------------------------------------------------------------

## 11. TELEMETRY MONITORING

Body temperature, blood pressure, and electrocardiogram (ECG) signals will be collected continuously [REDACTED]. All animals will be unrestrained for monitoring.

The following parameters will be derived from the telemetry signals:

Signal	Derived Parameters
Body Temperature	<ul style="list-style-type: none"> <li>• Body temperature</li> </ul>
Blood Pressure	<ul style="list-style-type: none"> <li>• Systolic pressure</li> <li>• Diastolic pressure</li> <li>• Mean arterial pressure</li> <li>• Heart rate</li> </ul>
ECG	<ul style="list-style-type: none"> <li>• Heart rate</li> <li>• RR interval</li> <li>• PR interval</li> <li>• QRS duration</li> <li>• QT interval</li> </ul>
Activity	<ul style="list-style-type: none"> <li>• Total activity (may not be reported; see below)</li> </ul>

**Baseline Data:**

All animals will be monitored for at least 24 hours within 2 weeks of transfer to study, while housed on the Testing Facility stock colony. The heart rate data (derived from the blood pressure, unless otherwise specified) will be summarized in 1-minute intervals and used in the calculation of the heart rate-corrected QT interval for the Main Study data. The baseline data will not be reported but will be maintained in the study file. The Study Director may determine suitability of the animals for study based on these data. The reason for excluding any animal will be documented in the raw data.

**Main Study Data:**

All animals will be monitored for at least 2 hours predose and for at least 24 hours postdose for each dose administration. All data will be collected and summarized in 1-minute intervals and reported in approximately 60-minute intervals. Other data summary intervals may be used at the discretion of the Study Director to optimize the telemetry evaluations based on the results of the study. Two hours of predose data will be reported but may not reflect the exact 120-minute interval prior to vehicle or test article administration.

**Additional Information:**

The heart rate-corrected QT intervals will be calculated using a method based on Spence and modified by Miyazaki & Tagawa and reported.<sup>1,2</sup> An individual animal may be retested with one or more of the scheduled doses of test article or vehicle if the Study Director has determined; 1) that the animal did not receive an adequate dose (i.e., due to vomiting); 2) an equipment malfunction that limited or failed to provide sufficient or reliable raw data to analyze; or 3) other unforeseen circumstances. In the case of such retesting the requisite washout periods between doses will be initiated prior to retesting in each animal, unless indicated otherwise by the Study Director, and the retest session(s) will be documented in the

study file. The data from the initial monitoring period may not be reported but will be retained in the study file.

Total activity (movements within the cage) will be measured continuously [REDACTED] and collected in the same intervals as the cardiovascular data. Although collected, data from the activity measurement will not be summarized or reported unless it is determined by the Study Director, in consultation with the Sponsor, that they may help to clarify results obtained from the cardiovascular and/or body temperature data. All raw activity data collected will be maintained in the study file.

## 12. BIOANALYSIS

### 12.1. Sample Collection

#### Bioanalytical Sample Collection

Treatment Nos.	Postdose Collection Intervals – Each Day of Dosing
	6 hours
1-4	X

X = Sample to be collected

Method/Comments: Jugular, or other suitable vein

The blood samples will be collected within  $\pm 15$  minutes of the stated collection time. Samples collected outside of this time range will be documented as a collection time deviation and the actual collection times may be used. Any sample collection time deviations will be communicated to the Study Director and the Principal Investigator for Bioanalysis in a timely manner.

Volume (mL): 1 mL

Additional blood samples may be obtained (e.g. due to sample quality) if permissible sampling frequency and blood volume are not exceeded.

Anticoagulant: K<sub>2</sub>EDTA

Fasting: The animals will not be fasted before blood collection.

Whole Blood Storage: Wet ice or ice block until centrifuged.

Processing: Plasma

Final Storage Temperature: Frozen (-60 to -90°C)

## 12.2. Bioanalytical Sample Processing

Additional Container: Blood collection and 2D barcoded (2 mL Greiner cryovial #122263-2DG) storage tubes and their labels will be provided by Testing Facility. The labels for the plasma storage tubes will contain the Testing Facility study number, Sponsor's study number, animal number, species, test item number, matrix of sample, interval and timepoint relative to dosing, and analysis type, aliquot number. The 2D barcodes will be included on the sample manifest.

Processing Details: Within 60 minutes of collection, blood samples will be centrifuged (1100 to 1600 g for separation of plasma). The temperature of the centrifuge will be within operating range of 2 to 8°C.

The resultant plasma will be transferred to a labeled 2 mL polypropylene Greiner tube and stored frozen (-60°C to -90°C) until shipped to the Sponsor for analysis. The time and date that the samples are placed in the freezer will be recorded.

Bioanalytical Sample: All samples to be analyzed will be shipped to the Sponsor for analysis.  
Shipping: See [Attachment A](#) for shipping details.

Contact/Details:

Plasma samples will be shipped Monday through Wednesday for next day delivery. [REDACTED] Sample Receiving will be notified prior to shipment and will provide authorization for shipment. The Principal Investigator for Bioanalysis will also be notified. The inventory documentation accompanying the samples will specify the type and number of samples, the date on which each sample was collected, the barcode for each sample, and the storage conditions. Any deviations from the protocol during the study with regard to sample collection, processing, and storage will be included in the inventory documentation and communicated to the Principal Investigator for Bioanalysis in a timely manner.

Upon receipt at the Test Site, the samples will be stored in a freezer set to maintain -70°C.

## 12.3. Bioanalytical Sample Analysis

Analysis Performed By: The plasma will be analyzed for [REDACTED] concentration. All analytical work will be conducted by the Sponsor, using an analytical method developed and validated by that laboratory (to be added by amendment).

Analysis Details: Concentration levels will be combined and averaged by treatment (rather than by study day). Drug analysis data will be reported as mean  $\pm$  SEM. Mean  $\pm$  SEM plasma concentrations for each of the three test item treatments (Treatments 2, 3, and 4) will be plotted on a single graph. Data

presentation can be adjusted as deemed appropriate by the Principal Investigator after consultation with the Sponsor Representative, or designee. The Study Director will be informed of any adjustments to the data presentation.

**Regulatory Requirements:**

The work performed in conjunction with this study will be conducted in compliance with GLPs and subject to review by the Quality Assurance Unit (QAU) of that laboratory. The findings of their QAU will be submitted to the Principal Investigator and the Principal Investigator's management as well as to the Testing Facility Study Director and Testing Facility Management. A Final Report, including a Quality Assurance Statement and Statement of Compliance, will be prepared and submitted to Testing Facility for inclusion as an appendix in the main study Final Report.

### **13. TERMINAL PROCEDURES**

No terminal procedures are scheduled.

#### **13.1. Animal Disposition**

At termination of the study, all surviving animals and all extra animals transferred to this study, but not placed on study, will be transferred to a Testing Facility stock colony, unless otherwise directed. The final disposition of each animal will be documented in the study records.

Companion animals will be returned to a Testing Facility stock or training colony when no longer needed.

#### **13.2. Unscheduled Euthanasia**

Any moribund animals will be euthanized for humane reasons. All animals euthanized in extremis or found dead will be subjected to a routine necropsy to determine a cause of death and for removal of the telemetry transmitters. No tissues will be saved and carcasses will be discarded.

#### **13.3. Method of Euthanasia**

Euthanasia will be by euthanasia solution administration, under sedation if necessary (e.g. acepromazine and/or Telazol®), followed by a Testing Facility SOP approved method to ensure death, e.g. exsanguination.

### **14. HISTOLOGY AND MICROSCOPIC EVALUATION**

No postmortem evaluations are scheduled; however, in the event of unexpected death or euthanasia, a routine necropsy will be performed, and the telemetry transmitters will be removed. No tissues will be saved.

## 15. STATISTICAL ANALYSIS

The following presents a proposed statistical analysis plan. Statistical plans are data dependent, and this analysis plan may require modification if standard data assumptions are not met. Other conceptually equivalent statistical testing routines may also be employed at the discretion of the statistician. The actual analysis plan will be documented in the Final Report.

### 15.1. Statistical Comparisons

Control Treatment	Comparison Treatments
1	2, 3, 4

### 15.2. Statistical Analysis

#### 15.2.1. Descriptive Statistics

Endpoints: Body Temperature

Cardiovascular Endpoints  
Systolic, Diastolic, and Mean Blood Pressures  
Heart Rate  
ECG (RR, PR, QRS, QT, and QTc)

Description: Descriptive statistics will consist of means, standard deviations, and group size for each time period.

#### 15.2.2. Paired Sample T-Test Comparison

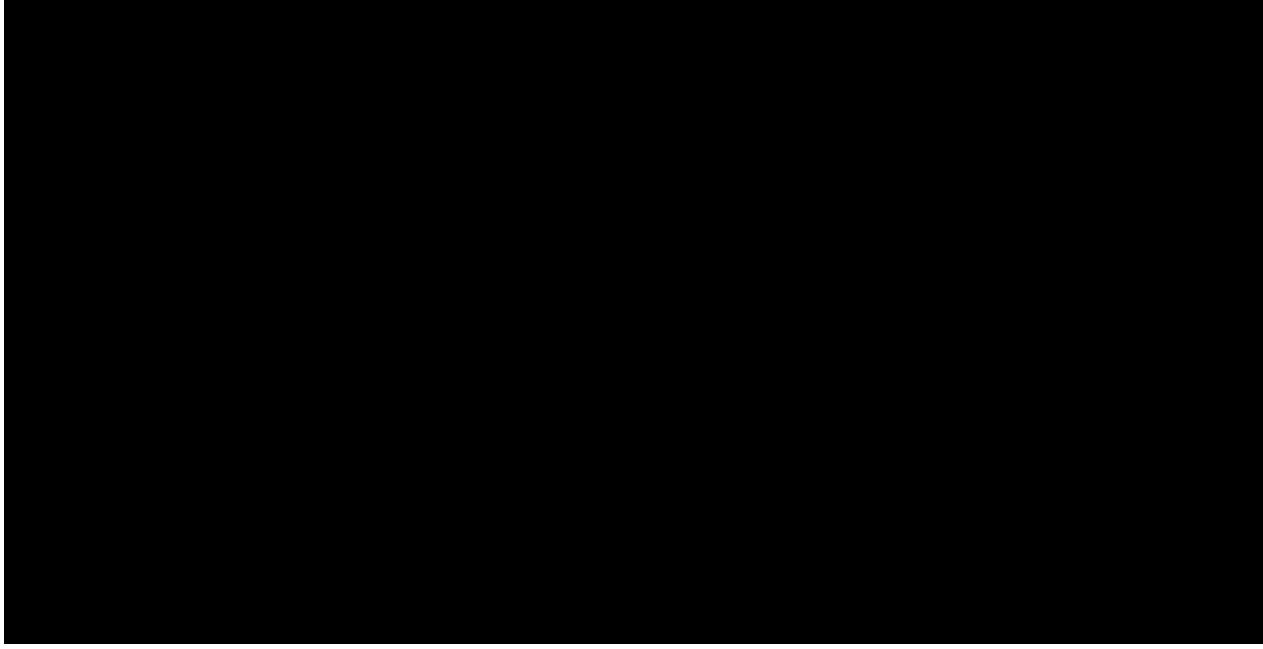
Endpoints: Body Temperature

Cardiovascular Endpoints  
Systolic, Diastolic, and Mean Blood Pressures  
Heart Rate and ECG (RR, PR, QRS, QT, and QTc)

Description: For each specified endpoint and for each time interval a Paired Sample t-test<sup>3</sup> will be used to test for no treatment effect. For each treatment, each subject will serve as its own control to generate a calculated difference between treatment and control. The mean of this difference will be tested against a mean of 0, for no change. A Bonferroni correction will be applied. Results of the comparison will be reported at the 0.05 and 0.01 significance levels. The step-down Sidak method will be applied to previously obtained p-values to adjust for multiple testing. All endpoints will be analyzed using two-tailed tests unless indicated otherwise.

## **16. COMPUTER SYSTEMS**

The following are the proposed computer systems to be used during the conduct of this study and their primary function. The actual systems and versions used will be documented in the Final Report.



## **17. REGULATORY COMPLIANCE**

The study will be performed in accordance with the U.S. Department of Health and Human Services, Food and Drug Administration, United States Code of Federal Regulations, Title 21, Part 58: Good Laboratory Practice for Nonclinical Laboratory Studies and as accepted by Regulatory Authorities throughout the European Union (OECD Principles of Good Laboratory Practice), Japan (MHLW), and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

Exceptions to GLPs include the following study elements:

The initial bulk test item characterization was conducted by the Sponsor using validated methods in a Good Manufacturing Practices (GMP) based quality system.

## **18. QUALITY ASSURANCE**

### **18.1. Testing Facility**

The Testing Facility Quality Assurance Unit (QAU) will monitor the study to assure the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with Good Laboratory Practice regulations. The QAU will review the protocol, conduct inspections at intervals adequate to assure the integrity of the study, and audit the Final Report to

assure that it accurately describes the methods and standard operating procedures and that the reported results accurately reflect the raw data of the study.

#### **18.2. Test Site(s)/Subcontractor(s)**

For all study phase(s) inspected by test site/subcontractor QAU(s), copies of each periodic inspection report will be made available to the Study Director, Testing Facility Management, and the Testing Facility QAU.

#### **19. AMENDMENTS AND DEVIATIONS**

Changes to the approved protocol shall be made in the form of an amendment, which will be signed and dated by the Study Director. Every reasonable effort will be made to discuss any necessary protocol changes in advance with the Sponsor. The Study Director will notify the Sponsor of deviations that may result in a significant impact on the study as soon as possible.

#### **20. RETENTION AND DISPOSITION OF RECORDS, SAMPLES, AND SPECIMENS**

Report will be archived by no later than the date of Final Report issue. All retained materials will be archived at [REDACTED] unless specified by the Sponsor. At least 1 year after issue of the Draft Report, the Sponsor will be contacted.

Samples for clinical pathology evaluations are discarded per Testing Facility SOP unless otherwise indicated in the table below.

Disposition of retained analytical samples will be as described in the table below.

**Disposition of Retained Samples**

<b>Sample Type</b>	<b>Disposition</b>	<b>Schedule</b>
Dose Formulation Samples	Discard	Any remaining formulation samples will be discarded after acceptance of the analytical results by the Study Director or upon receipt of authorization to finalize the report.

Records to be maintained will include, but will not be limited to, documentation and data for the following:

- Protocol, protocol amendments, and deviations
- Study schedule
- Study-related correspondence
- Test system receipt, health, and husbandry
- Statistical analysis results
- Test and control item receipt, identification, preparation, and analysis
- In-life measurements and observations

#### **21. STUDY CLASSIFICATION**

Study Category: Safety Pharmacology

Study Type: Cardiovascular Pharmacology

Study Design: Latin Square

Primary Treatment CAS Registry Number:	Not Available
Primary Treatment Unique Ingredient ID:	Not Available
Class of Compound:	Small Molecule

## 22. REPORTING

A comprehensive Draft Report will be prepared following completion of the study and will be finalized following consultation with the Sponsor. The report will include all information necessary to provide a complete and accurate description of the experimental methods and results and any circumstances that may have affected the quality or integrity of the study.

The Sponsor will receive an electronic version of the Draft and Final Report provided in Adobe Acrobat PDF format (hyperlinked and searchable at final). The PDF document will be created from native electronic files to the extent possible, including text and tables generated by the Testing Facility. Report components not available in native electronic files and/or original signature pages will be scanned and converted to PDF image files for incorporation.

Reports should be finalized within 6 months of issue of the Draft Report. If the Sponsor has not provided comments to the report within 6 months of draft issue, the report will be finalized by the Testing Facility unless other arrangements are made by the Sponsor.

### 22.1. SEND Datasets

SEND datasets will be generated and provided outside the context of the Final GLP Report. These datasets will not be subject to QA Audit nor will they be used as the basis for the Study Director interpretation of the study results. SEND datasets will be provided following the Final Report.

An electronic version of all data collected in support of this study at a Test Site (i.e., formulation analysis), should be provided to Testing Facility.

## 23. JUSTIFICATIONS AND GUIDELINES

### 23.1. Justification of Test System and Number of Animals

The beagle is the usual non-rodent model used for evaluating the cardiovascular safety of various test articles and for which there is a large historical database.<sup>4</sup> There are no known or expected differences between male and female animals relative to exposure levels or the effects of the test article on cardiovascular function; therefore, only males will be used to conserve animals.

The total number of animals to be used in this study is considered to be the minimum required to properly characterize the effects of the test article and has been designed such that it does not require an unnecessary number of animals to accomplish its objectives.

### 23.2. Justification of Route and Dose Levels

The oral route is the intended route of administration of this test article in humans.

In a previous repeat dose range finding toxicity study in dogs, [REDACTED] was tolerated up to 150 mg/kg/day. Test-item-related findings were noted in heart, kidney, gall bladder, and stomach. Based upon the results of that study, the highest dose may produce some toxic effects, but not lethality or excessive toxicity that would prevent meaningful evaluation. The mid-dose level is expected to produce minimal to moderate effects. The low-dose level should produce no observable effects.

### 23.3. Guidelines for Study

The design of this study was based on the study objective(s), the overall product development strategy for the test article, and the following study design guidelines:

- ICH Harmonised Tripartite Guideline M3 (R2). *Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*.
- ICH Harmonised Tripartite Guideline S7A. *Guideline on Safety Pharmacology Studies for Human Pharmaceuticals*.
- ICH Harmonised Tripartite Guideline S7B. *The Non-Clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals*.

## 24. ANIMAL WELFARE

This study will comply with all applicable sections of the Final Rules of the Animal Welfare Act regulations (Code of Federal Regulations, Title 9), the *Public Health Service Policy on Humane Care and Use of Laboratory Animals* from the Office of Laboratory Animal Welfare, and the *Guide for the Care and Use of Laboratory Animals* from the National Research Council.<sup>5,6</sup> The protocol and any amendments or procedures involving the care or use of animals in this study will be reviewed and approved by the Testing Facility Institutional Animal Care and Use Committee before the initiation of such procedures.

If an animal is determined to be in overt pain/distress, or appears moribund and is beyond the point where recovery appears reasonable, the animal will be euthanized for humane reasons in accordance with the *American Veterinary Medical Association (AVMA) Guidelines on Euthanasia* and with the procedures outlined in the protocol.<sup>7</sup>

By approving this protocol, the Sponsor affirms that there are no acceptable non-animal alternatives for this study, that this study is required by a relevant government regulatory agency(ies) and that it does not unnecessarily duplicate any previous experiments.

### 24.1. Institutional Animal Care and Use Committee Approval

The protocol and any amendment(s) or procedures involving the care and use of animals in this study will be reviewed and approved by [REDACTED] Institutional Animal Care and Use

Committee (IACUC) before conduct. During the study, the care and use of animals will be conducted with guidance from the guidelines of the USA National Research Council.

## 25. REFERENCES

1. Spence S. The Heart Rate-Corrected QT Interval of Conscious Beagle Dogs: A Formula Based on Analysis of Covariance. *Toxicological Sciences*. 1998;45(2):247-258.
2. Miyazaki H, Tagawa M. Rate-Correction Technique for QT Interval in Long-Term Telemetry ECG Recording in Beagle Dogs. *Experimental Animals*. 2002;51(5):465-475.
3. Guidance for industry, investigators, and reviewers: exploratory IND studies. U.S. FDA Center for Drug Evaluation and Research (CDER), 2006 Jan.
4. Office of Laboratory Animal Welfare. *Public Health Services Policy on Humane Care and Use of Laboratory Animals*. Bethesda, MD: National Institutes of Health. Current edition.
5. National Research Council. *Guide for the Care and Use of Laboratory Animals*. Washington, DC: National Academy Press. Current edition.
6. American Veterinary Medical Association. *AVMA Guidelines on Euthanasia*. Current edition.

## **DEVIATIONS**

All SOP deviations that occurred during the study have been authorized/acknowledged by the Study Director, assessed for impact, and documented in the study records. None of the SOP deviations were considered to have impacted the overall integrity of the study or the interpretation of the study results and conclusions. No protocol deviations occurred during the study.

**Appendix 2**  
**Test Item Characterization**

Appendix 3  
Dose Formulation Analysis Report

**Appendix 4**  
**Individual Detailed Clinical Observations**

On occasion, clinical findings may have been observed more than once during the interval and were recorded accordingly. The individual clinical observations table of this appendix reports the findings observed, not the number of times observed.

## Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs

Individual Detailed Clinical Observations  
Predose

Sex: Male	Animal	Observation Type: Routine	From Day 1 (Start Date) to 42 (Start Date)
0 mg kg	1001	Calculus	1
		Gums discolored, Red, Mouth	1
		Teeth discolored, Yellow	1
	1002	Calculus	36
		Calculus	1
	1003	Gums discolored, Red	1
		Teeth discolored, Brown	1
	1004	Calculus	36
		Calculus	11
	1005	Gums discolored, Red, Mouth	11
		Teeth discolored, Yellow	11
	1006	No abnormalities detected	22

Values=Interval seen

## Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs

Individual Detailed Clinical Observations  
Predose

Sex: Male	Animal	Observation Type: Routine	From Day 1 (Start Date) to 42 (Start Date)
20 mg kg	1001	Calculus	11
		Gums discolored, Red, Mouth	11
		Teeth discolored, Yellow	11
	1002	No abnormalities detected	22
	1003	Calculus	22
		Teeth discolored, Brown	22
	1004	Gums discolored, Red, Mouth	11
	1005	Gums discolored, Red, Mouth	1
	1006	Calculus	36

Values=Interval seen

## Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs

Individual Detailed Clinical Observations  
Predose

Sex: Male	Animal	Observation Type: Routine	From Day 1 (Start Date) to 42 (Start Date)
50 mg kg	1001	No abnormalities detected	22
	1002	Calculus	11
		Gums discolored, Red, Mouth	11
		Teeth discolored, Yellow	11
		Thin	11
	1003	Calculus	11
		Gums discolored, Red, Mouth	11
		Teeth discolored, Yellow	11
	1004	No abnormalities detected	22
	1005	Calculus	36
	1006	No abnormalities detected	1

Values=Interval seen

## Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs

Individual Detailed Clinical Observations  
Predose

Sex: Male	Animal	Observation Type: Routine	From Day 1 (Start Date) to 42 (Start Date)
150 mg kg	1001	Calculus	36
	1002	Calculus	1
		Teeth discolored, Yellow	1
	1003	Calculus	36
	1004	No abnormalities detected	1
	1005	Lacrimation, Eye/left	22
	1006	Calculus	11
		Gums discolored, Red, Mouth	11
		Teeth discolored, Yellow	11

Values=Interval seen

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle DogsIndividual Detailed Clinical Observations  
1 hour postdose

Sex: Male	Animal	Observation Type: Routine	From Day 1 (Start Date) to 42 (Start Date)
0 mg kg	1001	No abnormalities detected	1
	1002	No abnormalities detected	36
	1003	No abnormalities detected	1
	1004	No abnormalities detected	36
	1005	No abnormalities detected	11
	1006	No abnormalities detected	22

Values=Interval seen

## Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs

Individual Detailed Clinical Observations  
1 hour postdose

Sex: Male	Animal	Observation Type: Routine	From Day 1 (Start Date) to 42 (Start Date)
20 mg kg	1001	No abnormalities detected	11
	1002	No abnormalities detected	22
	1003	No abnormalities detected	22
	1004	No abnormalities detected	11
	1005	No abnormalities detected	1
	1006	No abnormalities detected	36

Values=Interval seen

## Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs

Individual Detailed Clinical Observations  
1 hour postdose

Sex: Male	Animal	Observation Type: Routine	From Day 1 (Start Date) to 42 (Start Date)
50 mg kg	1001	No abnormalities detected	22
	1002	No abnormalities detected	11
	1003	No abnormalities detected	11
	1004	No abnormalities detected	22
	1005	No abnormalities detected	36
	1006	No abnormalities detected	1

Values=Interval seen

## Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs

Individual Detailed Clinical Observations  
1 hour postdose

Sex: Male	Animal	Observation Type: Routine	From Day 1 (Start Date) to 42 (Start Date)
150 mg kg	1001	No abnormalities detected	36
	1002	No abnormalities detected	1
	1003	No abnormalities detected	36
	1004	No abnormalities detected	1
	1005	No abnormalities detected	22
	1006	No abnormalities detected	11

Values=Interval seen

## Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs

Individual Detailed Clinical Observations  
End of monitoring

Sex: Male	Animal	Observation Type: Routine	From Day 1 (Start Date) to 42 (Start Date)
0 mg kg	1001	Gums discolored, Red, Mouth	2
	1002	No abnormalities detected	37
	1003	Gums discolored, Red, Mouth	2
	1004	Teeth discolored, Yellow	2
	1005	No abnormalities detected	37
	1006	Lacrimation, Eye/left	12
		Calculus	23

Values=Interval seen

## Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs

Individual Detailed Clinical Observations  
End of monitoring

Sex: Male	Animal	Observation Type: Routine	From Day 1 (Start Date) to 42 (Start Date)
20 mg kg	1001	No abnormalities detected	12
	1002	Calculus	23
	1003	No abnormalities detected	23
	1004	No abnormalities detected	12
	1005	Gums discolored, Red, Mouth	2
	1006	Lacrimation, Eye/left Teeth discolored, Yellow Teeth discolored, Brown	2 2 37

Values=Interval seen

## Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs

Individual Detailed Clinical Observations  
End of monitoring

Sex: Male	Animal	Observation Type: Routine	From Day 1 (Start Date) to 42 (Start Date)
50 mg kg	1001	Calculus	23
	1002	No abnormalities detected	12
	1003	Calculus	12
		Scabbed area, Blood collection site	12
		Teeth discolored, Brown	12
	1004	No abnormalities detected	23
	1005	Lacrimation, Eye/left	37
	1006	Gums discolored, Red, Mouth	2
		Teeth discolored, Yellow	2

Values=Interval seen

## Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs

Individual Detailed Clinical Observations  
End of monitoring

Sex: Male	Animal	Observation Type: Routine	From Day 1 (Start Date) to 42 (Start Date)
150 mg kg	1001	Gums discolored, Red, Mouth	37
		Teeth discolored, Brown	37
	1002	Gums discolored, Red, Mouth	2
		Teeth discolored, Yellow	2
	1003	Teeth discolored, Brown	37
		Vomitus, Tan, Food like	37
	1004	No abnormalities detected	2
	1005	Feces soft	23
		Vomitus, Tan, Food like	23
	1006	No abnormalities detected	12

Values=Interval seen

## Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs

Individual Detailed Clinical Observations  
Unscheduled

Sex: Male	Animal	Observation Type: Unscheduled	Time Sign Present (Hour:Minute:Second) <sup>a</sup>	From Day 1 (Start Date) to 42 (Start Date) <sup>b</sup>
0 mg kg	1002	Feces soft	115:39:44, 139:43:05	41, 42
	1003	Vomitus, Tan, Food like	68:41:52	4
	1006	Feces discolored, Yellow	259:59:35	33
		Feces mucoid	188:19:47	30

<sup>a</sup>In relation to time of dose<sup>b</sup>Values=Interval seen

## Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs

Individual Detailed Clinical Observations  
Unscheduled

Sex: Male	Animal	Observation Type: Unscheduled	Time Sign Present (Hour:Minute:Second) <sup>a</sup>	From Day 1 (Start Date) to 42 (Start Date) <sup>b</sup>
20 mg kg	1001	Inappetence	Predose	11
	1004	Feces mucoid	145:36:12	17
		Feces soft	48:48:51, 68:11:20	13, 14
	1006	Feces soft	139:39:38	42

<sup>a</sup>In relation to time of dose<sup>b</sup>Values=Interval seen

## Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs

Individual Detailed Clinical Observations  
Unscheduled

Sex: Male	Animal	Observation Type: Unscheduled	Time Sign Present (Hour:Minute:Second) <sup>a</sup>	From Day 1 (Start Date) to 42 (Start Date) <sup>b</sup>
50 mg kg	1001	Feces discolored, Yellow	259:53:49	33
		Feces mucoid	188:14:08	30
	1002	Emesis, Tan, Food like	0:01:49	11
		Feces discolored, Yellow	Predose	11
		Feces mucoid	Predose	11
	1005	Feces soft	115:33:09, 139:35:51	41, 42

<sup>a</sup>In relation to time of dose<sup>b</sup>Values=Interval seen

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle DogsIndividual Detailed Clinical Observations  
Unscheduled

Sex: Male	Animal	Observation Type: Unscheduled	Time Sign Present (Hour:Minute:Second) <sup>a</sup>	From Day 1 (Start Date) to 42 (Start Date) <sup>b</sup>
150 mg kg	1001	Feces soft	139:34:43	42

<sup>a</sup>In relation to time of dose<sup>b</sup>Values=Interval seen

**Appendix 5**  
**Individual Body Weight Values**

Dosing Schedule

<b>Animal No.</b>	<b>Dose level (mg/kg)</b>				<b>Return to Stock</b>
	<b>0</b>	<b>20</b>	<b>50</b>	<b>150</b>	
1001	Day 1	Day 11	Day 22	Day 36	Day 44
1002	Day 36	Day 22	Day 11	Day 1	Day 44
1003	Day 1	Day 22	Day 11	Day 36	Day 44
1004	Day 36	Day 11	Day 22	Day 1	Day 44
1005	Day 11	Day 1	Day 36	Day 22	Day 44
1006	Day 22	Day 36	Day 1	Day 11	Day 44

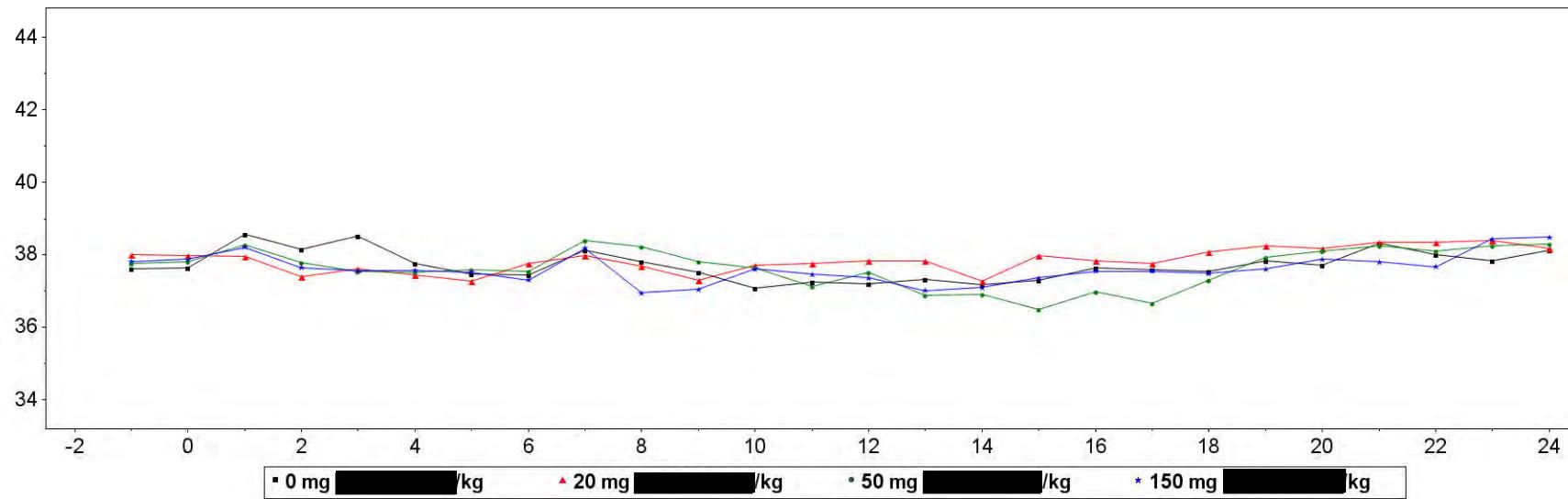
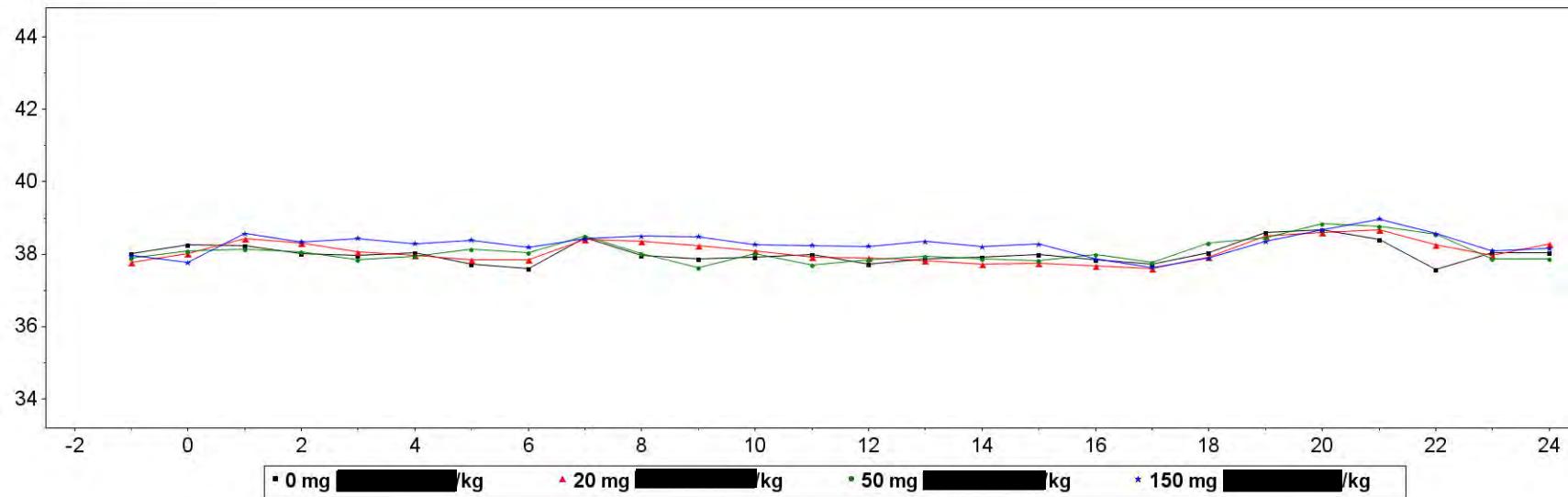
[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs

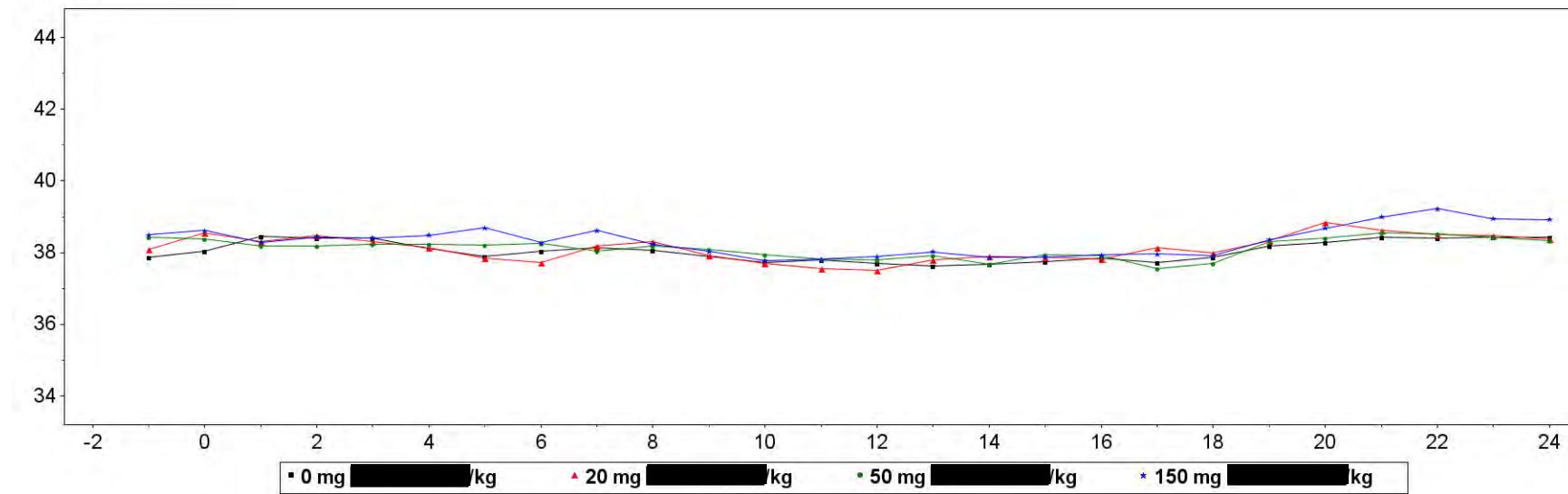
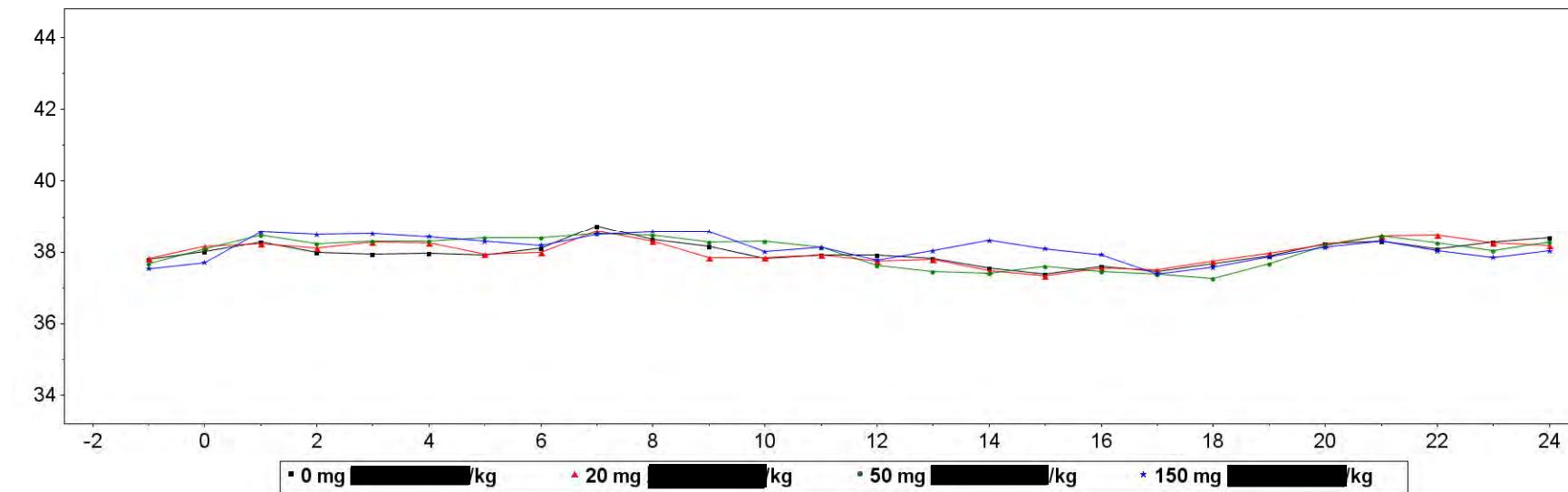
## Individual Body Weight Values

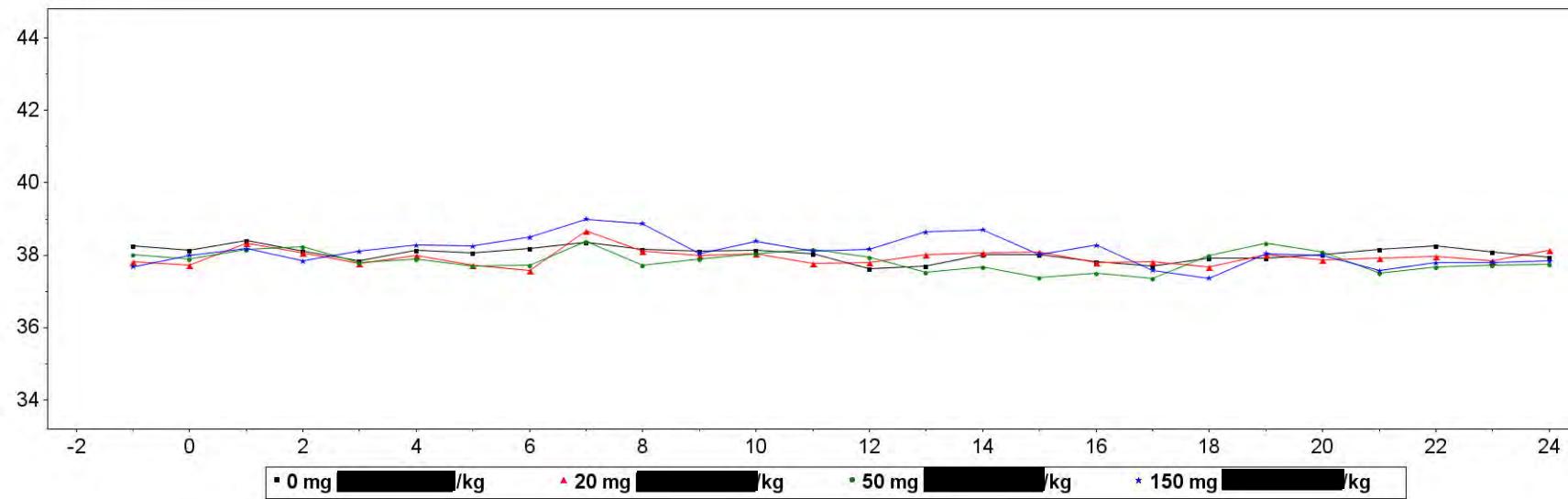
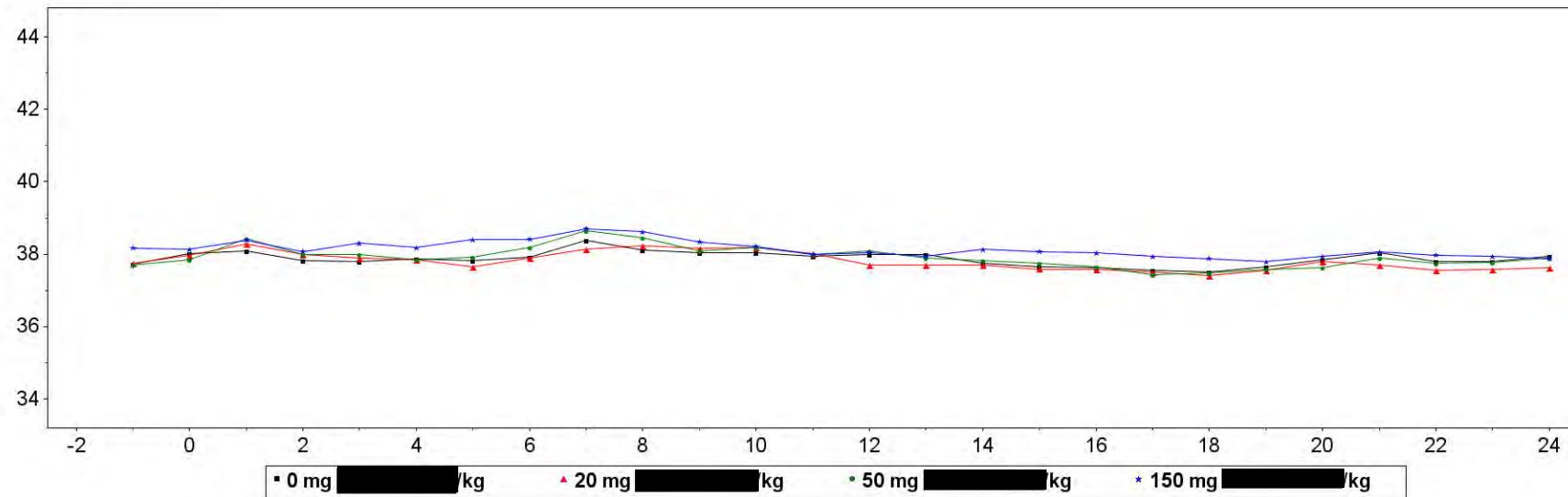
Sex: Male    Body Weight (kg)

kg	Day(s) Relative to Start Date				
	-1	10	21	35	44
1001	8.45	8.55	8.50	8.90	8.80
1002	9.10	9.20	9.60	9.90	9.90
1003	10.65	10.55	10.70	10.90	10.55
1004	10.10	10.35	10.35	10.35	10.45
1005	8.20	8.25	8.55	8.25	7.95
1006	7.85	7.80	7.85	8.00	7.85

**Appendix 6**  
**Individual Body Temperature**

**Individual Body Temperature, °C vs. Time, Hour****1001 M****1002 M**

**Individual Body Temperature, °C vs. Time, Hour****1003 M****1004 M**

**Individual Body Temperature, °C vs. Time, Hour****1005 M****1006 M**

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual Body Temperature, °C - MALE**

Group, Animal Number	Study Interval (hour:minute)	Individual Body Temperature, °C - MALE								
		-1:00	0:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00
<b>0 mg [REDACTED] kg</b>										
1001		37.6	37.6	38.6	38.1	38.5	37.8	37.5	37.4	38.1
1002		38.0	38.3	38.2	38.0	38.0	38.0	37.7	37.6	38.5
1003		37.9	38.0	38.5	38.4	38.4	38.1	37.9	38.1	38.1
1004		37.8	38.0	38.3	38.0	37.9	38.0	37.9	38.1	38.7
1005		38.3	38.1	38.4	38.1	37.8	38.1	38.1	38.2	38.4
1006		37.7	38.0	38.1	37.8	37.8	37.9	37.8	37.9	38.4
<b>20 mg [REDACTED] kg</b>										
1001		38.0	38.0	37.9	37.4	37.6	37.4	37.3	37.7	38.0
1002		37.8	38.0	38.4	38.3	38.1	38.0	37.8	37.8	38.4
1003		38.1	38.5	38.3	38.5	38.3	38.1	37.9	37.7	38.2
1004		37.8	38.2	38.2	38.1	38.3	38.3	38.0	38.0	38.6
1005		37.8	37.7	38.3	38.1	37.8	38.0	37.7	37.6	38.7
1006		37.7	38.0	38.3	38.0	37.9	37.8	37.7	37.9	38.1
<b>50 mg [REDACTED] kg</b>										
1001		37.8	37.8	38.3	37.8	37.5	37.5	37.6	37.5	38.4
1002		37.9	38.1	38.1	38.1	37.8	37.9	38.1	38.0	38.5
1003		38.4	38.4	38.2	38.2	38.2	38.2	38.2	38.2	38.0
1004		37.7	38.1	38.5	38.2	38.3	38.3	38.4	38.4	38.5
1005		38.0	37.9	38.2	38.2	37.8	37.9	37.7	37.7	38.4
1006		37.7	37.8	38.4	38.0	38.0	37.8	37.9	38.2	38.6
<b>150 mg [REDACTED] kg</b>										
1001		37.8	37.9	38.2	37.6	37.5	37.6	37.5	37.3	38.2
1002		38.0	37.8	38.6	38.3	38.4	38.3	38.4	38.2	38.4
1003		38.5	38.6	38.3	38.4	38.4	38.5	38.7	38.3	38.6

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual Body Temperature, °C - MALE**

Group, Animal Number	Study Interval (hour:minute)	Individual Body Temperature, °C - MALE								
		-1:00	0:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00
<u>150 mg [REDACTED] kg</u>										
1004		37.5	37.7	38.6	38.5	38.5	38.4	38.3	38.2	38.5
1005		37.7	38.0	38.2	37.8	38.1	38.3	38.3	38.5	39.0
1006		38.2	38.1	38.4	38.1	38.3	38.2	38.4	38.4	38.7

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual Body Temperature, °C - MALE**

Group, Animal Number	Study Interval (hour:minute)	Individual Body Temperature, °C - MALE								
		8:00	9:00	10:00	11:00	12:00	13:00	14:00	15:00	16:00
<b>0 mg [REDACTED] kg</b>										
1001		37.8	37.5	37.1	37.2	37.2	37.3	37.2	37.3	37.6
1002		38.0	37.9	37.9	38.0	37.7	37.9	37.9	38.0	37.9
1003		38.1	37.9	37.7	37.8	37.7	37.6	37.7	37.8	37.8
1004		38.4	38.2	37.8	37.9	37.9	37.8	37.6	37.4	37.6
1005		38.2	38.1	38.1	38.1	37.6	37.7	38.0	38.0	37.8
1006		38.1	38.0	38.0	38.0	38.0	38.0	37.8	37.7	37.6
<b>20 mg [REDACTED] kg</b>										
1001		37.7	37.3	37.7	37.7	37.8	37.8	37.3	38.0	37.8
1002		38.4	38.2	38.1	37.9	37.9	37.8	37.7	37.7	37.7
1003		38.3	37.9	37.7	37.5	37.5	37.8	37.9	37.9	37.8
1004		38.3	37.8	37.8	37.9	37.8	37.8	37.5	37.3	37.6
1005		38.1	38.0	38.1	37.8	37.8	38.0	38.1	38.1	37.8
1006		38.2	38.2	38.2	38.0	37.7	37.7	37.7	37.6	37.6
<b>50 mg [REDACTED] kg</b>										
1001		38.2	37.8	37.6	37.1	37.5	36.9	36.9	36.5	37.0
1002		38.0	37.6	38.0	37.7	37.9	37.9	37.9	37.8	38.0
1003		38.2	38.1	37.9	37.8	37.8	37.9	37.7	37.9	37.9
1004		38.5	38.3	38.3	38.1	37.6	37.5	37.4	37.6	37.4
1005		37.7	37.9	38.0	38.2	37.9	37.5	37.7	37.4	37.5
1006		38.5	38.1	38.2	38.0	38.1	37.9	37.8	37.7	37.6
<b>150 mg [REDACTED] kg</b>										
1001		36.9	37.0	37.6	37.4	37.4	37.0	37.1	37.4	37.5
1002		38.5	38.5	38.3	38.2	38.2	38.4	38.2	38.3	37.9
1003		38.2	38.0	37.8	37.8	37.9	38.0	37.9	37.9	37.9

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual Body Temperature, °C - MALE**

Group, Animal Number	Study Interval (hour:minute)	Individual Body Temperature, °C - MALE								
		8:00	9:00	10:00	11:00	12:00	13:00	14:00	15:00	16:00
<u>150 mg [REDACTED] kg</u>										
1004		38.6	38.6	38.0	38.1	37.8	38.0	38.3	38.1	37.9
1005		38.9	38.1	38.4	38.1	38.2	38.6	38.7	38.0	38.3
1006		38.6	38.3	38.2	38.0	38.0	37.9	38.1	38.1	38.0

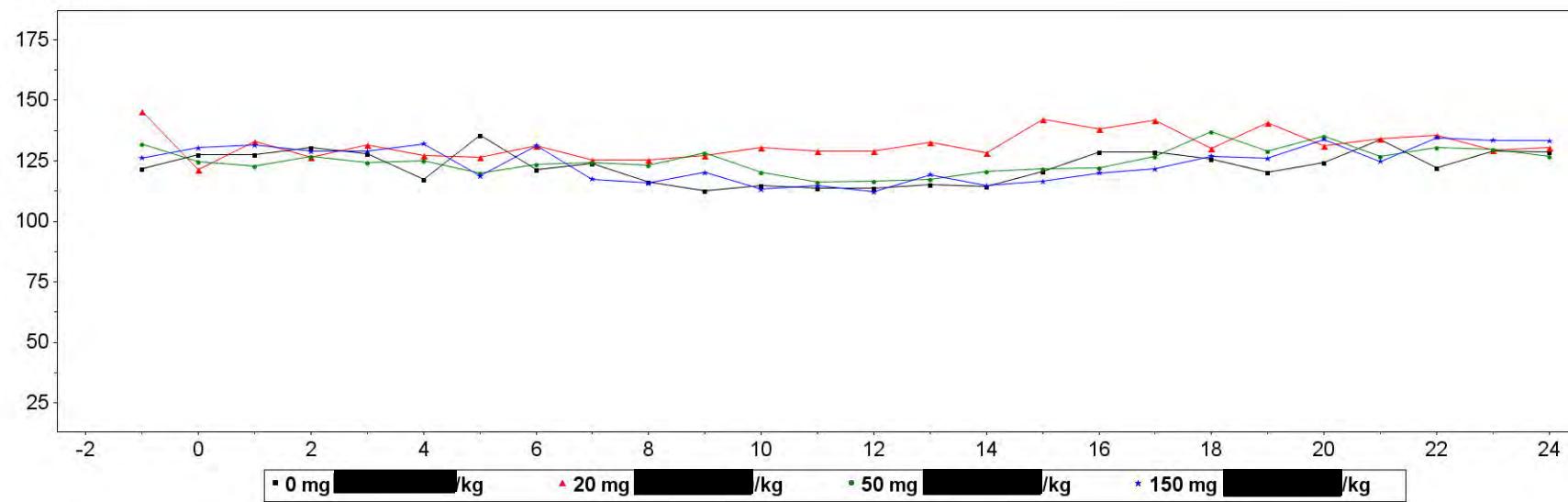
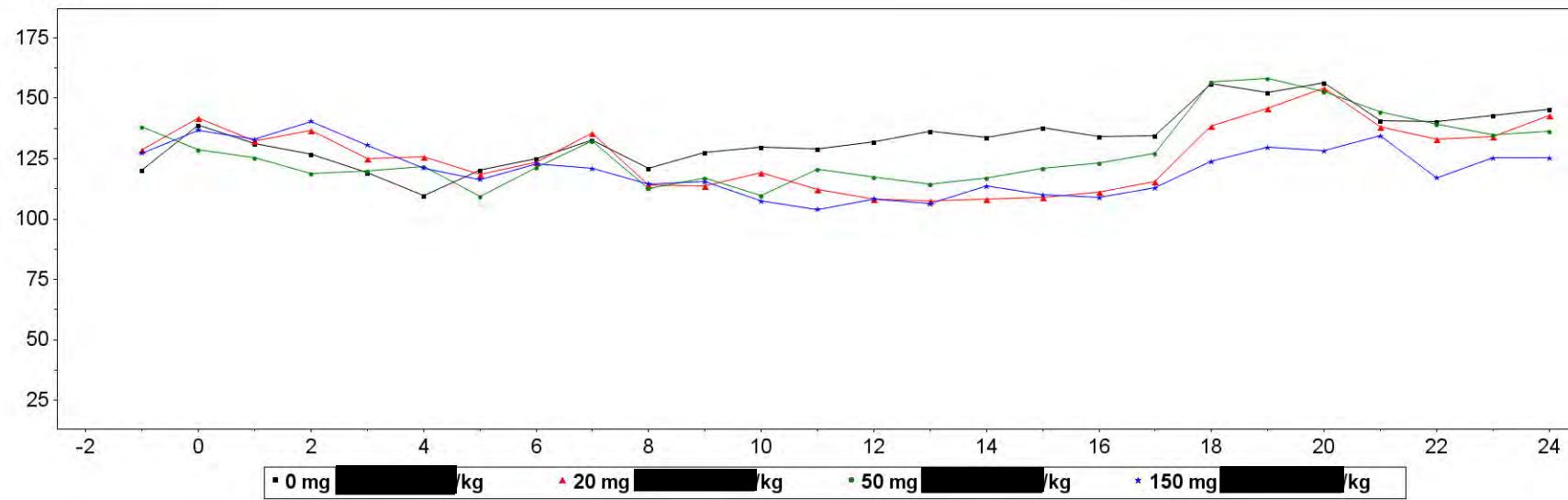
[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual Body Temperature, °C - MALE**

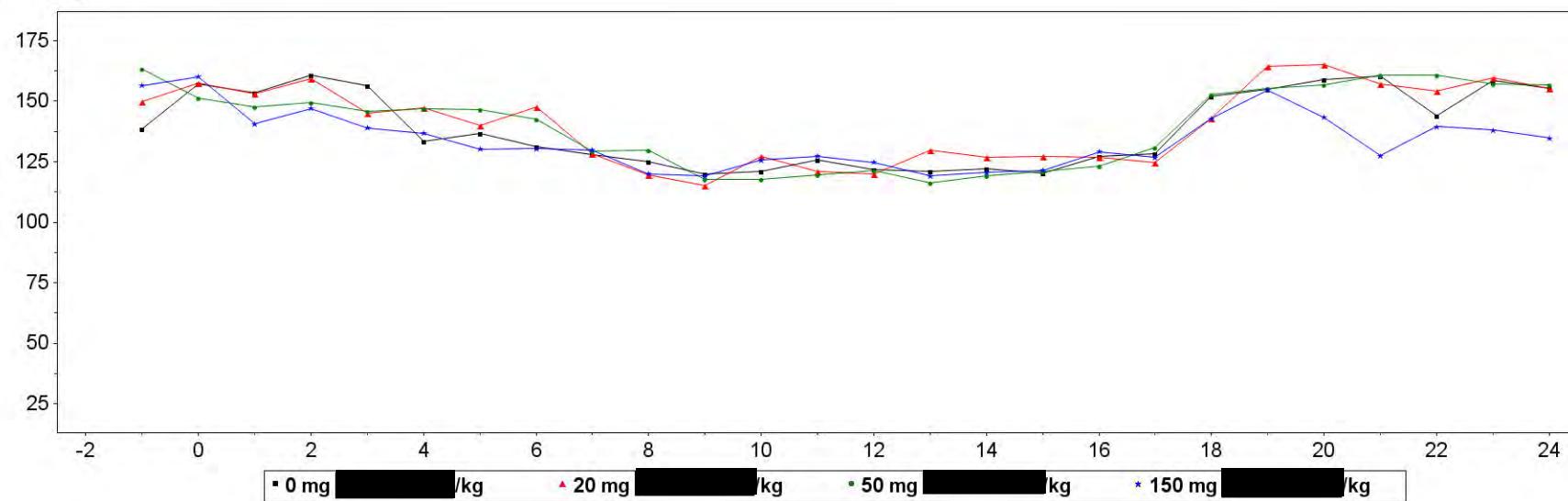
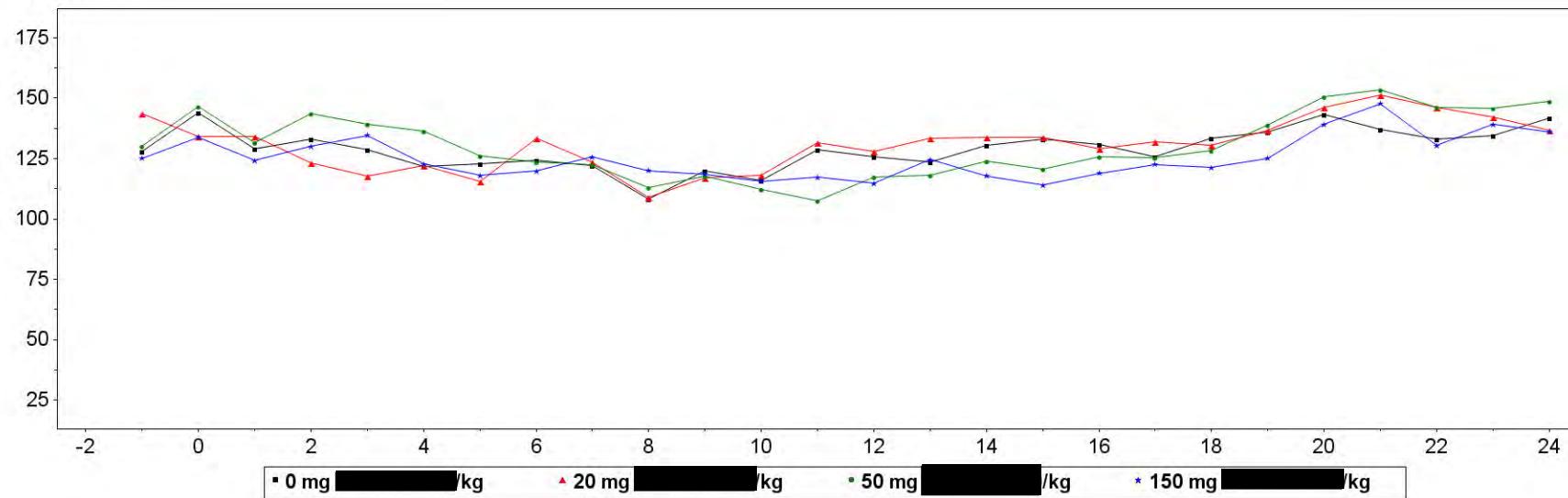
Group, Animal Number	Study Interval (hour:minute)	Individual Body Temperature, °C - MALE						
		17:00	18:00	19:00	20:00	21:00	22:00	23:00
<b>0 mg [REDACTED] kg</b>								
1001		37.6	37.5	37.8	37.7	38.3	38.0	37.8
1002		37.7	38.0	38.6	38.7	38.4	37.6	38.0
1003		37.7	37.9	38.2	38.3	38.4	38.4	38.4
1004		37.5	37.7	37.9	38.2	38.3	38.1	38.3
1005		37.7	37.9	37.9	38.0	38.2	38.3	37.9
1006		37.6	37.5	37.6	37.8	38.0	37.8	37.9
<b>20 mg [REDACTED] kg</b>								
1001		37.8	38.1	38.2	38.2	38.3	38.3	38.4
1002		37.6	37.9	38.5	38.6	38.7	38.3	38.0
1003		38.1	38.0	38.3	38.8	38.6	38.5	38.5
1004		37.5	37.8	38.0	38.2	38.5	38.5	38.3
1005		37.8	37.7	38.0	37.9	37.9	38.0	37.9
1006		37.5	37.4	37.6	37.8	37.7	37.6	37.6
<b>50 mg [REDACTED] kg</b>								
1001		36.6	37.3	37.9	38.1	38.2	38.1	38.2
1002		37.8	38.3	38.5	38.8	38.8	38.5	37.9
1003		37.6	37.7	38.3	38.4	38.6	38.5	38.4
1004		37.4	37.3	37.7	38.2	38.4	38.3	38.0
1005		37.4	38.0	38.3	38.1	37.5	37.7	37.7
1006		37.4	37.5	37.6	37.6	37.9	37.8	37.9
<b>150 mg [REDACTED] kg</b>								
1001		37.5	37.5	37.6	37.9	37.8	37.7	38.4
1002		37.6	37.9	38.4	38.7	39.0	38.6	38.1
1003		38.0	37.9	38.4	38.7	39.0	39.2	39.0

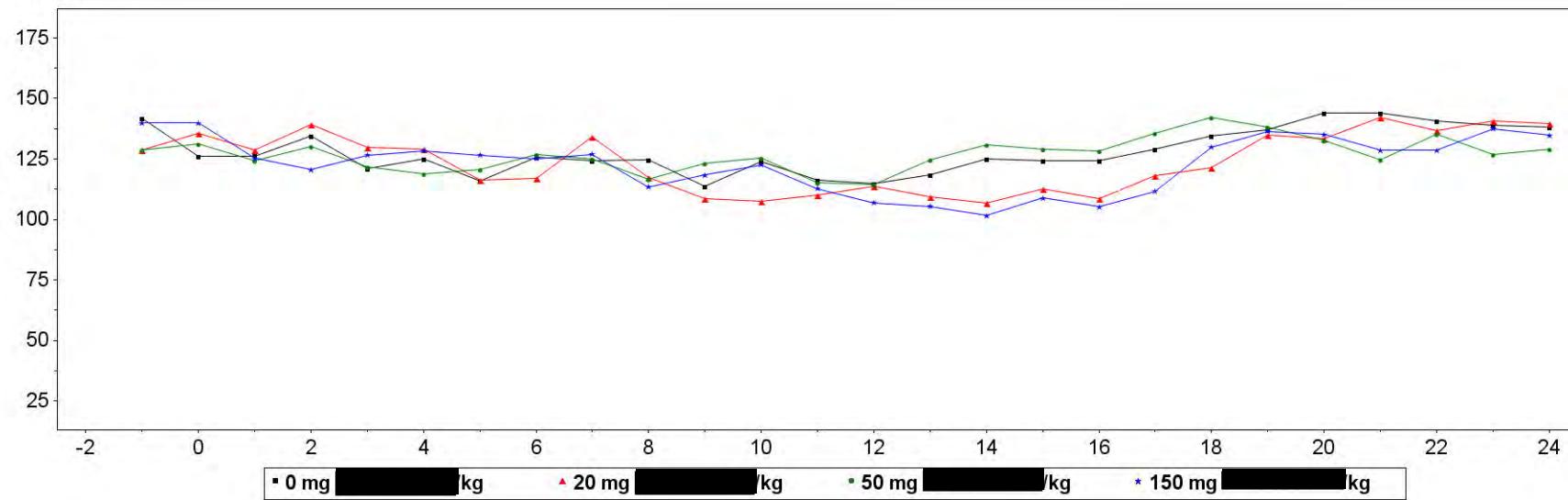
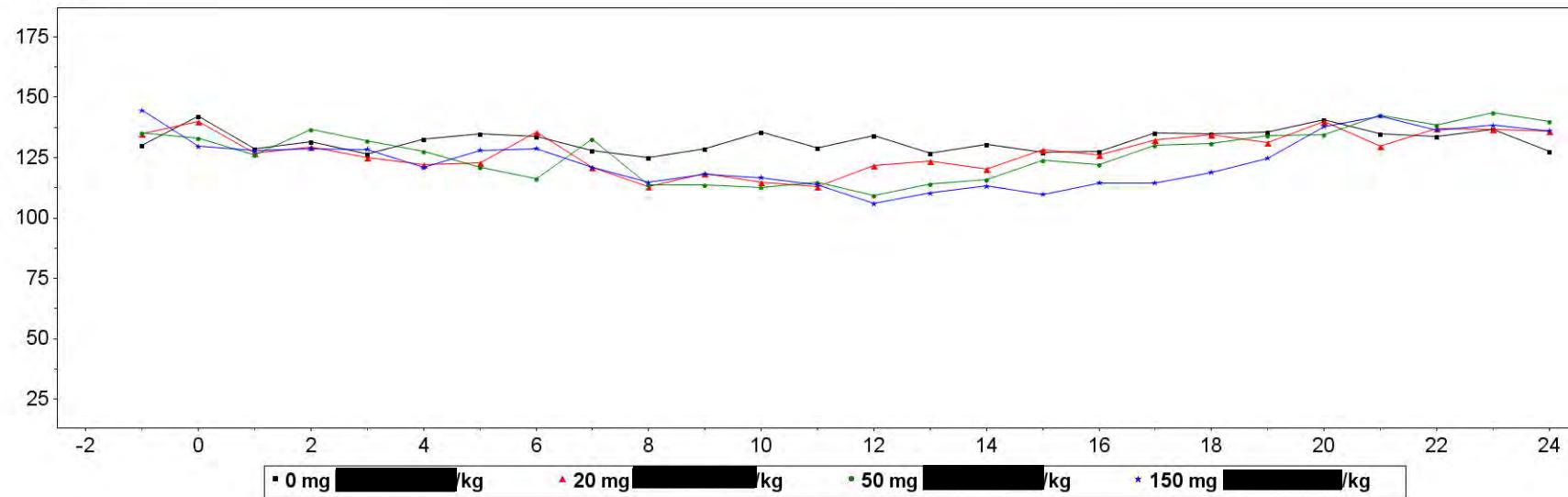
[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual Body Temperature, °C - MALE**

Group, Animal Number	Study Interval (hour:minute)							
	17:00	18:00	19:00	20:00	21:00	22:00	23:00	24:00
<u>150 mg [REDACTED] kg</u>								
1004	37.4	37.6	37.9	38.1	38.3	38.0	37.9	38.0
1005	37.6	37.4	38.0	38.0	37.6	37.8	37.8	37.8
1006	37.9	37.9	37.8	37.9	38.1	38.0	37.9	37.9

**Appendix 7**  
**Individual Systolic Blood Pressure**

**Individual Systolic Blood Pressure, mmHg vs. Time, Hour****1001 M****1002 M**

**Individual Systolic Blood Pressure, mmHg vs. Time, Hour****1003 M****1004 M**

**Individual Systolic Blood Pressure, mmHg vs. Time, Hour****1005 M****1006 M**

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual Systolic Blood Pressure, mmHg - MALE**

Group, Animal Number	Study Interval (hour:minute)	-1:00	0:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00
	<u>0 mg [REDACTED] kg</u>									
1001		122	128	128	130	128	117	136	121	124
1002		120	139	131	127	119	110	120	125	133
1003		138	157	154	161	156	133	137	131	128
1004		128	144	129	133	129	122	123	124	122
1005		142	126	126	134	121	125	116	126	124
1006		130	142	129	132	127	133	135	134	128
	<u>20 mg [REDACTED] kg</u>									
1001		146	121	133	127	132	127	126	131	125
1002		129	142	132	137	125	126	119	124	136
1003		150	158	153	159	145	147	140	148	128
1004		143	134	134	123	118	122	115	134	124
1005		129	136	129	139	130	129	116	117	134
1006		135	140	127	129	125	122	123	136	121
	<u>50 mg [REDACTED] kg</u>									
1001		132	125	123	127	124	125	120	124	124
1002		138	129	125	119	120	122	109	122	132
1003		163	151	148	149	146	147	146	143	129
1004		130	146	131	144	139	136	126	123	122
1005		129	131	124	130	122	119	121	127	125
1006		135	133	126	137	132	128	121	116	133
	<u>150 mg [REDACTED] kg</u>									
1001		126	130	131	129	129	132	119	131	117
1002		127	137	133	140	131	121	116	123	121
1003		156	160	141	147	139	137	130	130	130

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual Systolic Blood Pressure, mmHg - MALE**

Group, Animal Number	Study Interval (hour:minute)	Individual Systolic Blood Pressure, mmHg - MALE								
		-1:00	0:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00
<u>150 mg [REDACTED] kg</u>										
1004		125	134	124	130	135	123	118	120	126
1005		140	140	125	121	127	128	127	125	127
1006		145	130	128	129	128	121	128	129	121

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual Systolic Blood Pressure, mmHg - MALE**

Group, Animal Number	Study Interval (hour:minute)	8:00	9:00	10:00	11:00	12:00	13:00	14:00	15:00	16:00
	<u>0 mg [REDACTED] kg</u>									
1001		116	113	115	114	114	115	114	120	129
1002		121	128	130	129	132	136	134	138	134
1003		125	120	121	126	122	121	122	120	127
1004		108	120	116	129	126	124	130	133	131
1005		124	114	124	116	115	119	125	124	124
1006		125	129	136	129	134	127	130	127	128
	<u>20 mg [REDACTED] kg</u>									
1001		125	127	130	129	129	133	128	142	138
1002		114	114	119	112	108	108	108	109	111
1003		120	115	127	121	120	130	127	127	127
1004		109	117	118	131	128	133	134	134	129
1005		117	109	108	110	114	109	107	113	109
1006		113	119	115	113	122	123	120	128	126
	<u>50 mg [REDACTED] kg</u>									
1001		123	128	120	116	116	117	121	122	122
1002		113	117	110	121	117	114	117	121	123
1003		130	118	118	119	121	116	119	121	123
1004		113	118	112	107	117	118	124	121	126
1005		117	123	125	115	114	125	131	129	128
1006		114	114	113	115	109	114	116	124	122
	<u>150 mg [REDACTED] kg</u>									
1001		116	120	113	115	112	119	115	116	120
1002		115	115	107	104	108	106	114	110	109
1003		120	119	126	127	125	119	121	122	129

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual Systolic Blood Pressure, mmHg - MALE**

Group, Animal Number	Study Interval (hour:minute)	8:00	9:00	10:00	11:00	12:00	13:00	14:00	15:00	16:00
	150 mg [REDACTED] kg									
1004		120	119	116	117	115	125	118	114	119
1005		113	118	123	113	107	105	102	109	105
1006		115	118	117	114	106	110	113	110	114

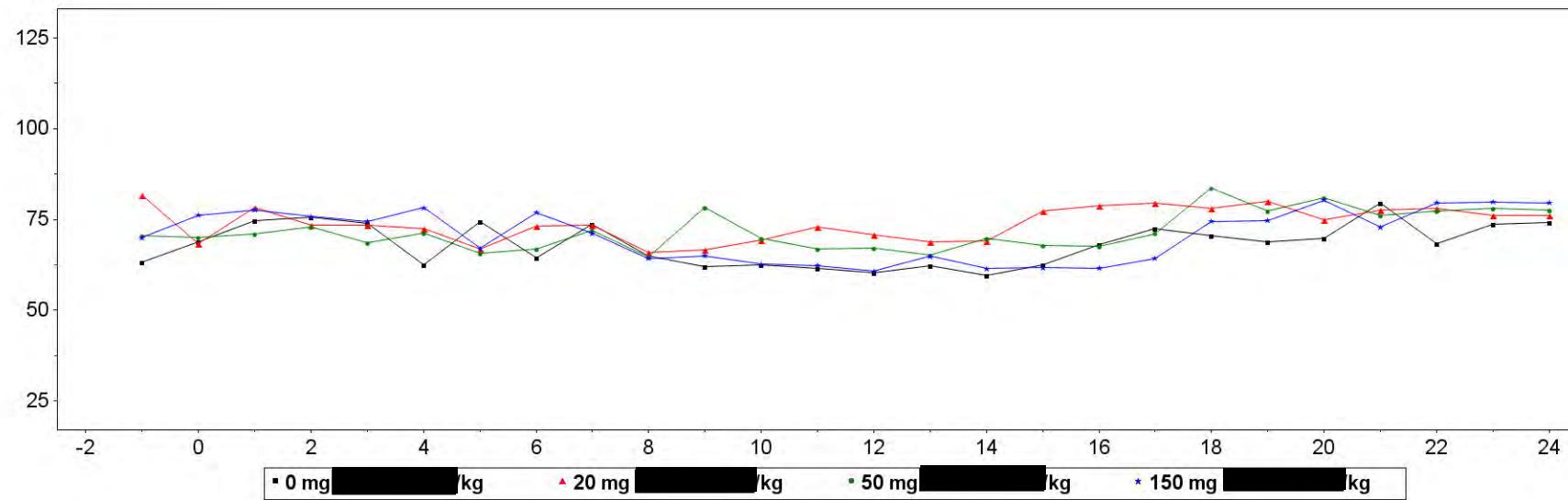
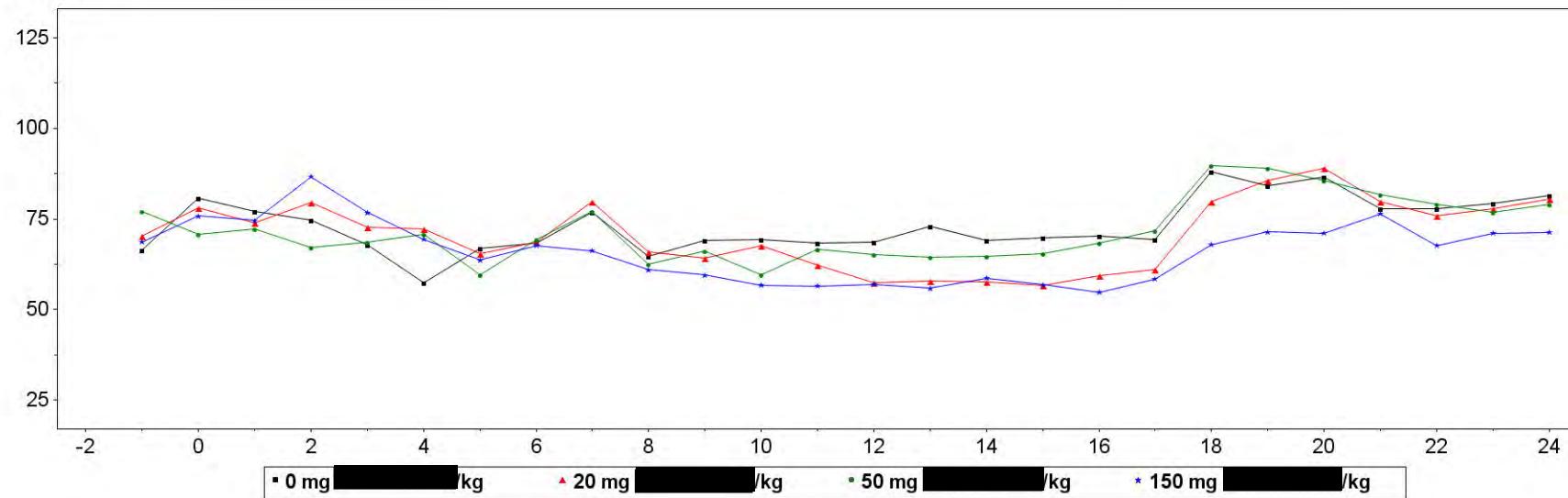
[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual Systolic Blood Pressure, mmHg - MALE**

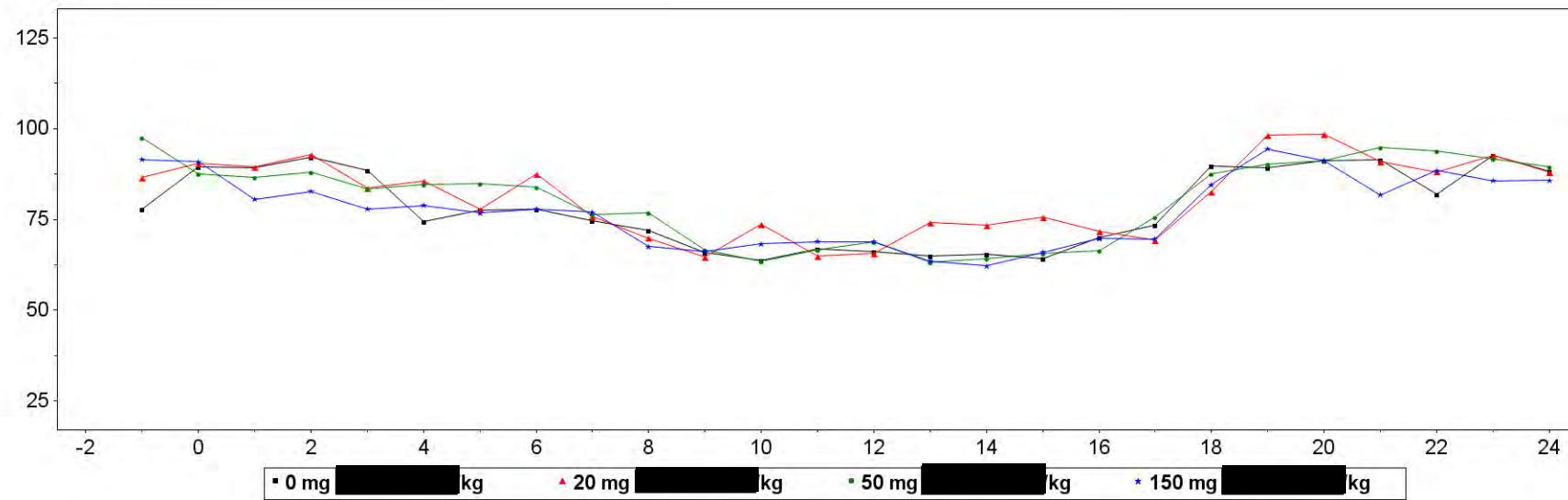
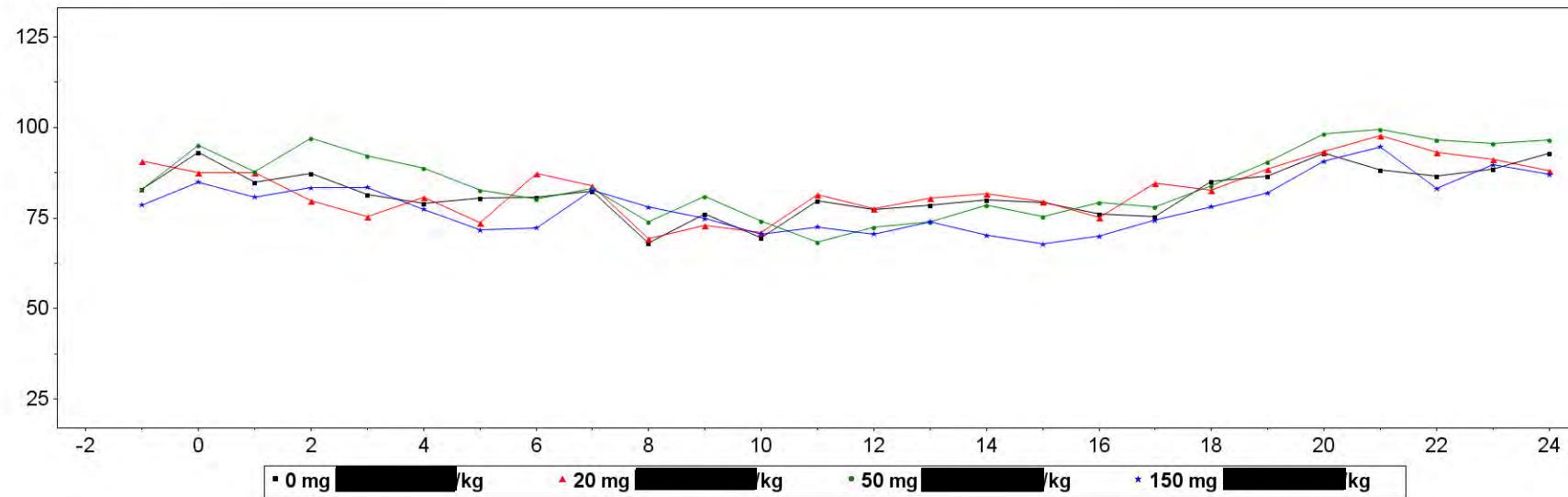
Group, Animal Number	Study Interval (hour:minute)	17:00	18:00	19:00	20:00	21:00	22:00	23:00	24:00
<b>0 mg [REDACTED] kg</b>									
1001		129	126	120	124	134	122	129	129
1002		135	156	152	157	141	140	143	145
1003		128	152	155	159	160	144	158	155
1004		126	133	136	143	137	133	134	142
1005		129	135	137	144	144	141	139	138
1006		135	135	135	141	135	134	137	128
<b>20 mg [REDACTED] kg</b>									
1001		142	130	141	131	134	136	129	130
1002		115	138	146	154	138	133	134	143
1003		125	143	164	165	157	154	160	155
1004		132	130	137	146	151	146	142	137
1005		118	121	135	134	142	137	141	140
1006		132	135	131	140	130	137	137	136
<b>50 mg [REDACTED] kg</b>									
1001		127	137	129	135	127	130	130	127
1002		127	157	158	153	144	139	135	136
1003		131	153	155	157	161	161	157	157
1004		125	128	139	150	153	146	146	149
1005		135	142	138	133	125	135	127	129
1006		130	131	134	135	142	138	143	140
<b>150 mg [REDACTED] kg</b>									
1001		122	127	126	134	125	135	134	133
1002		113	124	130	128	134	117	125	125
1003		127	143	155	143	127	139	138	135

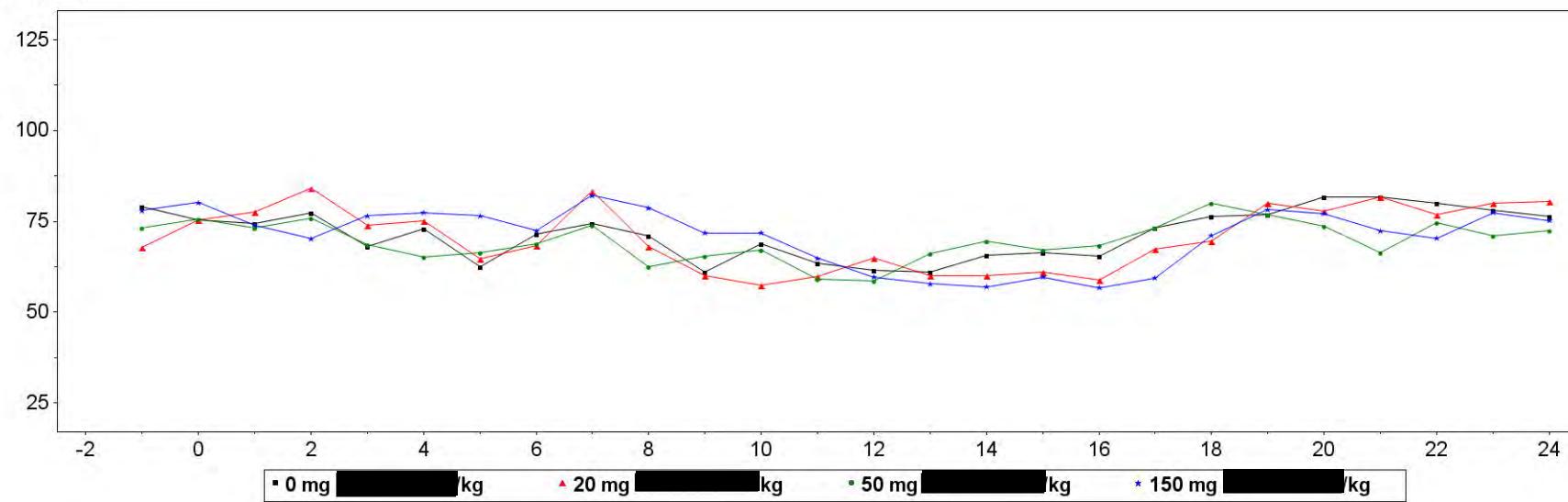
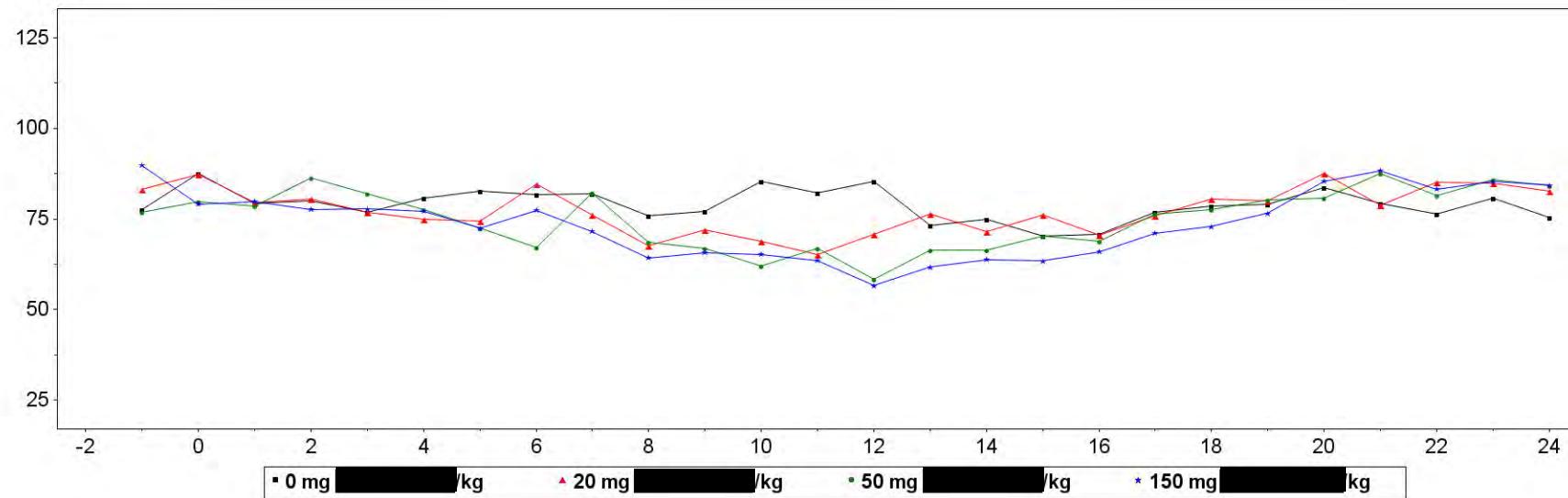
[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual Systolic Blood Pressure, mmHg - MALE**

Group, Animal Number	Study Interval (hour:minute)							
	17:00	18:00	19:00	20:00	21:00	22:00	23:00	24:00
<u>150 mg [REDACTED] kg</u>								
1004		122	121	125	139	148	130	139
1005		112	130	136	135	129	129	137
1006		115	119	125	138	142	136	138

**Appendix 8**  
**Individual Diastolic Blood Pressure**

**Individual Diastolic Blood Pressure, mmHg vs. Time, Hour****1001 M****1002 M**

**Individual Diastolic Blood Pressure, mmHg vs. Time, Hour****1003 M****1004 M**

**Individual Diastolic Blood Pressure, mmHg vs. Time, Hour****1005 M****1006 M**

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual Diastolic Blood Pressure, mmHg - MALE**

Group, Animal Number	Study Interval (hour:minute)	Individual Diastolic Blood Pressure, mmHg - MALE								
		-1:00	0:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00
<b>0 mg [REDACTED] kg</b>										
1001		63	69	75	76	74	62	74	64	74
1002		66	81	77	75	68	57	67	68	77
1003		78	89	89	92	89	74	78	78	75
1004		83	93	85	87	81	79	81	81	82
1005		79	75	74	77	68	73	62	71	74
1006		78	87	79	80	77	81	83	82	82
<b>20 mg [REDACTED] kg</b>										
1001		82	68	78	73	73	72	67	73	73
1002		70	78	74	80	73	72	65	69	80
1003		86	90	90	93	84	86	78	88	76
1004		91	88	87	80	75	81	74	87	84
1005		68	75	78	84	74	75	65	68	83
1006		83	87	80	81	77	75	74	85	76
<b>50 mg [REDACTED] kg</b>										
1001		71	70	71	73	69	71	66	67	72
1002		77	71	72	67	69	71	60	69	77
1003		97	87	87	88	83	85	85	84	76
1004		83	95	88	97	92	89	83	80	83
1005		73	76	73	76	68	65	66	69	74
1006		77	80	78	86	82	78	72	67	82
<b>150 mg [REDACTED] kg</b>										
1001		70	76	78	76	74	78	67	77	71
1002		69	76	75	87	77	69	64	68	66
1003		91	91	81	83	78	79	77	78	77

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual Diastolic Blood Pressure, mmHg - MALE**

Group, Animal Number	Study Interval (hour:minute)	Individual Diastolic Blood Pressure, mmHg - MALE								
		-1:00	0:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00
<u>150 mg [REDACTED] kg</u>										
1004		79	85	81	83	83	77	72	72	83
1005		78	80	74	70	77	77	77	72	82
1006		90	79	80	78	78	77	72	77	72

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual Diastolic Blood Pressure, mmHg - MALE**

Group, Animal Number	Study Interval (hour:minute)	Individual Diastolic Blood Pressure, mmHg - MALE								
		8:00	9:00	10:00	11:00	12:00	13:00	14:00	15:00	16:00
<b>0 mg [REDACTED] kg</b>										
1001		65	62	63	61	60	62	59	63	68
1002		65	69	69	68	69	73	69	70	70
1003		72	66	64	67	66	65	65	64	70
1004		68	76	69	80	77	79	80	79	76
1005		71	61	69	63	62	61	66	66	65
1006		76	77	85	82	85	73	75	70	71
<b>20 mg [REDACTED] kg</b>										
1001		66	67	69	73	71	69	69	77	79
1002		66	64	68	62	57	58	58	57	59
1003		70	65	74	65	66	74	73	76	72
1004		69	73	71	81	77	81	82	79	75
1005		68	60	57	60	65	60	60	61	59
1006		67	72	69	65	71	76	71	76	71
<b>50 mg [REDACTED] kg</b>										
1001		65	78	70	67	67	65	70	68	68
1002		62	66	60	67	65	64	65	65	68
1003		77	67	64	67	69	63	64	66	66
1004		74	81	74	68	72	74	79	75	79
1005		63	65	67	59	58	66	69	67	68
1006		68	67	62	67	58	66	66	70	69
<b>150 mg [REDACTED] kg</b>										
1001		64	65	63	62	61	65	61	62	62
1002		61	59	57	56	57	56	59	57	55
1003		67	66	68	69	69	63	62	66	70

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual Diastolic Blood Pressure, mmHg - MALE**

Group, Animal Number	Study Interval (hour:minute)	Individual Diastolic Blood Pressure, mmHg - MALE								
		8:00	9:00	10:00	11:00	12:00	13:00	14:00	15:00	16:00
<u>150 mg [REDACTED] kg</u>										
1004		78	75	71	73	71	74	70	68	70
1005		79	72	72	65	60	58	57	60	57
1006		64	66	65	64	57	62	64	63	66

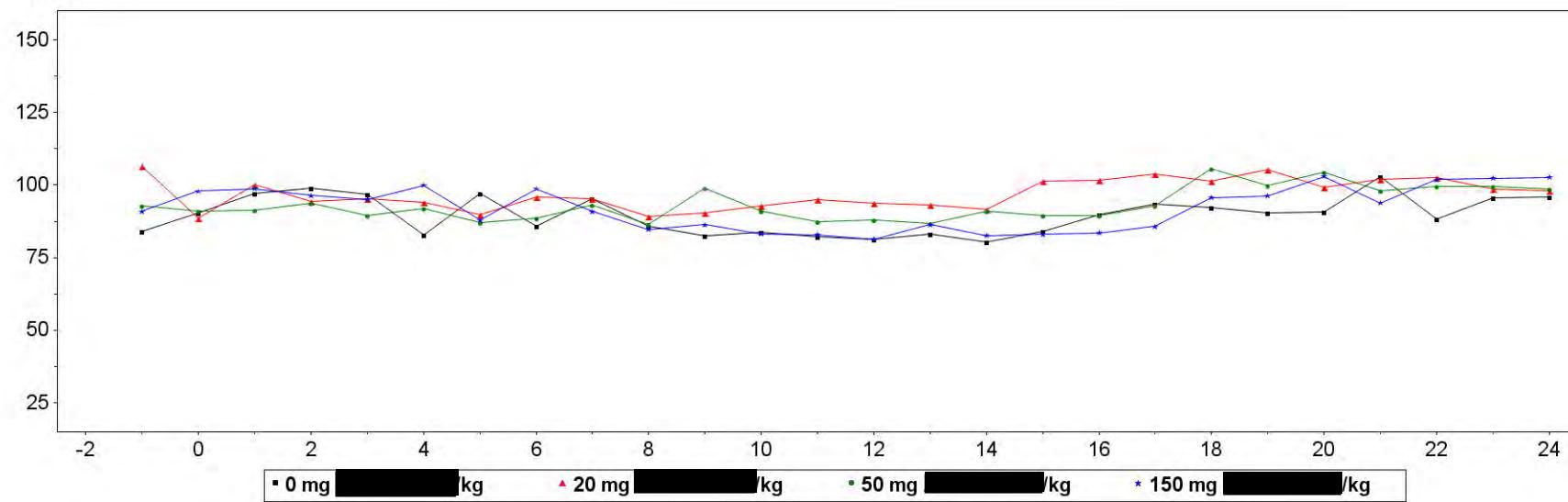
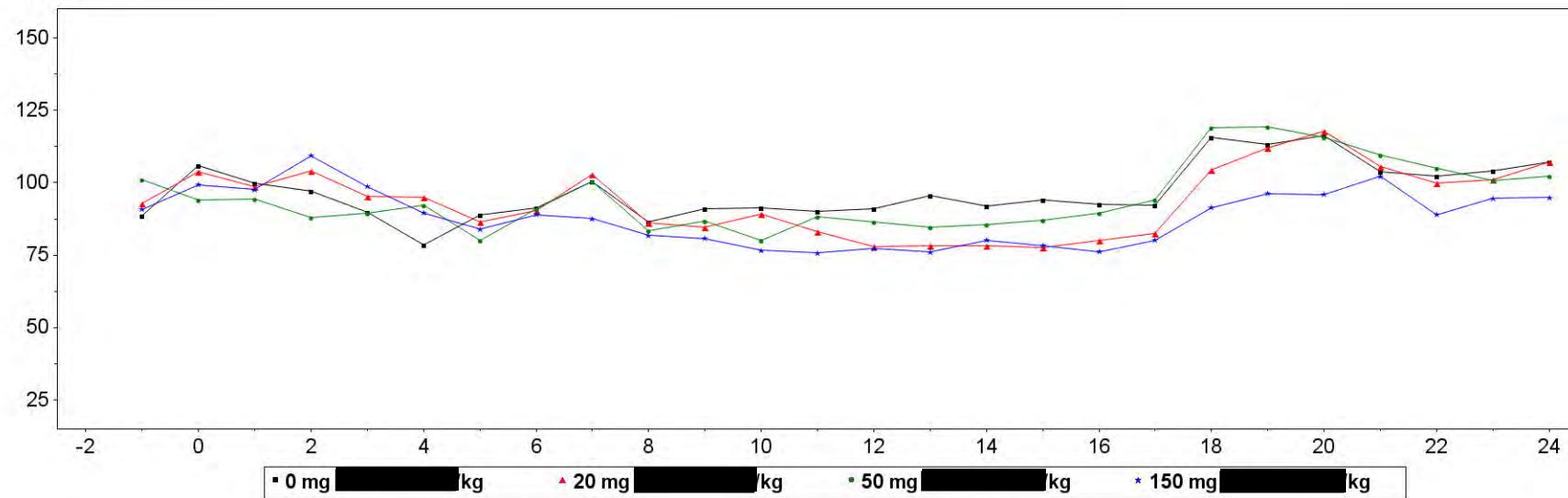
[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual Diastolic Blood Pressure, mmHg - MALE**

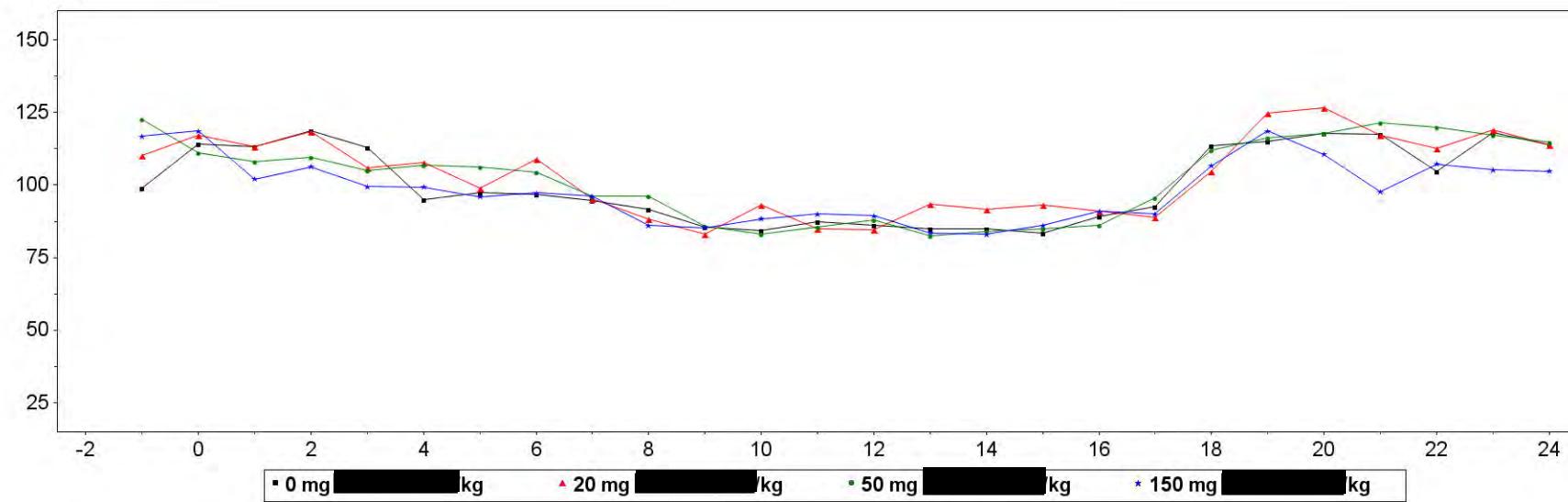
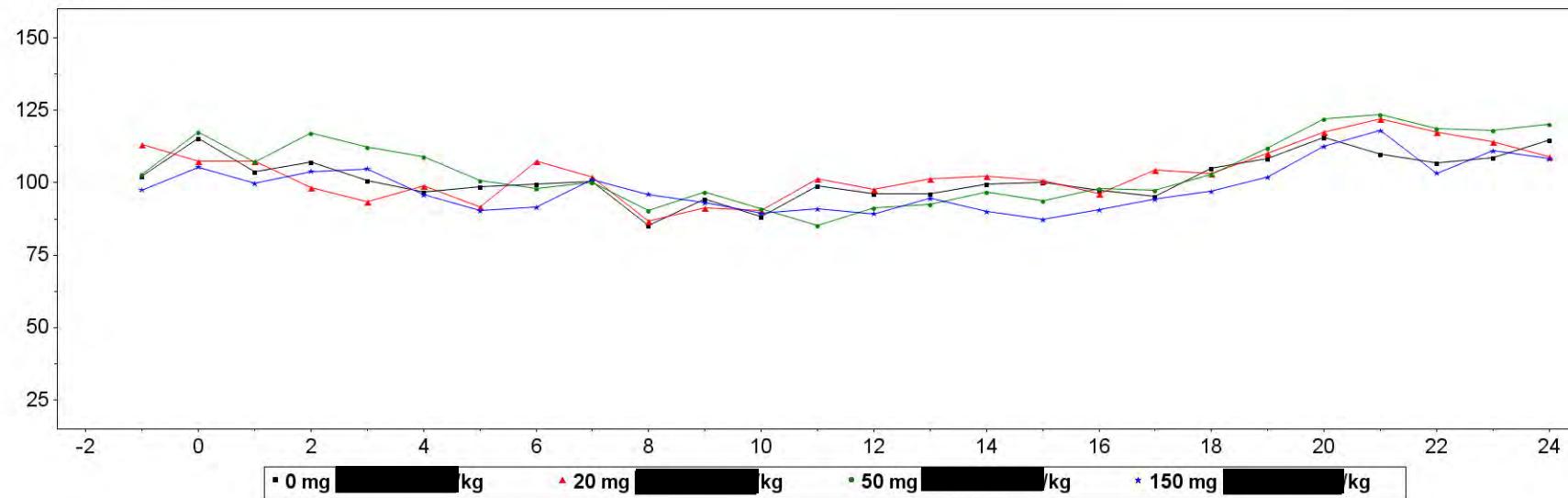
Group, Animal Number	Study Interval (hour:minute)	Individual Diastolic Blood Pressure, mmHg - MALE						
		17:00	18:00	19:00	20:00	21:00	22:00	23:00
0 mg [REDACTED] kg								
1001		72	70	69	70	80	68	74
1002		69	88	84	87	78	78	79
1003		73	90	89	91	91	82	93
1004		75	85	87	93	88	87	89
1005		73	76	77	82	82	80	78
1006		77	79	79	84	79	76	81
20 mg [REDACTED] kg								
1001		79	78	80	75	78	78	76
1002		61	80	85	89	80	76	78
1003		69	83	98	99	91	88	93
1004		85	83	88	93	98	93	91
1005		67	69	80	78	82	77	80
1006		76	81	80	88	79	85	85
50 mg [REDACTED] kg								
1001		71	84	77	81	76	77	78
1002		72	90	89	86	82	79	77
1003		76	88	90	91	95	94	92
1004		78	84	90	98	99	97	96
1005		73	80	77	74	66	75	71
1006		76	78	80	81	88	81	86
150 mg [REDACTED] kg								
1001		64	74	75	80	73	80	80
1002		58	68	71	71	76	68	71
1003		70	85	94	91	82	88	86

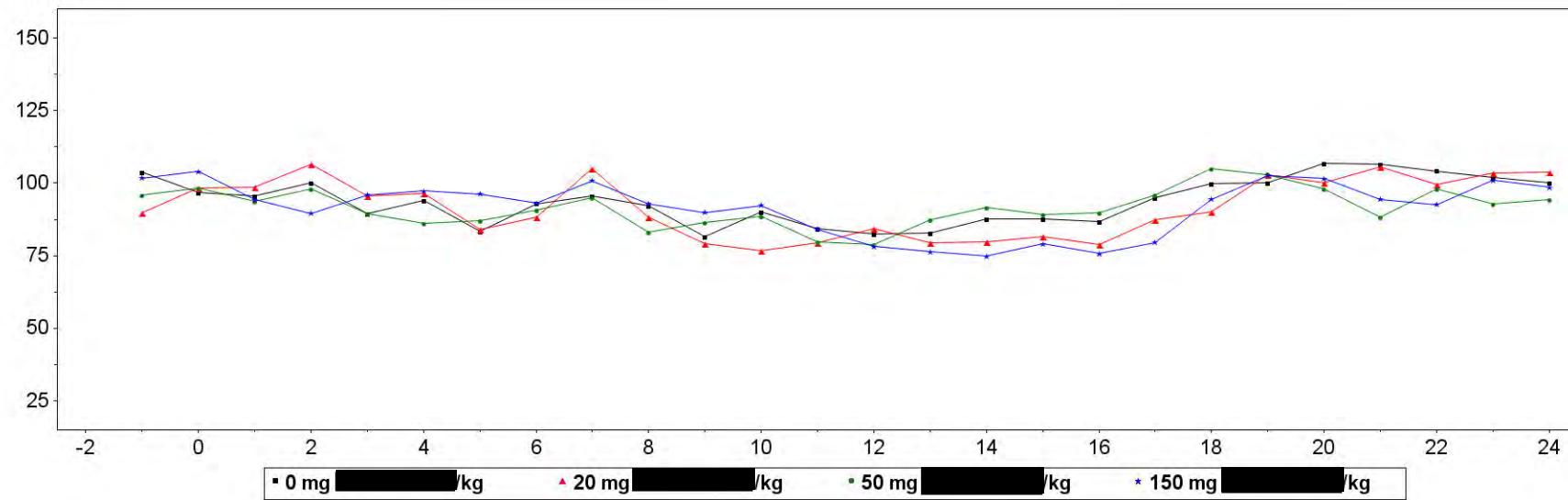
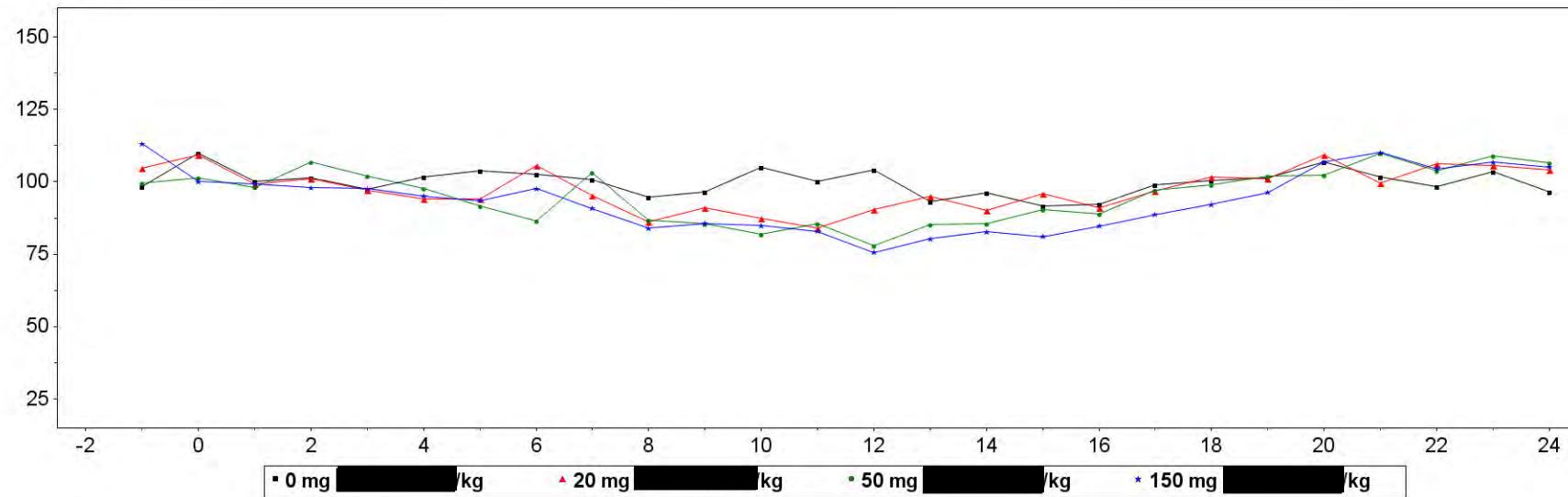
[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual Diastolic Blood Pressure, mmHg - MALE**

Group, Animal Number	Study Interval (hour:minute)							
	17:00	18:00	19:00	20:00	21:00	22:00	23:00	24:00
<u>150 mg [REDACTED] kg</u>								
1004	74	78	82	91	95	83	90	87
1005	59	71	78	77	72	70	77	75
1006	71	73	77	85	88	83	85	84

**Appendix 9**  
**Individual Mean Arterial Blood Pressure**

**Individual Mean Arterial Blood Pressure, mmHg vs. Time, Hour****1001 M****1002 M**

**Individual Mean Arterial Blood Pressure, mmHg vs. Time, Hour****1003 M****1004 M**

**Individual Mean Arterial Blood Pressure, mmHg vs. Time, Hour****1005 M****1006 M**

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual Mean Arterial Blood Pressure, mmHg - MALE**

Group, Animal Number	Study Interval (hour:minute)	Individual Mean Arterial Blood Pressure, mmHg - MALE								
		-1:00	0:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00
<b>0 mg [REDACTED] kg</b>										
1001		84	91	97	99	97	83	97	86	95
1002		89	106	100	97	90	79	89	91	100
1003		99	114	113	119	113	95	97	97	95
1004		102	115	104	107	101	97	99	100	100
1005		104	97	96	100	89	94	83	93	96
1006		98	110	100	101	97	102	104	103	101
<b>20 mg [REDACTED] kg</b>										
1001		107	89	100	94	95	94	90	96	95
1002		93	104	99	104	95	95	87	90	103
1003		110	117	113	118	106	108	99	109	95
1004		113	108	107	98	93	99	92	107	102
1005		90	98	99	107	95	96	84	88	105
1006		105	109	99	101	97	94	94	106	95
<b>50 mg [REDACTED] kg</b>										
1001		93	91	91	94	89	92	87	89	93
1002		101	94	94	88	89	92	80	91	100
1003		123	111	108	110	105	107	106	104	96
1004		103	118	107	117	112	109	101	98	100
1005		96	98	94	98	90	86	87	91	95
1006		100	101	98	107	102	98	92	87	103
<b>150 mg [REDACTED] kg</b>										
1001		91	98	99	96	95	100	88	99	91
1002		91	99	98	109	99	90	84	89	88
1003		117	119	102	106	99	99	96	97	96

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual Mean Arterial Blood Pressure, mmHg - MALE**

Group, Animal Number	Study Interval (hour:minute)	Individual Mean Arterial Blood Pressure, mmHg - MALE								
		-1:00	0:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00
<u>150 mg [REDACTED] kg</u>										
1004		97	105	100	104	105	96	90	92	101
1005		102	104	94	90	96	97	96	93	101
1006		113	100	99	98	98	95	94	98	91

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual Mean Arterial Blood Pressure, mmHg - MALE**

Group, Animal Number	Study Interval (hour:minute)	Individual Mean Arterial Blood Pressure, mmHg - MALE								
		8:00	9:00	10:00	11:00	12:00	13:00	14:00	15:00	16:00
<b>0 mg [REDACTED] kg</b>										
1001		86	83	84	82	81	83	80	84	90
1002		86	91	91	90	91	96	92	94	93
1003		91	85	84	87	86	85	85	83	89
1004		85	94	88	99	96	96	99	100	97
1005		92	82	90	84	82	83	88	88	87
1006		95	96	105	100	104	93	96	92	92
<b>20 mg [REDACTED] kg</b>										
1001		89	90	93	95	94	93	92	101	102
1002		86	85	89	83	78	78	78	78	80
1003		88	83	93	85	85	94	92	93	91
1004		87	91	90	101	98	101	102	101	96
1005		88	79	77	80	84	79	80	82	79
1006		86	91	87	84	90	95	90	96	91
<b>50 mg [REDACTED] kg</b>										
1001		86	99	91	87	88	87	91	90	90
1002		83	87	80	88	87	85	85	87	90
1003		96	86	83	86	88	82	84	85	86
1004		90	97	91	85	91	92	97	94	98
1005		83	87	89	80	79	87	92	89	90
1006		87	85	82	86	78	85	85	91	89
<b>150 mg [REDACTED] kg</b>										
1001		85	86	83	83	81	86	83	83	83
1002		82	81	77	76	77	76	80	78	76
1003		86	85	88	90	89	83	83	86	91

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual Mean Arterial Blood Pressure, mmHg - MALE**

Group, Animal Number	Study Interval (hour:minute)	Individual Mean Arterial Blood Pressure, mmHg - MALE								
		8:00	9:00	10:00	11:00	12:00	13:00	14:00	15:00	16:00
150 mg [REDACTED] kg										
1004		96	93	89	91	89	95	90	87	91
1005		93	90	92	84	78	76	75	79	76
1006		84	86	85	83	76	80	83	81	85

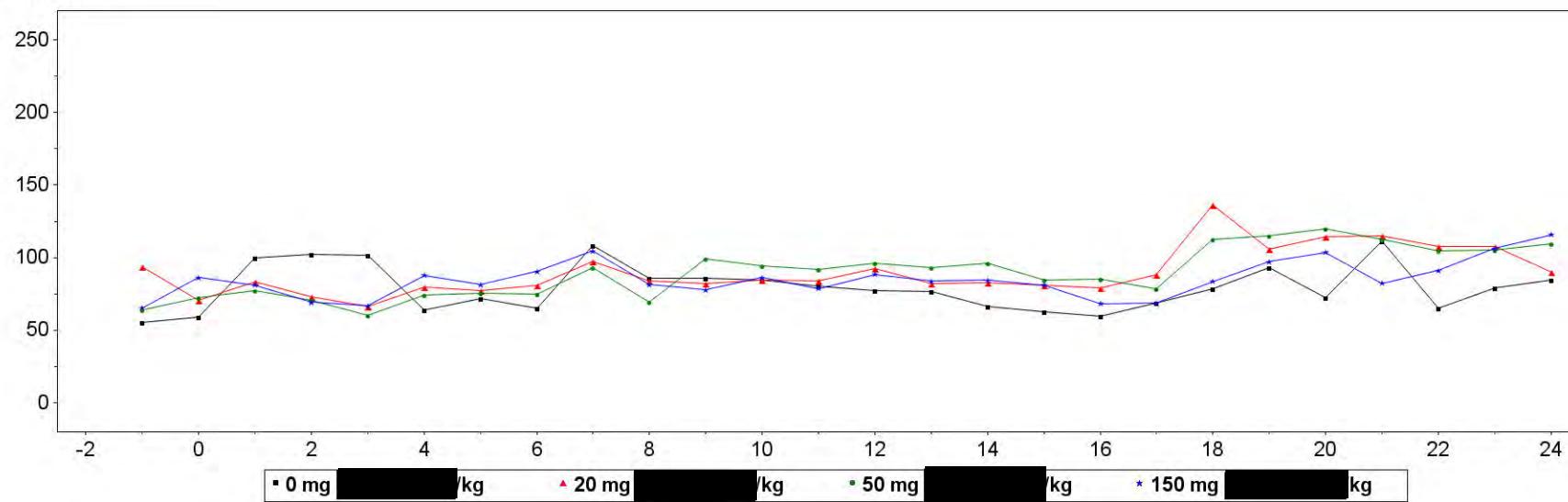
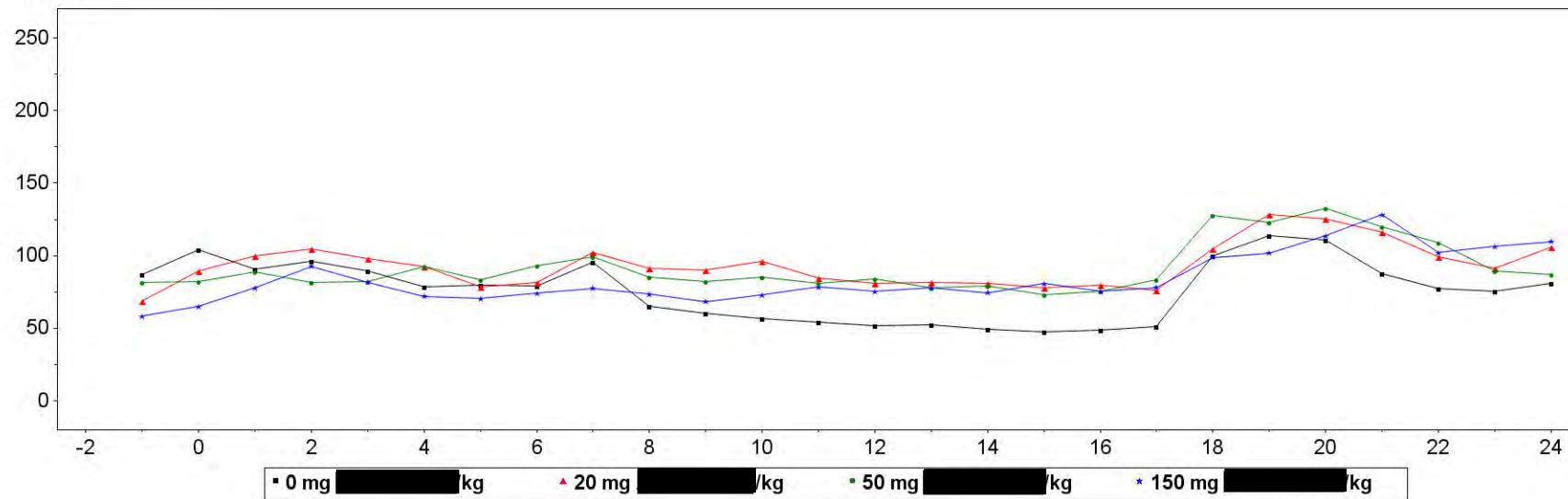
[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual Mean Arterial Blood Pressure, mmHg - MALE**

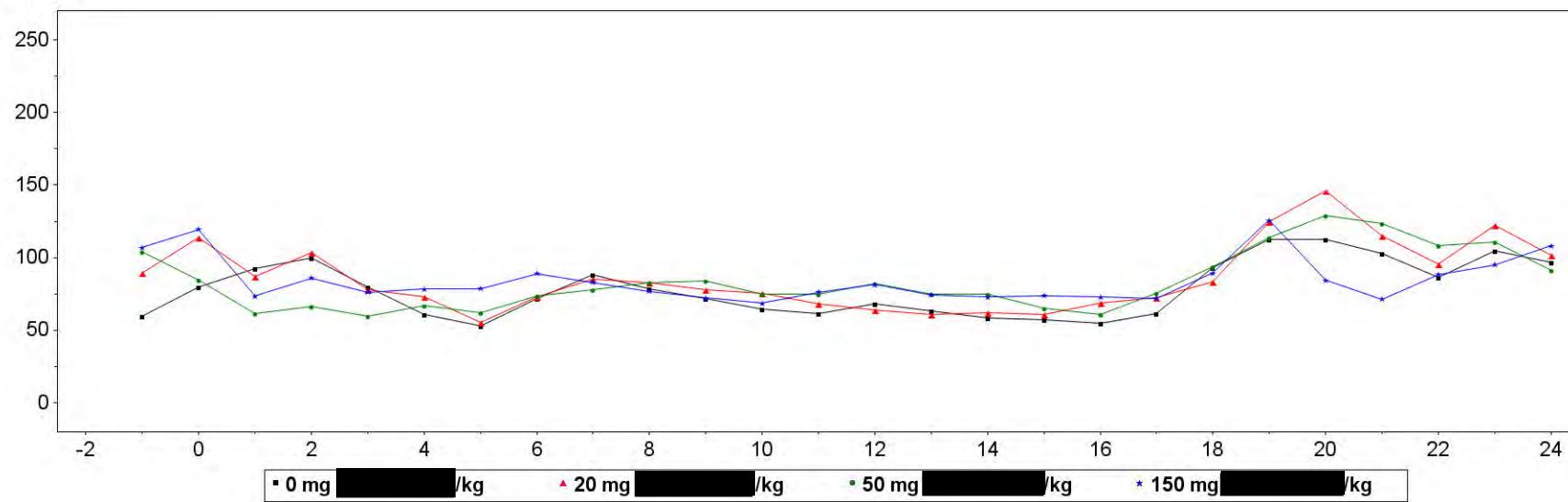
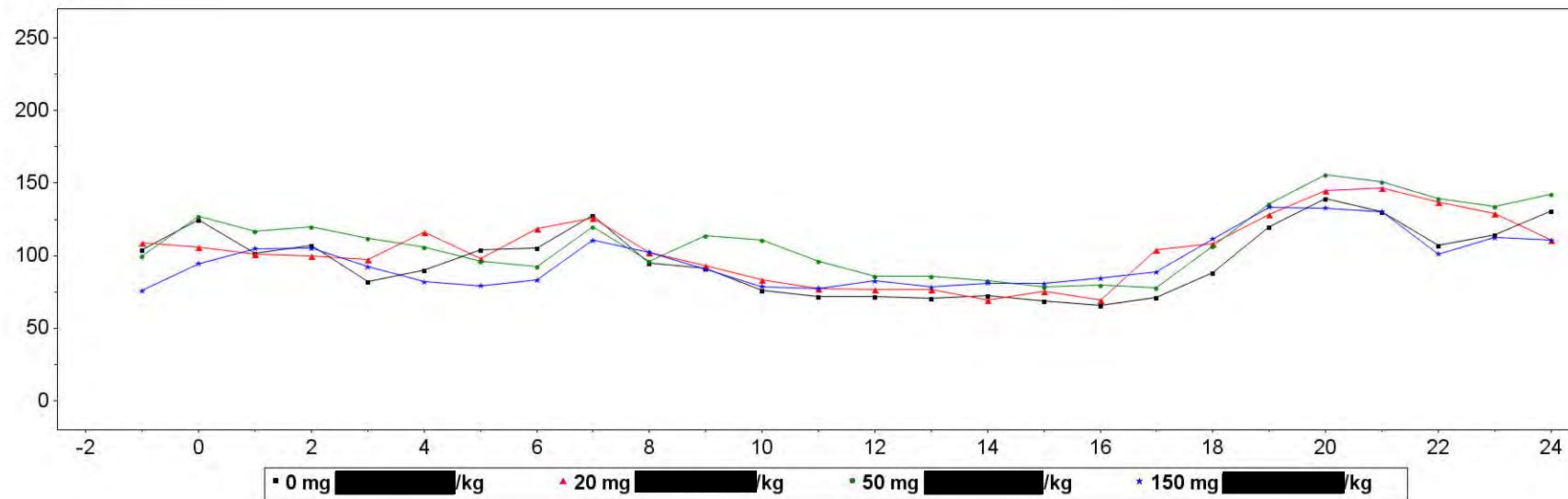
Group, Animal Number	Study Interval (hour:minute)	Individual Mean Arterial Blood Pressure, mmHg - MALE						
		17:00	18:00	19:00	20:00	21:00	22:00	23:00
<b>0 mg [REDACTED] kg</b>								
1001		93	92	90	91	103	88	96
1002		92	116	113	116	104	102	104
1003		93	114	115	118	118	105	118
1004		95	105	108	116	110	107	109
1005		95	100	100	107	107	104	102
1006		99	100	101	107	102	98	103
<b>20 mg [REDACTED] kg</b>								
1001		104	101	105	99	102	102	99
1002		83	104	112	118	105	100	101
1003		89	105	125	127	117	113	119
1004		104	103	110	118	122	117	114
1005		87	90	103	100	106	100	104
1006		97	102	101	109	100	106	104
<b>50 mg [REDACTED] kg</b>								
1001		93	106	100	104	98	100	100
1002		94	119	119	116	109	105	101
1003		96	112	116	118	121	120	117
1004		97	103	112	122	124	119	118
1005		96	105	103	98	88	98	93
1006		97	99	102	102	110	104	109
<b>150 mg [REDACTED] kg</b>								
1001		86	96	96	103	94	102	102
1002		80	91	96	96	102	89	95
1003		90	107	119	111	98	107	105

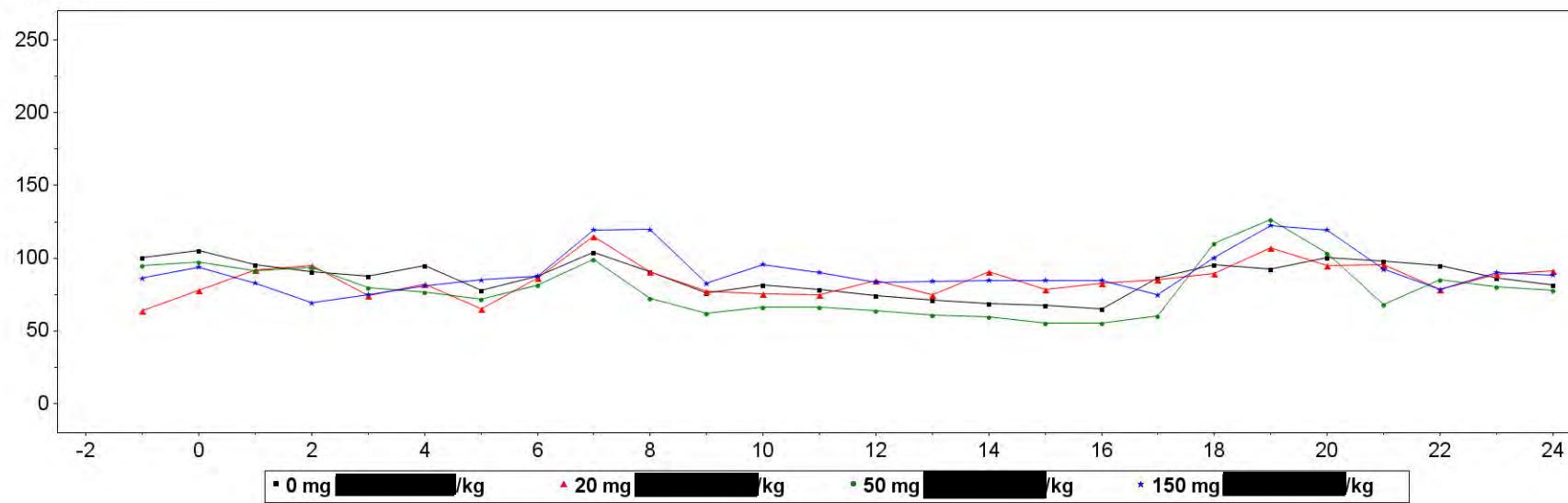
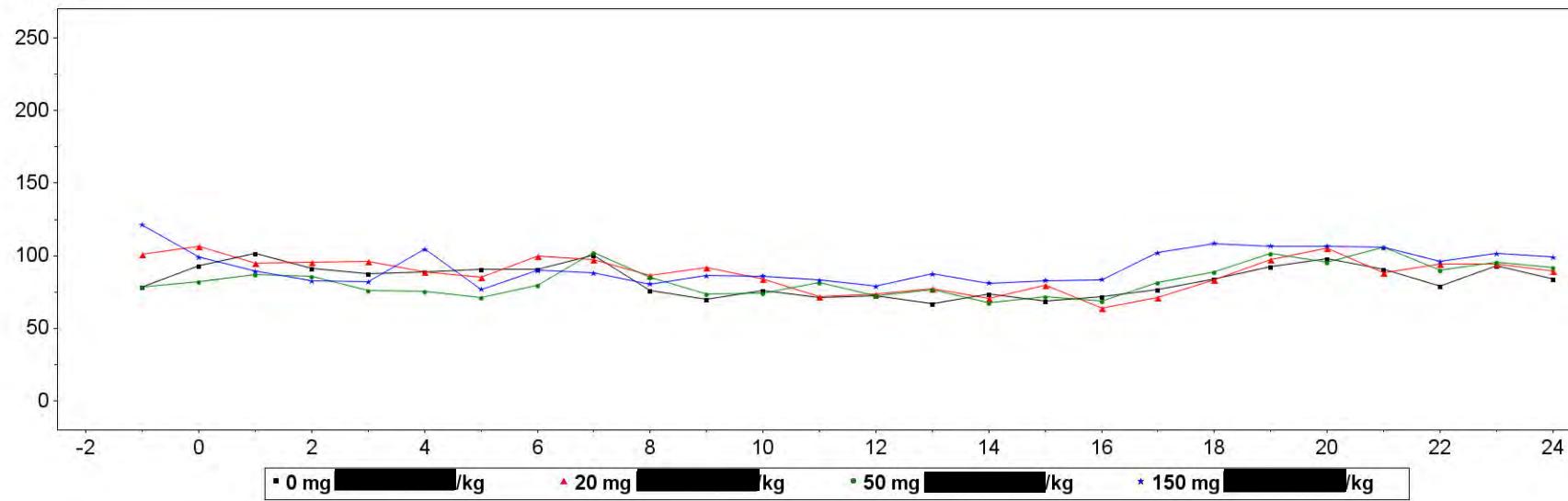
[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual Mean Arterial Blood Pressure, mmHg - MALE**

Group, Animal Number	Study Interval (hour:minute)							
	17:00	18:00	19:00	20:00	21:00	22:00	23:00	24:00
<u>150 mg [REDACTED] kg</u>								
1004	94	97	102	113	118	103	111	108
1005	80	94	103	102	94	93	101	98
1006	89	92	96	107	110	104	107	105

Appendix 10  
Individual Heart Rate

**Individual Heart Rate, beats/minute vs. Time, Hour****1001 M****1002 M**

**Individual Heart Rate, beats/minute vs. Time, Hour****1003 M****1004 M**

**Individual Heart Rate, beats/minute vs. Time, Hour****1005 M****1006 M**

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual Heart Rate, beats/minute - MALE**

Group, Animal Number	Study Interval (hour:minute)	Individual Heart Rate, beats/minute - MALE							
		-1:00	0:00	1:00	2:00	3:00	4:00	5:00	6:00
<b>0 mg [REDACTED] kg</b>									
1001	55	59	100	102	101	64	72	65	108
1002	87	104	91	96	89	79	80	79	95
1003	60	80	92	100	79	61	53	72	88
1004	104	124	102	107	82	90	104	105	128
1005	100	105	96	91	88	95	78	87	104
1006	78	93	102	92	88	89	91	91	100
<b>20 mg [REDACTED] kg</b>									
1001	94	70	83	73	66	80	77	81	97
1002	68	90	100	105	98	93	79	82	102
1003	90	114	87	104	78	73	55	73	85
1004	109	106	101	100	98	116	98	119	126
1005	64	78	92	95	74	82	65	86	115
1006	101	107	95	95	96	89	85	100	97
<b>50 mg [REDACTED] kg</b>									
1001	64	73	77	70	60	74	76	75	93
1002	81	82	89	81	82	93	83	93	99
1003	104	85	61	66	60	67	62	74	78
1004	100	127	117	120	112	106	96	93	120
1005	95	97	91	94	79	77	72	82	99
1006	78	82	87	86	76	76	71	80	102
<b>150 mg [REDACTED] kg</b>									
1001	65	86	81	69	67	88	81	91	105
1002	58	65	78	93	82	72	70	74	77
1003	107	119	73	86	76	78	79	89	83

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual Heart Rate, beats/minute - MALE**

Group, Animal Number	Study Interval (hour:minute)	Individual Heart Rate, beats/minute - MALE								
		-1:00	0:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00
<u>150 mg [REDACTED] kg</u>										
1004		76	94	105	105	92	82	79	83	111
1005		86	94	83	69	75	81	85	88	119
1006		121	99	89	83	82	104	77	90	88

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual Heart Rate, beats/minute - MALE**

Group, Animal Number	Study Interval (hour:minute)	Individual Heart Rate, beats/minute - MALE								
		8:00	9:00	10:00	11:00	12:00	13:00	14:00	15:00	16:00
<b>0 mg [REDACTED] kg</b>										
1001		86	86	84	80	78	77	66	63	60
1002		65	60	57	54	52	52	49	48	49
1003		78	72	65	62	68	64	58	57	55
1004		95	91	76	72	72	71	72	69	66
1005		91	76	82	78	74	71	69	68	65
1006		76	70	76	71	73	67	74	69	72
<b>20 mg [REDACTED] kg</b>										
1001		84	82	84	84	93	82	83	81	79
1002		92	90	96	85	81	82	81	78	79
1003		83	78	76	68	64	61	62	61	69
1004		102	93	84	77	77	77	69	75	69
1005		91	77	75	75	85	75	91	79	83
1006		87	92	84	72	74	77	70	79	64
<b>50 mg [REDACTED] kg</b>										
1001		69	99	94	92	96	93	96	85	85
1002		85	82	85	81	84	78	79	73	75
1003		83	84	75	75	82	75	75	65	61
1004		96	114	111	96	86	86	83	78	80
1005		73	62	67	67	64	61	59	55	55
1006		85	74	74	82	73	77	68	72	68
<b>150 mg [REDACTED] kg</b>										
1001		81	78	86	79	88	84	85	81	68
1002		74	68	73	78	75	78	74	81	75
1003		77	72	69	76	82	75	73	74	73

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual Heart Rate, beats/minute - MALE**

Group, Animal Number	Study Interval (hour:minute)	Individual Heart Rate, beats/minute - MALE								
		8:00	9:00	10:00	11:00	12:00	13:00	14:00	15:00	16:00
<u>150 mg [REDACTED] kg</u>										
1004		102	91	79	77	83	78	81	81	84
1005		120	83	96	90	84	84	85	85	85
1006		80	86	86	83	79	88	81	83	84

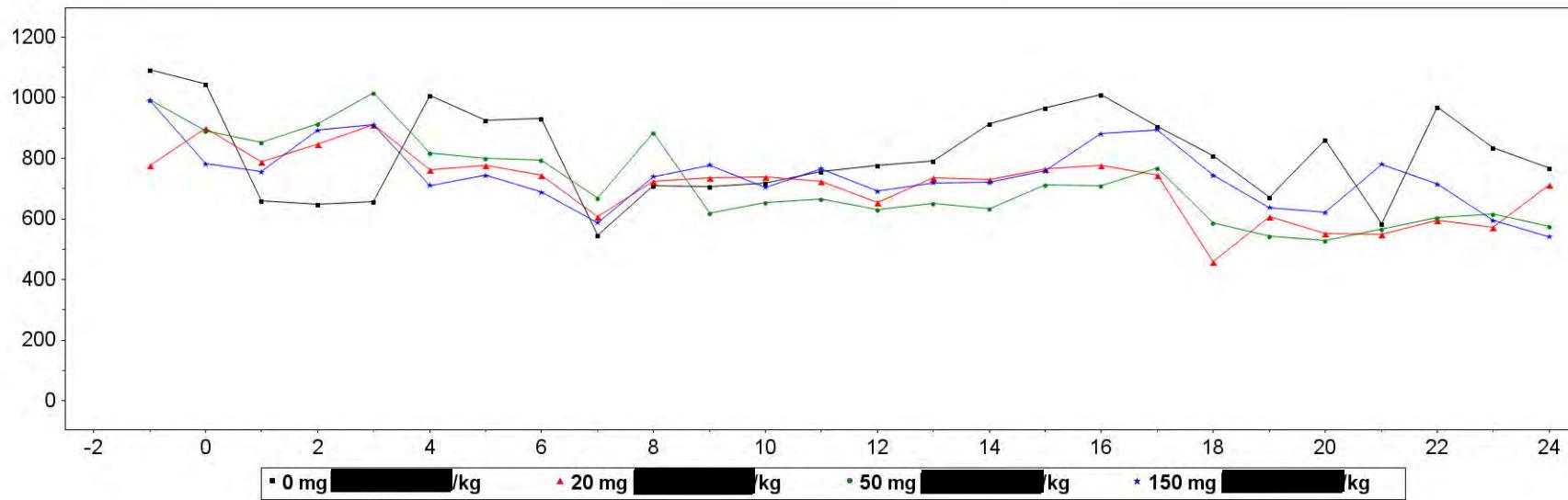
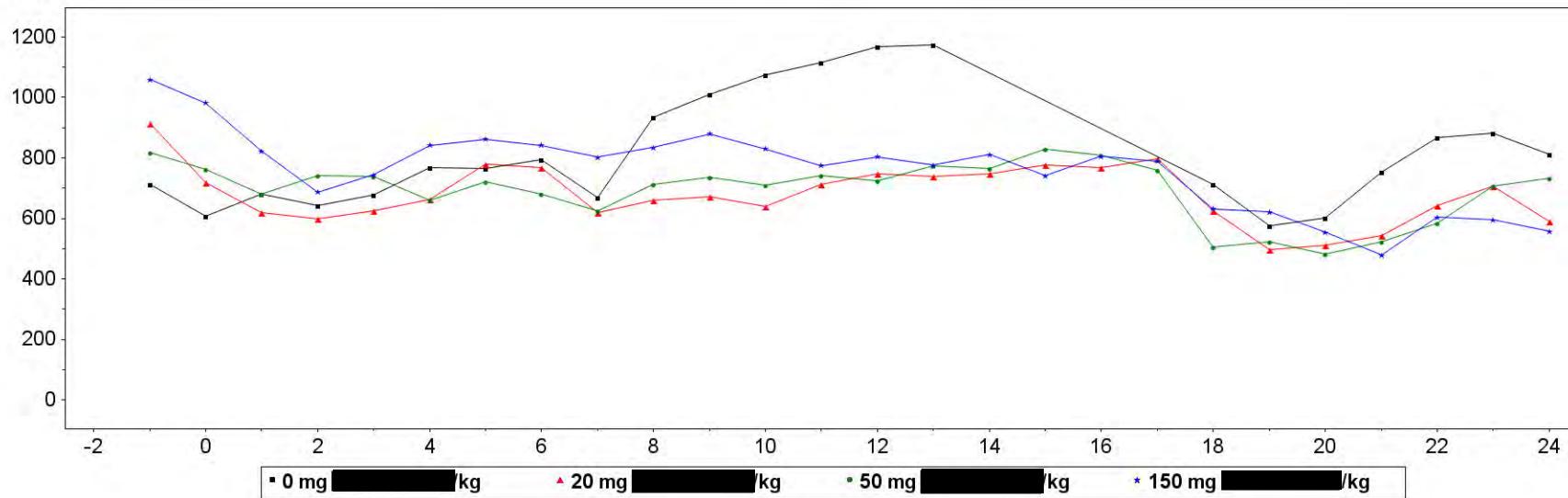
[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual Heart Rate, beats/minute - MALE**

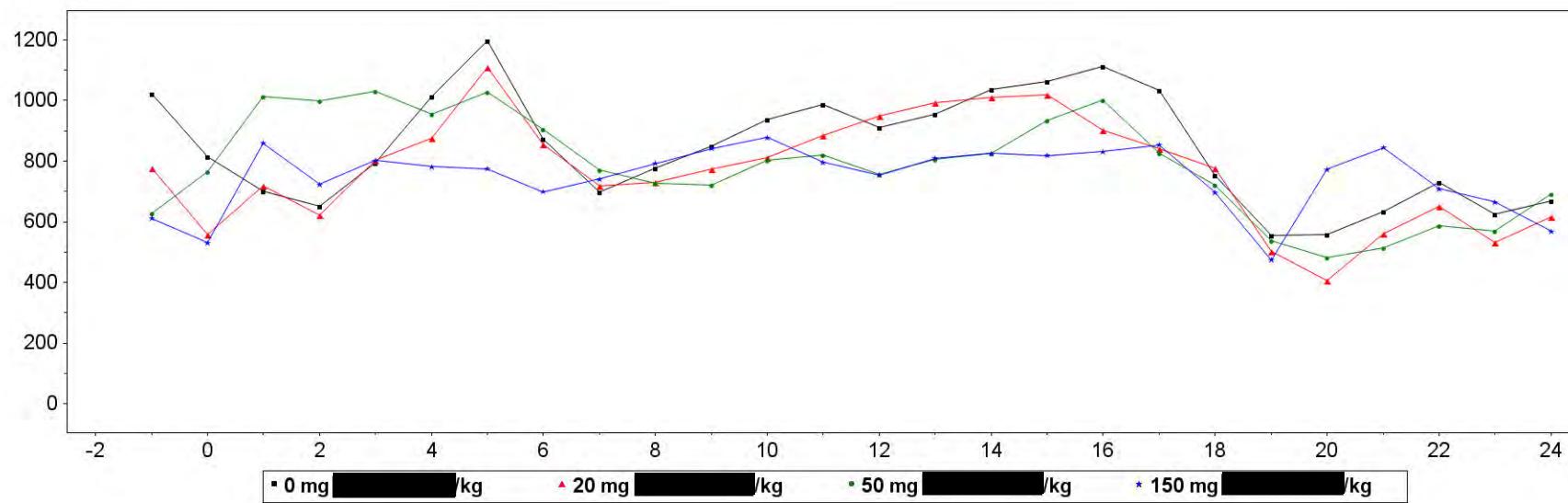
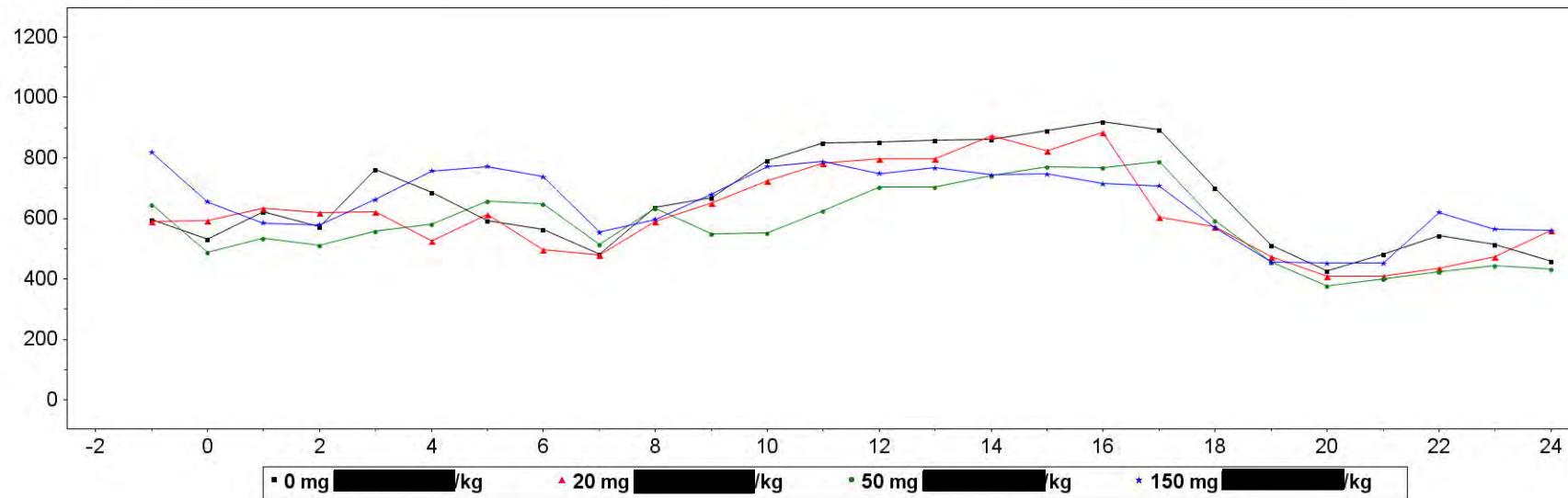
Group, Animal Number	Study Interval (hour:minute)	Individual Heart Rate, beats/minute - MALE						
		17:00	18:00	19:00	20:00	21:00	22:00	23:00
0 mg [REDACTED] kg								
1001		69	79	93	72	111	65	79
1002		51	100	113	111	87	78	75
1003		62	93	113	112	103	86	104
1004		71	88	120	140	130	107	114
1005		87	95	93	100	98	95	86
1006		77	84	92	98	91	79	93
20 mg [REDACTED] kg								
1001		88	136	106	115	115	108	108
1002		76	105	128	125	116	99	92
1003		73	84	125	146	115	96	122
1004		104	108	128	145	146	137	129
1005		85	89	107	95	95	79	89
1006		71	83	97	106	88	94	94
50 mg [REDACTED] kg								
1001		78	113	115	120	113	105	105
1002		84	128	123	133	120	109	89
1003		76	94	114	129	124	109	111
1004		78	106	136	156	151	139	134
1005		60	110	126	103	68	85	81
1006		82	89	101	95	106	90	96
150 mg [REDACTED] kg								
1001		69	83	97	104	82	91	106
1002		78	99	102	114	128	102	106
1003		72	89	126	84	71	88	95

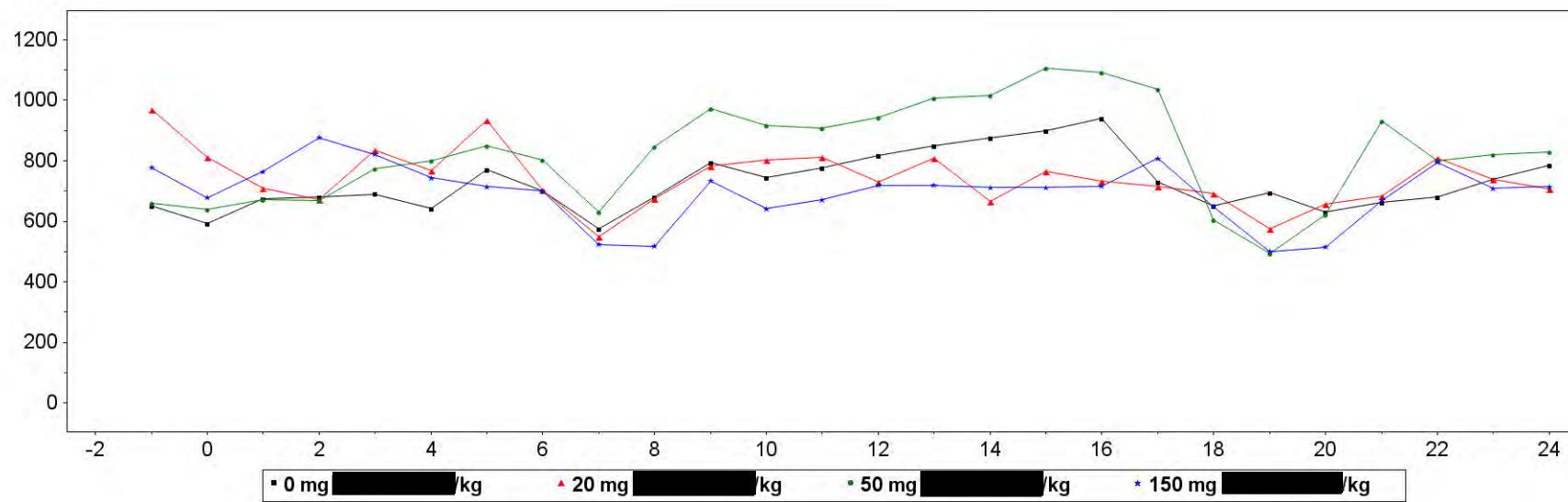
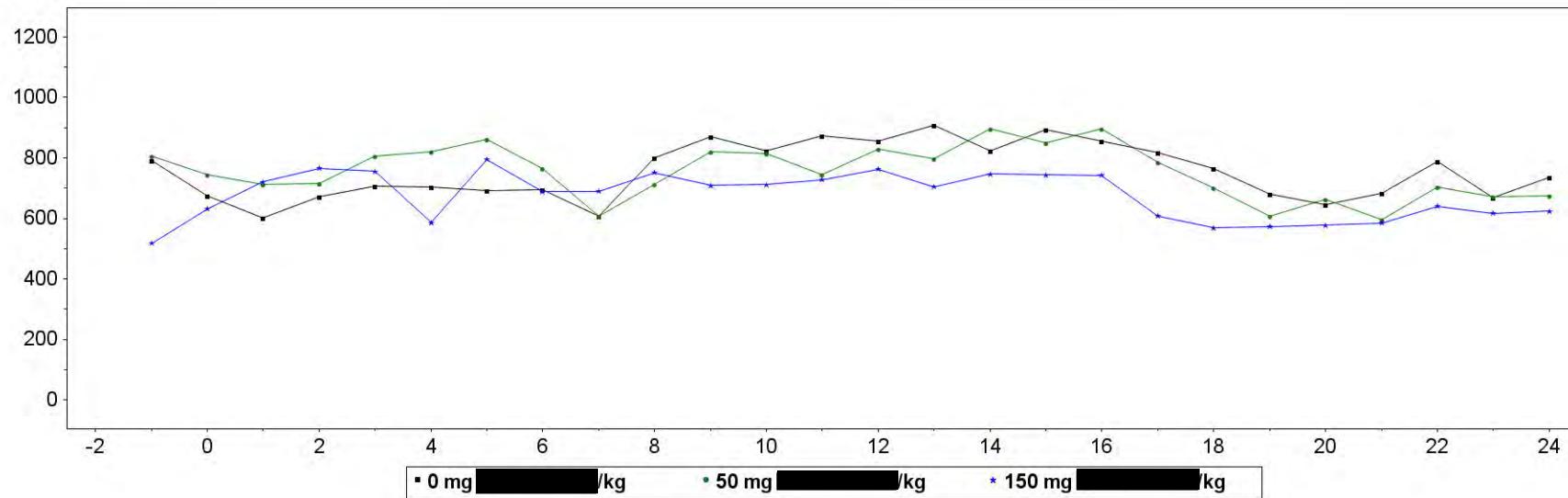
[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual Heart Rate, beats/minute - MALE**

Group, Animal Number	Study Interval (hour:minute)							
	17:00	18:00	19:00	20:00	21:00	22:00	23:00	24:00
<u>150 mg [REDACTED] kg</u>								
1004	89	112	133	133	130	101	112	110
1005	75	100	122	119	92	78	90	88
1006	102	108	106	106	106	96	101	99

Appendix 11  
Individual RR Interval

**Individual RR Interval, msec vs. Time, Hour****1001 M****1002 M**

**Individual RR Interval, msec vs. Time, Hour****1003 M****1004 M**

**Individual RR Interval, msec vs. Time, Hour****1005 M****1006 M**

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual RR Interval, msec - MALE**

Group, Animal Number	Study Interval (hour:minute)	Individual RR Interval, msec - MALE								
		-1:00	0:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00
<b>0 mg [REDACTED] kg</b>										
1001	1091	1046	661	647	656	1008	926	930	547	
1002	713	608	680	643	678	769	764	795	669	
1003	1023	814	700	653	795	1014	1196	873	697	
1004	595	530	623	571	763	685	593	563	482	
1005	651	591	675	679	691	644	771	700	574	
1006	792	674	603	673	706	703	692	696	608	
<b>20 mg [REDACTED] kg</b>										
1001	778	899	787	847	911	763	777	743	608	
1002	914	718	620	598	625	662	779	768	620	
1003	777	557	718	622	803	876	1110	855	719	
1004	591	593	634	620	623	526	613	495	480	
1005	971	812	710	673	836	768	934	702	549	
<b>50 mg [REDACTED] kg</b>										
1001	993	891	854	914	1016	817	799	795	670	
1002	816	761	679	743	738	659	722	681	625	
1003	629	766	1014	997	1030	955	1028	905	771	
1004	644	486	535	512	557	580	657	647	513	
1005	659	640	671	667	774	801	851	804	631	
1006	807	744	712	715	805	820	860	764	609	
<b>150 mg [REDACTED] kg</b>										
1001	990	781	755	892	910	711	744	689	588	
1002	1059	982	823	687	744	842	862	842	803	
1003	611	531	859	723	803	781	774	699	742	
1004	819	654	585	578	662	756	771	738	554	

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual RR Interval, msec - MALE**

Group, Animal Number	Study Interval (hour:minute)	Individual RR Interval, msec - MALE								
		-1:00	0:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00
<u>150 mg [REDACTED] kg</u>										
1005		778	679	765	877	821	744	715	700	524
1006		517	631	720	766	755	587	796	688	689

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs

## Individual RR Interval, msec - MALE

Group, Animal Number	Study Interval (hour:minute)	Individual RR Interval, msec - MALE								
		8:00	9:00	10:00	11:00	12:00	13:00	14:00	15:00	16:00
<u>0 mg [REDACTED] kg</u>										
1001		711	706	717	756	777	790	914	965	1011
1002		934	1010	1073	1115	1167	1175	1234	1264	1257
1003		776	849	936	988	912	955	1037	1062	1113
1004		637	668	790	849	852	857	862	892	919
1005		680	794	744	775	818	850	875	899	939
1006		801	869	824	873	854	909	824	894	855
<u>20 mg [REDACTED] kg</u>										
1001		724	736	737	724	654	735	731	765	776
1002		661	672	640	712	746	740	746	775	767
1003		730	773	810	885	950	993	1010	1018	903
1004		590	650	725	782	798	797	873	822	883
1005		676	782	803	813	730	809	667	765	733
<u>50 mg [REDACTED] kg</u>										
1001		886	620	654	666	631	651	633	712	709
1002		712	737	709	743	724	773	764	829	810
1003		728	721	803	821	757	806	826	933	1002
1004		635	549	552	626	704	705	741	772	767
1005		848	971	917	908	945	1007	1015	1107	1093
1006		712	820	814	743	828	797	895	851	896
<u>150 mg [REDACTED] kg</u>										
1001		740	777	705	766	692	719	721	758	881
1002		835	879	830	774	803	776	811	741	805
1003		792	842	879	796	754	810	826	819	831
1004		597	680	771	788	748	767	744	747	715

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual RR Interval, msec - MALE**

Group, Animal Number	Study Interval (hour:minute)	Individual RR Interval, msec - MALE								
		8:00	9:00	10:00	11:00	12:00	13:00	14:00	15:00	16:00
150 mg [REDACTED] kg										
1005		518	734	641	671	719	719	712	712	716
1006		751	709	712	728	763	704	747	744	742

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs

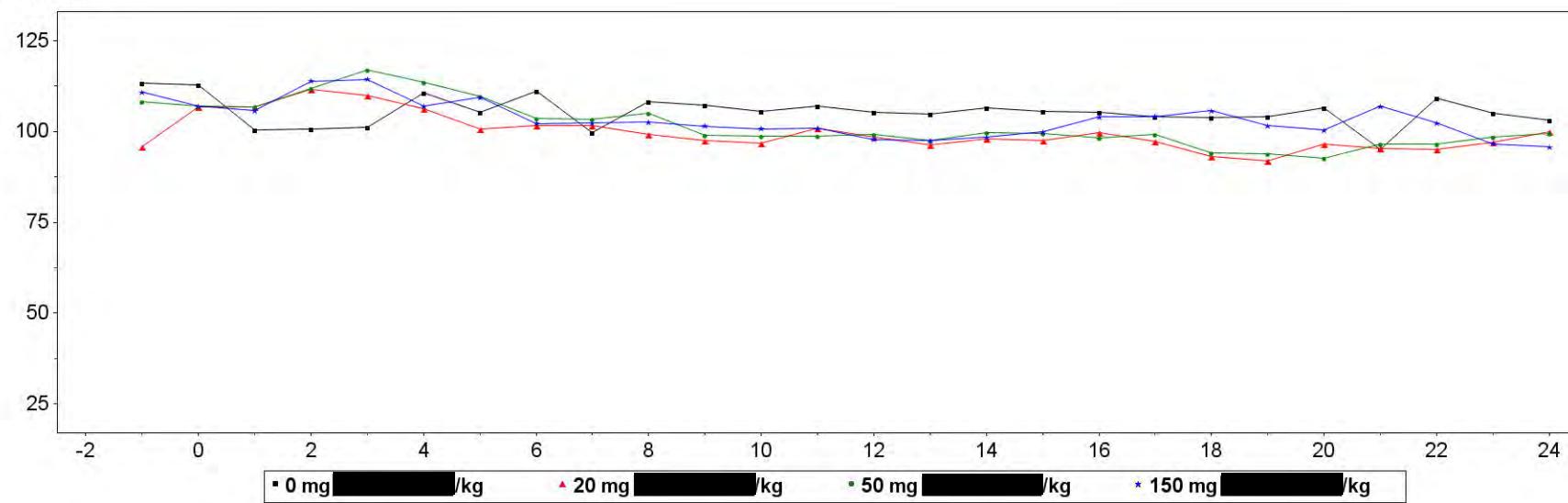
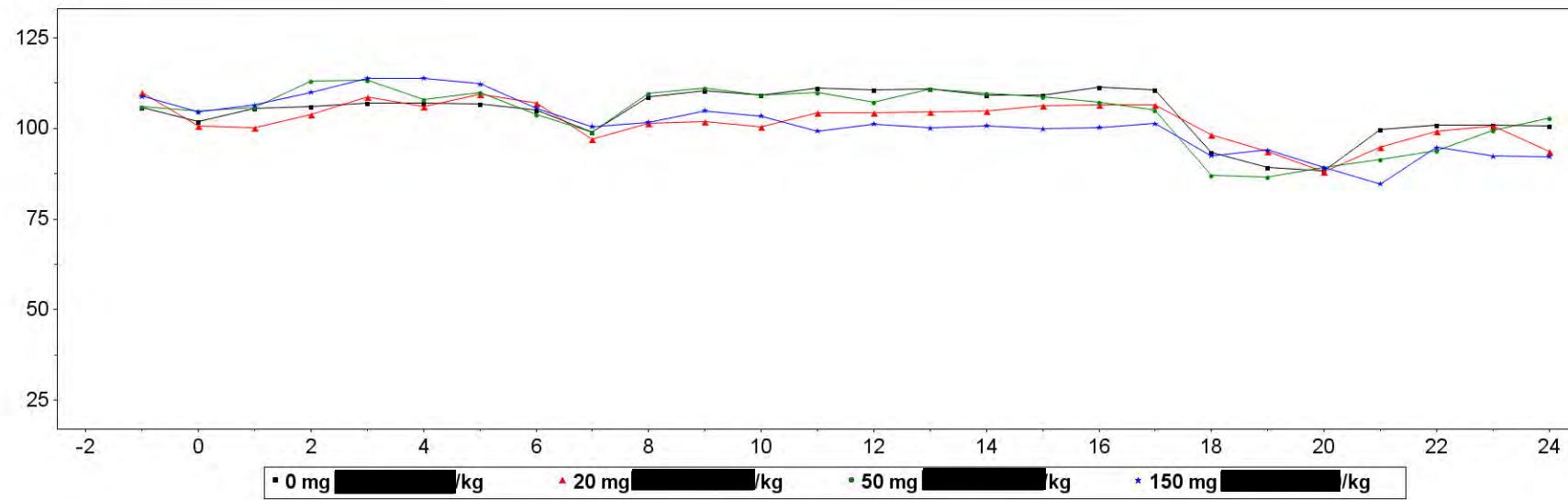
## Individual RR Interval, msec - MALE

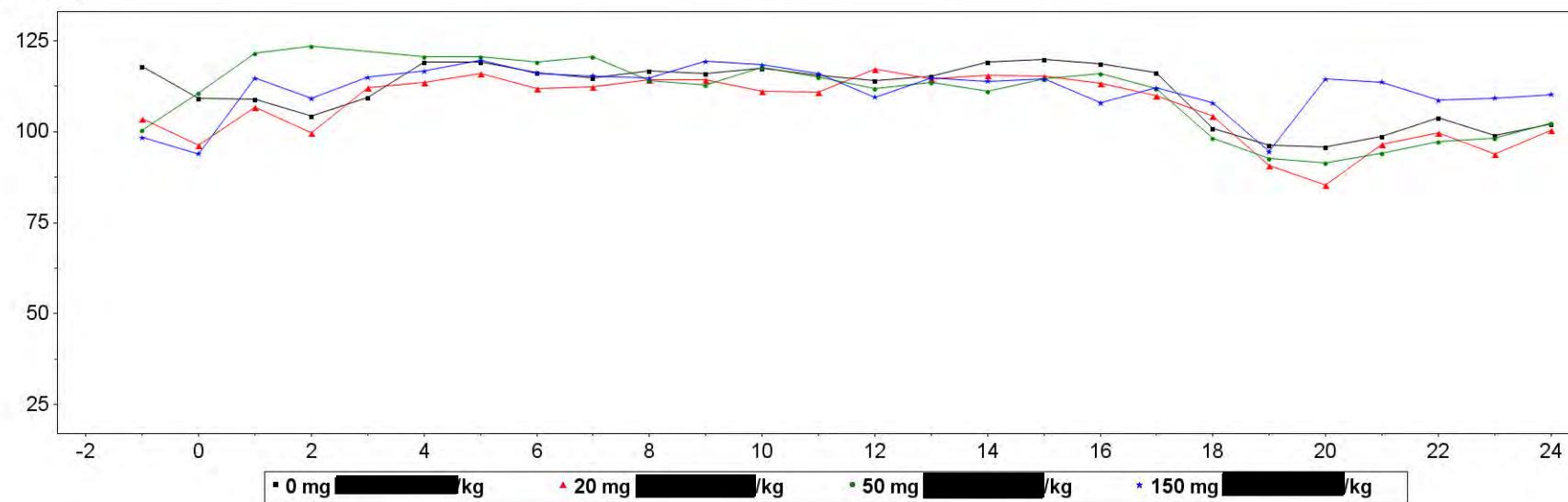
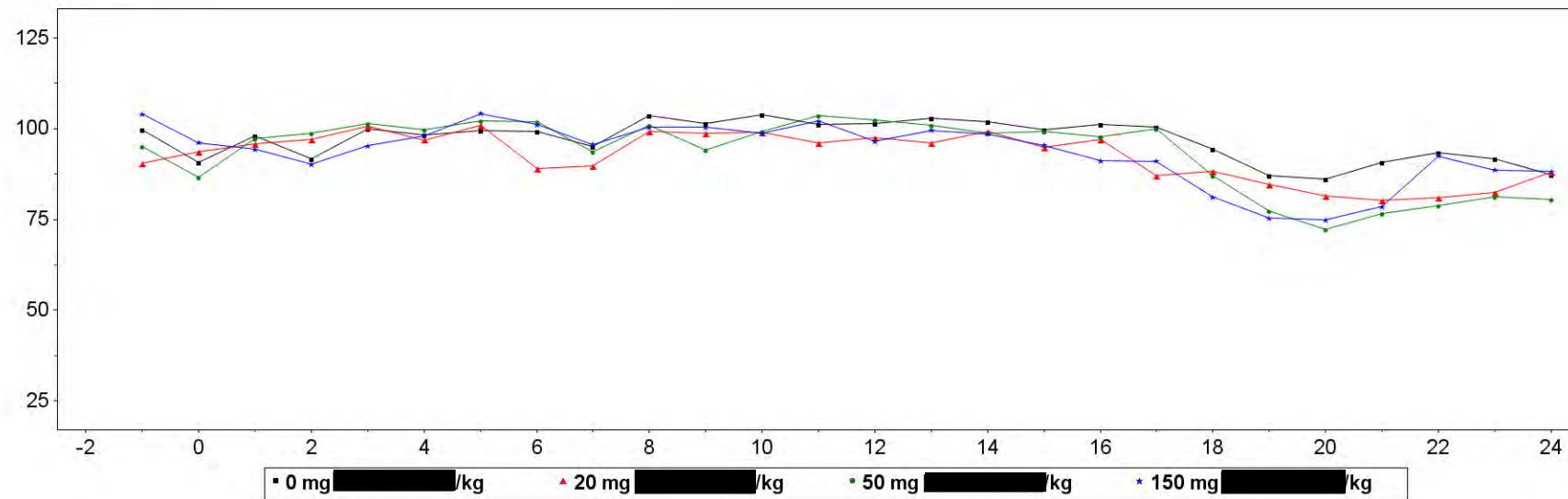
Group, Animal Number	Study Interval (hour:minute)	Individual RR Interval, msec - MALE						
		17:00	18:00	19:00	20:00	21:00	22:00	23:00
<b>0 mg [REDACTED] kg</b>								
1001		906	809	672	861	585	969	834
1002		1223	711	575	603	755	868	882
1003		1034	754	554	558	634	729	626
1004		895	700	511	427	482	543	514
1005		731	652	696	631	664	679	740
1006		816	765	679	644	682	788	669
<b>20 mg [REDACTED] kg</b>								
1001		743	460	608	553	549	595	573
1002		797	625	495	510	543	643	707
1003		842	777	502	406	562	651	531
1004		605	573	473	408	409	436	474
1005		716	693	576	658	684	810	740
<b>50 mg [REDACTED] kg</b>								
1001		769	587	542	527	566	605	615
1002		761	506	523	483	523	585	705
1003		828	720	536	482	514	588	569
1004		790	593	455	375	402	423	444
1005		1036	604	494	623	931	799	821
1006		785	702	608	662	596	704	670
<b>150 mg [REDACTED] kg</b>								
1001		894	745	638	621	780	714	595
1002		789	631	622	554	478	604	594
1003		853	697	474	773	844	708	665
1004		707	570	455	451	453	620	565

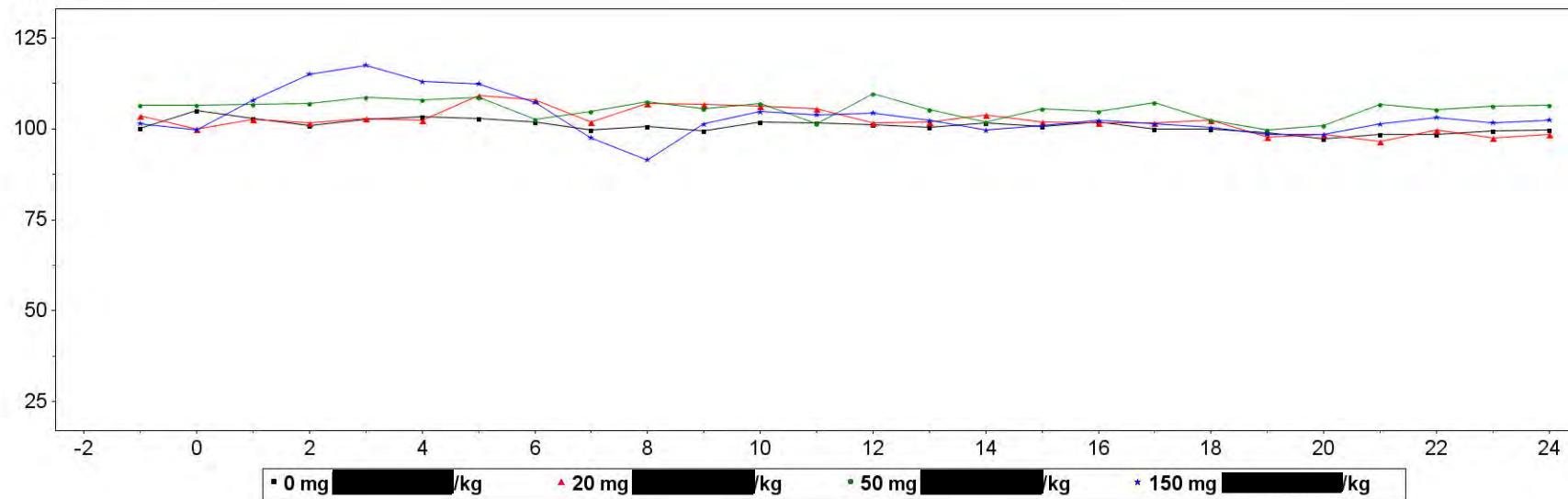
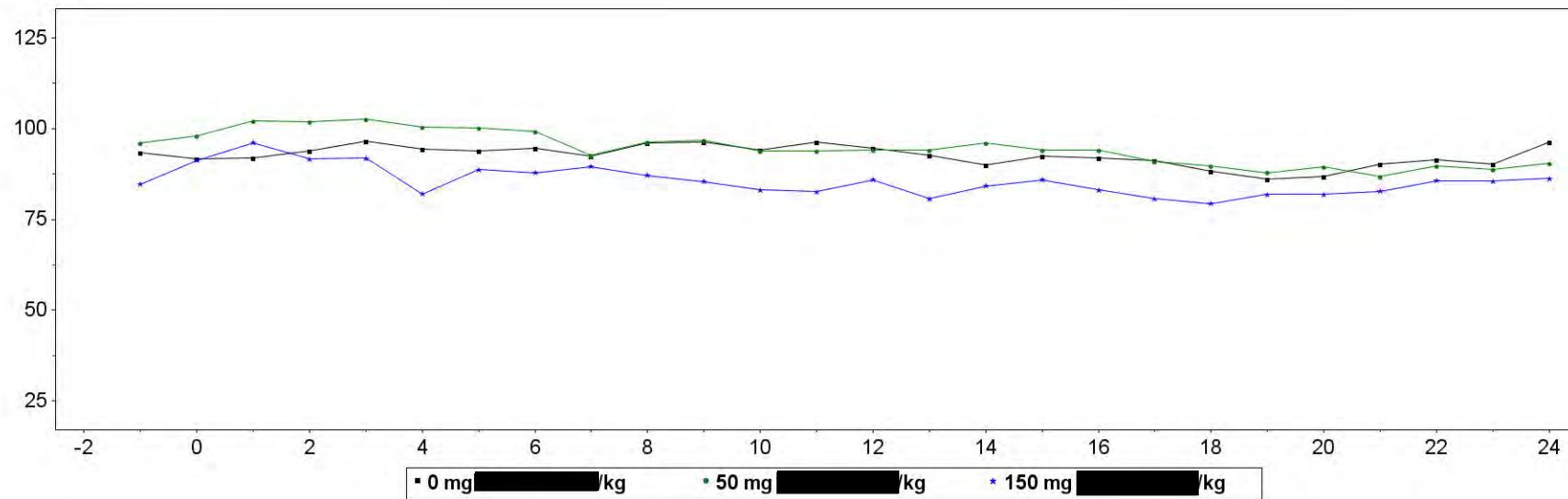
[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual RR Interval, msec - MALE**

Group, Animal Number	Study Interval (hour:minute)							
	17:00	18:00	19:00	20:00	21:00	22:00	23:00	24:00
<u>150 mg [REDACTED] kg</u>								
1005	808	649	500	515	669	795	709	714
1006	607	569	573	578	584	640	616	624

Appendix 12  
Individual PR Interval

**Individual PR Interval, msec vs. Time, Hour****1001 M****1002 M**

**Individual PR Interval, msec vs. Time, Hour****1003 M****1004 M**

**Individual PR Interval, msec vs. Time, Hour****1005 M****1006 M**

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual PR Interval, msec - MALE**

Group, Animal Number	Study Interval (hour:minute)	-1:00	0:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00
	<u>0 mg [REDACTED] kg</u>									
1001		113	113	101	101	101	111	105	111	100
1002		106	102	106	106	107	107	107	105	99
1003		118	109	109	104	110	119	119	116	115
1004		100	91	98	92	100	98	100	99	95
1005		100	105	103	101	103	103	103	102	100
1006		93	92	92	94	97	94	94	95	92
	<u>20 mg [REDACTED] kg</u>									
1001		96	107	107	112	110	106	101	102	102
1002		110	101	100	104	109	106	109	107	97
1003		104	96	107	100	112	113	116	112	112
1004		91	94	96	97	101	97	101	89	90
1005		104	100	103	102	103	102	109	108	102
	<u>50 mg [REDACTED] kg</u>									
1001		108	107	107	112	117	114	110	104	103
1002		106	105	106	113	113	108	110	104	99
1003		100	111	122	123	127	121	121	119	121
1004		95	86	97	99	101	100	102	102	94
1005		106	106	107	107	109	108	109	103	105
1006		96	98	102	102	103	100	100	99	93
	<u>150 mg [REDACTED] kg</u>									
1001		111	107	106	114	114	107	109	102	102
1002		109	105	106	110	114	114	112	106	100
1003		98	94	115	109	115	117	120	116	115
1004		104	96	94	90	95	98	104	101	96

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual PR Interval, msec - MALE**

Group, Animal Number	Study Interval (hour:minute)	Individual PR Interval, msec - MALE								
		-1:00	0:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00
<u>150 mg</u> [REDACTED] kg										
1005		101	100	108	115	118	113	112	107	98
1006		85	91	96	92	92	82	89	88	89

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual PR Interval, msec - MALE**

Group, Animal Number	Study Interval (hour:minute)	Individual PR Interval, msec - MALE								
		8:00	9:00	10:00	11:00	12:00	13:00	14:00	15:00	16:00
<b>0 mg [REDACTED] kg</b>										
1001		108	107	106	107	105	105	106	106	105
1002		109	110	109	111	111	111	109	109	111
1003		117	116	117	116	114	115	119	120	119
1004		104	101	104	101	101	103	102	100	101
1005		101	99	102	102	101	100	102	101	102
1006		96	96	94	96	95	93	90	93	92
<b>20 mg [REDACTED] kg</b>										
1001		99	98	97	101	99	96	98	97	100
1002		101	102	100	104	104	105	105	106	106
1003		114	114	111	111	117	114	115	115	113
1004		99	99	99	96	97	96	99	95	97
1005		107	107	106	106	102	102	104	102	102
<b>50 mg [REDACTED] kg</b>										
1001		105	99	99	99	99	97	100	99	98
1002		110	111	109	110	107	111	110	109	107
1003		114	113	118	115	112	114	111	115	116
1004		101	94	99	104	102	101	99	99	98
1005		107	105	107	101	110	105	102	106	105
1006		96	97	94	94	94	94	96	94	94
<b>150 mg [REDACTED] kg</b>										
1001		103	102	101	101	98	97	98	100	104
1002		102	105	103	99	101	100	101	100	100
1003		115	119	118	116	109	115	114	114	108
1004		100	100	99	102	96	100	98	95	91

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual PR Interval, msec - MALE**

Group, Animal Number	Study Interval (hour:minute)	Individual PR Interval, msec - MALE								
		8:00	9:00	10:00	11:00	12:00	13:00	14:00	15:00	16:00
150 mg [REDACTED] kg										
1005		91	101	105	104	104	102	100	101	102
1006		87	85	83	83	86	81	84	86	83

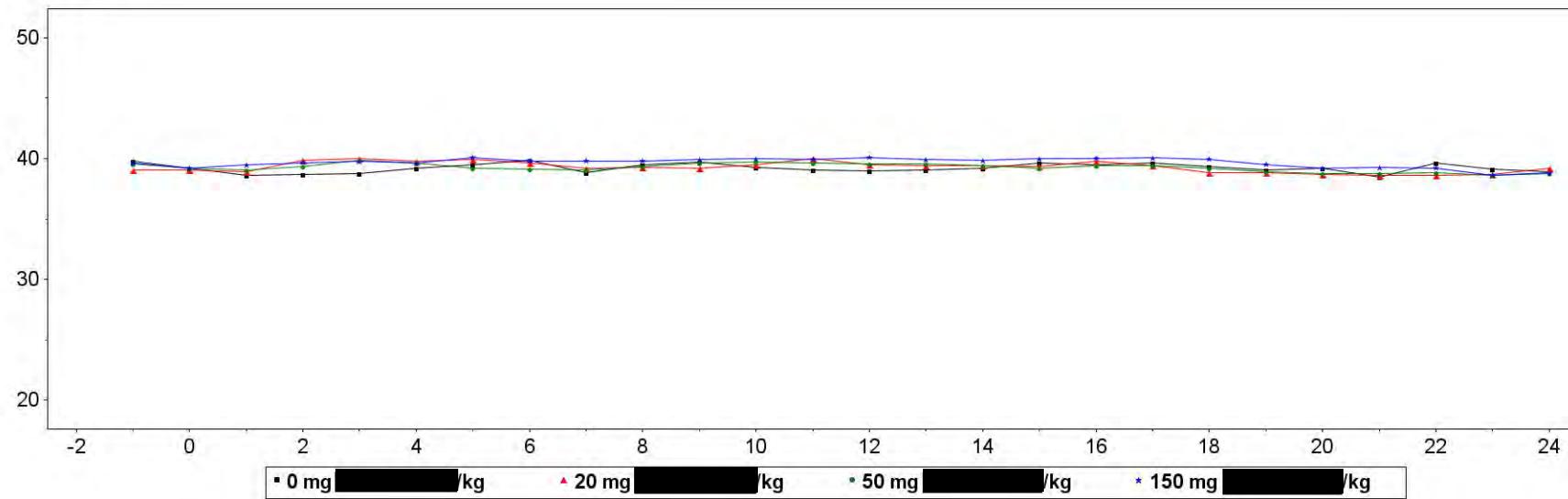
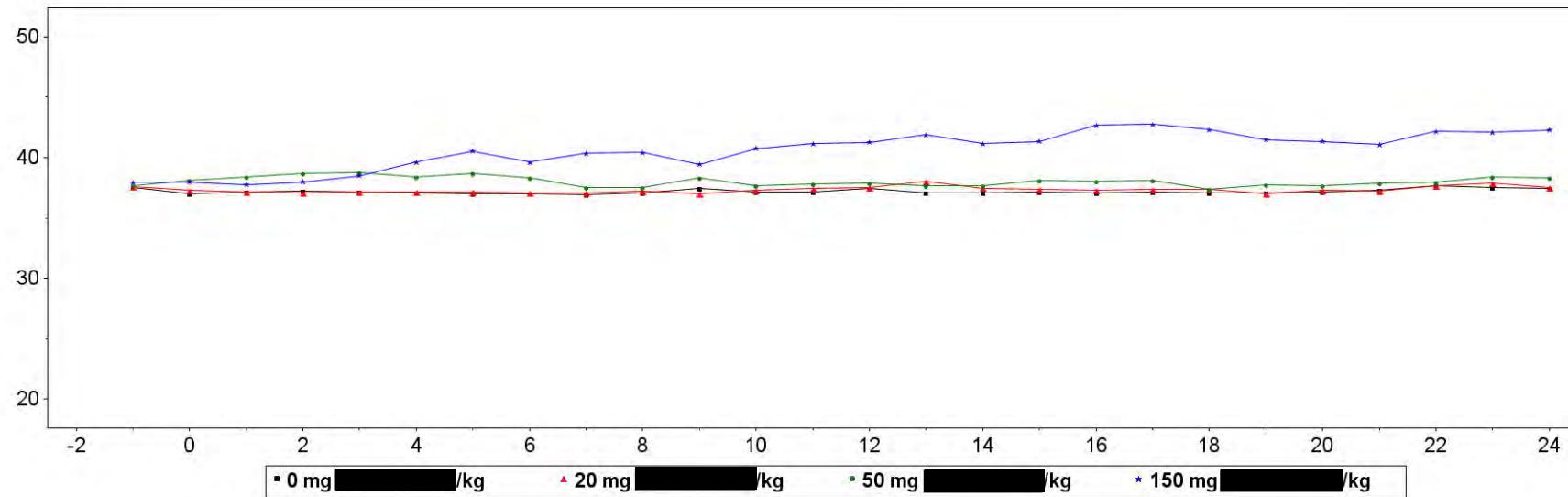
[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual PR Interval, msec - MALE**

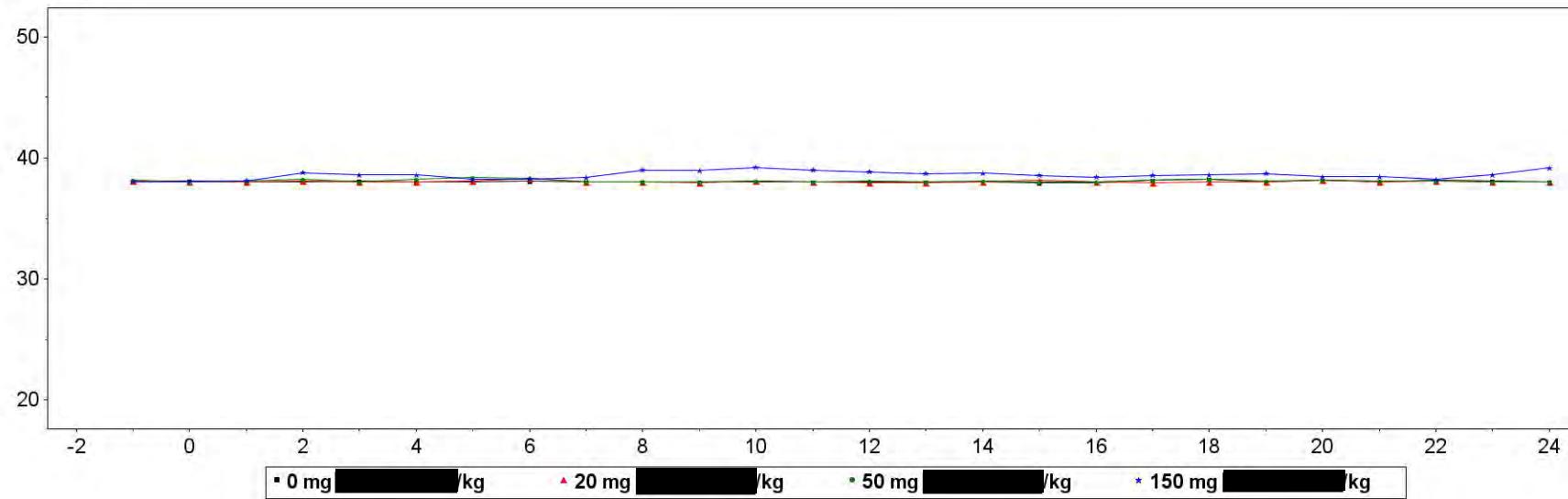
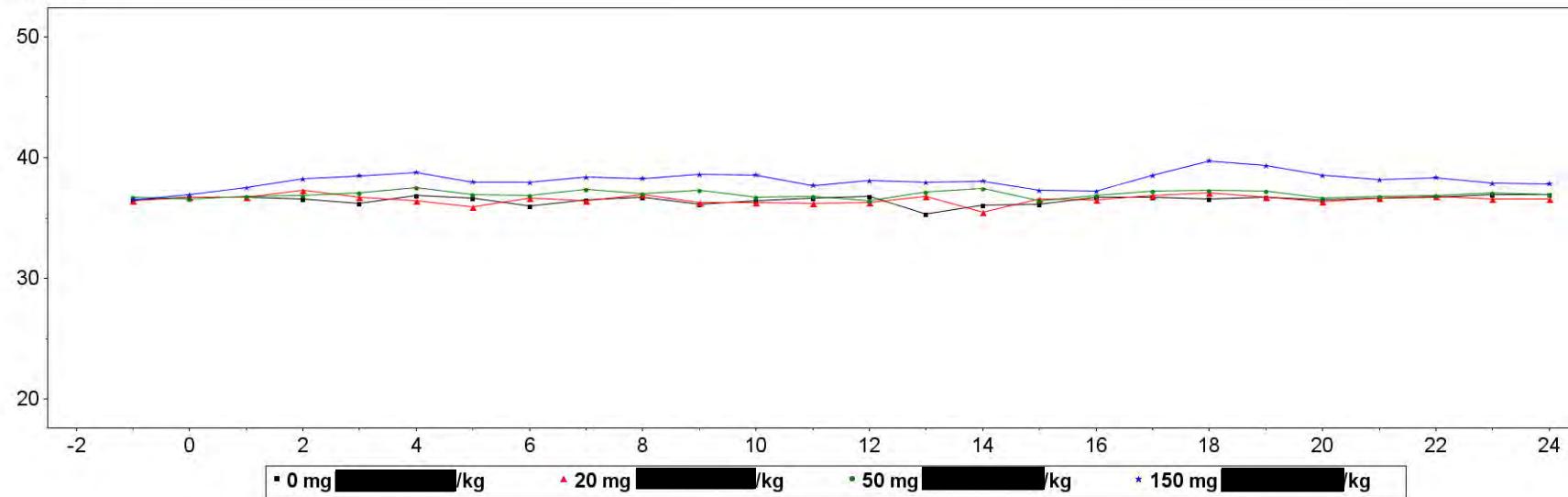
Group, Animal Number	Study Interval (hour:minute)	Individual PR Interval, msec - MALE						
		17:00	18:00	19:00	20:00	21:00	22:00	23:00
<b>0 mg [REDACTED] kg</b>								
1001		104	104	104	107	95	109	105
1002		111	93	89	88	100	101	101
1003		116	101	96	96	99	104	99
1004		101	94	87	86	91	93	92
1005		100	100	99	97	98	98	100
1006		91	88	86	87	90	91	90
<b>20 mg [REDACTED] kg</b>								
1001		97	93	92	96	95	95	97
1002		106	98	94	88	95	99	101
1003		110	104	91	85	97	100	94
1004		87	88	85	82	80	81	82
1005		102	102	98	99	97	100	98
<b>50 mg [REDACTED] kg</b>								
1001		99	94	94	93	96	97	99
1002		105	87	87	89	91	94	100
1003		112	98	93	91	94	97	98
1004		100	87	77	72	76	79	81
1005		107	102	100	101	107	105	106
1006		91	90	88	89	87	90	89
<b>150 mg [REDACTED] kg</b>								
1001		104	106	102	100	107	102	97
1002		101	93	94	89	85	95	92
1003		112	108	94	114	114	109	109
1004		91	81	75	75	78	93	89

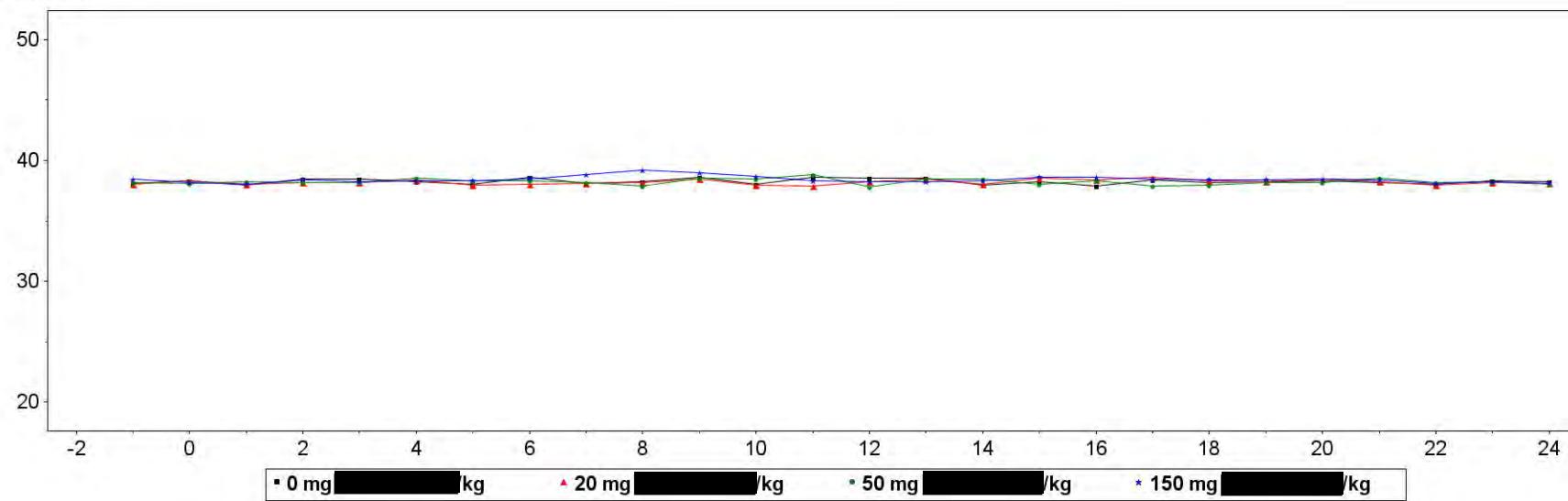
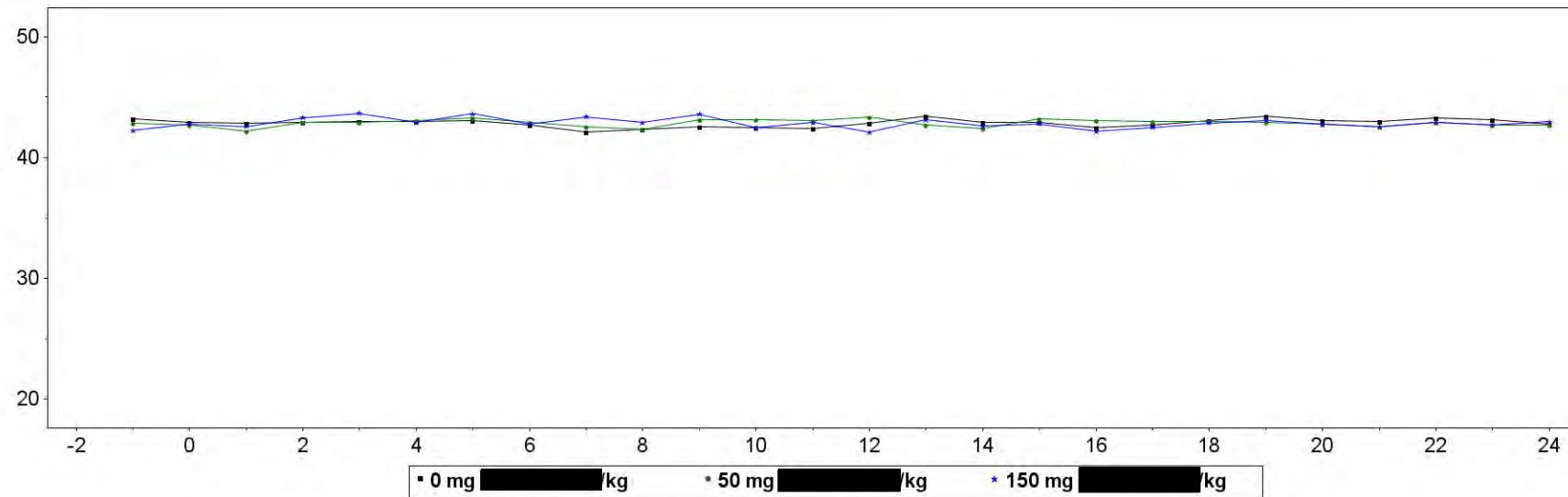
[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual PR Interval, msec - MALE**

Group, Animal Number	Study Interval (hour:minute)							
	17:00	18:00	19:00	20:00	21:00	22:00	23:00	24:00
<u>150 mg [REDACTED] kg</u>								
1005	101	100	99	98	101	103	102	102
1006	81	79	82	82	83	86	86	86

Appendix 13  
Individual QRS Duration

**Individual QRS Duration, msec vs. Time, Hour****1001 M****1002 M**

**Individual QRS Duration, msec vs. Time, Hour****1003 M****1004 M**

**Individual QRS Duration, msec vs. Time, Hour****1005 M****1006 M**

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual QRS Duration, msec - MALE**

Group, Animal Number	Study Interval (hour:minute)	Individual QRS Duration, msec - MALE								
		-1:00	0:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00
<b>0 mg [REDACTED] kg</b>										
1001		40	39	39	39	39	39	39	40	39
1002		38	37	37	37	37	37	37	37	37
1003		38	38	38	38	38	38	38	38	38
1004		37	37	37	37	36	37	37	36	36
1005		38	38	38	39	39	38	38	39	38
1006		43	43	43	43	43	43	43	43	42
<b>20 mg [REDACTED] kg</b>										
1001		39	39	39	40	40	40	40	40	39
1002		38	37	37	37	37	37	37	37	37
1003		38	38	38	38	38	38	38	38	38
1004		36	37	37	37	37	36	36	37	36
1005		38	38	38	38	38	38	38	38	38
<b>50 mg [REDACTED] kg</b>										
1001		40	39	39	39	40	40	39	39	39
1002		38	38	38	39	39	38	39	38	38
1003		38	38	38	38	38	38	38	38	38
1004		37	37	37	37	37	38	37	37	37
1005		38	38	38	38	38	39	38	38	38
1006		43	43	42	43	43	43	43	43	43
<b>150 mg [REDACTED] kg</b>										
1001		40	39	39	40	40	40	40	40	40
1002		38	38	38	38	39	40	41	40	40
1003		38	38	38	39	39	39	38	38	38
1004		37	37	38	38	38	39	38	38	38

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual QRS Duration, msec - MALE**

Group, Animal Number	Study Interval (hour:minute)	Individual QRS Duration, msec - MALE								
		-1:00	0:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00
<u>150 mg [REDACTED] kg</u>										
1005		38	38	38	38	38	38	38	38	39
1006		42	43	43	43	44	43	44	43	43

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual QRS Duration, msec - MALE**

Group, Animal Number	Study Interval (hour:minute)	Individual QRS Duration, msec - MALE								
		8:00	9:00	10:00	11:00	12:00	13:00	14:00	15:00	16:00
<b>0 mg [REDACTED] kg</b>										
1001		40	40	39	39	39	39	39	40	40
1002		37	37	37	37	37	37	37	37	37
1003		38	38	38	38	38	38	38	38	38
1004		37	36	36	37	37	35	36	36	37
1005		38	39	38	39	39	39	38	38	38
1006		42	43	42	42	43	43	43	43	42
<b>20 mg [REDACTED] kg</b>										
1001		39	39	39	40	40	39	39	39	40
1002		37	37	37	37	38	38	37	37	37
1003		38	38	38	38	38	38	38	38	38
1004		37	36	36	36	36	37	35	37	36
1005		38	38	38	38	38	38	38	39	38
<b>50 mg [REDACTED] kg</b>										
1001		39	40	40	40	40	40	39	39	39
1002		38	38	38	38	38	38	38	38	38
1003		38	38	38	38	38	38	38	38	38
1004		37	37	37	37	36	37	37	36	37
1005		38	39	38	39	38	39	38	38	38
1006		42	43	43	43	43	43	42	43	43
<b>150 mg [REDACTED] kg</b>										
1001		40	40	40	40	40	40	40	40	40
1002		40	39	41	41	41	42	41	41	43
1003		39	39	39	39	39	39	39	39	38
1004		38	39	39	38	38	38	38	37	37

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual QRS Duration, msec - MALE**

Group, Animal Number	Study Interval (hour:minute)	Individual QRS Duration, msec - MALE								
		8:00	9:00	10:00	11:00	12:00	13:00	14:00	15:00	16:00
150 mg [REDACTED] kg										
1005		39	39	39	38	38	38	38	39	39
1006		43	44	42	43	42	43	43	43	42

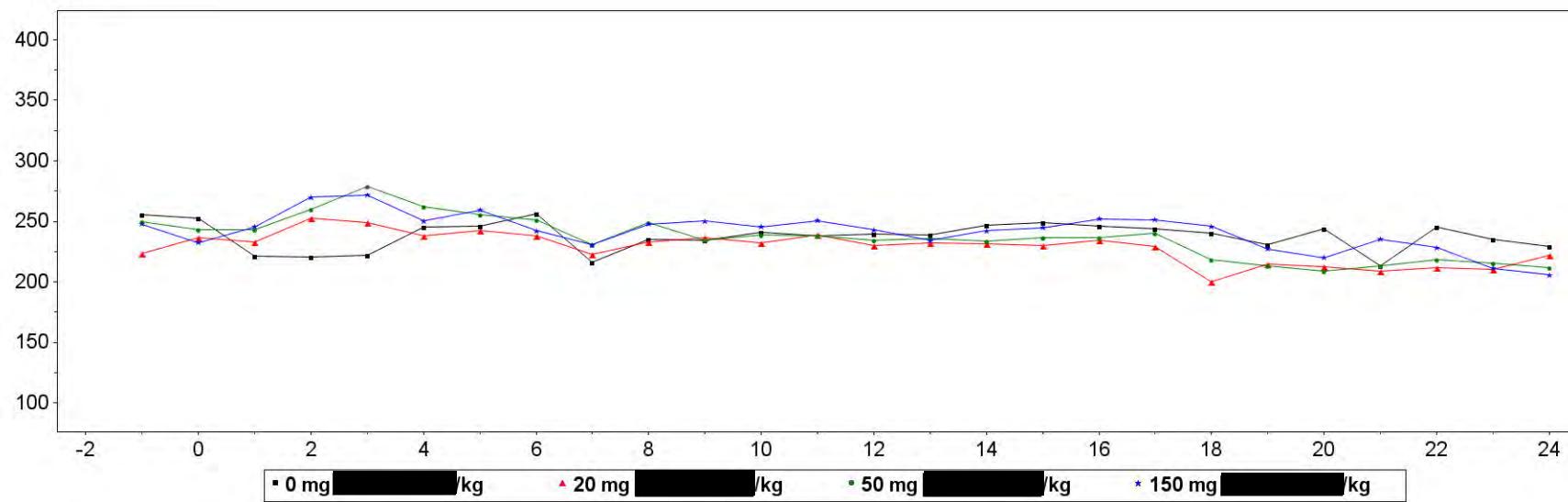
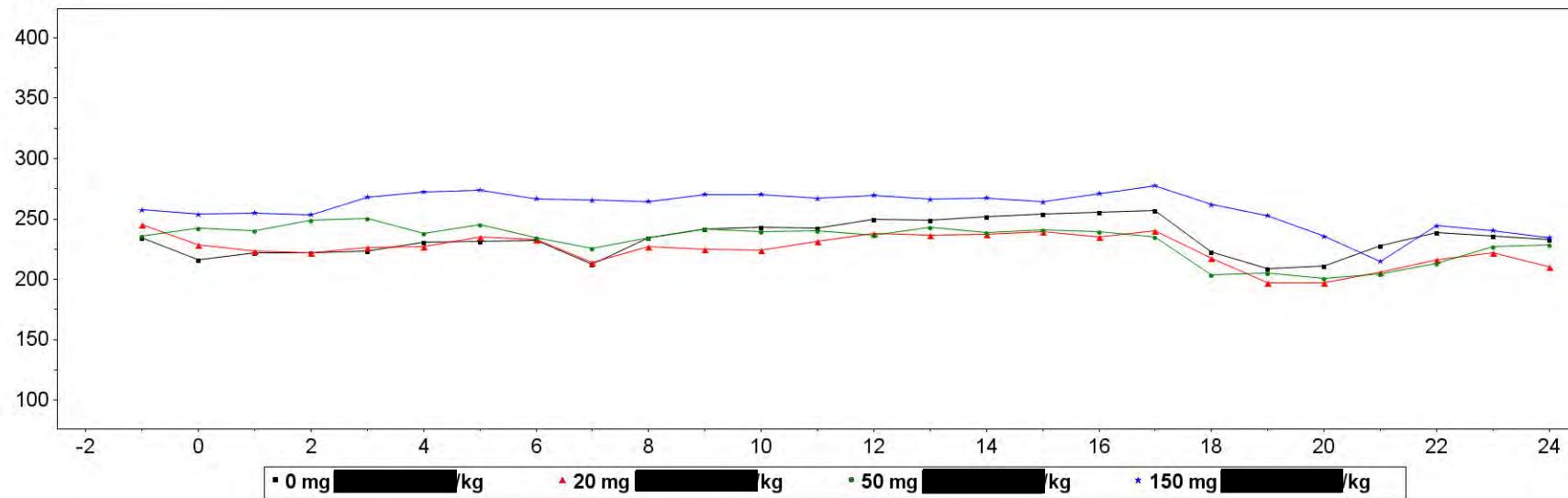
[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual QRS Duration, msec - MALE**

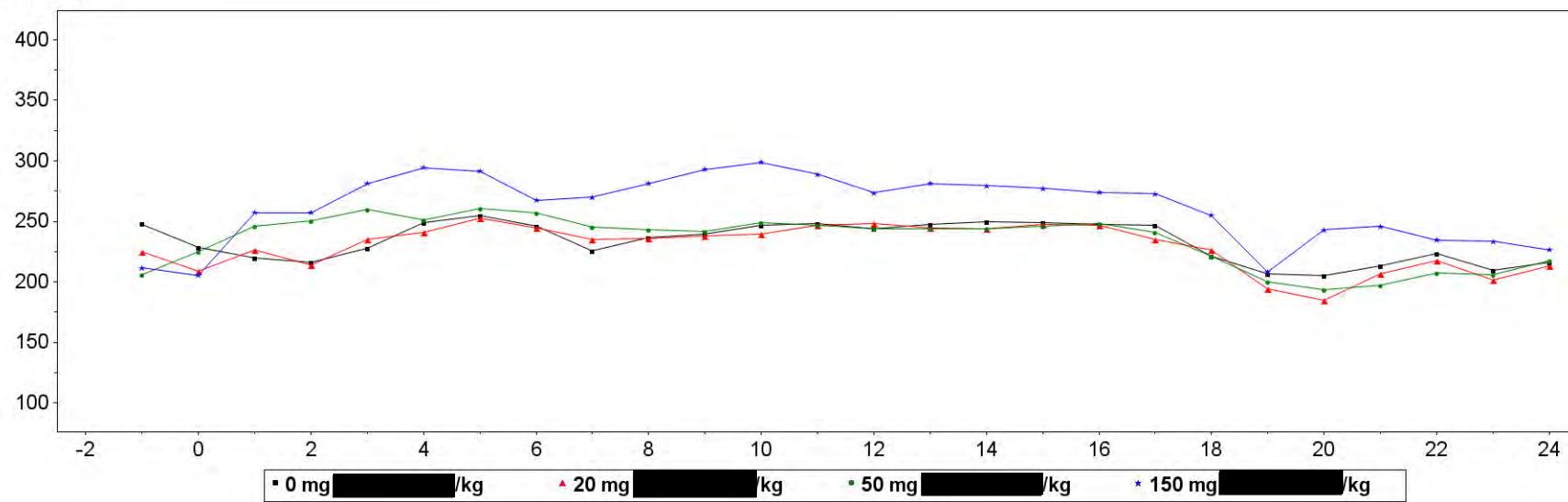
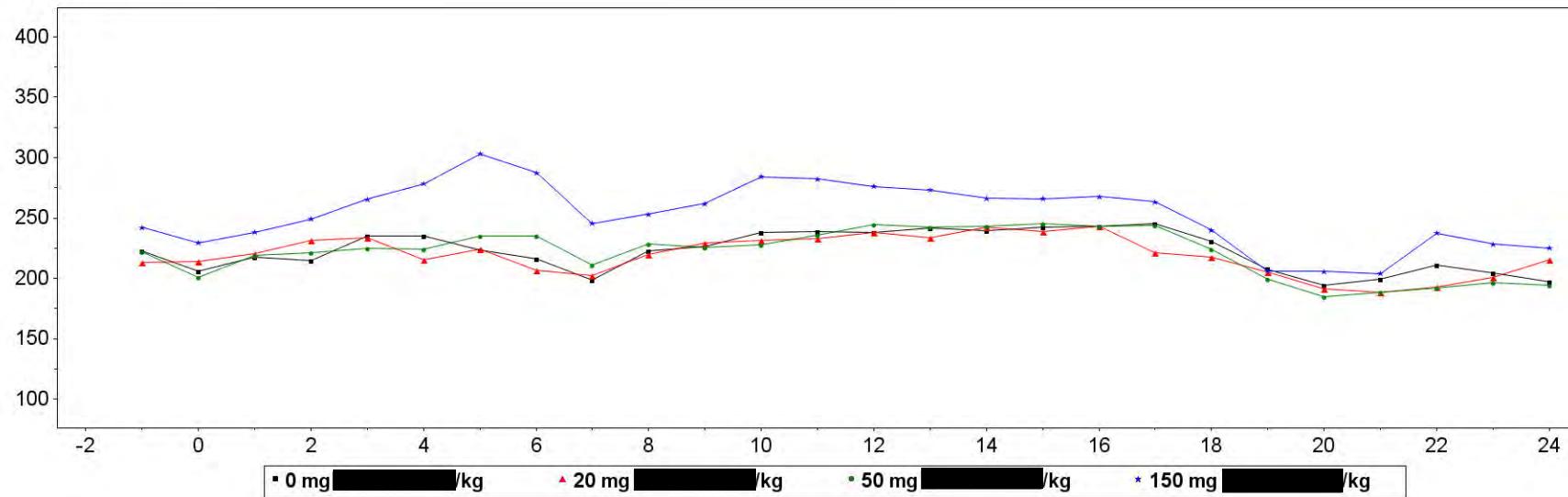
Group, Animal Number	Study Interval (hour:minute)	Individual QRS Duration, msec - MALE							
		17:00	18:00	19:00	20:00	21:00	22:00	23:00	24:00
<b>0 mg [REDACTED] kg</b>									
1001		40	39	39	39	39	40	39	39
1002		37	37	37	37	37	38	38	37
1003		38	38	38	38	38	38	38	38
1004		37	37	37	37	37	37	37	37
1005		38	38	38	38	38	38	38	38
1006		43	43	43	43	43	43	43	43
<b>20 mg [REDACTED] kg</b>									
1001		39	39	39	39	39	39	39	39
1002		37	37	37	37	37	38	38	38
1003		38	38	38	38	38	38	38	38
1004		37	37	37	36	37	37	37	37
1005		39	38	38	38	38	38	38	38
<b>50 mg [REDACTED] kg</b>									
1001		39	39	39	39	39	39	39	39
1002		38	37	38	38	38	38	38	38
1003		38	38	38	38	38	38	38	38
1004		37	37	37	37	37	37	37	37
1005		38	38	38	38	39	38	38	38
1006		43	43	43	43	43	43	43	43
<b>150 mg [REDACTED] kg</b>									
1001		40	40	40	39	39	39	39	39
1002		43	42	41	41	41	42	42	42
1003		39	39	39	38	38	38	39	39
1004		39	40	39	39	38	38	38	38

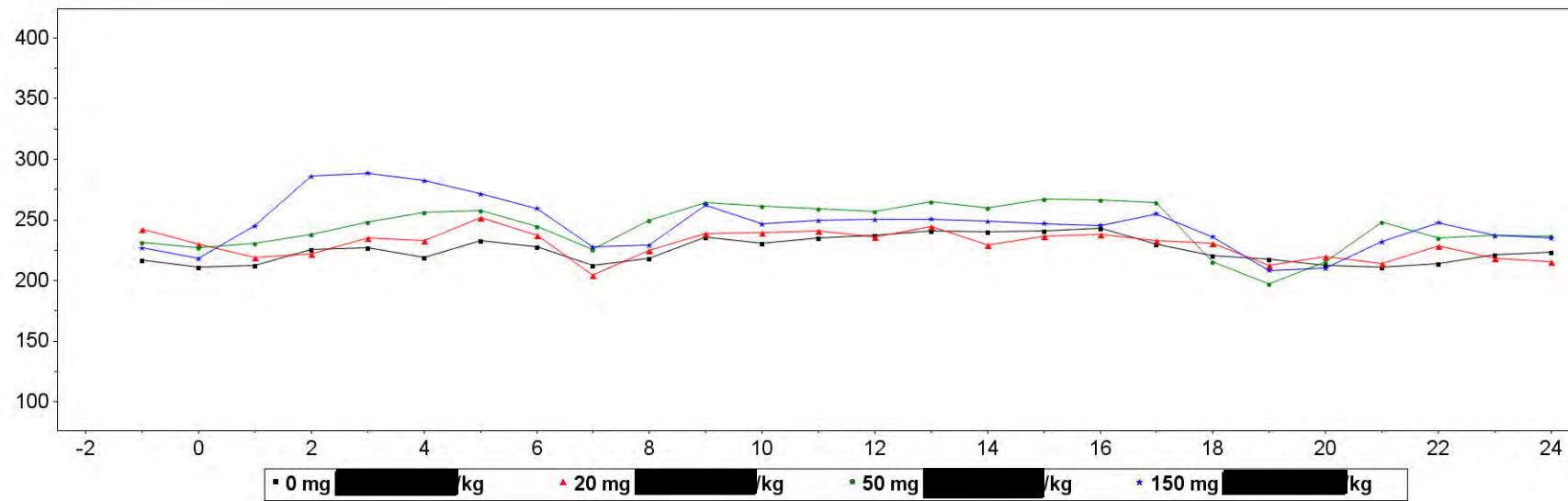
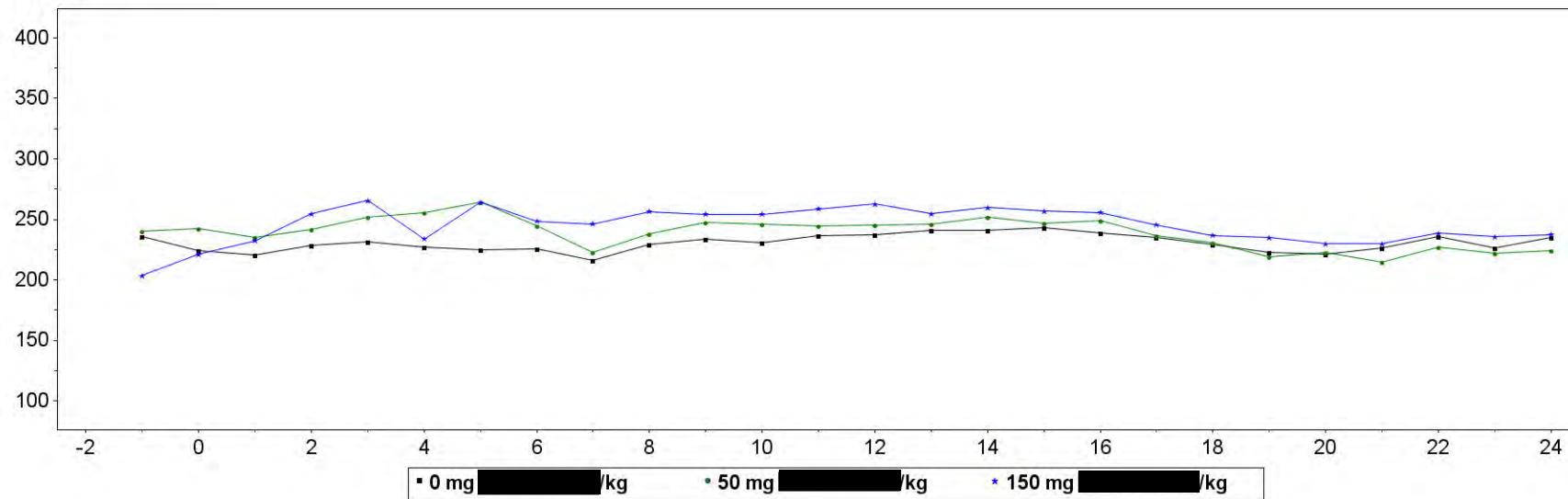
## Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs

**Individual QRS Duration, msec - MALE**

Appendix 14  
Individual QT Interval

**Individual QT Interval, msec vs. Time, Hour****1001 M****1002 M**

**Individual QT Interval, msec vs. Time, Hour****1003 M****1004 M**

**Individual QT Interval, msec vs. Time, Hour****1005 M****1006 M**

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual QT Interval, msec - MALE**

Group, Animal Number	Study Interval (hour:minute)	Individual QT Interval, msec - MALE								
		-1:00	0:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00
<b>0 mg [REDACTED] kg</b>										
1001	256	252	221	220	222	245	246	256	216	
1002	235	216	222	222	224	231	231	232	213	
1003	248	229	219	216	228	249	255	246	226	
1004	222	206	217	215	235	235	223	216	198	
1005	217	211	213	226	227	219	233	228	213	
1006	235	224	221	228	231	227	225	225	216	
<b>20 mg [REDACTED] kg</b>										
1001	223	237	233	253	249	238	242	238	223	
1002	246	229	223	222	226	227	235	233	214	
1003	225	209	226	214	235	241	253	244	235	
1004	213	214	221	232	234	216	224	207	202	
1005	243	230	219	222	235	233	252	237	204	
<b>50 mg [REDACTED] kg</b>										
1001	249	243	243	260	279	262	256	251	230	
1002	236	242	240	249	250	238	245	235	226	
1003	206	225	246	250	260	251	260	257	245	
1004	222	201	219	221	225	224	235	235	211	
1005	231	227	231	238	248	256	257	245	225	
1006	240	242	235	242	252	256	264	245	223	
<b>150 mg [REDACTED] kg</b>										
1001	248	232	246	270	272	250	259	242	231	
1002	258	254	255	254	268	273	274	266	266	
1003	212	205	257	257	281	295	291	267	270	
1004	242	229	238	249	266	278	303	288	245	

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual QT Interval, msec - MALE**

Group, Animal Number	Study Interval (hour:minute)	Individual QT Interval, msec - MALE								
		-1:00	0:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00
<u>150 mg [REDACTED] kg</u>										
1005		227	218	245	286	288	282	271	259	228
1006		204	221	232	254	266	234	264	248	246

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual QT Interval, msec - MALE**

Group, Animal Number	Study Interval (hour:minute)	Individual QT Interval, msec - MALE								
		8:00	9:00	10:00	11:00	12:00	13:00	14:00	15:00	16:00
<b>0 mg [REDACTED] kg</b>										
1001	235	235	241	238	239	239	246	249	246	
1002	234	242	243	243	250	249	252	254	255	
1003	237	240	247	248	244	247	249	249	248	
1004	223	227	238	238	238	242	240	242	243	
1005	219	236	231	235	237	241	240	241	243	
1006	230	234	231	236	237	241	241	243	239	
<b>20 mg [REDACTED] kg</b>										
1001	233	237	232	239	230	232	232	230	234	
1002	227	225	224	231	238	237	237	239	235	
1003	236	238	240	247	248	244	244	247	247	
1004	220	229	232	233	238	234	243	239	243	
1005	225	239	240	241	236	244	229	237	238	
<b>50 mg [REDACTED] kg</b>										
1001	249	235	238	238	234	236	234	237	237	
1002	235	242	240	240	237	243	239	241	240	
1003	243	242	249	247	244	244	244	246	248	
1004	229	226	228	236	245	243	243	246	243	
1005	250	264	262	259	257	265	260	267	266	
1006	238	248	246	245	245	246	252	247	249	
<b>150 mg [REDACTED] kg</b>										
1001	248	250	246	250	243	234	242	245	252	
1002	265	270	270	267	270	266	267	264	271	
1003	281	293	299	289	274	281	280	277	274	
1004	253	262	284	282	276	273	266	266	268	

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual QT Interval, msec - MALE**

Group, Animal Number	Study Interval (hour:minute)	Individual QT Interval, msec - MALE								
		8:00	9:00	10:00	11:00	12:00	13:00	14:00	15:00	16:00
150 mg [REDACTED] kg										
1005		229	262	247	250	250	250	249	247	245
1006		256	254	254	259	262	255	260	257	256

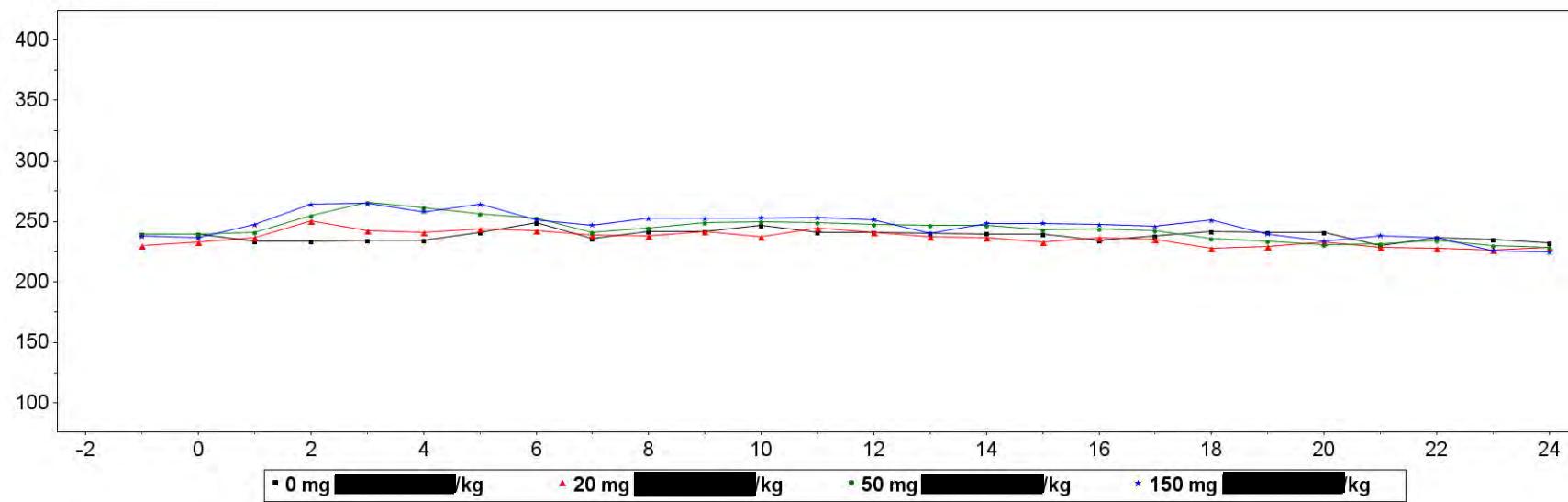
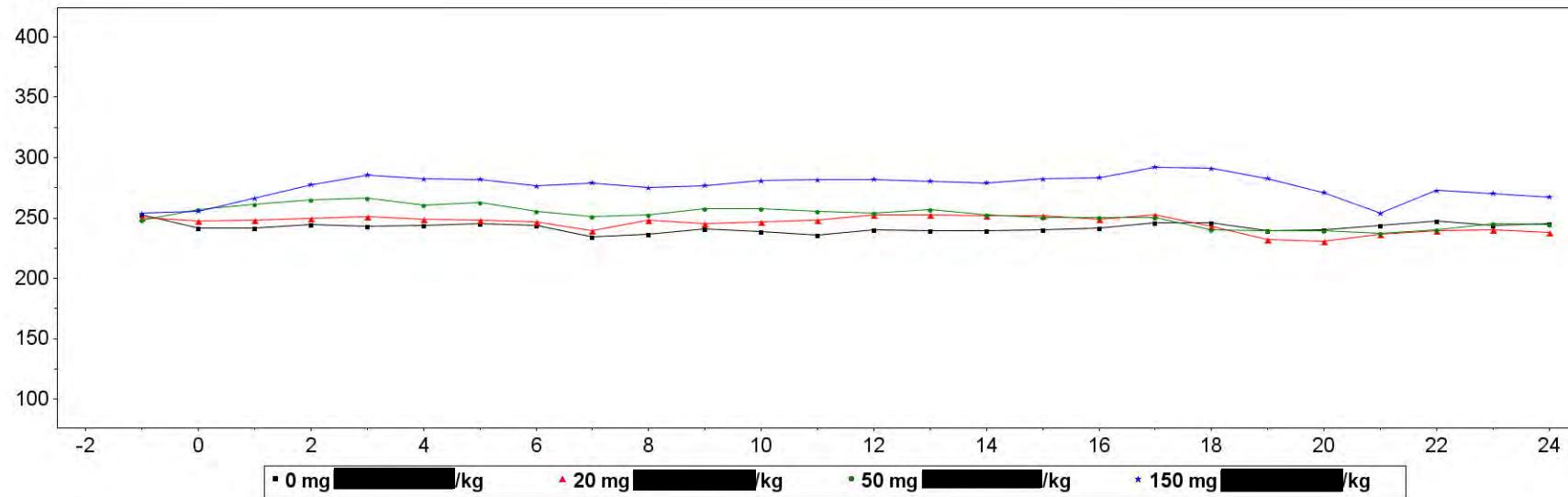
[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual QT Interval, msec - MALE**

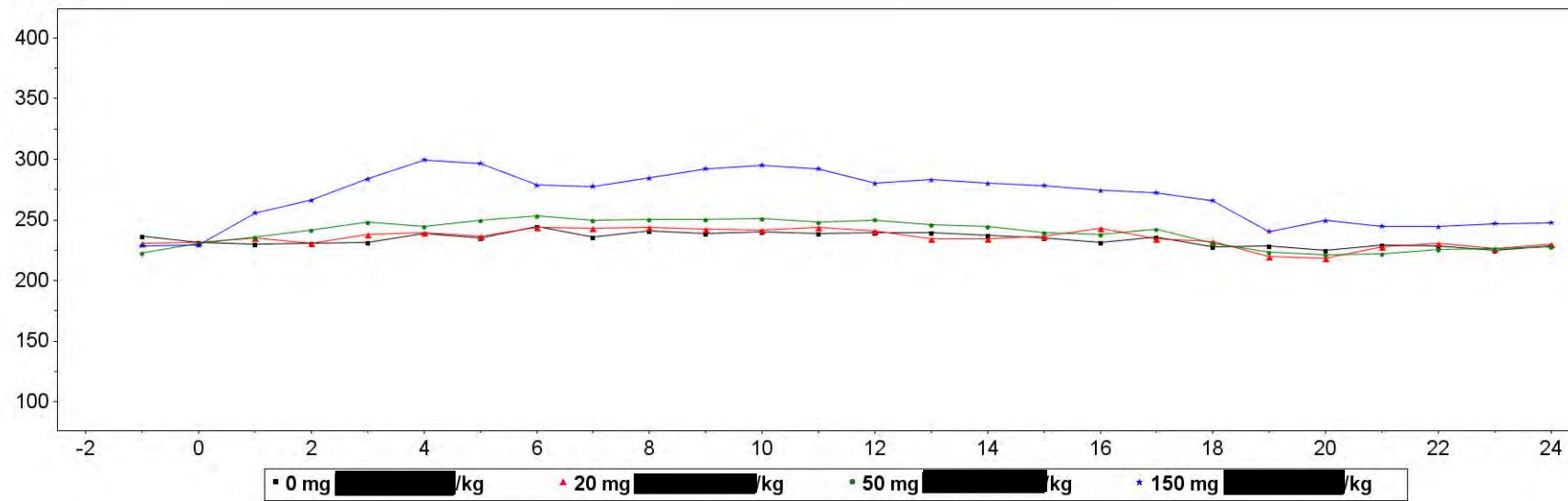
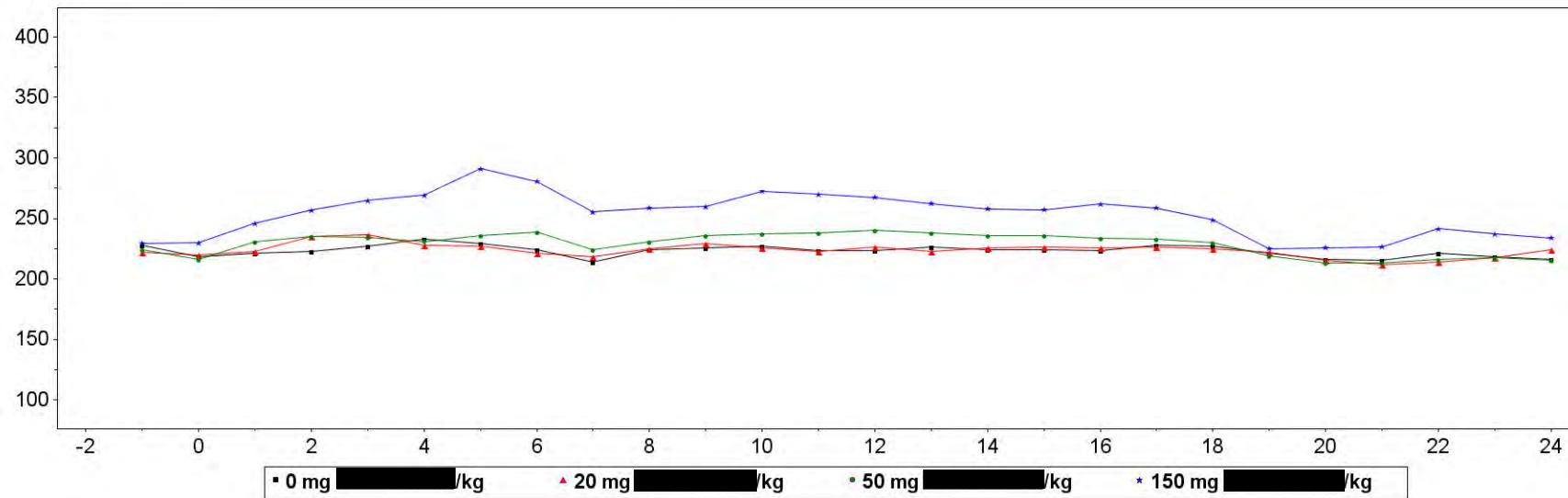
Group, Animal Number	Study Interval (hour:minute)	Individual QT Interval, msec - MALE						
		17:00	18:00	19:00	20:00	21:00	22:00	23:00
<b>0 mg [REDACTED] kg</b>								
1001		243	240	231	244	213	245	235
1002		257	223	209	211	228	238	236
1003		247	221	207	205	213	223	210
1004		245	231	208	194	199	211	204
1005		230	221	218	212	211	214	221
1006		235	230	223	221	227	236	226
<b>20 mg [REDACTED] kg</b>								
1001		229	200	215	213	208	212	211
1002		241	217	197	197	206	216	222
1003		235	226	194	184	207	218	201
1004		221	217	205	191	188	193	201
1005		233	231	212	219	214	229	218
<b>50 mg [REDACTED] kg</b>								
1001		240	218	213	209	213	219	215
1002		235	204	205	201	205	213	227
1003		241	221	200	193	197	207	206
1004		244	224	199	185	188	192	196
1005		264	215	197	215	248	235	238
1006		237	231	219	223	214	227	222
<b>150 mg [REDACTED] kg</b>								
1001		251	246	227	220	235	228	211
1002		278	262	253	235	215	244	240
1003		273	255	208	243	246	235	234
1004		263	240	206	206	204	237	228

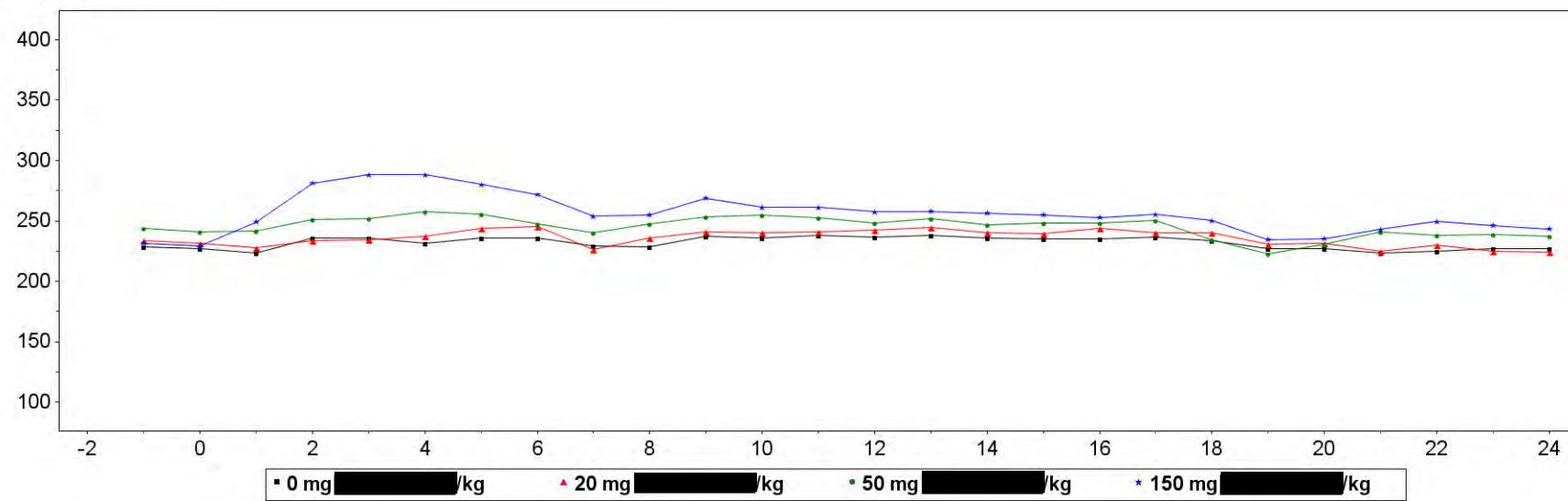
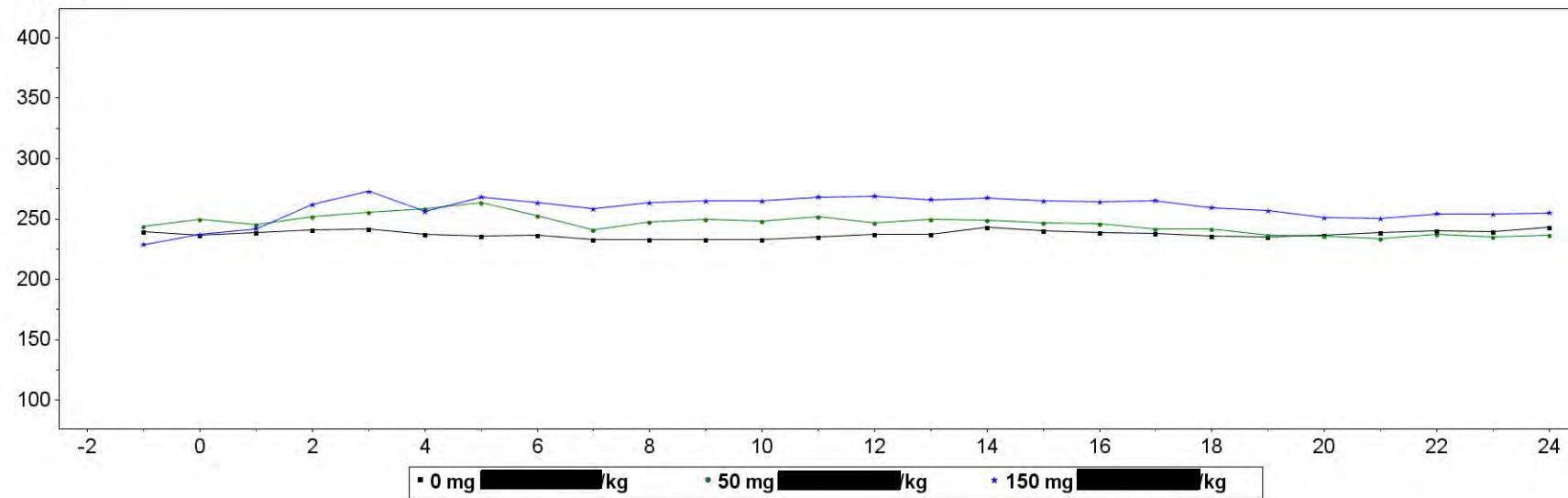
[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual QT Interval, msec - MALE**

Group, Animal Number	Study Interval (hour:minute)							
	17:00	18:00	19:00	20:00	21:00	22:00	23:00	24:00
<u>150 mg [REDACTED] kg</u>								
1005	255	236	208	210	232	248	237	235
1006	245	237	235	230	230	238	236	238

Appendix 15  
Individual Corrected QT Interval

**Individual Corrected QT Interval, msec vs. Time, Hour****1001 M****1002 M**

**Individual Corrected QT Interval, msec vs. Time, Hour****1003 M****1004 M**

**Individual Corrected QT Interval, msec vs. Time, Hour****1005 M****1006 M**

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual Corrected QT Interval, msec - MALE**

Group, Animal Number	Study Interval (hour:minute)	Individual Corrected QT Interval, msec - MALE							
		-1:00	0:00	1:00	2:00	3:00	4:00	5:00	6:00
<b>0 mg [REDACTED] kg</b>									
1001	239	239	234	234	234	235	241	249	236
1002	253	242	242	245	243	244	245	244	235
1003	237	232	230	231	231	238	235	244	236
1004	228	218	221	223	227	233	229	224	214
1005	228	227	224	236	236	231	236	236	229
1006	240	237	239	241	242	237	236	236	233
<b>20 mg [REDACTED] kg</b>									
1001	230	233	236	250	242	241	244	242	239
1002	250	247	248	249	251	249	248	247	239
1003	230	231	235	230	238	239	237	244	243
1004	222	220	223	235	237	228	227	221	218
1005	233	231	228	234	234	238	244	245	226
<b>50 mg [REDACTED] kg</b>									
1001	239	239	241	254	266	261	256	253	241
1002	248	257	261	265	267	261	263	255	251
1003	223	230	236	242	248	244	250	253	250
1004	224	216	230	235	235	231	236	238	224
1005	244	241	242	251	252	258	255	247	240
1006	244	250	245	252	255	258	264	253	241
<b>150 mg [REDACTED] kg</b>									
1001	238	236	247	264	265	258	264	251	247
1002	254	256	266	277	286	282	282	276	279
1003	229	229	256	266	284	299	297	279	278
1004	230	230	246	257	265	269	291	281	255

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual Corrected QT Interval, msec - MALE**

Group, Animal Number	Study Interval (hour:minute)	Individual Corrected QT Interval, msec - MALE								
		-1:00	0:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00
<u>150 mg [REDACTED] kg</u>										
1005		232	229	249	281	288	288	280	272	254
1006		229	237	242	262	273	256	268	263	258

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual Corrected QT Interval, msec - MALE**

Group, Animal Number	Study Interval (hour:minute)	Individual Corrected QT Interval, msec - MALE								
		8:00	9:00	10:00	11:00	12:00	13:00	14:00	15:00	16:00
<b>0 mg [REDACTED] kg</b>										
1001	242	241	247	241	241	240	240	239	234	
1002	237	241	239	236	240	239	239	240	242	
1003	241	239	240	239	240	240	237	235	232	
1004	224	225	227	224	223	226	224	224	223	
1005	229	237	236	238	237	238	236	235	235	
1006	233	233	233	235	238	238	243	241	239	
<b>20 mg [REDACTED] kg</b>										
1001	238	241	237	245	241	237	236	233	236	
1002	248	245	247	248	253	252	252	252	249	
1003	244	242	242	244	241	235	234	237	243	
1004	225	230	226	223	227	223	226	226	226	
1005	236	241	240	241	243	245	240	240	244	
<b>50 mg [REDACTED] kg</b>										
1001	244	249	250	249	247	247	247	243	244	
1002	252	258	258	256	254	257	253	250	251	
1003	251	250	251	248	250	246	244	240	238	
1004	230	236	237	238	240	238	236	236	234	
1005	248	253	255	253	248	252	247	248	248	
1006	248	250	248	252	247	250	249	247	246	
<b>150 mg [REDACTED] kg</b>										
1001	252	252	253	253	251	240	249	248	247	
1002	275	277	281	282	282	281	279	282	283	
1003	285	292	295	292	280	283	280	278	274	
1004	259	260	273	270	267	262	258	257	262	

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual Corrected QT Interval, msec - MALE**

Group, Animal Number	Study Interval (hour:minute)								
	8:00	9:00	10:00	11:00	12:00	13:00	14:00	15:00	16:00
<u>150 mg [REDACTED] kg</u>									
1005	255	269	261	261	258	258	256	255	253
1006	263	265	265	268	269	266	267	265	264

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual Corrected QT Interval, msec - MALE**

Group, Animal Number	Study Interval (hour:minute)	Individual Corrected QT Interval, msec - MALE						
		17:00	18:00	19:00	20:00	21:00	22:00	23:00
<b>0 mg [REDACTED] kg</b>								
1001		238	241	241	241	230	237	235
1002		246	246	239	240	244	247	244
1003		236	228	228	225	229	228	225
1004		228	227	221	216	215	221	218
1005		237	233	227	227	223	225	227
1006		238	236	235	236	239	240	239
<b>20 mg [REDACTED] kg</b>								
1001		235	228	229	233	228	228	226
1002		252	243	232	231	237	239	240
1003		235	232	220	219	227	231	226
1004		226	225	222	215	212	214	218
1005		240	240	231	231	225	230	225
<b>50 mg [REDACTED] kg</b>								
1001		242	236	234	231	231	234	230
1002		250	240	239	239	237	240	245
1003		242	231	223	221	222	226	226
1004		233	230	219	213	213	216	218
1005		251	234	223	231	241	238	239
1006		242	241	236	236	233	237	235
<b>150 mg [REDACTED] kg</b>								
1001		246	251	240	234	238	236	226
1002		292	291	283	271	254	273	270
1003		272	266	240	250	245	244	247
1004		259	249	225	226	227	242	237

[REDACTED]  
Cardiovascular Safety Evaluation of Orally Administered [REDACTED] in Beagle Dogs**Individual Corrected QT Interval, msec - MALE**

Group, Animal Number	Study Interval (hour:minute)							
	17:00	18:00	19:00	20:00	21:00	22:00	23:00	24:00
<b>150 mg [REDACTED] kg</b>								
1005	255	250	234	235	243	249	246	243
1006	265	259	257	251	250	254	254	255

Appendix 16  
Bioanalysis Report

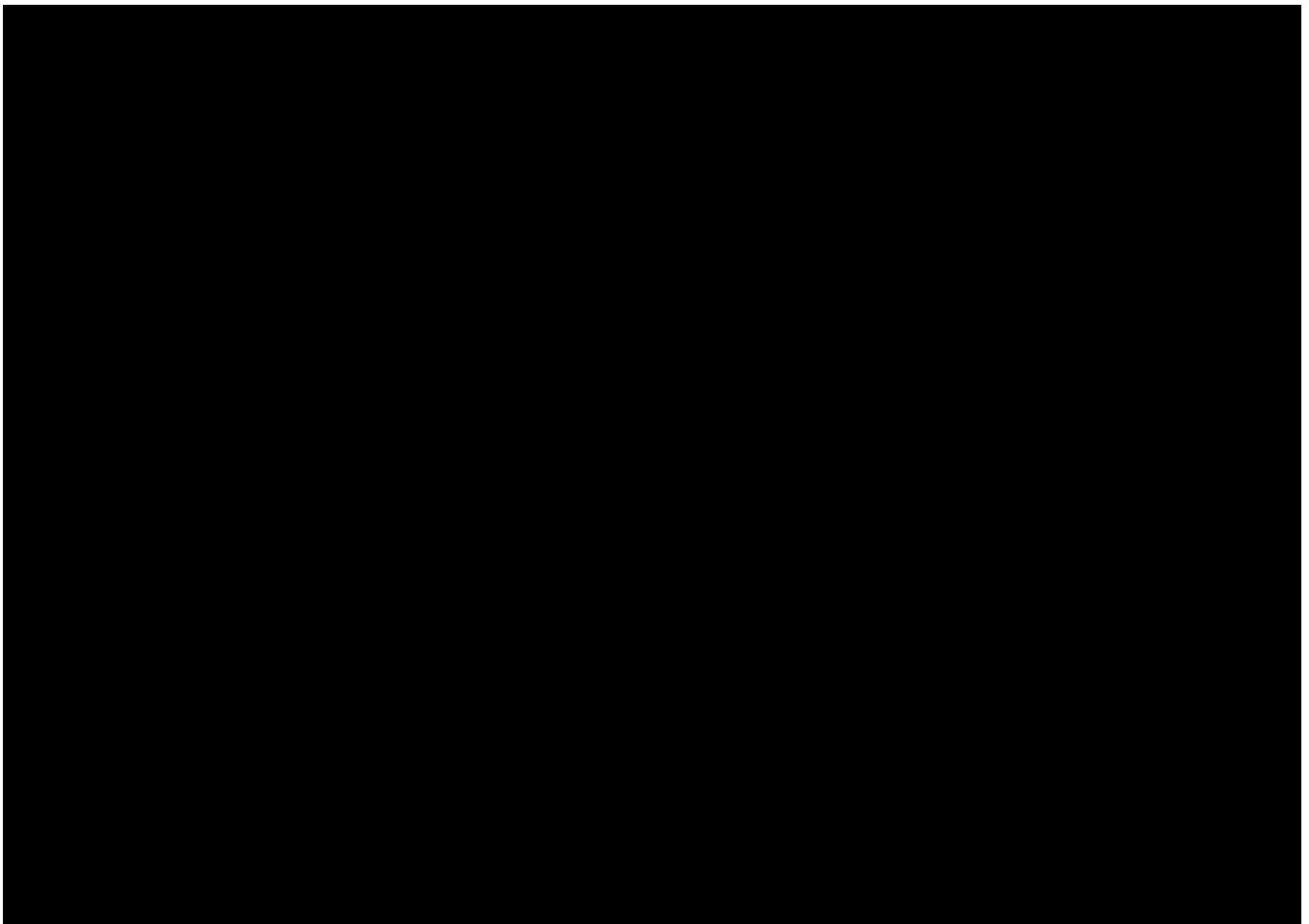
**1.0**

**Title Page**

Concentration Determination for Cardiovascular  
Safety Evaluation of Orally Administered [REDACTED]  
[REDACTED] in Beagle Dogs

Study Plan [REDACTED]

[REDACTED] Study Number: [REDACTED]



---

**2.0 Table of Contents**

<b>1.0</b>	<b>Title Page .....</b>	<b>1</b>
<b>2.0</b>	<b>Table of Contents .....</b>	<b>2</b>
<b>3.0</b>	<b>Quality Assurance Statement .....</b>	<b>4</b>
<b>4.0</b>	<b>Compliance with Good Laboratory Practice</b>	
	<b>Regulations .....</b>	<b>5</b>
<b>5.0</b>	<b>Study Plan Information.....</b>	<b>6</b>
<b>6.0</b>	<b>Experimental .....</b>	<b>6</b>
<b>7.0</b>	<b>Results and Discussion.....</b>	<b>7</b>
<b>8.0</b>	<b>Summary of Analytical Method .....</b>	<b>8</b>
<b>9.0</b>	<b>Summary of Sample Analysis .....</b>	<b>8</b>
9.1	Analyte(s) and Internal Standard(s).....	8
9.2	Performance of the Assay during Sample Analysis .....	9
9.3	Reassay History .....	9
9.4	Deactivated Samples .....	9
9.5	Incurred Sample Reproducibility .....	9
9.6	Sample Tracking and Stability .....	10
9.7	Quantitation .....	10
9.8	Data Storage .....	11
9.9	Deviations.....	12
9.10	Discussion.....	12
9.11	Source of Data .....	13
9.12	Revision History .....	14
<b>10.0</b>	<b>Tables .....</b>	<b>15</b>
<b>11.0</b>	<b>Figures.....</b>	<b>23</b>

**List of Tables**

Table 1.	Plasma Concentrations of [REDACTED] for Individual Animals at 6h Post dose in Treatments 2, 3, 4 (20, 50, 150 mg/kg).....	15
----------	---------------------------------------------------------------------------------------------------------------------------	----

---

Table 2.	Summary of Calibration Curves for [REDACTED] .....	16
Table 3.	Statistical Summary of Calibration Curves for Linearity for [REDACTED] .....	18
Table 4.	Summary of Quality Control Samples for [REDACTED] .....	19
Table 5.	Summary of Dilution Quality Control Samples for [REDACTED] .....	20
Table 6.	Summary of Study Samples Repeated for [REDACTED] .....	21
Table 7.	Plasma Concentrations of [REDACTED] for Individual Animals at 6h Post dose in Treatment 1 (0 mg/kg/day in 0.5% hydroxypropylmethylcellulose (HPMC; low viscosity), 0.1% Tween 80 in NANOPure Diamond Ultrapure water (w/v)) .....	22

## List of Figures

Figure 1.	Plot of [REDACTED] QC.3 Samples .....	23
Figure 2.	Plot of [REDACTED] QC.2 Samples .....	24
Figure 3.	Plot of [REDACTED] QC.1 Samples .....	25
Figure 4.	Representative Chromatogram of a Blank Dog Plasma Sample from Study [REDACTED] .....	26
Figure 5.	Representative Chromatogram from an LLOQ Calibration Standard from Study [REDACTED] .....	27
Figure 6.	Representative Chromatogram from a Sample from Study [REDACTED] (Animal 1005 Day 1 6 h).....	28
Figure 7.	Mean ( $\pm$ SEM) Plasma Concentrations of [REDACTED] versus Time in Dog after Dosing in Treatments 2, 3, 4 .....	29

## List of Appendices

Appendix A.	List of Abbreviations .....	30
Appendix B.	Certificate(s) of Analysis.....	31

**4.0****Compliance with Good Laboratory Practice  
Regulations**

The portion of "Cardiovascular Safety Evaluation of Orally Administered [REDACTED]  
Free Form in Beagle Dogs [REDACTED] conducted by [REDACTED]  
[REDACTED] and described in this report entitled: Concentration Determination  
for Cardiovascular Safety Evaluation of Orally Administered [REDACTED] Free Form in  
Beagle Dogs was performed in compliance with:

- Food and Drug Administration, United States Code of Federal Regulations,  
Title 21, Part 58: Good Laboratory Practice for Nonclinical Laboratory  
Studies

---

## 5.0 Study Plan Information

The numeric codes describing drug and study number in this report may omit dashes separating the numeric suffix. These descriptors are synonymous to the codes containing dashes.

**Study Plan Title:** Cardiovascular Safety Evaluation of Orally Administered [REDACTED]  
[REDACTED] in Beagle Dogs.

**Study Plan Number:** [REDACTED]

**Objectives:** The purpose of this phase of the study was to determine plasma concentrations of [REDACTED] and to evaluate exposure.

**Testing Site and Principal Investigator:** The bioanalytical portion of this study was conducted by [REDACTED]  
[REDACTED].

**Personnel:** [REDACTED]  
[REDACTED].

**Analytical Target:** [REDACTED]

## 6.0 Experimental

**Sample Analysis:** The concentration of [REDACTED] in plasma was determined in the [REDACTED] using a validated LC-MS/MS method. A brief description of the method is presented in [Section 8.0](#) of this report. The method and summary of sample analysis is described in [Section 9.0](#) of this report.

**Data Treatment:** None

---

## 7.0 Results and Discussion

The plasma concentrations from individual animals in Treatment Groups 2, 3, and 4 are tabulated in [Table 1](#). Samples from Treatment Group 1 (0 mg/kg [REDACTED] were analyzed to determine if drug was present in animals dosed with vehicle only. No quantifiable levels of [REDACTED] were present in animals from Treatment Group 1. Plasma concentrations from individual animals in Treatment Group 1 are tabulated in [Table 7](#). A log-linear plot of the plasma concentration versus time curves are presented in [Figure 7](#).

## 8.0 Summary of Analytical Method

**Analytical Method:** Bioanalytical Method for the Determination of [REDACTED] and [REDACTED] in Dog Plasma K<sub>2</sub>EDTA using Liquid-Liquid Extraction Followed by LC-MS/MS Detection, issued July 2019.

## 9.0 Summary of Sample Analysis

The following table summarizes information relating to the assay of samples from this study.

Scope	Analysis of [REDACTED] in Dog Plasma K <sub>2</sub> EDTA
Sample Volume	25 µL
Calibration Standards	8 standard levels ranging from 249 ng/mL to 251000 ng/mL
Sample Container	Polypropylene tubes
Analytical Method	Liquid-Liquid Extraction Followed by LC-MS/MS Detection
Analysis Site	[REDACTED]
Blinding	None
Assayed by	Animal
Randomization of Chromatograms for Regulatory Submission	If requested, chromatograms from run ID 1 will be submitted.
Lower Limit of Quantitation for sample analysis	249 ng/mL
Number of Samples Received	24
Number of Samples Analyzed	24

## 9.1 Analyte(s) and Internal Standard(s)

Name	Potency	Source	Lot Number
[REDACTED]	99.5%	[REDACTED]	[REDACTED]
[REDACTED]	NA	[REDACTED]	[REDACTED]

\*Refer to Appendix B for the certificate of analysis

**9.2****Performance of the Assay during Sample Analysis**

The performance of the assay during sample analysis is presented in the following table.

Names	Results for [REDACTED]	Data
Calibration Standards	Mean Bias -2.4% at LLOQ Mean Bias between -8.8 and 11.6% at higher standard levels $r^2 \geq 0.994101$ All standards accepted with a final bias $\leq 15\%$ except at LLOQ which were $\leq 20\%$ .	<a href="#">Table 2</a> <a href="#">Table 3</a>
QCs	$\geq 2/3$ of QCs in each run were biased $\leq 15\%$ from theory. $\geq 50\%$ of QCs at each concentration were biased $\leq 15\%$ from theory. Mean Bias between -9.8 and 4.5% $CV \leq 3.6\%$	<a href="#">Table 4</a>
Dilution QCs	$\geq 2/3$ of dilution QCs in each run with accepted dilution results were biased $\leq 15\%$ from theory. Mean Bias = 5.2% $CV = 6.9\%$	<a href="#">Table 5</a>

Concentrations are reported to three significant figures. Graphical representation of QC performance is presented as [Figure 1- Figure 3](#).

**9.3****Reassay History**

No reassays were performed in this study.

**9.4****Deactivated Samples**

No study samples were deactivated in this study.

**9.5****Incurred Sample Reproducibility**

Incurred samples reproducibility was not performed as part of this study.

## 9.6 Sample Tracking and Stability

First Sampling Date	15-Jul-2019	Sample conditions upon receipt	Frozen
First Shipping Date	16-Jul-2019		
First and Last Receiving Dates	17-Jul-2019 and 21-Aug-2019	Storage conditions after sample received	~ -70°C
Extraction Date	22-Aug-2019		
Maximum Storage Period	38 days at ~ -70°C*		
Validated Storage Stability	71 days at ~ -70°C		
Maximum Number of Freeze Thaw Cycles and Time at Room Temperature Experienced by Study Samples during the Conduct of the Analysis	1 cycle and 3 hours at room temperature*		
Number of Validated Freeze Thaw Cycles and Time at Room Temperature	6 cycles and 17 hours at room temperature		

\*Maximum storage period and maximum number of freeze thaw cycles and time at room temperature experienced by study samples during the conduct of analysis was calculated using [REDACTED]. Refer to Section 9.11 Source of Data for the reference to [REDACTED] where the sample storage tracking calculations and information can be found.

## 9.7 Quantitation

Peak areas of the analyte(s) and internal standard(s) were obtained using [REDACTED]  
[REDACTED] All samples within a run used the same integration parameters.

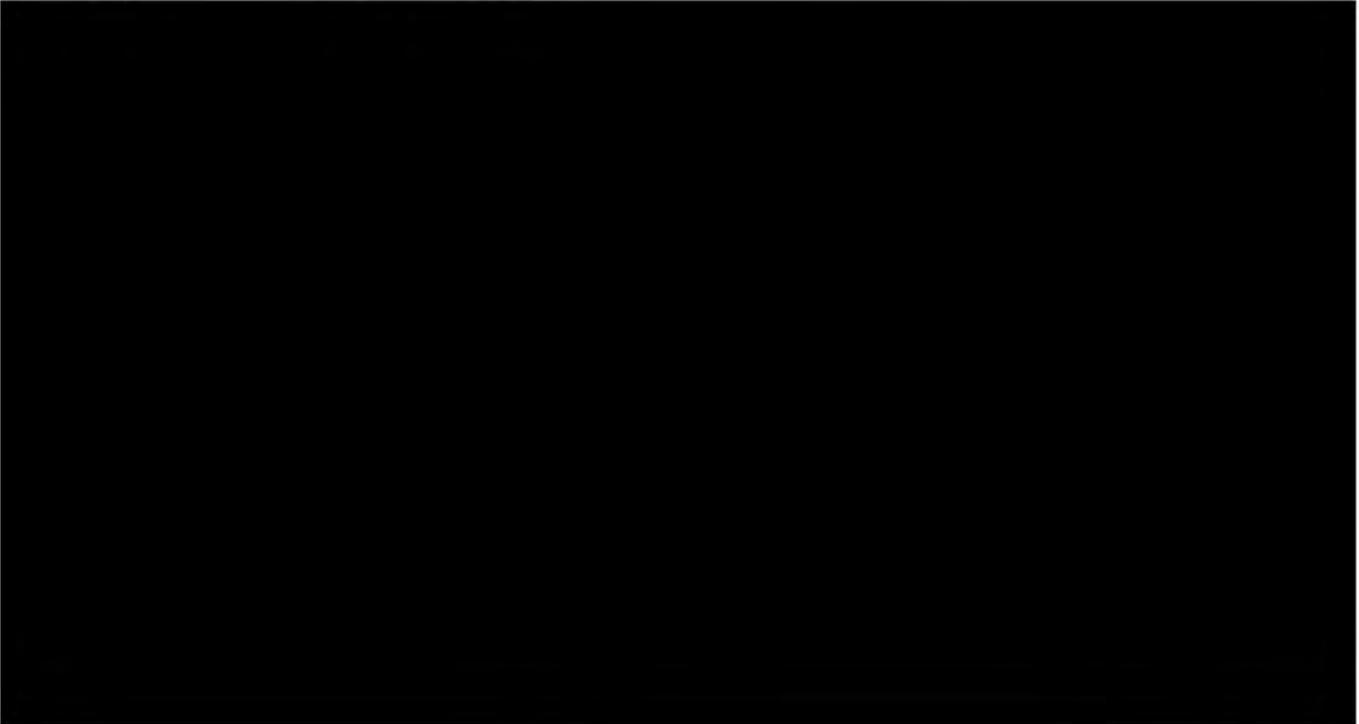
The integration data was imported into the LIMS for regression and quantitation. A calibration curve was derived from the peak area ratio versus the concentration of the standards. A weighting of  $1/x^2$  (where x is the concentration of a given standard) was used for curve fitting. The regression equation for the calibration curve was then used to back-calculate the measured concentrations. For each standard and QC, the results were compared to the theoretical concentrations to obtain the accuracy of each level measured. Results from the QC samples were used to verify accuracy and precision of the analytical

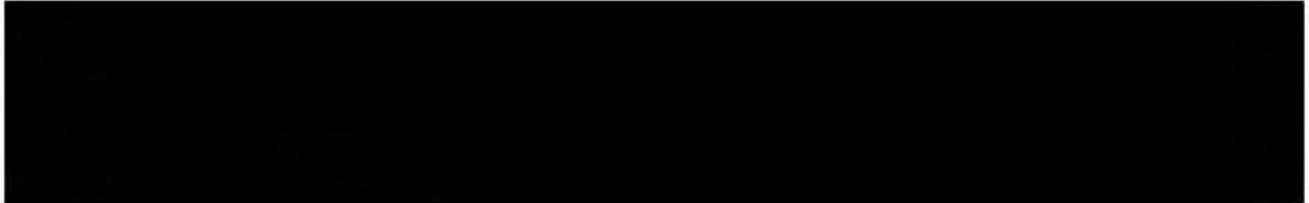
results for the study samples. Samples with concentrations above the upper limit of quantitation (AQL) for any given run were diluted and assayed with a set of QC samples with the same dilution factor. All reported results were generated within the quantitation limits established by the run calibration curves. Values that were less than the lower limit of quantitation for a given run were reported as BQL.

All individual sample analyte concentrations presented in this report were produced by [REDACTED] All remaining summary statistical calculations presented in this report were produced by [REDACTED] Where applicable, exceptions are indicated as footnotes to the affected tables. Where such exceptions involve additional systems used to perform calculations (*e.g.*, spreadsheets), software validation status is also indicated. Simple mathematical calculations (*e.g.*, *via* calculator) are not attributed.

Representative chromatograms from a blank sample, LLOQ calibration standard, and a study sample from Study [REDACTED] are presented in [Figure 4-Figure 6](#).

#### **9.8 Data Storage**





**9.9 Deviations**

None.

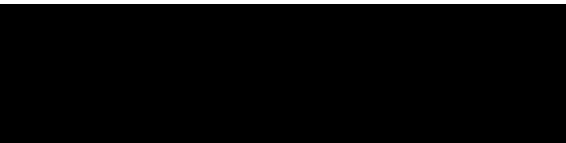
**9.10 Discussion**

The method performed as expected during the course of sample analysis.



**9.12                  Revision History**

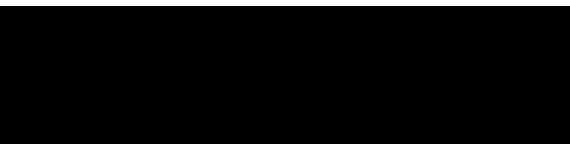
Version 1.0 New Document



## 10.0 Tables

**Table 1. Plasma Concentrations of [REDACTED] for Individual Animals at 6h Post dose in Treatments 2, 3, 4 (20, 50, 150 mg/kg)**

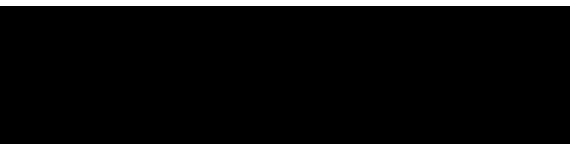
Sex	Animal	Plasma Concentration (µg/mL)		
		20	50	150 mg/kg
Male	1001	32.5	122	213
	1002	32.1	86.1	451
	1003	48.9	117	445
	1004	26.5	157	354
	1005	26.8	69.6	436
	1006	20.4	126	450
Overall	Mean	31.2	113	392
	SEM	3.97	12.7	38.8
	n	6	6	6

**Table 2.** Summary of Calibration Curves for [REDACTED]

Run Date	Run Number	Calculated Concentration ( $\mu\text{g/mL}$ ) and %Bias							
		STD 8		STD 7		STD 6		STD 5	
		<b>0.249</b>	%Bias	<b>0.500</b>	%Bias	<b>1.73</b>	%Bias	<b>5.76</b>	%Bias
26-Aug-2019	1	0.243	-2.4	0.503	0.6	1.93	11.6	6.19	7.5
Mean		0.243		0.503		1.93		6.19	
S.D.		0.00		0.00		0.00		0.00	
%CV		0.0		0.0		0.0		0.0	
%Bias		-2.4		0.6		11.6		7.5	
n		1		1		1		1	

Values in bold are theoretical concentrations.

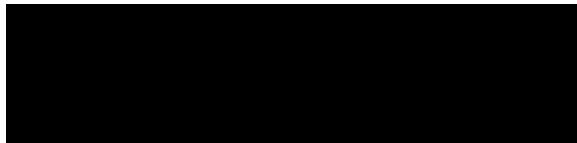


**Table 2.** Summary of Calibration Curves for [REDACTED] (Cont.)

Run Date	Run Number	Calculated Concentration ( $\mu\text{g/mL}$ ) and %Bias							
		STD 4		STD 3		STD 2		STD 1	
		<b>19.0</b>	%Bias	<b>62.1</b>	%Bias	<b>215</b>	%Bias	<b>251</b>	%Bias
26-Aug-2019	1	19.4	2.1	60.5	-2.6	196	-8.8	232	-7.6
Mean		19.4		60.5		196		232	
S.D.		0.00		0.00		0.00		0.00	
%CV		0.0		0.0		0.0		0.0	
%Bias		2.1		-2.6		-8.8		-7.6	
n		1		1		1		1	

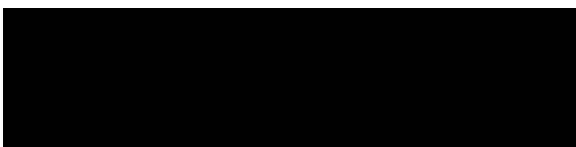
Values in bold are theoretical concentrations.



**Table 3. Statistical Summary of Calibration Curves for Linearity for [REDACTED]**

Run Date	Run Number	Slope	Intercept	r <sup>2</sup>
26-Aug-2019	1	0.000027	0.001612	0.994101



**Table 4.** Summary of Quality Control Samples for [REDACTED]

Run Date	Run Number	Calculated Concentration ( $\mu\text{g/mL}$ ) and %Bias					
		QC.3	QC.2	QC.1			
		<b>0.624</b>	%Bias	<b>11.2</b>	%Bias	<b>204</b>	%Bias
26-Aug-2019	1	0.586	-6.1	11.7	4.5	186	-8.8
		0.612	-1.9	11.2	0.0	185	-9.3
		0.632	1.3	11.8	5.4	179	-12.3
		0.633	1.4	12.2	8.9	185	-9.3
Mean		0.616		11.7		184	
S.D.		0.0221		0.411		3.20	
%CV		3.6		3.5		1.7	
%Bias		-1.3		4.5		-9.8	
n		4		4		4	

Values in bold are theoretical concentrations.



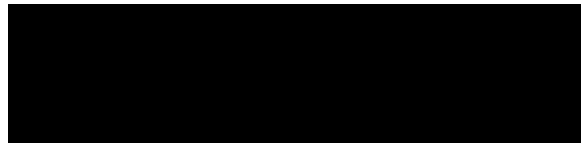
**Table 5. Summary of Dilution Quality Control Samples for [REDACTED]**

Run Date	Run Number	Dilution Factor	Calculated Concentration ( $\mu\text{g/mL}$ ) and %Bias	
			<b>501</b>	%Bias
26-Aug-2019	1	10	506	1.0
			545	8.8
			529	5.6
			~579	15.6
			531	6.0
			471	-6.0
Mean			527	
S.D.			36.4	
%CV			6.9	
%Bias			5.2	
n			6	

Values in bold are theoretical concentrations.

~ &gt; 15% Theoretical



**Table 6. Summary of Study Samples Repeated for [REDACTED]**

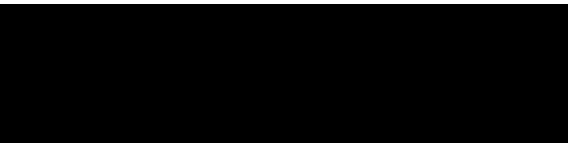
<b>Reason for Repeat Analysis</b>	<b>Number of Repeat Samples</b>	<b>% of Total Analyzed Samples</b>
Run rejected	0	0.0
Total*	0	0.0

\* A sample may be included in more than one reason category.

Total Number of Analyzed Samples = 24

% of Total Analyzed Samples = (Number of Repeat Samples/Total Number of Analyzed Samples) \* 100





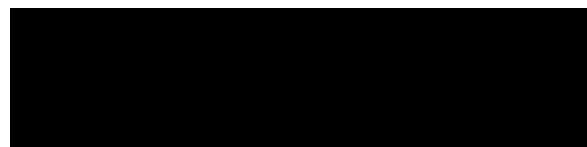
**Table 7. Plasma Concentrations of [REDACTED] for Individual Animals at 6h Post dose in Treatment 1 (0 mg/kg/day in 0.5% hydroxypropylmethylcellulose (HPMC; low viscosity), 0.1% Tween 80 in NANOPure Diamond Ultrapure water (w/v))**

Sex	Animal	Plasma Concentration ( $\mu\text{g/mL}$ )
		0 mg/kg
Male	1001	BQL <sup>1</sup>
Male	1002	BQL <sup>1</sup>
Male	1003	BQL <sup>1</sup>
Male	1004	BQL <sup>1</sup>
Male	1005	BQL <sup>1</sup>
Male	1006	BQL <sup>1</sup>

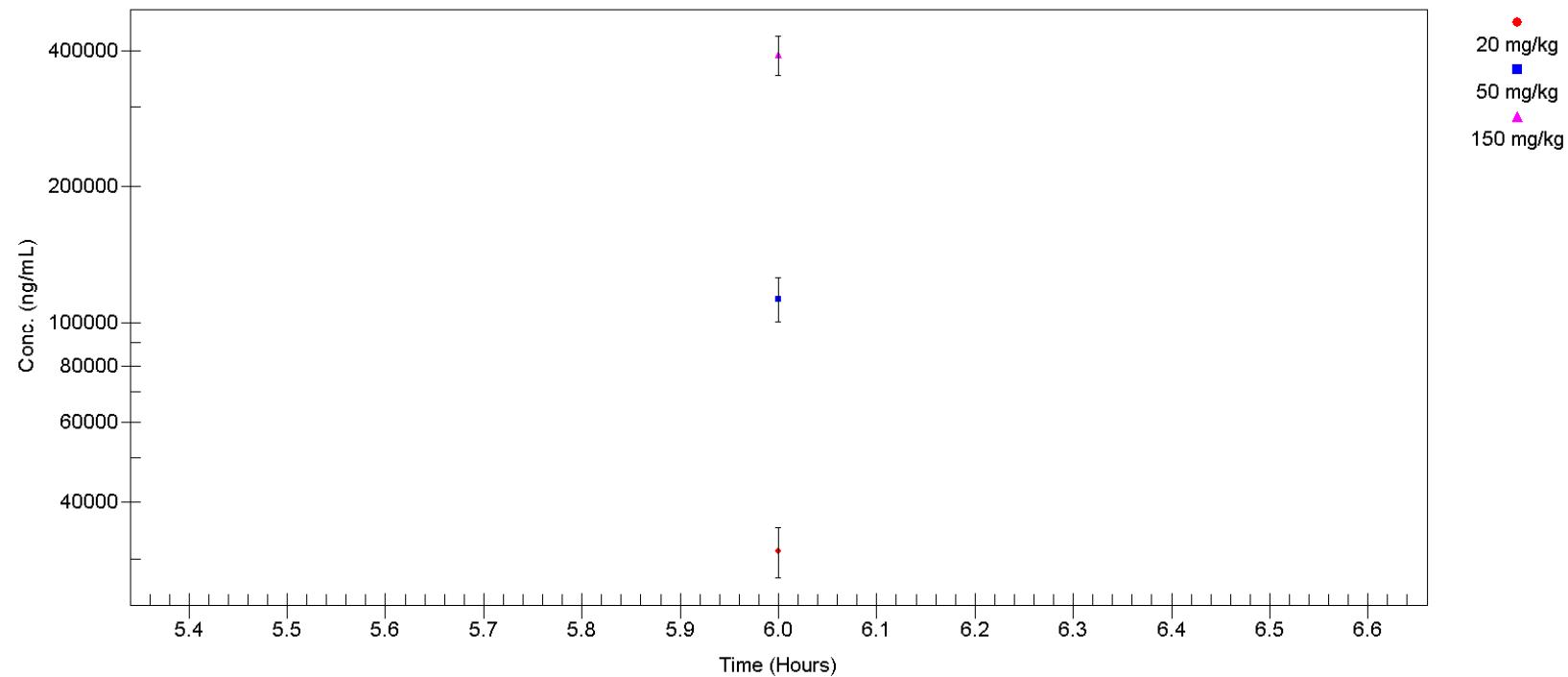
<sup>1</sup> BQL – Concentration < 0.249  $\mu\text{g/mL}$

This table was manually added using data from LIMS.





**Figure 7. Mean ( $\pm$ SEM) Plasma Concentrations of [REDACTED] versus Time in Dog after Dosing in Treatments 2, 3, 4**



This figure was manually added [REDACTED]



**Appendix A. List of Abbreviations****List of Abbreviations**

<b>Abbreviation</b>	<b>Definitions</b>
BA-ELN or BA ELN	Bioanalytical Electronic Laboratory Notebook
BQL	Below the lower quantitation limit
Conc.	Concentration
CV	Coefficient of variation, a measure of precision
GDA	Global Drug Analysis
ID	Identification
LC	HPLC, High-performance liquid chromatography
LIMS	Laboratory Information Management System
LLOQ	Lower limit of quantitation
MS/MS	Tandem mass spectrometer or tandem mass spectrometric
n	Number
NA	Not applicable
QC	Quality control sample
r <sup>2</sup>	Coefficient of determination
SD	Standard deviation
SDMS	Scientific Data Management System
STD	Calibration standard