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14. ABSTRACT

The purpose of this study was to evaluate the therapeutic capacity of 3,4-diaminopyridine phosphate (amifampridine phosphate drug substance; 3,4-DAPP) treatment to acutely reverse toxicity in cynomolgus monkeys systemically intoxicated with botulinum neurotoxin serotype A1 (BoNT/A1). To accomplish this, male cynomolgus monkeys (of Mauritius origin) were subjected to systemic intoxication with BoNT/A1 was achieved in all animals by a single intramuscular (IM) injection of a BoNT/A1 dosing solution into the right calf muscle at a a challenge level of 2.5x the BoNT/A1 median lethal dose (LD50) for IM intoxication in cynomolgus monkeys. Following challenge, animals were observed for toxic signs commonly associated with botulism (e.g., ptosis, muscular weakness, respiratory distress, oral/nasal discharge). Clinical severity scoring was performed based on the presence and/or severity of select toxic signs. A clinical severity score of 1 or greater of a clinical sign associated with toxicity from botulinum toxin (ptosis, muscular weakness, respiratory distress, oral or nasal discharge) served as a trigger to initiate subcutaneous (SC) treatments approximately two hours after the initial trigger. As the objective of this study was to show reversal of toxicity, a 2-hour delay from the initial trigger was instituted to ensure sufficient toxicity was present prior to treatment. Animals received SC treatment with either vehicle (saline), 2.06 mg/kg of 3,4-DAPP, or 4.12 mg/kg of 3,4-DAPP. Repeat treatments were performed at approximately 4-hour intervals thereafter. Following IM administration of BoNT/A1 at a challenge level of 2.5x LD50, all animals were observed to remain in clinically normal status on average for approximately 48 hours. The time-to-first observation of toxicity following challenge ranged from 35 hours and 21 minutes to 67 hours and 42 minutes. Leading signs of intoxication included ataxia, labored breathing, shallow respirations, coughing, oral/nasal discharge, and hunched posture. The number and severity of abnormal observations increased over time as disease progressed. Other abnormal clinical signs commonly observed following challenge were ptosis, lethargy, gasping, prostrate posture, and death. All abnormal observations were considered specifically attributed to administration of the challenge agent (BoNT/A1). At the dosing frequency interval employed in this study (~4 hour intervals), SC treatment with 3,4-DAPP at 2.06 or 4.12 mg/kg did not completely prevent disease progression after initial presentation of toxicity as all animals on study succumbed to challenge prior to scheduled euthanasia at 7-days post-challenge. Cage-side observations provided subjective evidence of acute toxicity reversal following 3,4-DAPP dosing was found to be supported by a general trend of reductions in clinical severity scores at 15- and 120-minutes after treatment administration. An observed reversal effect was found to be more frequent and more robust at earlier treatment time-points and in animals receiving the higher dose of 3,4-DAPP (4.12 mg/kg), including 2 of 3 animals returning to clinical severity scores of 0 after initial presentation of disease. In general, 3,4-DAPP treatments subjectively (per cage-side observations) appeared less effective at resolving toxicity at the late-stages of disease when severity scores were greater, and mortality was imminent. However, 3,4-DAPP treatment at the higher dose level tested (4.12 mg/kg) appeared to prolong survival, as evidenced by greater time-to-death values following initial presentation of toxicity. Evidence of 3,4-DAPP mediated reversal of BoNT/A1 toxicity was supported by improvements in ABG measurements following treatment dosing in a limited sample set (n = 1 for each group). As disease severity progressed following BoNT/A1 challenge, ABG profiles were generally characterized by a reduction of pO2, an increase in pCO2, and a decrease in pH. At the 15-minute post-treatment sampling time-point, with one exception, 3,4-DAPP dosing at 2.06 mg/kg or 4.12 mg/kg generally improved blood gas parameters by increasing pO2, decreasing pCO2, and restoring pH. However, sustained improvement in ABG parameters following 3,4-DAPP dosing was not achieved as ABG values for pO2 were generally decreased at the next sampling time-point approximately 4 hours later. While treatment with 3,4-DAPP did not appear to acutely alter telemetry endpoints, it did appear to positively alter the clinical trajectory of physiologic function after repeated treatments. Compared to animals treated with saline, animals treated with 3,4-DAPP sustained respiratory rate for a greater length of time. Similarly, 3,4-DAPP treatment (at the 4.12 mg/kg dose level) was found to sustain body temperature for a longer period compared to other groups. Analysis of cardiac function and animal activity was less conclusive. In contrast to other groups, animals receiving 4.12 mg/kg of 3,4-DAPP generally displayed more dynamic heart rate effects, with varying increases and decreases in heart rate occurring throughout the dosing period until animal death.

15. SUBJECT TERMS

3,4-diaminopyridine phosphate, amifampridine, firdapse, 3,4-DAP, monkey, nonhuman primate, botulinum neurotoxin, subcutaneous, arterial blood gas, telemetry

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Efficacy Evaluation of 3,4-Diaminopyridine to Acutely Reverse Toxicity in Cynomolgus Monkeys Intoxicated by Botulinum Neurotoxin Serotype A1

Final Report

On

June 30, 2022

For

Study Number B05929

To

SPONSOR:
Defense Threat Reduction Agency
Chemical & Biological Technologies Department
Vaccines/Therapeutics Division (CBM)
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by

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GLP COMPLIANCE STATEMENT

This study was conducted at the Battelle Biomedical Research Center (BBRC) using practices consistent with, but not in strict accordance with, 21 CFR Part 58, Good Laboratory Practice (GLP) Regulations. Facility standard operating procedures (SOPs) and practices were followed.

SUMMARY

The purpose of this study was to evaluate the therapeutic capacity of 3,4-diaminopyridine phosphate (amifampridine phosphate drug substance; 3,4-DAPP) treatment to acutely reverse toxicity in cynomolgus monkeys systemically intoxicated with botulinum neurotoxin serotype A1 (BoNT/A1). To accomplish this, male cynomolgus monkeys (of Mauritius origin) were surgically implanted with Data Sciences International (DSI) L11R telemetry units capable of collecting continuous activity, respiratory, cardiac, and body temperature measurements. A select subset of animals (3 of 8) additionally had previously implanted vascular access ports (VAPs) for the collection of arterial blood to be used for arterial blood gas (ABG) analysis. Animals were randomized by body weight to one of three groups to ensure each group was represented with an animal that had a functioning arterial VAP. Systemic intoxication with BoNT/A1 was achieved in all animals by a single intramuscular (IM) injection of a BoNT/A1 dosing solution into the right calf muscle at a challenge level of 2.5x the BoNT/A1 median lethal dose (LD_{50}) for IM intoxication in cynomolgus monkeys. Following challenge, animals were observed for toxic signs commonly associated with botulism (e.g., ptosis, muscular weakness, respiratory distress, oral/nasal discharge). Clinical severity scoring was performed based on the presence and/or severity of select toxic signs. A clinical severity score of 1 or greater of a clinical sign associated with toxicity from botulinum toxin (ptosis, muscular weakness, respiratory distress, oral or nasal discharge) served as a trigger to initiate subcutaneous (SC) treatments approximately two hours after the initial trigger. As the objective of this study was to show reversal of toxicity, a 2-hour delay from the initial trigger was instituted to ensure sufficient toxicity was present prior to treatment. Animals received SC treatment with either vehicle (saline), 2.06 mg/kg of 3,4-DAPP, or 4.12 mg/kg of 3,4-DAPP. Repeat treatments were performed at approximately 4-hour intervals thereafter. The 4-hour interval was chosen based on efficacy data associated with the use of 3,4-DAPP for the treatment of Lambert-Eaton Mysasthenic syndrome (LEMS) as well as to maintain consistency and allow association with the pharmacokinetic evaluation (PK) performed using the same interval. Additional post-treatment observations were performed 15 minutes (± 2 minutes) after each administration of 3,4-DAPP. Endpoints used to evaluate potential reversal of BoNT/A1-induced toxicity with 3,4-DAPP treatment included clinical observations and associated clinical severity scores, ABG analysis, respiratory telemetry, cardiac telemetry, and body temperature. While not designed specifically as a survival study, time-to-death calculations were performed based on mortality outcomes.

Following IM administration of BoNT/A1 at a challenge level of 2.5x LD_{50}, all animals were observed to remain in clinically normal status on average for approximately 48 hours. The time-to-first observation of toxicity following challenge ranged from 35 hours and 21 minutes to 67 hours and 42 minutes. Leading signs of intoxication included ataxia, labored breathing, shallow respirations, coughing, oral/nasal discharge, and hunched posture. The number and severity of abnormal observations increased over time as disease progressed. Other abnormal clinical signs commonly observed following challenge were ptosis, lethargy, gasping, prostrate posture, and death. All abnormal observations were considered specifically attributed to administration of the challenge agent (BoNT/A1). In general, the overall frequency and severity of clinical observations following BoNT/A1 challenge was similar across all treatment

groups (saline, 2.06 mg/kg of 3,4-DAPP, or 4.12 mg/kg of 3,4-DAPP) throughout the post-challenge observation period. At the dosing frequency interval employed in this study (~4 hour intervals), SC treatment with 3,4-DAPP at 2.06 or 4.12 mg/kg did not completely prevent disease progression after initial presentation of toxicity as all animals on study succumbed to challenge prior to scheduled euthanasia at 7-days post-challenge. Cage-side observations provided subjective evidence of acute toxicity reversal following 3,4-DAPP dosing was found to be supported by a general trend of reductions in clinical severity scores at 15- and 120-minutes after treatment administration. An observed reversal effect was found to be more frequent and more robust at earlier treatment time-points and in animals receiving the higher dose of 3,4-DAPP (4.12 mg/kg), including 2 of 3 animals returning to clinical severity scores of 0 after initial presentation of disease. Partial reversal in some animals following 3,4-DAPP dosing was evidenced by resolution of oral/nasal discharge, reductions in muscular weakness (postural improvements), resolution of ptosis, and general improvements in observed respiratory patterns. In general, 3,4-DAPP treatments subjectively (per cage-side observations) appeared less effective at resolving toxicity at the late-stages of disease when severity scores were greater, and mortality was imminent. However, 3,4-DAPP treatment at the higher dose level tested (4.12 mg/kg) appeared to prolong survival, as evidenced by greater time-to-death values following initial presentation of toxicity.

Evidence of 3,4-DAPP mediated reversal of BoNT/A1 toxicity was supported by improvements in ABG measurements following treatment dosing in a limited sample set (n = 1 for each group). As disease severity progressed following BoNT/A1 challenge, ABG profiles were generally characterized by a reduction of pO_2, an increase in pCO_2, and a decrease in pH. At the 15-minute post-treatment sampling time-point, with one exception, 3,4-DAPP dosing at 2.06 mg/kg or 4.12 mg/kg generally improved blood gas parameters by increasing pO_2, decreasing pCO_2, and restoring pH. However, sustained improvement in ABG parameters following 3,4-DAPP dosing was not achieved as ABG values for pO_2 were generally decreased at the next sampling time-point approximately 4 hours later.

While treatment with 3,4-DAPP did not appear to acutely alter telemetry endpoints, it did appear to positively alter the clinical trajectory of physiologic function after repeated treatments. Compared to animals treated with saline, animals treated with 3,4-DAPP sustained respiratory rate for a greater length of time. Similarly, 3,4-DAPP treatment (at the 4.12 mg/kg dose level) was found to sustain body temperature for a longer period compared to other groups. Analysis of cardiac function and animal activity was less conclusive. In contrast to other groups, animals receiving 4.12 mg/kg of 3,4-DAPP generally displayed more dynamic heart rate effects, with varying increases and decreases in heart rate occurring throughout the dosing period until animal death.

Collectively, given the copious data obtained from BoNT/A1-intoxicated cynomolgus monkeys, the study objective of evaluating the potential therapeutic capacity of 3,4-DAPP treatment was considered to be successfully met.

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1 INTRODUCTION

The purpose of this study was to evaluate the therapeutic capacity of 3,4-diaminopyridine phosphate (amifampridine phosphate drug substance; 3,4-DAPP) to acutely reverse toxicity in cynomolgus monkeys systemically intoxicated with botulinum neurotoxin serotype A1 (BoNT/A1).

This study was conducted at the Battelle Biomedical Research Center (BBRC) under the direction of Phillip H. Beske, PhD, DABT. The study was initiated on June 1, 2021, with the signing of the protocol. The in-life portion of the study began on September 13, 2021, with the initiation of BoNT/A1 challenge and was concluded on September 17, 2021 when the final animal succumbed to challenge.

Intramuscular challenge administration of BoNT/A1 was performed on a single challenge day. Post-challenge subcutaneous treatments with vehicle (saline) or test article (2.06 mg/kg 3,4-DAPP or 4.12 mg/kg of 3,4-DAPP) were animal specific and were initiated after the manifestation of select toxic signs associated with botulism (i.e. muscular weakness, respiratory distress, oral/nasal discharge). Repeat dosing was performed with a dosing interval of approximately 4 hours. Clinical parameters used to evaluate reversal of toxicity were survival, clinical observations, clinical severity scores, arterial blood gas analysis (in select animals, and continuous telemetry for activity, respiratory impedance measurements, electrocardiograms (ECGs), and body temperatures.

AmplifyBio (West Jefferson, OH) was designated as the test site for pre-surgery animal holding, surgery for telemeter implantation, and post-surgical animal recovery. Carolyn Fetzek, DVM, was designated as the animal surgeon. Data Sciences International (DSI; St. Paul, MN) was designated as the test site for telemetry data analysis. Heather Simenson, BS, CRAT, was designated as the Principal Investigator for analysis. Larry P. Tilley, DVM, DACVIM (Vet Med Consultants, Inc., Santa Fe, NM) was designated as a contributing scientist for electrocardiography interpretation and review.

Defense Threat Reduction Agency was the Sponsor of the study. Lindsay Odell, PhD, was designated as the Sponsor Representative.

The study protocol and a summary of deviations are presented in Appendix A and Appendix C, respectively.

2 MATERIALS AND METHODS

2.1 CHALLENGE MATERIAL, TEST ARTICLE, AND VEHICLE

2.1.1 Challenge Material

The BoNT/A1 challenge material was identified as follows:

Product Name:	Botulinum neurotoxin complex serotype A1 (BoNT/A1)
Description:	BoNT/A1 provided by Metabiologics, Inc. Diluted in sterile gel phosphate buffer (pH 6.2) containing 0.2% (w/v) gelatin to achieve a final dosing solution of 1,000x mouse intraperitoneal LD_{50s}/mL ($MIPLD_{50}$)
Batch/Lot Number:	A081508-01
Potency:	Stock potency solution determined by Battelle in May 2021 to be 521,330 $MIPLD_{50}$/mL.
Storage Conditions:	Frozen at ≤ -60°C until formulation, then stored at 2 to 8°C for up to 4 hours before administration.
Expiration Date:	Not assigned. Stability is assessed upon use per cumulative sum control charting (CUSUM) of assay performance and not on the original manufacturer's expiration date assignment of 08/15/2009.

The original manufacturers Certificate of Analysis (CoA) and updated potency characterization for the challenge material are included in Appendix D.

2.1.2 Test Article

The 3,4-diaminopyridine phosphate (3,4-DAPP) test article was identified as follows:

Product Name:	Amifampridine Phosphate Drug Substance (synonym 3,4-diaminoprydine phosphate; abbreviated 3,4-DAPP)
Batch/Lot Number:	P528FPM-19-002
Purity:	99.2% (by HPLC)
Storage Conditions:	Powder stored at controlled room temperature until formulation at 2 mg/mL in saline. Formulated test article was stored at 2 to 8°C for up to 6 hours before

	administration (reference Deviation Report (DR)-B05929-BBRC-0004, Appendix C)
Retest Date:	December 2022

A Certificate of Analysis and stability/retest information for the test article are included in Appendix E.

2.1.3 Vehicle

The vehicle for preparation of 3,4-DAPP dosing solutions and for vehicle treatments (Group 1 animals) were identified as follows:

Name:	0.9% Sodium Chloride for Injection USP
Batch/Lot Number:	Y340786
Expiration Date:	October 2021
Storage Conditions:	Controlled room temperature
Supplier:	Baxter Healthcare Corporation

A verified photocopy of the label characterization for the vehicle is included in Appendix E.

2.2 CHALLENGE MATERIAL POTENCY ANALYSIS

The mouse potency assay, performed under Battelle Study 521-C1176424, was used to quantify the toxicity of the challenge material prior to use on this study. Assays were performed in quadruplicate per procedures contained in Battelle SOP Number BBRC.X-014. Diluted BoNT solutions were prepared on the day of testing from frozen working stock samples of Lot A081508-01 Batch 4a. To prepare the dilutions for the bioassays, 100 µL from the stock vial of BoNT/A Lot A081508-01 was initially diluted 1:100 using sterile gel phosphate buffer, pH 6.3. From this initial 1:100 dilution, an additional 1:100 dilution was performed prior to final dilution into the various concentrations of the assay. Four replicate potency assays were performed using 6 dilution groups at concentrations ranging from a 1:27,500 to a 1:434,000 dilution of the stock material with 6 mice per group weighing between 18.1-22.0 grams(g) on the day of dosing. All mice were challenged IP at a dose volume of 500 µL using a 1-cc syringe with a fixed 27-gauge, ½-inch needle. Lethality was recorded twice daily for 96 ± 2 hours following BoNT/A1 challenge. The number of animals found dead over the total number of animals challenged was tabulated at the end of the observation period for each assay. The lethality results from each assay ($MIPLD_{50}$/mL) were then determined by probit analysis using R version 2.11.0 statistical software. The individual result for each replicate as well as the average from all four replicates was reported. The stock concentration for toxin Lot A081508-01 Batch 4a was determined to be 521,330 $MIPLD_{50}$/mL.

2.3 CHALLENGE MATERIAL PREPARATION

One hundred (100) µL of BoNT/A1 stock (521,330 $MIPLD_{50}$/mL) was diluted into 9.9 mL of gel phosphate diluent to produce an initial diluted working solution (5,213.3 $MIPLD_{50}$/mL). A second dilution was performed by diluting 1.919 mL of the working solution into 8.081 mL of

gel phosphate diluent. The resulting formulation produce a total volume of 10 mL of a final BoNT/A1 dosing solution with a potency of 1,000 $MIPLD_{50}$/mL.

2.4 TEST ARTICLE PREPARATION

3,4-DAPP was prepared at a concentration of 2 mg/mL in 0.9% sodium chloride. 3,4-DAPP dose formulations were prepared fresh throughout the day and night when dosing activities were required. 3,4-DAPP solutions were maintained on wet ice after preparation and were replaced with fresh solutions within 6 hours. Maintenance of some early dosing solution preparations on wet ice when not in use was not explicitly documented (reference DR-B05929-BBRC-0004).

2.5 TEST ARTICLE ANALYSIS

Formulation analysis of the test article dosing solutions in saline were not performed.

2.6 RESERVE SAMPLES

Reserve samples were not collected nor required for this non-GLP study.

2.7 DISPOSITION OF CHALLENGE MATERIAL AND TEST ARTICLE

Unused stocks of the challenge material were retained at the Battelle Biomedical Research Center (BBRC) for use on future BoNT studies. The residual challenge dosing solution was discarded according to facility procedures.

Unused bulk test article was retained at the BBRC for use on future studies. Residual prepared test article dosing solutions were discarded after use.

2.8 EXPERIMENTAL ANIMALS

A total of nine male cynomolgus monkeys (of Mauritius origin) were transferred to Battelle Study B05929 on June 24, 2021. Eight animals were previously procured from PrimGen (Lehigh Acres, FL) and were used at as a test system on a previous pharmacokinetic study for 3,4-DAPP conducted at AmplifyBio (formerly Battelle-West Jefferson). One research naïve animal (SA180D) was originally procured from Charles River Houston (Houston, TX) and was transferred to study from a facility holding colony. All animals had previous surgeries for placement of vascular access ports (VAPs) under Study B05928 (January-February, 2021), except Animal SA180D who had surgeries for VAPs performed under the facility holding protocol (January, 2021).

Due to erosion and infection complications associated with long-term VAP use and maintenance, VAPs were previously removed per surgeon recommendation in all but three animals (G180JD, VL90IA, SA180D) prior to transfer to Battelle Study B05929. Quarantine exams, fecal exams, tuberculous testing, physical exams, and clinical pathology health screens (hematology and serum chemistry) were performed prior to transfer to Battelle Study B05929.

One (1) animal (AL110O) was humanely euthanized due to post-surgical complications prior to placement on in-life study. Animal AL110O was not replaced.

Eight (8) total animals were relocated from the AmplifyBio test site to the BBRC testing facility on September 2, 2021 (Study Day -11). Animals were weighed on September 10, 2021 (Study Day -3) for group assignment by body weight. Male animals were approximately 3 to 4 years of age at group assignment with body weights ranging from 3.72 to 4.88 kg. A complete listing of animal identification numbers, study group assignments, birth dates, and body weights are presented below in Table 1.

Table 1. Group Assignment, Animal Identification, Age, and Body Weight

Group 1			Group 2			Group 3		
Animal ID	**Date of Birth**	**Weight (kg)**	**Animal ID**	**Date of Birth**	**Weight (kg)**	**Animal ID**	**Date of Birth**	**Weight (kg)**
G180JD	8/21/2018	3.98	VL90IA	8/27/2018	4.77	SA180D	11/30/2017	3.72
N378ALE	8/20/2018	4.15	YR895FD	8/13/2018	4.04	BF873I	8/16/2018	4.19
			AL793H	8/27/2018	4.62	AP55D	7/3/2018	4.88

2.8.1 Housing and Environmental Conditions

General procedures for animal care and housing met current AAALAC International recommendations, current requirements stated in the "Guide for Care and Use of Laboratory Animals" (National Research Council [NRC]), current requirements as stated by the U.S. Department of Agriculture through the Animal Welfare Act, as amended, and conformed to testing facility SOP.

Animals were housed in stainless steel cages. Animals were socially housed (to the extent possible) during holding and prior to telemeter surgery. Following telemeter surgery, animals were single housed for recovery. Prior to challenge (Study Day -3), animals were separated into single housing arrangements and remained single housed throughout the duration of the study. During periods of single housing, socialization was achieved by housing animals in the same room with visual and auditory contact.

The light/dark cycle was controlled by electronic timers set to maintain 12 hours of light and 12 hours of dark each day using fluorescent lighting set to start at 6:00 AM each day. Following challenge, the lighting cycle was suspended and lights were turned on for observation and study activities when required. Room temperature and relative humidity controls were set to maintain ranges of 64 to 84°F (set point of 74°F) and 30 to 70% (set point of 40.0%), respectively.

2.8.2 Feed and Water

Animals were offered PMI, Inc. Certified Monkey Chow. Analytical reports of each feed lot were provided by the manufacturer.

Fresh water from the Village of West Jefferson municipal water supply was provided *ad libitum* to the animals by an automatic watering system except when removed from the home cage.

2.8.3 Environmental Enrichment

Animals were provided fresh fruits or fresh vegetables and/or other enrichment items to promote and enhance psychological well-being. Additional environmental enrichment was provided in the room with a radio.

2.8.4 Animal Identification and Group Assignment

Animals were identified by the supplier's tattoo designation. Animals were weighed on September 10, 2021 (Study Day -3) and assigned to dose groups using a stratified randomization program (Provantis) designed to maintain similar group mean body weights.

2.8.5 Animal Surgery

Animals were surgically implanted with DSI L11R telemeters capable of monitoring respiratory function, cardiac function, body temperature, and activity. Surgical implantation was performed in the AmplifyBio surgical suite from July 6, 2021 – July 13, 2021. For implantation, animals were maintained under operative inhaled isoflurane anesthesia. Pre-operative antibiotic, anti-inflammatory, and pain medications were provided. DSI L11R units were implanted intramuscularly on the anterior abdomen. ECG leads were placed on the thorax in a lead II configuration. Respiratory leads were placed on the right and left side of the thorax. Following lead placements, incisions were closed with absorbable sutures and tissue glue (as appropriate). Animals were monitored for recovery and provided post-operative antibiotic, anti-inflammatory, and pain medications. A complete listing of surgical dates is provided below in Table 2.

Table 2. Telemeter Surgery Schedule

Group 1		Group 2		Group 3	
Animal ID	**Surgery Date**	**Animal ID**	**Surgery Date**	**Animal ID**	**Surgery Date**
G180JD	7/8/2021	VL90IA	7/7/2021	SA180D	7/6/2021
N378ALE	7/6/2021	YR895FD	7/13/2021	BF873I	7/8/2021
		AL793H	7/7/2021	AP55D	7/12/2021

2.8.6 Post-Surgical Animal Health

Following DSI L11R telemeter surgery, some animals displayed varying health concerns including the appearance of foot and extremity lesions that developed 3-9 days after surgery. An investigation by the AmplifyBio test site was initiated to identify the root cause of the adverse outcomes. Due to the appearance and progression of the lesions, the timing in which the lesions presented post-operatively, and the number of lesions observed; thermal injuries (1st to 2nd degree) became the presumptive diagnosis. Improper placement of the Bair Hugger blower, designed to provide warmth and maintain body temperature during surgery, was identified as a likely root cause. A complete description of the investigation report is provided in Appendix F.

Veterinary guided treatments including carprofen and Clavamox were provided for pain management and to prevent infection, respectively (reference DR-B05929-AMP-0001, Appendix C). Wounds were cleaned, topical treatments applied, and lesions were wrapped as warranted. Complete records of veterinary care are maintained in the study file. All wounds

were resolved prior to transfer to the BBRC testing facility on September 2, 2021. All animals were observed to be clinically normal prior to BoNT/A1 challenge on September 13, 2021.

One (1) animal (AL110O) was humanely euthanized on July 13, 2021 due to animal health concerns (decrease in appetite, activity level, and attitude) and an unlikely prognosis for recovery. The reason for euthanasia was related to right leg swelling and was attributed to complications that were secondary to previous VAP placement and not thermal injuries. A gross necropsy was performed and no cause for the leg swelling was identified.

3 EXPERIMENTAL DESIGN

Eight (8) male cynomolgus monkeys were assigned to challenge and treatments groups as presented in the table below.

Table 3. Study Design

Group	Animal ID	Challenge; Dose; Route	Treatment; Dose; Route*	Clinical Parameters Collected
1	G180JD**	BoNT/A1; 2.5x LD_{50}; IM	Vehicle; 0 mg/kg; SC	Clinical Observations Clinical Severity Scores Respiratory Telemetry Cardiac Telemetry Body Temperature Arterial Blood Gas**
	N378ALE			
2	VL90IA**		3,4-DAPP; 2.06 mg/kg; SC	
	YR895FD			
	AL793H			
3	SA180D**		3,4-DAPP; 4.12 mg/kg; SC	
	BF873I			
	AP55D			

IM = intramuscular; SC = subcutaneous
*Treatments initiated 2 hours after a clinical severity score of 1 or greater. Repeat treatments delivered at a target interval of every 4 hours thereafter (reference DR-B05929-BBRC-0001, Appendix C).
**Arterial VAP was present and patent in the animal for arterial blood gas collection.

3.1 CHALLENGE ADMINISTRATION

The study was conducted on a single challenge day. The day of challenge was defined as Study Day 1. Unanesthetized animals were chair restrained for the challenge administration procedures. Systemic intoxication with BoNT/A1 was achieved by a single IM injection of the BoNT/A1 dosing solution into the right calf muscle at a dose level of 97.5 $MIPLD_{50}$/kg, corresponding to 2.5x the LD_{50} for IM intoxication in cynomolgus monkeys with BoNT/A1 (Scott and Suzuki, 1988). Intramuscular challenge volumes ranged from 0.36 to 0.48 mL to achieve the specific challenge level based on animal weight. After challenge, animals were returned to their home caging for observation. A complete listing of BoNT/A1 challenge dose volumes is presented below in Table 4.

Table 4. Intramuscular BoNT/A1 Challenge Volumes

Group	Animal ID	BoNT/A1 Challenge Volume (mL)
1	G180JD	0.39
	N378ALE	0.40
2	VL90IA	0.47
	YR895FD	0.39
	AL793H	0.45
3	SA180D	0.36
	BF873I	0.41
	AP55D	0.48

3.2 TREATMENT ADMINISTRATION

Repeat treatment with 3,4-DAPP (or saline) was administered as a SC bolus at alternating sites on the hip/thigh area. A clinical severity score of 1 or greater served as a trigger to initiate 3,4-DAPP (or saline) treatment starting at the following observation time-point ~2 hours later (to ensure sufficient toxicity was present prior to treatment). Repeat treatments were administered at a targeted 4-hour interval thereafter(based upon efficacy data from LEMS and dosing interval used in PK study [B05928]). Actual intervals between treatments ranged from 3 hours and 40 minutes to 4 hours and 16 minutes. A complete listing of treatment times and treatment intervals are provided in Appendix G.

Saline was administered as received without further manipulation or preparation. Saline dosing volumes were matched to the highest dosing volume employed for 3,4-DAPP dosing (2.06 mL/kg). 3,4-DAPP was administered using a 2 mg/mL dosing solution, prepared from 3,4-DAPP powder with saline as the vehicle. 3,4-DAPP dosing solutions were maintained on ice after preparation and when not in use (reference DR-B05929-BBRC-0004, Appendix C) and were replaced with freshly prepared solutions approximately every 6 hours. Animals receiving 2.06 mg/kg of 3,4-DAPP were dosed at 1.03 mL/kg. Animals receiving 4.12 mg/kg of 3,4-DAPP were dosed at 2.06 mL/kg. Dosing volumes for all groups ranged from 4.16 to 10.05 mLs per treatment. A complete listing of treatment dose volumes and number of treatments is presented below in Table 5.

Table 5. Subcutaneous Treatments

Group	Treatment (dose)	Animal ID	Treatment Volume (mL)	Number of Treatments Administered	Total Volume Administered (mL)
1	Saline (0 mg/kg)	G180JD	8.20	4	32.80
		N378ALE	8.55	5	42.75
2	3,4-DAPP (2.06 mg/kg)	VL90IA	4.91	4	19.64
		YR895FD	4.16	3	12.48
		AL793H	4.76	3	14.28
3	3,4-DAPP (4.12 mg/kg)	SA180D	7.66	7	53.62
		BF873I	8.63	9	77.67
		AP55D	10.05	5	50.25

3.3 CLINICAL OBSERVATIONS AND SEVERITY SCORING

Observations for moribundity and mortality were performed a minimum of twice daily during the pre-study period.

On the day of challenge (Study Day 1), a morning observation was performed prior to BoNT/A1 administration. Following BoNT/A1 challenge, a single PM observation was performed. Scheduled routine observations were performed every 2 hours starting at 0800 the day after challenge (Study Day 2). Animals were observed for signs commonly associated with botulism (e.g., ptosis, muscular weakness, respiratory distress, oral/nasal discharge) and clinical severity scoring was performed according to Table 6 at each observation time-point. Additional post-treatment observations and associated clinical severity scores were performed 15 minutes (± 2 minutes) after each administration of 3,4-DAPP (or saline).

Table 6. Clinical Severity Scoring

Clinical Signs	Observation	Clinical Severity Score Assigned
Ptosis	Absent	0
	Slight	1
	Marked	2
Muscular Weakness	Normal	0
	Hunched Posture	1
	Prostrate but able to rise	2
	Prostrate but unable to rise	3
Respiratory Distress	Normal breathing	0
	Open mouth shallow (thoracic)	1
	Gasping and jerking (abdominal)	3
Oral Discharge	Absent	0
	Present	1
Nasal Discharge	Absent	0
	Present	1
Lethality	Alive	0
	Dead	10

3.4 BODY WEIGHTS

Animals were weighed at the AmplifyBio test site prior to surgery on June 29, 2021 (Study Day -76). An additional body weight check was performed for Animal VL90IA on August 31, 2021 (Study Day -13) prior to transport to the BBRC testing facility. Body weights were collected at the BBRC testing facility on September 10, 2021 (Study Day -3). Study Day -3 body weights were used for challenge and treatment dose calculations.

3.5 ARTERIAL BLOOD GAS

For animals with functioning VAPs (Animals G180JD; VL90IA; SA180D), whole blood samples (target volume 1.0 mL) were collected from unanesthetized animals using the arterial VAP (reference DR-B05929-BBRC-0007, Appendix C) and placed in selfPICO Self-Filling Syringes at the following time points: prior to challenge (baseline), immediately prior to the first treatment administration, 15 minutes (± 3 minutes) after the first treatment administration, immediately prior to the second treatment administration, 15 minutes (± 3 minutes) after the second treatment administration, immediately prior to the third treatment administration, and 15 minutes (± 3 minutes) after the third treatment administration (reference DR-B05929-BBRC-0006, Appendix C). Collected samples were analyzed using an ABL90 Flex Blood Gas Analyzer within 30 minutes of collection. Parameters analyzed and reported included pH, pCO_2 (torr), pO_2 (torr), ctHb (g/dL), sO_2 (%), FO_2Hb (%), FHHb (%), cK^+ (meq/L), cNa^+ (meq/L), cCa^{2+} (meq/L), cCl^- (meq/L), cGlu (mg/dL), and cLac (mmol/L).

3.6 TELEMETRY

3.6.1 Respiratory

Respiratory telemetry data captured from the DSI L11R implants was continuously collected on study, starting on September 10, 2021 (Study Day -3) and continuing through study termination. All data collection was performed according to Battelle SOP Number BBRC.VI-186. At the conclusion of in-life, collected respiratory data was collated and received at DSI on October 27, 2021 for analysis with Ponemah® software. A narrative of analysis with graphs and tables (as appropriate) was provided to Battelle by DSI for inclusion in the Final Report. Respiratory parameters analyzed and reported included tidal volume, minute volume, and respiration rate.

3.6.2 Cardiac

Cardiac telemetry data captured from the DSI L11R implants was continuously collected on study, starting on September 10, 2021 (Study Day -3) and continuing through study termination. All data collection was performed according to Battelle SOP Number BBRC.VI-186. At the conclusion of in-life, collected cardiac data was collated and received at DSI on October 27, 2021 for analysis with Ponemah® software. A narrative of analysis with graphs and tables (as appropriate) was provided to Battelle by DSI for inclusion in the Final Report. Parameters analyzed and reported included RR interval, heart rate (derived from RR), PR interval, QRS duration, QT interval, heart rate corrected QT interval Bazett's (QTcB), and individual heart rate corrected QT interval Bazett's (QTc). The number of T waves present was

analyzed but only used for quality control purposes. A cardiologist review of electrocardiograms (ECGs) was performed to investigate and/or diagnose potential arrhythmias.

3.6.3 Body Temperature

Body temperature data captured from the DSI L11R implants was continuously collected on study, starting on September 10, 2021 (Study Day -3) and continuing through study termination. All data collection was performed according to Battelle SOP Number BBRC.IV-087. At the conclusion of in-life, body temperature data was collated and received at DSI on October 27, 2021 for analysis with Ponemah® software. A narrative of analysis with graphs and tables (as appropriate) was provided to Battelle by DSI for inclusion in the Final Report. Parameters analyzed and reported included mean temperature.

3.6.4 Activity

Activity data captured from the DSI L11R implants was continuously collected on study, starting on September 10, 2021 (Study Day -3) and continuing through study termination. All data collection was performed according to Battelle SOP Number BBRC.IV-087. At the conclusion of in-life, body temperature data was collated and received at DSI on October 27, 2021 for analysis with Ponemah® software. A narrative of analysis with graphs and tables (as appropriate) was provided to Battelle by DSI for inclusion in the Final Report. Parameters analyzed and reported included mean activity.

3.7 STUDY TERMINATION

The in-life phase of Battelle Study B05929 was concluded on September 17, 2021 (Study Day 5) when the final animal succumbed to challenge.

4 COMPUTER SYSTEMS FOR DATA MANAGEMENT

The following computer systems were used for toxicology data management:

Table 7. Computer Systems

Computer System	Version No.	Manufacturer	Data Type
ECMS	3.13	Siemens	Animal Facility Environmental
Insight, InfoCenter Suite, and APOGEE	3.9.1	Siemens	Building Monitoring (Room Temperatures, Light Cycles, Pressure, Humidity, Air Flow, Cold Storage Unit Temperature)
Provantis	10.1.0.0	Instem	Clinical observations, body weights, randomizations
Ponemah	5.5	ECG PRO	Telemetry Data
Origin Pro	Origin 2019b	Origin Pro	Graphing
GraphPad Prism	7.05	GraphPad Software	Descriptive statistics, graphing

5 STATISTICAL ANALYSIS

Descriptive statistics (group mean and standard error) of clinical severity scores was performed in GraphPad Prism. Statistical analysis of telemetry data was not performed.

6 STORAGE OF STUDY MATERIALS AND RECORDS RETENTION

The final report and all records generated at the BBRC testing facility, AmplifyBio test site, and DSI test site that would be required to reconstruct the study are archived at the Battelle archives.

Unused frozen bulk working stock aliquots of the BoNT/A1 used on this study are retained at the BBRC for use on future studies. The prepared BoNT/A1 challenge solution was discarded after use. The unused bulk stock of 3,4-DAPP powder was retained at the BBRC for use on future studies. Individual 3,4-DAPP dosing solutions and vehicle were discarded after use. Following arterial blood gas analysis, blood specimens were discarded.

7 RESULTS

7.1 MORTALITY

Individual Mortality Data: Appendix H

All eight animals placed on study and challenged with BoNT/A1 succumbed to challenge prior to scheduled euthanasia and removal from the study at 7 days post-challenge (Study Day 8). All animals were found dead, with the exception of animal SA180D (Group 3) who was euthanized in a moribund state at 77 hours and 59 minutes post-challenge. Mortality was expected following systemic exposure to BoNT/A1 at the challenge levels employed (2.5x LD_{50}) and was considered specifically attributed to administration of the challenge material.

Relative to the time of BoNT/A1 challenge (2.5x LD_{50}), time-to-death for Group 1 animals receiving saline treatment ranged from 69 hours and 28 minutes to 89 hours and 52 minutes. Post-challenge time-to-death for Group 2 animals receiving 2.06 mg/kg of 3,4-DAPP treatment ranged from 61 hours and 18 minutes to 67 hours and 21 minutes. Post-challenge time-to-death for Group 3 animals receiving 4.12 mg/kg of 3,4-DAPP treatment ranged from 57 hours and 15 minutes to 91 hours and 35 minutes.

However, given the varying post-challenge latency times it took for individual animals to reach trigger-to-treatment criteria, ranging from 35 hours and 21 minutes to 67 hours and 42 minutes, interpretation of mortality results strictly relative to challenge time does not account for survival time relative to treatment. As such, additional analysis was performed to investigate potential treatment effects on survival time after animals displayed toxicity and treatments were initiated. This was accomplished by examining the difference between time-to-death as it relates to the time-to-trigger criteria and may be interpreted as a more accurate measure of potential test article-effects on altering clinical trajectory after presentation of toxic signs associated with botulism. Of note, while often similar, the first observation of toxicity did not always correspond to a clinical severity score of ≥ 1 which would trigger the initiation of treatments. Some animals initially presented with ataxia or labored breathing that did not meet the open mouth shallow (thoracic) criteria in the severity scoring system. Therefore, the time-to-trigger (based on clinical severity scores) varies in some animals in relation to the first abnormal observation.

Following post-challenge treatment trigger criteria (clinical severity score of ≥ 1), time-to-death for Group 1 animals receiving saline treatment ranged from 18 hours and 2 minutes to 22 hours and 10 minutes. Post-trigger time-to-death for Group 2 animals receiving 2.06 mg/kg of 3,4-DAPP treatment ranged from 12 hours and 55 minutes to 18 hours. Post-trigger time-to-death for Group 3 animals receiving 4.12 mg/kg of 3,4-DAPP treatment ranged from 19 hours and 54 minutes to 38 hours and 4 minutes. A complete listing of challenge times, times to toxicity and trigger, and times to death relative to challenge, toxicity, and trigger are presented for all animals in Appendix H. An abbreviated summary is provided below in Table 8.

Table 8. Time-to-Death

Group	Treatment (dose)	Animal ID	Time-to-Death after BoNT/A1 Challenge (hrs:min)	Time-to-Death after Trigger Criteria (hrs:min)
1	Saline (0 mg/kg)	G180JD	69:28	18:02
		N378ALE	89:52	22:10
2	3,4-DAPP (2.06 mg/kg)	VL90IA	65:06	18:00
		YR895FD	67:21	13:53
		AL793H	61:18	11:55
3	3,4-DAPP (4.12 mg/kg)	SA180D	77:59*	30:27
		BF873I	91:35	38:04
		AP55D	57:15	19:54

hrs:min = hours:minutes
*Animal SA180D was euthanized in a moribund state.

Compared to saline-treated controls, no apparent survival benefit was evident with the lower dose level of 3,4-DAPP tested (2.06 mg/kg). However, repeat SC treatment with 3,4-DAPP at a dose-level of 4.12 mg/kg appeared to generally prolong survival, as evidenced by greater time-to-death values following initial presentation of signs associated with botulism. As such, indications of prolonged survival times following toxicity was considered attributable to test article administration at the 4.12 mg/kg dose level.

7.2 CLINICAL OBSERVATIONS

Scheduled Clinical Observations: Appendix I
Pre- and Post-Treatment Clinical Observations: Appendix J

7.2.1 Scheduled Observations

Regularly scheduled descriptive observations were performed per the unit clock at ~2 hour intervals (starting on Study Day 2). All animals were observed as clinically normal on Study Day 1 prior to BoNT/A1 challenge. Following challenge, all animals remained in clinically normal status until the evening of Study Day 2 where the first animal (AP55D) displayed signs associated with botulism (i.e., oral and nasal discharge). The time-to-first observation of toxicity following challenge ranged from 35 hours and 21 minutes to 67 hours and 42 minutes. Leading signs of intoxication generally included ataxia, labored breathing, shallow respirations, oral/nasal discharge, and hunched posture. The number of abnormal observations generally increased over time as toxicity progressed. Other abnormal clinical signs commonly observed following challenge were ptosis, lethargy, gasping, coughing, prostrate posture, and

death. Manifestation of these toxic signs are consistent with systemic botulism (Rao *et al.* 2021) and were considered specifically attributable to BoNT/A1 challenge.

7.2.2 Pre- and Post-Treatment Observations

Additional descriptive observations were performed at ~15 minutes after SC administration of test article (or vehicle). At the dosing level and dosing frequency interval employed in this study, SC treatment with 3,4-DAPP at 2.06 or 4.12 mg/kg did not completely prevent disease progression nor fully restore animal health after initial presentation of toxicity. Partial reversal in some animals following 3,4-DAPP dosing was evidenced by resolution of oral/nasal discharge, reductions in muscular weakness (postural improvements), resolution of ptosis, and general improvements in observed respiratory patterns. Improvement effects were generally more frequent and more robust in animals receiving the higher dose of 3,4-DAPP (4.12 mg/kg). In general, 3,4-DAPP treatments appeared less effective at overtly resolving toxicity at the late-stages of disease where toxic observations were numerous as mortality approached.

7.3 CLINICAL SEVERITY SCORING

Scheduled Clinical Severity Scores: Appendix K
Pre- and Post-Treatment Clinical Severity Scores: Appendix L

7.3.1 Scheduled Clinical Severity Scoring

All animals were observed with clinical severity scores of 0 on Study Day 1 prior to BoNT/A1 challenge. Following challenge, all animals remained in clinically normal status until the evening of Study Day 2 where the first animal (AP55D) displayed a clinical severity score of 2. The time-to-first clinical severity score of ≥ 1 following challenge ranged from 35 hours and 21 minutes to 67 hours and 42 minutes (as was identical with scheduled clinical observations). Clinical severity scores initially presented at a range of 1 to 2 in all animals. With some exceptions, as toxicity progressed from initial presentation, clinical severity scores generally increased to a range of 3 to 5 prior to mortality (score of 10). Presentation of clinical severity scores of 10 (death) was expected following systemic exposure to BoNT/A1 at the challenge levels employed (2.5x LD_{50}) and was considered specifically attributed to administration of the challenge material.

7.3.2 Pre- and Post-Treatment Clinical Severity Scoring

In general, the overall frequency and severity of clinical observations following BoNT/A1 challenge was similar across all treatment groups (saline, 2.06 mg/kg 3,4-DAPP, 4.12 mg/kg 3,4-DAPP). At the dosing level and dosing frequency interval employed in this study, SC treatment with 3,4-DAPP at 2.06 or 4.12 mg/kg did not completely prevent clinical severity progression when treatments were administered after initial presentation of toxicity. Severity reversal following 3,4-DAPP dosing is supported by cage-side observations showing a general trend of a reduction in clinical severity scores at 15- and 120-minutes after dose administration. This effect was more frequent and more robust in animals receiving the higher dose of 3,4-DAPP (4.12 mg/kg), including 2 of 3 animals returning to clinical severity scores of 0 after initial presentation of disease (Animals BF873I and AP55D) following the first three treatment administrations. Animals receiving 4.12 mg/kg of 3,4-DAPP generally had lower pre-

treatment severity scores, indicating an overall trend towards severity improvement between treatments. A summary table and graphical plot of pre- and post-treatment clinical severity scores at 15-minutes and 2-hours post-treatment through the first 4 treatments (the last treatment where data from all study groups are represented) is presented below in Table 9 and Figure 1, respectively. Severity scores of 10 (death) were excluded when applicable.

Table 9. Group Summary of Mean (± Standard Error) Clinical Severity Scores

Group	Treatment (dose)	Pre-Treatment	15-min Post-Treatment	2-hr Post-Treatment
1	Saline	2.75 ± 0.45 (n = 8)	2.88 ± 0.55 (n = 8)	2.88 ± 0.48 (n = 8)
2	3,4-DAPP (2.06 mg/kg)	3.50 ± 0.48 (n = 10)	3.00 ± 0.49 (n = 10)	2.78 ± 0.32 (n = 9)
3	3,4-DAPP (4.12 mg/kg)	2.90 ± 0.38 (n = 10)	3.10 ± 0.50 (n = 10)	2.40 ± 0.43 (n = 10)

NOTE: Data beyond the 4th treatment is not included in this table as all groups would not contain available data. Severity scores of 10 (death) were excluded when applicable.

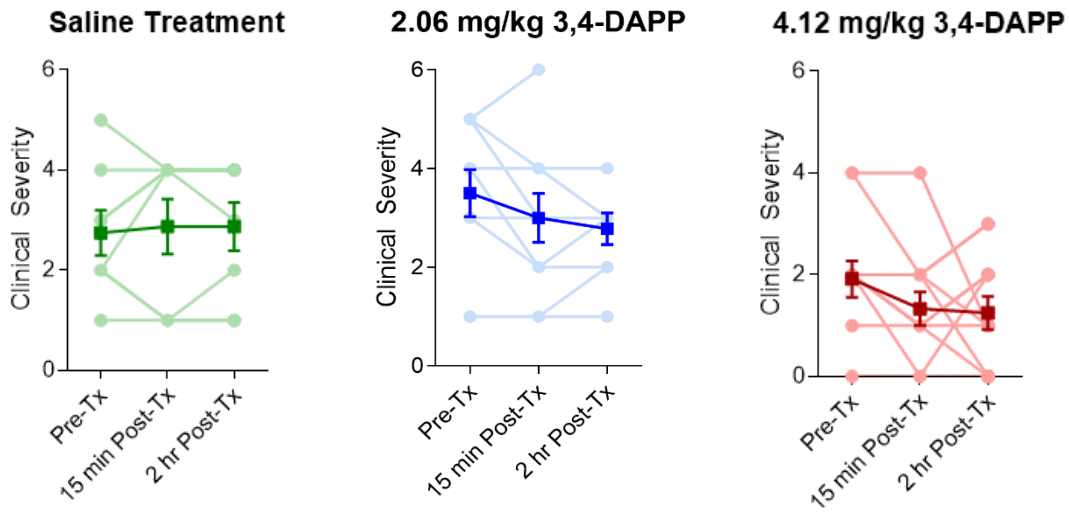

Figure 1. Clinical Severity Before and After Vehicle or 3,4-DAPP Treatment

Clinical severity was assessed before (Pre-Tx) and after administering treatment (15 min and 2 hr Post-Tx). Dimmed background lines represent individual pre- and post-treatment scores. The bold line represents the mean ± standard error of all individual pre- and post-treatment scores. NOTE: Data beyond the 4th treatment is not included in this graphical representation as all groups would not contain data available for plotting. Severity scores of 10 (death) were excluded when applicable.

7.4 ARTERIAL BLOOD GAS

Individual Arterial Blood Gas Data: Appendix L

While a limited sample set (n=1 for each group), preliminary evidence of 3,4-DAPP mediated reversal of BoNT/A1 toxicity is supported by improvements in arterial blood gas (ABG) measurements 15-minutes following subcutaneous dosing. As disease severity progressed

following BoNT/A1 challenge, ABG profiles were generally characterized by a reduction of pO_2, an increase in pCO_2, and a decrease in pH. At the 15-minute post-treatment sampling time-point, with one exception (Group 2, 1st treatment), 3,4-DAPP dosing at 2.06 mg/kg or 4.12 mg/kg generally improved blood gas parameters by increasing pO_2, decreasing pCO_2, and restoring pH. Sustained improvement in ABG parameters following 3,4-DAPP dosing was not achieved as values were generally decreased at the next sampling time-point approximately 4 hours later. A complete listing of blood gas, oximetry, electrolyte, and metabolite profiles for each animal evaluated are presented in Appendix M. A summary of blood gas parameters for pO_2 and pCO_2 are provided below in Table 12 and Table 11, respectively.

Table 10. Arterial Blood Gas – pO_2 (torr)

Group	Animal ID	Treatment (dose)	Pre-Challenge Baseline	Pre-Tx_1	Post-Tx_1	Pre-Tx_2	Post-Tx_2	Pre-Tx_3	Post-Tx_3
1	G180JD	Saline (0 mg/kg)	94.2	99.0	95.9	84.7	86.5	NR	NR
2	VL90IA	3,4-DAPP (2.06 mg/kg)	93.2	82.3	77.5	77.2	90.1	63.3	84.0
3	SA180D	3,4-DAPP (4.12 mg/kg)	106	90.0	94.0	82.5	94.2	76.5	88.4

NR = not reported (reference DR-B05929-BBRC-0006, Appendix C); Pre-Tx = before treatment; Post-Tx = 15 minutes after treatment; Tx_1 = first treatment; Tx_2 = second treatment; Tx_3 = third treatment

Table 11. Arterial Blood Gas – pCO_2 (torr)

Group	Animal ID	Treatment (dose)	Pre-Challenge Baseline	Pre-Tx_1	Post-Tx_1	Pre-Tx_2	Post-Tx_2	Pre-Tx_3	Post-Tx_3
1	G180JD	Saline	32.5	35.7	36.6	38.3	37.8	NR	NR
2	VL90IA	3,4-DAPP (2.06 mg/kg)	32.9	54.2	51.4	51.9	44.5	66.4	56.4
3	SA180D	3,4-DAPP (4.12 mg/kg)	29.8	43.2	36.7	41.4	34.7	42.8	37.3

NR = not reported (reference DR-B05929-BBRC-0006, Appendix C); Pre-Tx = before treatment; Post-Tx = 15 minutes after treatment; Tx_1 = first treatment; Tx_2 = second treatment; Tx_3 = third treatment

7.5 TELEMETRY DATA

DSI Telemetry Data Analysis Report: Appendix M

A complete listing and presentation of all parameters analyzed is reported in the DSI Telemetry Data Analysis report. A select summary is provided below, with particular focus on physiologic responses following initiation of vehicle (saline) or 3,4-DAPP treatment.

7.5.1 Respiratory Parameters

For animals receiving repeat vehicle (saline) treatments, mean minute volumes and tidal volumes generally increased for 0.75 hours following the first treatment. However, these measurements were not sustained, as minute volumes and tidal volumes were generally

decreased by 8.5 hours through approximately 16 hours and eventual animal death. Decreases in respiratory rate were observed in a similar time-frame, starting at 8.75 hours.

For animals receiving treatments with 2.06 mg/kg of 3,4-DAPP, minute and tidal volumes were similar to vehicle (saline) treatments, characterized generally by decreases in minute and tidal volumes around 6.75 to 8.75 hours, respectively, through 14 hours and eventual animal death. Respiratory rate was initially increased from 0.75 hours until 2 hours after the first treatment, followed by a delayed decrease starting at 11.25 hours and continuing through animal death.

For animals receiving treatments with 4.12 mg/kg of 3,4-DAPP, minute volume and tidal volume was similarly characterized by an initial increase in response to the first treatment from 0.25 to 0.5 hours post-treatment followed by general decreases starting at 6.75 and 6.00 hours, respectively. However, in contrast to other groups, animals receiving 4.12 mg/kg of 3,4-DAPP displayed an extended time before evidence of a decreased respiratory rate was observed. While a decrease in respiratory rate was observed at 8.75 hours for saline treated animals and at 11.25 hours for 3,4-DAPP treated animals at 2.06 mg/kg, treatment with 4.12 mg/kg of 3,4-DAPP sustained respiratory rate until 18.75 hours. The effect of treatments on mean respiratory rate following the onset of clinical signs is provided below in Figure 2.

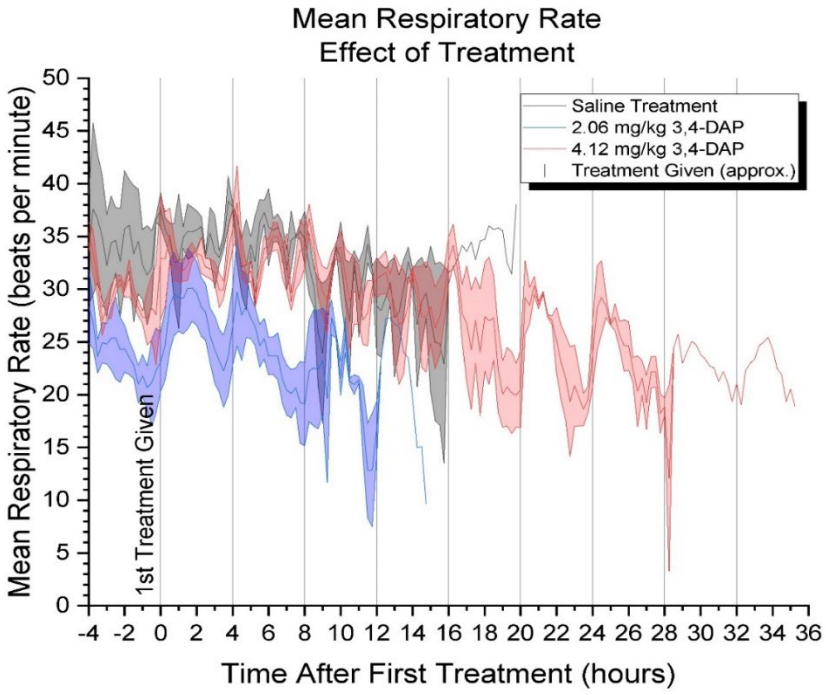

Figure 2. Respiratory Rate Before and After Vehicle or 3,4-DAPP Treatment

Respiratory rate was collected from DSI L11R telemeters and analyzed compared to the pre-treatment baseline (-4 to 0 hours). The darkened traces represent the group mean. The shaded area represents the standard error. The vertical lines represent the approximate time a treatment was administered. NOTE: The first clinical severity score of ≥ 1 roughly corresponds to -2 hours, with the first subcutaneous treatment performed 2 hours later at t = 0.

7.5.2 Cardiac Parameters

For animals receiving repeat vehicle (saline) treatments, following the first treatment, there was an overall increase in mean heart rate until 12.5 hours followed by a decrease in mean rate at 15.5 hours until animal death. QT intervals were increased at 15.5 hours and remained elevated until the time of death.

For animals receiving treatments with 2.06 mg/kg of 3,4-DAPP, no changes were observed following the first dosing. Mean heart rate and QT intervals were generally decreased at 7.50 and 10.25 hours, respectively, until the time of death.

For animals receiving treatments with 4.12 mg/kg of 3,4-DAPP, in contrast to other groups, heart rate and QT intervals proved more dynamic, characterized by varying increases and decreases occurring throughout the dosing period until animal death. Changes were evident as early as 0.5 and 1.25 hours after the first dosing, with an increased heart rate and QT interval, respectively. The effect of treatments on mean heart rate following the onset of clinical signs is provided below in Figure 3.

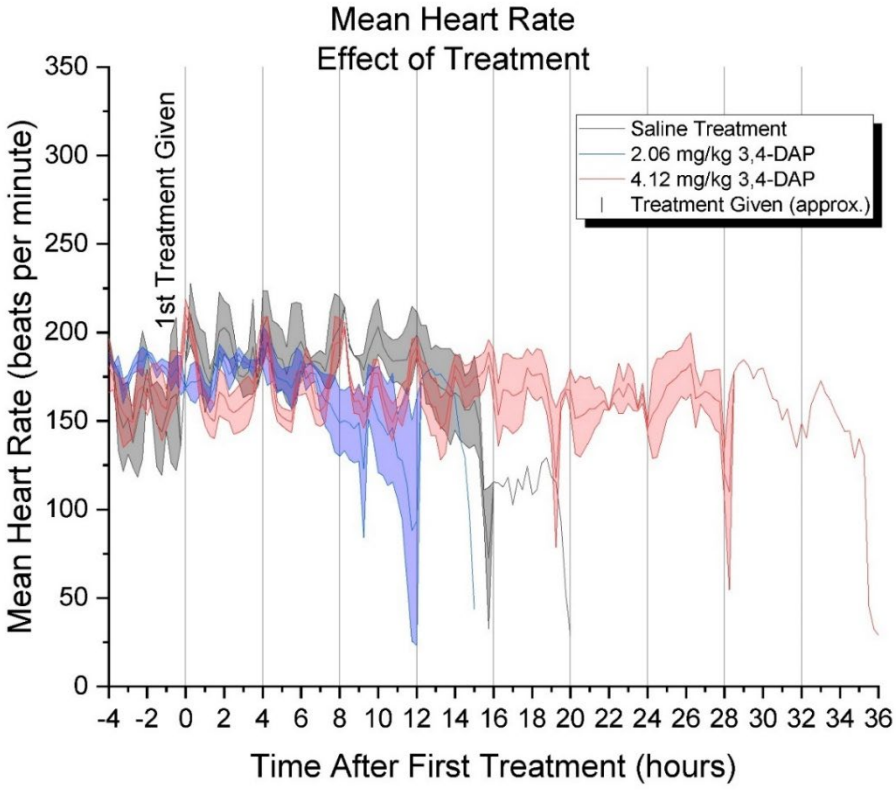

Figure 3. Heart Rate Before and After Vehicle or 3,4-DAPP Treatment

Heart rate was collected from DSI L11R telemeter and analyzed compared to the pre-treatment baseline (-4 to 0 hours). The darkened traces represent the group mean. The shaded area represents the standard error. The vertical lines represent the approximate time a treatment was administered. NOTE: The first clinical severity score of ≥ 1 roughly corresponds to -2 hours, with the first subcutaneous treatment performed 2 hours later at t = 0.

7.5.2.1 Cardiac Arrhythmias

The isolated changes for the heart rate, QTc, QRS, and PR intervals during the study were within the normal range for the cynomolgus monkeys and were not considered test article-related. The heart rate changes that occurred were considered to be related to the administration of the botulinum neurotoxin. A normal fluctuation of the heart rate occurred throughout the study in all animals and in all phases with no consistent pattern of a test article effect from the therapeutic capacity of 3,4-DAPP.

Cardiac arrhythmias were noted during a cardiologist review of the ECG data. Arrhythmias identified included: Ventricular Premature Complex/Premature Ventricular Contraction (VPC/PVC), Second Degree Atrioventricular Heart Block (2AVHB), junctional and ventricular escape rhythms, intermittent supraventricular tachycardia, ventricular tachycardia, ST segment depression/bundle branch block with intermittent ventricular rhythm, and Sino atrial arrest-junctional escape complexes/ST segment elevation and depression.

For all three groups, the incidence of arrhythmias was very similar for the terminal ECG patterns. Compared to baseline, the frequency of ventricular premature complexes was similar for all three groups during the post-dosing phase. The junctional escape complexes and the periods of second-degree atrioventricular block were not deemed to be of concern in this study. Arrhythmias often took place during baseline and were often seen at time-periods when there are changes in the heart rate. As there were no striking differences for the frequency of ventricular arrhythmias when comparing the two 3,4-DAPP dosing groups (2.06 mg/kg and 4.12 mg/kg) to the saline group, arrythmias were not considered to be test-article related and was considered to be the result of systemic intoxication with botulinum neurotoxin.

7.5.3 Body Temperature

For animals receiving repeat vehicle (saline) treatments, following the first treatment, there was a general decrease in mean body temperature starting at 7.00 hours until death. Animals receiving 2.06 mg/kg of 3,4-DAPP showed a similar trend, except for a period of decreased body temperature at 0.25 hours, which then increased at 2.5 hours before beginning a decreased trajectory at 7.00 hours until death. In contrast to other groups, animals treated with 4.12 mg/kg of 3,4-DAPP maintained body temperature for a longer period of time, with decreases in body temperatures not observed until 12.25 hours through 24 hours post first treatment. Thereafter, body temperature decreased until animal death. The effect of treatments on body temperature following the onset of clinical signs is provided below in Figure 4.

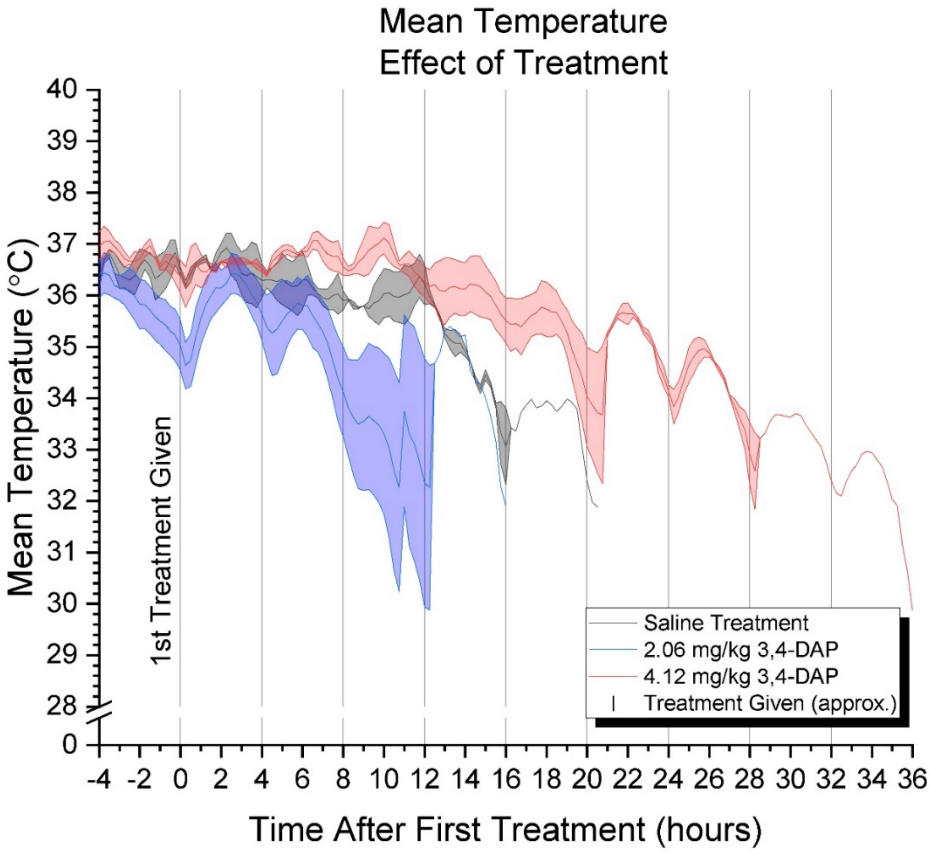

Figure 4. Body Temperature Before and After Vehicle or 3,4-DAPP Treatment

Body temperature was collected from DSI L11R telemeter and analyzed compared to the pre-treatment baseline (-4 to 0 hours). The darkened traces represent the group mean. The shaded area represents the standard error. The vertical lines represent the approximate time a treatment was administered. NOTE: The first clinical severity score of ≥ 1 roughly corresponds to -2 hours, with the first subcutaneous treatment performed 2 hours later at t = 0.

7.5.4 Activity

For animals receiving repeat vehicle (saline) treatments, activity was increased around the first and second treatments. A decrease in activity was noted around 19.75 hours prior to animal death. Animals receiving 2.06 mg/kg of 3,4-DAPP showed a similar, but not identical trend, with an increase in activity around the second treatment. Activity was noted as decreased at varying times between 9.25 until the time of animal death at 16 hours post first treatment. In contrast, for animals receiving 4.12 mg/kg of 3,4-DAPP, activity was increased at the first, second, and fourth treatments. Activity decreased for periods in between treatments and at times leading up to animal death. The effect of treatments on animal activity following the onset of clinical signs is provided below in Figure 5.

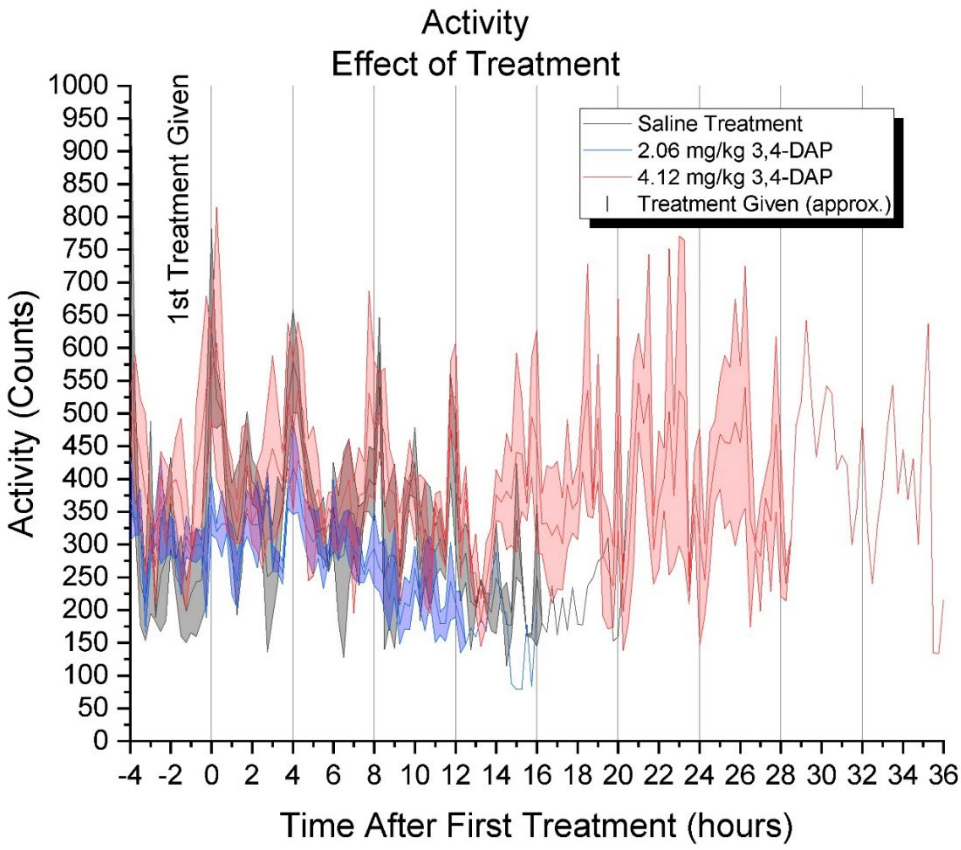

Figure 5. Animal Activity Before and After Vehicle or 3,4-DAPP Treatment

Animal activity was collected from DSI L11R telemeter and analyzed compared to the pre-treatment baseline (-4 to 0 hours). The darkened traces represent the group mean. The shaded area represents the standard error. The vertical lines represent the approximate time a treatment was administered. NOTE: The first clinical severity score of ≥ 1 roughly corresponds to -2 hours, with the first subcutaneous treatment performed 2 hours later at t = 0.

8 DISCUSSION

In this study, a previously developed cynomolgus monkeys (*Macaca fascicularis)* model for post-exposure BoNT countermeasure efficacy testing (Beske, 2019) was utilized using a lethal IM challenge dose of 2.5xLD_{50} of BoNT/A1 (97.5 MIPLD_{50}/kg; Scott and Suzuki, 1988). Results obtained in this study were consistent with this previous work, with observed induction of systemic toxicity (based upon clinical observations of oral and nasal discharge, ataxia, hunched posture or labored/shallow respirations) apparent within 1.5 to 2.75 days after BoNT/A1 challenge. Similarly, after the manifestation of early toxic signs consistent with the onset of systemic botulism (i.e. muscle weakness, oral/nasal discharge), disease progression led to severe respiratory distress and eventual death. Collectively, these studies further corroborate the reliability and practical utility of the IM BoNT/A1 challenge model in cynomolgus monkeys. Despite the variance in the BoNT challenge route for NHP studies,

whether intravenous (Kodihalli *et al.* 2017), inhalational (Sanford *et al*. 2010), or intramuscular (Scott and Suzuki, 1988; Beske, 2019), a recognized pattern of disease progression appears to result regardless of the toxin exposure route. Given the high cost and labor-intensive nature of inhalation studies, should manifestation of systemic toxicity and subsequent evaluation of test article-effects be the primary objective, intoxication by the IM route appears to present a reliable and cost-effective alternative. The IM intoxication approach allows for a greater challenge throughput (if required) while simultaneously utilizing smaller amounts of costly challenge material. These attributes, as well as considerations for staff safety, should be considered as an advantage over other NHP BoNT intoxication modalities.

3,4-Diaminopyridine is the only reported botulism reversal agent (Siegel *et al.* 1986, Mayorov *et al.* 2010; Friggeri *et al.* 2013; Beske *et al.* 2017; Bradford *et al.* 2018; Beske, 2019; Vazquez-Cintron *et al*. 2020). The data collected in this study are generally consistent with these findings. Evidence of toxicity reversal was apparent through clinical severity scoring and arterial blood gas measurements. At early treatment administrations associated with earlier stages of disease progression, SC treatment with 3,4-DAPP, particularly at the 4.12 mg/kg dose level, showed subjective evidence of improving overall animal health. Clinical severity scores were reduced following 4.12 mg/kg of 3,4-DAPP treatment and remained lower compared to other groups. The finding from this study that 3,4-DAPP can improve neuromuscular function after the onset of botulism is consistent with pilot studies performed in humans (Friggeri *et al*. 2013. . In general, clinical severity scores were reduced following 4.12 mg/kg of 3,4-DAPP treatment and remained lower compared to other groups. Fifteen minutes and 2-hours post treatment, clinical severity scores decreased by one to two levels (lowest score = 1) in 33% (3 of 9) of the total number of observations (accounting for total number of observations from all animals alive in the group at each time point) associated with the saline control group and 40% (4 of 10) of the total number of observations associated with the group receiving 2.06 mg/kg of 3,4-DAPP. Comparatively, with regards to the group receiving 4.12 mg/kg of 3,4-DAPP, clinical severity scores experienced a greater decrease (up to three levels; lowest score = 0) but occurred less frequently (24%; 5 of 21) in the total number of observations recorded 1 5-minutes post-treatment. At 2-hours post treatment this group experienced both a greater level of decrease (up to three levels; lowest score = 0) and at a greater frequency of decrease (53%; 10 of 21) in` clinical severity score in comparison to the saline and 2.06 mg/kg 3,4-DAPP treatment groups. The findings from this study that 3,4-DAPP can improve neuromuscular function after the onset of botulism is consistent with pilot studies performed in humans (Friggeri *et al*. 2013). Similarly consistent to pilot human studies, the magnitude of improvement appeared to vary among subjects, with some animals showing a greater improvement following treatment than others. Of note, treatment with 3,4-DAPP did not appear to worsen the overall condition of the animals. As such, administration of 3,4-DAPP may be considered as a treatment of "low regret" in which the risk of an adverse outcome is minimal and the benefit may be significant. In previous pharmacokinetic work (Study B05928), with many of the same animals used on this study, evidence of foamy emesis was observed in some naïve animals in response to intravenous and SC dosing at the 4.12 mg/kg dose level of 3,4-DAPP. In the BoNT/A1-challenged animals under this study, when 4.12 mg/kg of 3,4-DAPP was administered at time-points after the manifestation of signs associated with botulism, foamy emesis was not observed. If foamy emesis in naïve subjects

is attributed to increased cholinergic action following dose administration, these results support the hypothesis that a similarly high degree of cholinergic activity is not achieved in BoNT/A1-intoxicated synapses in response to 3,4-DAPP treatment. Of note, vomiting was observed in one animal (VL90IA) receiving dosing with 2.06 mg/kg of 3,4-DAPP. However, this was considered attributable to intoxication with BoNT/A1 as observations of vomiting were not previously observed in naïve animals at the 2.06 mg/kg dose level of 3,4-DAPP by any route of administration in Study B05928.

Over timeframes of observed improvements in clinical scoring, SC treatment with 3,4-DAPP appeared to improve blood gas parameters but due to the limited sample set, a degree of significance could not be established. In response to 3,4-DAPP dosing, improvements were characterized by increasing pO_2, decreasing pCO_2, and restoring pH at approximately 15-minutes post-treatment. This appears to be a novel finding, as to date, a comprehensive search of available literature did not return any previous work reporting blood gas analysis following 3,4-DAPP dosing.

In contrast to 3,4-DAP studies in BoNT/A-intoxicated mice, which were characterized by a sharp increase in respiratory function in response to 3,4-DAP treatment (Vazquez-Cintron *et al*. 2020), a similar phenomenon was not observed in NHPs in this study. Notably, beyond the obvious difference in the test system utilized (mice vs. NHPs), the method of respiratory data collection was also different between studies. In Vazquez-Cintron *et al*. (2020), mice were monitored with metabolic cages and the volume of oxygen (VO_2) and exhaled carbon dioxide (VCO_2) was reported as a surrogate for respiratory function. In this study, telemeter leads that were surgically implanted in NHPs served to directly capture respiratory rate and depth using impedance measurements. Parameters such as tidal volume and minute volume were then derived from respiratory waveforms. While each approach has its own unique advantages and disadvantages (direct vs. indirect measurement; invasive vs. non-invasive, etc), it should be noted that dissimilarities in results may not be solely attributed to a species difference and may include unique study design considerations and variations in the methods for data collection.

While treatment with 3,4-DAPP did not appear to acutely alter telemetry endpoints, it did appear to positively alter the clinical trajectory of physiologic function after repeated treatments. Compared to animals treated with saline, which displayed a general decrease in respiratory rate at 8.5 hours after treatment was initiated, animals receiving 3,4-DAPP treatment did not show a general decrease in respiratory rate until 11.25 and 18.75 hours after treatment was initiated at the 2.06 and 4.12 mg/kg dose level, respectively. Similarly, 3,4-DAPP treatment at the 4.12 mg/kg was found to sustain body temperature for a greater period of time compared to other groups. Analysis of cardiac function and animal activity was less conclusive. Notably, whereas animals receiving saline or 2.06 mg/kg of 3,4-DAPP showed a more linear downward trend in heart rate between dosing periods and eventual animal death, animals receiving 4.12 mg/kg of 3,4-DAPP displayed more dynamic heart rate effects, with varying increases and decreases in heart rate occurring throughout the dosing period until animal death.

While not a specific objective of this study, the collective benefit of post-exposure 3,4-DAPP treatment is further supported by evidence of sustained survival following the onset of systemic botulism. On average, animals receiving 4.12 mg/kg of 3,4-DAPP survived approximately 10 hours longer than other groups, with 2 of 3 animals surviving beyond 30 hours after the onset of signs associated with botulism. While specific survival studies will eventually be required to more definitively determine survival effects, the results obtained in this study offer promising preliminary evidence that, if required, licensure of 3,4-DAPP under the "Animal Rule" using survival as a primary endpoint of efficacy may serve a possible approach (U.S. Food and Drug Administration, 2015). Utilizing the 4.12 mg/kg dose of 3,4-DAPP, shortening the dosing interval may confer additional prolongation of survival as results obtained in this study suggest that the durability in maintaining the reduced clinical severity effect was not always sustained beyond 2 hours.

Collectively, given the abundance of direct and supportive evidence for the therapeutic capacity of 3,4-DAPP to serve as a BoNT/A1 medical countermeasure obtained in this study utilizing the cynomolgus monkey test system, the objective of this study was considered to be successfully met.

9 ACKNOWLEDGEMENTS

Acknowledgements of the principal contributors participating in the performance of this study are presented below.

Table 12. Principal Contributors

Role	Name
Study Director	Phillip H. Beske, PhD, DABT/Michelle L. Vassar, BS
Lead Animal Technicians	Bradley Brown Jay Bruskotter
Attending Veterinarian	Tracy A. Peace, DVM, MS, DACLAM
Study Surgeon/Veterinarian (AmplifyBio)	Carolyn Fetzek, DVM
Lead Chemist	Brent McCracken, BA
Telemetry Data Acquisition Lead	Ashley Hay
Select Agent, Principal Investigator	Michelle Vassar
Quality Control Review	J.D. Vrabel (in-life data) Jennifer Webb (report)
Telemetry Data Analysis, Principal Investigator (DSI)	Heather Simenson, BS, CRAT
Electrocardiography, Contributing Scientist (VetMed Consultant Inc.)	Larry P. Tilley, DVM, DACVIM

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Appendix A Protocol

Efficacy Evaluation of 3,4-Diaminopyridine to Acutely Reverse Toxicity in Cynomolgus Monkeys Intoxicated by Botulinum Neurotoxin Serotype A1

Study Protocol

May 13, 2021

Study Number B05929

Defense Threat Reduction Agency
Chemical & Biological Technologies Department
Vaccines/Therapeutics Division (CBM)
8725 John J Kingman Rd MS 6201, Fort Belvoir, VA 22060

GLP Compliance Status: non-GLP

Battelle Memorial Institute
505 King Ave
Columbus, OH, 43201

Testing Facility:
Battelle Biomedical Research Center
1425 Plain City-Georgesville Road
West Jefferson, OH 43162

SIGNATURES

APPROVED, TESTING FACILITY:

Phillip H. Beske, Ph.D., D.A.B.T.
Study Director

01 June 2021
Date

Kemla Siddoway, B.S.
Manager, High Hazard Containment – Chemistry

6/1/2021
Date

APPROVED, SPONSOR: ODELL.LINDSAY.THOMAS.1242936830

Digitally signed by ODELL.LINDSAY.THOMAS.1242936830
Date: 2021.05.13 11:20:23 -04'00'

Lindsay Odell, Ph.D.
Sponsor Representative
Defense Threat Reduction Agency

Date

CDC Select Agent PI Assurance

The CDC Principal Investigator has read and reviewed the following protocol. All methods pertaining to the production, use, storage, and destruction of Biological Select Agent or Toxin are in accordance with Battelle approved procedures that adhere to the Biosafety in Microbiological and Biomedical Laboratories (BMBL) 5th Edition.

CDC Principal Investigator: Michelle Vassar 01 June 2021
Signature/Date

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1.0 INTRODUCTION

Botulinum neurotoxins (BoNTs) are bacterial protein toxins that include antigenically distinct serotypes, labeled A-G [1]. Debate continues as to the presence of other unique serotypes, including BoNT/H [2] and BoNT/X [3]. The toxin itself consists of a heavy chain, which mediates neuron-specific binding and uptake, and a catalytically active light chain. Upon translocation to the presynaptic cytosol, the light chain proteolytically cleaves one of three SNARE proteins critically involved in neurotransmitter exocytosis: synaptosomal-associated protein 25 (BoNT/A, BoNT/C, BoNT/E); synaptobrevin-1/2 (BoNT/B, BoNT/D, BoNT/F, BoNT/G); or syntaxin (BoNT/C) [4]. The resulting inactivation of SNARE-dependent neurotransmitter release prevents the activation of postsynaptic receptors, ultimately manifesting in a flaccid paralysis. Depending on the serotype, intoxication can persist from weeks to months. At lethal doses, paralysis of muscles involved in respiratory function can lead to death by asphyxiation.

While the post-exposure administration of antibody-based antitoxin can extract and inactivate circulating BoNT, any toxin that has already entered the presynaptic compartment is inaccessible to antibody treatments. As such, the current post-exposure BoNT countermeasure approach is rendered largely ineffective after clinical manifestation of disease. Further complicating matters, the criteria for administration of antitoxin requires clinical evidence of flaccid paralysis. As such, even patients who receive antitoxin in a timely manner are likely to experience some symptoms of botulism. In severe cases of poisoning, the only treatment options include intensive supportive care (e.g., mechanical ventilation and parenteral nutrition), which may be needed for weeks to months once flaccid paralysis has manifested. Thus, there exists a critical need for novel late-acting post-symptomatic BoNT countermeasures that acutely reverse botulism symptoms, delay lethality, and/or accelerate disease recovery.

A promising candidate countermeasure to therapeutically treat the symptoms associated with botulism is 3,4-diaminopyridine (3,4-DAP). 3,4-DAP exerts positive modulation of neurotransmitter release through K^+ channel antagonism [5], thereby prolonging action potential duration, increasing presynaptic Ca^{2+} uptake, and potentiating Ca^{2+}-dependent vesicle acetylcholine release. Given the recent approval (November 2018) from the US Food and Drug Administration for Catalyst Pharmaceutical, Inc. to market 3,4-DAP (brand name Firdapse®) as a symptomatic treatment for Lambert-Eaton myasthenic syndrome (LEMS), an accelerated pathway towards repurposing 3,4-DAP as a BoNT countermeasure may now be possible. As non-clinical studies performed in NHPs are seen as an important part of predicting the human efficacy of candidate countermeasures, demonstrating initial proof-of-concept therapeutic benefit of 3,4-DAP in BoNT-intoxicated NHPs is an important step prior to further efficacy evaluation.

2.0 PURPOSE

Following systemic intoxication with botulinum neurotoxin serotype A1 (BoNT/A1), the objective of this study is to evaluate the therapeutic capacity of 3,4-diaminopyridine (3,4-DAP) to acutely reverse toxicity in the cynomolgus monkey model.

3.0 REGULATORY COMPLIANCE

This study will be conducted consistent with, but not in strict compliance with, the current version of the United States Food and Drug Administration's (FDA) Good Laboratory Practice (GLP) Regulations, 21 CFR Part 58 for the conduct of non-clinical laboratory studies.

Any deviations from the study protocol will be documented in the study file and presented in the final report. Deviations from GLP and SOPs will be documented in the study file and presented in the final report as warranted.

4.0 TESTING FACILITY AND STUDY DIRECTOR

4.1 TESTING FACILITY

Battelle Biomedical Research Center
1425 Plain City-Georgesville Road
West Jefferson, OH 43162

4.2 STUDY DIRECTOR

Phillip Beske, Ph.D., D.A.B.T.
Telephone: (614) 424-3277
Email: beske@battelle.org

5.0 TEST SITE AND PRINCIPAL INVESTIGATORS

5.1 AMPLIFYBIO

Test Site for:	Animal Holding and Animal Surgery
Address:	AmplifyBio 1425 State Route 142 (Plain City-Georgesville Road) West Jefferson, OH 43162
Surgeon:	Carolyn Fetzek, D.V.M

5.2 DATA SCIENCES INTERNATIONAL

Test Site for:	Respiratory, cardiac, and body temperature telemetry data analysis
Address:	Data Sciences International 119 14th Street NW St. Paul, MN 55112
Principal Investigator:	To be assigned by Data Sciences International

6.0 SPONSOR AND SPONSOR'S REPRESENTATIVE

6.1 SPONSOR

Defense Threat Reduction Agency
Chemical & Biological Technologies Department
Vaccines/Therapeutics Division (CBM)
8725 John J Kingman Rd MS 6201, Fort Belvoir, VA 22060

6.2 SPONSOR'S REPRESENTATIVE

Lindsay Odell, Ph.D.
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7.0 PROPOSED STUDY SCHEDULE

Proposed dates for selected study events are listed below.

Animal Surgery:	June 2021
In-Life:	July 2021
Sample Analysis and Reporting:	July 2021 – September 2021

8.0 CHALLENGE MATERIAL, TEST ARTICLE, AND PLACEBO

Paper documentation and/or the Inventory and Dispense modules under Provantis will be utilized for challenge material, test article or placebo inventory and preparation. Records of receipt, use, and distribution of materials used on study will be maintained in the study file.

8.1 CHALLENGE MATERIAL

Name:	Botulinum neurotoxin serotype A1 (BoNT/A1).
Description:	BoNT/A1 provided by Metabiologics, Inc. Diluted in sterile 30 mM PBS (pH 6.1-6.3) containing 0.2% (w/v) gelatin to achieve a final dosing solution of 1,000x mouse intraperitoneal LD_{50s}/mL ($MIPLD_{50}$)
Batch/Lot Number:	A081508-01
Storage Conditions:	Frozen at ≤ -60°C until formulation, then 2-8°C for up to 4 hours before administration.
Stability:	Assess upon use per cumulative sum control charting (CUSUM) of assay performance.
Expiration Date:	None assigned

The BoNT/A1 used on study is currently stored at Battelle. The provided certificate of analysis (CoA) for the specific lot used on study will be maintained in the study file. Documentation of synthesis will be maintained by the manufacturer. The expiration date and nominal potency provided in the CoA will not be used. Rather, the potency of the specific BoNT/A1 lot used on study will be verified by a mouse lethality assay performed in quadruplicate per SOP BBRC. X-014 under Battelle Study 521-C1176424. Briefly, for each assay, 6 graded dilutions of the BoNT/A stock will be prepared using 0.2% gelatin phosphate buffer (GPB). Each dilution will be injected intraperitoneally (IP) at a volume of 0.5mL into 6 male CD-1 mice weighing 18.0-22.0g using a 0.5 - 1mL tuberculin syringe containing a 27G ½ inch needle. Beginning in the PM time frame on the day of dosing, mortality observations (# dead/# alive) will be recorded for each group at least once a day for up to 96 ± 2 hours after the dose time that is recorded for each group. At the conclusion of the post-challenge observation period, mortality results will be tallied with the final number alive per group recorded.

The final potency value ($MIPLD_{50}$/mL) for each assay will be determined using probit analysis. Results from analysis will be used to determine appropriate dilutions for preparation of final BoNT/A1 dosing solutions with a target potency of 1,000x $MIPLD_{50}$/mL.

8.2 TEST ARTICLE

Name:	3,4-diaminopyridine phosphate (3,4-DAP)
Description:	Active Pharmaceutical Ingredient (API) powder of Firdapse®; provided by Catalyst

	Pharmaceuticals. Final dosing solutions in saline or water will be prepared by Battelle. All dosing solutions will be prepared fresh on the day of use, maintained at 2-8°C when not in use, and will be visually inspected prior to administration.
Batch/Lot Number:	Lot number to be included in final report
Storage Conditions:	Controlled room temperature (CRT) until formulation, then a target of 2-8°C for up to 6 hours before administration
Stability:	Stability data of Firdapse® API powder at CRT to be provided by Catalyst Pharmaceuticals.
Expiration Date:	To be included in final report

3,4-DAP will be provided to Battelle by Catalyst Pharmaceuticals. A Certificate of Analysis (CoA) and/or equivalent documentation of test article identity, strength, purity, composition and other defining characteristics will be obtained for a specific lot utilized. Documentation of synthesis will be maintained by the manufacturer.

The concentration of dosing solutions will be prepared so as to allow dose administration to remain within IACUC-approved dose administration volumes. Initial characterization of dosing solutions may be performed to include visual determination of solubility and determination of pH. The pH of dosing solutions may be buffered towards physiologic pH if necessary.

8.3 VEHICLE

Name:	0.9% sodium chloride for injection (if IV or SC) or distilled deionized water (DDI) or water for injection, if PO
Batch/Lot Number:	To be included in final report
Storage Conditions:	Controlled room temperature
Stability:	Stable at room temperature until the expiration date when stored according to the manufacturer instructions.
Expiration Date:	To be included in final report

The saline (0.9% sodium chloride for injection) and DDI water (or water for injection) for dose solution preparation will be characterized by its labeling. Documentation of synthesis will be maintained by the manufacturer as applicable. A copy of the package insert or Certificate of Analysis (CoA) and/or equivalent documentation of control article identity, strength, purity, composition and other defining characteristics will be obtained for a specific lot utilized, if possible.

9.0 TEST SYSTEM

Species:	Cynomolgus Monkey, *Macaca fascicularis*
Strain:	Mauritius Origin
Source:	PreLabs (Lehigh Acres, FL) or other acceptable vendor
Anticipated Age of Animals on Day 1:	2 to 4 years, but not a requirement for placement on study
Anticipated Weight of Animals on Day 1:	3.0-5.0 kilograms
Number of Animals Required for Study:	9 total males (8 on study, 1 extra)
Special Considerations:	Previously implanted vascular access port(s) (target of 1 venous and 1 arterial). Data Sciences International (DSI) L11R telemeters (or equivalent) to be implanted at Battelle prior to challenge.

9.1 ANIMALS

Animals will not be research naïve and will have been utilized as part of the test system on Battelle Study B05928 entitled "Pharmacokinetic Analysis of 3,4-Diaminopyridine in the Cynomolgus Monkey". Following the conclusion of in-life activities for Battelle Study B05928, animals will be transferred to the current study and allowed to recover from previous in-life activities for a minimum of 28 days prior to challenge activities. Animals will be maintained at the AmplifyBio test facility for recovery. Previously implanted dual vascular access ports (VAPs) will be maintained according to facility SOPs.

Only animals in good health, free of malformations that would otherwise interfere with the study and exhibiting no signs of clinical disease will be used on study. Animals that do not meet these criteria will be replaced by animals assigned as extras (if available). Extra animals(s) may be used as replacements on study as necessary including in events of unexpected mortality or technical difficulty.

9.2 ANIMAL IDENTIFICATION

Tattoos, cage cards, and ID chips (if present) will be used to identify each animal. Tattoo and ID chip placement will have occurred prior to this study. The cage card will state, at a minimum, the species/strain, tattoo number, study number, and gender.

9.3 ANIMAL SURGERY

Surgeries will be performed aseptically in accordance with SOPs ARF2-038, ARF2-039, ARF3-011, and ARF2-047. Animals will be implanted with DSI L11R telemeters (or equivalent) at the AmplifyBio surgical suite.

The telemetry unit will be implanted intramuscularly, subcutaneously, subperitoneally or intraperitoneally depending on animal size and tissue depth. The unit's antenna will be placed perpendicular to the unit and the biopotential leads will be oriented cranially. The positive ECG lead will be secured to the abdominal side of the diaphragm if the unit is placed subperitoneally or intraperitoneally. Alternatively, it may be placed subcutaneously on the thorax. The telemetry unit will be secured inside a pocket of tissue with non-absorbable sutures. The antenna will be inserted into a small pocket created on the side opposite of the implant. If incised, the abdominal muscle will be closed in a simple interrupted pattern with absorbable sutures. Small incisions will be made on the thorax where the respiratory and ECG leads will be secured. The respiratory and ECG lead(s) will be passed through tunnels made using a trochar passed in the subcutaneous tissue between the abdominal incision to the small incisions made on the thorax. The subcutaneous tissue at the abdominal incision site will be closed with absorbable suture in a simple interrupted pattern. The skin will be closed with either absorbable sutures in an intradermal pattern or staples. The abdominal skin will then be glued closed. ECG leads will be placed in a lead II configuration. If the positive lead is not placed on the diaphragm, the lead will be placed subcutaneously or in a small intramuscular pockets over the middle of the left ribcage approximately level with the xiphoid process. A loop will be created with the wire and secured with non-absorbable suture. The muscular pocket if created will be closed with absorbable suture and the skin closed with absorbable suture and tissue glue. The negative ECG lead will be placed on the right pectoral muscle in an analogous manner to the positive ECG lead. The negative respiratory impedance leads will be placed on the right side of the thorax and the positive leads will be placed on the left side of the thorax. One lead on the right and left side is placed cranial to the 7th rib and one lead on the right and left side is placed caudal to the 7th rib with approximately 2 cm of distance between the leads on each side. Small loops are created at the distal tip of the leads. The leads will be repositioned as needed to obtain an optimal telemetry signal. They will then be secured with non-absorbable suture. The muscle and skin will be closed with absorbable suture. Tissue glue will be placed on the skin incisions.

Anesthetics, analgesics, and antibiotics will be used pre-operatively, operatively, and post-operatively. A target list of anesthetics, analgesics, and antibiotics for each stage is provided below. All dosage and treatment regimens will be performed according to facility regimens or at veterinary discretion. Animals will be monitored from induction to recovery. Supplemental heat and fluids will be provided.

Pre-operative: ketamine, isoflurane, buprenorphine, lidocaine (or bupivacaine), enrofloxacin, carprofen

Operative: isoflurane

Post-operative: buprenorphine, carprofen, enrofloxacin (3 days), then a switch to oral antibiotics for 3 days (Clavamox)

A list of target dose, dose routes, and dose frequencies for each anesthetic, analgesic, and antibiotic is presented below:

Ketamine: 20 mg/kg; pre-operatively; IM

Buprenorphine: 0.03 mg/kg; IM; BID on the day of surgery and IM BID for one additional day

Lidocaine (or bupivacaine): 0.3 mL SC; pre-operatively at telemetry incision site

Carprofen: 4 mg/kg; pre-operatively IM; and SID IM for 3 days post-operatively

Enrofloxacin: 5 mg/kg; pre-operatively IM and for 3 days post-operatively

Clavamox: 16 mg/kg; PO; BID after enrofloxacin administered for three additional days (seven total days of antibiotics)

Following surgical recovery and veterinary assessment of suitability, animals will be transferred to the BBRC for facility acclimation prior to challenge.

10.0 EXPERIMENTAL DESIGN

This study will be conducted in accordance with the protocol, protocol amendments, and applicable Battelle SOPs. An abbreviated list of procedures used in this study can be found in Section 17.0. This study will evaluate the proof-of-concept efficacy of 3,4-DAP to reverse toxicity in BoNT/A1-intoxicated cynomolgus monkeys.

Prior to challenge (Day -3, Day -2, or Day -1), animals will be weighed for dose calculations and the challenge site will be clipped. On the day of challenge (Study Day 1), animals will be chair restrained and a single intramuscular (IM) injection of BoNT/A1 will be injected into the right calf muscle. The IM volume for challenge administration will not exceed 0.5 mL. BoNT/A1 will be delivered at a target dose of 97.5 MIP_{LD50s}/kg, corresponding to 2.5x the published IM LD_{50} of BoNT/A for cynomolgus monkeys [6].

Following BoNT/A1 administration, twice daily AM/PM observations will be performed for the first 24 hours after challenge as manifestation of toxic signs is not anticipated during this timeframe. From ~24 hours after challenge until study termination (7 days post-challenge), animals will be clinically monitored at 2-hour intervals (± 15 minutes) for toxic signs of systemic botulism in accordance with (IAW) Battelle SOP CORV-005. Criteria for initiation of 3,4-DAP treatment (or placebo) will be animal-specific and will be determined through clinical severity scoring of select toxic signs (ptosis, muscular weakness, respiratory distress, oral/nasal discharge). A clinical severity score of 1 or greater will serve as a trigger to initiate 3,4-DAP (or placebo) treatment at the following observation time-point, ~2 hours after the first observed toxic sign. Additional post-treatment observations will be performed 15 minutes (± 2 minutes) after each administration of 3,4-DAP (or placebo).

3,4-DAP treatment will be performed by the intravenous (IV), subcutaneous (SC), or oral (PO) dosing route and the specific route will be determined in consultation with the Sponsor pending results of the pharmacokinetic (PK) analysis performed under Battelle Study B05928. Treatments will be delivered in bolus fashion. All dose volumes will not exceed 5 mL/kg. 3,4-DAP treatment will be performed at two dosing levels (TBD_1 mg/kg and TBD_2 mg/kg) and will be determined in consultation with the Sponsor pending results of the PK analysis performed under Battelle Study B05928. Placebo dose volumes will be matched to the highest dose volume employed for 3,4-DAP treatment. Repeat treatment frequency with 3,4-DAP (or placebo) will be performed at an interval determined in consultation with the Sponsor pending results of the PK analysis performed under Battelle Study B05928. Final treatment conditions including dose concentration, dosing route, and dosing frequency will be documented by amendment.

Animals that are judged to be moribund (complete lack of activity or total paralysis of body movement) by a trained animal technician or veterinarian will be euthanized.

A summary of the Study Design is presented in Table 1. Detailed procedures for collected endpoints are presented below in subsequent sections (see Sections 10.3 through 10.8).

Table 1. Study Design

Group	Challenge; Dose; Route	Treatment; Dose; Route*	Endpoints	# of Animals
1	BoNT/A1 2.5x LD_{50}; IM	Vehicle; 0 mg/kg; TBD	Clinical Observations Respiratory Telemetry Cardiac Telemetry Body Temperature Arterial Blood Gas**	2
2		3,4-DAP; TBD_1 mg/kg; TBD		3
3		3,4-DAP; TBD_2 mg/kg; TBD		3

* Dose route and 3,4-DAP doses to be determined in consultation with the Sponsor.
** If an arterial VAP is present and patent in the animal

10.1 ANIMAL RANDOMIZATION

Animals will be randomized to groups by weights collected prior to challenge activities (Day -3, Day -2, or Day-1). Randomization will be performed using the Provantis computer system in accordance with Battelle SOP Number COR.4-006 to ensure similar group mean weights. In the event of animal illness or injury prior to the start of the study, extra replacement animals will be assigned to groups by the Study Director.

10.2 BODY WEIGHTS

Animals will be weighed during quarantine and re-weighed as necessary for medical monitoring purposes. Animals will be weighed prior to the day of challenge for randomization to groups by body weight (Day -3, Day -2, or Day -1) and for challenge and treatment dose calculations. Additional weights may be taken at any time for medical monitoring purposes for any health or veterinarian related issues. Body weights will be collected in accordance with Battelle SOP COR.4-012 and will be recorded in Provantis in accordance with SOP COR.4-008.

10.3 ANIMAL OBSERVATIONS

10.3.1 Prior to Challenge

AM/PM clinical observations will be performed twice daily in accordance with Battelle SOP COR.5-005. A single AM observation will be made before challenge with BoNT/A1. Clinical observations will be recorded in Provantis in accordance with Battelle SOP COR.4-009.

10.3.2 Post-Challenge

A single PM observation will be performed on the day of challenge, after BoNT/A1 challenge. On Study Day 2, per the 24-hour clock, animals will be observed at 2-hour intervals (± 15 minutes) starting at 0800 and continuing at 1000, 1200, 1400, 1600, 1800, 2000, 2200, 2400, 0200, 0400, and 0600 through study termination (Study Day 8). Clinical observations will be recorded in Provantis according to Battelle SOP Number COR.4-009. Paper documentation of observations may be performed if required.

10.3.3 Post-Treatment

Following each 3,4-DAP (or placebo) treatment, an additional observation will be collected at 15 minutes (± 2 minutes) after administration. Clinical observations will be recorded in Provantis according to Battelle SOP Number COR.4-009. Paper documentation of observations may be performed if required.

10.3.4 Clinical Severity Scoring

At each clinical observation time-point, including post-treatment observations, clinical severity scoring will be performed IAW the Table 2 criteria. Paper documentation of clinical severity scores will be performed.

Table 2. Clinical Severity Scoring

Clinical Signs	Observation	Clinical Severity Score Assigned
Ptosis	Absent	0
	Slight	1
	Marked	2
Muscular Weakness	Normal	0
	Hunched Posture	1
	Prostrate but able to rise	2
	Prostrate but unable to rise	3
Respiratory Distress	Normal breathing	0
	Open mouth shallow (thoracic)	1
	Gasping and jerking (abdominal)	3
Oral Discharge	Absent	0
	Present	1
Nasal Discharge	Absent	0
	Present	1
Lethality	Alive	0
	Dead	10

10.4 RESPIRATORY TELEMETRY

Respiratory telemetry data captured from the DSI L11R implants will be continuously collected on study, starting at least 2 days before BoNT/A1 challenge (baseline) and continuing through study termination. All data collection will be performed according to Battelle SOP Number BBRC.IV-087. Data may not be collected during study activities requiring the removal of animal from home caging. At the conclusion of in-life, collected telemetry data will be collated and provided to DSI for analysis with Ponemah® Software. A narrative of analysis with graphs and tables (as appropriate) will be provided to Battelle by DSI for inclusion in the Final Report. Respiratory parameters analyzed may include breaths per minute, minute volume, and tidal volume. Additional or alternate analysis of unique study specific results may be performed by DSI with Study Director and Sponsor concurrence.

10.5 CARDIAC TELEMETRY

Cardiac telemetry data captured from the DSI L11R implants will be continuously collected on study, starting at least 2 days before BoNT/A1 challenge (baseline) and continuing through

study termination. All data collection will be performed according to Battelle SOP Number BBRC.IV-087. Data may not be collected during study activities requiring the removal of animal from home caging. At the conclusion of in-life, collected cardiac data will be collated and provided to DSI for analysis with Ponemah® Software. A narrative of analysis with graphs and tables (as appropriate) will be provided to Battelle by DSI for inclusion in the Final Report. Cardiac parameters analyzed may include heart rate and QT interval. A cardiologist review of electrocardiograms (ECGs) may be performed with Study Director and Sponsor concurrence to investigate and/or diagnose potential arrhythmias.

10.6 BODY TEMPERATURE

Body temperature data captured directly from the DSI L11R implants will be continuously collected on study, starting at least 2 days before BoNT/A1 challenge (baseline) and continuing through study termination. All data collection will be performed according to Battelle SOP Number BBRC.IV-087. Data may not be collected during study activities requiring the removal of animal from home caging. At the conclusion of in-life, collected body temperature data will be collated and provided to DSI for analysis. A narrative of analysis with graphs and tables (as appropriate) will be provided to Battelle by DSI for inclusion in the Final Report. Body temperature data may be averaged over time.

10.7 BLOOD COLLECTION AND ARTERIAL BLOOD GAS ANALYSIS

All blood will be collected IAW Battelle SOP Number BBRC.VII-077 and Battelle SOP Number COR.5-018 as applicable. Whole blood samples will be collected from unanesthetized animals using the arterial VAP. Animals will be chair restrained for all collections. To reduce handling, animals may remain in chair restraint for the pre- and 15-minute post-treatment blood collections outlined below. Analysis will be restricted to samples that are obtained. If the arterial VAP is not present or not patent, a sample will not be collected for arterial blood gas (ABG) analysis and a reason for the failed collection will be documented.

A target of one (1) mL of blood with selfPICO Self-Filling Syringes via the arterial VAP (if present and if patent) at the following time points for measurement of ABGs using an ABL90 Flex Blood Gas Analyzer IAW Battelle SOP BBRC. VI-133: prior to challenge (baseline), immediately prior to the first 3,4-DAP (or placebo) administration, 15 minutes (± 3 minutes) after the first 3,4-DAP (or placebo) administration, immediately prior to the second 3,4-DAP (or placebo) administration, 15 minutes (± 3 minutes) after the second 3,4-DAP (or placebo) administration, immediately prior to the third 3,4-DAP (or placebo) administration, and 15 minutes (± 3 minutes) after the third 3,4-DAP (or placebo) administration. ABG analysis will include, at a minimum, pH, pCO_2, pO_2, and sO_2. All ABG samples will be analyzed within 30 minutes of collection.

11.0 ANIMAL CARE, HOUSING, AND ENVIRONMENTAL CONDITIONS

General procedures for animal care and housing will meet the AAALAC International recommendations, current requirements stated in the current "Guide for Care and Use of Laboratory Animals," current requirements as stated by the U.S. Department of Agriculture through the Animal Welfare Act, as amended, and will conform to the testing facility SOPs. Prior to study initiation the protocol will be reviewed and approved by the Institutional Animals Care and Use Committee (IACUC).

11.1 RECEIPT, QUARANTINE, AND TRANSFER

Prior to transfer to this study, receipt and quarantine of animals will have been previously performed in accordance with Battelle SOPs under a previous study (Study B05928). Previous testing of NHPs under Study B05928 will be used to verify negative status tuberculosis and to confirm that they are seronegative for Simian Immunodeficiency Virus (SIV), Simian T-Lymphotrophic Virus-I (STLV-1), and Macacine herpesvirus 1 (Herpes B virus), and negative for Simian Retrovirus (SRVl & SRV2) by polymerase chain reaction (PCR).

Pole/collar and other training will have been performed under the previous study (Study B05928) and will continue into the pre-challenge period for this study, as necessary. Prior to challenge, all animals will be acclimated to chair restraint IAW Battelle policies.

Animals will be visually examined through detailed clinical observation by a Battelle veterinarian prior to transfer. Only NHPs that are determined to be healthy by a Battelle clinical veterinarian will be transferred to this study protocol. Documentation of the transfer to this study will be retained in the study file. If any NHP is considered unacceptable for study purposes by a veterinarian or the Study Director, it will be removed from the study.

11.2 VETERINARY CARE

Animals will be observed by laboratory personnel prior to and following dosing. Animals that develop non-study-related illness or injury will be evaluated by a Battelle veterinarian for determination of treatment or disposition. In such cases, and if in the opinion of a Battelle veterinarian, an animal who is in a moribund state prior to challenge will be euthanized in accordance with Battelle SOPs.

11.3 PAIN AND DISTRESS

Discomfort and distress will be limited to that which is unavoidable in the conduct of scientifically valuable research. Early euthanasia will be performed for any moribund animals. The use of a vascular access ports for blood collection is intended to reduce the distress associated with repeated blood collections.

Animals that develop non-study-related illness or injury will be evaluated by a Battelle veterinarian for determination of treatment or disposition. In such cases, if in the opinion of the Study Director and a Battelle veterinarian, an animal is unfit for placement on study or in a moribund state prior to study the animal will be euthanized.

11.4 CRITERIA FOR EUTHANASIA

As death is not an endpoint of efficacy in this study, animals that are judged to be moribund (complete lack of activity or total paralysis of body movement) by a trained animal technician or veterinarian will be euthanized. If required, NHPs will be anesthetized and euthanized with an American Veterinary Medical Association (AVMA) accepted method of euthanasia. The absence of a heartbeat determined stethoscopically or by palpation, will be used to verify death and will be documented. The staff member who decides to euthanize each animal will record the reason for euthanasia (in sufficient detail for an independent review to recreate the activities that occurred) and the time the animal was euthanized. This documentation will be included in the study file.

11.5 ANIMAL HOUSING AND ENVIRONMENTAL CONDITIONS

11.5.1 Housing

Animals may be socially housed (to the extent possible) prior to telemeter surgery. Following telemeter surgery, animals will be single housed for approximately 3-5 days for recovery or at veterinary discretion. After surgery but prior to challenge, animals may be single housed or socially housed (to the extent possible) at veterinary discretion. For pre-challenge baseline and all post-challenge telemeter data capture, animals will be single housed. Socialization will be achieved by housing animals in the same room with visual and auditory contact.

11.5.2 Lighting

The light/dark cycle will be approximately 12 hours each per day using fluorescent lighting, in accordance with Battelle SOP BBRC.IV-002, with the exception of during study activities where lights may be on longer than 12 hours if necessary.

11.5.3 Temperature

Animal room temperatures will be controlled, monitored, and documented according to Battelle SOP BBRC.IV-008. Animal room temperature will be maintained at SOP defined criteria (64-84ºF). Excursions will be evaluated by the Study Director to assess impact.

11.5.4 Humidity

The relative humidity of animal rooms will be maintained according to Battelle SOP BBRC.IV-008. The relative humidity of animal rooms will be maintained at SOP-defined criteria (30- 70%). Excursions will be evaluated by the Study Director to assess impact.

11.5.5 Air Handling

The air pressure and air changes of animal rooms will be maintained according to Battelle SOP COR.5-015.

11.5.6 Diet

NHPs will be fed Purina Certified Monkey Chow IAW Battelle SOP BBRC.VII-014. No contaminants that would affect the results of the study are known to be present in the feed.

Analytical reports of each lot of feed will be provided by the manufacturer. Analytical reports will be reviewed according to Battelle SOP BBRC.VII-002 to ensure acceptable standards and freedom from levels of contaminants that may interfere with the purpose or conduct of the study.

11.5.7 Water

Cages will be equipped with an automatic watering system. Water will be supplied from the West Jefferson municipal water system and will be available ad libitum during the study. Water is analyzed at least once per year. Analysis is carried out IAW Battelle SOP BBRC. VIII-003. No contaminants that would affect the results of the study are known to be present in the water. Analytical results will be retained in facility records.

11.5.8 Enrichment

To promote and enhance the psychological well-being of the NHPs, both food and environmental enrichment will be provided as described in Battelle SOP COR.5-008. Documentation of the supplementation will be maintained in the study files.

12.0 COMPUTER SYSTEMS FOR DATA MANAGEMENT

The following computer systems may be used for data management:

Table 3. Data Acquisition Systems

Computer System*	Manufacturer	Data Type
ECMS	Siemens	Animal Facility Environmental
Insight, InfoCenter Suite, and APOGEE	Siemens	Building Monitoring (Room Temperatures, Light Cycles, Pressure, Humidity, Air Flow, Cold Storage Unit Temperature)

Provantis®	Instem	Clinical observations, body weights, randomizations
Sample Tracking System#	Battelle	Barcoded sample tracking for sample disposition and location
SAS®	SAS	Statistical Analysis
Stata	StataCorp, LLC	Statistical Analysis
Prism	GraphPad	Graphing
Ponemah®	DSI	Telemetry data acquisition

* Version numbers to be included in the final report.
\# Does not have archival capabilities but is otherwise validated as Part 11 compliant.

13.0 STATISTICAL ANALYSIS

Statistical analysis of pre- and post-treatment clinical severity scores, breaths per minute, minute volumes, tidal volumes, heart rates, QT intervals, body temperatures, and ABG parameters may be performed using appropriate statistical tests amongst individual animals and/or across group means. Where appropriate, data may be averaged over unit time. The use of repeated-measures testing will be utilized to the extent possible to increase statistical power. Additional or alternate analysis may be performed with Study Director and Sponsor concurrence in consultation with a Statistician. The final results of statistical analysis and all employed statistical methods will be provided as a Contributing Scientist Report for inclusion in the Final Report.

14.0 REPORTING

A draft report will be prepared and submitted to the Sponsor. The Sponsor shall submit comments on the draft report. Additional reviews and comments may be performed. A final report will be submitted to the Sponsor following receipt of the Sponsor's final comments.

15.0 STORAGE OF STUDY MATERIALS AND RECORDS RETENTION

The disposition of study materials (data, documentation, samples, and/or specimens) is outlined in the following table.

Table 4. Storage of Study Materials

Study Material	Location or Disposition
Raw data from Battelle	Raw data will be archived at Battelle
Residual test article	Retention samples will not be archived. Residual test article will be retained for use on a future study.
Animals	NHPs used on study will be euthanized at the protocol-defined terminal time-point. Any unused extra animals may be euthanized, transferred to a training protocol, or transferred to another study.
Final Report	Report will be archived at Battelle

16.0 BIOSAFETY CONSIDERATIONS

A Battelle Environment, Safety, and Health Officer has been provided the opportunity to review this animal use protocol and all procedures required to execute this study.

17.0 REFERENCES

References

1. Simpson, L.L., *Identification of the major steps in botulinum toxin action*. Annu Rev Pharmacol Toxicol, 2004. **44**:167-193.
2. Barash, J.R., Arnon, S.S. *A novel strain of Clostridium botulinum that produces type B and type H botulinum toxins*. J Infect Dis, 2014. **209**(2):183-191.
3. Zhang, S., et al., *Identification and characterization of a novel botulinum neurotoxin*. Nat Commun, 2017. **8**:14130.
4. Montecucco, C., Schiavo, G. *Mechanism of action of tetanus and botulinum neurotoxins*. Mol Microbiol, 1994. **3**(1):1-8.
5. Kirsch, G.E, Narahashi, T. *3,4-diaminopyridine. A potent new potassium channel blocker*. Biophys J, 1978. 22(3):507-512.

6. Scott, A.B., and Suzuki, D. *Systemic Toxicity of Botulinum Toxin by Intramuscular Injection in the Monkey*. Movement Disorders, 1988. 3(4): 333-335.

Standard Operating Procedures

1. Battelle SOP BBRC.IV-002, "Monitoring Room Lighting in Animal Rooms."

2. Battelle SOP BBRC.IV-008, "Monitoring Temperature and Humidity Conditions Using Automated HVAC Control and Monitoring Systems."

3. Battelle SOP BBRC.VI-133, "Operation and Maintenance of the ABL90 Flex Blood Gas Analyzer."

4. Battelle SOP BBRC.VI-087, "Standard Operating Procedure for Use and Maintenance of the Data Sciences International Telemetry System."

5. Battelle SOP BBRC.VII-002, "Feed Source, Storage, Handling, and Analysis."

6. Battelle SOP BBRC.VII-006, "Animal Euthanasia at the Battelle Biomedical Research Center (BBRC)."

7. Battelle SOP BBRC.VII-014, "Care of Nonhuman Primates."

8. Battelle SOP BBRC.VII-026, "Receipt, Transfer, Quarantine, Monitoring, and Release of Experimental Animals."

9. Battelle SOP BBRC.VII-077, "Collection of Blood Samples and Maintenance of Vascular Access Ports in Multiple Animal Species Used at the BBRC."

10. Battelle SOP BBRC.VIII-003, "Supplying Water and Monitoring Water Quality of the Manual and Automatic Watering Systems."

11. Battelle SOP BBRC.VIII-010, "Operating the Pathological Incinerator."

12. Battelle SOP BBRC.X-014, "Detection, Quantitation and Optimal Dose Calibration of Botulinum Toxins and Antitoxins (Antibodies) Using the Mouse Bioassay."

13. Battelle SOP COR.1-002, "Operation of Archives."

14. Battelle SOP COR.4-006, "Randomization and Animal Management in the Provantis Computer System."

15. Battelle SOP COR.4-007, “Defining In-Life Data Entry Sessions in the Provantis Computer System.”

16. Battelle SOP COR.4 -008, “Entering Body Weights, Recording Generalized Results, and Marking Animals Dead in the Provantis Computer System.”

17. Battelle SOP COR.4-009, “Entering Clinical Observations in the Provantis Computer System.”

18. Battelle SOP COR.5-005, “Conducting Clinical Observations.”

19. Battelle SOP COR.5-007, “Oral Dosing of Animals.”

20. Battelle SOP COR.5-008, “Environmental Enrichment of Nonhuman Primates.”

21. Battelle SOP COR.5-009, “Injections.”

22. Battelle SOP COR.5-012, “Measuring Body Weight, Food Consumption, and Water Consumption.”

23. Battelle SOP COR.5-015, “HVAC Systems in Animal Resources.”

24. Battelle SOP COR.5-018, “Blood Collection.”

Appendix B Summary of Deviations

SUMMARY OF DEVIATIONS

Deviations from GLP or the study protocol are summarized below; SOP deviations are maintained in the study file.

Deviation Number	Date Occurred	Description	Impact
DR-B05929-BBRC-0001	09/14/2021	Section 10.0 (EXPERIMENTAL DESIGN) of the Study Protocol states: "Repeat treatment frequency with 3,4-DAP (or placebo) will be performed at an interval determined in consultation with the Sponsor pending results of the PK analysis performed under Battelle Study B05928. Final treatment conditions including dose concentration, dosing route, and dosing frequency will be documented by amendment." Documentation of Sponsor concurrence on the dose concentration (2.06 and 4.12 mg/kg), dosing route (subcutaneous), and dosing frequency (4 hour dosing interval) is present in the Study File e-mails. Documentation exists that the Study Director provided direction to staff to perform treatment administration per Sponsor/Study Director concurrence. However, the final treatment dosing conditions were not documented by amendment, per protocol.	There is no adverse impact to the study objective or interpretation of study results for the missing amendment. The dosing conditions outlined with Sponsor/Study Director concurrence (2.06 and 4.12 mg/kg of 3,4-diaminopyridine phosphate; subcutaneous route; 4- hour dosing interval) were performed as intended.
DR-B05929-BBRC-0004	9/14/2021	Protocol section 8.2 'Test Article' states, "Storage Conditions: Controlled room temperature (CRT) until formulation, then a target of 2-8°C for up to 6 hours before administration." Dosing paperwork (form named "3,4-Diaminopyridine Phosphate Dose Form) is missing indication that Test Article was kept on ice or at 2-8 degrees Celsius. Error occurred on the following forms: Animal ID AP55D - 9/14/21; 9/15/21 Animal ID BF873I - 9/15/21 Animal ID N378ALE - 9/16/21 Animal ID AL793H - 9/15/21 Animal ID YR895FD - 9/15/21	Documentation for storage of the test article solutions on wet ice after preparation is present on all of dosing solution preparation paperwork. Most dose administration forms (excepting the above examples) have additional comments documented that solutions were stored on ice when not in use. The partial omission of this comment on some of the early dose forms does not adversely impact overall interpretation of study results.

Deviation Number	Date Occurred	Description	Impact
DR-B05929-BBRC-0006	9/15/2021	Protocol section 10.7 'Blood Collection and Arterial Blood Gas Analysis' states, "A target of one (1) mL of blood with selfPICO Self-Filling Syringes via the arterial VAP (if present and if patent) at the following time points for measurement of ABGs using an ABL90 Flex Blood Gas Analyzer IAW Battelle SOP BBRC. VI-133: prior to challenge (baseline), immediately prior to the first 3,4-DAP (or placebo) administration, 15 minutes (± 3 minutes) after the first 3,4-DAP (or placebo) administration, immediately prior to the second 3,4-DAP (or placebo) administration, 15 minutes (± 3 minutes) after the second 3,4-DAP (or placebo) administration, immediately prior to the third 3,4-DAP (or placebo) administration, and 15 minutes (± 3 minutes) after the third 3,4-DAP (or placebo) administration." 1. On Collection, Transfer, and Storage of Whole Specimens (form VII-020A-00) for Animal ID G180JD Treatment 3 - the 15 Min Post Treatment collection is documented to be collected on 9/15/21 @ 22:06. On Dosing Form titled "3,4 Diaminopyridine Phosphate Dose Form" for Animal ID G180JD dated 9/15/21 shows that the 3rd Treatment occurred at 9/15/21 @22:10. Therefore, the collection which was supposed to occur 15 mins post treatment, was actually collected 4 mins before treatment occurred. 2. All ABG samples were supposed to be analyzed within 30mins of collection. Animal ID G180JD sample #590 was recorded on the Radiometer ABL90 Series Printout as being analyzed at 9/15/21 @ 10:02PM. Animal ID G180JD sample #590 was the pre-treatment 3 collection per the records on form ABL90 Blood Gas Sample Tracking Sheet. Animal ID G180JD collection form titled "Sample Description Treatment 3" shows that Pre Treatment collection occurred at 21:01 on 9/15/21 Per paperwork it appears that the specimen was collected at 09:01 PM on 9/15/21, and was analyzed at 10:05 PM (with adjustment time see ABL90 clock discrepancy memo) on 9/15/21 which is outside the 30mins allowed on the protocol by a total of 34mins	The inaccurate and/or conflicting sample collection times in relation to SC treatment times and ultimate ABL90 sample analysis times does not allow for a reasonable re-construction of study events or interpretation of results. Therefore, all ABG data for Treatment #3 for Animal GJ180JD (pre- and post-dose) will be excluded from analysis and reporting. The exclusion of this data adversely impacts interpretation of ABG results for Treatment #3 as Animal GJ180JD served as the only subject in the control group. The overall study objective and other endpoints of the study are not adversely impacted.

Deviation Number	Date Occurred	Description	Impact
DR-B05929-BBRC-0007	9/15/2021	Per the Battelle Study B05929 protocol Section 10.7 Blood Collection and Arterial Blood Gas Analysis, "Whole blood samples will be collected from unanesthetized animals using the arterial VAP." The collection site was not indicated on the Collection, Transfer and Storage of Whole Specimens form (form VII-020A-00) for the following animals and time points: Group 1: Animal G180JD Treatment 1: Pre-treatment sample and 15 minute post-treatment sample. Animal G180JD Treatment 2: Pre-treatment sample and 15 minute post-treatment sample. Animal G180JD Treatment 3: Pre-treatment sample and 15 minute post-treatment sample. Group 2: Animal VL90IA Treatment 2: Pre-treatment sample and 15 minute post-treatment sample. Animal VL90IA Treatment 3: Pre-treatment sample and 15 minute post-treatment sample. Group 3: Animal SA180D Treatment 2: Pre-treatment sample and 15 minute post-treatment sample. Animal SA180D Treatment 3: Pre-treatment sample and 15 minute post-treatment sample.	Notation on the "Collection, Transfer, and Storage of Whole Specimens" study paperwork forms states that "Unless otherwise noted, prior to accessing the VAP system for all animals, the area of the port was cleaned with 3 antimicrobial wipes and one alcohol wipe per the SOP." Blood samples were not collected by needle stick from animals that did not have arterial VAPs. It is therefore reasonable to assume that samples were collected from the site that was documented as being cleaned per SOP. Previous baseline samples were collected and documented to have come from the arterial catheter in the same animals prior to the partial omissions on the documentation instructions at later times to "circle one" collection site on the paperwork. Unless otherwise noted, all ABG data will be reported with annotation of this deviation report for reference. Therefore, there is no adverse impact to the overall study objective for this partial omission of documentation.

Appendix C Challenge Article COA and Characterization

METABIOLOGICS, INC
505 S. ROSA RD, SUITE 18
MADISON WI 53719
(608) 441-2730 fax (608) 441-2731

Certificate of Analysis

Description: Clostridium botulinum Complex Type A

Lot No. #: A081508-01

Volume of toxin shipped : 5.0 ml 25 mg Total

Concentration of toxin: 5.0 mg/ml

Specific Activity: 3.5 X 10^7 LD50/mg

The toxin was shipped in 0.05 M Sodium Phosphate + 0.2 M sodium chloride buffer, pH 6.2. Toxin was passed through a 0.22 micron syringe filter.

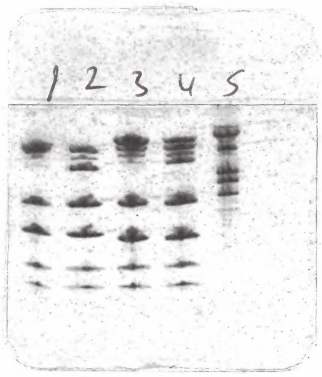
The toxin described above was tested for specific activity by mouse bioassay, identity by type specific antibody neutralization and purity by SDS-PAGE.

Lot number A081508-01 of Type A toxin complex has been released.

Released by: _____

Date: 8/15/08

Storage conditions: Refrigerate (2-8 C) short term or freeze.
Expires 8/15/09



SDS-PAGE

1 A complex
2 1 reduced
3 B complex
4 3 reduced
5 HMW markers

Serotype A BoNT Lot# A081508-01 Batch 4a Potency Check

Study Number: 521-C1176424
Study Date: 05/24/2021

Test	Study Date	Serotype	ExpNum	MIPLD$_{50}$/mL
Toxin Potency	05/24/2021	A	11702	508,472
			11703	512,704
			11704	614,875
			11705	449,267
			AVERAGE	***521,330***

Report Printed By/Date MV 6.2.21

QC Review Performed By/Date MH 6/2/2021

Appendix D Test Article and Vehicle

Patheon
A HEALTHIER WORLD. DELIVERED.

Patheon API Manufacturing
309 Delaware Street
Greenville, SC 29605
864-299-8600
Patheon.com

CERTIFICATE OF ANALYSIS

Project Code: CAY528
Lot Number: P528FPM-19-002
Product Name: Amifampridine Phosphate Drug Substance
Manufacturing Date: 12/16/2019
Inventory Code: PR-PRD-CAY01
Date of Analysis: 03/11/2020

TEST	SPECIFICATION		RESULTS	
Description	White Crystalline Powder		White Crystalline Powder	
Identification (FTIR)	Conforms to reference		Conforms to reference	
Identification (Phosphate)	Conforms		Conforms	
Assay (HPLC) on dried basis	98.0 – 102.0%		99.2%	
Related Substances	4-aminopyridine (AMPY, 4-AP)	≤ 0.05%	4-aminopyridine (AMPY, 4-AP)	< 0.05%
	3-nitro-4-aminopyridine (ANPB)	≤ 0.05%	3-nitro-4-aminopyridine <0.05%(ANPB)	< 0.05%
	Individual Unidentified	≤ 0.10%	Individual Unidentified	< 0.05%
	Total	≤ 0.50%	Total	< 0.50%
Residual Solvents	Ethanol	NMT 3000 ppm	Ethanol	< 397 ppm
	1,2-Dichloroethane	NMT 5 ppm	1,2-Dichloroethane	< 2 ppm
	Triethylamine	NMT 125 ppm	Triethylamine	< 58 ppm
3-nitro-4-pyridinyl-ether ester	NMT 0.001%		ND (<0.001%)	
Clarity and color of solution	Clear, colorless solution		Clear, colorless solution	

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Greenville, SC 29605
864-299-8600
Patheon.com

CERTIFICATE OF ANALYSIS

TEST	SPECIFICATON	RESULTS
Solubility	Easily soluble in Water	Easily soluble in Water
Melting Point (ID)	225-231°C	229°C
pH (ID), 1% (w/v) in water	4.2 - 4.6	4.5
Loss on Drying	NMT 1.0%	0.3%
Palladium	NMT 15 ppm	< 5 ppm
Water Content (KF)	NMT 1.0%	<0.05% (0.02%)
Particle Size	D(v, 0.9) ≤ 50 µm	37 µm
Total aerobic count	NMT 1000 CFU/g	< 10 CFU/g
Yeast and mold (Fungi)	NMT 100 CFU/g	< 10 CFU/g
Absence of E. Coli	Absent in 1 g	Absent in 1 g

Storage: Store in tight containers at warehouse conditions

Re-test date: 12/2022

Record of Revision

Version:	Effective Date:	Reason:
1	JUN 08 2020	New

Patheon
A HEALTHIER WORLD. DELIVERED.

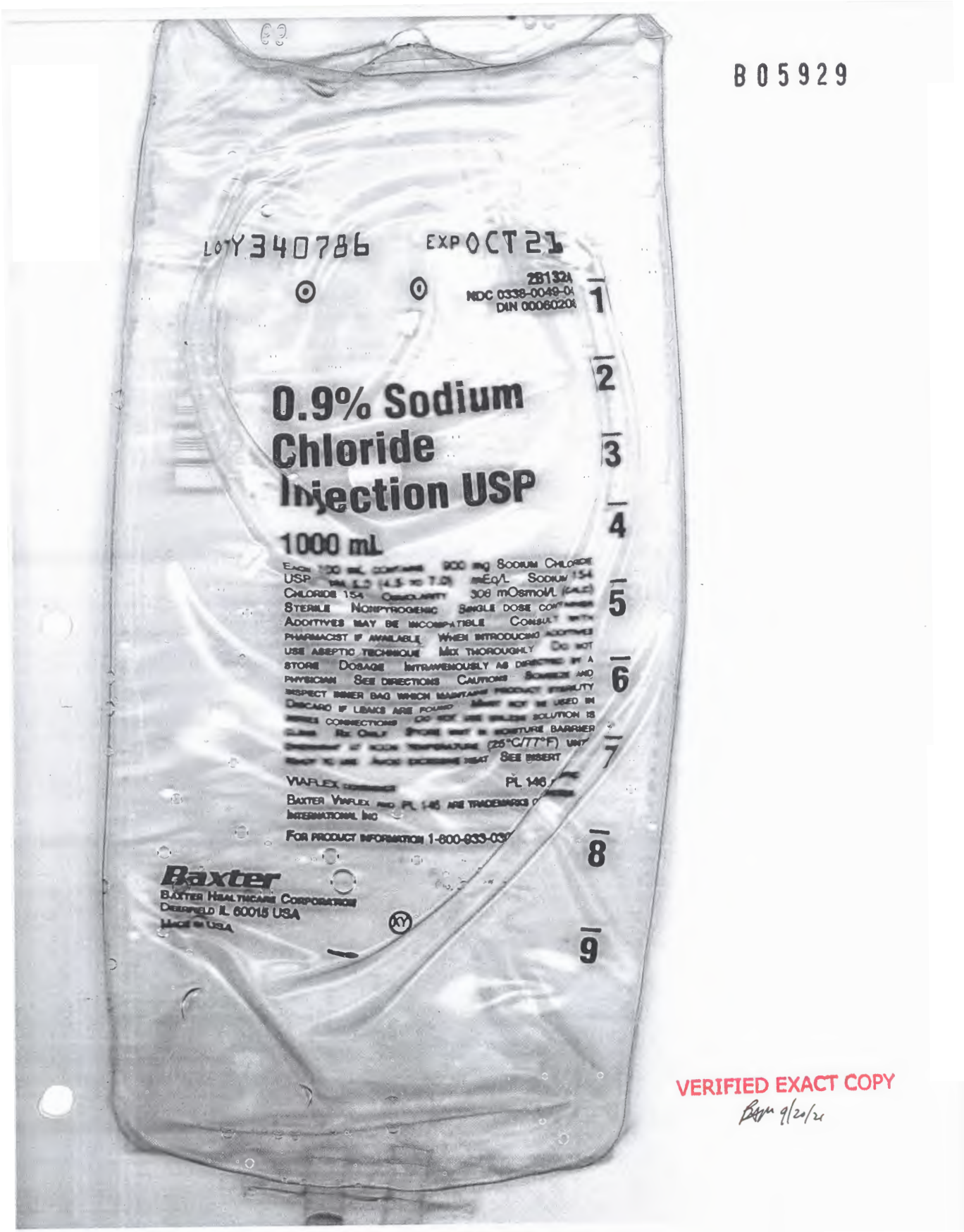
Patheon API Manufacturing
309 Delaware Street
Greenville, SC 29605
864-299-8600
Patheon.com

CERTIFICATE OF ANALYSIS

This lot was manufactured in accordance with the requirements for production of Active Pharmaceutical Ingredients (APIs) as outlined in ICH Q7 "Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients".

Quality Control — Date: 05/29/2020

Quality Assurance — Date: 05/29/2020


B05929
LOT Y340786
EXP OCT 21
0.9% Sodium Chloride Injection USP
1000 mL
Baxter
Baxter Healthcare Corporation
Deerfield IL 60015 USA
VERIFIED EXACT COPY
9/20/21

Appendix E Animal Surgery Investigation Report

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INVESTIGATION REPORT FORM

Describe issue and reason for investigation:

The following investigation describes the details of the foot and extremity lesions that developed approximately 3-9 days post-telemetry surgery on Study B05929.

Description of the telemetry surgery: The nonhuman primates (NHPs) were sedated with ketamine and administered buprenorphine, enrofloxacin, and carprofen for the surgical placement of telemetry units. They were induced with isoflurane and intubated. Their vital signs were monitored and recorded. The thorax and abdomen were prepared aseptically. Animals were moved to the surgery room table and placed in dorsal recumbency on a heated surgical table (warmed to 104F) on top of a Bair Hugger warming blanket covered by a drape and second sterile drape. Their legs were gently restrained to the surgery table. The animals were aseptically draped using sterile adhesive towels and a large surgical drape. Once draped, a second Bair Hugger warming unit was used to blow warm air on the caudal aspect of the animals. The Bair Huggers were set to maintain a temperature of 109F. The Bair Huggers were adjusted (turned down or off) to maintain a normal body temperature (101F). All surgery procedures were conducted according to the study protocol using trained staff to complete the responsibilities of the study including being up to date on the required surgical SOPs, including: AMPARF2-039 Care of Anesthetized Animals, AMPARF2-038 Preparation to Perform Surgery on Animal Models, AMPARF2-004 Handling of Nonhuman Primates, AMPARF2-023 Restraint of Animals and Use of Restraining Devices for Species other than Rats and Mice and training sessions: Large Animal Data Collection Vital Signs, and Animal Welfare Training.

A total of 9 animals underwent surgery as follows:

Animal ID	Surgery Date
N378ALE	06 July 2021
SA180D	06 July 2021
AL793H	07 July 2021
VL90IA	07 July 2021
G180JD	08 July 2021
BF873I	08 July 2021
AL110O	09 July 2021
AP55D	12 July 2021
YR895FD	13 July 2021

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INVESTIGATION REPORT FORM

The following is a time course of the observations:

Friday July 9: All animals appeared normal (surgeries were completed on 7 of the 9 animals).

Saturday July 10: Animal AL110O (one day post-surgery) was reported for swelling of the right leg. The animal was suspected to have decreased hind limb perfusion due to previous history of a venous and arterial access port (VAP) placed in the affected limb. The animal was being treated with carprofen and enrofloxacin. Buprenorphine was extended an additional day. All other animals appeared normal on 7/10.

Sunday July 11: No additional abnormal observations reported. The leg swelling for Animal AL110O remained unchanged from July 10.

Monday July 12: Animals AL110O (three days post-surgery) and SA180D (six days post-surgery) were reported with foot wounds. The epidermis on one of the toes of the right foot of animal AL110O had sloughed and the right limb remained severely swollen. The epidermis on multiple toes and the bottom of the right foot of Animal SA180D appeared to have of sloughed and/or was gone eight days post-surgery. As this observation was on the limb that had been previously catheterized with an arterial and venous port, a perfusion issue was also suspected due to the previous VAP surgery, but no limb swelling was present. A small, but similar sloughed lesion was located on one of the opposite foot's toes. Due to the location of the smaller lesion, thermal injury (first to second degree burns) was considered as a differential diagnosis for the lesions. The study director was contacted by the veterinary surgeon via email and the differentials diagnoses were listed. The animals were treated with carprofen and Clavamox.

Tuesday July 13. Animal VL901A (six days post-surgery) and Animal G180JD (five days post-surgery) were both observed to have similar lesions on the toes of the right and left foot respectively. The animals were treated with carprofen and Clavamox. As a treatment, the lesions on the feet of VL901A and G180JD were covered with bandage material; animal SA180D was dressed in clothing which covered his wounds. The study director was notified of the status of the animals.

Animal AL110O's attitude, appetite and activity level had decreased. The animal appeared uncomfortable, and the leg was unlikely to improve based on the judgement of the clinical veterinarian. The study director and attending veterinarian were contacted to discuss the status of AL110O; the animal was subsequently euthanized for humane reasons related to the leg swelling and not thermal injuries. A gross necropsy was performed; no cause for the leg swelling was determined.

A preliminary root cause analysis was initiated. Attempts were made to ascertain the max heat that could be produced utilizing two Bair Huggers in a similar fashion as used during the NHP surgeries. A Bair Hugger blanket was set to high (109F) and

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INVESTIGATION REPORT FORM

placed on top of the heated operating table (also set to 104F). A second Bair Hugger was set to high and blown directly onto a temperature probe and the probe and blower were covered with drapes. The max temperature observed was 110F.

Since the second Bair Hugger was considered a contributing factor for the lesions on the animals that previously underwent surgery, it was not utilized to blow air on the caudal aspect of the animal during the final surgery on 7/13.

Wednesday July 14. Animals BF873I (six days post-surgery) and AP55D (two days post-surgery) were found to have small ulcerations on their genitals that did not slough and the epidermis remained intact (presumed first degree burn). Animal N378ALE (8 days post-surgery) was found to have lesions on the heel of the right foot. The epidermis of the left foot of Animal G180JD (six days post-surgery) was removed.

Current status. Affected animals were treated with carprofen and Clavamox as warranted for pain management and to prevent infection. The wounds have been cleaned, topical treatments applied, and lesions wrapped as warranted. By 7/23, four of the six remaining affected NHPs had healed and were no longer being treated for thermal injuries. As of August 6rd, Animals G180JD and VL901A continue to have open wounds on their caudal heels which are slowly healing and are anticipated to be completely resolved by the transfer date of September 2, 2021 and will be used on study.

Discussion and Conclusion. Due to the appearance and progression of the lesions on 7 of the 9 animals, the timing in which the lesions presented post-operatively, and the number of lesions observed; thermal injuries (1st to 2nd degree) became the presumptive diagnosis. As the lesions were observed on the caudal aspect of the animals in the location where the Bair Hugger blower was most likely to impact, the source of the thermal injuries was presumed to be the Bair Hugger blower. Two animals did not have lesions; Animal AL793H (surgery on July 7) and Animal YR895FD (surgery on 7/13 without the use of the second Bair Hugger).

As an immediate preventative action, the Bair Hugger was no longer used as a blower on this study as soon as the lesions were identified and thermal injury considered the differential diagnosis; however, it took seven days for wounds to become apparent on the first animal and all but one of animals had already undergone surgery by this time. It takes several days to a week for burned skin cells to slough. The animals were being treated with pain medication for four days post-operatively, so they did not show signs of pain until the end of the post-operative recovery period.

Utilization of a warming unit in this manner was recommended by a Senior Research Surgeon from Data Sciences International (DSI) who is a surgical team subject matter expert (SME). This SME indicated the DSI surgical team uses the technique regularly to increase body temperatures of monkeys and first discovered the technique when visiting another lab which uses a Bair Hugger as a warmer by blowing the warm air on

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INVESTIGATION REPORT FORM

the animal. The Bair Hugger was used as a blower during recent surgeries on 42 NHPs on various projects without incident. It was speculated that the technician placed the blower end (portion where the heated air exited the instrument) closer to the animals than had been when used previously.

The Bair Huggers are assessed by Universal Medical Services biannually and were last inspected in March 2021 and found to be operating as expected. The surgical table and Cardell thermometer are inspected annually and were inspected in September 2020 and found to be operating as expected.

In Summary, this investigation has reached the following conclusions:

- The protocol was followed using trained staff.
- Seven of the nine animals that underwent surgery showed signs of thermal injuries. The animals were examined by a veterinarian and prescribed the appropriate treatments.
- The use Bair Hugger as a heat bower designed to maintain body temperature during surgery was hypothesized to contribute to the thermal injuries; the distance from the extremities, the length of time the blower was used, and the insulating/shielding capacity of the amount of fur (or lack of fur) on the animal's extremities were factors that contributed to the thermal injuries.
- The use of the Bair Hugger was recommended by a surgical subject matter expert and was successfully used on other projects without incident.
- The use of the Bair Hugger was immediately discontinued after it became apparent that it was the cause of the injuries.
- There was no additional perceived pain and distress due to the thermal injuries since the animals were already prescribed analgesics and anti-inflammatory medications during the post-surgery period.
- One of the nine animals was euthanized 4 days after surgery due to a decrease in attitude, appetite and activity level resulting from right limb swelling that was secondary to the VAP placement. The reason for euthanasia was unrelated to the thermal injuries.
- If the Bair Hugger is used in the future as a heat blower designed to maintain body temperature during surgery, an optimal use (proximity, time, and distance) will be determined.
- Six of the remaining eight animals are fully healed at the time of this report. The remaining 2 animals are expected to make a full recovery.
- The Study Director was informed of the unanticipated complications by the veterinary surgeon as they were identified.
- All animals are scheduled to be transferred on September 2, 2021 at which time they will be completely healed and ready to use on study.

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INVESTIGATION REPORT FORM

Check applicable boxes:

☑ Verified instrument/equipment setup and conditions
☑ Verified instrument/equipment calibration
☐ Performed instrument/equipment check
☑ Verified analysis/operation procedures
☑ Verified sample/reagent/standard expiration date, labeling, storage and preparation
☑ Verified calculations
☑ Verified all other operation/ facility requirements
☐ Notified Sponsor (See attached email)
☐ Verified operator training

Completed By signature/date: Rory Barnard 8/6/2021

Reviewed By signature/date: [signature] 8/6/2021

Appendix F Treatment Times

Study B05929
Treatment Times and Treatment Dosing Intervals

				Treatment Key (Date and Time)								
Group	Animal ID	IM Challenge	SC Treatment*	1st Treatment (Date & Time)	2nd Treatment (Date & Time)	3rd Treatment (Date & Time)	4th Treatment (Date & Time)	5th Treatment (Date & Time)	6th Treatment (Date & Time)	7th Treatment (Date & Time)	8th Treatment (Date & Time)	9th Treatment (Date & Time)
1	G180JD	BoNT/A1	saline (0 mg/kg)	9/15/2021 14:21	9/15/2021 18:12	9/15/2021 22:10	9/16/2021 1:57					
	N378ALE			9/16/2021 6:00	9/16/2021 10:01	9/16/2021 14:10	9/16/2021 17:53	9/16/2021 21:50				
2	VL90IA	BoNT/A1	3,4-DAPP (2.06 mg/kg)	9/15/2021 10:23	9/15/2021 14:18	9/15/2021 18:16	9/15/2021 22:07					
	YR895FD			9/15/2021 16:08	9/15/2021 19:58	9/16/2021 0:08						
	AL793H			9/15/2021 11:53	9/15/2021 16:09	9/15/2021 20:01						
3	SA180D	BoNT/A1	3,4-DAPP (4.12 mg/kg)	9/15/2021 10:14	9/15/2021 14:12	9/15/2021 18:09	9/15/2021 22:04	9/16/2021 1:54	9/16/2021 6:04	9/16/2021 9:56		
	BF873I			9/15/2021 16:04	9/15/2021 19:55	9/16/2021 0:04	9/16/2021 3:55	9/16/2021 7:59	9/16/2021 12:01	9/16/2021 15:51	9/16/2021 19:54	9/17/2021 0:03
	AP55D			9/14/2021 21:52	9/15/2021 2:02	9/15/2021 6:03	9/15/2021 10:18	9/15/2021 13:58				

				Treatment Key (Time Interval Between Repeat Treatments)								
Group	Animal ID	IM Challenge	SC Treatment*	1st Treatment	Δ 1st and 2nd Treatment (hrs:min)	Δ 2nd and 3rd Treatment (hrs:min)	Δ 3rd and 4th Treatment (hrs:min)	Δ 4th and 5th Treatment (hrs:min)	Δ 5th and 6th Treatment (hrs:min)	Δ 6th and 7th Treatment (hrs:min)	Δ 7th and 8th Treatment (hrs:min)	Δ 8th and 9th Treatment (hrs:min)
1	G180JD	BoNT/A1	saline (0 mg/kg)		3:51	3:58	3:47					
	N378ALE				4:01	4:09	3:43	3:57				
2	VL90IA	BoNT/A1	3,4-DAPP (2.06 mg/kg)		3:55	3:58	3:51					
	YR895FD				3:50	4:10						
	AL793H				4:16	3:52						
3	SA180D	BoNT/A1	3,4-DAPP (4.12 mg/kg)		3:58	3:57	3:55	3:50	4:10	3:52		
	BF873I				3:51	4:09	3:51	4:04	4:02	3:50	4:03	4:09
	AP55D				4:10	4:01	4:15	3:40				

* Subcutaneous dosing performed at alternating right and left sites on the hip/thigh area; Δ = difference between treatments; hrs:min = hours:minutes; IM = intramuscular; SC = subcutaneous

Prepard by: PHB 25 Feb 2022
QC Review by: JDV 2/25/2022

Appendix G Mortality

Study B05929
Mortality

Group	Animal ID	IM Challenge	SC Treatment	Challenge (Date & Time)	First Observation of Toxicity (Date & Time)	Trigger Criteria Met for Subsequent Treatments (Date & Time)#	Time of Death (Date & Time)	Time-to-First Observation of Toxicity after Challenge (hrs:min)	Time-to-Trigger Criteria after Challenge (hrs:min)#	Time-to-Death after Challenge (hrs:min)	Time-to-Death after First Observation of Toxicity (hrs:min)	Time-to-Death after Trigger Criteria (hrs:min)#
1	G180JD	BoNT/A1 (97.5 $MIPLD_{50}$/kg)	saline (0 mg/kg)	9/13/2021 8:22	9/15/2021 5:57	9/15/2021 11:48	9/16/2021 5:50	45:35	51:26	69:28	23:53	18:02
	N378ALE			9/13/2021 8:05	9/16/2021 3:47	9/16/2021 3:47	9/17/2021 1:57	67:42	67:42	89:52	22:10	22:10
2	VL90IA	BoNT/A1 (97.5 $MIPLD_{50}$/kg)	3,4-DAPP (2.06 mg/kg)	9/13/2021 8:42	9/15/2021 3:57	9/15/2021 7:48	9/16/2021 1:48	43:15	47:06	65:06	21:51	18:00
	YR895FD			9/13/2021 8:29	9/15/2021 5:58	9/15/2021 13:57	9/16/2021 3:50	45:29	53:28	67:21	21:52	13:53
	AL793H			9/13/2021 8:27	9/15/2021 1:56	9/15/2021 9:50	9/15/2021 22:45	41:29	49:23	62:18	20:49	12:55
3	SA180D*	BoNT/A1 (97.5 $MIPLD_{50}$/kg)	3,4-DAPP (4.12 mg/kg)	9/13/2021 8:15	9/15/2021 7:47	9/15/2021 7:47	9/16/2021 14:14	47:32	47:32	77:59	30:27	30:27
	BF873I			9/13/2021 8:17	9/15/2021 11:46	9/15/2021 13:48	9/17/2021 3:52	51:29	53:31	91:35	40:06	38:04
	AP55D			9/13/2021 8:30	9/14/2021 21:51	9/14/2021 21:51	9/15/2021 17:45	37:21	37:21	57:15	19:54	19:54

trigger criteria defined as Clinical Severity Score ≥ 1; *denotes moribund euthanasia; hrs:min = hours:minutes; IM = intramuscular; $MIPLD_{50}$ = mouse interperitoneal LD_{50}; SC = subcutaneous

Prepard by: PHB 25 Feb 2022
QC Review by: JDV 2/25/22

Appendix H Scheduled Clinical Observations

Study B05929
Scheduled Clinicel Observations

Group	Animal ID	IM Challenge	SC Treatment*	Study Day 1 AM	Study Day 1 PM	Study Day 2 Time Slot (± 15 minutes) 0800	1000	1200	1400	1600	1800	2000	2200	2400
1	G180JD	BoNT/A1	saline (0 mg/kg)	N	N	N	N, C1	N	N	N	N	N	N	N
	N378ALE			N	N	N	N	N	N	N	N	N	N	N
2	VL90IA	BoNT/A1	3,4-DAPP (2.06 mg/kg)	N	N	N	N, C1	N	N	N	N	N	N	N
	YR895FD			N	N	N	N, C1	N	N	N	N	N	N	N
	AL793H			N	N	N	N	N	N	N	N	N	N	N
3	SA180D	BoNT/A1	3,4-DAPP (4.12 mg/kg)	N	N	N	N, C1	N, C1	N	N	N	N	N	N
	BF873I			N	N	N	N	N	N	N	N	N	N	N
	AP55D			N	N	N	N	N	N	N	N	OD, ND	LB, OD, ND	LB

Group	Animal ID	IM Challenge	SC Treatment*	Study Day 3 Time Slot (± 15 minutes) 0200	0400	0600	0800	1000	1200	1400	1600	1800	2000	2200	2400
1	G180JD	BoNT/A1	saline (0 mg/kg)	N	N	LB	LB	LB	LB, P	LB, P	LB, P	LB, OD, P	LB, P	LB, P, H	LB, P, H
	N378ALE			N	N	N	N	N	N	N	N	N	N	N	N
2	VL90IA	BoNT/A1	3,4-DAPP (2.06 mg/kg)	N	LB	LB	LB, C, SR	LB, C, SR, V	LB, SR, V	LB, SR, V	LB, SR, H	LB, SR, H, P, OD, C2	LB, SR, H, P, C2	LB, SR, H, P, OD, C2	LB, SR, H, P, OD
	YR895FD			N	N	LB, A	LB, A	LB	LB, A	LB, SR, H, P	LB, SR, H, L, OD, P	LB, SR, A, H, OD, P	LB, SR, A, H, P	LB, G, H, L, P	LB, G, Pr, A, L, OD, P
	AL793H			A	LB, A	LB, A	LB, A	SR, C, A	SR, C, H, OD	SR, C, H	SR, G, H, OD, ND, P	SR, G, H, P	SR, G, H, L, P, OD	FD	
3	SA180D	BoNT/A1	3,4-DAPP (4.12 mg/kg)	N	N	N	H	H	LB, H, OD	LB, H, OD	LB, H, OD	LB, H, P	LB, H, OD, P	LB, H, OD, ND, P	LB, H, OD, P
	BF873I			N	N	N	N	N	LB	LB, H	SR, H, ND, P	SR, H	SR	LB, SR	LB, SR, H, P
	AP55D			LB	LB	LB, OD, ND	LB	SR, OD	SR	LB, SR, C4, NS	LB, H, NS	FD			

Group	Animal ID	IM Challenge	SC Treatment*	Study Day 4 Time Slot (± 15 minutes) 0200	0400	0600	0800	1000	1200	1400	1600	1800	2000	2200	2400
1	G180JD	BoNT/A1	saline (0 mg/kg)	LB, P, H	LB, P, H, OD, G	FD									
	N378ALE			N	LB, SR, H	LB, SR, H, ND	LB, SR, H, ND	SR, H, ND	SR, H, ND, P	SR, H, ND, OD, P	SR, C, H, ND, P	SR, G, H, ND, P	SR, G, H, ND, P	SR, G, H, ND, P	SR, G, H, L, P
2	VL90IA	BoNT/A1	3,4-DAPP (2.06 mg/kg)	FD											
	YR895FD			LB, H, P, L, OD	FD										
	AL793H														
3	SA180D	BoNT/A1	3,4-DAPP (4.12 mg/kg)	LB, H, OD, P	LB, H, OD, P	LB, H, OD, P	LB, SR, H, OD, P	SR, H, OD, P	SR, A, H, P	SR, H, OD, Pr, P, A, C3, E					
	BF873I			LB, SR, H, L, P	LB, SR, H, L, P	LB, P	LB, SR, H, P	LB, SR, H, P	SR, H, Pr, A, P	SR, H, A, P	SR, H, Pr, A, L, P	SR, H, Pr, A, L, P	SR, G, H, Pr, A, L, P	SR, H, A, L, P	SR, G, H, Pr, L, ND, OD, P
	AP55D														

Group	Animal ID	IM Challenge	SC Treatment*	Study Day 5 Time Slot (± 15 minutes) 0200	0400	0600	0800	1000	1200	1400	1600	1800	2000	2200	2400
1	G180JD	BoNT/A1	saline (0 mg/kg)												
	N378ALE			FD											
2	VL90IA	BoNT/A1	3,4-DAPP (2.06 mg/kg)												
	YR895FD														
	AL793H														
3	SA180D	BoNT/A1	3,4-DAPP (4.12 mg/kg)												
	BF873I			SR, G, H, A, L, P	FD										
	AP55D														

* Subcutaneous dosing performed at alternating right and left sites on the hip/thigh area; IM = intramuscular; SC = subcutaneous

Observation Key	
A = ataxia	OD = oral discharge
C = coughing	P = ptosis
E = euthanized	Pr = prostrate
FD = found dead	SR = shallow respirations
G = gasping	V = vomiting
H = hunched	*Additional Comments*
L = lethargic	C1 = no stool observed (cage cleaning removed feces prior)
LB = labored respirations	C2 = right hind limb weakness
ND = nasal discharge	C3 = animal observed as moribund (prostrate and non-reponsive) 5 minutes after initial observation was conducted
NS = no stool	C4 = limb impairment

Prepared by: PHB 25 Feb 2022
QC Review by: JDV 2/25/2022

Appendix I Pre- and Post-Treatment Clinical Observations

Study B05929
Pre- and Post-Treatment Clinical Severity Scores

				1st Treatment					2nd Treatment					3rd Treatment				
Group	Animal ID	IM Challenge	SC Treatment*	Pre-Tx	15 min Post-Tx	2 hr Post-Tx	Δ 15 min	Δ 2 hr	Pre-Tx	15 min Post-Tx	2 hr Post-Tx	Δ 15 min	Δ 2 hr	Pre-Tx	15 min Post-Tx	2 hr Post-Tx	Δ 15 min	Δ 2 hr
1	G180JD	BoNT/A1	saline (0 mg/kg)	1	1	1	0	0	2	1	1	-1	-1	2	1	2	-1	0
	N378ALE			3	4	3	+1	0	3	4	4	+1	1	5	4	4	-1	-1
2	VL90IA	BoNT/A1	3,4-DAPP (2.06 mg/kg)	1	1	1	0	0	1	1	2	0	1	4	2	3	-2	-1
	YR895FD			4	4	4	0	0	3	3	3	0	0	5	4	3	-1	-2
	AL793H			3	2	2	-1	-1	5	3	3	-2	-2	5	6	10	+1	+5
3	SA180D	BoNT/A1	3,4-DAPP (4.12 mg/kg)	1	1	2	0	+1	2	1	2	-1	0	2	2	3	0	+1
	BF873I			4	4	1	0	-3	0	0	0	0	0	2	0	2	-2	0
	AP55D			2	1	0	-1	-2	0	0	0	0	0	2	2	0	0	-2

				4th Treatment					5th Treatment					6th Treatment				
Group	Animal ID	IM Challenge	SC Treatment*	Pre-Tx	15 min Post-Tx	2 hr Post-Tx	Δ 15 min	Δ 2 hr	Pre-Tx	15 min Post-Tx	2 hr Post-Tx	Δ 15 min	Δ 2 hr	Pre-Tx	15 min Post-Tx	2 hr Post-Tx	Δ 15 min	Δ 2 hr
1	G180JD	BoNT/A1	saline (0 mg/kg)	2	4	4	+2	+2										
	N378ALE			4	4	4	0	0	5	5	3	0	-2					
2	VL90IA	BoNT/A1	3,4-DAPP (2.06 mg/kg)	4	4	4	0	0										
	YR895FD																	
	AL793H																	
3	SA180D	BoNT/A1	3,4-DAPP (4.12 mg/kg)	4	2	3	-2	-1	3	3	3	0	0	3	3	4	0	+1
	BF873I			2	2	1	0	-1	3	4	3	+1	0	4	5	3	+1	-1
	AP55D			2	1	1	-1	-1	1	1	1	0	0					

				7th Treatment					8th Treatment					9th Tretment				
Group	Animal ID	IM Challenge	SC Treatment*	Pre-Tx	15 min Post-Tx	2 hr Post-Tx	Δ 15 min	Δ 2 hr	Pre-Tx	15 min Post-Tx	2 hr Post-Tx	Δ 15 min	Δ 2 hr	Pre-Tx	15 min Post-Tx	2 hr Post-Tx	Δ 15 min	Δ 2 hr
1	G180JD	BoNT/A1	saline (0 mg/kg)															
	N378ALE																	
2	VL90IA	BoNT/A1	3,4-DAPP (2.06 mg/kg)															
	YR895FD																	
	AL793H																	
3	SA180D	BoNT/A1	3,4-DAPP (4.12 mg/kg)	4	4	3	0	-1	5 (10) C1									
	BF873I			4	5	4	+1	0	4	5	3	+1	-1	6	3	3	-3	-3
	AP55D																	

* Subcutaneous dosing performed at alternating right and left sites on the hip/thigh area; Δ = difference between Post-Tx and Pre-Tx value; IM = Intramuscular; kg = kilogram; SC = subcutaneous; Tx = treatment
C1 = animal was euthanized in moribund state after observation

Prepared by: PHB 25 Feb 2022
QC Review by: JDV 2/25/2022

Appendix J Scheduled Clinical Severity Scores

Study B05929
Scheduled Clinical Severity Scores

Group	Animal ID	IM Challenge	SC Treatment*	Study Day 1		Study Day 2 Time Slot (± 15 minutes)								
				AM	PM	0800	1000	1200	1400	1600	1800	2000	2200	2400
1	G180JD	BoNT/A1	saline (0 mg/kg)	0	0	0	0	0	0	0	0	0	0	0
	N378ALE			0	0	0	0	0	0	0	0	0	0	0
2	VL90IA	BoNT/A1	3,4-DAPP (2.06 mg/kg)	0	0	0	0	0	0	0	0	0	0	0
	YR895FD			0	0	0	0	0	0	0	0	0	0	0
	AL793H			0	0	0	0	0	0	0	0	0	0	0
3	SA180D	BoNT/A1	3,4-DAP (4.12 mg/kg)	0	0	0	0	0	0	0	0	0	0	0
	BF873I			0	0	0	0	0	0	0	0	0	0	0
	AP55D			0	0	0	0	0	0	0	0	2	2	0

Group	Animal ID	IM Challenge	SC Treatment*	Study Day 3 Time Slot (± 15 minutes)											
				0200	0400	0600	0800	1000	1200	1400	1600	1800	2000	2200	2400
1	G180JD	BoNT/A1	saline (0 mg/kg)	0	0	0	0	0	1	1	1	2	1	2	2
	N378ALE			0	0	0	0	0	0	0	0	0	0	0	0
2	VL90IA	BoNT/A1	3,4-DAPP (2.06 mg/kg)	0	0	0	1	1	1	1	2	4	3	4	4
	YR895FD			0	0	0	0	0	0	2	4	4	3	3	5
	AL793H			0	0	0	0	1	3	2	5	3	5	10	
3	SA180D	BoNT/A1	3,4-DAPP (4.12 mg/kg)	0	0	0	1	1	2	2	2	2	3	4	3
	BF873I			0	0	0	0	0	0	1	4	1	0	0	2
	AP55D			0	0	2	0	2	1	1	1	10			

Group	Animal ID	IM Challenge	SC Treatment*	Study Day 4 Time Slot (± 15 minutes)											
				0200	0400	0600	0800	1000	1200	1400	1600	1800	2000	2200	2400
1	G180JD	BoNT/A1	saline (0 mg/kg)	2	4	10									
	N378ALE			0	2	3	3	3	4	5	4	4	4	5	3
2	VL90IA	BoNT/A1	3,4-DAPP (2.06 mg/kg)	10											
	YR895FD			3	10										
	AL793H														
3	SA180D	BoNT/A1	3,4-DAPP (4.12 mg/kg)	3	3	3	4	4	3	5 (10) C1					
	BFB73I			2	2	1	3	3	4	3	4	4	4	3	6
	AP55D														

Group	Animal ID	IM Challenge	SC Treatment*	Study Day 5 Time Slot (± 15 minutes)											
				0200	0400	0600	0800	1000	1200	1400	1600	1800	2000	2200	2400
1	G180JD	BoNT/A1	saline (0 mg/kg)												
	N378ALE			10											
2	VL90IA	BoNT/A1	3,4-DAPP (2.06 mg/kg)												
	YR895FD														
	AL793H														
3	SA180D	BoNT/A1	3,4-DAPP (4.12 mg/kg)												
	BF873I			3	10										
	AP55D														

* Subcutaneous dosing performed at alternating right and left sites on the hip/thigh area; C1 = animal was euthanized in moribund state after observation; IM = intramuscular; SC = subcutaneous

Prepard by: PHB 25 Feb 2022
QC Review by: JDV 2/25/2022

Appendix K Pre- and Post-Treatment Clinical Severity Scores

Study B05929
Pre- and Post-Treatment Clinical Severity Scores

				1st Treatment					2nd Treatment					3rd Treatment				
Group	Animal ID	IM Challenge	SC Treatment*	Pre-Tx	15 min Post-Tx	2 hr Post-Tx	Δ 15 min	Δ 2 hr	Pre-Tx	15 min Post-Tx	2 hr Post-Tx	Δ 15 min	Δ 2 hr	Pre-Tx	15 min Post-Tx	2 hr Post-Tx	Δ 15 min	Δ 2 hr
1	G180JD	BoNT/A1	saline (0 mg/kg)	1	1	1	0	0	2	1	1	-1	-1	2	1	2	-1	0
	N378ALE			3	4	3	+1	0	3	4	4	+1	1	5	4	4	-1	-1
2	VL90IA	BoNT/A1	3,4-DAPP (2.06 mg/kg)	1	1	1	0	0	1	1	2	0	1	4	2	3	-2	-1
	YR895FD			4	4	4	0	0	3	3	3	0	0	5	4	3	-1	-2
	AL793H			3	2	2	-1	-1	5	3	3	-2	-2	5	6	10	+1	+5
3	SA180D	BoNT/A1	3,4-DAPP (4.12 mg/kg)	1	1	2	0	+1	2	1	2	-1	0	2	2	3	0	+1
	BF873I			4	4	1	0	-3	0	0	0	0	0	2	0	2	-2	0
	AP55D			2	1	0	-1	-2	0	0	0	0	0	2	2	0	0	-2

				4th Treatment					5th Treatment					6th Treatment				
Group	Animal ID	IM Challenge	SC Treatment*	Pre-Tx	15 min Post-Tx	2 hr Post-Tx	Δ 15 min	Δ 2 hr	Pre-Tx	15 min Post-Tx	2 hr Post-Tx	Δ 15 min	Δ 2 hr	Pre-Tx	15 min Post-Tx	2 hr Post-Tx	Δ 15 min	Δ 2 hr
1	G180ID	BoNT/A1	saline (0 mg/kg)	2	4	4	+2	+2										
	N378ALE			4	4	4	0	0	5	5	3	0	-2					
2	VL90IA	BoNT/A1	3,4-DAPP (2.06 mg/kg)	4	4	4	0	0										
	YR895FD																	
	AL793H																	
3	SA180D	BoNT/A1	3,4-DAPP (4.12 mg/kg)	4	2	3	-2	-1	3	3	3	0	0	3	3	4	0	+1
	BF873I			2	2	1	0	-1	3	4	3	+1	0	4	5	3	+1	-1
	AP55D			2	1	1	-1	-1	1	1	1	0	0					

				7th Treatment					8th Treatment					9th Tretment				
Group	Animal ID	IM Challenge	SC Treatment*	Pre-Tx	15 min Post-Tx	2 hr Post-Tx	Δ 15 min	Δ 2 hr	Pre-Tx	15 min Post-Tx	2 hr Post-Tx	Δ 15 min	Δ 2 hr	Pre-Tx	15 min Post-Tx	2 hr Post-Tx	Δ 15 min	Δ 2 hr
1	G180JD	BoNT/A1	saline (0 mg/kg)															
	N378ALE																	
2	VL90IA	BoNT/A1	3,4-DAPP (2.06 mg/kg)															
	YR895FD																	
	AL793H																	
3	SA180D	BoNT/A1	3,4-DAPP (4.12 mg/kg)	4	4	3	0	-1	5 (10) C1									
	BF873I			4	5	4	+1	0	4	5	3	+1	-1	6	3	3	-3	-3
	AP55D																	

* Subcutaneous dosing performed at alternating right and left sites on the hip/thigh area; Δ = difference between Post-Tx and Pre-Tx value; IM = intramuscular; kg = kilogram; SC = subcutaneous; Tx = treatment

C1 = animal was euthanized in moribund state after observation

Prepared by: PHB 25 Feb 2022
QC Review by: JDV 2/25/2022

Appendix L Arterial Blood Gas

Study B05929
Arterial Blood Gas Data

Group	Animal ID	IM Challenge	SC Treatment	Parameter	Baseline	2 hrs after trigger*			6 hrs after trigger*			10 hrs after trigger*		
						Pre-Tx#	15 min Post-Tx_1#	Δ	Pre-Tx#	15 min Post-Tx_2#	Δ	Pre-Tx	15 min Post-Tx_3	Δ
				Blood Gas										
				pH	7.469	7.470	7.487	+0.017	7.431	7.455	+0.024			
				$p CO_2$ (torr)	32.5	35.7	36.6	+0.9	38.3	37.8	-0.5			
				$p O_2$ (torr)	94.2	99.0	95.9	-3.1	84.7	86.5	+1.8			
				Oximetry										
				c tHb (g/dL)	9.3	9.4	9.3	-0.1	9.2	9.1	-0.1			
				$s O_2$ (%)	96.7	97.2	97.1	-0.1	94.6	95.2	+0.6			
				$F O_2$Hb (%)	95.9	96.5	96.3	-0.2	94.2	94.3	+0.1			
1	G180JD	BoNT/A1 (97.5 $MIPLD_{50}$/kg)	Saline (0 mg/kg)	F HHb (%)	3.3	2.8	2.9	+0.1	5.4	4.8	-0.6			
				Electrolyte										
				$c K^+$ (meq/L)	3.7	3.5	3.3	-0.2	3.6	3.5	-0.1			
				$c Na^+$ (meq/L)	150	150	151	+1	151	151	0			
				$c Ca^{2+}$ (meq/L)	2.30	2.33	2.31	-0.02	2.31	2.27	-0.04			
				$c Cl^-$ (meq/L)	110	110	110	0	111	111	0			
				Metabolite										
				c Glu (mg/dL)	93	79	71	-8	77	70	-7			
				c Lac (mmol/L)	6.2	2.4	1.0	-1.4	2.1	1.2	-0.9			

*trigger defined as clinical severity score of ≥ 1; Δ = difference between Post-Tx and Pre-Tx value; IM = intramuscular; kg = kilogram; $MIPLD_{50}$ = mouse intraperitoneal LD_{50}; SC = subcutaneous; Tx = treatment

denotes "not reported" (reference DR-B05929-BBRC-0006); # = reference DR-B05929-BBRC-0007

Prepard by: PHB 25 Feb 2022
QC Review by: JDV 2/25/2022

Study B05929
Arterial Blood Gas Data

Group	Animal ID	IM Challenge	SC Treatment	Parameter	Baseline	2 hrs after trigger*			6 hrs after trigger*			10 hrs after trigger*		
						Pre-Tx	15 min Post-Tx_1	Δ	Pre-Tx#	15 min Post-Tx_2#	Δ	Pre-Tx#	15 min Post-Tx_3#	Δ
				Blood Gas										
				pH	7.496	7.341	7.367	+0.026	7.347	7.394	+0.047	7.272	7.323	0.051
				$p CO_2$ (torr)	32.9	54.2	51.4	-2.8	51.9	44.5	-7.4	66.4	56.4	-10.0
				$p O_2$ (torr)	93.2	82.3	77.5	-4.8	77.2	90.1	+12.9	63.3	84.0	+20.7
				Oximetry										
				c tHb (g/dL)	14.0	15.5	15.5	0	15.2	15.2	0.0	14.9	14.9	0
				$s O_2$ (%)	97.0	92.3	92.6	+0.3	92.0	95.3	+3.3	83.4	93.0	+9.6
2	VL90IA	BoNT/A1 (97.5 $MIPLD_{50}$/kg)	3,4-DAPP (2.06 mg/kg)	$F O_2Hb$ (%)	96.5	91.7	92.1	+0.4	91.6	94.7	+3.1	83	92.5	+9.5
				F HHb (%)	3.0	7.7	7.4	-0.3	8.0	4.7	-3.3	16.5	7.0	-9.5
				Electrolyte										
				$c K^+$ (meq/L)	3.5	3.8	4.0	+0.2	3.6	3.5	-0.1	3.5	3.4	-0.1
				$c Na^+$ (meq/L)	149	151	150	-1.0	152	152	0	154	153	-1
				$c Ca^{2+}$ (meq/L)	2.31	2.38	2.43	+0.1	2.32	2.3	-0.02	2.38	2.31	-0.07
				$c Cl^-$ (meq/L)	109	108	108	0	109	109	0	109	110	+1
				Metabolite										
				c Glu (mg/dL)	79	80	86	+6	77	93	+16	94	98	+4
				c Lac (mmol/L)	2.9	1.2	1.3	+0.1	2.0	2.3	+0.3	1.3	1.3	0

*trigger defined as clinical severity score of ≥ 1; Δ = difference between Post-Tx and Pre-Tx value; IM = intramuscular; kg = kilogram; $MIPLD_{50}$ = mouse intraperitoneal LD_{50}; SC = subcutaneous; Tx = treatment

= reference DR-B05929-BBRC-0007

Prepared by: PHB 25 Feb 2022
QC Review by: JDV 2/25/2022

Study B05929
Arterial Blood Gas Data

Group	Animal ID	IM Challenge	SC Treatment	Parameter	Baseline	2 hrs after trigger*			6 hrs after trigger*			10 hrs after trigger*		
						Pre-Tx	15 min Post-Tx_1	Δ	Pre-Tx#	15 min Post-Tx_2#	Δ	Pre-Tx#	15 min Post-Tx_3#	Δ
3	SA180D	BoNT/A1 (97.5 $MIPLD_{50}$/kg)	3,4-DAPP (4.12 mg/kg)	***Blood Gas***										
				pH	7.407	7.337	7.439	+0.102	7.364	7.404	+0.040	7.366	7.435	+0.069
				p CO_2 (torr)	29.8	43.2	36.7	-6.5	41.4	34.7	-6.7	42.8	37.3	-5.5
				p O_2 (torr)	106	90.0	94.0	+4.0	82.5	94.2	+11.7	76.5	88.4	+11.9
				Oximetry										
				c tHb (g/dL)	13.9	14.4	14.1	-0.3	13.5	13.3	-0.2	13.2	12.9	-0.3
				s O_2 (%)	96.8	94.1	96.1	+2.0	92.8	95.7	+2.9	91.3	95.3	+4.0
				F O_2Hb (%)	96.4	93.4	95.6	+2.2	92.2	95.1	+2.9	90.8	94.9	+4.1
				F HHb (%)	3.2	5.9	3.9	-2.0	7.2	4.3	-2.9	8.7	4.7	-4.0
				Electrolyte										
				c K^+ (meq/L)	3.7	3.8	3.7	-0.1	3.6	3.4	-0.2	3.6	3.6	0
				c Na^+ (meq/L)	150	152	152	0	154	153	-1	154	154	0
				c Ca^{2+} (meq/L)	2.29	2.36	2.33	-0.03	2.31	2.24	-0.07	2.26	2.25	-0.01
				c Cl^- (meq/L)	110	112	110	-2	112	111	-1	113	112	-1
				Metabolite										
				c Glu (mg/dL)	104	81	90	+9	94	101	+7	82	86	+4
				c Lac (mmol/L)	9.4	5.9	4.1	-1.8	5.6	6.7	+1.1	4.0	2.9	-1.1

*trigger defined as clinical severity score of ≥ 1; Δ = difference between Post-Tx and Pre-Tx value; IM = intramuscular; kg = kilogram; $MIPLD_{50}$ = mouse intraperitoneal LD_{50}; SC = subcutaneous; Tx = treatment

= reference DR-B05929-BBRC-0007

Prepard by: PHB 25 Feb 2022
QC Review by: JDV 2/25/2022

Appendix M Telemetry Contributing Scientist Report

Battelle		Status:	Final
Study Number	B05929	Page	1 of 220
PI's Reference No:	360-0002		

Phase Report - Analysis of Telemetry Data

Efficacy Evaluation of 3,4-Diaminopyridine to Acutely Reverse Toxicity in Cynomolgus Monkeys Intoxicated by Botulinum Neurotoxin Serotype A1

3,4-Diaminopyridine

Author

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Testing Facility

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Battelle		Status:	Final
Study Number	B05929	Page	2 of 220
PI's Reference No:	360-0002		

Principal Investigator's Authentication

Report title: Efficacy Evaluation of 3,4-Diaminopyridine to Acutely Reverse Toxicity in Cynomolgus Monkeys Intoxicated by Botulinum Neurotoxin Serotype A1

Test Site: Data Sciences International (DSI)

DSI Scientific Services
119 14th St NW, Suite 100
St. Paul, MN 55112
USA

Study No. : **B05929**

PI's ref. no.: **360-0002**

The phase of the study described in this report "Efficacy Evaluation of 3,4-Diaminopyridine to Acutely Reverse Toxicity in Cynomolgus Monkeys Intoxicated by Botulinum Neurotoxin Serotype A1" was conducted under my supervision and responsibility and is in compliance with standard operating procedures.

The report is a complete and accurate account of the methods employed and the data obtained.

Date: 23-May-2022

DocuSigned by:
Heather Simenson
Signer Name: Heather Simenson
Signing Reason: I approve this document
Signing Time: 23-May-2022 | 12:30:39 PM CDT
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Principal Investigator
Data Sciences International (DSI)

Battelle		Status:	Final
Study Number	B05929	Page	3 of 220
PI's Reference No:	360-0002		

General Information

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End of experimental work study phase: (finalization of report) 23 May 2022

GLP status:

Non-GLP. This phase of the study was conducted in accordance with internal standard operating procedures.

Archive:

Battelle

Battelle		Status:	Final
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1 Introduction

Following systemic intoxication with botulinum neurotoxin serotype A1 (BoNT/A1), the objective of this study is to evaluate the therapeutic capacity of 3,4-diaminopyridine (3,4-DAP) to acutely reverse toxicity in the cynomolgus monkey model.

2 Materials and Methods

2.1 Study Design

Ponemah version 5.50 (Data Sciences International, St. Paul, MN, USA) was used to review the telemetry data. The electrocardiogram (ECG) temperature, and respiration waveforms were reported from the L11R implanted device (DSI, St.Paul, MN, U.S.A.). Data was obtained at least 2 days prior to IM LD_{50} BoNT/A1 challenge (baseline) and continuing through study termination. The 3,4-DAP treatment, or saline, was started upon animal-specific clinical severity scoring of select toxic signs (Ptosis, muscular weakness, respiratory distress, oral/nasal discharge). After initiation of treatment, animals were given subsequent treatment doses every 4.0 ± 0.3 hours. Table 1 displays the challenges and treatment times.

Table 1: Treatments Given

Group	Animal ID	SC Treatment*	Challenge	1st Treatment (days post challenge)	2nd Treatment (days post challenge)	3rd Treatment (days post challenge)	4th Treatment (days post challenge)
1	G180JD	saline (0 mg/kg)	9/13/2021 8:22	9/15/2021 14:21 (2.25 days)	9/15/2021 18:12 (2.41 days)	9/15/2021 22:10 (2.57 days)	9/16/2021 1:57 (2.73 days)
	N378ALE		9/13/2021 8:05	9/16/2021 6:00 (2.91 days)	9/16/2021 10:01 (3.08 days)	9/16/2021 14:10 (3.25 days)	9/16/2021 17:53 (3.41 days)
2	VL90IA	3,4-DAP (2.06 mg/kg)	9/13/2021 8:42	9/15/2021 10:23 (2.07 days)	9/15/2021 14:18 (2.23 days)	9/15/2021 18:16 (2.40 days)	9/15/2021 22:07 (2.56 days)
	YR895FD		9/13/2021 8:29	9/15/2021 16:08 (2.32 days)	9/15/2021 19:58 (2.48 days)	9/16/2021 0:08 (2.65 days)	
	AL793H		9/13/2021 8:27	9/15/2021 11:53 (2.14 days)	9/15/2021 16:09 (2.32 days)	9/15/2021 20:01 (2.48 days)	
3	SA180D	3,4-DAP (4.12 mg/kg)	9/13/2021 8:15	9/15/2021 10:14 (2.08 days)	9/15/2021 14:12 (2.25 days)	9/15/2021 18:09 (2.41 days)	9/15/2021 22:04 (2.58 days)
	BF873I		9/13/2021 8:17	9/15/2021 16:04 (2.32 days)	9/15/2021 19:55 (2.48 days)	9/16/2021 0:04 (2.66 days)	9/16/2021 3:55 (2.82 days)
	AP55D		9/13/2021 8:30	9/14/2021 21:52 (1.56 days)	9/15/2021 2:02 (1.73 days)	9/15/2021 6:03 (1.90 days)	9/15/2021 10:18 (2.08 days)

Group	Animal ID	SC Treatment*	5th Treatment (days post challenge)	6th Treatment (days post challenge)	7th Treatment (days post challenge)	8th Treatment (days post challenge)	9th Treatment (days post challenge)
1	G180JD	saline (0 mg/kg)					
	N378ALE		9/16/2021 21:50 (3.57 days)				
2	VL90IA	3,4-DAP (2.06 mg/kg)					
	YR895FD						
	AL793H						
3	SA180D	3,4-DAP (4.12 mg/kg)	9/16/2021 1:54 (2.74 days)	9/16/2021 6:04 (2.91 days)	9/16/2021 9:56 (3.07 days)		
	BF873I		9/16/2021 7:59 (2.99 days)	9/16/2021 12:01 (3.16 days)	9/16/2021 15:51 (3.32 days)	9/16/2021 19:54 (3.48 days)	9/17/2021 0:03 (3.66 days)
	AP55D		9/15/2021 13:58 (2.23 days)				

2.2 Data Review

Data were analyzed and assessed for quality. Data were omitted if the signals were not of sufficient quality to be analyzed, in the case of signal drop out, and/or non-physiological values. The parameters reported are mean temperature and mean activity. The report also contains the absolute and percent change of each parameter, with respect to the baseline values hourly mean.

ECG data were reviewed for correct placement of each signal's fiducial points (validation marks) in accordance with standard procedures. The ECG data were evaluated using ECG Pattern Recognition (ECG PRO, Ponemah v5.5). A representative collection of ECG waveforms were selected, reviewed, and placed into a template library. All of the complexes used in calculations also included all the necessary validation marks (e.g. P start, Q, R, S end, and T end validation marks). ECG template libraries within Ponemah were quality checked to ensure consistent and appropriate placement of validation marks.

The respiratory (impedance) signal was calibrated using a portion of the baseline data at resting respiratory rates along with estimated tidal volume, determined by their body weight. The body weights of the subjects were multiplied by 14.3 mL/kg to give an estimated tidal volume, per recommendations from the Handbook of Veterinary Anesthesia, Muir, Hubbell et al. 2nd ed 1995: pg 215, for animals less than 50 kg. This estimated total volume was applied to the Ponemah's Qualitative Diagnostic Calibration (QDC) within the Ponemah software to determine the slope and intercept. The slope and intercept were applied to each animal's individual respiratory signal for the duration of the study.

The following parameters were calculated:

Respiration Channel

- Tidal Volume
- Minute Volume
- Respiration Rate

Electrocardiogram (ECG) Channel

- RR Interval
- Heart Rate (Derived from RR)
- PR Interval
- QRS Duration
- QT Interval
- Heart Rate Corrected QT Interval Bazett's (QTcB)
- Individual Heart Rate Corrected QT Interval Bazett's (QTc)
- TCt, Number of T wave present (For QC Purpose)

Temperature Channel

- Mean Temperature

Activity Channel
- Mean Temperature

Abnormality in ECG rhythm or shape was assessed using Data Insights (Ponemah v5.5) Arrhythmias reported through Data Insights default settings were First Degree Atrioventricular (AV) Heart Block, 2nd Degree AV Heart Block, Junctional Escape beats, Premature Atrial Complex and Ventricular Ectopic Complexes (couplet, triplets, bigeminy, trigeminy, and ventricular tachycardia. Table 40 summarizes the arrhythmias found.

Data were averaged and reported in hourly segments. Individual and group mean data (with standard error) reported using Microsoft Excel spreadsheets (Microsoft Office 365).

Following analysis, the ECG template libraries were reviewed by the contributing scientist for ECG to ensure consistent placement of the P, Q, R, S, and T markings. The resultant data, tables and graphs, and areas of concern were provided to the contributing scientist for interpretation. No changes or adjustments were required following the contributing scientist's review.

The figures presented in this report were prepared using Origin Pro (Origin 2019b). Ponemah output files were concatenated and treatment group averages were calculated using a validated MATLAB program. The treatment group averages were imported into Origin Pro for graphical presentation.

2.3 Deviations

There were no work plan, protocol, or SOP deviations that affected the quality or integrity of the data to report.

2.4 Archive

Study-related electronic documentation will be transferred via secure FTP or hard media to Battelle for archiving.

After finalization of the PI report, the following study-related documentation will be transferred to Battelle for archiving:

- PI Study Plan
- PI Study Plan amendments
- All generated data
- Final PI report

3 Results

Data points prior to death of each animal were removed for reporting of the disease progression/treatment data, to look at underlying trends. The acute data has all available data leading up to death.

The Figure section contains plots of the group means, while the Results section reports individual subject data. Tables containing both individual and group means are displayed in the Table section.

Two separate analyses were performed, a complete history from baseline to death after the challenge with BoNT/A1 and acute changes in response to treatments. The complete history of the data from start to finish relative to before and after challenge with BoNT/A1 provides a complete timeline of the study, it does not account for the different times that animals displayed toxic sign and different times that animals received treatments. The focused analysis of acute changes in response to treatments provides a better view of the effect(s) in response to treatments, it does not account for the different times the treatments occurred relative to challenge.

Complete History Analysis of BoNT/A1 Challenge (Challenge Complete History)

A 48-hour baseline collection period (pre-challenge), 10 September 2021 16:00 until 12 September 2021 16:00, was collapsed into hourly averages. Each hourly timepoint was averaged together to give an overall baseline value for each hour of the day.

Data outside of 10% change from baseline for ECG intervals, 20% change from baseline for respiratory parameters, 0.5°C for temperature, and 50% change from baseline for activity for 3 or more consecutive time points are reported.

Focused Acute Changes in Response to Treatments (Acute Treatment Response)

The baseline (pre-treatment) used for the acute treatment comparison was the 4-hour average prior to the first treatment dose. A quick overview of the group summary changes in the physiological signals, when compared to the baseline value is found in Table 2 and Table 3.

For the acute treatment group changes mentioned in this section, a 10% change from baseline for ECG intervals, 20% change from baseline for respiratory parameters, 0.5°C for temperature, and 50% change from baseline for activity for 2 or more consecutive time points are reported.

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Table 2: Mean ECG Parameters Acute Changes (compared to pre-treatment baseline)

	Heart Rate (bpm)		PR Interval (ms)		QRS Duration (ms)		QT Interval (ms)	
Day	**PRE: 4-hour Ave**	**Post Dose**	**PRE: 4-hour Ave**	**Post Dose**	**PRE: 4-hour Ave**	**Post Dose**	**PRE: 4-hour Ave**	**Post Dose**
Group 1	159.78±4.10	↑ 0.25-12.5 hrs ↓15.5 hrs until death	77.96±0.94	↓ various post throughout the first 12 hours	37.41±0.33	↑16 hrs until death	224.28±3.04	↓ various post throughout the first 12 hours ↑15.5 hrs until death
Group 2	179.23±1.47	↓various time points from 7.5 hrs until death	72.42±0.52	↑ 8.25-9.25 ↑10.75-11 hrs	34.02±0.24	↓10.25-10.5 hrs	195.63±0.86	↑various time points from 8.25 hrs until death
Group 3	168.20±3.50	↑ 0.25-0.5 hrs ↑3.75-4.25 hrs ↓5.25-5.5 hrs ↑7.75-8.25 hrs ↑11.75-12.0 hrs ↓13.25-13.5 hrs, ↓19-19.25 hrs, ↓28-28.25 hrs, ↓31.5-32.25 hrs ↓34 hrs until death	74.54±0.78	↑28-28.25 hrs ↑31.75 until death	37.03±0.18	No change	209.17±3.04	↑1.25-1.5 hrs ↑5-5.5 hrs, ↑13.25-13.5 hrs ↑20.25-20.5 hrs ↑24-24.5 hrs ↑various time points from 30.25 hrs until death

	QTc Interval (ms)	
Day	**PRE: 4-hour Ave**	**Post Dose**
Group 1	362.13±0.90	No change
Group 2	337.75±1.01	↑12.25-12.5 hrs
Group 3	347.55±1.68	↓28-28.25 hrs ↑28.5 hrs until death

Mean±SEM. Data were aligned based on the event of the first treatment dose. All comparison was made from the average of the 4 hours preceding the first treatment dose.

Table 3: Mean Respiratory, Temperature, &Activity Parameters Acute Changes (compared to pre-treatment baseline)

	Respiratory Rate (bpm)		Minute Volume		Tidal Volume		Temperature	
Day	PRE: 4-hour Ave	Post Dose	PRE: 4-hour Ave	Post Dose	PRE: 4-hour Ave	Post Dose	PRE: 4-hour Ave	Post Dose
Group 1	34.49±0.48	↓Various points starting at 8.75 hrs until death	2730±224.78	↑0.25-0.75 hrs ↑3.75-4 hrs ↓Various points starting at 8.5 hrs until death	78.66±5.75	↑0.25-0.75 hrs ↑4-4.5 hrs ↓Various points starting at 5.5 hrs until death, exception ↑15.75-16 hrs	36.53±0.04	↓Various points starting at 7 hrs until death
Group 2	23.78±0.51	↑0.75-2 hrs ↓Various points starting at 11.25 hrs until death	1293.33±44.36	↑0.5-0.75 hrs, ↓Various points starting at 6.75 hrs until death, exception ↑10-10.25 hrs	54.73±1.30	↓Various points starting at 8.75 hrs until death	35.83±0.10	↓0.25-0.75 hrs ↑2.5-3 hrs ↓Various points starting at 7 hrs until death
Group 3	29.81±0.58	↓Various points starting at 22.25 hrs until death	2259.80±95.25	↑ 0.25 - 0.5hrs ↓6.75-7.25 hrs ↓Various points starting at 9.25 hrs until death	75.30±1.77	↓6.00-7.25 hrs ↓Various points starting at 9.25 hrs until death	36.76±0.05	↓12.25 hrs until death

	Activity	
Day	PRE: 4-hour Ave	Post Dose
Group 1	36.29±0.04	↑0.25-0.5 hrs ↑3.75-4.25 hrs ↓19.75-20 hrs
Group 2	10.27±0.10	↑3.75-4.25 hrs ↓9.25-9.75 hrs ↓10.25-10.5 hrs ↓11-13.5 hrs ↓14.25-16 hrs
Group 3	20.46±0.05	↑0.25-0.5 hrs ↑4.25-4.5 hrs ↓10.5-10.75 hrs ↑11.75-12 hrs ↓12.75-13.75 hrs ↓19.25-19.75 hrs ↓20.25-20.5 hrs ↑23-23.25 hrs

Mean±SEM. Data were aligned based on the event of the first treatment dose. All comparison was made from the average of the 4 hours preceding the first treatment dose.

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3.1 Group 1 Treatment with Saline

Table 4: Group 1 Challenge Timeline

Animal ID	Challenge (Date & Time)	First Observation of Toxicity (Date & Time)	Trigger Criteria Met for Subsequent Treatments (Date & Time)#	Time of Death (Date & Time)	Time-to-First Observation of Toxicity after Challenge (hrs:min)	Time-to-Trigger Criteria after Challenge (hrs:min)#	Time-to-Death after Challenge (hrs:min)	Time-to-Death after First Observation of Toxicity (hrs:min)	Time-to-Death after Trigger Criteria (hrs:min)#
G180JD	9/13/2021 8:22	9/15/2021 5:57	9/15/2021 11:48	9/16/2021 5:50	45:35	51:26	69:28	23:53	18:02
N378ALE	9/13/2021 8:05	9/16/2021 3:47	9/16/2021 3:47	9/17/2021 1:57	67:42	67:42	89:52	22:10	22:10

trigger criteria defined as Clinical Severity Score ≥ 1; *denotes moribund euthanasia; hrs:min = hours:minutes; IM = intramuscular; $MIPLD_{50}$ = mouse intraperitoneal LD_{50}; SC = subcutaneous

3.1.1 ECG Parameters

3.1.1.1 Challenge Complete History

Figure 1 - Figure 12 are the graphical representation of the ECG parameters for the Challenge Complete History data.

G180JD and N378ALE, when compared to pre-challenge baseline, had a decrease in heart rate the night prior to the challenge and following the challenge, had an increase in heart rate.

G180JD, had an increase in heart rate on 9/15/2021 0100 hrs until 0300 hrs (1.7-1.8 days post challenge), then again prior to death 9/15/2021 1700 hrs until 9/16/2021 0400 hrs (2.4-2.8 days post challenge).

N378ALE, had an increase in heart rate on 9/14/2021 0900 hrs until 1200 hrs (1.0-1.2 days post challenge), on 9/14/2021 2200 hrs until 9/15/2021 0000 hrs (1.6-1.7 days post challenge). A decrease in heart rate and PR interval was noted on 9/15/2021 0500 hrs until 0700 hrs (1.9 days post challenge); PR interval decrease lasted an additional hour until 0800 hrs. A decrease in heart rate occurred just prior to death on 9/15/2021 1000 hrs until 9/16/2021 2000 hrs (2.1-3.5 days post challenge), while PR and QT interval were decreased started on 9/15/2021 at 1300 hrs until 9/16/2021 2000 hrs (2.2-3.5 days post challenge).

3.1.1.2 Acute Treatment Response Post First Treatment

Figure 13 - Figure 18 are the graphical representation of the ECG parameters for the Acute Treatment Response.

There was an overall increase in mean heart rate, QRS duration, and QT interval for the saline treatment group when compared to the 4-hour average prior to the first treatment dose. There was an increase in mean heart rate from the time of post treatment until 12.5 hours post

treatment, with few spurious points below 10% increase. There was an increase in QRS duration from 16 hours post treatment until the end of data/death. There was an increase in QT interval from 15.5 hours post treatment until the end of data/death.

There was an overall decrease in mean heart rate, PR interval, and QT interval for this treatment group, when compared to the 4-hour average prior to treatment dose. There was a decrease in mean heart rate from 15.5 hours post treatment until the end of data/death. There was a decrease in PR interval during the following post treatment timepoints, 0.25 to 0.50 hours, 1.75 to 2.25 hours, 4.00 to 4.25 hours, 7.75 to 8.50 hours, 9.5 to 10.0 hours, and 11.75 to 12.0 hours. There was a decrease in QT interval during the following post treatment timepoints, 0.25 to 0.75 hours, 1.75 to 2.25 hours, and 4.00 to 4.25 hours.

3.1.2 Respiratory Parameters

3.1.2.1 Challenge Complete History

Figure 19 - Figure 24 are the graphical representation of the respiratory parameters for the Challenge Complete History data.

G180JD, when compared to pre-challenge baseline, had a decrease in tidal volume on 9/15/2021 from 1000 hrs until 1800 hrs (~2.1-2.4 days post challenge) with a decrease in minute volume on 9/15/2021 from 1600 hrs until 1800 hrs. A decrease in tidal volume and minute volume is also detected at 2100 until 9/16/2021 0400 hrs, prior to death.

N378ALE, when compared to pre-challenge baseline, had an increase in tidal volume and minute volume on 9/13/2021 at 1600 hrs until 1900 hrs after receiving the challenge on 9/13/2021 at 8:05 hrs. A decrease in tidal volume and minute volume is noted on 9/13/2021 from 2300 hrs until 9/14/2021 0100 hrs (~0.6-0.7 days post challenge); the decrease in minute volume lasted an additional hour until 9/14/2021 0200 hrs. An increase in respiration rate is noted on 9/15/2021 at 1100 hrs until 1500 hrs (2.1-2.3 days post challenge). An increase in minute volume was noted on 9/15/2021 1800 hrs until 2000 hrs (2.4 – 2.5 days post challenge). An increase in respiration rate was noted on 9/15/2021 from 2300 hrs until 9/16/2021 0100 hrs. A decrease in tidal volume and minute volume occurred on 9/16/2021 at 0700 for tidal volume and 0800 for minute volume (approximately 2.9 days post challenge) and continued until death, with spurious points under 20% change from baseline.

3.1.2.2 Acute Treatment Response Post First Treatment

Figure 25- Figure 27 are the graphical representation of the respiratory parameters for the Acute Treatment Response.

There was an increase in mean minute volume and tidal volume when compared to the 4-hour average prior to the first treatment dose of saline, from the time of post treatment until 0.75 hours post first treatment dose. An increase in minute volume when compared to the 4-hour average

prior to treatment from 3.75 hours until 4 hours post first treatment, while tidal volume was increased from 4 until 4.5 hours post first treatment. A decrease in respiration rate was observed from 8.75 until 9 hours and again from 15 until 15.75 hours post first treatment dose. A decrease in minute volume, when compared to the 4-hour average prior to the first treatment dose from 8.5 until 9.25 hours, from 10.25 until 11.5 hours, from 12 until 19.25 hours post first treatment dose. Tidal volume was decreased from 12.5 until 14 hours, 14.5 until 14.75 hours, from 16.25 until 19.25 hours post first treatment dose. There was a period where an increase in tidal volume is observed from 15.75 until 16 hours post first treatment dose.

3.1.3 Temperature and Activity

3.1.3.1 Challenge Complete History

Figure 28- Figure 31 are the graphical representation of the Temperature and Activity parameters for the Challenge Complete History data.

G180JD, when compared to baseline, had an increase in temperature prior to challenge on 9/12/2021 1600 hrs until 1900 hrs, followed by a decrease in temperature on 9/13/2021 from 0100 hrs until 0300 hrs. An increase in temperature on 9/13/2021 from 1100 hrs until 1400 hrs was noted just after receiving challenge on 9/13/2021 at 0822 hrs. A decrease in temperature was detected just prior to death. An increase in activity, when compared to baseline is noted on 9/15/2021 0100 hrs until 9/15/2021 0300 hrs. Additionally activity was increased from 9/15/2021 1900 hrs until death on 9/16/2021 0400 hrs (although the last data point prior to death was just under 50% increase).

N378ALE, when compared to baseline, had an increase in temperature on 9/13/2021 at 0800 hrs until 1000 hrs after receiving the challenge on 9/13/2021 at 8:05 hrs. An increase in temperature, when compared to baseline is noted on 9/14/2021 2300 hrs until 9/15/2021 0100 hrs (~1.6-1.7 days post challenge), 9/15/2021 1300 hrs until 1600 hrs (~2.2-2.3 days post challenge), and then again on 9/15/2021 1900 hrs until 9/16/2021 0100 hrs (~2.4-2.7 days post challenge). A decrease in temperature was detected prior to death. An increase in activity is noted following the challenge on 9/13/2021 1600 hrs until 9/13/2021 1900 hrs. Additionally, an increase in activity is noted on 9/14/2021 1600 hrs until 9/14/2021 1800 hrs, on 9/15/2021 0100 hrs until 9/15/2021 0500 hrs, and then again on 9/15/2021 1900 hrs until 9/16/2021 0000 hrs.

3.1.3.2 Acute Treatment Response Post First Treatment

Figure 32 - Figure 33 are the graphical representation of the Temperature and Activity parameters for the Challenge Complete History data.

There was a decrease in mean temperature when compared to the 4-hour average prior to treatment dose, from 7 hours until 7.5 hours, 8 hours until 9.75 hours, 10.5 until 11 hours, 12.25 hours until 20.5 hours (end of data/death) post first treatment dose. An increase in activity is seen around the first and second treatments (from 0.25 hours until 0.5 hours and from 3.75 hours

until 4.25 hours post first treatment). A decrease in activity is noted from 19.75 hours until 20 hours post first treatment.

3.2 Group 2 Treatment with 3,4-DAP (2.06 mg/kg)

Table 5 Group 2 Challenge Timeline

Animal ID	Challenge (Date & Time)	First Observation of Toxicity (Date & Time)	Trigger Criteria Met for Subsequent Treatments (Date & Time)#	Time of Death (Date & Time)	Time-to-First Observation of Toxicity after Challenge (hrs:min)	Time-to-Trigger Criteria after Challenge (hrs:min)#	Time-to-Death after Challenge (hrs:min)	Time-to-Death after First Observation of Toxicity (hrs:min)	Time-to-Death after Trigger Criteria (hrs:min)#
VL90IA	9/13/2021 8:42	9/15/2021 3:57	9/15/2021 7:48	9/16/2021 1:48	43:15	47:06	65:06	21:51	18:00
YR895FD	9/13/2021 8:29	9/15/2021 5:58	9/15/2021 13:57	9/16/2021 3:50	45:29	53:28	67:21	21:52	13:53
AL793H	9/13/2021 8:27	9/15/2021 1:56	9/15/2021 9:50	9/15/2021 22:45	41:29	49:23	62:18	20:49	12:55

trigger criteria defined as Clinical Severity Score ≥ 1; *denotes moribund euthanasia; hrs:min = hours:minutes; IM = intramuscular; MIPLD$_{50}$ = mouse intraperitoneal LD$_{50}$; SC = subcutaneous

3.2.1 ECG Parameters

3.2.1.1 Challenge Complete History

Figure 1 - Figure 12 are the graphical representation of the ECG parameters for the Challenge Complete History data.

VL90IA, YR895FD and AL793H, when compared to baseline, had a decrease in heart rate the night prior to the challenge, with YR895FD having only 1 point greater than 10%. Following the challenge, with the exception of VL90IA, there was an increase in heart rate. YR895FD's increase in heart rate also had a decrease in QT interval from 9/13/2021 0900 hrs until 1200 hrs.

VL90IA, had a decrease in heart rate on 9/13/2021 2100 hrs until 9/14/2021 0300 hrs (0.5 -0.8 days post challenge), then again on 9/14/2021 from 1600 hrs until 1800 hrs (1.3-1.4 days post challenge). An increase in heart rate and decrease in QT interval was observed on 9/14/2021 from 2300 hrs until time of death on 9/15/2021 2100 hrs (1.6 – 2.5 days post challenge). The PR interval was also decreased from 9/15/2021 0700 hrs until 1100 hrs (1.9-2.1 days post challenge).

YR895FD had an increase in heart rate on 9/14/2021 from 2200 hrs until time of death on 9/15/2021 1900 hrs (1.6 – 2.5 days post challenge). The PR interval was also decreased from 9/15/2021 0300 hrs until 0500 hrs (1.8-1.9 days post challenge) and again from 1000 hrs until 1300 hrs on 9/15/2021 (2.1-2.2 days post challenge). The QT Interval was decreased during this same period on 9/15/2021 from 0300 hrs until 1200 hrs (1.8-2.1 days post challenge).

Prior to death on 9/14/2021, AL793H, had an increase in heart rate starting at 2100 hrs until 9/15/2021 1000 hrs (1.5-2.1 days post challenge). During this period the PR interval was decreased on 9/14/2021 2000 hrs until 2300 hrs (1.5-1.6 days post challenge) and again from 9/15/2021 0200 hrs until 1000 hrs (1.7-2.1 days post challenge). The QT interval was also decreased during this period starting at 9/15/2021 0100 hrs until 1000 hrs (1.7-2.1 days post challenge).

3.2.1.2 Acute Treatment Response Post First Treatment

Figure 13 - Figure 18 are the graphical representation of the ECG parameters for the Acute Treatment Response.

When compared to the 4-hour average prior to treatment dose, there were no changes observed immediately (within the first 2 hours post dose) following the first treatment in ECG parameters.

There was an overall increase in PR interval, QT interval, and QTc interval for this treatment group, when compared to the 4-hour average prior to treatment dose. There was an increase in PR interval during the following post treatment timepoints, 8.25 to 9.25 hours and 10.75 to 11.00 hours. There was an increase in QT interval from 8.25 to 9.25 hours post treatment. There was an increase in QTc interval from 12.25 to 12.50 hours post treatment.

There was an overall decrease in mean heart rate and QT interval for this treatment group, when compared to the 4-hour average prior to treatment dose. There was a decrease in mean heart rate during the following post treatment timepoints, 7.50 to 9.25 hours, 9.75 to 12.0 hours, and 14.25 hours until the end of data/death. There was a decrease in QT interval during the following post treatment timepoints, 10.25 to 11.00 hours, 12.25 to 12.50 hours, and 14.25 hours until the end of data/death.

3.2.2 Respiratory Parameters

3.2.2.1 Challenge Complete History

Figure 19 - Figure 24 are the graphical representation of the respiratory parameters for the Challenge Complete History data.

VL90IA, when compared to baseline, had a decrease in tidal volume and minute volume just prior to death on 9/15/2021 from 0800 hrs until 2100 hrs (~2.0-2.5 days post challenge).

YR895FD had an increase in respiration on 9/14/2021 from 2200 hrs until 9/15/2021 0900 hrs (1.6-2.0 days post challenge). Tidal volume and minute volume as decreased from 9/15/2021 0700 until time of death on 9/15/2021 at 1900 hrs.

Starting 3 hours period to death on 9/14/2021, AL793H, had a decrease in tidal volume and minute volume starting at 0800 hrs until 1000 hrs. Respiration rate was also decreased during this time but only 2 of 3 the three time points were greater than 20%.

3.2.2.2 Acute Treatment Response Post First Treatment

Figure 25- Figure 27 are the graphical representation of the respiratory parameters for the Acute Treatment Response.

There was an increase in mean respiratory rate, when compared to the 4-hour average prior to treatment dose, from 0.75 until 2 hours post first treatment dose. Additionally, mean minute volume was increased from 0.5 until 0.75 hours post first treatment dose.

A decrease in minute volume when compared to the 4-hour average prior to treatment Minute volume was decreased from 6.75 hours until 8.25 hours, from 8.75 hours until 9.75 hours, and from 10.5 hours until 14.75 hours (end of data/death) post first treatment dose. Tidal volume was decreased from 8.75 hours until 9.75 hours, 10.5 hours until 11.5 hours, 12.25 hours until 14 hours post first treatment dose. There was a decrease in respiratory rate, when compared to 4-hour average prior to treatment, at the following post treatment timepoints, 11.25 to 12 hours and 14.25 hours until the end of data/death.

3.2.3 Temperature

3.2.3.1 Challenge Complete History

Figure 28- Figure 31 are the graphical representation of the Temperature and Activity parameters for the Challenge Complete History data.

VL90IA, when compared to baseline, had a decrease in temperature on 9/14/2021 from 1800 hrs until 2000 hrs (1.4-1.5 days post challenge) then another decrease prior to death starting on 9/15/2021 at 1100 hrs (2.1 days post challenge) until 1900, 2 hours prior to death. Prior to death, a decrease in activity occurred from 9/15/2021 0800 hrs until 9/15/2021 1800 hrs (1300 hrs and 1600 hrs were at 45.2% and 44.2%, respectively), followed by an increase in activity on 9/15/2021 1900 hrs until 9/15/2021 2100 hrs (death).

YR895FD, when compared to baseline, had a decrease prior to death starting on 9/15/2021 at 1100 hrs (2.1 days post challenge) and continuing until one hour prior to death. A decrease in activity is noted prior to death on 9/15/2021 0700 hrs until 9/15/2021 1000 hrs and then again from 9/15/2021 1300 hrs until 9/15/2021 1800 hrs (death), with the exception of an increase of 52.7% on 9/15/2021 1900 hrs.

AL793H, when compared to baseline, had an increase in temperature on 9/14/2021 2300 hrs until 9/15/2021 0500 hrs, with one time point at 0200 hrs, where the increase was not greater than 0.5°C. The decrease in temperature prior to death started on 9/15/2021 at 0800 hrs (2.0 days post challenge) and continuing until death. An increase in activity is noted from 9/15/2021 0100 hrs until 9/15/2021 0600 hrs.

3.2.3.2 Acute Treatment Response Post First Treatment

Figure 32 - Figure 33 are the graphical representation of the Temperature and Activity parameters for the Challenge Complete History data.

There was a decrease in mean temperature when compared to the 4-hour average prior to treatment dose, from 0.25 hours until 0.75 hours post first treatment dose. This was followed by an increase in temperature at 2.5 hours until 3 hours post first treatment dose. Temperature was decreased from 7 hours until 16 hours (end of data/death) post first treatment dose, with the exception at 13.25 hours post first treatment where the temperature was less than 0.5°C change from pre-treatment average. An increase in activity is noted at approximately the same time the 2nd treatment was given, from 3.75 until 4.25 hours post first treatment. A decrease in activity is noted from 9.25 hours until 9.75 hours, 10.25 hours until 10.5 hours, 11 hours until 13.5 hours, and then from 14.25 hours until 16 hours (end of data) post first treatment.

3.3 Group 3 Treatment with 3,4-DAP (4.12 mg/kg)

Table 6 Group 3 Challenge Timeline

Animal ID	Challenge (Date & Time)	First Observation of Toxicity (Date & Time)	Trigger Criteria Met for Subsequent Treatments (Date & Time)#	Time of Death (Date & Time)	Time-to-First Observation of Toxicity after Challenge (hrs:min)	Time-to-Trigger Criteria after Challenge (hrs:min)#	Time-to-Death after Challenge (hrs:min)	Time-to-Death after First Observation of Toxicity (hrs:min)	Time-to-Death after Trigger Criteria (hrs:min)#
SA180D*	9/13/2021 8:15	9/15/2021 7:47	9/15/2021 7:47	9/16/2021 14:14	47:32	47:32	77:59	30:27	30:27
BF873I	9/13/2021 8:17	9/15/2021 11:46	9/15/2021 13:48	9/17/2021 3:52	51:29	53:31	91:35	40:06	38:04
AP55D	9/13/2021 8:30	9/14/2021 21:51	9/14/2021 21:51	9/15/2021 17:45	37:21	37:21	57:15	19:54	19:54

trigger criteria defined as Clinical Severity Score ≥ 1; *denotes moribund euthanasia; hrs:min = hours:minutes; IM = intramuscular; $MIPLD_{50}$ = mouse intraperitoneal LD_{50}; SC = subcutaneous

3.3.1 ECG Parameters

3.3.1.1 Challenge Complete History

Figure 1 - Figure 12 are the graphical representation of the ECG parameters for the Challenge Complete History data.

SA180D, BF873I, and AP55D, when compared to baseline, had a decrease in heart rate the night prior to the challenge and following the challenge, had an increase in heart rate with decrease in QT Interval.

SA180D had an increase in heart rate from 9/15/2021 0100 hrs until time of death on 9/16/2021 0900 hrs (1.7-3.0 days post challenge). PR and QT Interval were decreased from 9/15/2021 0500 hrs until 1200 hrs (1.9-2.2 days post challenge) and again from 9/15/2021 1800 hrs for QT interval and 1900 hrs for PR Interval until death, with spurious point less than 10% change from baseline.

BF873I had an increase in heart rate from 9/15/2021 1000 hrs until 9/16/2021 until 0200 hrs (2.1-2.7 days post challenge) and then again, just prior to death from 9/16/2021 0800 hrs until 1000 hrs (3.0-3.1 days post challenge). PR interval was decreased from 9/15/2021 1000 hrs until 1200 hrs (2.1-2.2 days post challenge). QT interval was decreased from 9/15/2021 2300 hrs until 9/16/2021 0100 hrs (2.6-2.7 days post challenge).

AP55D had an increase in heart rate and decrease in PR interval from 9/14/2021 1900 hrs until time of death on 9/15/2021 1400 hrs (1.4-2.2 days post challenge), with 2 time points on 9/15/2021 at 0000 hrs and 0100 hrs where the PR interval was less than 10% change from baseline. Also during this time the QT interval was decreased from 9/14/2021 2000 hrs until 9/15/2021 0600 hrs (1.5-1.9 days post challenge).

3.3.1.2 Acute Treatment Response Post First Treatment

Figure 13 - Figure 18 are the graphical representation of the ECG parameters for the Acute Treatment Response.

There was an increase in mean heart rate, when compared to the 4-hour average prior to treatment dose, from the time of post treatment until 0.5 hours post treatment, from 3.75 hours until 4.25 hours post first treatment. A decrease in heart rate, when compared to the 4-hour average prior to treatment dose, from 5.25 until 5.5 hours post first treatment, followed by an increase from 7.75 until 8.25 hours and 11.75 until 12 hours post first treatment. A decrease in heart rate was observed from 13.25 hours until 13.5 hour, from 19 until 19.25 hours, from 28 until 28.25 hours, from 31.5 until 32.25 hours, then finally from 34 until 36 (end of the data/death) hours post first treatment dose. An increase in QT interval is observed from 1.25 until 1.5 hours, 5 until 5.5 hours, 13.25 until 13.5 hours, 20.25 until 20.5 hours, 24 until 24.5 hours, and lastly prior to end of data/death from 30.25 until 32.5 hours post first treatment dose (with one spurious point at 33 hours post first treatment dose not above 10% change). PR interval was increased, when compared to the 4-hour average prior to treatment dose, from 28 to 28.25 hours post treatment prior to death/end of data, and from 31.75 until 32 hours and 33.25 until 35 hours post first treatment dose. There was an increase and a decrease in QTc interval, when compared to the 4-hour average prior to treatment dose. There was a decrease in QTc interval from 28.00 to 28.25 hours post treatment. There was an increase in QTc interval from 28.5 hours post treatment until the end of data/death.

3.3.2 Respiratory Parameters

3.3.2.1 Challenge Complete History

Figure 19 - Figure 24 are the graphical representation of the respiratory parameters for the Challenge Complete History data.

Prior to the challenge, SA180D, had an increase in minute volume on 9/12/2021 from 1900 hrs until 2100 hrs (0.6-0.5 days *prior* to challenge). An increase in tidal volume and minute volume occurred on 9/13/2021 at 1400 hrs until 1900 hrs (0.2-0.4 days post challenge), with one time point at 1500 hrs, where tidal volume was not greater than 20% change. A decrease in tidal volume and minute volume occurred from 9/14/2021 1700 hrs until 1900 hrs (1.4 days post challenge). Tidal volume was decreased on 9/15/2021 0400 hrs until 1800 hrs (1.8-2.4 days post challenge) then prior to death on 9/16/2021 0600 hrs until 0900 hrs (2.9-3.0 days post challenge). Minute volume was decreased on 9/15/2021 at 0800 hrs until 1000 hrs (2.0-2.1 days post challenge), then again prior to death on 9/16/2021 at 0400 hrs – 0900 hrs (2.8-3.0 days post challenge). Respiratory rate was increased from 9/15/2021 0000 hrs until 0700 hrs (1.7-1.9 days post challenge), from 9/15/2021 1000 hrs until 1200 hrs (2.1-2.2 days post challenge), and from 9/15/2021 1700 hrs until 2000 hrs (2.4-2.5 days post challenge). A decrease in respiration rate occurred starting 6 hours prior to death from 9/16/2021 0400 hrs until 0600 hrs (2.8-2.9 days post challenge).

BF873I, when compared to baseline, had a increase in minute volume on 9/14/2021 2000 hrs until 9/15/2021 0000 hrs (1.5-1.7 days post challenge), followed by a decrease in minute volume from 9/15/2021 0700 hrs until 0900 hrs (1.9-2.0 days post challenge) and again from 1100 hrs until 1800 hrs (2.1-2.4 days post challenge) Tidal volume was decreased from 9/15/2021 0700 hrs until 2300 hrs, with one time point at 2000 hrs where the change was less than 20%. Just prior to death tidal volume was again decreased from 9/16/2021 0300 hrs until 9/16/2021 1100 hrs (2.8-3.1 days post challenge). Respiration rate was elevated from 9/15/2021 1900 hrs until 2300 hrs (2.4-2.7 days post challenge).

Prior to the challenge, AP55D, had a decrease in minute volume on 9/13/2021 from 0100 hrs until 0500 hrs (0.3-0.1 days prior to challenge). Both tidal volume and minute volume were decreased from 9/14/2021 0000 hrs until 0200 hrs (0.6-0.7 days post challenge). Minute volume was increased on 9/14/2021 2300 hrs until 9/15/2021 0100 hrs (1.6-1.7 days post challenge). Respiration was increased from 9/15/2021 0300 hrs until 0500 hrs (1.8-1.9 days post challenge).

Prior to death, both minute volume and tidal volume were decreased from 9/15/2021 0700 hrs until prior to death, 1400 hrs (1.9-2.2 days post challenge).

3.3.2.2 Acute Treatment Response Post First Treatment

Figure 25- Figure 27 are the graphical representation of the respiratory parameters for the Acute Treatment Response.

There was an overall increase in minute volume for this treatment group, when compared to the 4-hour average prior to treatment dose. There was an increase in minute volume from 0.25 to 0.5 hours post treatment.

There was an overall decrease in respiratory rate, minute volume, and tidal volume for this treatment group, when compared to the 4-hour average prior to treatment dose. There was a decrease in respiratory rate for the following post treatment timepoints, 18.75 to 20.0 hours, 22.25 to 23.75 hours, 26.25 to 28.25 hours, 30.0 to 33.0 hours, and 34.25 hours until the end of data/death. There was a decrease in minute volume for the following post treatment timepoints, 6.75 to 7.25 hours, 9.25 to 9.5 hours, 10.25 to 11.50 hours, 12.5 to 13.75 hours, 14.25 to 20.5 hours, 21.5 to 24.5 hours, 25.25 hours until the end of data/death. There was a decrease in tidal volume for the following post treatment timepoints, 6.00 to 7.25 hours, 9.25 to 11.5 hours, 12.5 to 20.5 hours, 21.75 to 24.50 hours, and 28.5 to 35 hours.

3.3.3 Temperature and Activity

3.3.3.1 Challenge Complete History

Figure 28- Figure 31 are the graphical representation of the Temperature and Activity parameters for the Challenge Complete History data.

SA180D, when compared to baseline, had an increase in temperature following the challenge on 9/13/2021 0900 hrs until 1100 hrs. SA180D, when compared to baseline, had an increase in temperature on 9/15/2021 2000 hrs until 9/16/2021 0500 hrs (2.5-2.9 days post challenge). The decrease in temperature prior to death started on 9/16/2021 at 0600 hrs (2.9 days post challenge) and continuing until death. An increase in activity is noted from 9/15/2021 0100 hrs until 9/15/2021 0600 hrs, as well as an increase from 9/16/2021 0100 hrs until 9/16/2021 0300 hrs.

BF873I, when compared to baseline, had a decrease in temperature on 9/15/2021 0800 hrs until 1000 hrs (2.0-2.1 days post challenge), then again from 9/15/2021 1300 hrs until 1800 hrs (2.2-2.4 days post challenge). The decrease in temperature prior to death starting on 9/16/2021 at 0700 hrs (2.9 days post challenge) and continuing until death. An increase in activity is noted from 9/15/2021 2200 hrs until 9/16/2021 0200 hrs. A decrease in activity was noted on 9/15/2021 1800 hrs, followed by an increase from 9/15/2021 1900 hrs to 9/15/2021 2000 hrs.

AP55D, when compared to baseline, had an increase in temperature on 9/14/2021 2100 hrs until 9/15/2021 0600 hrs (1.5-1.9 days post challenge). The decrease in temperature prior to death started on 9/15/2021 at 1000 hrs (2.1 days post challenge) and continuing until death. An increase in activity is noted from 9/14/2021 2000 hrs until 9/15/2021 0600 hrs.

3.3.3.2 Acute Treatment Response Post First Treatment

Figure 32 - Figure 33 are the graphical representation of the Temperature and Activity parameters for the Challenge Complete History data.

There was a decrease in mean temperature when compared to the 4-hour average prior to treatment dose, from 12.25 hours until 24 hours (end of data/death) post first treatment dose. An increase in activity is seen around the first, second, and fourth times the treatment was given (from 0.25 hours until 0.5 hours, from 4.25 hours until 4.5 hours, and 11.75 until 12 hours post first treatment). A decrease in activity is seen from 10.5 hours until 10.75 hours, 12.75 hours until 13.75 hours, 19.25 hours until 19.75 hours, 20.25 hours until 20.5 hours. An increase is seen in activity from 23 hours until 23.25 hours.

4 Qualitative ECG (Arrhythmia) Summary

Following systemic intoxication with botulinum neurotoxin serotype A1 (BoNT/A1), the objective of this study was to evaluate the therapeutic capacity of 3,4-diaminopyridine (3,4-DAP) to acutely reverse toxicity in the cynomolgus monkey model.

A 4-hour average ("baseline") prior to the first treatment dose was done; because the 4-hour timeframe was due to the animals getting sick just prior to the treatment. Below is a Summary analysis of both the qualitative and quantitative analysis for this study. Refer to the following respective sections and graphs for a more detailed analysis:

- Table 4: Group 1 Challenge Timeline
- Table 5 Group 2 Challenge Timeline
- Table 6 Group 3 Challenge Timeline
- Table 2: Mean ECG Parameters Acute Changes (compared to pre-treatment baseline)
- Table 40: Incidences of Arrhythmia
- **Section 8.1** ECG Graphs

Quantitative Analysis. The isolated changes for the heart rate, QTc, QRS, and PR intervals during the study were within the normal range for the cynomolgus monkeys and are not test article-related. The heart rate changes that occurred were considered to be related to the administration of the botulinum neurotoxin. A normal fluctuation of the heart rate occurred throughout the study in all animals and in all phases with no consistent pattern of a test article effect from the therapeutic capacity of 3,4-diaminopyridine (3,4-DAP). The changes in the mean heart rate during the study were within the normal range for cynomolgus monkeys (162 to 270 beats per minute) (Gauvin et al. 2006). When comparing the percentage change in QTc at each interval with the time matched percentage change in QTc for the saline group animals; the QTc changes were below the 10% increase reported in the JPMA QT PRODACT data of cynomolgus monkeys exposed to therapeutic concentrations of drugs known to cause QT prolongation in humans. Changes in the PR interval in this study is a partial normal physiologic response to the respective changes in the heart rate at that same timepoints.

Qualitative Analysis. Table 40 summarizes the arrhythmias found. Spontaneous cardiac arrhythmias are known to occur in monkeys. Ventricular premature complexes can be observed as an incidental finding in cynomolgus monkeys. In one study with cynomolgus monkeys; 8% of the 62 monkeys had ventricular premature complexes (Macallum and Houston, 1993). In another study, ECG recordings were collected from 1563 monkeys and ventricular premature complexes were noted in six animals (0.38%), with one animal (0.06%) having intermittent ventricular bigeminy and with recordings approximately 10 seconds in duration (Gauvin et al., 2009). The arrhythmia was also seen during prestudy. The telemetry method with the continuous recording and qualitative assessment provides a much larger data pool than the conventional 'snapshot' approaches, such that low-frequency incidental ECG findings that were almost undetectable with sparse sampling methods are more likely to be recorded.

In this study, the incidence of arrhythmias was very similar for the terminal ECG patterns for all three groups. Compared to baseline, the frequency of ventricular premature complexes was very similar for all three groups at postdose phases in the study. The junctional escape complexes and the periods of second-degree atrioventricular block were not of concern in this study. These arrhythmias often took place during baseline and are often seen when there are changes in the heart rate. Primary concern in primates is the ventricular arrhythmias which were very common in this study; especially during the terminal phases, but also during the postdose phases. There were no striking differences for the frequency of ventricular arrhythmias when comparing the two different dosing groups including the saline group. The systemic intoxication with botulinum neurotoxin causes myocarditis resulting in ventricular arrhythmias.

Time-to-Death after Challenge/First Observation of Toxicity/Trigger Criteria

The below time- to- death values comparing the three test groups clearly shows that the treatment with 3,4-DAP at the dose level of 4.12 mg/kg was very effective in treating the systemic intoxication from botulinum neurotoxin serotype A1 (BoNT/A1). The three animals lived longer compared to the animals in Group 1 and Group 2. The time- to- death values for the Group 1 and 2 were very similar, indicating that the lower dose of 3,4-DAP at the dose level of 2.06 mg/kg was not as effective in countering the systemic intoxication with botulinum neurotoxin.

Group 1: Treatment with Saline

Time-to-Death after Challenge (hrs:min)	Time-to-Death after First Observation of Toxicity (hrs:min)	Time-to-Death after Trigger Criteria (hrs:min)#
69:28	23:53	18:02
89:52	22:10	22:10

Group 2: Treatment with 3,4-DAP (2.06 mg/kg)

Time-to-Death after Challenge (hrs:min)	Time-to-Death after First Observation of Toxicity (hrs:min)	Time-to-Death after Trigger Criteria (hrs:min)#
65:06	21:51	18:00
67:21	21:52	13:53
62:18	20:49	12:55

Group 3: Treatment with 3,4-DAP (4.12 mg/kg)

Time-to-Death after Challenge (hrs:min)	Time-to-Death after First Observation of Toxicity (hrs:min)	Time-to-Death after Trigger Criteria (hrs:min)#
77:59	30:27	30:27
91:35	40:06	38:04
57:15	19:54	19:54

5 Conclusions

Following the systemic intoxication with botulinum neurotoxin serotype A1 (BoNT/A1), the therapeutic capacity of 3,4-diaminopyridine (3,4-DAP) clearly shows that the treatment with 3,4-DAP at the dose level of 4.12 mg/kg helps to acutely reverse toxicity in the cynomolgus monkey model.

6 List of Abbreviations and Definitions

ECG	Electrocardiograms; A recording of the electrical fields generated by the heart
RR Interval	The time between ventricular depolarizations (Cunningham 2002). The RR interval is the inverse of heart rate.
PR Interval	The duration of time for atrial depolarization and conduction through the AV node to occur. A prolongation may represent first degree AV block. A shortening may occur when accessory pathways bypass the AV node (Tilley et al. 2008).
QRS Duration	The duration of time for the ventricles to depolarize. A prolongation can occur with an enlarged left ventricle, right or left bundle branch, and complexes of ventricular origin (Tilley et al. 2008).
QT Interval	The duration of time for the ventricles to depolarize and repolarize. The QT interval is heart rate dependent (Tilley et al. 2008).
QTc	Heart rate correction of the QT interval. Prolongation can progress to ventricular tachycardia, ventricular fibrillation, and torsades de pointes (Tilley et al. 2008).
VPC/PVC	Ventricular Premature Complex/Premature Ventricular Contraction. "Cardiac impulses initiated within the ventricles instead of the sinus node" (Tilley & Burtnick 1999).

APC/PAC	Atrial Premature Complex/Premature Atrial Contraction
AV	Atrioventricular
2AVHB	Second Degree Atrioventricular Heart Block
Escape Rhythms	"The pacemaker with the highest automaticity (usually the sinoatrial node) either slows down or stops" (Tilley & Burtnick 1999).

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Holzgrefe, H., Ferber, G., Champeroux, P., Gill, M., Honda, M., Andrea-Greiter-Wilke, Baird, T., Meyer, O., Saulnier, M. Preclinical QT Safety Assessment: Cross-Species Comparisons and Human Translation from an industry Consortium. *Journal of Pharmacological and Toxicological Methods*. 69:61-101, 2014

8 Figures

8.1 ECG Graphs

8.1.1 Challenge Complete History

Figure 1 Heart Rate, Percent Change from Baseline (Challenge History)

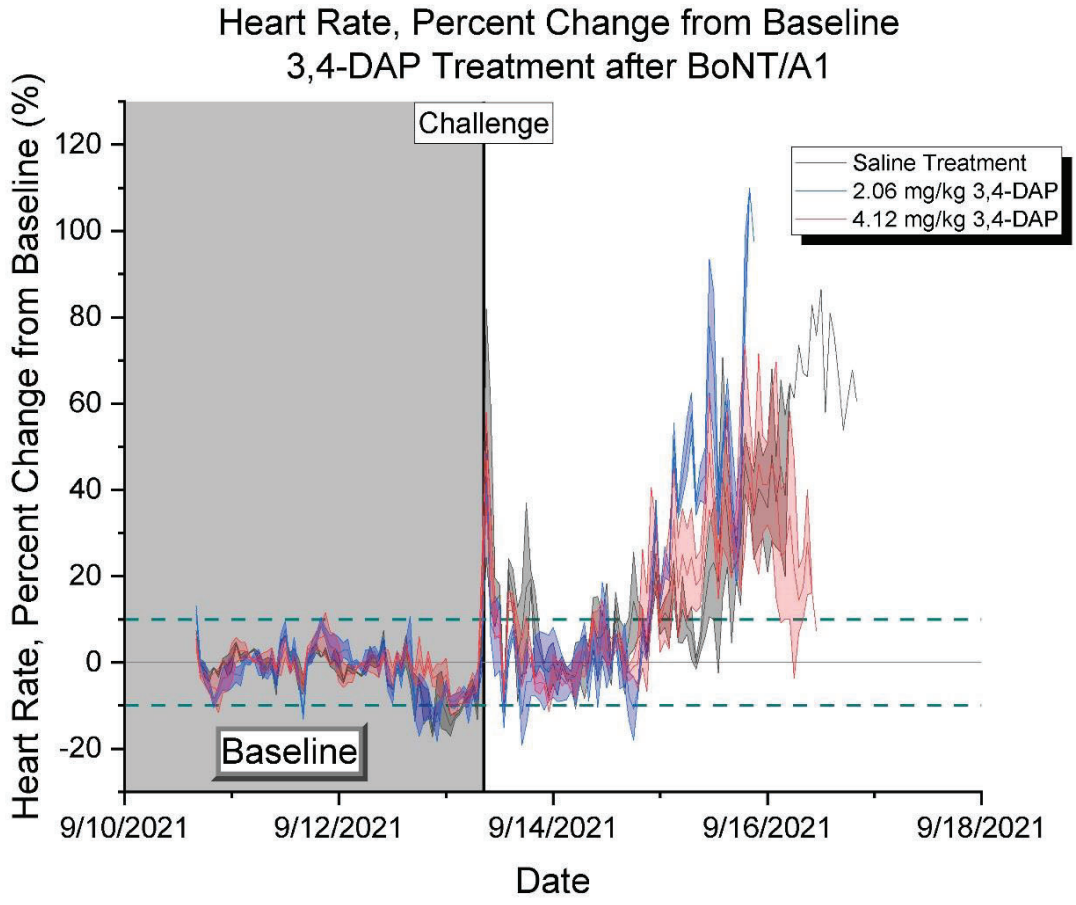

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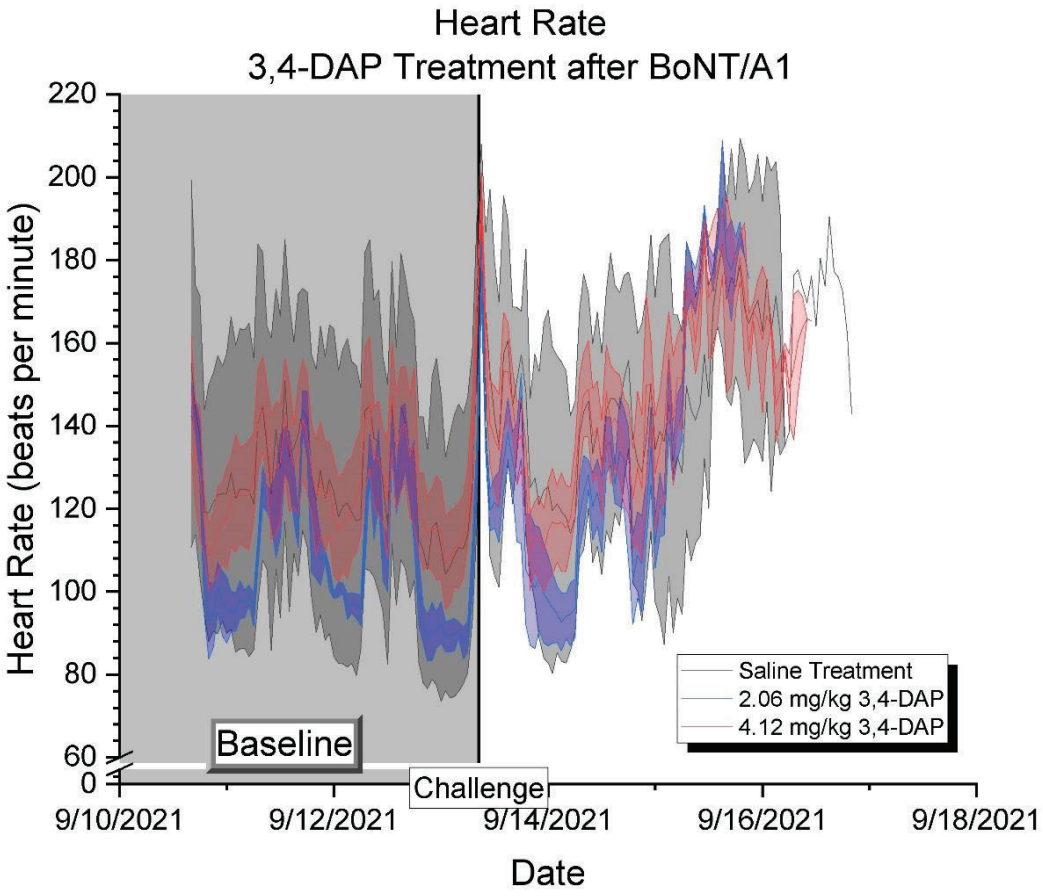
Figure 2 Heart Rate (Challenge History)



Battelle		Status:	Final
Study Number	B05929	Page	32 of 220
PI's Reference No:	360-0002		

Figure 3 PR Interval, Percent Change from Baseline (Challenge History)

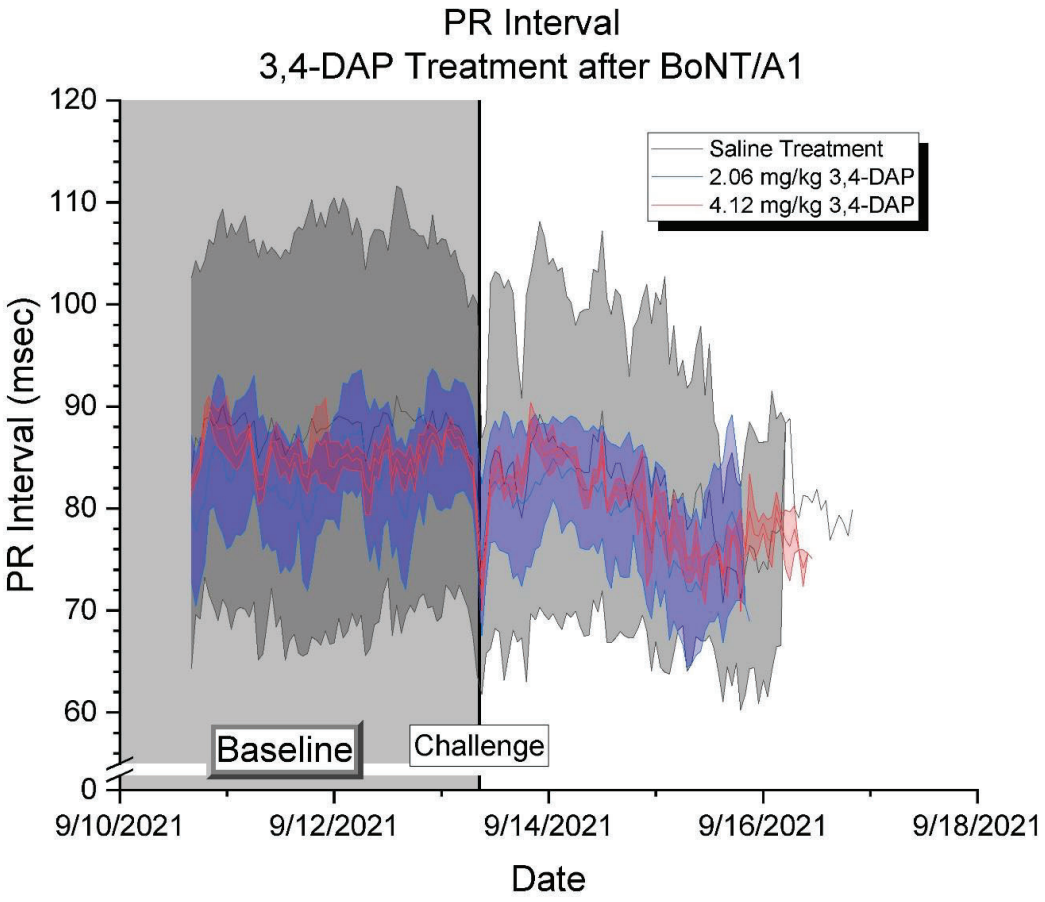


Figure 4 PR Interval (Challenge History)

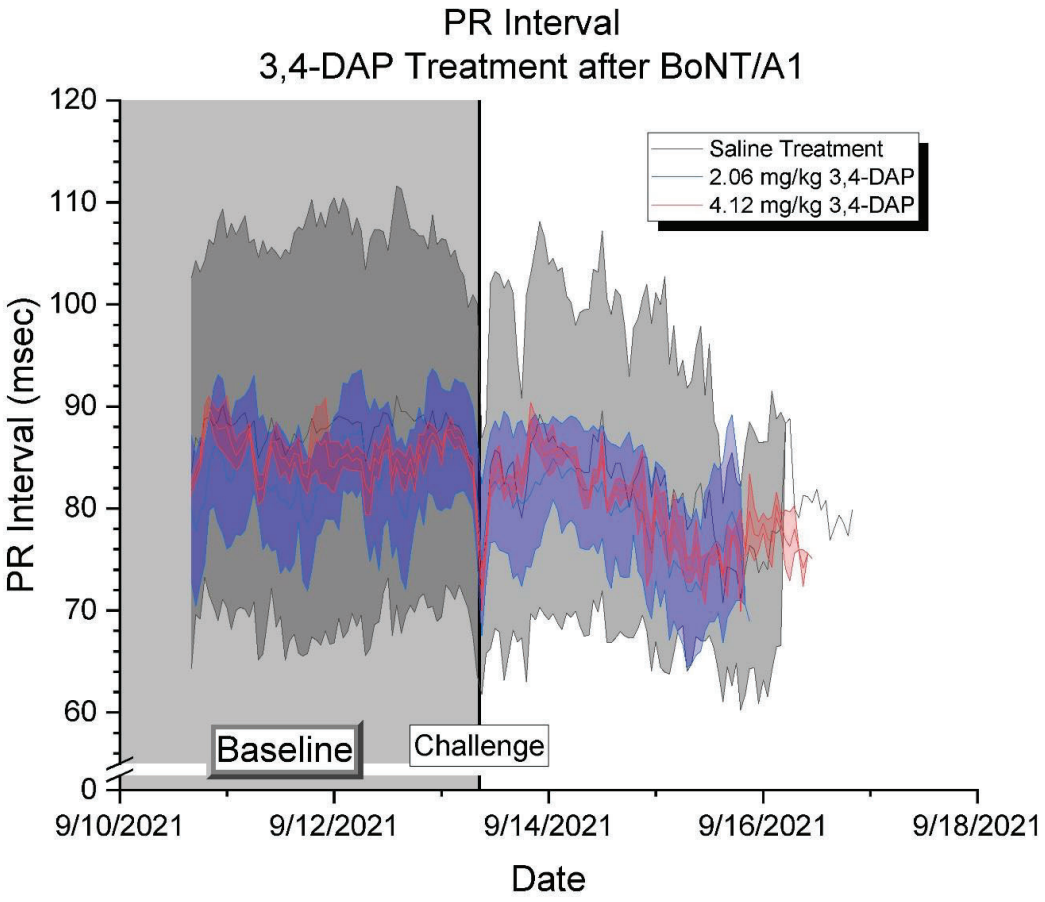


Figure 5 QRS Duration, Percent Change from Baseline (Challenge History)

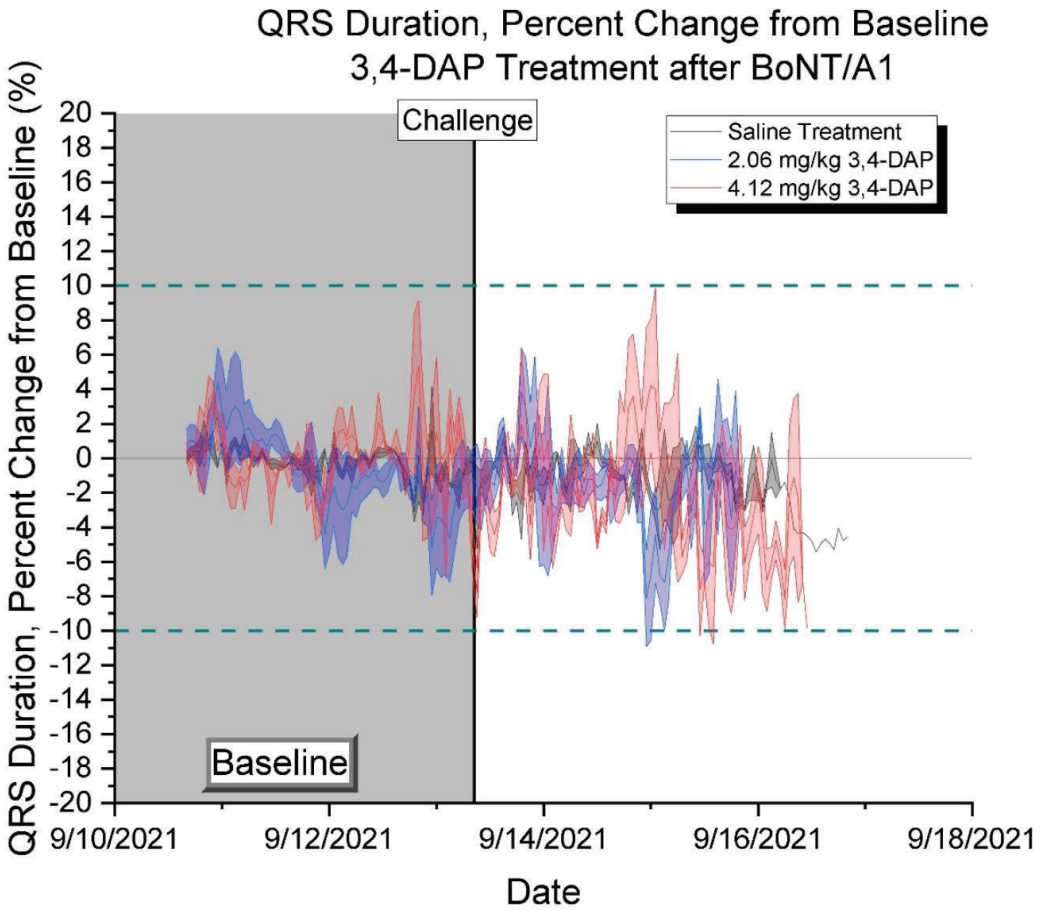


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Figure 6 QRS Duration (Challenge History)

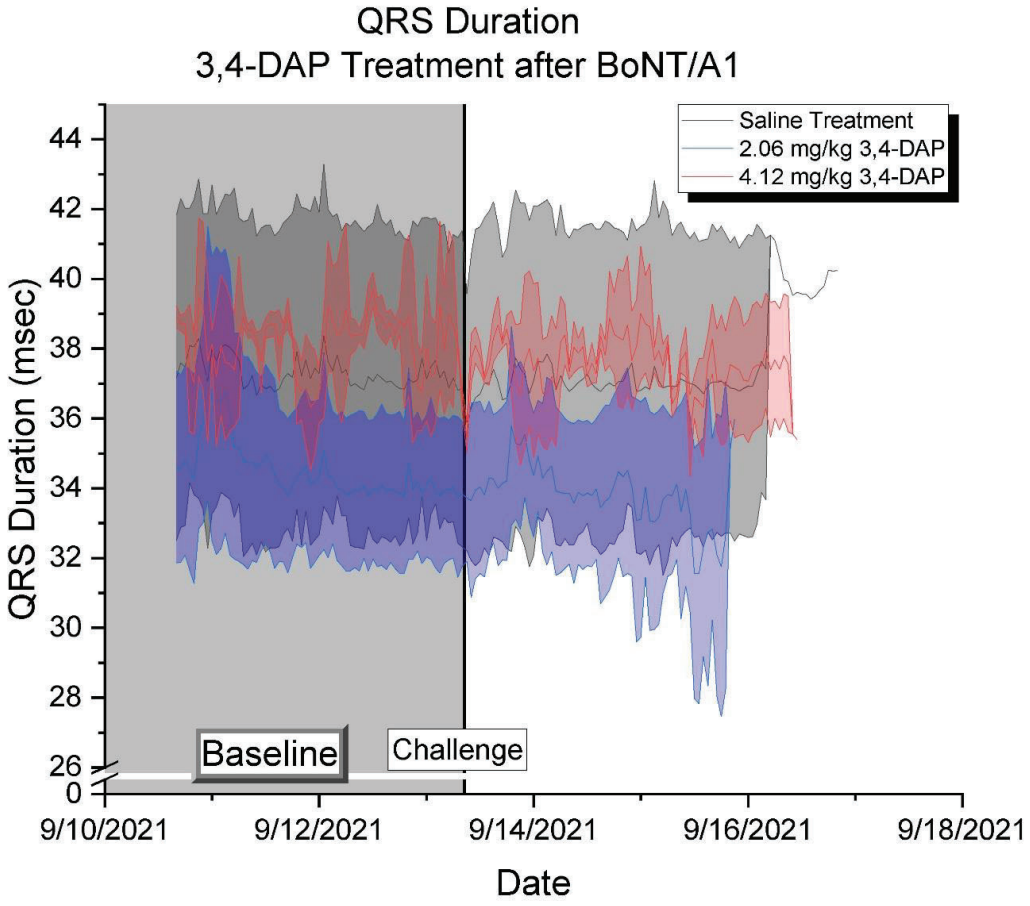

Figure 7 QTc, Percent Change from Baseline (Challenge History)

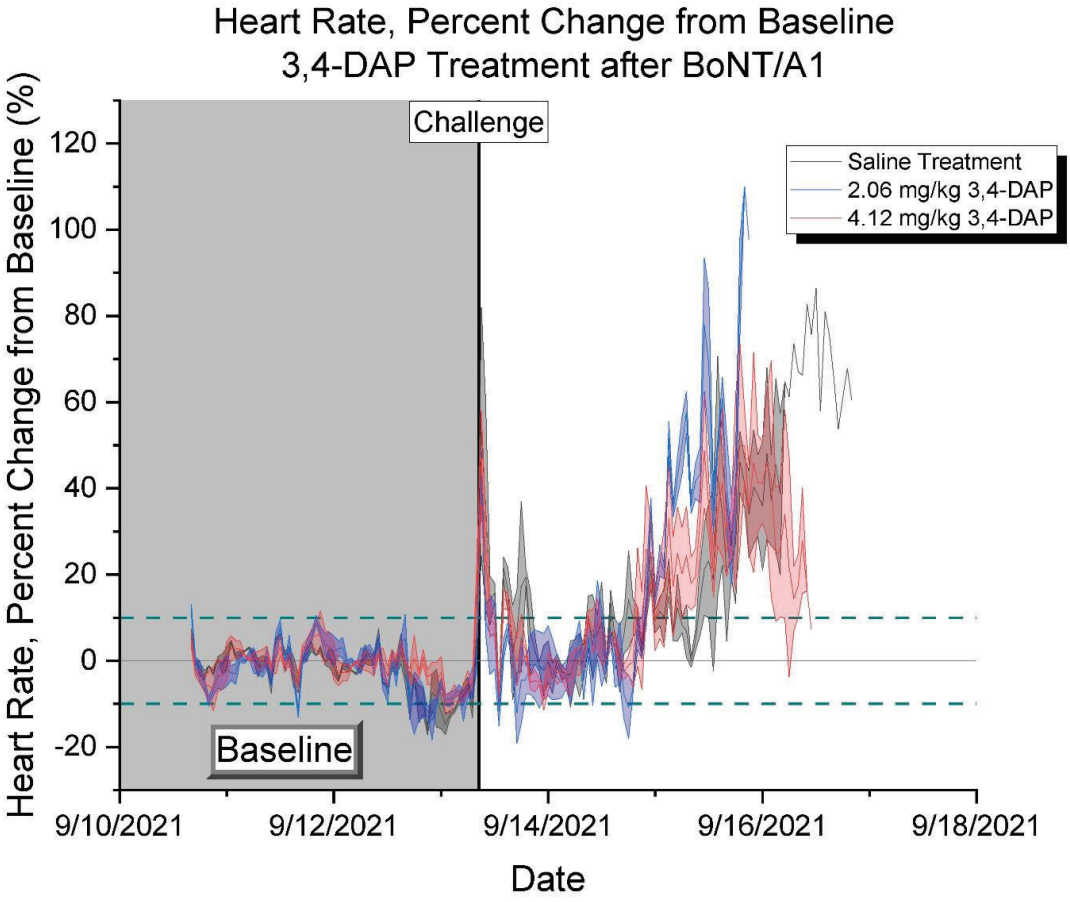

Figure 8 QTc (Challenge History)

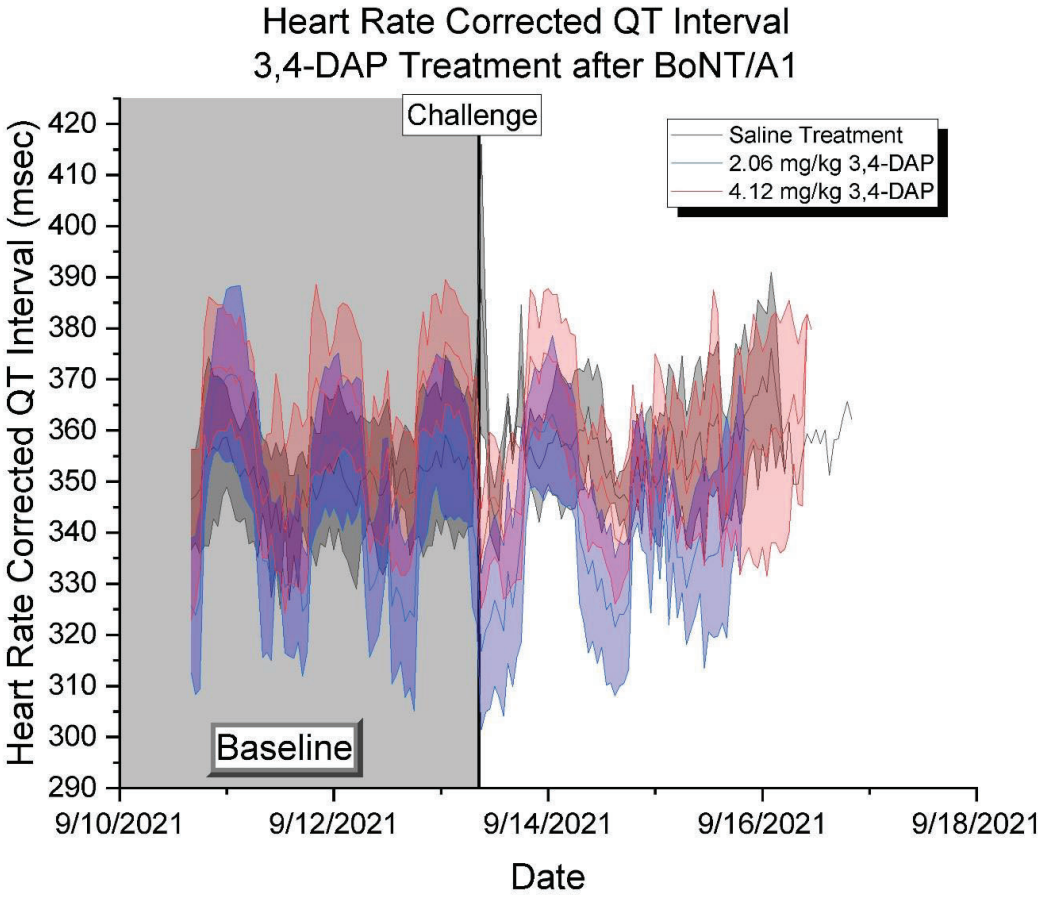

Figure 9 QT Interval, Percent Change from Baseline (Challenge History)

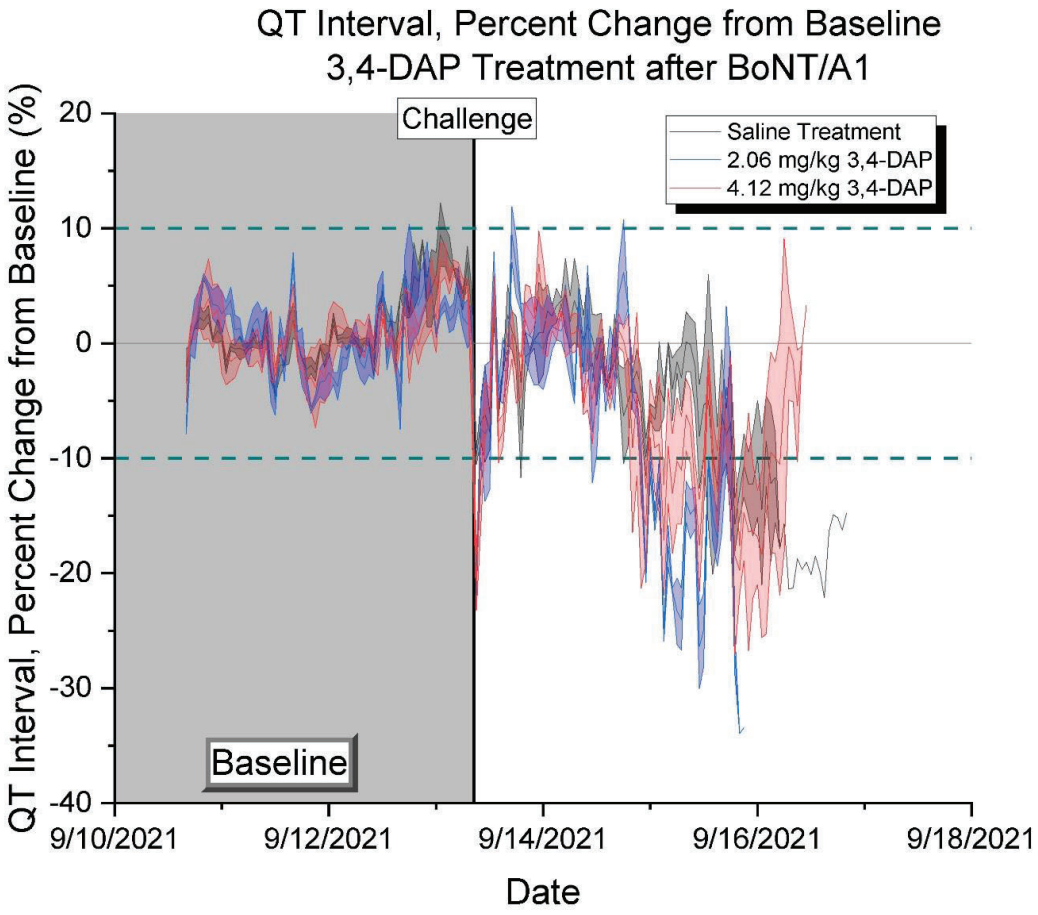

Figure 10 QT Interval (Challenge History)

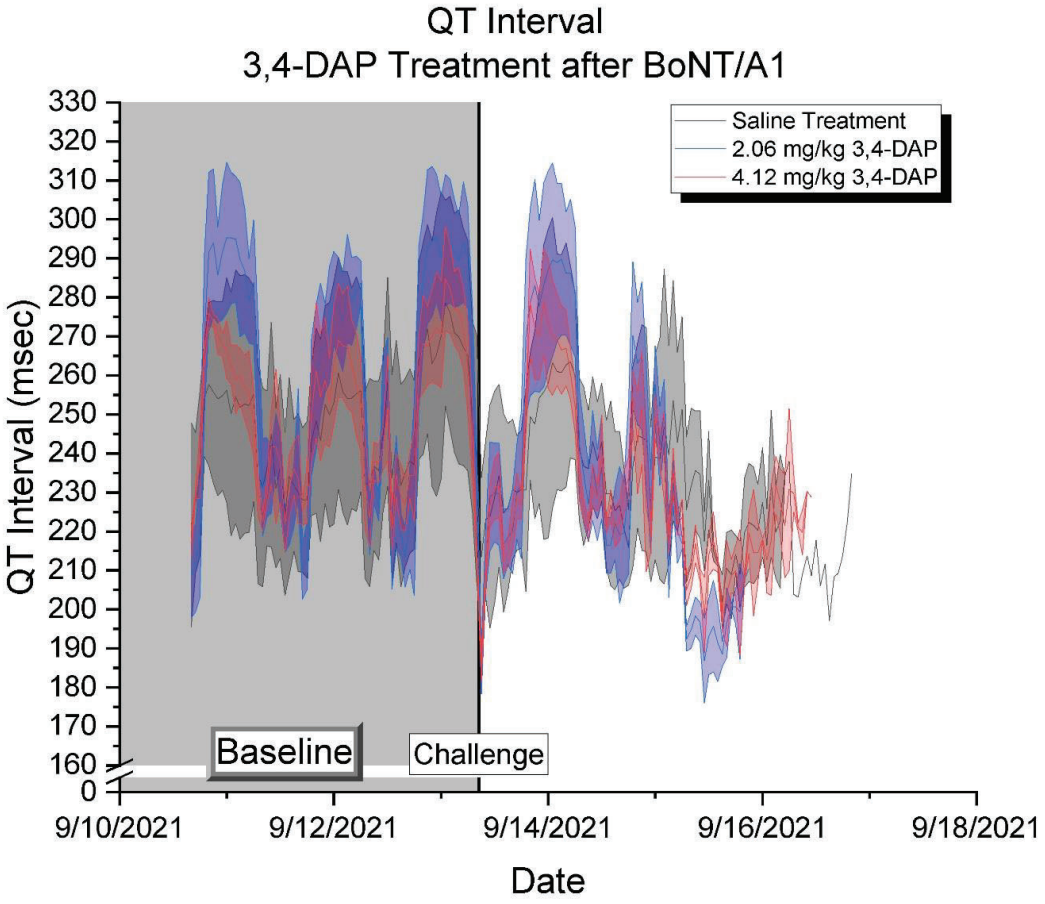

Figure 11 RR Interval, Percent Change from Baseline (Challenge History)

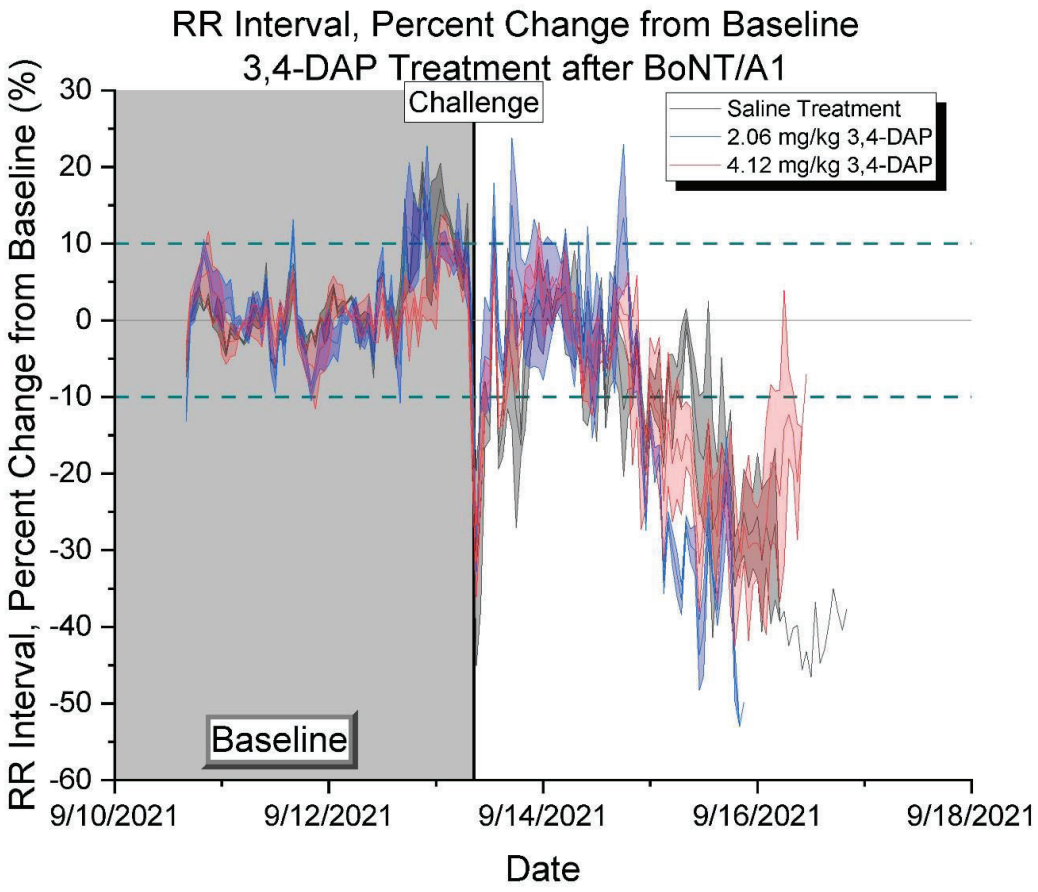

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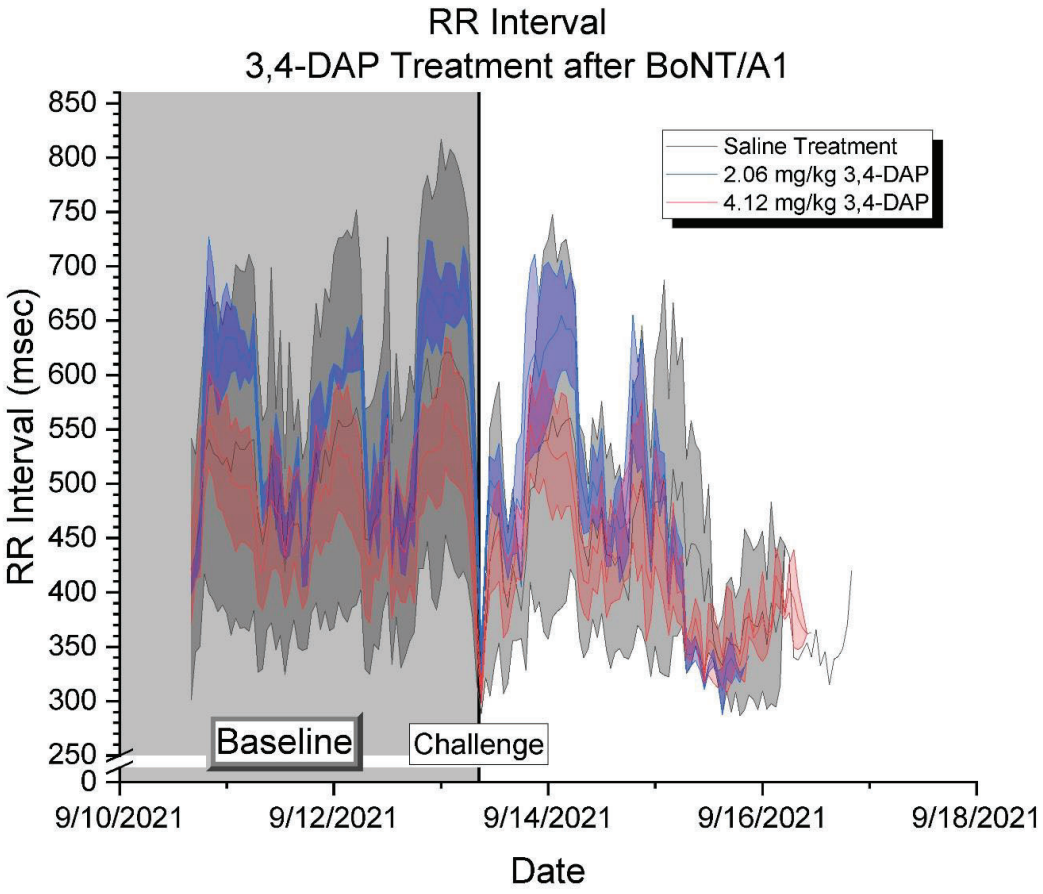
Figure 12 RR Interval (Challenge History)



8.1.2 Acute Treatment Response

Figure 13 Mean Heart Rate, Time After First Treatment

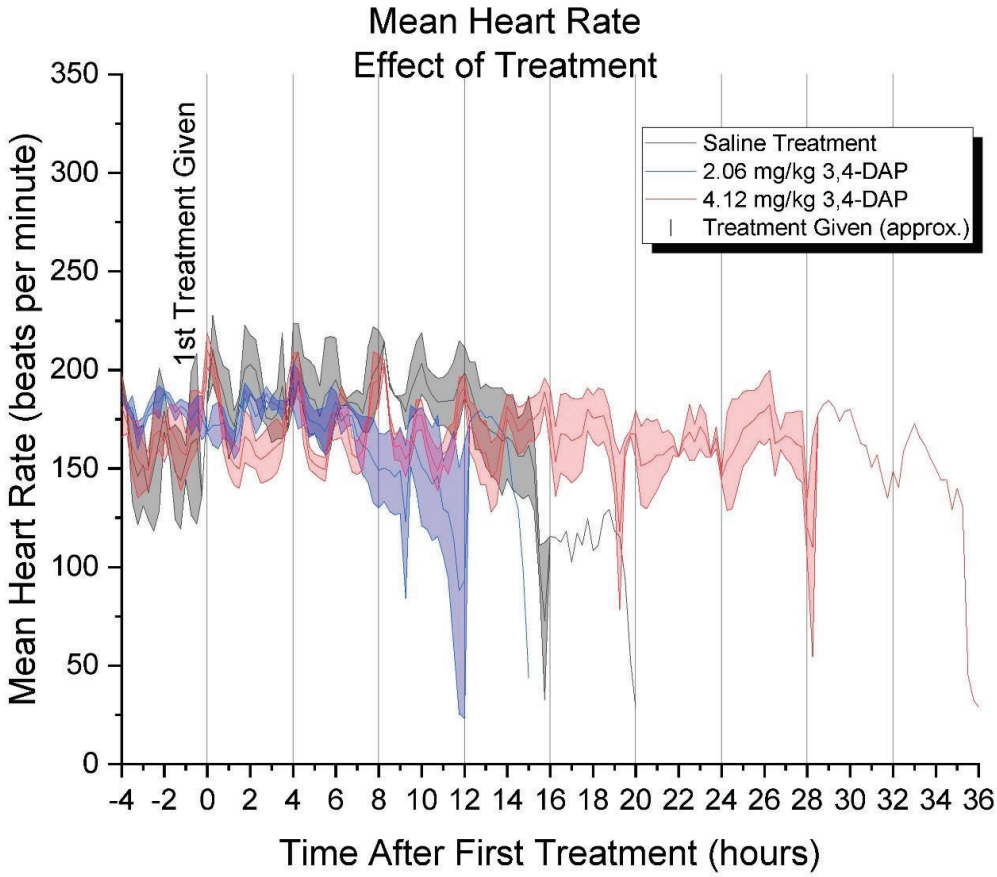


Figure 14 PR Interval, Time After First Treatment

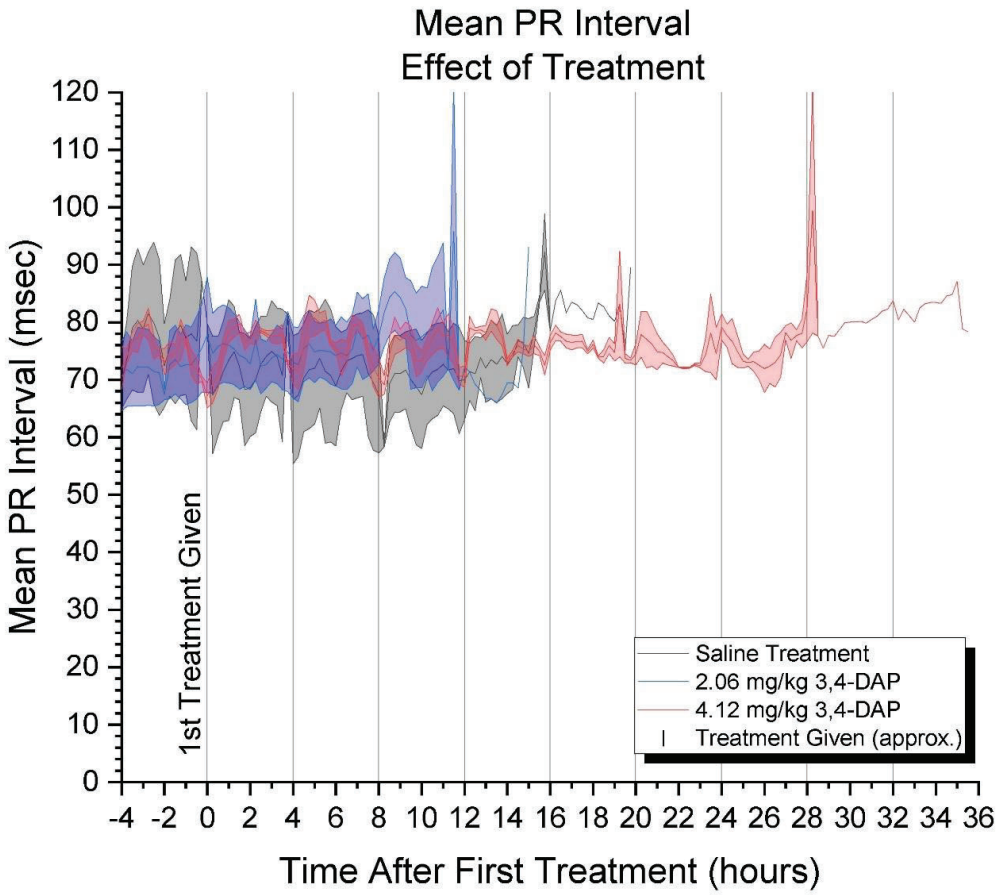


Figure 15 QRS Duration, Time After First Treatment

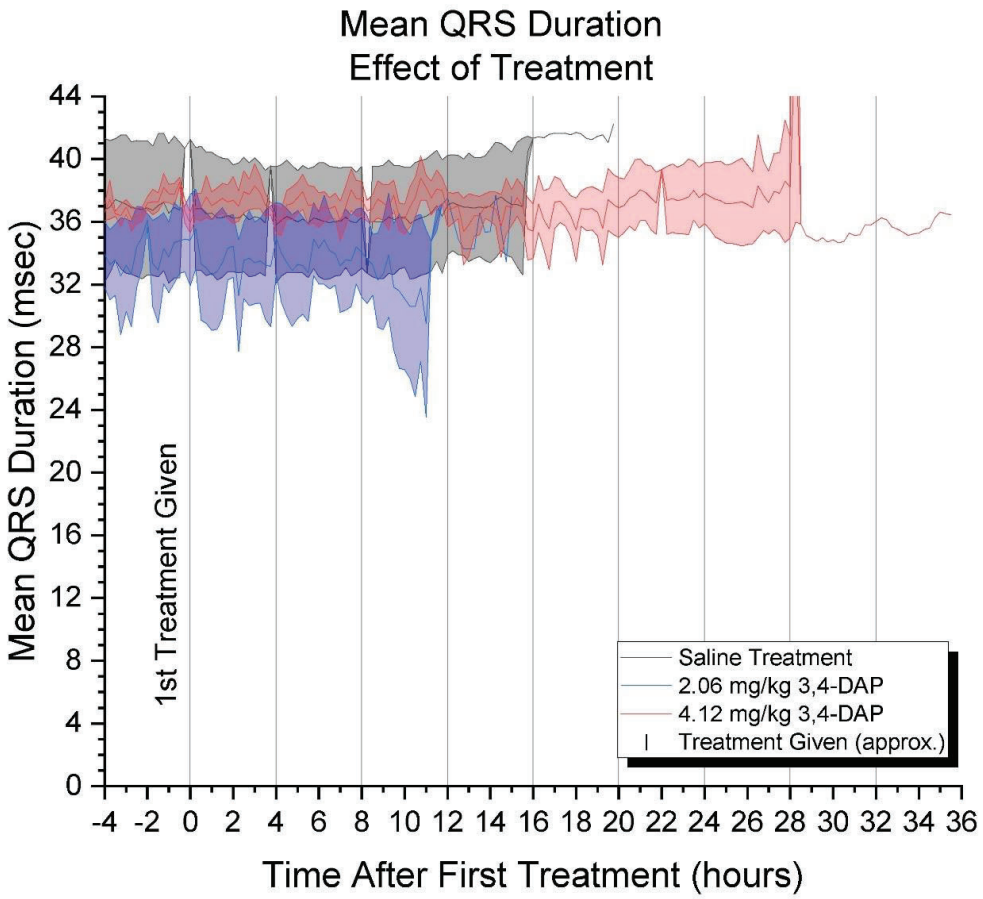


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Figure 16 QTc, Time After First Treatment

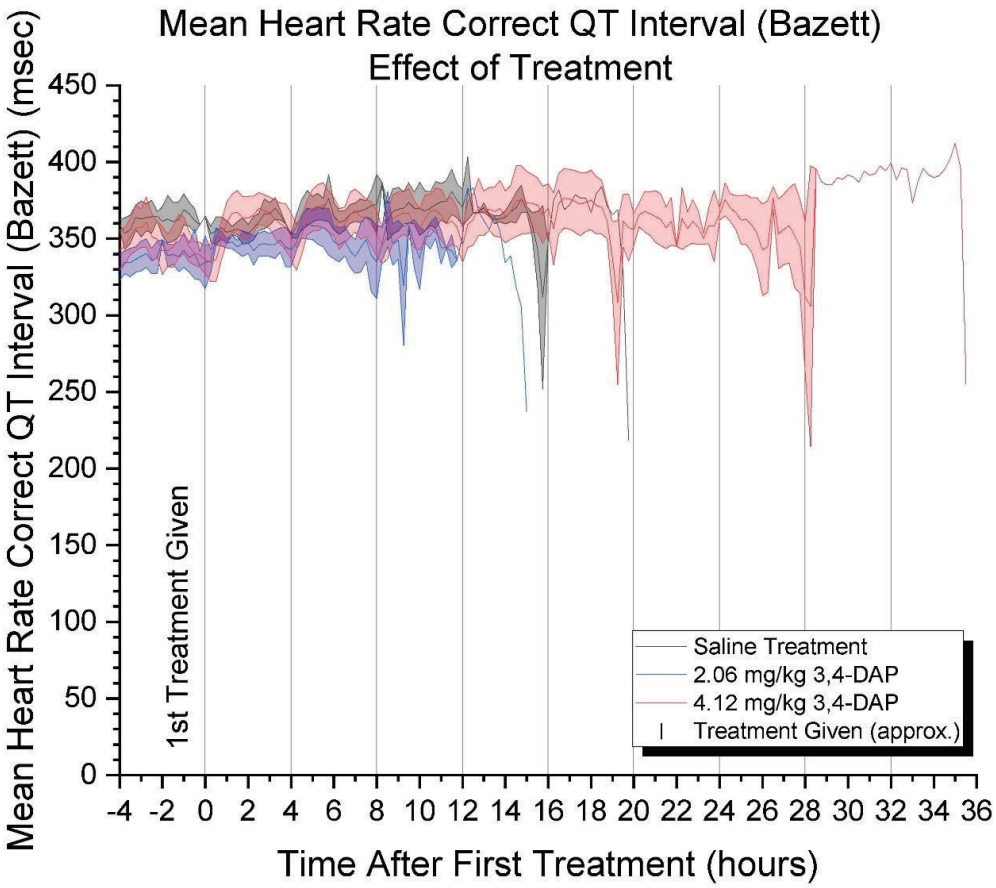


Figure 17 QT Interval, Time After First Treatment

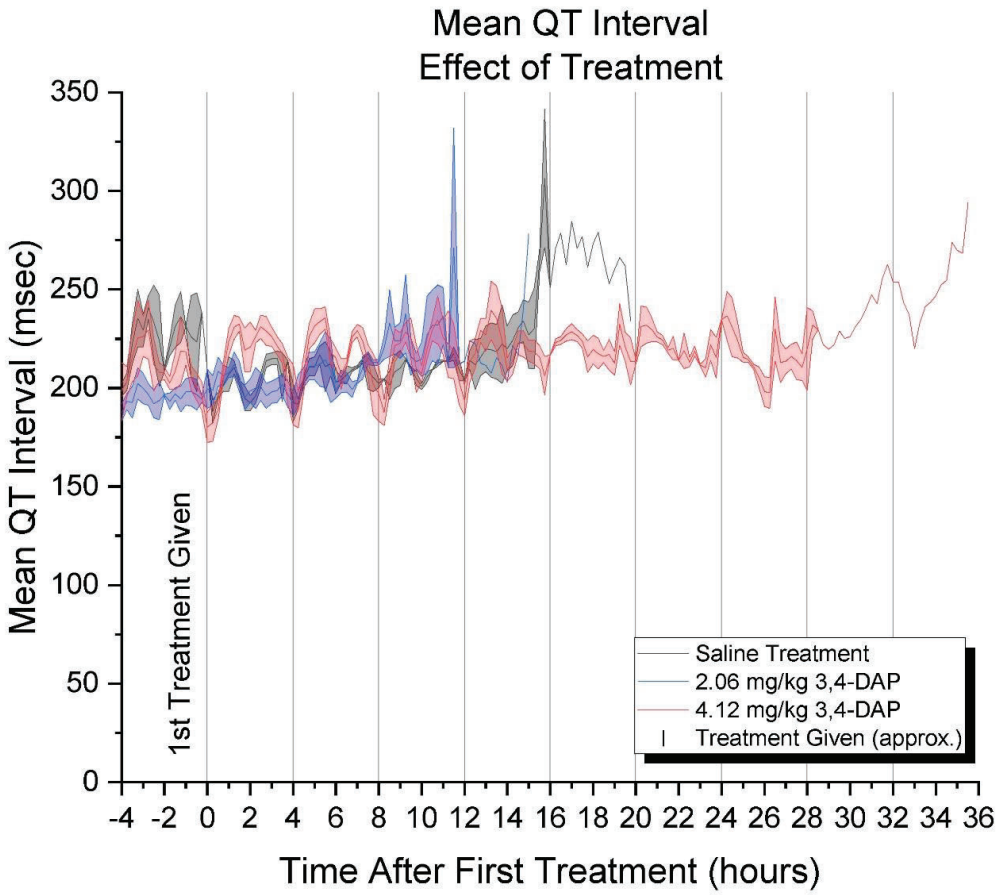
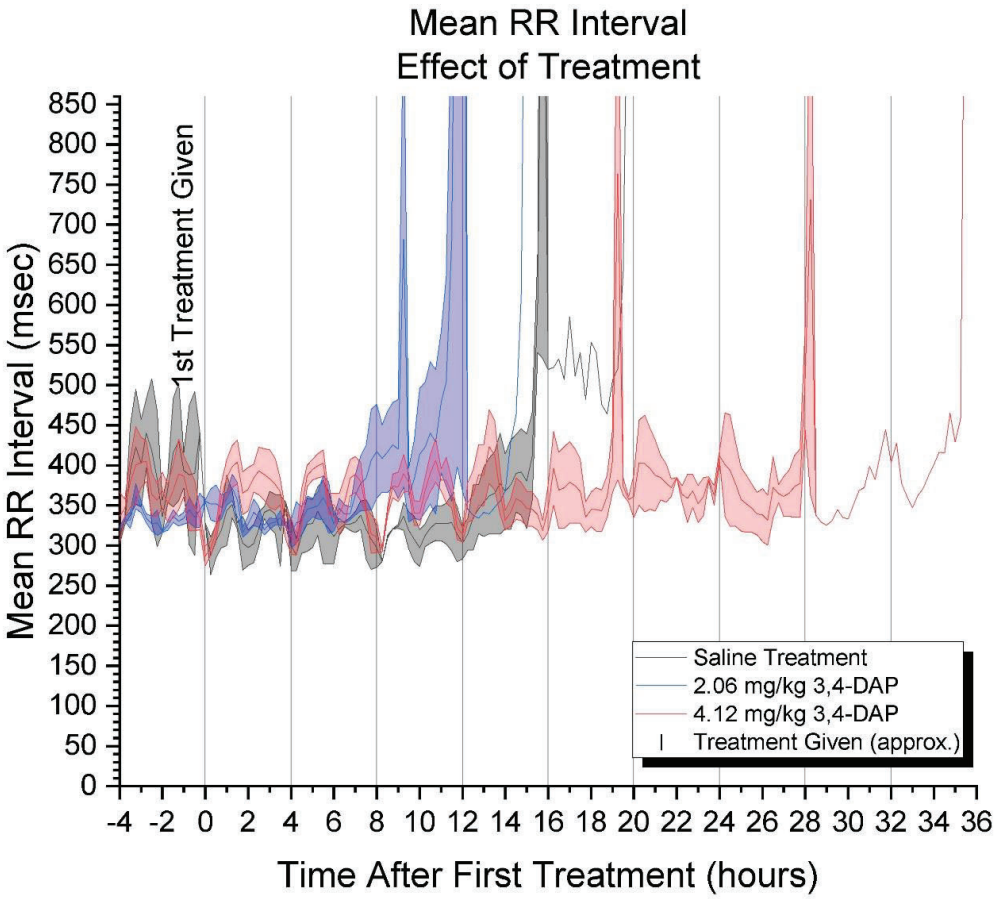


Figure 18 RR Interval, Time After First Treatment



8.2 Respiratory Graphs

8.2.1 Challenge Complete History

Figure 19 Tidal Volume, Percent Change from Baseline (Challenge History)

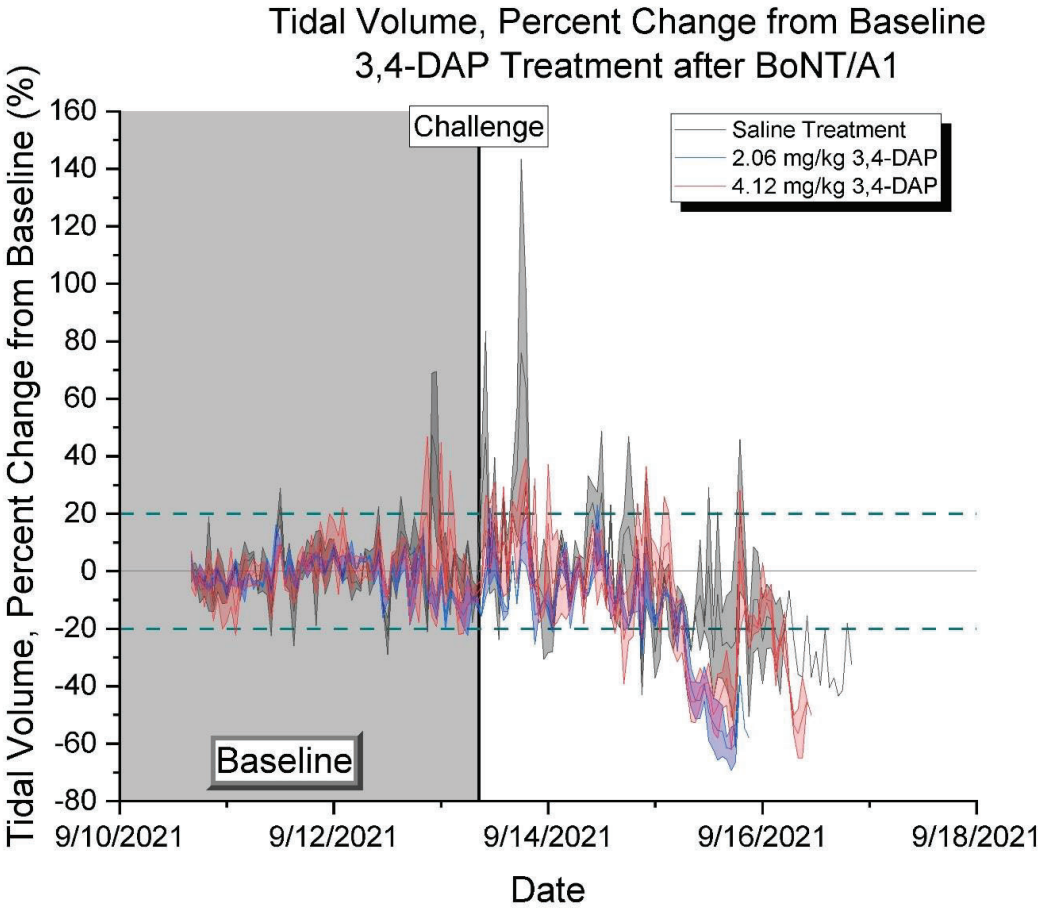


Figure 20 Tidal Volume (Challenge History)

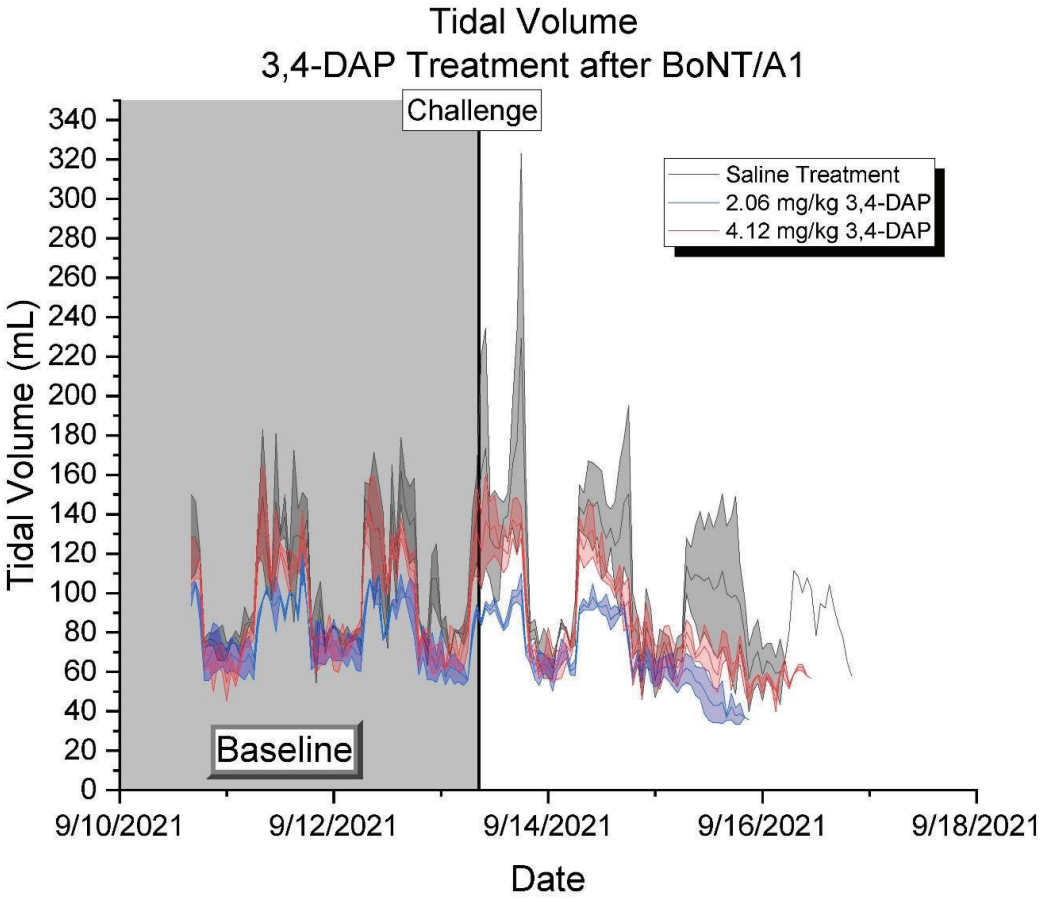


Figure 21 Respiration Rate, Percent Change from Baseline (Challenge History)

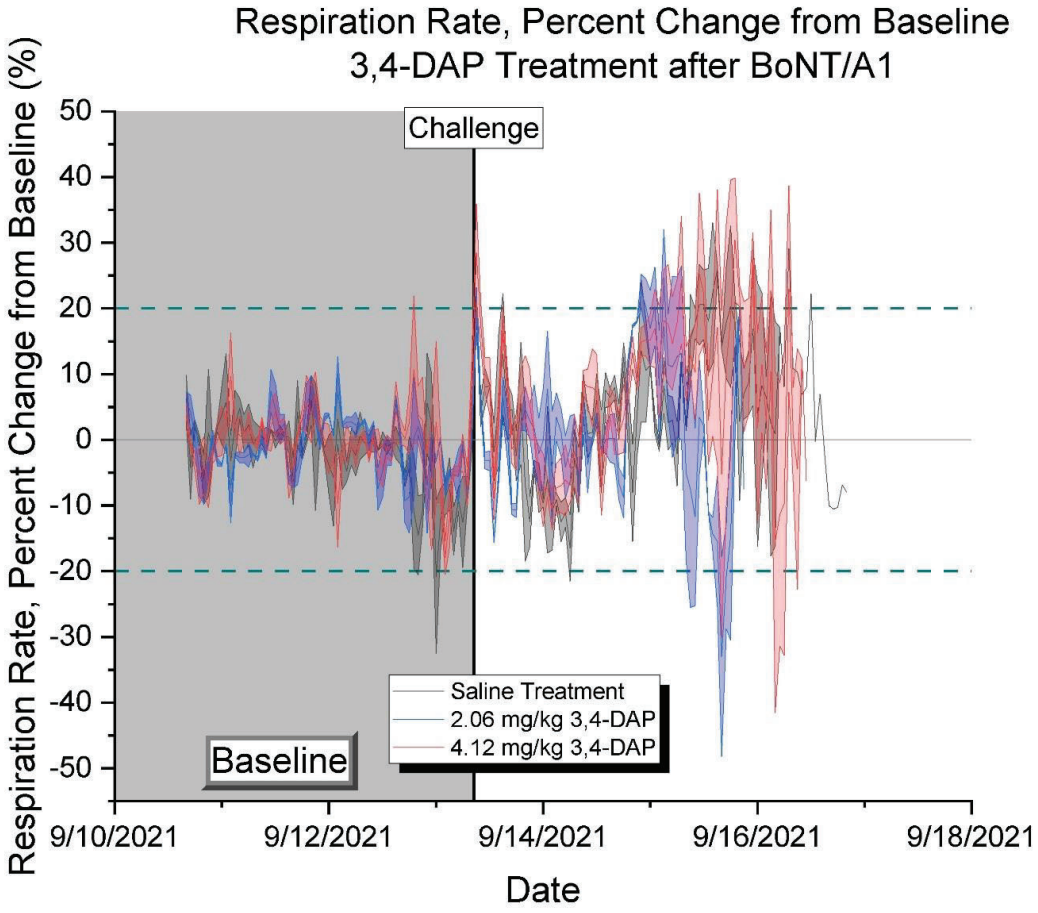


Figure 22 Respiration Rate (Challenge History)

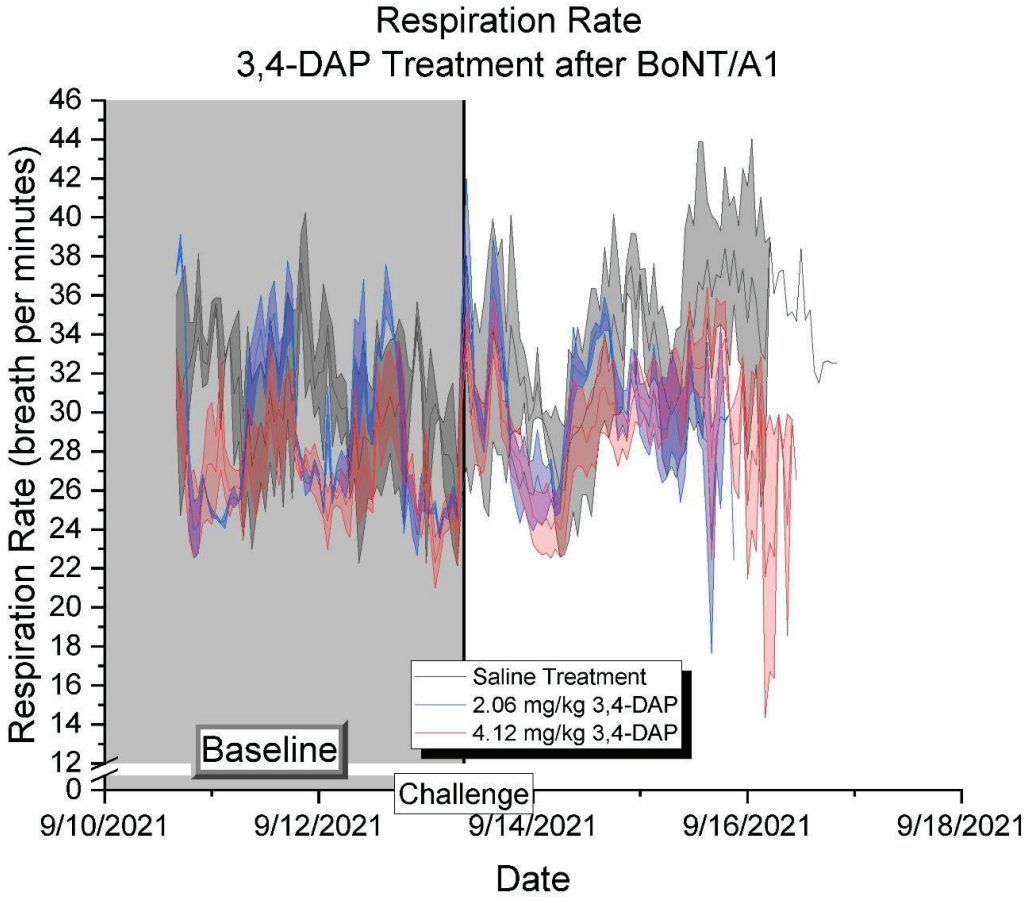


Figure 23 Minute Volume, Percent Change from Baseline (Challenge History)

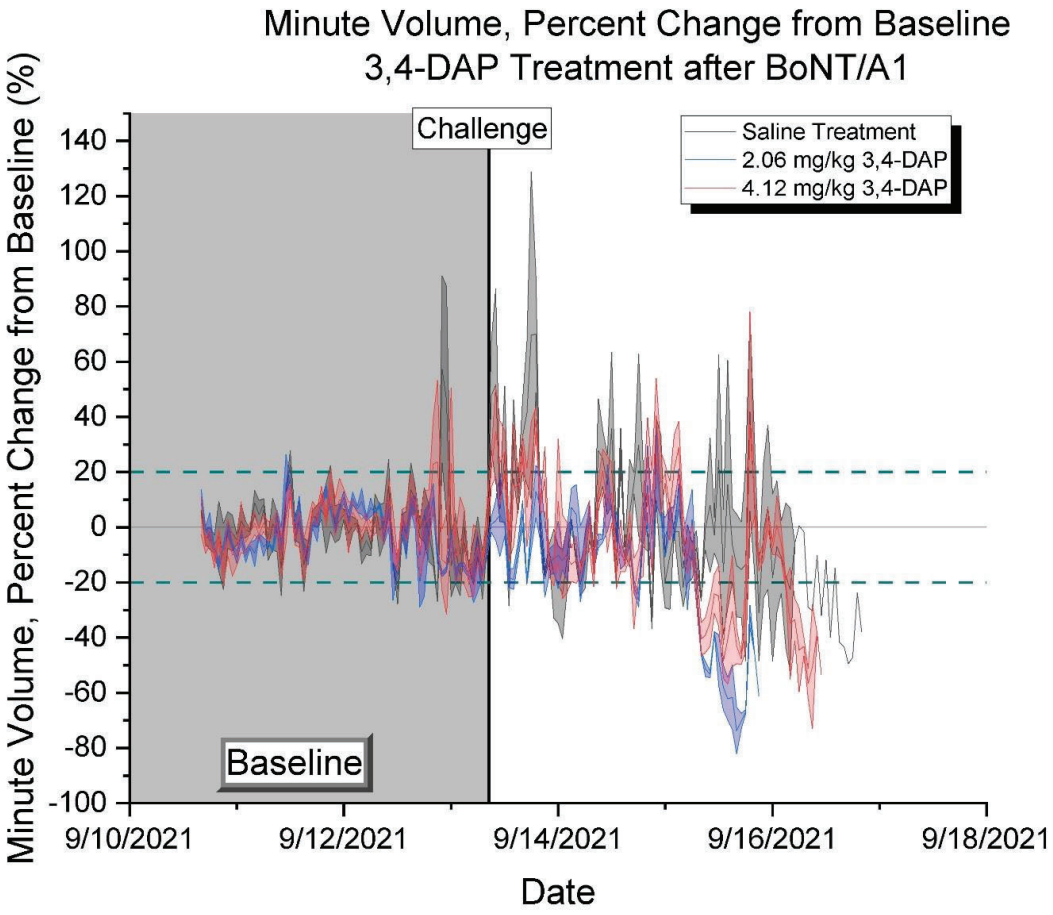
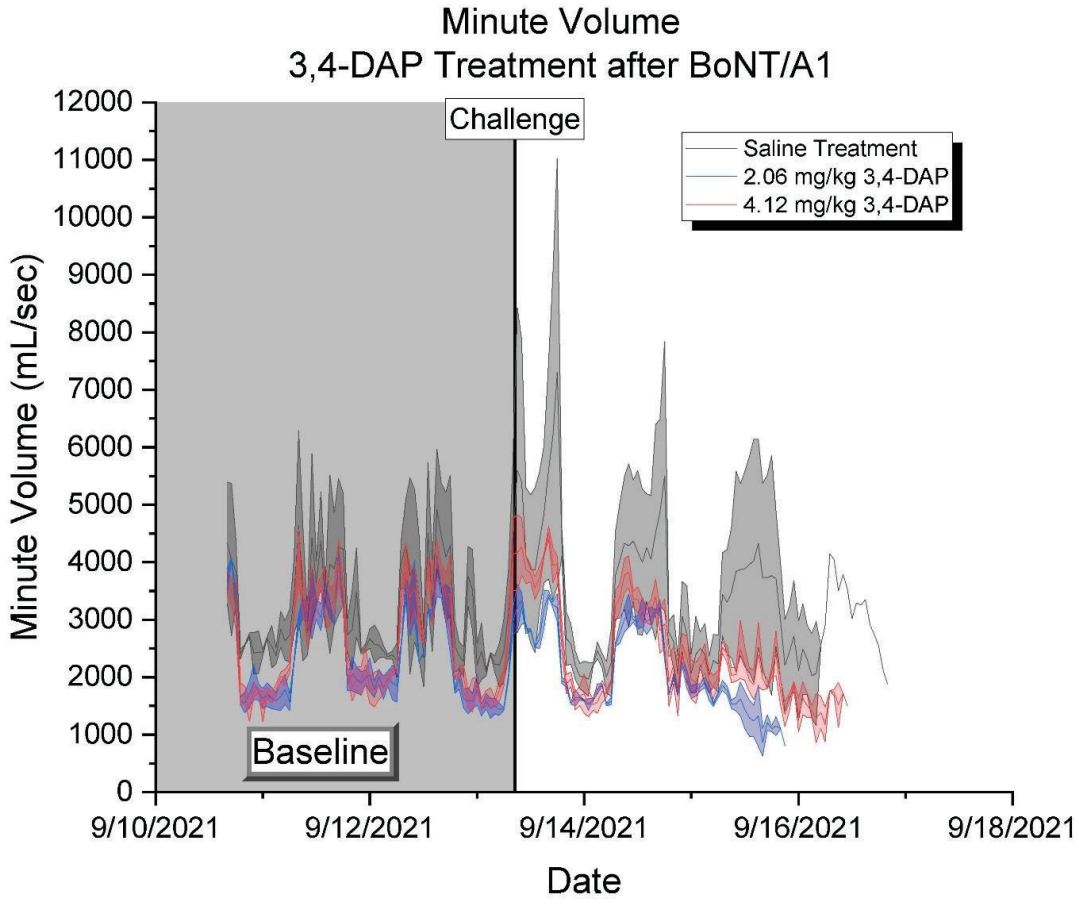


Figure 24 Minute Volume (Challenge History)



8.2.2 Acute Treatment Response

Figure 25 Tidal Volume, Time After First Treatment

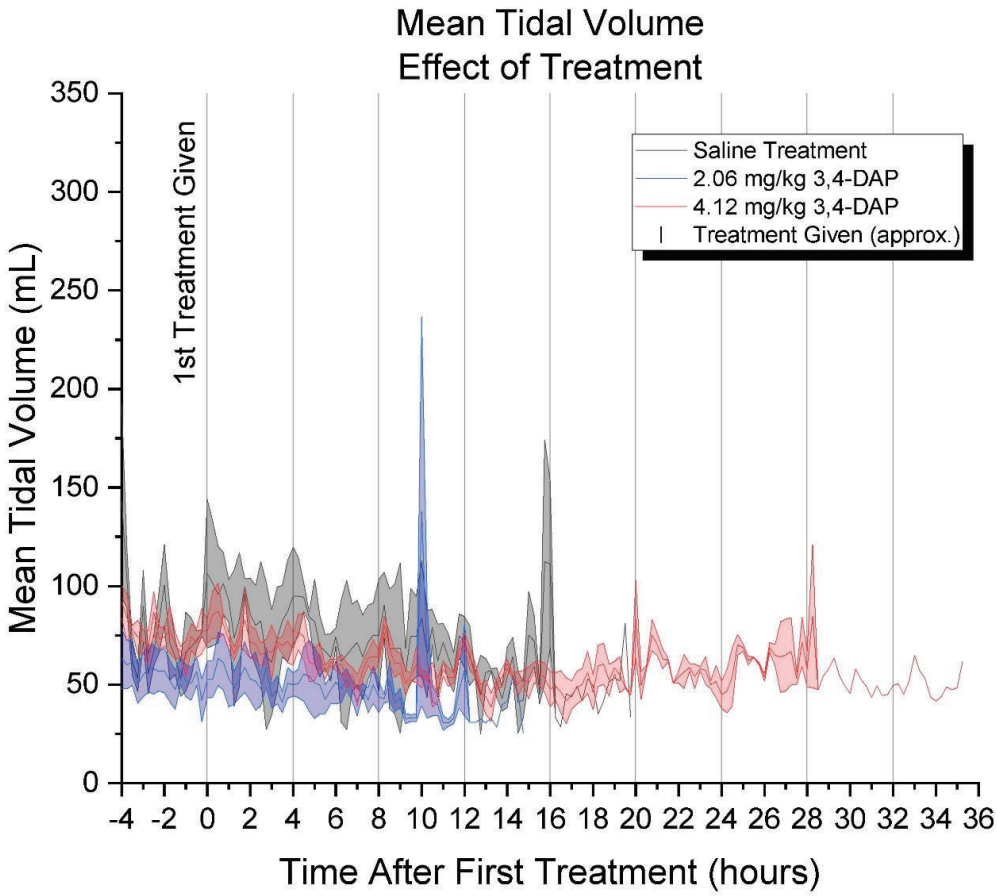


Figure 26 Respiration Rate, Time After First Treatment

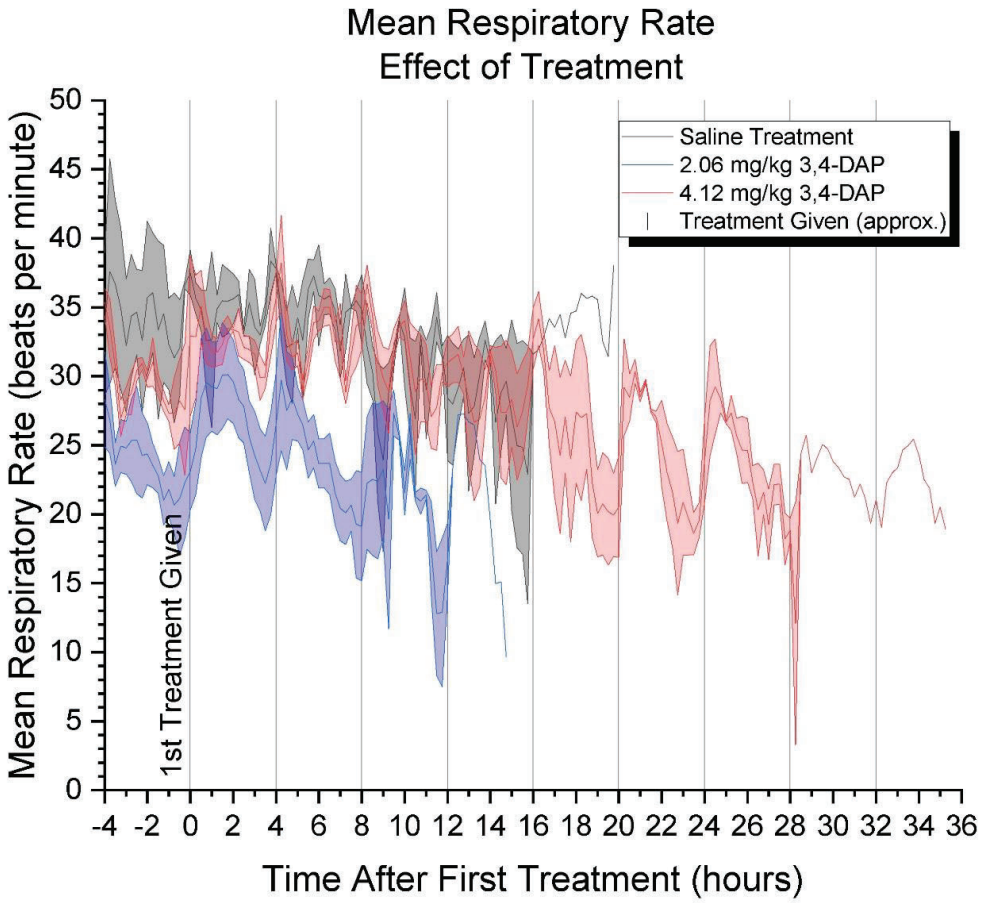
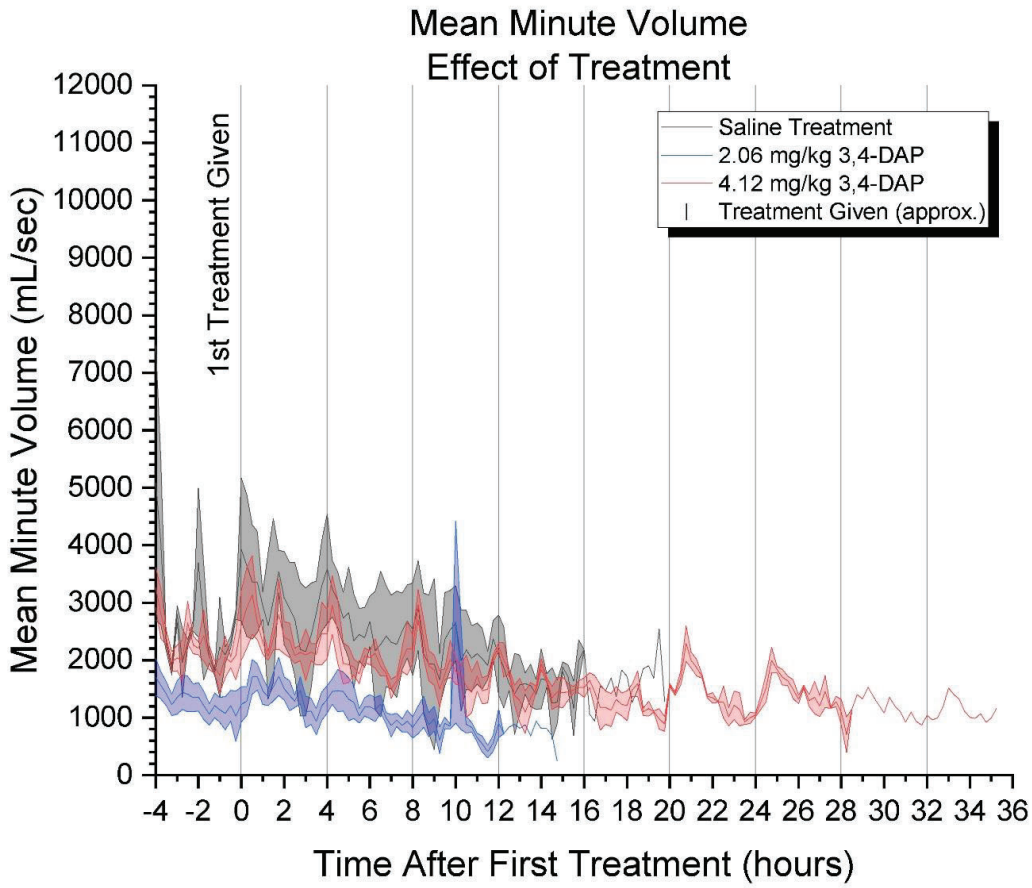


Figure 27 Minute Volume, Time After First Treatment



8.3 Temperature and Activity Graphs

8.3.1 Challenge Complete History

Figure 28 Mean Temperature, Absolute Change from Baseline (Challenge History)

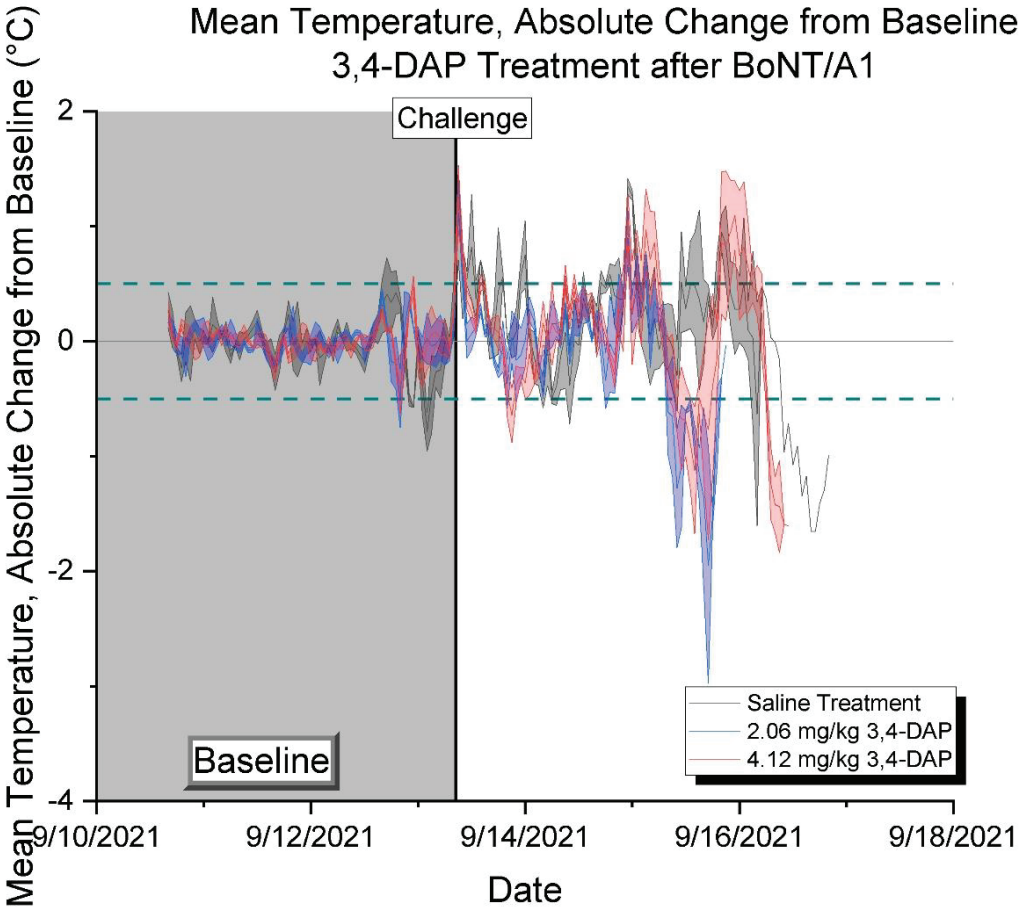


Figure 29 Mean Temperature (Challenge History)

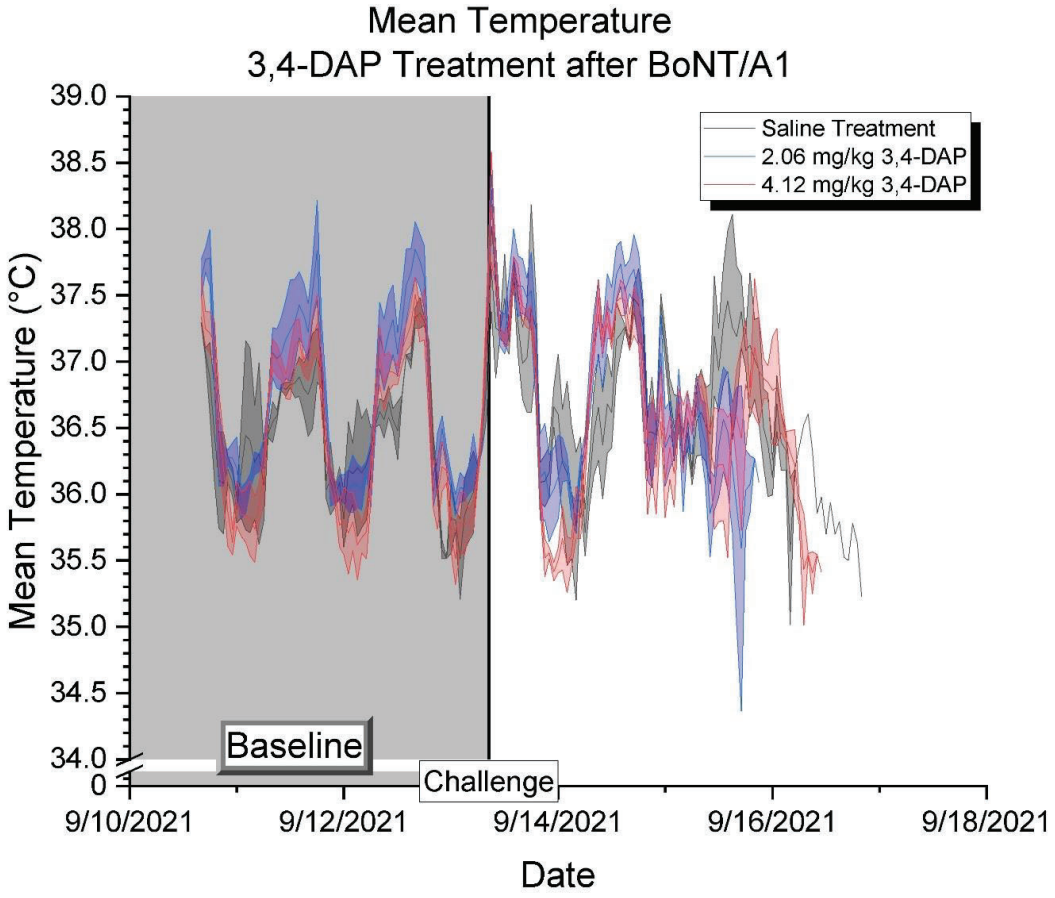


Figure 30 Activity, Percent Change from Baseline (Challenge History)

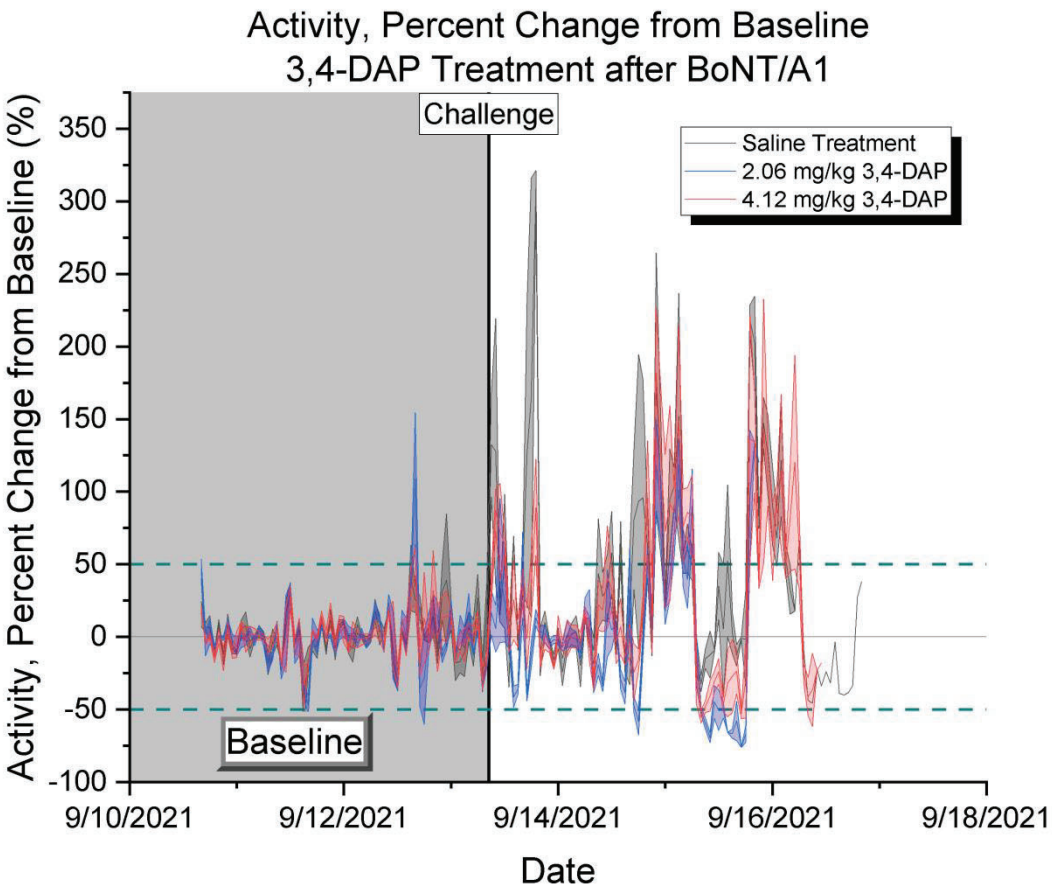
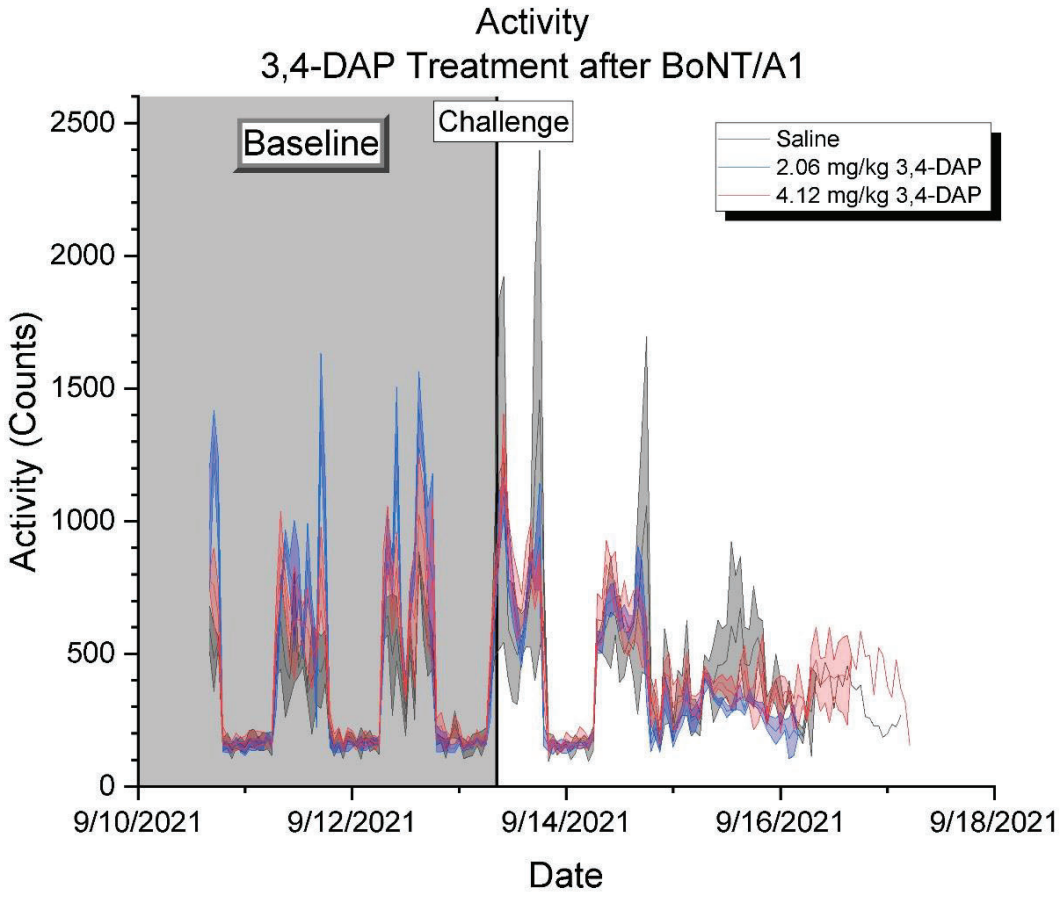


Figure 31 Activity (Challenge History)



8.3.2 Acute Treatment Response

Figure 32 Mean Temperature, Time After First Treatment

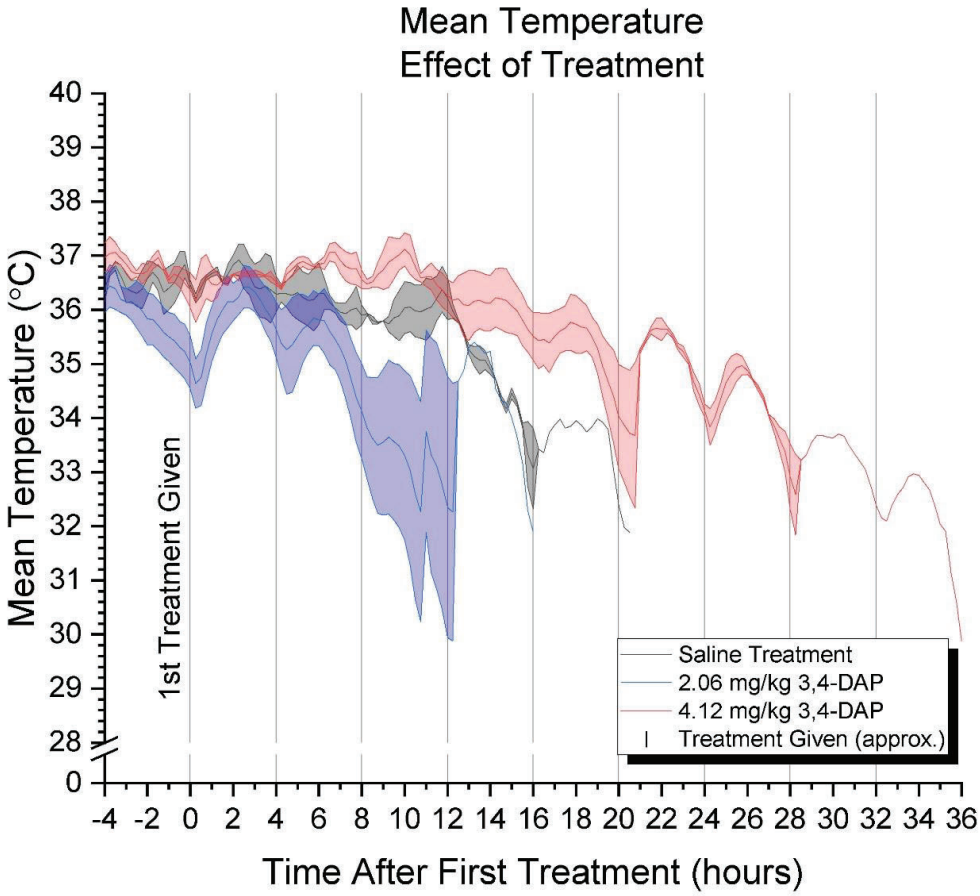
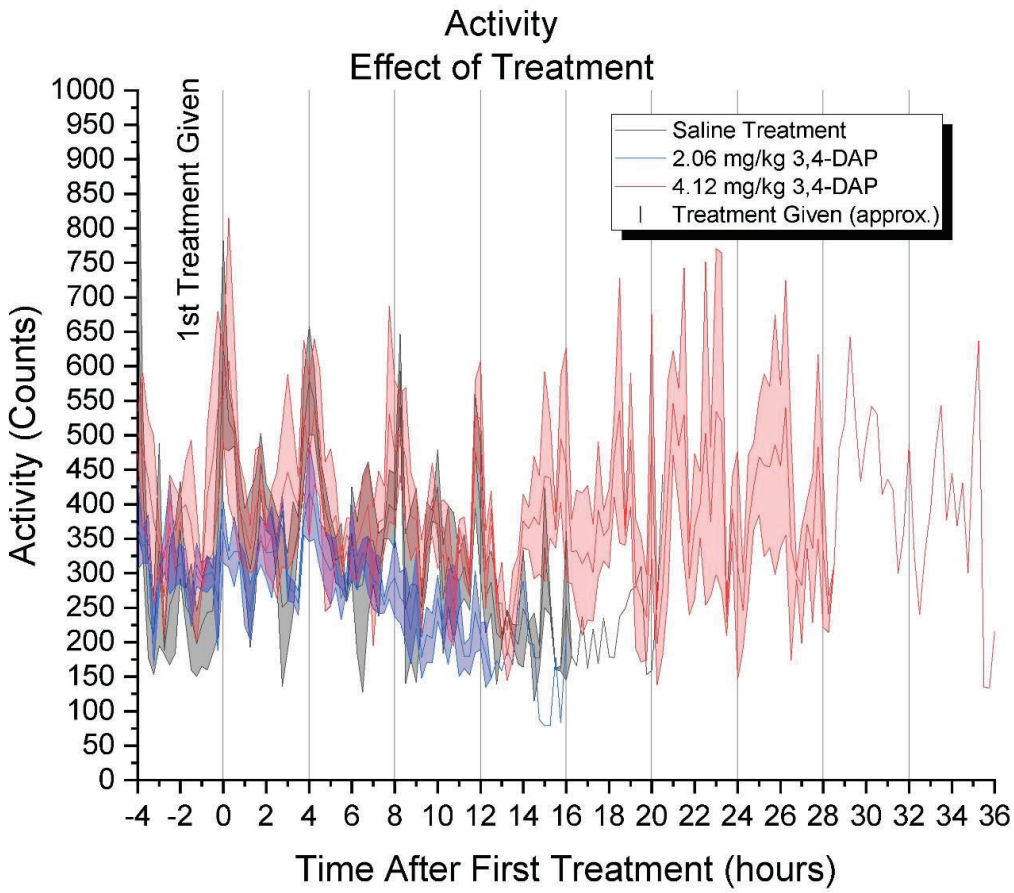


Figure 33 Activity, Time After First Treatment



9 Tables

9.1 Saline Treatment

9.1.1 Temperature and Activity – Saline Treatment

Table 7: Temperature (°C) Saline Treatment

Saline Treatment						
Temperature (°C)						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/10/2021 16:00	37.3	37.3	37.3	0.0	0.0	2
9/10/2021 17:00	37.0	37.1	37.1	0.0	0.1	2
9/10/2021 18:00	36.6	37.1	36.9	0.3	0.4	2
9/10/2021 19:00	36.1	36.8	36.5	0.4	0.5	2
9/10/2021 20:00	35.7	36.5	36.1	0.4	0.5	2
9/10/2021 21:00	35.7	36.5	36.1	0.4	0.5	2
9/10/2021 22:00	36.1	36.3	36.2	0.1	0.1	2
9/10/2021 23:00	36.0	36.2	36.1	0.1	0.2	2
9/11/2021 0:00	36.0	35.8	35.9	0.1	0.1	2
9/11/2021 1:00	36.5	35.8	36.2	0.3	0.5	2
9/11/2021 2:00	37.2	35.7	36.4	0.7	1.0	2
9/11/2021 3:00	37.1	35.7	36.4	0.7	1.0	2
9/11/2021 4:00	36.7	35.8	36.2	0.4	0.6	2
9/11/2021 5:00	37.0	35.6	36.3	0.7	1.0	2
9/11/2021 6:00	36.3	35.8	36.1	0.3	0.4	2
9/11/2021 7:00	36.4	36.5	36.4	0.0	0.0	2
9/11/2021 8:00	36.4	36.7	36.5	0.2	0.2	2
9/11/2021 9:00	36.6	36.6	36.6	0.0	0.1	2
9/11/2021 10:00	36.8	36.8	36.8	0.0	0.0	2
9/11/2021 11:00	36.8	36.7	36.8	0.1	0.1	2
9/11/2021 12:00	36.8	36.8	36.8	0.0	0.0	2
9/11/2021 13:00	36.7	36.9	36.8	0.1	0.2	2
9/11/2021 14:00	36.7	37.0	36.9	0.1	0.2	2
9/11/2021 15:00	36.6	37.0	36.8	0.2	0.3	2
9/11/2021 16:00	36.4	37.1	36.8	0.3	0.4	2
9/11/2021 17:00	36.5	37.2	36.9	0.4	0.5	2
9/11/2021 18:00	36.8	37.2	37.0	0.2	0.3	2

Saline Treatment						
Temperature (°C)						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/11/2021 19:00	36.8	37.0	36.9	0.1	0.2	2
9/11/2021 20:00	36.1	36.0	36.0	0.1	0.1	2
9/11/2021 21:00	36.4	35.8	36.1	0.3	0.4	2
9/11/2021 22:00	36.1	35.9	36.0	0.1	0.1	2
9/11/2021 23:00	36.2	36.0	36.1	0.1	0.2	2
9/12/2021 0:00	36.0	35.6	35.8	0.2	0.3	2
9/12/2021 1:00	36.5	35.8	36.2	0.4	0.5	2
9/12/2021 2:00	36.4	35.9	36.2	0.2	0.3	2
9/12/2021 3:00	36.7	35.7	36.2	0.5	0.7	2
9/12/2021 4:00	36.6	35.8	36.2	0.4	0.6	2
9/12/2021 5:00	36.6	35.8	36.2	0.4	0.6	2
9/12/2021 6:00	36.5	36.2	36.3	0.2	0.2	2
9/12/2021 7:00	36.5	36.5	36.5	0.0	0.0	2
9/12/2021 8:00	36.7	36.5	36.6	0.1	0.1	2
9/12/2021 9:00	36.7	36.4	36.6	0.1	0.2	2
9/12/2021 10:00	36.6	36.8	36.7	0.1	0.2	2
9/12/2021 11:00	36.5	36.6	36.6	0.1	0.1	2
9/12/2021 12:00	36.3	36.7	36.5	0.2	0.3	2
9/12/2021 13:00	36.7	36.7	36.7	0.0	0.0	2
9/12/2021 14:00	37.0	37.1	37.1	0.0	0.0	2
9/12/2021 15:00	37.1	36.9	37.0	0.1	0.1	2
9/12/2021 16:00	37.4	37.3	37.3	0.1	0.1	2
9/12/2021 17:00	37.5	37.3	37.4	0.1	0.2	2
9/12/2021 18:00	37.3	37.3	37.3	0.0	0.0	2
9/12/2021 19:00	37.1	37.2	37.1	0.0	0.1	2
9/12/2021 20:00	36.3	36.5	36.4	0.1	0.1	2
9/12/2021 21:00	36.1	36.0	36.0	0.1	0.1	2
9/12/2021 22:00	35.5	35.7	35.6	0.1	0.1	2
9/12/2021 23:00	35.5	35.5	35.5	0.0	0.0	2
9/13/2021 0:00	36.1	35.6	35.8	0.3	0.4	2
9/13/2021 1:00	35.9	35.7	35.8	0.1	0.1	2
9/13/2021 2:00	35.8	35.2	35.5	0.3	0.4	2

Saline Treatment						
Temperature (°C)						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/13/2021 3:00	36.1	35.6	35.8	0.3	0.4	2
9/13/2021 4:00	36.2	35.6	35.9	0.3	0.4	2
9/13/2021 5:00	36.3	35.7	36.0	0.3	0.4	2
9/13/2021 6:00	36.2	36.2	36.2	0.0	0.0	2
9/13/2021 7:00	36.3	36.5	36.4	0.1	0.1	2
9/13/2021 8:00	36.6	37.1	36.9	0.3	0.4	2
9/13/2021 9:00	37.4	38.0	37.7	0.3	0.5	2
9/13/2021 10:00	36.9	37.6	37.3	0.4	0.5	2
9/13/2021 11:00	37.3	37.2	37.2	0.0	0.1	2
9/13/2021 12:00	37.8	37.1	37.5	0.3	0.5	2
9/13/2021 13:00	37.3	37.1	37.2	0.1	0.1	2
9/13/2021 14:00	37.6	37.8	37.7	0.1	0.1	2
9/13/2021 15:00	37.1	37.5	37.3	0.2	0.3	2
9/13/2021 16:00	36.7	37.3	37.0	0.3	0.4	2
9/13/2021 17:00	36.6	37.4	37.0	0.4	0.6	2
9/13/2021 18:00	36.6	38.2	37.4	0.8	1.1	2
9/13/2021 19:00	37.0	37.5	37.2	0.3	0.4	2
9/13/2021 20:00	35.9	36.2	36.1	0.1	0.2	2
9/13/2021 21:00	35.9	36.3	36.1	0.2	0.3	2
9/13/2021 22:00	36.4	36.0	36.2	0.2	0.3	2
9/13/2021 23:00	36.8	36.5	36.7	0.2	0.2	2
9/14/2021 0:00	37.1	36.2	36.6	0.5	0.6	2
9/14/2021 1:00	36.6	35.8	36.2	0.4	0.6	2
9/14/2021 2:00	36.9	35.5	36.2	0.7	1.0	2
9/14/2021 3:00	36.5	35.5	36.0	0.5	0.7	2
9/14/2021 4:00	36.3	35.2	35.8	0.6	0.8	2
9/14/2021 5:00	36.4	36.0	36.2	0.2	0.3	2
9/14/2021 6:00	35.9	35.5	35.7	0.2	0.2	2
9/14/2021 7:00	35.9	36.3	36.1	0.2	0.3	2
9/14/2021 8:00	36.1	36.8	36.5	0.3	0.4	2
9/14/2021 9:00	36.3	37.1	36.7	0.4	0.6	2
9/14/2021 10:00	36.0	36.8	36.4	0.4	0.6	2

Saline Treatment						
Temperature (°C)						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/14/2021 11:00	36.3	37.1	36.7	0.4	0.5	2
9/14/2021 12:00	36.4	36.9	36.6	0.3	0.4	2
9/14/2021 13:00	36.9	37.5	37.2	0.3	0.4	2
9/14/2021 14:00	37.1	37.4	37.2	0.1	0.2	2
9/14/2021 15:00	37.2	37.3	37.3	0.0	0.0	2
9/14/2021 16:00	37.2	37.1	37.1	0.0	0.1	2
9/14/2021 17:00	37.4	37.6	37.5	0.1	0.1	2
9/14/2021 18:00	37.1	37.7	37.4	0.3	0.4	2
9/14/2021 19:00	37.1	37.4	37.3	0.1	0.2	2
9/14/2021 20:00	36.6	36.4	36.5	0.1	0.2	2
9/14/2021 21:00	36.1	36.9	36.5	0.4	0.6	2
9/14/2021 22:00	36.4	36.5	36.5	0.1	0.1	2
9/14/2021 23:00	37.5	37.4	37.4	0.1	0.1	2
9/15/2021 0:00	37.2	37.0	37.1	0.1	0.2	2
9/15/2021 1:00	36.9	36.6	36.8	0.1	0.2	2
9/15/2021 2:00	36.8	36.3	36.5	0.2	0.4	2
9/15/2021 3:00	36.7	36.5	36.6	0.1	0.2	2
9/15/2021 4:00	36.2	36.2	36.2	0.0	0.0	2
9/15/2021 5:00	36.6	36.4	36.5	0.1	0.1	2
9/15/2021 6:00	36.2	36.1	36.1	0.1	0.1	2
9/15/2021 7:00	36.3	36.8	36.5	0.3	0.4	2
9/15/2021 8:00	36.3	36.9	36.6	0.3	0.5	2
9/15/2021 9:00	36.2	36.8	36.5	0.3	0.4	2
9/15/2021 10:00	36.1	36.8	36.5	0.4	0.5	2
9/15/2021 11:00	36.7	37.6	37.2	0.5	0.6	2
9/15/2021 12:00	36.6	37.3	36.9	0.3	0.4	2
9/15/2021 13:00	36.8	37.7	37.3	0.4	0.6	2
9/15/2021 14:00	36.9	38.0	37.5	0.5	0.7	2
9/15/2021 15:00	36.4	38.1	37.3	0.9	1.2	2
9/15/2021 16:00	36.7	37.7	37.2	0.5	0.8	2
9/15/2021 17:00	37.1	37.7	37.4	0.3	0.4	2
9/15/2021 18:00	37.0	37.2	37.1	0.1	0.2	2

Saline Treatment						
Temperature (°C)						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/15/2021 19:00	36.6	37.7	37.1	0.5	0.8	2
9/15/2021 20:00	36.7	37.3	37.0	0.3	0.4	2
9/15/2021 21:00	36.5	37.3	36.9	0.4	0.6	2
9/15/2021 22:00	36.2	36.8	36.5	0.3	0.4	2
9/15/2021 23:00	36.0	36.8	36.4	0.4	0.6	2
9/16/2021 0:00	36.0	36.3	36.1	0.1	0.2	2
9/16/2021 1:00	36.5	36.9	36.7	0.2	0.3	2
9/16/2021 2:00	36.6	36.2	36.4	0.2	0.3	2
9/16/2021 3:00	36.2	36.5	36.3	0.1	0.2	2
9/16/2021 4:00	35.0	36.1	35.6	0.6	0.8	2
9/16/2021 5:00	NaN	36.2	36.2	0.0	0.0	1
9/16/2021 6:00	NaN	36.4	36.4	0.0	0.0	1
9/16/2021 7:00	NaN	36.5	36.5	0.0	0.0	1
9/16/2021 8:00	NaN	36.6	36.6	0.0	0.0	1
9/16/2021 9:00	NaN	36.3	36.3	0.0	0.0	1
9/16/2021 10:00	NaN	35.9	35.9	0.0	0.0	1
9/16/2021 11:00	NaN	36.0	36.0	0.0	0.0	1
9/16/2021 12:00	NaN	35.7	35.7	0.0	0.0	1
9/16/2021 13:00	NaN	35.9	35.9	0.0	0.0	1
9/16/2021 14:00	NaN	35.7	35.7	0.0	0.0	1
9/16/2021 15:00	NaN	35.8	35.8	0.0	0.0	1
9/16/2021 16:00	NaN	35.5	35.5	0.0	0.0	1
9/16/2021 17:00	NaN	35.5	35.5	0.0	0.0	1
9/16/2021 18:00	NaN	35.8	35.8	0.0	0.0	1
9/16/2021 19:00	NaN	35.6	35.6	0.0	0.0	1
9/16/2021 20:00	NaN	35.2	35.2	0.0	0.0	1

Table 8: Activity Saline Treatment

Saline Treatment						
Activity						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/10/2021 16:00	506.9	679.5	593.2	86.3	122.1	2
9/10/2021 17:00	357.3	608.4	482.8	125.5	177.5	2
9/10/2021 18:00	521.8	566.9	544.3	22.5	31.9	2
9/10/2021 19:00	134.6	178.3	156.5	21.9	30.9	2
9/10/2021 20:00	144.7	201.7	173.2	28.5	40.3	2
9/10/2021 21:00	104.9	169.6	137.2	32.3	45.7	2
9/10/2021 22:00	144.4	166.0	155.2	10.8	15.3	2
9/10/2021 23:00	136.2	187.1	161.6	25.5	36.0	2
9/11/2021 0:00	125.8	167.6	146.7	20.9	29.5	2
9/11/2021 1:00	149.3	212.9	181.1	31.8	45.0	2
9/11/2021 2:00	145.6	214.5	180.0	34.4	48.7	2
9/11/2021 3:00	137.7	180.6	159.1	21.5	30.4	2
9/11/2021 4:00	134.0	204.6	169.3	35.3	49.9	2
9/11/2021 5:00	143.5	199.8	171.6	28.1	39.8	2
9/11/2021 6:00	116.4	206.7	161.5	45.1	63.8	2
9/11/2021 7:00	410.5	442.3	426.4	15.9	22.5	2
9/11/2021 8:00	443.2	798.5	620.8	177.7	251.3	2
9/11/2021 9:00	260.6	647.8	454.2	193.6	273.8	2
9/11/2021 10:00	323.8	488.4	406.1	82.3	116.4	2
9/11/2021 11:00	392.3	810.7	601.5	209.2	295.8	2
9/11/2021 12:00	417.5	478.2	447.9	30.4	42.9	2
9/11/2021 13:00	451.6	592.1	521.8	70.2	99.3	2
9/11/2021 14:00	322.5	383.6	353.0	30.6	43.2	2
9/11/2021 15:00	198.2	608.0	403.1	204.9	289.8	2
9/11/2021 16:00	307.2	588.4	447.8	140.6	198.8	2
9/11/2021 17:00	294.3	569.1	431.7	137.4	194.3	2
9/11/2021 18:00	387.8	585.8	486.8	99.0	140.0	2
9/11/2021 19:00	161.2	235.9	198.6	37.4	52.8	2
9/11/2021 20:00	113.6	171.9	142.8	29.2	41.2	2
9/11/2021 21:00	154.0	215.0	184.5	30.5	43.1	2
9/11/2021 22:00	105.0	160.3	132.6	27.6	39.1	2

Saline Treatment						
Activity						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/11/2021 23:00	172.7	208.2	190.4	17.8	25.2	2
9/12/2021 0:00	158.7	202.6	180.7	22.0	31.1	2
9/12/2021 1:00	151.7	169.8	160.7	9.0	12.8	2
9/12/2021 2:00	102.7	221.3	162.0	59.3	83.9	2
9/12/2021 3:00	182.2	191.0	186.6	4.4	6.2	2
9/12/2021 4:00	130.9	212.8	171.9	41.0	57.9	2
9/12/2021 5:00	144.7	170.9	157.8	13.1	18.5	2
9/12/2021 6:00	121.0	192.3	156.6	35.7	50.5	2
9/12/2021 7:00	696.8	549.0	622.9	73.9	104.5	2
9/12/2021 8:00	571.8	715.5	643.7	71.9	101.7	2
9/12/2021 9:00	267.3	725.9	496.6	229.3	324.3	2
9/12/2021 10:00	473.1	716.2	594.6	121.6	171.9	2
9/12/2021 11:00	335.2	485.7	410.4	75.2	106.4	2
9/12/2021 12:00	190.4	295.1	242.8	52.4	74.0	2
9/12/2021 13:00	494.3	639.9	567.1	72.8	102.9	2
9/12/2021 14:00	251.4	393.6	322.5	71.1	100.5	2
9/12/2021 15:00	885.2	878.2	881.7	3.5	5.0	2
9/12/2021 16:00	549.4	740.0	644.7	95.3	134.7	2
9/12/2021 17:00	417.4	657.0	537.2	119.8	169.4	2
9/12/2021 18:00	445.4	583.6	514.5	69.1	97.7	2
9/12/2021 19:00	158.4	198.9	178.6	20.3	28.7	2
9/12/2021 20:00	164.9	187.4	176.2	11.2	15.9	2
9/12/2021 21:00	106.0	177.1	141.6	35.6	50.3	2
9/12/2021 22:00	187.8	182.2	185.0	2.8	3.9	2
9/12/2021 23:00	285.3	184.4	234.9	50.4	71.3	2
9/13/2021 0:00	177.3	194.5	185.9	8.6	12.2	2
9/13/2021 1:00	105.4	180.0	142.7	37.3	52.8	2
9/13/2021 2:00	112.9	164.4	138.6	25.8	36.5	2
9/13/2021 3:00	116.2	195.7	155.9	39.8	56.2	2
9/13/2021 4:00	155.2	201.9	178.5	23.4	33.0	2
9/13/2021 5:00	115.0	207.5	161.2	46.2	65.4	2
9/13/2021 6:00	170.0	220.5	195.3	25.3	35.8	2

Saline Treatment						
Activity						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/13/2021 7:00	344.2	424.0	384.1	39.9	56.4	2
9/13/2021 8:00	491.6	1033.8	762.7	271.1	383.4	2
9/13/2021 9:00	518.5	1841.5	1180.0	661.5	935.5	2
9/13/2021 10:00	542.9	1922.0	1232.5	689.5	975.1	2
9/13/2021 11:00	401.2	779.4	590.3	189.1	267.4	2
9/13/2021 12:00	321.8	766.7	544.3	222.4	314.6	2
9/13/2021 13:00	309.5	679.2	494.3	184.9	261.5	2
9/13/2021 14:00	486.4	650.3	568.3	82.0	115.9	2
9/13/2021 15:00	526.9	673.9	600.4	73.5	104.0	2
9/13/2021 16:00	523.5	963.3	743.4	219.9	310.9	2
9/13/2021 17:00	399.5	1939.2	1169.4	769.8	1088.7	2
9/13/2021 18:00	514.7	2398.0	1456.4	941.6	1331.7	2
9/13/2021 19:00	623.0	820.3	721.6	98.7	139.5	2
9/13/2021 20:00	94.4	199.0	146.7	52.3	73.9	2
9/13/2021 21:00	152.7	196.8	174.7	22.0	31.1	2
9/13/2021 22:00	119.6	162.8	141.2	21.6	30.5	2
9/13/2021 23:00	135.9	159.3	147.6	11.7	16.5	2
9/14/2021 0:00	151.1	170.3	160.7	9.6	13.5	2
9/14/2021 1:00	99.9	163.1	131.5	31.6	44.7	2
9/14/2021 2:00	124.7	195.2	159.9	35.3	49.9	2
9/14/2021 3:00	174.7	175.9	175.3	0.6	0.8	2
9/14/2021 4:00	151.8	193.0	172.4	20.6	29.1	2
9/14/2021 5:00	94.7	176.9	135.8	41.1	58.1	2
9/14/2021 6:00	133.9	224.2	179.1	45.2	63.9	2
9/14/2021 7:00	517.1	558.8	538.0	20.9	29.5	2
9/14/2021 8:00	504.4	620.1	562.2	57.8	81.8	2
9/14/2021 9:00	478.3	730.5	604.4	126.1	178.3	2
9/14/2021 10:00	445.0	869.5	657.3	212.2	300.2	2
9/14/2021 11:00	571.3	714.6	643.0	71.7	101.3	2
9/14/2021 12:00	393.0	720.4	556.7	163.7	231.5	2
9/14/2021 13:00	416.2	584.3	500.2	84.1	118.9	2
9/14/2021 14:00	514.5	581.2	547.9	33.4	47.2	2

Saline Treatment						
Activity						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/14/2021 15:00	411.1	618.8	514.9	103.8	146.8	2
9/14/2021 16:00	273.3	1019.5	646.4	373.1	527.6	2
9/14/2021 17:00	431.7	1348.4	890.1	458.3	648.2	2
9/14/2021 18:00	420.4	1697.1	1058.7	638.4	902.8	2
9/14/2021 19:00	410.7	236.4	323.6	87.2	123.3	2
9/14/2021 20:00	181.3	343.9	262.6	81.3	115.0	2
9/14/2021 21:00	129.9	167.0	148.5	18.6	26.3	2
9/14/2021 22:00	232.6	594.7	413.6	181.0	256.0	2
9/14/2021 23:00	239.8	491.0	365.4	125.6	177.6	2
9/15/2021 0:00	169.3	238.9	204.1	34.8	49.3	2
9/15/2021 1:00	241.1	439.1	340.1	99.0	140.0	2
9/15/2021 2:00	269.3	415.2	342.3	73.0	103.2	2
9/15/2021 3:00	267.6	625.8	446.7	179.1	253.3	2
9/15/2021 4:00	190.2	328.2	259.2	69.0	97.6	2
9/15/2021 5:00	207.9	329.3	268.6	60.7	85.8	2
9/15/2021 6:00	189.6	277.1	233.4	43.8	61.9	2
9/15/2021 7:00	409.2	497.0	453.1	43.9	62.0	2
9/15/2021 8:00	372.5	471.9	422.2	49.7	70.3	2
9/15/2021 9:00	242.1	537.0	389.6	147.5	208.5	2
9/15/2021 10:00	285.0	626.9	456.0	171.0	241.8	2
9/15/2021 11:00	325.1	594.5	459.8	134.7	190.5	2
9/15/2021 12:00	340.6	611.6	476.1	135.5	191.7	2
9/15/2021 13:00	287.9	923.1	605.5	317.6	449.2	2
9/15/2021 14:00	286.6	795.6	541.1	254.5	359.9	2
9/15/2021 15:00	478.6	867.5	673.0	194.5	275.0	2
9/15/2021 16:00	325.8	600.1	462.9	137.2	194.0	2
9/15/2021 17:00	318.7	591.6	455.1	136.5	193.0	2
9/15/2021 18:00	300.4	755.3	527.8	227.5	321.7	2
9/15/2021 19:00	486.1	637.6	561.9	75.7	107.1	2
9/15/2021 20:00	350.3	624.9	487.6	137.3	194.1	2
9/15/2021 21:00	237.2	335.9	286.5	49.4	69.8	2
9/15/2021 22:00	330.4	374.6	352.5	22.1	31.3	2

Saline Treatment						
Activity						
Date	**G180JD**	**N378ALE**	**Mean**	**SE**	**SD**	**n**
9/15/2021 23:00	305.4	499.9	402.6	97.2	137.5	2
9/16/2021 0:00	231.7	401.4	316.6	84.9	120.0	2
9/16/2021 1:00	281.9	284.7	283.3	1.4	2.0	2
9/16/2021 2:00	323.1	398.5	360.8	37.7	53.3	2
9/16/2021 3:00	261.4	264.6	263.0	1.6	2.3	2
9/16/2021 4:00	198.2	241.5	219.8	21.6	30.6	2
9/16/2021 5:00	NaN	218.3	218.3	0.0	0.0	1
9/16/2021 6:00	NaN	332.2	332.2	0.0	0.0	1
9/16/2021 7:00	NaN	449.5	449.5	0.0	0.0	1
9/16/2021 8:00	NaN	425.5	425.5	0.0	0.0	1
9/16/2021 9:00	NaN	374.0	374.0	0.0	0.0	1
9/16/2021 10:00	NaN	468.2	468.2	0.0	0.0	1
9/16/2021 11:00	NaN	428.5	428.5	0.0	0.0	1
9/16/2021 12:00	NaN	294.7	294.7	0.0	0.0	1
9/16/2021 13:00	NaN	421.8	421.8	0.0	0.0	1
9/16/2021 14:00	NaN	375.5	375.5	0.0	0.0	1
9/16/2021 15:00	NaN	454.9	454.9	0.0	0.0	1
9/16/2021 16:00	NaN	380.9	380.9	0.0	0.0	1
9/16/2021 17:00	NaN	363.6	363.6	0.0	0.0	1
9/16/2021 18:00	NaN	382.5	382.5	0.0	0.0	1
9/16/2021 19:00	NaN	263.8	263.8	0.0	0.0	1
9/16/2021 20:00	NaN	257.9	257.9	0.0	0.0	1

9.1.2 Respiratory Parameters – Saline Treatment

Table 9: Tidal Volume (mL) Saline Treatment

Saline Treatment						
Tidal Volume (mL)						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/10/2021 16:00	107.0	150.0	128.5	21.5	30.4	2
9/10/2021 17:00	110.1	146.5	128.3	18.2	25.8	2
9/10/2021 18:00	122.8	118.1	120.4	2.3	3.3	2
9/10/2021 19:00	76.9	72.1	74.5	2.4	3.4	2
9/10/2021 20:00	79.9	73.7	76.8	3.1	4.4	2
9/10/2021 21:00	72.8	79.6	76.2	3.4	4.8	2
9/10/2021 22:00	65.9	81.5	73.7	7.8	11.0	2
9/10/2021 23:00	65.4	83.9	74.7	9.2	13.1	2
9/11/2021 0:00	66.6	74.6	70.6	4.0	5.7	2
9/11/2021 1:00	74.3	76.3	75.3	1.0	1.4	2
9/11/2021 2:00	74.3	80.9	77.6	3.3	4.7	2
9/11/2021 3:00	67.9	77.5	72.7	4.8	6.8	2
9/11/2021 4:00	74.5	93.0	83.7	9.3	13.1	2
9/11/2021 5:00	84.2	86.3	85.2	1.1	1.5	2
9/11/2021 6:00	79.3	90.6	85.0	5.7	8.0	2
9/11/2021 7:00	118.2	136.8	127.5	9.3	13.2	2
9/11/2021 8:00	115.6	182.9	149.3	33.6	47.6	2
9/11/2021 9:00	99.4	145.5	122.5	23.1	32.6	2
9/11/2021 10:00	96.1	98.9	97.5	1.4	2.0	2
9/11/2021 11:00	111.7	180.9	146.3	34.6	48.9	2
9/11/2021 12:00	130.5	126.7	128.6	1.9	2.7	2
9/11/2021 13:00	128.4	150.1	139.2	10.9	15.4	2
9/11/2021 14:00	115.7	108.1	111.9	3.8	5.4	2
9/11/2021 15:00	85.3	172.5	128.9	43.6	61.7	2
9/11/2021 16:00	115.3	143.0	129.2	13.8	19.5	2
9/11/2021 17:00	103.8	151.0	127.4	23.6	33.3	2
9/11/2021 18:00	127.3	147.6	137.5	10.2	14.4	2
9/11/2021 19:00	82.4	85.7	84.1	1.6	2.3	2
9/11/2021 20:00	54.4	97.4	75.9	21.5	30.5	2
9/11/2021 21:00	87.8	105.8	96.8	9.0	12.7	2

Saline Treatment						
Tidal Volume (mL)						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/11/2021 22:00	75.8	69.5	72.6	3.2	4.5	2
9/11/2021 23:00	82.2	78.9	80.5	1.6	2.3	2
9/12/2021 0:00	82.9	83.7	83.3	0.4	0.6	2
9/12/2021 1:00	81.6	79.5	80.6	1.1	1.5	2
9/12/2021 2:00	69.3	78.7	74.0	4.7	6.6	2
9/12/2021 3:00	83.3	74.3	78.8	4.5	6.4	2
9/12/2021 4:00	77.4	75.7	76.6	0.8	1.2	2
9/12/2021 5:00	81.8	76.7	79.3	2.6	3.6	2
9/12/2021 6:00	69.0	82.0	75.5	6.5	9.2	2
9/12/2021 7:00	138.4	156.5	147.4	9.0	12.7	2
9/12/2021 8:00	132.7	154.8	143.8	11.1	15.7	2
9/12/2021 9:00	92.2	171.5	131.9	39.7	56.1	2
9/12/2021 10:00	109.9	156.4	133.2	23.3	32.9	2
9/12/2021 11:00	90.0	141.6	115.8	25.8	36.5	2
9/12/2021 12:00	71.9	91.2	81.6	9.7	13.7	2
9/12/2021 13:00	124.8	165.1	145.0	20.1	28.5	2
9/12/2021 14:00	95.2	123.8	109.5	14.3	20.3	2
9/12/2021 15:00	145.3	179.0	162.1	16.8	23.8	2
9/12/2021 16:00	127.0	159.6	143.3	16.3	23.0	2
9/12/2021 17:00	114.9	154.3	134.6	19.7	27.8	2
9/12/2021 18:00	117.8	158.3	138.1	20.2	28.6	2
9/12/2021 19:00	86.7	87.2	86.9	0.3	0.4	2
9/12/2021 20:00	75.5	80.6	78.0	2.5	3.6	2
9/12/2021 21:00	63.3	79.1	71.2	7.9	11.2	2
9/12/2021 22:00	119.7	94.9	107.3	12.4	17.6	2
9/12/2021 23:00	125.1	89.8	107.4	17.7	25.0	2
9/13/2021 0:00	82.0	84.7	83.4	1.4	1.9	2
9/13/2021 1:00	74.2	88.4	81.3	7.1	10.1	2
9/13/2021 2:00	69.0	67.7	68.4	0.6	0.9	2
9/13/2021 3:00	81.6	80.1	80.9	0.7	1.0	2
9/13/2021 4:00	79.5	80.7	80.1	0.6	0.8	2
9/13/2021 5:00	73.8	83.9	78.9	5.1	7.2	2

Saline Treatment						
Tidal Volume (mL)						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/13/2021 6:00	82.0	95.2	88.6	6.6	9.3	2
9/13/2021 7:00	105.4	142.2	123.8	18.4	26.0	2
9/13/2021 8:00	115.3	160.0	137.7	22.3	31.6	2
9/13/2021 9:00	102.1	221.5	161.8	59.7	84.5	2
9/13/2021 10:00	113.0	234.4	173.7	60.7	85.9	2
9/13/2021 11:00	107.0	148.7	127.9	20.8	29.4	2
9/13/2021 12:00	95.0	152.0	123.5	28.5	40.3	2
9/13/2021 13:00	96.5	148.3	122.4	25.9	36.7	2
9/13/2021 14:00	129.3	146.0	137.7	8.4	11.9	2
9/13/2021 15:00	127.8	151.0	139.4	11.6	16.4	2
9/13/2021 16:00	133.4	197.5	165.5	32.1	45.3	2
9/13/2021 17:00	120.4	232.8	176.6	56.2	79.5	2
9/13/2021 18:00	135.8	323.3	229.5	93.8	132.6	2
9/13/2021 19:00	158.2	102.3	130.2	28.0	39.5	2
9/13/2021 20:00	75.8	84.5	80.2	4.3	6.1	2
9/13/2021 21:00	77.2	86.7	82.0	4.7	6.7	2
9/13/2021 22:00	64.4	74.1	69.2	4.8	6.8	2
9/13/2021 23:00	82.0	56.5	69.3	12.8	18.1	2
9/14/2021 0:00	77.0	56.8	66.9	10.1	14.3	2
9/14/2021 1:00	67.7	56.2	61.9	5.8	8.1	2
9/14/2021 2:00	75.4	74.3	74.9	0.5	0.8	2
9/14/2021 3:00	82.5	86.8	84.7	2.1	3.0	2
9/14/2021 4:00	80.7	81.3	81.0	0.3	0.5	2
9/14/2021 5:00	71.9	74.8	73.4	1.4	2.0	2
9/14/2021 6:00	73.6	95.7	84.6	11.1	15.6	2
9/14/2021 7:00	132.3	154.9	143.6	11.3	16.0	2
9/14/2021 8:00	129.6	150.8	140.2	10.6	15.0	2
9/14/2021 9:00	127.7	167.1	147.4	19.7	27.8	2
9/14/2021 10:00	121.3	166.1	143.7	22.4	31.6	2
9/14/2021 11:00	128.5	164.2	146.3	17.9	25.3	2
9/14/2021 12:00	106.9	162.0	134.5	27.6	39.0	2
9/14/2021 13:00	110.5	145.0	127.7	17.3	24.5	2

Saline Treatment						
Tidal Volume (mL)						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/14/2021 14:00	123.1	142.8	132.9	9.9	13.9	2
9/14/2021 15:00	101.8	146.5	124.2	22.3	31.6	2
9/14/2021 16:00	89.3	166.3	127.8	38.5	54.5	2
9/14/2021 17:00	113.3	177.9	145.6	32.3	45.6	2
9/14/2021 18:00	105.6	195.3	150.4	44.8	63.4	2
9/14/2021 19:00	99.6	67.6	83.6	16.0	22.6	2
9/14/2021 20:00	71.2	87.8	79.5	8.3	11.8	2
9/14/2021 21:00	45.8	65.7	55.7	9.9	14.1	2
9/14/2021 22:00	62.5	102.4	82.4	19.9	28.2	2
9/14/2021 23:00	60.7	91.7	76.2	15.5	21.9	2
9/15/2021 0:00	47.0	64.2	55.6	8.6	12.2	2
9/15/2021 1:00	53.8	81.8	67.8	14.0	19.8	2
9/15/2021 2:00	70.8	79.7	75.3	4.5	6.3	2
9/15/2021 3:00	58.7	77.9	68.3	9.6	13.6	2
9/15/2021 4:00	54.9	67.5	61.2	6.3	8.9	2
9/15/2021 5:00	66.5	77.4	71.9	5.4	7.7	2
9/15/2021 6:00	64.9	79.6	72.2	7.3	10.4	2
9/15/2021 7:00	100.0	128.1	114.1	14.1	19.9	2
9/15/2021 8:00	89.7	123.2	106.4	16.7	23.7	2
9/15/2021 9:00	84.5	134.2	109.3	24.8	35.1	2
9/15/2021 10:00	74.6	141.6	108.1	33.5	47.3	2
9/15/2021 11:00	80.0	132.0	106.0	26.0	36.7	2
9/15/2021 12:00	75.3	140.9	108.1	32.8	46.3	2
9/15/2021 13:00	70.4	133.1	101.7	31.3	44.3	2
9/15/2021 14:00	66.6	139.8	103.2	36.6	51.7	2
9/15/2021 15:00	72.3	150.2	111.3	39.0	55.1	2
9/15/2021 16:00	65.7	134.0	99.9	34.1	48.3	2
9/15/2021 17:00	56.8	138.6	97.7	40.9	57.8	2
9/15/2021 18:00	48.6	149.2	98.9	50.3	71.1	2
9/15/2021 19:00	74.0	115.1	94.5	20.5	29.1	2
9/15/2021 20:00	60.3	97.5	78.9	18.6	26.3	2
9/15/2021 21:00	39.7	73.1	56.4	16.7	23.6	2

Saline Treatment						
Tidal Volume (mL)						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/15/2021 22:00	50.8	81.9	66.3	15.6	22.0	2
9/15/2021 23:00	54.2	86.7	70.4	16.3	23.0	2
9/16/2021 0:00	45.4	71.6	58.5	13.1	18.5	2
9/16/2021 1:00	57.0	74.3	65.7	8.7	12.3	2
9/16/2021 2:00	52.7	74.5	63.6	10.9	15.4	2
9/16/2021 3:00	51.2	67.2	59.2	8.0	11.4	2
9/16/2021 4:00	43.4	76.7	60.1	16.6	23.5	2
9/16/2021 5:00	NaN	65.7	65.7	0.0	0.0	1
9/16/2021 6:00	NaN	80.5	80.5	0.0	0.0	1
9/16/2021 7:00	NaN	111.5	111.5	0.0	0.0	1
9/16/2021 8:00	NaN	108.4	108.4	0.0	0.0	1
9/16/2021 9:00	NaN	100.1	100.1	0.0	0.0	1
9/16/2021 10:00	NaN	107.9	107.9	0.0	0.0	1
9/16/2021 11:00	NaN	101.7	101.7	0.0	0.0	1
9/16/2021 12:00	NaN	78.6	78.6	0.0	0.0	1
9/16/2021 13:00	NaN	94.9	94.9	0.0	0.0	1
9/16/2021 14:00	NaN	92.3	92.3	0.0	0.0	1
9/16/2021 15:00	NaN	104.4	104.4	0.0	0.0	1
9/16/2021 16:00	NaN	92.3	92.3	0.0	0.0	1
9/16/2021 17:00	NaN	84.1	84.1	0.0	0.0	1
9/16/2021 18:00	NaN	77.9	77.9	0.0	0.0	1
9/16/2021 19:00	NaN	64.7	64.7	0.0	0.0	1
9/16/2021 20:00	NaN	57.9	57.9	0.0	0.0	1

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Table 10: Minute Volume (mL/sec) Saline Treatment

Saline Treatment						
Minute Volume (mL/sec)						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/10/2021 16:00	3279.2	5394.9	4337.1	1057.9	1496.0	2
9/10/2021 17:00	2721.3	5366.5	4043.9	1322.6	1870.4	2
9/10/2021 18:00	3256.5	4430.7	3843.6	587.1	830.3	2
9/10/2021 19:00	2320.8	2495.6	2408.2	87.4	123.6	2
9/10/2021 20:00	2572.1	2550.2	2561.2	11.0	15.5	2
9/10/2021 21:00	2776.4	2694.1	2735.3	41.2	58.2	2
9/10/2021 22:00	2062.4	2771.6	2417.0	354.6	501.5	2
9/10/2021 23:00	2061.6	2805.2	2433.4	371.8	525.8	2
9/11/2021 0:00	2374.9	2489.5	2432.2	57.3	81.0	2
9/11/2021 1:00	2665.9	2696.1	2681.0	15.1	21.4	2
9/11/2021 2:00	2164.9	2901.6	2533.3	368.4	520.9	2
9/11/2021 3:00	2230.3	2517.8	2374.1	143.8	203.3	2
9/11/2021 4:00	2522.4	3149.5	2836.0	313.6	443.4	2
9/11/2021 5:00	2295.6	2984.8	2640.2	344.6	487.3	2
9/11/2021 6:00	2260.6	3190.7	2725.7	465.1	657.7	2
9/11/2021 7:00	2770.6	4055.7	3413.2	642.6	908.7	2
9/11/2021 8:00	2997.6	6290.7	4644.2	1646.6	2328.6	2
9/11/2021 9:00	2285.5	4584.0	3434.8	1149.3	1625.3	2
9/11/2021 10:00	2377.6	3174.5	2776.1	398.5	563.5	2
9/11/2021 11:00	2949.7	5894.5	4422.1	1472.4	2082.3	2
9/11/2021 12:00	3251.2	4014.1	3632.7	381.5	539.5	2
9/11/2021 13:00	3520.4	5228.4	4374.4	854.0	1207.7	2
9/11/2021 14:00	2973.0	3600.8	3286.9	313.9	443.9	2
9/11/2021 15:00	2411.5	5515.5	3963.5	1552.0	2194.9	2
9/11/2021 16:00	2899.8	4868.9	3884.4	984.6	1392.4	2
9/11/2021 17:00	3077.1	5456.7	4266.9	1189.8	1682.6	2
9/11/2021 18:00	3254.0	5204.2	4229.1	975.1	1379.0	2
9/11/2021 19:00	2455.3	3020.0	2737.7	282.4	399.3	2
9/11/2021 20:00	2130.4	3520.9	2825.7	695.3	983.2	2
9/11/2021 21:00	2698.3	4257.4	3477.9	779.6	1102.5	2
9/11/2021 22:00	2405.4	2478.8	2442.1	36.7	51.9	2

Saline Treatment						
Minute Volume (mL/sec)						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/11/2021 23:00	2443.7	2574.5	2509.1	65.4	92.5	2
9/12/2021 0:00	2511.2	2831.2	2671.2	160.0	226.3	2
9/12/2021 1:00	2249.5	2909.1	2579.3	329.8	466.4	2
9/12/2021 2:00	2331.3	2782.3	2556.8	225.5	318.9	2
9/12/2021 3:00	2352.3	2557.2	2454.8	102.5	144.9	2
9/12/2021 4:00	2308.4	2404.2	2356.3	47.9	67.7	2
9/12/2021 5:00	2316.0	2454.4	2385.2	69.2	97.9	2
9/12/2021 6:00	1998.8	2588.2	2293.5	294.7	416.8	2
9/12/2021 7:00	3535.8	4372.6	3954.2	418.4	591.7	2
9/12/2021 8:00	3533.6	5089.7	4311.7	778.1	1100.3	2
9/12/2021 9:00	2052.9	5470.6	3761.8	1708.9	2416.7	2
9/12/2021 10:00	2617.8	5266.8	3942.3	1324.5	1873.1	2
9/12/2021 11:00	2301.9	4476.1	3389.0	1087.1	1537.4	2
9/12/2021 12:00	1835.9	2840.4	2338.2	502.3	710.3	2
9/12/2021 13:00	3277.1	5735.7	4506.4	1229.3	1738.5	2
9/12/2021 14:00	2446.2	4040.6	3243.4	797.2	1127.4	2
9/12/2021 15:00	3878.2	5963.8	4921.0	1042.8	1474.7	2
9/12/2021 16:00	3542.4	5382.3	4462.4	920.0	1301.0	2
9/12/2021 17:00	2963.5	5218.1	4090.8	1127.3	1594.2	2
9/12/2021 18:00	3083.9	5508.2	4296.1	1212.2	1714.2	2
9/12/2021 19:00	2089.7	2977.5	2533.6	443.9	627.8	2
9/12/2021 20:00	2140.4	2607.4	2373.9	233.5	330.2	2
9/12/2021 21:00	1998.6	2538.6	2268.6	270.0	381.8	2
9/12/2021 22:00	4269.0	3237.3	3753.2	515.9	729.5	2
9/12/2021 23:00	4221.7	2814.4	3518.1	703.7	995.1	2
9/13/2021 0:00	1825.2	2584.8	2205.0	379.8	537.1	2
9/13/2021 1:00	1957.7	2944.0	2450.9	493.2	697.4	2
9/13/2021 2:00	2027.5	2136.4	2082.0	54.5	77.0	2
9/13/2021 3:00	2424.3	2392.8	2408.6	15.8	22.3	2
9/13/2021 4:00	2087.6	2375.5	2231.6	144.0	203.6	2
9/13/2021 5:00	1826.9	2590.9	2208.9	382.0	540.2	2
9/13/2021 6:00	1898.7	2999.4	2449.1	550.4	778.3	2

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Saline Treatment						
Minute Volume (mL/sec)						
Date	**G180JD**	**N378ALE**	**Mean**	**SE**	**SD**	**n**
9/13/2021 7:00	2332.2	3867.0	3099.6	767.4	1085.3	2
9/13/2021 8:00	2967.9	5690.4	4329.2	1361.3	1925.1	2
9/13/2021 9:00	2773.3	8425.7	5599.5	2826.2	3996.9	2
9/13/2021 10:00	2920.8	7866.0	5393.4	2472.6	3496.8	2
9/13/2021 11:00	2926.0	5292.8	4109.4	1183.4	1673.6	2
9/13/2021 12:00	2587.9	5181.4	3884.7	1296.8	1833.9	2
9/13/2021 13:00	2428.4	5292.9	3860.7	1432.3	2025.5	2
9/13/2021 14:00	3186.8	5586.7	4386.8	1200.0	1697.0	2
9/13/2021 15:00	3644.2	6030.0	4837.1	1192.9	1687.0	2
9/13/2021 16:00	3710.5	7508.9	5609.7	1899.2	2685.9	2
9/13/2021 17:00	3350.0	9052.3	6201.2	2851.2	4032.1	2
9/13/2021 18:00	3584.1	11028.0	7306.1	3722.0	5263.6	2
9/13/2021 19:00	4565.9	4101.4	4333.7	232.3	328.5	2
9/13/2021 20:00	2205.7	3138.2	2672.0	466.3	659.4	2
9/13/2021 21:00	2227.8	2932.4	2580.1	352.3	498.2	2
9/13/2021 22:00	1964.4	2461.0	2212.7	248.3	351.1	2
9/13/2021 23:00	2235.0	1800.6	2017.8	217.2	307.2	2
9/14/2021 0:00	2280.2	1734.7	2007.5	272.8	385.7	2
9/14/2021 1:00	2255.7	1671.6	1963.7	292.1	413.0	2
9/14/2021 2:00	2253.1	2202.3	2227.7	25.4	35.9	2
9/14/2021 3:00	2315.8	2612.2	2464.0	148.2	209.6	2
9/14/2021 4:00	2170.8	2415.6	2293.2	122.4	173.1	2
9/14/2021 5:00	1734.0	2270.2	2002.1	268.1	379.2	2
9/14/2021 6:00	1659.9	2827.9	2243.9	584.0	825.9	2
9/14/2021 7:00	3007.2	4531.8	3769.5	762.3	1078.1	2
9/14/2021 8:00	3031.7	5014.7	4023.2	991.5	1402.2	2
9/14/2021 9:00	3177.7	5480.5	4329.1	1151.4	1628.3	2
9/14/2021 10:00	2866.7	5711.4	4289.1	1422.4	2011.5	2
9/14/2021 11:00	3314.5	5427.2	4370.9	1056.4	1493.9	2
9/14/2021 12:00	2752.7	5601.1	4176.9	1424.2	2014.1	2
9/14/2021 13:00	2724.4	5274.2	3999.3	1274.9	1803.0	2
9/14/2021 14:00	3319.3	5189.6	4254.5	935.2	1322.5	2

Saline Treatment						
Minute Volume (mL/sec)						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/14/2021 15:00	2943.5	5157.0	4050.3	1106.8	1565.2	2
9/14/2021 16:00	2642.8	6399.4	4521.1	1878.3	2656.3	2
9/14/2021 17:00	3249.5	6481.0	4865.3	1615.8	2285.0	2
9/14/2021 18:00	3156.7	7841.9	5499.3	2342.6	3312.9	2
9/14/2021 19:00	2974.5	2566.2	2770.4	204.2	288.7	2
9/14/2021 20:00	2148.6	3086.7	2617.7	469.1	663.3	2
9/14/2021 21:00	1729.0	2370.8	2049.9	320.9	453.8	2
9/14/2021 22:00	2449.7	3662.6	3056.2	606.5	857.6	2
9/14/2021 23:00	1910.1	3589.8	2750.0	839.9	1187.7	2
9/15/2021 0:00	1729.4	2397.5	2063.5	334.1	472.4	2
9/15/2021 1:00	1724.5	3056.8	2390.7	666.2	942.1	2
9/15/2021 2:00	2216.4	2789.1	2502.8	286.4	405.0	2
9/15/2021 3:00	1866.4	2933.4	2399.9	533.5	754.5	2
9/15/2021 4:00	1721.8	2363.2	2042.5	320.7	453.5	2
9/15/2021 5:00	1839.2	2744.2	2291.7	452.5	639.9	2
9/15/2021 6:00	1734.0	2729.9	2232.0	498.0	704.2	2
9/15/2021 7:00	2724.5	4164.4	3444.5	720.0	1018.2	2
9/15/2021 8:00	2389.0	4218.3	3303.7	914.7	1293.5	2
9/15/2021 9:00	2335.6	4614.3	3475.0	1139.4	1611.3	2
9/15/2021 10:00	2091.0	5587.0	3839.0	1748.0	2472.0	2
9/15/2021 11:00	2381.0	5366.7	3873.9	1492.9	2111.2	2
9/15/2021 12:00	2191.6	5570.2	3880.9	1689.3	2389.0	2
9/15/2021 13:00	2080.3	5837.4	3958.9	1878.6	2656.7	2
9/15/2021 14:00	1911.2	6133.1	4022.2	2111.0	2985.3	2
9/15/2021 15:00	2518.6	6133.7	4326.2	1807.6	2556.3	2
9/15/2021 16:00	2086.1	5376.0	3731.1	1645.0	2326.3	2
9/15/2021 17:00	1951.7	5517.2	3734.5	1782.8	2521.2	2
9/15/2021 18:00	1676.5	5858.9	3767.7	2091.2	2957.4	2
9/15/2021 19:00	2530.4	4899.1	3714.8	1184.4	1674.9	2
9/15/2021 20:00	1952.9	3958.8	2955.9	1003.0	1418.4	2
9/15/2021 21:00	1409.9	3004.5	2207.2	797.3	1127.6	2
9/15/2021 22:00	1659.9	3240.0	2450.0	790.1	1117.3	2

Saline Treatment						
Minute Volume (mL/sec)						
Date	**G180JD**	**N378ALE**	**Mean**	**SE**	**SD**	**n**
9/15/2021 23:00	1745.4	3686.9	2716.2	970.8	1372.8	2
9/16/2021 0:00	1254.2	2977.2	2115.7	861.5	1218.3	2
9/16/2021 1:00	1699.5	3272.8	2486.2	786.7	1112.5	2
9/16/2021 2:00	1709.6	2907.0	2308.3	598.7	846.7	2
9/16/2021 3:00	1286.4	2759.5	2023.0	736.6	1041.6	2
9/16/2021 4:00	1158.7	2969.7	2064.2	905.5	1280.6	2
9/16/2021 5:00	NaN	2560.5	2560.5	0.0	0.0	1
9/16/2021 6:00	NaN	2904.1	2904.1	0.0	0.0	1
9/16/2021 7:00	NaN	4145.1	4145.1	0.0	0.0	1
9/16/2021 8:00	NaN	4041.8	4041.8	0.0	0.0	1
9/16/2021 9:00	NaN	3499.1	3499.1	0.0	0.0	1
9/16/2021 10:00	NaN	3793.4	3793.4	0.0	0.0	1
9/16/2021 11:00	NaN	3525.5	3525.5	0.0	0.0	1
9/16/2021 12:00	NaN	3016.6	3016.6	0.0	0.0	1
9/16/2021 13:00	NaN	3292.6	3292.6	0.0	0.0	1
9/16/2021 14:00	NaN	3255.0	3255.0	0.0	0.0	1
9/16/2021 15:00	NaN	3349.2	3349.2	0.0	0.0	1
9/16/2021 16:00	NaN	2907.9	2907.9	0.0	0.0	1
9/16/2021 17:00	NaN	2738.8	2738.8	0.0	0.0	1
9/16/2021 18:00	NaN	2542.5	2542.5	0.0	0.0	1
9/16/2021 19:00	NaN	2106.0	2106.0	0.0	0.0	1
9/16/2021 20:00	NaN	1883.4	1883.4	0.0	0.0	1

Table 11: Respiration Rate (bpm) Saline Treatment

Saline Treatment						
Respiration Rate (bpm)						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/10/2021 16:00	30.7	36.0	33.3	2.7	3.8	2
9/10/2021 17:00	24.7	36.6	30.7	6.0	8.4	2
9/10/2021 18:00	26.5	37.5	32.0	5.5	7.8	2
9/10/2021 19:00	30.2	34.6	32.4	2.2	3.1	2
9/10/2021 20:00	32.2	34.6	33.4	1.2	1.7	2
9/10/2021 21:00	38.1	33.8	36.0	2.1	3.0	2
9/10/2021 22:00	31.3	34.0	32.6	1.4	1.9	2
9/10/2021 23:00	31.5	33.4	32.5	1.0	1.4	2
9/11/2021 0:00	35.7	33.4	34.5	1.2	1.6	2
9/11/2021 1:00	35.9	35.4	35.6	0.3	0.4	2
9/11/2021 2:00	29.1	35.8	32.5	3.4	4.8	2
9/11/2021 3:00	32.9	32.5	32.7	0.2	0.3	2
9/11/2021 4:00	33.9	33.9	33.9	0.0	0.0	2
9/11/2021 5:00	27.3	34.6	30.9	3.7	5.2	2
9/11/2021 6:00	28.5	35.2	31.9	3.4	4.7	2
9/11/2021 7:00	23.4	29.7	26.5	3.1	4.4	2
9/11/2021 8:00	25.9	34.4	30.2	4.2	6.0	2
9/11/2021 9:00	23.0	31.5	27.2	4.3	6.0	2
9/11/2021 10:00	24.7	32.1	28.4	3.7	5.2	2
9/11/2021 11:00	26.4	32.6	29.5	3.1	4.4	2
9/11/2021 12:00	24.9	31.7	28.3	3.4	4.8	2
9/11/2021 13:00	27.4	34.8	31.1	3.7	5.2	2
9/11/2021 14:00	25.7	33.3	29.5	3.8	5.4	2
9/11/2021 15:00	28.3	32.0	30.1	1.8	2.6	2
9/11/2021 16:00	25.1	34.1	29.6	4.5	6.3	2
9/11/2021 17:00	29.6	36.1	32.9	3.3	4.6	2
9/11/2021 18:00	25.6	35.3	30.4	4.8	6.9	2
9/11/2021 19:00	29.8	35.2	32.5	2.7	3.9	2
9/11/2021 20:00	39.2	36.1	37.7	1.5	2.2	2
9/11/2021 21:00	30.7	40.2	35.5	4.8	6.7	2
9/11/2021 22:00	31.7	35.7	33.7	2.0	2.8	2

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Saline Treatment						
Respiration Rate (bpm)						
Date	**G180JD**	**N378ALE**	**Mean**	**SE**	**SD**	**n**
9/11/2021 23:00	29.7	32.6	31.2	1.5	2.1	2
9/12/2021 0:00	30.3	33.8	32.0	1.8	2.5	2
9/12/2021 1:00	27.6	36.6	32.1	4.5	6.4	2
9/12/2021 2:00	33.6	35.3	34.5	0.9	1.2	2
9/12/2021 3:00	28.2	34.4	31.3	3.1	4.4	2
9/12/2021 4:00	29.8	31.7	30.8	1.0	1.4	2
9/12/2021 5:00	28.3	32.0	30.2	1.8	2.6	2
9/12/2021 6:00	29.0	31.6	30.3	1.3	1.8	2
9/12/2021 7:00	25.5	27.9	26.7	1.2	1.7	2
9/12/2021 8:00	26.6	32.9	29.8	3.1	4.4	2
9/12/2021 9:00	22.3	31.9	27.1	4.8	6.8	2
9/12/2021 10:00	23.8	33.7	28.7	4.9	7.0	2
9/12/2021 11:00	25.6	31.6	28.6	3.0	4.3	2
9/12/2021 12:00	25.5	31.1	28.3	2.8	4.0	2
9/12/2021 13:00	26.3	34.7	30.5	4.2	6.0	2
9/12/2021 14:00	25.7	32.6	29.2	3.5	4.9	2
9/12/2021 15:00	26.7	33.3	30.0	3.3	4.7	2
9/12/2021 16:00	27.9	33.7	30.8	2.9	4.1	2
9/12/2021 17:00	25.8	33.8	29.8	4.0	5.7	2
9/12/2021 18:00	26.2	34.8	30.5	4.3	6.1	2
9/12/2021 19:00	24.1	34.1	29.1	5.0	7.1	2
9/12/2021 20:00	28.3	32.4	30.4	2.0	2.8	2
9/12/2021 21:00	31.6	32.1	31.8	0.3	0.4	2
9/12/2021 22:00	35.7	34.1	34.9	0.8	1.1	2
9/12/2021 23:00	33.7	31.3	32.5	1.2	1.7	2
9/13/2021 0:00	22.3	30.5	26.4	4.1	5.8	2
9/13/2021 1:00	26.4	33.3	29.8	3.4	4.9	2
9/13/2021 2:00	29.4	31.5	30.5	1.1	1.5	2
9/13/2021 3:00	29.7	29.9	29.8	0.1	0.1	2
9/13/2021 4:00	26.3	29.5	27.9	1.6	2.3	2
9/13/2021 5:00	24.8	30.9	27.8	3.1	4.3	2
9/13/2021 6:00	23.2	31.5	27.3	4.2	5.9	2

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Saline Treatment						
Respiration Rate (bpm)						
Date	**G180JD**	**N378ALE**	**Mean**	**SE**	**SD**	**n**
9/13/2021 7:00	22.1	27.2	24.7	2.5	3.6	2
9/13/2021 8:00	25.7	35.6	30.7	4.9	7.0	2
9/13/2021 9:00	27.2	38.0	32.6	5.4	7.7	2
9/13/2021 10:00	25.9	33.6	29.7	3.8	5.4	2
9/13/2021 11:00	27.3	35.6	31.5	4.1	5.8	2
9/13/2021 12:00	27.2	34.1	30.7	3.4	4.8	2
9/13/2021 13:00	25.2	35.7	30.4	5.3	7.4	2
9/13/2021 14:00	24.7	38.3	31.5	6.8	9.6	2
9/13/2021 15:00	28.5	39.9	34.2	5.7	8.1	2
9/13/2021 16:00	27.8	38.0	32.9	5.1	7.2	2
9/13/2021 17:00	27.8	38.9	33.4	5.5	7.8	2
9/13/2021 18:00	26.4	34.1	30.3	3.9	5.5	2
9/13/2021 19:00	28.9	40.1	34.5	5.6	8.0	2
9/13/2021 20:00	29.1	37.1	33.1	4.0	5.7	2
9/13/2021 21:00	28.9	33.8	31.3	2.5	3.5	2
9/13/2021 22:00	30.5	33.2	31.9	1.4	1.9	2
9/13/2021 23:00	27.2	31.9	29.6	2.3	3.3	2
9/14/2021 0:00	29.6	30.6	30.1	0.5	0.7	2
9/14/2021 1:00	33.3	29.8	31.6	1.8	2.5	2
9/14/2021 2:00	29.9	29.6	29.8	0.1	0.2	2
9/14/2021 3:00	28.1	30.1	29.1	1.0	1.4	2
9/14/2021 4:00	26.9	29.7	28.3	1.4	2.0	2
9/14/2021 5:00	24.1	30.4	27.2	3.1	4.4	2
9/14/2021 6:00	22.6	29.6	26.1	3.5	4.9	2
9/14/2021 7:00	22.7	29.3	26.0	3.3	4.6	2
9/14/2021 8:00	23.4	33.3	28.3	4.9	7.0	2
9/14/2021 9:00	24.9	32.8	28.8	4.0	5.6	2
9/14/2021 10:00	23.6	34.4	29.0	5.4	7.6	2
9/14/2021 11:00	25.8	33.1	29.4	3.6	5.1	2
9/14/2021 12:00	25.7	34.6	30.2	4.4	6.2	2
9/14/2021 13:00	24.7	36.4	30.5	5.8	8.3	2
9/14/2021 14:00	27.0	36.3	31.7	4.7	6.6	2

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Saline Treatment						
Respiration Rate (bpm)						
Date	**G180JD**	**N378ALE**	**Mean**	**SE**	**SD**	**n**
9/14/2021 15:00	28.9	35.2	32.1	3.1	4.5	2
9/14/2021 16:00	29.6	38.5	34.0	4.4	6.3	2
9/14/2021 17:00	28.7	36.4	32.6	3.9	5.5	2
9/14/2021 18:00	29.9	40.2	35.0	5.1	7.3	2
9/14/2021 19:00	29.9	38.0	33.9	4.1	5.7	2
9/14/2021 20:00	30.2	35.1	32.7	2.5	3.5	2
9/14/2021 21:00	37.8	36.1	36.9	0.8	1.2	2
9/14/2021 22:00	39.2	35.8	37.5	1.7	2.4	2
9/14/2021 23:00	31.4	39.1	35.3	3.8	5.4	2
9/15/2021 0:00	36.8	37.3	37.1	0.3	0.4	2
9/15/2021 1:00	32.0	37.4	34.7	2.7	3.8	2
9/15/2021 2:00	31.3	35.0	33.1	1.8	2.6	2
9/15/2021 3:00	31.8	37.6	34.7	2.9	4.1	2
9/15/2021 4:00	31.3	35.0	33.2	1.8	2.6	2
9/15/2021 5:00	27.7	35.5	31.6	3.9	5.5	2
9/15/2021 6:00	26.7	34.3	30.5	3.8	5.4	2
9/15/2021 7:00	27.2	32.5	29.9	2.6	3.7	2
9/15/2021 8:00	26.6	34.3	30.4	3.8	5.4	2
9/15/2021 9:00	27.6	34.4	31.0	3.4	4.8	2
9/15/2021 10:00	28.0	39.5	33.7	5.7	8.1	2
9/15/2021 11:00	29.8	40.7	35.2	5.5	7.7	2
9/15/2021 12:00	29.1	39.5	34.3	5.2	7.4	2
9/15/2021 13:00	29.5	43.9	36.7	7.2	10.1	2
9/15/2021 14:00	28.7	43.9	36.3	7.6	10.8	2
9/15/2021 15:00	34.8	40.8	37.8	3.0	4.2	2
9/15/2021 16:00	31.7	40.1	35.9	4.2	5.9	2
9/15/2021 17:00	34.3	39.8	37.1	2.7	3.9	2
9/15/2021 18:00	34.5	39.3	36.9	2.4	3.4	2
9/15/2021 19:00	34.2	42.6	38.4	4.2	5.9	2
9/15/2021 20:00	32.4	40.6	36.5	4.1	5.8	2
9/15/2021 21:00	35.5	41.1	38.3	2.8	3.9	2
9/15/2021 22:00	32.7	39.6	36.1	3.4	4.9	2

Saline Treatment						
Respiration Rate (bpm)						
Date	**G180JD**	**N378ALE**	**Mean**	**SE**	**SD**	**n**
9/15/2021 23:00	32.2	42.5	37.4	5.1	7.3	2
9/16/2021 0:00	27.6	41.6	34.6	7.0	9.9	2
9/16/2021 1:00	29.8	44.0	36.9	7.1	10.1	2
9/16/2021 2:00	32.5	39.0	35.7	3.3	4.6	2
9/16/2021 3:00	25.1	41.1	33.1	8.0	11.2	2
9/16/2021 4:00	26.7	38.7	32.7	6.0	8.5	2
9/16/2021 5:00	NaN	39.0	39.0	0.0	0.0	1
9/16/2021 6:00	NaN	36.1	36.1	0.0	0.0	1
9/16/2021 7:00	NaN	37.2	37.2	0.0	0.0	1
9/16/2021 8:00	NaN	37.3	37.3	0.0	0.0	1
9/16/2021 9:00	NaN	34.9	34.9	0.0	0.0	1
9/16/2021 10:00	NaN	35.2	35.2	0.0	0.0	1
9/16/2021 11:00	NaN	34.7	34.7	0.0	0.0	1
9/16/2021 12:00	NaN	38.4	38.4	0.0	0.0	1
9/16/2021 13:00	NaN	34.7	34.7	0.0	0.0	1
9/16/2021 14:00	NaN	35.3	35.3	0.0	0.0	1
9/16/2021 15:00	NaN	32.1	32.1	0.0	0.0	1
9/16/2021 16:00	NaN	31.5	31.5	0.0	0.0	1
9/16/2021 17:00	NaN	32.6	32.6	0.0	0.0	1
9/16/2021 18:00	NaN	32.6	32.6	0.0	0.0	1
9/16/2021 19:00	NaN	32.5	32.5	0.0	0.0	1
9/16/2021 20:00	NaN	32.5	32.5	0.0	0.0	1

9.1.3 ECG Parameters – Saline Treatment

Table 12: Heart Rate (bpm) Saline Treatment

Saline Treatment						
Heart Rate (bpm)						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/10/2021 16:00	199.4	110.7	155.0	44.3	62.7	2
9/10/2021 17:00	173.9	113.8	143.8	30.0	42.4	2
9/10/2021 18:00	171.5	103.6	137.5	33.9	48.0	2
9/10/2021 19:00	143.9	94.4	119.2	24.8	35.0	2
9/10/2021 20:00	150.1	87.9	119.0	31.1	43.9	2
9/10/2021 21:00	152.8	90.4	121.6	31.2	44.1	2
9/10/2021 22:00	157.0	89.9	123.4	33.6	47.4	2
9/10/2021 23:00	154.4	92.9	123.6	30.8	43.5	2
9/11/2021 0:00	157.6	89.9	123.8	33.8	47.9	2
9/11/2021 1:00	166.4	90.9	128.7	37.7	53.4	2
9/11/2021 2:00	159.4	85.5	122.5	37.0	52.3	2
9/11/2021 3:00	163.4	86.2	124.8	38.6	54.6	2
9/11/2021 4:00	163.1	86.4	124.7	38.4	54.3	2
9/11/2021 5:00	164.8	84.4	124.6	40.2	56.8	2
9/11/2021 6:00	156.4	85.9	121.1	35.2	49.8	2
9/11/2021 7:00	183.8	97.7	140.8	43.1	60.9	2
9/11/2021 8:00	181.9	107.6	144.8	37.2	52.6	2
9/11/2021 9:00	164.0	105.3	134.7	29.4	41.5	2
9/11/2021 10:00	161.3	85.9	123.6	37.7	53.3	2
9/11/2021 11:00	173.0	105.5	139.3	33.7	47.7	2
9/11/2021 12:00	166.5	93.6	130.0	36.4	51.5	2
9/11/2021 13:00	185.0	116.8	150.9	34.1	48.2	2
9/11/2021 14:00	169.8	95.2	132.5	37.3	52.8	2
9/11/2021 15:00	160.2	109.3	134.7	25.5	36.0	2
9/11/2021 16:00	171.8	103.9	137.8	34.0	48.1	2
9/11/2021 17:00	173.2	114.8	144.0	29.2	41.3	2
9/11/2021 18:00	172.3	110.8	141.5	30.8	43.5	2
9/11/2021 19:00	157.3	98.8	128.1	29.3	41.4	2
9/11/2021 20:00	153.6	90.1	121.9	31.8	44.9	2
9/11/2021 21:00	164.1	94.5	129.3	34.8	49.2	2

Saline Treatment						
Heart Rate (bpm)						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/11/2021 22:00	156.7	88.3	122.5	34.2	48.4	2
9/11/2021 23:00	164.4	89.9	127.1	37.2	52.6	2
9/12/2021 0:00	163.5	84.4	123.9	39.5	55.9	2
9/12/2021 1:00	153.4	82.7	118.0	35.4	50.0	2
9/12/2021 2:00	158.5	82.6	120.6	38.0	53.7	2
9/12/2021 3:00	161.1	81.8	121.5	39.6	56.1	2
9/12/2021 4:00	155.6	82.7	119.1	36.4	51.5	2
9/12/2021 5:00	154.5	79.8	117.1	37.4	52.8	2
9/12/2021 6:00	149.2	85.9	117.6	31.6	44.7	2
9/12/2021 7:00	182.0	105.5	143.7	38.2	54.1	2
9/12/2021 8:00	184.9	105.1	145.0	39.9	56.4	2
9/12/2021 9:00	170.4	103.5	136.9	33.4	47.3	2
9/12/2021 10:00	172.8	99.8	136.3	36.5	51.7	2
9/12/2021 11:00	156.7	95.0	125.8	30.8	43.6	2
9/12/2021 12:00	150.0	82.5	116.3	33.7	47.7	2
9/12/2021 13:00	179.8	111.6	145.7	34.1	48.2	2
9/12/2021 14:00	159.0	96.8	127.9	31.1	44.0	2
9/12/2021 15:00	181.6	107.7	144.7	36.9	52.2	2
9/12/2021 16:00	175.9	105.7	140.8	35.1	49.6	2
9/12/2021 17:00	168.8	98.6	133.7	35.1	49.6	2
9/12/2021 18:00	165.2	102.7	134.0	31.3	44.2	2
9/12/2021 19:00	142.2	82.7	112.4	29.7	42.0	2
9/12/2021 20:00	142.2	78.0	110.1	32.1	45.5	2
9/12/2021 21:00	134.3	76.6	105.4	28.9	40.8	2
9/12/2021 22:00	152.1	78.8	115.4	36.6	51.8	2
9/12/2021 23:00	156.3	77.4	116.8	39.4	55.8	2
9/13/2021 0:00	147.3	73.4	110.4	37.0	52.3	2
9/13/2021 1:00	132.5	76.1	104.3	28.2	39.9	2
9/13/2021 2:00	138.1	74.3	106.2	31.9	45.1	2
9/13/2021 3:00	142.7	74.8	108.8	34.0	48.0	2
9/13/2021 4:00	145.4	76.0	110.7	34.7	49.1	2
9/13/2021 5:00	143.0	77.8	110.4	32.6	46.1	2

Battelle		Status:	Final
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Saline Treatment						
Heart Rate (bpm)						
Date	**G180JD**	**N378ALE**	**Mean**	**SE**	**SD**	**n**
9/13/2021 6:00	147.0	80.4	113.7	33.3	47.1	2
9/13/2021 7:00	158.7	93.2	125.9	32.7	46.3	2
9/13/2021 8:00	189.3	115.3	152.3	37.0	52.3	2
9/13/2021 9:00	208.0	190.0	199.0	9.0	12.7	2
9/13/2021 10:00	186.7	148.4	167.5	19.2	27.1	2
9/13/2021 11:00	197.1	108.7	152.9	44.2	62.5	2
9/13/2021 12:00	179.5	103.9	141.7	37.8	53.4	2
9/13/2021 13:00	169.8	101.1	135.4	34.4	48.6	2
9/13/2021 14:00	195.5	119.1	157.3	38.2	54.0	2
9/13/2021 15:00	189.5	131.9	160.7	28.8	40.7	2
9/13/2021 16:00	168.7	121.1	144.9	23.8	33.7	2
9/13/2021 17:00	168.6	133.2	150.9	17.7	25.1	2
9/13/2021 18:00	167.7	146.8	157.3	10.4	14.8	2
9/13/2021 19:00	182.7	113.5	148.1	34.6	48.9	2
9/13/2021 20:00	146.6	103.7	125.1	21.5	30.3	2
9/13/2021 21:00	157.4	97.6	127.5	29.9	42.3	2
9/13/2021 22:00	153.2	88.8	121.0	32.2	45.5	2
9/13/2021 23:00	165.0	84.0	124.5	40.5	57.3	2
9/14/2021 0:00	168.0	82.8	125.4	42.6	60.2	2
9/14/2021 1:00	159.1	80.2	119.6	39.4	55.8	2
9/14/2021 2:00	156.9	85.3	121.1	35.8	50.6	2
9/14/2021 3:00	155.5	83.2	119.4	36.1	51.1	2
9/14/2021 4:00	153.2	82.8	118.0	35.2	49.8	2
9/14/2021 5:00	142.4	85.8	114.1	28.3	40.1	2
9/14/2021 6:00	145.9	90.2	118.0	27.8	39.3	2
9/14/2021 7:00	167.6	108.2	137.9	29.7	42.0	2
9/14/2021 8:00	176.7	110.2	143.4	33.2	47.0	2
9/14/2021 9:00	172.0	120.1	146.0	25.9	36.7	2
9/14/2021 10:00	159.8	107.0	133.4	26.4	37.3	2
9/14/2021 11:00	167.5	111.0	139.2	28.2	39.9	2
9/14/2021 12:00	157.6	104.2	130.9	26.7	37.8	2
9/14/2021 13:00	172.7	114.8	143.7	29.0	41.0	2

Battelle		Status:	Final
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Saline Treatment						
Heart Rate (bpm)						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/14/2021 14:00	181.8	111.7	146.7	35.0	49.5	2
9/14/2021 15:00	174.0	119.0	146.5	27.5	38.9	2
9/14/2021 16:00	172.2	115.9	144.1	28.2	39.8	2
9/14/2021 17:00	176.3	126.3	151.3	25.0	35.3	2
9/14/2021 18:00	177.1	134.5	155.8	21.3	30.1	2
9/14/2021 19:00	172.3	102.0	137.1	35.1	49.7	2
9/14/2021 20:00	162.3	100.1	131.2	31.1	44.0	2
9/14/2021 21:00	164.7	93.0	128.9	35.9	50.7	2
9/14/2021 22:00	171.5	102.0	136.8	34.8	49.2	2
9/14/2021 23:00	186.0	114.5	150.3	35.8	50.6	2
9/15/2021 0:00	171.1	97.5	134.3	36.8	52.0	2
9/15/2021 1:00	183.6	93.8	138.7	44.9	63.5	2
9/15/2021 2:00	185.1	87.3	136.2	48.9	69.2	2
9/15/2021 3:00	186.3	103.8	145.1	41.2	58.3	2
9/15/2021 4:00	166.8	90.0	128.4	38.4	54.3	2
9/15/2021 5:00	166.8	98.5	132.7	34.1	48.3	2
9/15/2021 6:00	162.7	94.6	128.6	34.0	48.2	2
9/15/2021 7:00	184.5	114.9	149.7	34.8	49.2	2
9/15/2021 8:00	180.6	107.5	144.1	36.6	51.7	2
9/15/2021 9:00	171.1	111.7	141.4	29.7	42.0	2
9/15/2021 10:00	176.8	113.4	145.1	31.7	44.9	2
9/15/2021 11:00	182.4	132.1	157.2	25.1	35.6	2
9/15/2021 12:00	174.0	120.2	147.1	26.9	38.0	2
9/15/2021 13:00	177.8	159.8	168.8	9.0	12.7	2
9/15/2021 14:00	189.2	163.9	176.5	12.7	17.9	2
9/15/2021 15:00	208.9	158.6	183.8	25.1	35.5	2
9/15/2021 16:00	194.0	147.0	170.5	23.5	33.2	2
9/15/2021 17:00	206.9	144.9	175.9	31.0	43.9	2
9/15/2021 18:00	194.6	152.0	173.3	21.3	30.1	2
9/15/2021 19:00	209.5	148.0	178.7	30.8	43.5	2
9/15/2021 20:00	205.6	130.9	168.2	37.3	52.8	2
9/15/2021 21:00	196.3	133.2	164.8	31.6	44.6	2

Saline Treatment						
Heart Rate (bpm)						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/15/2021 22:00	199.1	136.8	168.0	31.2	44.1	2
9/15/2021 23:00	205.5	135.1	170.3	35.2	49.7	2
9/16/2021 0:00	194.1	131.5	162.8	31.3	44.3	2
9/16/2021 1:00	205.0	145.8	175.4	29.6	41.8	2
9/16/2021 2:00	201.5	124.1	162.8	38.7	54.7	2
9/16/2021 3:00	203.8	139.0	171.4	32.4	45.8	2
9/16/2021 4:00	191.1	133.0	162.1	29.1	41.1	2
9/16/2021 5:00	NaN	135.2	135.2	0.0	0.0	1
9/16/2021 6:00	NaN	138.6	138.6	0.0	0.0	1
9/16/2021 7:00	NaN	176.3	176.3	0.0	0.0	1
9/16/2021 8:00	NaN	177.7	177.7	0.0	0.0	1
9/16/2021 9:00	NaN	173.5	173.5	0.0	0.0	1
9/16/2021 10:00	NaN	169.7	169.7	0.0	0.0	1
9/16/2021 11:00	NaN	176.2	176.2	0.0	0.0	1
9/16/2021 12:00	NaN	164.1	164.1	0.0	0.0	1
9/16/2021 13:00	NaN	180.5	180.5	0.0	0.0	1
9/16/2021 14:00	NaN	173.7	173.7	0.0	0.0	1
9/16/2021 15:00	NaN	190.5	190.5	0.0	0.0	1
9/16/2021 16:00	NaN	177.2	177.2	0.0	0.0	1
9/16/2021 17:00	NaN	175.9	175.9	0.0	0.0	1
9/16/2021 18:00	NaN	172.5	172.5	0.0	0.0	1
9/16/2021 19:00	NaN	162.1	162.1	0.0	0.0	1
9/16/2021 20:00	NaN	142.9	142.9	0.0	0.0	1

Table 13: PR Interval (msec) Saline Treatment

Saline Treatment						
PR Interval (msec)						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/10/2021 16:00	64.3	102.6	83.5	19.2	27.1	2
9/10/2021 17:00	69.6	104.3	87.0	17.4	24.5	2
9/10/2021 18:00	69.2	103.1	86.1	17.0	24.0	2
9/10/2021 19:00	73.3	104.3	88.8	15.5	21.9	2
9/10/2021 20:00	71.5	106.4	88.9	17.4	24.6	2
9/10/2021 21:00	70.3	105.9	88.1	17.8	25.1	2
9/10/2021 22:00	69.0	108.2	88.6	19.6	27.7	2
9/10/2021 23:00	71.1	109.4	90.2	19.1	27.0	2
9/11/2021 0:00	70.3	106.5	88.4	18.1	25.6	2
9/11/2021 1:00	68.1	108.0	88.1	19.9	28.2	2
9/11/2021 2:00	70.0	106.8	88.4	18.4	26.1	2
9/11/2021 3:00	70.3	107.7	89.0	18.7	26.4	2
9/11/2021 4:00	70.1	108.7	89.4	19.3	27.3	2
9/11/2021 5:00	69.3	106.0	87.7	18.3	25.9	2
9/11/2021 6:00	70.9	106.4	88.6	17.8	25.1	2
9/11/2021 7:00	65.2	104.6	84.9	19.7	27.9	2
9/11/2021 8:00	65.7	106.3	86.0	20.3	28.7	2
9/11/2021 9:00	68.9	105.0	86.9	18.0	25.5	2
9/11/2021 10:00	72.2	105.6	88.9	16.7	23.6	2
9/11/2021 11:00	68.3	105.1	86.7	18.4	26.0	2
9/11/2021 12:00	69.4	104.5	86.9	17.5	24.8	2
9/11/2021 13:00	65.1	105.4	85.3	20.1	28.5	2
9/11/2021 14:00	67.0	104.9	86.0	19.0	26.8	2
9/11/2021 15:00	67.7	107.0	87.3	19.7	27.8	2
9/11/2021 16:00	65.8	107.6	86.7	20.9	29.5	2
9/11/2021 17:00	65.5	107.3	86.4	20.9	29.6	2
9/11/2021 18:00	65.8	108.8	87.3	21.5	30.4	2
9/11/2021 19:00	67.4	110.3	88.8	21.4	30.3	2
9/11/2021 20:00	67.1	107.6	87.4	20.3	28.7	2
9/11/2021 21:00	66.6	109.0	87.8	21.2	30.0	2
9/11/2021 22:00	68.0	107.6	87.8	19.8	28.0	2

Saline Treatment						
PR Interval (msec)						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/11/2021 23:00	66.7	109.6	88.1	21.5	30.3	2
9/12/2021 0:00	66.8	110.5	88.6	21.8	30.9	2
9/12/2021 1:00	69.3	108.9	89.1	19.8	28.0	2
9/12/2021 2:00	67.3	110.4	88.9	21.5	30.5	2
9/12/2021 3:00	68.0	109.4	88.7	20.7	29.3	2
9/12/2021 4:00	69.7	106.8	88.2	18.5	26.2	2
9/12/2021 5:00	68.4	108.5	88.5	20.0	28.3	2
9/12/2021 6:00	69.6	107.3	88.4	18.9	26.7	2
9/12/2021 7:00	65.6	103.4	84.5	18.9	26.7	2
9/12/2021 8:00	66.3	106.4	86.3	20.1	28.4	2
9/12/2021 9:00	68.6	107.3	87.9	19.4	27.4	2
9/12/2021 10:00	68.9	107.3	88.1	19.2	27.2	2
9/12/2021 11:00	71.7	107.1	89.4	17.7	25.1	2
9/12/2021 12:00	73.2	105.3	89.2	16.1	22.7	2
9/12/2021 13:00	67.5	108.5	88.0	20.5	29.0	2
9/12/2021 14:00	70.5	111.6	91.1	20.5	29.0	2
9/12/2021 15:00	67.8	111.3	89.5	21.8	30.8	2
9/12/2021 16:00	69.5	109.5	89.5	20.0	28.3	2
9/12/2021 17:00	70.5	107.5	89.0	18.5	26.1	2
9/12/2021 18:00	69.8	107.2	88.5	18.7	26.5	2
9/12/2021 19:00	71.2	106.7	89.0	17.7	25.1	2
9/12/2021 20:00	71.6	106.7	89.2	17.5	24.8	2
9/12/2021 21:00	70.2	105.4	87.8	17.6	24.9	2
9/12/2021 22:00	70.4	108.8	89.6	19.2	27.1	2
9/12/2021 23:00	68.9	105.9	87.4	18.5	26.1	2
9/13/2021 0:00	69.4	106.5	87.9	18.5	26.2	2
9/13/2021 1:00	72.5	106.3	89.4	16.9	23.9	2
9/13/2021 2:00	71.9	104.7	88.3	16.4	23.2	2
9/13/2021 3:00	71.1	105.3	88.2	17.1	24.2	2
9/13/2021 4:00	72.5	103.6	88.0	15.5	22.0	2
9/13/2021 5:00	71.3	102.8	87.1	15.7	22.3	2
9/13/2021 6:00	70.1	99.7	84.9	14.8	20.9	2

Saline Treatment						
PR Interval (msec)						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/13/2021 7:00	67.5	100.9	84.2	16.7	23.6	2
9/13/2021 8:00	63.6	100.1	81.9	18.2	25.8	2
9/13/2021 9:00	61.8	86.9	74.3	12.6	17.8	2
9/13/2021 10:00	65.8	88.4	77.1	11.3	16.0	2
9/13/2021 11:00	66.2	102.1	84.2	17.9	25.4	2
9/13/2021 12:00	68.2	103.2	85.7	17.5	24.7	2
9/13/2021 13:00	67.9	102.9	85.4	17.5	24.8	2
9/13/2021 14:00	63.1	101.6	82.4	19.2	27.2	2
9/13/2021 15:00	65.5	102.4	84.0	18.5	26.1	2
9/13/2021 16:00	68.1	101.1	84.6	16.5	23.4	2
9/13/2021 17:00	66.9	94.8	80.9	14.0	19.7	2
9/13/2021 18:00	67.3	90.8	79.1	11.7	16.6	2
9/13/2021 19:00	63.0	100.9	82.0	19.0	26.8	2
9/13/2021 20:00	69.7	103.0	86.3	16.7	23.6	2
9/13/2021 21:00	69.1	105.6	87.3	18.3	25.8	2
9/13/2021 22:00	70.3	108.1	89.2	18.9	26.7	2
9/13/2021 23:00	69.6	106.7	88.1	18.5	26.2	2
9/14/2021 0:00	69.1	103.9	86.5	17.4	24.6	2
9/14/2021 1:00	69.7	104.5	87.1	17.4	24.6	2
9/14/2021 2:00	68.7	103.3	86.0	17.3	24.4	2
9/14/2021 3:00	68.1	103.6	85.9	17.7	25.1	2
9/14/2021 4:00	69.7	100.8	85.3	15.5	22.0	2
9/14/2021 5:00	69.3	100.2	84.8	15.4	21.8	2
9/14/2021 6:00	69.9	98.0	83.9	14.0	19.8	2
9/14/2021 7:00	68.5	99.2	83.9	15.4	21.7	2
9/14/2021 8:00	67.5	99.5	83.5	16.0	22.6	2
9/14/2021 9:00	67.6	99.5	83.6	16.0	22.6	2
9/14/2021 10:00	71.0	103.5	87.2	16.2	22.9	2
9/14/2021 11:00	69.8	103.2	86.5	16.7	23.5	2
9/14/2021 12:00	71.9	107.2	89.6	17.7	25.0	2
9/14/2021 13:00	66.9	100.6	83.7	16.9	23.8	2
9/14/2021 14:00	66.8	99.0	82.9	16.1	22.7	2

Saline Treatment						
PR Interval (msec)						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/14/2021 15:00	67.3	101.5	84.4	17.1	24.2	2
9/14/2021 16:00	68.0	100.9	84.4	16.5	23.3	2
9/14/2021 17:00	67.5	98.0	82.7	15.2	21.5	2
9/14/2021 18:00	67.3	92.9	80.1	12.8	18.1	2
9/14/2021 19:00	67.4	97.7	82.5	15.2	21.4	2
9/14/2021 20:00	68.3	98.7	83.5	15.2	21.5	2
9/14/2021 21:00	69.5	100.6	85.1	15.5	21.9	2
9/14/2021 22:00	68.0	102.0	85.0	17.0	24.0	2
9/14/2021 23:00	64.1	98.1	81.1	17.0	24.1	2
9/15/2021 0:00	66.9	101.2	84.0	17.1	24.2	2
9/15/2021 1:00	64.4	100.0	82.2	17.8	25.2	2
9/15/2021 2:00	64.0	102.7	83.3	19.4	27.4	2
9/15/2021 3:00	63.7	94.1	78.9	15.2	21.5	2
9/15/2021 4:00	65.8	98.0	81.9	16.1	22.7	2
9/15/2021 5:00	68.0	93.0	80.5	12.5	17.6	2
9/15/2021 6:00	68.5	94.5	81.5	13.0	18.4	2
9/15/2021 7:00	64.0	91.8	77.9	13.9	19.6	2
9/15/2021 8:00	64.8	92.6	78.7	13.9	19.6	2
9/15/2021 9:00	67.4	95.8	81.6	14.2	20.0	2
9/15/2021 10:00	67.1	97.9	82.5	15.4	21.8	2
9/15/2021 11:00	67.0	91.1	79.0	12.1	17.1	2
9/15/2021 12:00	67.6	96.1	81.8	14.3	20.2	2
9/15/2021 13:00	66.3	88.6	77.4	11.2	15.8	2
9/15/2021 14:00	64.0	87.3	75.7	11.7	16.5	2
9/15/2021 15:00	61.0	80.5	70.8	9.7	13.8	2
9/15/2021 16:00	64.5	84.1	74.3	9.8	13.9	2
9/15/2021 17:00	62.6	85.5	74.1	11.4	16.2	2
9/15/2021 18:00	64.8	82.8	73.8	9.0	12.7	2
9/15/2021 19:00	60.2	82.1	71.2	10.9	15.5	2
9/15/2021 20:00	61.8	86.2	74.0	12.2	17.3	2
9/15/2021 21:00	64.3	88.5	76.4	12.1	17.1	2
9/15/2021 22:00	64.4	87.5	76.0	11.6	16.4	2

Saline Treatment						
PR Interval (msec)						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/15/2021 23:00	60.9	86.4	73.7	12.8	18.1	2
9/16/2021 0:00	63.2	86.5	74.8	11.7	16.5	2
9/16/2021 1:00	61.5	86.5	74.0	12.5	17.7	2
9/16/2021 2:00	64.1	91.5	77.8	13.7	19.4	2
9/16/2021 3:00	66.5	88.7	77.6	11.1	15.8	2
9/16/2021 4:00	66.5	89.4	78.0	11.4	16.2	2
9/16/2021 5:00	NaN	88.3	88.3	0.0	0.0	1
9/16/2021 6:00	NaN	88.8	88.8	0.0	0.0	1
9/16/2021 7:00	NaN	80.0	80.0	0.0	0.0	1
9/16/2021 8:00	NaN	79.1	79.1	0.0	0.0	1
9/16/2021 9:00	NaN	81.3	81.3	0.0	0.0	1
9/16/2021 10:00	NaN	81.1	81.1	0.0	0.0	1
9/16/2021 11:00	NaN	80.5	80.5	0.0	0.0	1
9/16/2021 12:00	NaN	81.9	81.9	0.0	0.0	1
9/16/2021 13:00	NaN	79.8	79.8	0.0	0.0	1
9/16/2021 14:00	NaN	80.8	80.8	0.0	0.0	1
9/16/2021 15:00	NaN	76.9	76.9	0.0	0.0	1
9/16/2021 16:00	NaN	78.2	78.2	0.0	0.0	1
9/16/2021 17:00	NaN	79.4	79.4	0.0	0.0	1
9/16/2021 18:00	NaN	78.6	78.6	0.0	0.0	1
9/16/2021 19:00	NaN	77.3	77.3	0.0	0.0	1
9/16/2021 20:00	NaN	79.9	79.9	0.0	0.0	1

Table 14: QRS Duration (msec) Saline Treatment

Saline Treatment						
QRS Duration (msec)						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/10/2021 16:00	32.5	41.8	37.2	4.7	6.6	2
9/10/2021 17:00	32.9	42.3	37.6	4.7	6.7	2
9/10/2021 18:00	32.9	42.0	37.5	4.5	6.4	2
9/10/2021 19:00	34.2	42.0	38.1	3.9	5.6	2
9/10/2021 20:00	33.8	42.3	38.0	4.2	6.0	2
9/10/2021 21:00	33.7	42.9	38.3	4.6	6.5	2
9/10/2021 22:00	33.4	41.9	37.6	4.2	6.0	2
9/10/2021 23:00	32.3	41.9	37.1	4.8	6.8	2
9/11/2021 0:00	33.3	42.7	38.0	4.7	6.7	2
9/11/2021 1:00	33.5	41.8	37.7	4.2	5.9	2
9/11/2021 2:00	33.9	42.2	38.0	4.1	5.8	2
9/11/2021 3:00	33.8	42.4	38.1	4.3	6.1	2
9/11/2021 4:00	33.7	42.4	38.0	4.4	6.2	2
9/11/2021 5:00	33.2	42.6	37.9	4.7	6.7	2
9/11/2021 6:00	33.6	41.8	37.7	4.1	5.8	2
9/11/2021 7:00	32.0	41.6	36.8	4.8	6.8	2
9/11/2021 8:00	32.2	41.7	36.9	4.7	6.7	2
9/11/2021 9:00	32.4	42.0	37.2	4.8	6.8	2
9/11/2021 10:00	32.1	41.2	36.7	4.6	6.5	2
9/11/2021 11:00	32.5	41.5	37.0	4.5	6.4	2
9/11/2021 12:00	32.2	41.5	36.9	4.7	6.6	2
9/11/2021 13:00	32.3	41.5	36.9	4.6	6.5	2
9/11/2021 14:00	32.3	41.2	36.8	4.5	6.3	2
9/11/2021 15:00	32.3	41.4	36.9	4.5	6.4	2
9/11/2021 16:00	32.7	41.6	37.1	4.5	6.3	2
9/11/2021 17:00	32.8	41.7	37.3	4.4	6.3	2
9/11/2021 18:00	32.5	41.9	37.2	4.7	6.7	2
9/11/2021 19:00	33.4	42.4	37.9	4.5	6.4	2
9/11/2021 20:00	32.4	42.0	37.2	4.8	6.8	2
9/11/2021 21:00	33.3	42.0	37.7	4.3	6.1	2
9/11/2021 22:00	32.4	41.9	37.1	4.8	6.8	2

Saline Treatment						
QRS Duration (msec)						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/11/2021 23:00	32.5	42.4	37.4	4.9	7.0	2
9/12/2021 0:00	32.7	41.9	37.3	4.6	6.5	2
9/12/2021 1:00	33.5	43.3	38.4	4.9	6.9	2
9/12/2021 2:00	33.3	42.0	37.6	4.4	6.2	2
9/12/2021 3:00	33.0	41.8	37.4	4.4	6.2	2
9/12/2021 4:00	33.8	41.9	37.8	4.0	5.7	2
9/12/2021 5:00	33.2	41.4	37.3	4.1	5.8	2
9/12/2021 6:00	33.2	41.6	37.4	4.2	5.9	2
9/12/2021 7:00	32.4	41.5	36.9	4.6	6.5	2
9/12/2021 8:00	32.3	41.7	37.0	4.7	6.6	2
9/12/2021 9:00	32.3	41.5	36.9	4.6	6.5	2
9/12/2021 10:00	32.3	41.4	36.8	4.5	6.4	2
9/12/2021 11:00	32.9	41.5	37.2	4.3	6.1	2
9/12/2021 12:00	32.5	41.6	37.1	4.5	6.4	2
9/12/2021 13:00	32.4	42.1	37.3	4.9	6.9	2
9/12/2021 14:00	32.6	41.7	37.2	4.5	6.4	2
9/12/2021 15:00	32.6	41.5	37.0	4.5	6.4	2
9/12/2021 16:00	32.5	41.7	37.1	4.6	6.5	2
9/12/2021 17:00	32.6	41.2	36.9	4.3	6.1	2
9/12/2021 18:00	32.4	41.4	36.9	4.5	6.4	2
9/12/2021 19:00	32.5	41.2	36.8	4.3	6.1	2
9/12/2021 20:00	33.2	41.1	37.1	4.0	5.6	2
9/12/2021 21:00	32.4	41.7	37.0	4.6	6.5	2
9/12/2021 22:00	32.7	41.5	37.1	4.4	6.2	2
9/12/2021 23:00	33.7	41.7	37.7	4.0	5.7	2
9/13/2021 0:00	32.5	41.8	37.1	4.6	6.6	2
9/13/2021 1:00	33.3	41.7	37.5	4.2	6.0	2
9/13/2021 2:00	33.6	41.8	37.7	4.1	5.8	2
9/13/2021 3:00	32.8	41.5	37.2	4.3	6.1	2
9/13/2021 4:00	33.2	41.6	37.4	4.2	6.0	2
9/13/2021 5:00	33.0	40.8	36.9	3.9	5.5	2
9/13/2021 6:00	33.0	41.3	37.2	4.1	5.8	2

Saline Treatment						
QRS Duration (msec)						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/13/2021 7:00	32.4	41.2	36.8	4.4	6.2	2
9/13/2021 8:00	32.3	41.4	36.9	4.5	6.4	2
9/13/2021 9:00	32.2	39.6	35.9	3.7	5.2	2
9/13/2021 10:00	31.9	40.7	36.3	4.4	6.2	2
9/13/2021 11:00	31.8	41.4	36.6	4.8	6.8	2
9/13/2021 12:00	31.9	41.5	36.7	4.8	6.8	2
9/13/2021 13:00	32.3	41.8	37.0	4.7	6.7	2
9/13/2021 14:00	32.1	41.9	37.0	4.9	7.0	2
9/13/2021 15:00	32.6	42.2	37.4	4.8	6.8	2
9/13/2021 16:00	32.5	41.5	37.0	4.5	6.4	2
9/13/2021 17:00	32.5	40.6	36.5	4.1	5.8	2
9/13/2021 18:00	32.3	40.9	36.6	4.3	6.1	2
9/13/2021 19:00	32.2	41.9	37.1	4.9	6.9	2
9/13/2021 20:00	32.9	42.5	37.7	4.8	6.8	2
9/13/2021 21:00	32.7	42.2	37.4	4.7	6.7	2
9/13/2021 22:00	32.3	42.2	37.3	4.9	7.0	2
9/13/2021 23:00	31.8	41.7	36.7	5.0	7.0	2
9/14/2021 0:00	32.1	42.1	37.1	5.0	7.1	2
9/14/2021 1:00	33.2	42.1	37.6	4.5	6.3	2
9/14/2021 2:00	33.0	42.2	37.6	4.6	6.5	2
9/14/2021 3:00	33.4	42.3	37.8	4.4	6.3	2
9/14/2021 4:00	33.1	42.0	37.6	4.5	6.3	2
9/14/2021 5:00	32.4	41.2	36.8	4.4	6.2	2
9/14/2021 6:00	32.3	42.1	37.2	4.9	6.9	2
9/14/2021 7:00	32.6	41.4	37.0	4.4	6.2	2
9/14/2021 8:00	32.4	41.2	36.8	4.4	6.2	2
9/14/2021 9:00	32.4	41.4	36.9	4.5	6.4	2
9/14/2021 10:00	32.7	41.4	37.0	4.4	6.2	2
9/14/2021 11:00	32.8	41.5	37.1	4.4	6.2	2
9/14/2021 12:00	33.0	41.6	37.3	4.3	6.1	2
9/14/2021 13:00	32.4	41.6	37.0	4.6	6.5	2
9/14/2021 14:00	32.3	41.4	36.9	4.6	6.5	2

Saline Treatment						
QRS Duration (msec)						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/14/2021 15:00	32.1	41.4	36.8	4.7	6.6	2
9/14/2021 16:00	32.2	41.6	36.9	4.7	6.7	2
9/14/2021 17:00	32.4	41.6	37.0	4.6	6.5	2
9/14/2021 18:00	32.4	41.5	36.9	4.5	6.4	2
9/14/2021 19:00	32.7	41.4	37.1	4.4	6.2	2
9/14/2021 20:00	32.8	41.3	37.1	4.3	6.0	2
9/14/2021 21:00	33.6	41.1	37.3	3.8	5.3	2
9/14/2021 22:00	33.4	41.7	37.6	4.1	5.9	2
9/14/2021 23:00	32.2	41.4	36.8	4.6	6.5	2
9/15/2021 0:00	32.1	41.5	36.8	4.7	6.7	2
9/15/2021 1:00	32.2	41.6	36.9	4.7	6.6	2
9/15/2021 2:00	31.8	41.8	36.8	5.0	7.1	2
9/15/2021 3:00	32.2	42.8	37.5	5.3	7.5	2
9/15/2021 4:00	32.4	41.7	37.1	4.7	6.6	2
9/15/2021 5:00	31.5	42.2	36.9	5.4	7.6	2
9/15/2021 6:00	31.9	42.0	36.9	5.0	7.1	2
9/15/2021 7:00	32.6	41.2	36.9	4.3	6.1	2
9/15/2021 8:00	32.3	41.5	36.9	4.6	6.5	2
9/15/2021 9:00	32.6	41.6	37.1	4.5	6.4	2
9/15/2021 10:00	32.8	41.3	37.1	4.3	6.1	2
9/15/2021 11:00	32.9	41.2	37.0	4.1	5.9	2
9/15/2021 12:00	32.6	41.3	37.0	4.4	6.2	2
9/15/2021 13:00	32.6	41.1	36.9	4.2	6.0	2
9/15/2021 14:00	32.3	41.1	36.7	4.4	6.2	2
9/15/2021 15:00	32.7	41.2	36.9	4.2	5.9	2
9/15/2021 16:00	32.5	41.6	37.0	4.5	6.4	2
9/15/2021 17:00	32.7	41.4	37.0	4.3	6.1	2
9/15/2021 18:00	32.6	41.5	37.1	4.4	6.3	2
9/15/2021 19:00	32.7	41.3	37.0	4.3	6.1	2
9/15/2021 20:00	32.7	41.0	36.9	4.2	5.9	2
9/15/2021 21:00	32.5	41.2	36.9	4.4	6.2	2
9/15/2021 22:00	32.7	40.9	36.8	4.1	5.8	2

Saline Treatment						
QRS Duration (msec)						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/15/2021 23:00	32.6	41.1	36.9	4.2	6.0	2
9/16/2021 0:00	32.6	41.3	36.9	4.3	6.1	2
9/16/2021 1:00	32.6	41.2	36.9	4.3	6.1	2
9/16/2021 2:00	33.0	41.6	37.3	4.3	6.1	2
9/16/2021 3:00	33.9	41.4	37.6	3.8	5.3	2
9/16/2021 4:00	33.7	41.2	37.4	3.7	5.3	2
9/16/2021 5:00	NaN	41.2	41.2	0.0	0.0	1
9/16/2021 6:00	NaN	41.1	41.1	0.0	0.0	1
9/16/2021 7:00	NaN	40.6	40.6	0.0	0.0	1
9/16/2021 8:00	NaN	40.0	40.0	0.0	0.0	1
9/16/2021 9:00	NaN	39.9	39.9	0.0	0.0	1
9/16/2021 10:00	NaN	39.5	39.5	0.0	0.0	1
9/16/2021 11:00	NaN	39.6	39.6	0.0	0.0	1
9/16/2021 12:00	NaN	39.6	39.6	0.0	0.0	1
9/16/2021 13:00	NaN	39.6	39.6	0.0	0.0	1
9/16/2021 14:00	NaN	39.4	39.4	0.0	0.0	1
9/16/2021 15:00	NaN	39.5	39.5	0.0	0.0	1
9/16/2021 16:00	NaN	39.7	39.7	0.0	0.0	1
9/16/2021 17:00	NaN	39.8	39.8	0.0	0.0	1
9/16/2021 18:00	NaN	40.3	40.3	0.0	0.0	1
9/16/2021 19:00	NaN	40.2	40.2	0.0	0.0	1
9/16/2021 20:00	NaN	40.2	40.2	0.0	0.0	1

Table 15: Heart Rate Corrected QT Interval (msec) Saline Treatment

Saline Treatment						
Heart Rate Corrected QT Interval (msec)						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/10/2021 16:00	356.3	336.7	346.5	9.8	13.9	2
9/10/2021 17:00	356.3	338.0	347.1	9.1	12.9	2
9/10/2021 18:00	361.1	335.8	348.5	12.6	17.8	2
9/10/2021 19:00	370.5	337.5	354.0	16.5	23.4	2
9/10/2021 20:00	374.5	337.3	355.9	18.6	26.3	2
9/10/2021 21:00	370.7	342.7	356.7	14.0	19.7	2
9/10/2021 22:00	370.6	341.3	355.9	14.7	20.8	2
9/10/2021 23:00	369.8	347.1	358.4	11.4	16.1	2
9/11/2021 0:00	368.5	349.0	358.7	9.8	13.8	2
9/11/2021 1:00	364.5	346.3	355.4	9.1	12.8	2
9/11/2021 2:00	362.0	342.5	352.3	9.7	13.8	2
9/11/2021 3:00	359.9	342.1	351.0	8.9	12.6	2
9/11/2021 4:00	362.0	342.9	352.5	9.5	13.5	2
9/11/2021 5:00	364.1	337.8	351.0	13.2	18.6	2
9/11/2021 6:00	367.6	338.4	353.0	14.6	20.6	2
9/11/2021 7:00	361.7	335.1	348.4	13.3	18.8	2
9/11/2021 8:00	358.4	343.8	351.1	7.3	10.3	2
9/11/2021 9:00	357.6	339.2	348.4	9.2	13.0	2
9/11/2021 10:00	354.3	327.3	340.8	13.5	19.0	2
9/11/2021 11:00	357.6	333.6	345.6	12.0	17.0	2
9/11/2021 12:00	355.0	325.0	340.0	15.0	21.2	2
9/11/2021 13:00	357.4	342.4	349.9	7.5	10.6	2
9/11/2021 14:00	351.2	326.8	339.0	12.2	17.3	2
9/11/2021 15:00	351.2	335.6	343.4	7.8	11.0	2
9/11/2021 16:00	354.9	329.3	342.1	12.8	18.1	2
9/11/2021 17:00	355.9	341.1	348.5	7.4	10.5	2
9/11/2021 18:00	352.5	337.4	344.9	7.6	10.7	2
9/11/2021 19:00	362.9	336.6	349.7	13.2	18.6	2
9/11/2021 20:00	359.4	333.4	346.4	13.0	18.4	2
9/11/2021 21:00	359.4	337.9	348.7	10.7	15.2	2
9/11/2021 22:00	367.1	337.2	352.1	15.0	21.1	2

Saline Treatment						
Heart Rate Corrected QT Interval (msec)						
Date	**G180JD**	**N378ALE**	**Mean**	**SE**	**SD**	**n**
9/11/2021 23:00	366.0	341.2	353.6	12.4	17.5	2
9/12/2021 0:00	366.2	336.7	351.4	14.8	20.9	2
9/12/2021 1:00	368.9	340.8	354.9	14.1	19.9	2
9/12/2021 2:00	365.7	336.3	351.0	14.7	20.8	2
9/12/2021 3:00	363.2	334.5	348.9	14.3	20.2	2
9/12/2021 4:00	363.7	331.6	347.6	16.1	22.7	2
9/12/2021 5:00	361.4	329.0	345.2	16.2	22.9	2
9/12/2021 6:00	362.8	337.5	350.2	12.7	17.9	2
9/12/2021 7:00	362.2	339.3	350.8	11.4	16.2	2
9/12/2021 8:00	361.4	343.0	352.2	9.2	13.0	2
9/12/2021 9:00	362.6	339.5	351.0	11.6	16.4	2
9/12/2021 10:00	360.9	333.5	347.2	13.7	19.3	2
9/12/2021 11:00	363.3	331.7	347.5	15.8	22.3	2
9/12/2021 12:00	366.1	334.4	350.3	15.9	22.4	2
9/12/2021 13:00	358.5	354.8	356.7	1.9	2.7	2
9/12/2021 14:00	353.3	341.7	347.5	5.8	8.2	2
9/12/2021 15:00	358.1	345.3	351.7	6.4	9.0	2
9/12/2021 16:00	361.1	344.1	352.6	8.5	12.0	2
9/12/2021 17:00	359.6	335.6	347.6	12.0	17.0	2
9/12/2021 18:00	357.5	338.5	348.0	9.5	13.5	2
9/12/2021 19:00	367.2	339.3	353.2	13.9	19.7	2
9/12/2021 20:00	369.2	335.2	352.2	17.0	24.1	2
9/12/2021 21:00	366.7	337.4	352.0	14.6	20.7	2
9/12/2021 22:00	368.5	337.4	353.0	15.6	22.0	2
9/12/2021 23:00	369.5	342.6	356.0	13.5	19.0	2
9/13/2021 0:00	365.8	339.6	352.7	13.1	18.6	2
9/13/2021 1:00	374.8	343.4	359.1	15.7	22.2	2
9/13/2021 2:00	373.3	340.4	356.9	16.4	23.2	2
9/13/2021 3:00	370.6	336.7	353.7	17.0	24.0	2
9/13/2021 4:00	369.5	340.3	354.9	14.6	20.6	2
9/13/2021 5:00	365.6	338.9	352.3	13.4	18.9	2
9/13/2021 6:00	368.7	341.1	354.9	13.8	19.6	2

Saline Treatment						
Heart Rate Corrected QT Interval (msec)						
Date	**G180JD**	**N378ALE**	**Mean**	**SE**	**SD**	**n**
9/13/2021 7:00	365.6	341.3	353.5	12.2	17.2	2
9/13/2021 8:00	367.7	374.9	371.3	3.6	5.0	2
9/13/2021 9:00	359.3	416.1	387.7	28.4	40.1	2
9/13/2021 10:00	358.1	382.6	370.3	12.2	17.3	2
9/13/2021 11:00	353.8	339.8	346.8	7.0	9.9	2
9/13/2021 12:00	348.8	336.9	342.8	6.0	8.5	2
9/13/2021 13:00	354.7	334.4	344.6	10.1	14.3	2
9/13/2021 14:00	359.9	352.4	356.2	3.7	5.3	2
9/13/2021 15:00	363.9	367.3	365.6	1.7	2.5	2
9/13/2021 16:00	357.0	353.5	355.3	1.8	2.5	2
9/13/2021 17:00	360.9	364.4	362.6	1.8	2.5	2
9/13/2021 18:00	360.6	384.6	372.6	12.0	17.0	2
9/13/2021 19:00	357.0	352.9	354.9	2.1	2.9	2
9/13/2021 20:00	364.4	349.4	356.9	7.5	10.6	2
9/13/2021 21:00	361.7	346.2	354.0	7.8	11.0	2
9/13/2021 22:00	363.0	342.1	352.6	10.5	14.8	2
9/13/2021 23:00	361.5	347.3	354.4	7.1	10.0	2
9/14/2021 0:00	365.5	349.5	357.5	8.0	11.3	2
9/14/2021 1:00	367.8	347.4	357.6	10.2	14.4	2
9/14/2021 2:00	373.1	347.2	360.2	13.0	18.3	2
9/14/2021 3:00	370.9	342.7	356.8	14.1	20.0	2
9/14/2021 4:00	369.8	345.2	357.5	12.3	17.4	2
9/14/2021 5:00	368.0	344.4	356.2	11.8	16.7	2
9/14/2021 6:00	371.7	344.8	358.3	13.5	19.0	2
9/14/2021 7:00	372.1	348.3	360.2	11.9	16.8	2
9/14/2021 8:00	371.5	348.3	359.9	11.6	16.4	2
9/14/2021 9:00	374.1	355.2	364.7	9.4	13.4	2
9/14/2021 10:00	369.8	346.8	358.3	11.5	16.3	2
9/14/2021 11:00	373.0	344.4	358.7	14.3	20.2	2
9/14/2021 12:00	369.3	339.9	354.6	14.7	20.8	2
9/14/2021 13:00	357.6	343.6	350.6	7.0	9.9	2
9/14/2021 14:00	358.7	345.7	352.2	6.5	9.2	2

Saline Treatment						
Heart Rate Corrected QT Interval (msec)						
Date	**G180JD**	**N378ALE**	**Mean**	**SE**	**SD**	**n**
9/14/2021 15:00	349.2	345.9	347.6	1.6	2.3	2
9/14/2021 16:00	352.0	341.3	346.6	5.3	7.5	2
9/14/2021 17:00	352.2	342.7	347.5	4.7	6.7	2
9/14/2021 18:00	354.3	337.7	346.0	8.3	11.7	2
9/14/2021 19:00	357.4	342.1	349.7	7.7	10.8	2
9/14/2021 20:00	363.3	346.6	354.9	8.3	11.8	2
9/14/2021 21:00	356.4	339.8	348.1	8.3	11.8	2
9/14/2021 22:00	363.2	354.8	359.0	4.2	5.9	2
9/14/2021 23:00	364.8	340.9	352.8	12.0	16.9	2
9/15/2021 0:00	359.3	338.3	348.8	10.5	14.8	2
9/15/2021 1:00	363.5	337.2	350.4	13.1	18.6	2
9/15/2021 2:00	362.8	346.5	354.6	8.1	11.5	2
9/15/2021 3:00	373.0	352.1	362.5	10.5	14.8	2
9/15/2021 4:00	371.4	348.3	359.9	11.6	16.4	2
9/15/2021 5:00	366.2	340.8	353.5	12.7	17.9	2
9/15/2021 6:00	374.6	345.3	359.9	14.7	20.7	2
9/15/2021 7:00	362.8	337.8	350.3	12.5	17.7	2
9/15/2021 8:00	366.9	336.8	351.8	15.1	21.3	2
9/15/2021 9:00	372.4	342.3	357.3	15.0	21.2	2
9/15/2021 10:00	374.5	345.0	359.7	14.8	20.9	2
9/15/2021 11:00	366.0	334.0	350.0	16.0	22.6	2
9/15/2021 12:00	375.3	347.8	361.5	13.8	19.5	2
9/15/2021 13:00	374.7	346.9	360.8	13.9	19.6	2
9/15/2021 14:00	377.4	348.9	363.2	14.2	20.1	2
9/15/2021 15:00	363.9	339.8	351.8	12.1	17.1	2
9/15/2021 16:00	362.2	343.9	353.1	9.2	13.0	2
9/15/2021 17:00	366.9	342.3	354.6	12.3	17.4	2
9/15/2021 18:00	377.1	348.4	362.7	14.4	20.3	2
9/15/2021 19:00	374.8	341.7	358.2	16.5	23.4	2
9/15/2021 20:00	380.8	345.3	363.0	17.8	25.1	2
9/15/2021 21:00	374.7	353.9	364.3	10.4	14.7	2
9/15/2021 22:00	376.4	357.1	366.7	9.6	13.6	2

Saline Treatment						
Heart Rate Corrected QT Interval (msec)						
Date	**G180JD**	**N378ALE**	**Mean**	**SE**	**SD**	**n**
9/15/2021 23:00	385.5	348.3	366.9	18.6	26.3	2
9/16/2021 0:00	384.0	357.4	370.7	13.3	18.8	2
9/16/2021 1:00	382.8	352.0	367.4	15.4	21.8	2
9/16/2021 2:00	391.0	361.2	376.1	14.9	21.0	2
9/16/2021 3:00	383.3	352.6	367.9	15.3	21.7	2
9/16/2021 4:00	366.7	357.0	361.9	4.9	6.9	2
9/16/2021 5:00	NaN	351.5	351.5	0.0	0.0	1
9/16/2021 6:00	NaN	361.7	361.7	0.0	0.0	1
9/16/2021 7:00	NaN	349.4	349.4	0.0	0.0	1
9/16/2021 8:00	NaN	349.6	349.6	0.0	0.0	1
9/16/2021 9:00	NaN	355.5	355.5	0.0	0.0	1
9/16/2021 10:00	NaN	359.4	359.4	0.0	0.0	1
9/16/2021 11:00	NaN	357.5	357.5	0.0	0.0	1
9/16/2021 12:00	NaN	360.2	360.2	0.0	0.0	1
9/16/2021 13:00	NaN	357.4	357.4	0.0	0.0	1
9/16/2021 14:00	NaN	360.1	360.1	0.0	0.0	1
9/16/2021 15:00	NaN	351.3	351.3	0.0	0.0	1
9/16/2021 16:00	NaN	358.1	358.1	0.0	0.0	1
9/16/2021 17:00	NaN	358.4	358.4	0.0	0.0	1
9/16/2021 18:00	NaN	362.3	362.3	0.0	0.0	1
9/16/2021 19:00	NaN	365.7	365.7	0.0	0.0	1
9/16/2021 20:00	NaN	362.3	362.3	0.0	0.0	1

Table 16: QT Interval (msec) Saline Treatment

Saline Treatment						
QT Interval (msec)						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/10/2021 16:00	195.5	247.9	221.7	26.2	37.0	2
9/10/2021 17:00	209.3	245.4	227.3	18.0	25.5	2
9/10/2021 18:00	213.6	255.6	234.6	21.0	29.7	2
9/10/2021 19:00	239.2	269.1	254.1	14.9	21.1	2
9/10/2021 20:00	236.8	278.7	257.7	20.9	29.6	2
9/10/2021 21:00	232.3	279.2	255.7	23.5	33.2	2
9/10/2021 22:00	229.1	278.8	254.0	24.8	35.1	2
9/10/2021 23:00	230.5	279.0	254.8	24.2	34.3	2
9/11/2021 0:00	227.4	285.0	256.2	28.8	40.8	2
9/11/2021 1:00	218.9	281.3	250.1	31.2	44.2	2
9/11/2021 2:00	222.1	287.0	254.5	32.5	45.9	2
9/11/2021 3:00	218.1	285.5	251.8	33.7	47.7	2
9/11/2021 4:00	219.5	285.8	252.7	33.1	46.9	2
9/11/2021 5:00	219.7	284.9	252.3	32.6	46.1	2
9/11/2021 6:00	227.7	282.8	255.2	27.5	38.9	2
9/11/2021 7:00	206.7	262.6	234.6	28.0	39.6	2
9/11/2021 8:00	205.8	256.8	231.3	25.5	36.0	2
9/11/2021 9:00	216.3	256.0	236.2	19.9	28.1	2
9/11/2021 10:00	216.1	273.6	244.9	28.8	40.7	2
9/11/2021 11:00	210.6	251.6	231.1	20.5	29.0	2
9/11/2021 12:00	213.1	260.2	236.7	23.5	33.3	2
9/11/2021 13:00	203.5	245.4	224.5	20.9	29.6	2
9/11/2021 14:00	208.8	259.4	234.1	25.3	35.8	2
9/11/2021 15:00	214.9	248.7	231.8	16.9	23.9	2
9/11/2021 16:00	209.7	250.3	230.0	20.3	28.7	2
9/11/2021 17:00	209.5	246.6	228.1	18.6	26.2	2
9/11/2021 18:00	208.0	248.3	228.2	20.1	28.5	2
9/11/2021 19:00	224.1	262.3	243.2	19.1	27.0	2
9/11/2021 20:00	224.6	272.1	248.3	23.7	33.6	2
9/11/2021 21:00	217.3	269.2	243.3	26.0	36.7	2
9/11/2021 22:00	227.2	278.0	252.6	25.4	35.9	2

Battelle		Status:	Final
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Saline Treatment						
QT Interval (msec)						
Date	**G180JD**	**N378ALE**	**Mean**	**SE**	**SD**	**n**
9/11/2021 23:00	221.1	278.7	249.9	28.8	40.7	2
9/12/2021 0:00	221.9	283.9	252.9	31.0	43.9	2
9/12/2021 1:00	230.8	290.4	260.6	29.8	42.2	2
9/12/2021 2:00	225.0	286.7	255.8	30.8	43.6	2
9/12/2021 3:00	221.6	286.5	254.1	32.4	45.9	2
9/12/2021 4:00	225.9	282.4	254.2	28.3	40.0	2
9/12/2021 5:00	225.2	285.4	255.3	30.1	42.5	2
9/12/2021 6:00	230.1	282.0	256.1	25.9	36.7	2
9/12/2021 7:00	208.0	255.9	231.9	24.0	33.9	2
9/12/2021 8:00	205.9	259.2	232.5	26.7	37.7	2
9/12/2021 9:00	215.2	258.5	236.8	21.6	30.6	2
9/12/2021 10:00	212.6	258.6	235.6	23.0	32.5	2
9/12/2021 11:00	224.9	263.6	244.2	19.4	27.4	2
9/12/2021 12:00	231.6	285.1	258.3	26.8	37.8	2
9/12/2021 13:00	207.1	260.1	233.6	26.5	37.4	2
9/12/2021 14:00	217.1	269.0	243.1	26.0	36.8	2
9/12/2021 15:00	205.8	257.7	231.8	25.9	36.7	2
9/12/2021 16:00	210.9	259.2	235.1	24.2	34.2	2
9/12/2021 17:00	214.4	261.7	238.1	23.6	33.4	2
9/12/2021 18:00	215.5	258.7	237.1	21.6	30.6	2
9/12/2021 19:00	238.6	288.9	263.7	25.2	35.6	2
9/12/2021 20:00	239.8	294.1	267.0	27.1	38.4	2
9/12/2021 21:00	245.1	298.7	271.9	26.8	37.9	2
9/12/2021 22:00	231.5	294.4	263.0	31.5	44.5	2
9/12/2021 23:00	228.9	301.7	265.3	36.4	51.4	2
9/13/2021 0:00	233.4	306.9	270.2	36.8	52.0	2
9/13/2021 1:00	252.2	305.0	278.6	26.4	37.3	2
9/13/2021 2:00	246.0	306.0	276.0	30.0	42.4	2
9/13/2021 3:00	240.3	301.5	270.9	30.6	43.3	2
9/13/2021 4:00	237.4	302.5	269.9	32.6	46.0	2
9/13/2021 5:00	236.8	297.6	267.2	30.4	43.0	2
9/13/2021 6:00	235.6	294.6	265.1	29.5	41.7	2

Saline Treatment						
QT Interval (msec)						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/13/2021 7:00	224.8	273.8	249.3	24.5	34.6	2
9/13/2021 8:00	207.1	270.4	238.7	31.7	44.8	2
9/13/2021 9:00	193.0	233.8	213.4	20.4	28.9	2
9/13/2021 10:00	203.0	243.3	223.1	20.1	28.5	2
9/13/2021 11:00	195.2	252.5	223.9	28.6	40.5	2
9/13/2021 12:00	201.7	256.0	228.8	27.1	38.4	2
9/13/2021 13:00	210.8	257.7	234.3	23.4	33.1	2
9/13/2021 14:00	199.4	250.2	224.8	25.4	35.9	2
9/13/2021 15:00	204.7	247.7	226.2	21.5	30.4	2
9/13/2021 16:00	212.9	248.8	230.8	18.0	25.4	2
9/13/2021 17:00	215.3	244.6	230.0	14.7	20.8	2
9/13/2021 18:00	215.7	245.9	230.8	15.1	21.3	2
9/13/2021 19:00	204.6	256.6	230.6	26.0	36.8	2
9/13/2021 20:00	233.2	265.8	249.5	16.3	23.1	2
9/13/2021 21:00	223.4	271.5	247.4	24.1	34.0	2
9/13/2021 22:00	227.2	281.2	254.2	27.0	38.2	2
9/13/2021 23:00	218.0	293.6	255.8	37.8	53.5	2
9/14/2021 0:00	218.4	297.4	257.9	39.5	55.9	2
9/14/2021 1:00	225.9	300.5	263.2	37.3	52.7	2
9/14/2021 2:00	230.8	291.1	261.0	30.2	42.7	2
9/14/2021 3:00	230.4	291.0	260.7	30.3	42.8	2
9/14/2021 4:00	231.4	293.9	262.7	31.2	44.2	2
9/14/2021 5:00	238.9	288.1	263.5	24.6	34.8	2
9/14/2021 6:00	238.4	281.2	259.8	21.4	30.2	2
9/14/2021 7:00	222.6	259.4	241.0	18.4	26.0	2
9/14/2021 8:00	216.5	257.1	236.8	20.3	28.7	2
9/14/2021 9:00	221.0	251.1	236.0	15.1	21.3	2
9/14/2021 10:00	226.6	259.7	243.1	16.5	23.4	2
9/14/2021 11:00	223.2	253.2	238.2	15.0	21.2	2
9/14/2021 12:00	227.9	258.0	242.9	15.1	21.3	2
9/14/2021 13:00	210.8	248.4	229.6	18.8	26.6	2
9/14/2021 14:00	206.1	253.4	229.7	23.6	33.4	2

Saline Treatment						
QT Interval (msec)						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/14/2021 15:00	205.0	245.7	225.3	20.3	28.7	2
9/14/2021 16:00	207.7	245.6	226.7	18.9	26.8	2
9/14/2021 17:00	205.5	236.2	220.9	15.4	21.7	2
9/14/2021 18:00	206.2	225.6	215.9	9.7	13.7	2
9/14/2021 19:00	210.9	262.3	236.6	25.7	36.4	2
9/14/2021 20:00	220.9	268.3	244.6	23.7	33.6	2
9/14/2021 21:00	215.1	273.0	244.0	28.9	40.9	2
9/14/2021 22:00	214.8	272.2	243.5	28.7	40.5	2
9/14/2021 23:00	207.2	246.8	227.0	19.8	28.0	2
9/15/2021 0:00	212.8	265.4	239.1	26.3	37.2	2
9/15/2021 1:00	207.8	269.6	238.7	30.9	43.8	2
9/15/2021 2:00	206.5	287.3	246.9	40.4	57.1	2
9/15/2021 3:00	211.7	267.6	239.6	28.0	39.6	2
9/15/2021 4:00	222.7	284.4	253.5	30.8	43.6	2
9/15/2021 5:00	219.6	266.0	242.8	23.2	32.8	2
9/15/2021 6:00	227.5	275.0	251.3	23.8	33.6	2
9/15/2021 7:00	206.9	244.2	225.5	18.6	26.3	2
9/15/2021 8:00	211.5	251.6	231.5	20.1	28.4	2
9/15/2021 9:00	220.5	250.9	235.7	15.2	21.5	2
9/15/2021 10:00	218.2	250.9	234.5	16.4	23.2	2
9/15/2021 11:00	209.9	225.1	217.5	7.6	10.7	2
9/15/2021 12:00	220.4	245.7	233.1	12.7	17.9	2
9/15/2021 13:00	217.7	212.6	215.1	2.5	3.6	2
9/15/2021 14:00	212.5	211.1	211.8	0.7	1.0	2
9/15/2021 15:00	195.0	209.0	202.0	7.0	9.9	2
9/15/2021 16:00	201.5	219.7	210.6	9.1	12.9	2
9/15/2021 17:00	197.6	220.3	209.0	11.4	16.1	2
9/15/2021 18:00	209.4	218.9	214.2	4.8	6.7	2
9/15/2021 19:00	200.6	217.6	209.1	8.5	12.0	2
9/15/2021 20:00	205.7	233.8	219.7	14.0	19.8	2
9/15/2021 21:00	207.1	237.5	222.3	15.2	21.5	2
9/15/2021 22:00	206.6	236.5	221.5	14.9	21.1	2

Saline Treatment						
QT Interval (msec)						
Date	**G180JD**	**N378ALE**	**Mean**	**SE**	**SD**	**n**
9/15/2021 23:00	208.3	232.1	220.2	11.9	16.8	2
9/16/2021 0:00	213.5	241.4	227.5	14.0	19.8	2
9/16/2021 1:00	207.1	225.8	216.5	9.3	13.2	2
9/16/2021 2:00	213.3	251.1	232.2	18.9	26.7	2
9/16/2021 3:00	208.0	231.7	219.8	11.9	16.8	2
9/16/2021 4:00	205.5	239.8	222.6	17.1	24.2	2
9/16/2021 5:00	NaN	234.2	234.2	0.0	0.0	1
9/16/2021 6:00	NaN	238.0	238.0	0.0	0.0	1
9/16/2021 7:00	NaN	203.9	203.9	0.0	0.0	1
9/16/2021 8:00	NaN	203.1	203.1	0.0	0.0	1
9/16/2021 9:00	NaN	209.1	209.1	0.0	0.0	1
9/16/2021 10:00	NaN	213.8	213.8	0.0	0.0	1
9/16/2021 11:00	NaN	208.6	208.6	0.0	0.0	1
9/16/2021 12:00	NaN	217.8	217.8	0.0	0.0	1
9/16/2021 13:00	NaN	206.1	206.1	0.0	0.0	1
9/16/2021 14:00	NaN	211.6	211.6	0.0	0.0	1
9/16/2021 15:00	NaN	197.1	197.1	0.0	0.0	1
9/16/2021 16:00	NaN	208.4	208.4	0.0	0.0	1
9/16/2021 17:00	NaN	209.3	209.3	0.0	0.0	1
9/16/2021 18:00	NaN	213.7	213.7	0.0	0.0	1
9/16/2021 19:00	NaN	222.5	222.5	0.0	0.0	1
9/16/2021 20:00	NaN	234.7	234.7	0.0	0.0	1

Table 17: RR Interval (msec) Saline Treatment

Saline Treatment						
RR Interval (msec)						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/10/2021 16:00	301.0	541.9	421.5	120.5	170.4	2
9/10/2021 17:00	345.1	527.1	436.1	91.0	128.7	2
9/10/2021 18:00	349.9	579.1	464.5	114.6	162.1	2
9/10/2021 19:00	416.8	635.7	526.2	109.4	154.7	2
9/10/2021 20:00	399.9	682.6	541.2	141.4	199.9	2
9/10/2021 21:00	392.7	663.5	528.1	135.4	191.5	2
9/10/2021 22:00	382.2	667.5	524.9	142.7	201.7	2
9/10/2021 23:00	388.6	646.2	517.4	128.8	182.1	2
9/11/2021 0:00	380.7	667.2	523.9	143.3	202.6	2
9/11/2021 1:00	360.6	660.0	510.3	149.7	211.7	2
9/11/2021 2:00	376.3	702.0	539.2	162.8	230.3	2
9/11/2021 3:00	367.2	696.4	531.8	164.6	232.8	2
9/11/2021 4:00	367.8	694.6	531.2	163.4	231.1	2
9/11/2021 5:00	364.2	711.2	537.7	173.5	245.4	2
9/11/2021 6:00	383.7	698.2	541.0	157.2	222.3	2
9/11/2021 7:00	326.4	614.0	470.2	143.8	203.4	2
9/11/2021 8:00	329.8	557.8	443.8	114.0	161.2	2
9/11/2021 9:00	365.8	569.9	467.8	102.0	144.3	2
9/11/2021 10:00	372.1	698.9	535.5	163.4	231.1	2
9/11/2021 11:00	346.8	568.6	457.7	110.9	156.8	2
9/11/2021 12:00	360.5	641.1	500.8	140.3	198.5	2
9/11/2021 13:00	324.4	513.7	419.0	94.7	133.9	2
9/11/2021 14:00	353.3	630.0	491.6	138.4	195.7	2
9/11/2021 15:00	374.5	549.1	461.8	87.3	123.5	2
9/11/2021 16:00	349.2	577.8	463.5	114.3	161.7	2
9/11/2021 17:00	346.5	522.7	434.6	88.1	124.6	2
9/11/2021 18:00	348.2	541.6	444.9	96.7	136.8	2
9/11/2021 19:00	381.4	607.3	494.4	113.0	159.8	2
9/11/2021 20:00	390.5	666.0	528.3	137.7	194.8	2
9/11/2021 21:00	365.7	634.8	500.3	134.5	190.3	2
9/11/2021 22:00	383.0	679.6	531.3	148.3	209.7	2

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Saline Treatment						
RR Interval (msec)						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/11/2021 23:00	365.1	667.2	516.1	151.1	213.6	2
9/12/2021 0:00	367.0	711.0	539.0	172.0	243.2	2
9/12/2021 1:00	391.3	725.9	558.6	167.3	236.7	2
9/12/2021 2:00	378.5	726.5	552.5	174.0	246.1	2
9/12/2021 3:00	372.4	733.4	552.9	180.5	255.2	2
9/12/2021 4:00	385.7	725.6	555.7	169.9	240.3	2
9/12/2021 5:00	388.4	752.3	570.4	181.9	257.3	2
9/12/2021 6:00	402.2	698.2	550.2	148.0	209.2	2
9/12/2021 7:00	329.8	568.7	449.2	119.5	169.0	2
9/12/2021 8:00	324.5	570.9	447.7	123.2	174.2	2
9/12/2021 9:00	352.2	579.7	465.9	113.7	160.8	2
9/12/2021 10:00	347.2	601.4	474.3	127.1	179.8	2
9/12/2021 11:00	383.0	631.6	507.3	124.3	175.8	2
9/12/2021 12:00	400.1	726.9	563.5	163.4	231.1	2
9/12/2021 13:00	333.8	537.5	435.6	101.8	144.0	2
9/12/2021 14:00	377.5	620.0	498.7	121.3	171.5	2
9/12/2021 15:00	330.4	557.0	443.7	113.3	160.2	2
9/12/2021 16:00	341.2	567.6	454.4	113.2	160.0	2
9/12/2021 17:00	355.5	608.3	481.9	126.4	178.7	2
9/12/2021 18:00	363.1	584.2	473.7	110.5	156.3	2
9/12/2021 19:00	422.1	725.1	573.6	151.5	214.3	2
9/12/2021 20:00	421.8	769.7	595.7	173.9	245.9	2
9/12/2021 21:00	446.8	783.7	615.2	168.4	238.2	2
9/12/2021 22:00	394.5	761.5	578.0	183.5	259.5	2
9/12/2021 23:00	383.9	775.3	579.6	195.7	276.7	2
9/13/2021 0:00	407.2	817.2	612.2	205.0	289.9	2
9/13/2021 1:00	453.0	788.5	620.7	167.8	237.2	2
9/13/2021 2:00	434.5	807.8	621.1	186.6	264.0	2
9/13/2021 3:00	420.4	802.2	611.3	190.9	269.9	2
9/13/2021 4:00	412.7	790.0	601.3	188.6	266.8	2
9/13/2021 5:00	419.6	771.4	595.5	175.9	248.8	2
9/13/2021 6:00	408.2	746.2	577.2	169.0	239.0	2

Saline Treatment						
RR Interval (msec)						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/13/2021 7:00	378.1	643.8	511.0	132.8	187.9	2
9/13/2021 8:00	317.0	520.3	418.7	101.6	143.7	2
9/13/2021 9:00	288.5	315.8	302.1	13.7	19.3	2
9/13/2021 10:00	321.4	404.4	362.9	41.5	58.7	2
9/13/2021 11:00	304.5	552.2	428.3	123.9	175.2	2
9/13/2021 12:00	334.4	577.4	455.9	121.5	171.8	2
9/13/2021 13:00	353.3	593.8	473.5	120.3	170.1	2
9/13/2021 14:00	306.9	503.8	405.3	98.4	139.2	2
9/13/2021 15:00	316.6	454.9	385.7	69.1	97.8	2
9/13/2021 16:00	355.6	495.4	425.5	69.9	98.8	2
9/13/2021 17:00	355.8	450.6	403.2	47.4	67.0	2
9/13/2021 18:00	357.8	408.6	383.2	25.4	36.0	2
9/13/2021 19:00	328.4	528.7	428.5	100.2	141.6	2
9/13/2021 20:00	409.4	578.9	494.1	84.7	119.8	2
9/13/2021 21:00	381.3	615.0	498.1	116.8	165.2	2
9/13/2021 22:00	391.6	675.6	533.6	142.0	200.8	2
9/13/2021 23:00	363.6	714.7	539.2	175.5	248.2	2
9/14/2021 0:00	357.1	724.4	540.7	183.6	259.7	2
9/14/2021 1:00	377.2	748.0	562.6	185.4	262.2	2
9/14/2021 2:00	382.5	703.2	542.8	160.3	226.7	2
9/14/2021 3:00	385.8	720.9	553.3	167.5	236.9	2
9/14/2021 4:00	391.7	725.0	558.3	166.7	235.7	2
9/14/2021 5:00	421.3	699.6	560.4	139.1	196.7	2
9/14/2021 6:00	411.3	664.9	538.1	126.8	179.3	2
9/14/2021 7:00	358.0	554.6	456.3	98.3	139.1	2
9/14/2021 8:00	339.7	544.6	442.2	102.5	144.9	2
9/14/2021 9:00	348.9	499.6	424.2	75.4	106.6	2
9/14/2021 10:00	375.4	560.6	468.0	92.6	131.0	2
9/14/2021 11:00	358.3	540.5	449.4	91.1	128.9	2
9/14/2021 12:00	380.7	575.9	478.3	97.6	138.0	2
9/14/2021 13:00	347.4	522.9	435.1	87.8	124.1	2
9/14/2021 14:00	330.1	537.3	433.7	103.6	146.5	2

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Saline Treatment						
RR Interval (msec)						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/14/2021 15:00	344.8	504.3	424.6	79.8	112.8	2
9/14/2021 16:00	348.4	517.7	433.1	84.7	119.7	2
9/14/2021 17:00	340.4	475.1	407.7	67.4	95.3	2
9/14/2021 18:00	338.8	446.0	392.4	53.6	75.8	2
9/14/2021 19:00	348.3	588.1	468.2	119.9	169.5	2
9/14/2021 20:00	369.7	599.4	484.6	114.9	162.4	2
9/14/2021 21:00	364.2	645.3	504.8	140.6	198.8	2
9/14/2021 22:00	349.8	588.3	469.1	119.2	168.6	2
9/14/2021 23:00	322.5	524.0	423.3	100.7	142.5	2
9/15/2021 0:00	350.7	615.2	482.9	132.2	187.0	2
9/15/2021 1:00	326.7	639.3	483.0	156.3	221.0	2
9/15/2021 2:00	324.1	687.6	505.9	181.8	257.0	2
9/15/2021 3:00	322.1	577.8	449.9	127.9	180.8	2
9/15/2021 4:00	359.6	666.6	513.1	153.5	217.0	2
9/15/2021 5:00	359.8	609.0	484.4	124.6	176.2	2
9/15/2021 6:00	368.8	634.5	501.6	132.8	187.8	2
9/15/2021 7:00	325.3	522.4	423.9	98.6	139.4	2
9/15/2021 8:00	332.2	558.1	445.1	113.0	159.7	2
9/15/2021 9:00	350.8	537.1	443.9	93.2	131.7	2
9/15/2021 10:00	339.3	529.1	434.2	94.9	134.2	2
9/15/2021 11:00	329.0	454.2	391.6	62.6	88.6	2
9/15/2021 12:00	344.9	499.3	422.1	77.2	109.1	2
9/15/2021 13:00	337.4	375.4	356.4	19.0	26.9	2
9/15/2021 14:00	317.1	366.2	341.6	24.5	34.7	2
9/15/2021 15:00	287.2	378.3	332.8	45.5	64.4	2
9/15/2021 16:00	309.3	408.2	358.7	49.4	69.9	2
9/15/2021 17:00	290.0	414.2	352.1	62.1	87.9	2
9/15/2021 18:00	308.3	394.8	351.6	43.3	61.2	2
9/15/2021 19:00	286.5	405.6	346.0	59.6	84.2	2
9/15/2021 20:00	291.9	458.4	375.1	83.2	117.7	2
9/15/2021 21:00	305.6	450.4	378.0	72.4	102.4	2
9/15/2021 22:00	301.3	438.6	369.9	68.6	97.1	2

Saline Treatment						
RR Interval (msec)						
Date	G180JD	N378ALE	Mean	SE	SD	n
9/15/2021 23:00	292.1	444.0	368.0	76.0	107.5	2
9/16/2021 0:00	309.1	456.5	382.8	73.7	104.2	2
9/16/2021 1:00	292.8	411.5	352.1	59.4	84.0	2
9/16/2021 2:00	297.8	483.3	390.5	92.8	131.2	2
9/16/2021 3:00	294.5	431.8	363.1	68.7	97.1	2
9/16/2021 4:00	313.9	451.1	382.5	68.6	97.0	2
9/16/2021 5:00	NaN	443.8	443.8	0.0	0.0	1
9/16/2021 6:00	NaN	433.1	433.1	0.0	0.0	1
9/16/2021 7:00	NaN	340.3	340.3	0.0	0.0	1
9/16/2021 8:00	NaN	337.7	337.7	0.0	0.0	1
9/16/2021 9:00	NaN	345.9	345.9	0.0	0.0	1
9/16/2021 10:00	NaN	353.7	353.7	0.0	0.0	1
9/16/2021 11:00	NaN	340.6	340.6	0.0	0.0	1
9/16/2021 12:00	NaN	365.6	365.6	0.0	0.0	1
9/16/2021 13:00	NaN	332.5	332.5	0.0	0.0	1
9/16/2021 14:00	NaN	345.3	345.3	0.0	0.0	1
9/16/2021 15:00	NaN	315.0	315.0	0.0	0.0	1
9/16/2021 16:00	NaN	338.6	338.6	0.0	0.0	1
9/16/2021 17:00	NaN	341.2	341.2	0.0	0.0	1
9/16/2021 18:00	NaN	347.9	347.9	0.0	0.0	1
9/16/2021 19:00	NaN	370.2	370.2	0.0	0.0	1
9/16/2021 20:00	NaN	419.9	419.9	0.0	0.0	1

9.2 2.06 mg/kg 3,4- diaminopyridine Treatment

9.2.1 Temperature and Activity – 2.06 mg/kg 3,4-diaminopyridine Treatment

Table 18: Temperature (°C) 2.06 mg/kg 3,4-diaminopyridine Treatment

2.06 mg/kg 3,4-diaminopyridine Treatment							
Temperature (°C)							
Date	VL90IA	YR895FD	AL793H	Mean	SE	SD	n
9/10/2021 16:00	37.6	37.4	37.9	37.6	0.1	0.2	3
9/10/2021 17:00	37.8	37.6	37.9	37.8	0.1	0.2	3
9/10/2021 18:00	37.7	37.5	38.2	37.8	0.2	0.4	3
9/10/2021 19:00	37.1	36.6	37.3	37.0	0.2	0.3	3
9/10/2021 20:00	36.7	35.8	36.5	36.4	0.3	0.5	3
9/10/2021 21:00	36.3	35.9	36.4	36.2	0.2	0.3	3
9/10/2021 22:00	36.3	36.4	36.2	36.3	0.1	0.1	3
9/10/2021 23:00	36.3	36.1	36.5	36.3	0.1	0.2	3
9/11/2021 0:00	36.0	36.0	36.7	36.2	0.2	0.4	3
9/11/2021 1:00	35.8	35.9	36.2	35.9	0.1	0.2	3
9/11/2021 2:00	36.1	35.7	36.1	36.0	0.1	0.2	3
9/11/2021 3:00	36.0	36.0	36.2	36.1	0.1	0.1	3
9/11/2021 4:00	36.4	36.1	36.3	36.2	0.1	0.1	3
9/11/2021 5:00	36.2	36.4	36.2	36.2	0.1	0.1	3
9/11/2021 6:00	36.2	36.3	36.5	36.3	0.1	0.2	3
9/11/2021 7:00	36.5	36.6	36.8	36.6	0.1	0.2	3
9/11/2021 8:00	37.2	36.7	37.3	37.1	0.2	0.3	3
9/11/2021 9:00	37.2	36.6	37.3	37.0	0.2	0.4	3
9/11/2021 10:00	37.3	36.5	37.3	37.1	0.3	0.5	3
9/11/2021 11:00	37.5	36.6	37.5	37.2	0.3	0.5	3
9/11/2021 12:00	37.6	36.5	37.6	37.2	0.4	0.7	3
9/11/2021 13:00	37.6	36.7	37.7	37.3	0.3	0.5	3
9/11/2021 14:00	37.7	36.9	37.6	37.4	0.2	0.4	3
9/11/2021 15:00	37.6	36.9	37.6	37.3	0.2	0.4	3
9/11/2021 16:00	37.1	36.9	37.6	37.2	0.2	0.4	3
9/11/2021 17:00	37.7	37.1	37.8	37.5	0.2	0.4	3
9/11/2021 18:00	37.9	37.2	38.4	37.8	0.4	0.7	3
9/11/2021 19:00	36.9	36.8	37.6	37.1	0.3	0.4	3

2.06 mg/kg 3,4-diaminopyridine Treatment							
Temperature (°C)							
Date	VL90IA	YR895FD	AL793H	Mean	SE	SD	n
9/11/2021 20:00	36.4	36.6	36.9	36.6	0.1	0.2	3
9/11/2021 21:00	35.9	35.9	36.4	36.1	0.2	0.3	3
9/11/2021 22:00	35.9	36.1	36.0	36.0	0.1	0.1	3
9/11/2021 23:00	35.9	36.1	36.2	36.0	0.1	0.2	3
9/12/2021 0:00	35.9	36.2	36.0	36.0	0.1	0.2	3
9/12/2021 1:00	36.3	35.8	35.9	36.0	0.2	0.3	3
9/12/2021 2:00	36.1	35.7	36.5	36.1	0.2	0.4	3
9/12/2021 3:00	35.9	35.9	36.4	36.1	0.2	0.3	3
9/12/2021 4:00	36.2	35.7	36.2	36.0	0.2	0.3	3
9/12/2021 5:00	36.2	36.1	36.3	36.2	0.1	0.1	3
9/12/2021 6:00	36.3	35.7	36.5	36.1	0.2	0.4	3
9/12/2021 7:00	36.7	36.2	36.8	36.6	0.2	0.3	3
9/12/2021 8:00	37.3	36.7	37.5	37.2	0.2	0.4	3
9/12/2021 9:00	37.2	36.5	37.4	37.1	0.3	0.5	3
9/12/2021 10:00	37.4	36.6	37.6	37.2	0.3	0.5	3
9/12/2021 11:00	37.5	36.8	37.6	37.3	0.3	0.5	3
9/12/2021 12:00	37.1	36.7	37.3	37.1	0.2	0.3	3
9/12/2021 13:00	37.4	36.9	37.7	37.3	0.2	0.4	3
9/12/2021 14:00	37.6	37.1	38.0	37.6	0.3	0.5	3
9/12/2021 15:00	37.7	37.4	38.0	37.7	0.2	0.3	3
9/12/2021 16:00	37.8	37.5	38.2	37.8	0.2	0.4	3
9/12/2021 17:00	37.8	37.4	38.1	37.8	0.2	0.4	3
9/12/2021 18:00	37.3	37.5	38.1	37.6	0.2	0.4	3
9/12/2021 19:00	36.6	37.0	37.0	36.8	0.1	0.2	3
9/12/2021 20:00	35.9	36.2	35.9	36.0	0.1	0.2	3
9/12/2021 21:00	35.9	36.6	36.2	36.3	0.2	0.4	3
9/12/2021 22:00	36.4	36.7	36.4	36.5	0.1	0.2	3
9/12/2021 23:00	36.2	36.2	36.4	36.3	0.1	0.1	3
9/13/2021 0:00	36.0	36.2	36.0	36.1	0.1	0.1	3
9/13/2021 1:00	35.8	35.9	36.1	35.9	0.1	0.1	3
9/13/2021 2:00	35.8	36.2	36.1	36.1	0.1	0.2	3
9/13/2021 3:00	35.9	36.2	36.0	36.0	0.1	0.1	3

2.06 mg/kg 3,4-diaminopyridine Treatment							
Temperature (°C)							
Date	VL90IA	YR895FD	AL793H	Mean	SE	SD	n
9/13/2021 4:00	35.9	36.2	36.2	36.1	0.1	0.2	3
9/13/2021 5:00	35.9	36.6	36.2	36.2	0.2	0.4	3
9/13/2021 6:00	36.1	36.2	36.2	36.2	0.1	0.1	3
9/13/2021 7:00	36.4	36.4	36.7	36.5	0.1	0.1	3
9/13/2021 8:00	37.4	36.9	37.5	37.3	0.2	0.3	3
9/13/2021 9:00	38.4	38.1	38.4	38.3	0.1	0.2	3
9/13/2021 10:00	37.9	37.3	37.9	37.7	0.2	0.3	3
9/13/2021 11:00	37.3	37.0	37.4	37.3	0.1	0.2	3
9/13/2021 12:00	37.2	36.9	37.5	37.2	0.1	0.3	3
9/13/2021 13:00	37.5	37.0	37.8	37.4	0.2	0.4	3
9/13/2021 14:00	37.9	37.4	38.1	37.8	0.2	0.4	3
9/13/2021 15:00	37.7	37.1	37.9	37.6	0.2	0.4	3
9/13/2021 16:00	37.7	37.2	37.9	37.6	0.2	0.4	3
9/13/2021 17:00	37.5	37.2	37.7	37.5	0.1	0.3	3
9/13/2021 18:00	37.4	37.1	38.1	37.5	0.3	0.5	3
9/13/2021 19:00	36.5	36.9	37.5	37.0	0.3	0.5	3
9/13/2021 20:00	35.9	35.7	36.8	36.1	0.3	0.6	3
9/13/2021 21:00	36.1	35.5	36.8	36.2	0.4	0.6	3
9/13/2021 22:00	35.8	35.5	36.6	36.0	0.3	0.6	3
9/13/2021 23:00	35.7	35.8	36.7	36.0	0.3	0.5	3
9/14/2021 0:00	36.0	35.6	36.7	36.1	0.3	0.5	3
9/14/2021 1:00	36.3	35.9	36.5	36.3	0.2	0.3	3
9/14/2021 2:00	36.2	36.1	36.4	36.2	0.1	0.2	3
9/14/2021 3:00	35.9	35.8	36.1	35.9	0.1	0.2	3
9/14/2021 4:00	35.6	35.8	36.0	35.8	0.1	0.2	3
9/14/2021 5:00	36.3	36.1	36.1	36.2	0.1	0.1	3
9/14/2021 6:00	36.5	36.4	36.2	36.4	0.1	0.1	3
9/14/2021 7:00	36.9	36.3	37.0	36.8	0.2	0.4	3
9/14/2021 8:00	37.2	36.7	37.5	37.1	0.2	0.4	3
9/14/2021 9:00	37.5	36.8	37.7	37.3	0.3	0.5	3
9/14/2021 10:00	37.1	36.6	37.4	37.0	0.2	0.4	3
9/14/2021 11:00	37.4	37.0	37.8	37.4	0.2	0.4	3

2.06 mg/kg 3,4-diaminopyridine Treatment							
Temperature (°C)							
Date	VL90IA	YR895FD	AL793H	Mean	SE	SD	n
9/14/2021 12:00	37.2	37.1	37.7	37.4	0.2	0.3	3
9/14/2021 13:00	37.6	37.3	38.1	37.7	0.2	0.4	3
9/14/2021 14:00	37.8	37.4	38.0	37.7	0.2	0.3	3
9/14/2021 15:00	37.6	37.2	37.8	37.5	0.2	0.3	3
9/14/2021 16:00	37.6	37.4	37.9	37.6	0.1	0.2	3
9/14/2021 17:00	37.4	37.4	38.2	37.7	0.3	0.5	3
9/14/2021 18:00	37.0	37.3	38.1	37.5	0.4	0.6	3
9/14/2021 19:00	36.1	37.2	37.7	37.0	0.5	0.8	3
9/14/2021 20:00	35.8	36.6	36.7	36.4	0.3	0.5	3
9/14/2021 21:00	35.7	36.7	36.7	36.4	0.3	0.6	3
9/14/2021 22:00	36.3	36.6	36.6	36.5	0.1	0.2	3
9/14/2021 23:00	36.6	37.0	37.6	37.1	0.3	0.5	3
9/15/2021 0:00	35.9	36.3	36.9	36.4	0.3	0.5	3
9/15/2021 1:00	35.9	36.7	36.7	36.4	0.3	0.4	3
9/15/2021 2:00	36.4	36.2	36.5	36.4	0.1	0.1	3
9/15/2021 3:00	36.4	36.7	37.1	36.7	0.2	0.4	3
9/15/2021 4:00	35.9	35.8	36.7	36.2	0.3	0.5	3
9/15/2021 5:00	36.4	36.4	37.0	36.6	0.2	0.3	3
9/15/2021 6:00	36.5	36.2	36.7	36.5	0.2	0.3	3
9/15/2021 7:00	37.0	36.7	36.7	36.8	0.1	0.2	3
9/15/2021 8:00	36.7	36.7	36.1	36.5	0.2	0.3	3
9/15/2021 9:00	36.6	36.8	35.8	36.4	0.3	0.5	3
9/15/2021 10:00	36.3	36.1	35.2	35.9	0.3	0.6	3
9/15/2021 11:00	35.9	36.1	NaN	36.0	0.1	0.2	2
9/15/2021 12:00	36.7	36.0	NaN	36.4	0.4	0.5	2
9/15/2021 13:00	37.0	36.2	NaN	36.6	0.4	0.6	2
9/15/2021 14:00	36.9	36.0	NaN	36.5	0.4	0.6	2
9/15/2021 15:00	36.7	35.7	NaN	36.2	0.5	0.7	2
9/15/2021 16:00	36.8	35.0	NaN	35.9	0.9	1.3	2
9/15/2021 17:00	36.8	34.4	NaN	35.6	1.2	1.7	2
9/15/2021 18:00	36.3	35.7	NaN	36.0	0.3	0.4	2
9/15/2021 19:00	35.9	36.3	NaN	36.1	0.2	0.3	2

2.06 mg/kg 3,4-diaminopyridine Treatment							
Temperature (°C)							
Date	**VL90IA**	**YR895FD**	**AL793H**	**Mean**	**SE**	**SD**	**n**
9/15/2021 20:00	36.3	NaN	NaN	36.3	0.0	0.0	1
9/15/2021 21:00	36.1	NaN	NaN	36.1	0.0	0.0	1

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Table 19: Activity 2.06 mg/kg 3,4-diaminopyridine Treatment

2.06 mg/kg 3,4-diaminopyridine Treatment							
Activity							
Date	VL90IA	YR895FD	AL793H	Mean	SE	SD	n
9/10/2021 16:00	686.9	1430.7	788.1	968.6	232.9	403.4	3
9/10/2021 17:00	1155.8	1500.3	1301.0	1319.0	99.9	173.0	3
9/10/2021 18:00	794.3	1377.2	1069.5	1080.3	168.3	291.6	3
9/10/2021 19:00	115.0	193.6	152.2	153.6	22.7	39.3	3
9/10/2021 20:00	112.9	168.8	151.9	144.5	16.5	28.6	3
9/10/2021 21:00	112.4	174.8	144.6	143.9	18.0	31.2	3
9/10/2021 22:00	162.9	185.7	186.2	178.2	7.7	13.3	3
9/10/2021 23:00	109.8	171.6	164.8	148.7	19.6	33.9	3
9/11/2021 0:00	97.8	190.9	143.6	144.1	26.9	46.6	3
9/11/2021 1:00	122.2	194.2	161.0	159.1	20.8	36.1	3
9/11/2021 2:00	115.9	178.9	162.6	152.5	18.9	32.7	3
9/11/2021 3:00	119.5	207.3	169.3	165.3	25.4	44.0	3
9/11/2021 4:00	121.4	167.3	169.9	152.9	15.7	27.3	3
9/11/2021 5:00	168.2	206.2	204.4	192.9	12.4	21.4	3
9/11/2021 6:00	129.0	200.0	153.9	161.0	20.8	36.0	3
9/11/2021 7:00	300.5	690.3	295.4	428.7	130.8	226.5	3
9/11/2021 8:00	664.6	773.3	700.3	712.8	32.0	55.4	3
9/11/2021 9:00	997.0	842.7	932.2	924.0	44.7	77.5	3
9/11/2021 10:00	923.0	727.3	764.4	804.9	60.0	104.0	3
9/11/2021 11:00	1073.0	269.7	924.0	755.6	246.7	427.3	3
9/11/2021 12:00	947.8	625.4	824.1	799.1	93.9	162.6	3
9/11/2021 13:00	504.9	462.0	600.6	522.5	41.0	71.0	3
9/11/2021 14:00	1100.6	615.5	839.5	851.9	140.2	242.8	3
9/11/2021 15:00	762.9	585.5	595.3	647.9	57.6	99.7	3
9/11/2021 16:00	225.4	707.5	220.7	384.5	161.5	279.7	3
9/11/2021 17:00	1425.9	1182.3	1773.4	1460.5	171.5	297.1	3
9/11/2021 18:00	752.1	941.6	1320.7	1004.8	167.2	289.5	3
9/11/2021 19:00	133.2	239.4	166.2	179.6	31.4	54.3	3
9/11/2021 20:00	113.1	168.9	148.5	143.5	16.3	28.2	3
9/11/2021 21:00	108.8	174.2	157.7	146.9	19.6	34.0	3
9/11/2021 22:00	120.8	173.3	154.1	149.4	15.3	26.6	3

2.06 mg/kg 3,4-diaminopyridine Treatment							
Activity							
Date	VL90IA	YR895FD	AL793H	Mean	SE	SD	n
9/11/2021 23:00	115.9	212.8	148.7	159.2	28.5	49.3	3
9/12/2021 0:00	137.9	171.6	165.4	158.3	10.4	17.9	3
9/12/2021 1:00	154.5	171.0	163.9	163.1	4.8	8.3	3
9/12/2021 2:00	120.4	212.3	151.2	161.3	27.0	46.8	3
9/12/2021 3:00	120.6	172.3	157.3	150.1	15.4	26.6	3
9/12/2021 4:00	134.0	192.1	165.5	163.8	16.8	29.1	3
9/12/2021 5:00	145.5	195.6	173.0	171.4	14.5	25.1	3
9/12/2021 6:00	153.4	176.9	165.9	165.4	6.8	11.7	3
9/12/2021 7:00	400.3	870.6	542.5	604.5	139.3	241.2	3
9/12/2021 8:00	772.4	1089.8	934.7	932.3	91.6	158.7	3
9/12/2021 9:00	923.4	674.5	755.5	784.5	73.3	126.9	3
9/12/2021 10:00	1491.3	976.8	1518.7	1328.9	176.3	305.3	3
9/12/2021 11:00	542.7	649.9	562.8	585.1	32.9	57.0	3
9/12/2021 12:00	411.9	410.2	404.9	409.0	2.1	3.7	3
9/12/2021 13:00	581.8	760.9	655.4	666.0	52.0	90.0	3
9/12/2021 14:00	742.5	989.0	800.7	844.1	74.4	128.9	3
9/12/2021 15:00	1547.5	1135.7	1579.9	1421.0	143.0	247.6	3
9/12/2021 16:00	1140.5	1267.1	1304.8	1237.5	49.7	86.1	3
9/12/2021 17:00	669.3	1207.7	799.7	892.2	162.2	280.9	3
9/12/2021 18:00	335.8	1575.5	435.7	782.3	397.6	688.7	3
9/12/2021 19:00	114.6	279.0	147.3	180.3	50.2	87.0	3
9/12/2021 20:00	113.2	242.7	154.5	170.1	38.2	66.1	3
9/12/2021 21:00	114.6	234.3	159.6	169.5	34.9	60.5	3
9/12/2021 22:00	111.4	165.0	151.9	142.8	16.2	28.0	3
9/12/2021 23:00	112.1	167.6	151.5	143.7	16.5	28.5	3
9/13/2021 0:00	144.8	184.0	196.2	175.0	15.5	26.9	3
9/13/2021 1:00	117.5	157.9	144.3	139.9	11.9	20.6	3
9/13/2021 2:00	140.5	170.9	172.4	161.3	10.4	18.0	3
9/13/2021 3:00	129.5	162.3	172.5	154.8	13.0	22.4	3
9/13/2021 4:00	180.9	172.5	187.5	180.3	4.3	7.5	3
9/13/2021 5:00	139.5	173.1	170.1	160.9	10.7	18.6	3
9/13/2021 6:00	148.0	192.6	166.3	168.9	12.9	22.4	3

2.06 mg/kg 3,4-diaminopyridine Treatment							
Activity							
Date	VL90IA	YR895FD	AL793H	Mean	SE	SD	n
9/13/2021 7:00	236.6	478.0	278.0	330.8	74.5	129.1	3
9/13/2021 8:00	605.0	699.9	670.0	658.3	28.0	48.5	3
9/13/2021 9:00	897.7	843.5	1229.5	990.2	120.7	209.0	3
9/13/2021 10:00	1159.9	1168.3	955.7	1094.6	69.5	120.4	3
9/13/2021 11:00	697.1	1123.6	792.4	871.0	129.2	223.9	3
9/13/2021 12:00	584.3	914.0	668.6	722.3	98.9	171.3	3
9/13/2021 13:00	473.3	707.4	617.8	599.5	68.2	118.1	3
9/13/2021 14:00	412.4	500.8	567.9	493.7	45.0	78.0	3
9/13/2021 15:00	668.5	552.8	759.0	660.1	59.7	103.4	3
9/13/2021 16:00	833.6	906.3	806.9	849.0	29.7	51.4	3
9/13/2021 17:00	696.0	795.3	964.2	818.5	78.3	135.6	3
9/13/2021 18:00	542.0	1088.5	1192.2	940.9	201.7	349.3	3
9/13/2021 19:00	126.5	260.2	187.2	191.3	38.7	67.0	3
9/13/2021 20:00	114.1	168.7	167.6	150.1	18.0	31.2	3
9/13/2021 21:00	104.1	198.1	148.2	150.1	27.1	47.0	3
9/13/2021 22:00	128.1	168.2	170.3	155.5	13.7	23.8	3
9/13/2021 23:00	109.2	199.4	147.7	152.1	26.1	45.2	3
9/14/2021 0:00	108.8	187.9	150.0	148.9	22.9	39.6	3
9/14/2021 1:00	121.9	174.1	154.7	150.2	15.3	26.4	3
9/14/2021 2:00	139.3	169.3	158.3	155.6	8.7	15.1	3
9/14/2021 3:00	129.4	165.2	169.0	154.5	12.6	21.8	3
9/14/2021 4:00	138.5	170.8	156.1	155.1	9.3	16.2	3
9/14/2021 5:00	127.7	184.7	177.5	163.3	17.9	31.0	3
9/14/2021 6:00	171.3	200.2	211.1	194.2	11.9	20.6	3
9/14/2021 7:00	466.9	612.7	552.2	543.9	42.3	73.2	3
9/14/2021 8:00	474.6	542.6	611.6	542.9	39.5	68.5	3
9/14/2021 9:00	635.0	662.5	758.8	685.4	37.5	65.0	3
9/14/2021 10:00	711.1	586.0	799.3	698.8	61.9	107.2	3
9/14/2021 11:00	619.8	802.3	724.1	715.4	52.9	91.6	3
9/14/2021 12:00	551.6	661.7	649.7	621.0	34.8	60.4	3
9/14/2021 13:00	569.1	670.1	700.1	646.4	39.6	68.6	3
9/14/2021 14:00	572.2	530.6	689.6	597.5	47.6	82.4	3

2.06 mg/kg 3,4-diaminopyridine Treatment							
Activity							
Date	VL90IA	YR895FD	AL793H	Mean	SE	SD	n
9/14/2021 15:00	599.1	662.7	607.6	623.1	19.9	34.5	3
9/14/2021 16:00	606.1	901.3	915.3	807.6	100.8	174.6	3
9/14/2021 17:00	548.2	766.0	917.7	743.9	107.2	185.8	3
9/14/2021 18:00	208.6	679.1	471.7	453.1	136.2	235.8	3
9/14/2021 19:00	104.1	197.5	178.0	159.9	28.5	49.3	3
9/14/2021 20:00	146.6	270.2	246.0	220.9	37.8	65.5	3
9/14/2021 21:00	105.0	195.2	172.9	157.7	27.1	47.0	3
9/14/2021 22:00	238.6	378.3	470.3	362.4	67.4	116.7	3
9/14/2021 23:00	182.3	335.6	356.7	291.5	55.0	95.2	3
9/15/2021 0:00	119.2	217.7	204.5	180.5	30.9	53.5	3
9/15/2021 1:00	172.4	232.9	277.1	227.5	30.3	52.6	3
9/15/2021 2:00	194.7	287.7	317.1	266.5	36.9	63.9	3
9/15/2021 3:00	231.8	401.0	412.4	348.4	58.4	101.1	3
9/15/2021 4:00	189.1	222.5	320.6	244.1	39.5	68.3	3
9/15/2021 5:00	166.3	276.6	331.0	258.0	48.4	83.9	3
9/15/2021 6:00	267.8	274.9	375.0	305.9	34.6	59.9	3
9/15/2021 7:00	325.5	385.9	461.3	390.9	39.3	68.0	3
9/15/2021 8:00	353.6	415.6	433.4	400.9	24.2	41.9	3
9/15/2021 9:00	321.1	360.6	339.3	340.3	11.4	19.8	3
9/15/2021 10:00	337.2	318.2	301.2	318.9	10.4	18.0	3
9/15/2021 11:00	354.4	305.7	NaN	330.0	24.3	34.4	2
9/15/2021 12:00	242.0	328.5	NaN	285.2	43.3	61.2	2
9/15/2021 13:00	297.7	270.1	NaN	283.9	13.8	19.6	2
9/15/2021 14:00	315.1	274.3	NaN	294.7	20.4	28.9	2
9/15/2021 15:00	422.0	259.6	NaN	340.8	81.2	114.8	2
9/15/2021 16:00	254.7	306.3	NaN	280.5	25.8	36.5	2
9/15/2021 17:00	314.0	322.7	NaN	318.4	4.3	6.1	2
9/15/2021 18:00	298.8	316.1	NaN	307.4	8.7	12.3	2
9/15/2021 19:00	300.8	330.6	NaN	315.7	14.9	21.1	2
9/15/2021 20:00	264.7	NaN	NaN	264.7	0.0	0.0	1
9/15/2021 21:00	243.7	NaN	NaN	243.7	0.0	0.0	1

9.2.2 Respiratory Parameters – 2.06 mg/kg 3,4-diaminopyridine Treatment

Table 20: Tidal Volume (mL) 2.06 mg/kg 3,4-diaminopyridine Treatment

2.06 mg/kg 3,4-diaminopyridine Treatment							
Tidal Volume (mL)							
Date	VL90IA	YR895FD	AL793H	Mean	SE	SD	n
9/10/2021 16:00	93.3	110.4	93.3	99.0	5.7	9.9	3
9/10/2021 17:00	104.3	106.7	104.3	105.1	0.8	1.4	3
9/10/2021 18:00	86.4	104.7	86.4	92.5	6.1	10.5	3
9/10/2021 19:00	69.5	48.4	69.5	62.5	7.0	12.2	3
9/10/2021 20:00	77.0	45.0	77.0	66.3	10.7	18.5	3
9/10/2021 21:00	85.1	46.4	85.1	72.2	12.9	22.3	3
9/10/2021 22:00	83.0	49.4	83.0	71.8	11.2	19.4	3
9/10/2021 23:00	73.5	57.6	73.5	68.2	5.3	9.2	3
9/11/2021 0:00	71.9	52.8	71.9	65.5	6.4	11.0	3
9/11/2021 1:00	77.7	51.8	77.7	69.0	8.6	14.9	3
9/11/2021 2:00	74.6	52.2	74.6	67.1	7.5	12.9	3
9/11/2021 3:00	71.9	51.0	71.9	65.0	7.0	12.1	3
9/11/2021 4:00	74.4	46.6	74.4	65.2	9.3	16.0	3
9/11/2021 5:00	78.0	51.7	78.0	69.3	8.8	15.2	3
9/11/2021 6:00	67.4	50.1	67.4	61.7	5.8	10.0	3
9/11/2021 7:00	81.9	93.3	81.9	85.7	3.8	6.6	3
9/11/2021 8:00	95.7	97.2	95.7	96.2	0.5	0.9	3
9/11/2021 9:00	101.5	104.3	101.5	102.4	0.9	1.6	3
9/11/2021 10:00	93.5	93.7	93.5	93.6	0.1	0.1	3
9/11/2021 11:00	108.5	66.2	108.5	94.4	14.1	24.4	3
9/11/2021 12:00	99.4	97.2	99.4	98.7	0.7	1.3	3
9/11/2021 13:00	90.8	82.8	90.8	88.1	2.6	4.6	3
9/11/2021 14:00	100.3	97.6	100.3	99.4	0.9	1.6	3
9/11/2021 15:00	98.8	99.1	98.8	98.9	0.1	0.2	3
9/11/2021 16:00	85.9	94.6	85.9	88.8	2.9	5.0	3
9/11/2021 17:00	111.1	126.5	111.1	116.2	5.1	8.9	3
9/11/2021 18:00	93.0	93.5	93.0	93.1	0.2	0.3	3
9/11/2021 19:00	70.3	56.7	70.3	65.8	4.5	7.9	3
9/11/2021 20:00	85.9	52.4	85.9	74.8	11.2	19.4	3
9/11/2021 21:00	84.8	54.0	84.8	74.5	10.3	17.8	3

2.06 mg/kg 3,4-diaminopyridine Treatment							
Tidal Volume (mL)							
Date	VL90IA	YR895FD	AL793H	Mean	SE	SD	n
9/11/2021 22:00	80.7	55.2	80.7	72.2	8.5	14.7	3
9/11/2021 23:00	78.1	62.7	78.1	73.0	5.1	8.9	3
9/12/2021 0:00	86.8	55.2	86.8	76.3	10.5	18.2	3
9/12/2021 1:00	77.6	59.7	77.6	71.6	6.0	10.4	3
9/12/2021 2:00	68.3	64.2	68.3	67.0	1.4	2.4	3
9/12/2021 3:00	79.8	53.9	79.8	71.2	8.7	15.0	3
9/12/2021 4:00	78.9	62.6	78.9	73.4	5.4	9.4	3
9/12/2021 5:00	78.5	52.0	78.5	69.7	8.8	15.3	3
9/12/2021 6:00	76.6	52.3	76.6	68.5	8.1	14.0	3
9/12/2021 7:00	87.0	99.9	87.0	91.3	4.3	7.5	3
9/12/2021 8:00	107.5	105.8	107.5	106.9	0.6	1.0	3
9/12/2021 9:00	103.1	89.8	103.1	98.7	4.4	7.7	3
9/12/2021 10:00	109.7	86.3	109.7	101.9	7.8	13.5	3
9/12/2021 11:00	78.2	75.0	78.2	77.1	1.0	1.8	3
9/12/2021 12:00	85.7	76.7	85.7	82.7	3.0	5.2	3
9/12/2021 13:00	94.6	96.9	94.6	95.3	0.8	1.3	3
9/12/2021 14:00	86.4	102.5	86.4	91.8	5.4	9.3	3
9/12/2021 15:00	109.5	90.9	109.5	103.3	6.2	10.7	3
9/12/2021 16:00	98.2	98.6	98.2	98.4	0.1	0.2	3
9/12/2021 17:00	87.5	117.9	87.5	97.6	10.1	17.5	3
9/12/2021 18:00	78.3	117.9	78.3	91.5	13.2	22.8	3
9/12/2021 19:00	72.4	51.3	72.4	65.4	7.0	12.2	3
9/12/2021 20:00	83.7	59.3	83.7	75.6	8.1	14.1	3
9/12/2021 21:00	75.5	46.2	75.5	65.7	9.8	16.9	3
9/12/2021 22:00	80.0	44.0	80.0	68.0	12.0	20.8	3
9/12/2021 23:00	68.4	47.9	68.4	61.6	6.9	11.9	3
9/13/2021 0:00	81.5	50.8	81.5	71.2	10.2	17.7	3
9/13/2021 1:00	61.8	49.1	61.8	57.6	4.2	7.3	3
9/13/2021 2:00	67.6	53.2	67.6	62.8	4.8	8.3	3
9/13/2021 3:00	69.3	46.0	69.3	61.5	7.8	13.5	3
9/13/2021 4:00	65.6	49.8	65.6	60.3	5.2	9.1	3
9/13/2021 5:00	63.0	48.3	63.0	58.1	4.9	8.4	3

2.06 mg/kg 3,4-diaminopyridine Treatment							
Tidal Volume (mL)							
Date	VL90IA	YR895FD	AL793H	Mean	SE	SD	n
9/13/2021 6:00	55.9	55.7	55.9	55.9	0.1	0.1	3
9/13/2021 7:00	76.1	87.8	76.1	80.0	3.9	6.8	3
9/13/2021 8:00	94.1	86.6	94.1	91.6	2.5	4.3	3
9/13/2021 9:00	86.3	82.0	86.3	84.8	1.4	2.4	3
9/13/2021 10:00	92.3	97.5	92.3	94.1	1.7	3.0	3
9/13/2021 11:00	88.8	95.7	88.8	91.1	2.3	4.0	3
9/13/2021 12:00	91.6	101.2	91.6	94.8	3.2	5.5	3
9/13/2021 13:00	85.8	93.7	85.8	88.4	2.7	4.6	3
9/13/2021 14:00	83.3	79.8	83.3	82.1	1.2	2.0	3
9/13/2021 15:00	90.1	80.5	90.1	86.9	3.2	5.6	3
9/13/2021 16:00	94.2	105.6	94.2	98.0	3.8	6.6	3
9/13/2021 17:00	95.5	104.1	95.5	98.4	2.9	5.0	3
9/13/2021 18:00	93.3	118.3	93.3	101.7	8.3	14.4	3
9/13/2021 19:00	71.4	66.8	71.4	69.9	1.5	2.7	3
9/13/2021 20:00	77.1	57.9	77.1	70.7	6.4	11.1	3
9/13/2021 21:00	63.3	52.8	63.3	59.8	3.5	6.0	3
9/13/2021 22:00	70.9	44.2	70.9	62.0	8.9	15.4	3
9/13/2021 23:00	68.6	54.7	68.6	64.0	4.6	8.0	3
9/14/2021 0:00	67.1	53.6	67.1	62.6	4.5	7.8	3
9/14/2021 1:00	66.5	41.9	66.5	58.3	8.2	14.2	3
9/14/2021 2:00	65.7	57.0	65.7	62.8	2.9	5.0	3
9/14/2021 3:00	76.4	57.3	76.4	70.0	6.4	11.1	3
9/14/2021 4:00	73.7	64.1	73.7	70.5	3.2	5.5	3
9/14/2021 5:00	62.7	56.3	62.7	60.6	2.1	3.7	3
9/14/2021 6:00	66.3	53.9	66.3	62.2	4.1	7.1	3
9/14/2021 7:00	89.2	94.7	89.2	91.1	1.8	3.1	3
9/14/2021 8:00	97.0	88.5	97.0	94.2	2.9	4.9	3
9/14/2021 9:00	93.9	89.8	93.9	92.5	1.4	2.4	3
9/14/2021 10:00	104.8	84.5	104.8	98.0	6.8	11.7	3
9/14/2021 11:00	93.4	95.1	93.4	93.9	0.6	1.0	3
9/14/2021 12:00	96.0	86.2	96.0	92.7	3.3	5.7	3
9/14/2021 13:00	99.5	82.6	99.5	93.9	5.6	9.7	3

2.06 mg/kg 3,4-diaminopyridine Treatment							
Tidal Volume (mL)							
Date	VL90IA	YR895FD	AL793H	Mean	SE	SD	n
9/14/2021 14:00	91.8	76.0	91.8	86.6	5.3	9.1	3
9/14/2021 15:00	93.8	79.2	93.8	88.9	4.9	8.4	3
9/14/2021 16:00	91.4	87.1	91.4	89.9	1.4	2.5	3
9/14/2021 17:00	95.8	87.1	95.8	92.9	2.9	5.0	3
9/14/2021 18:00	72.3	79.6	72.3	74.8	2.4	4.2	3
9/14/2021 19:00	59.7	50.3	59.7	56.6	3.1	5.4	3
9/14/2021 20:00	70.2	60.0	70.2	66.8	3.4	5.8	3
9/14/2021 21:00	60.4	50.9	60.4	57.2	3.2	5.5	3
9/14/2021 22:00	74.1	62.3	74.1	70.1	3.9	6.8	3
9/14/2021 23:00	69.3	47.9	69.3	62.2	7.1	12.4	3
9/15/2021 0:00	63.9	46.5	63.9	58.1	5.8	10.0	3
9/15/2021 1:00	66.9	47.3	66.9	60.4	6.5	11.3	3
9/15/2021 2:00	67.7	52.8	67.7	62.7	5.0	8.6	3
9/15/2021 3:00	69.0	48.3	69.0	62.1	6.9	11.9	3
9/15/2021 4:00	69.6	43.3	69.6	60.9	8.8	15.2	3
9/15/2021 5:00	56.4	45.8	56.4	52.9	3.5	6.1	3
9/15/2021 6:00	65.9	46.6	65.9	59.5	6.4	11.2	3
9/15/2021 7:00	69.5	47.0	69.5	62.0	7.5	13.0	3
9/15/2021 8:00	67.3	46.3	67.3	60.3	7.0	12.1	3
9/15/2021 9:00	62.9	40.9	62.9	55.6	7.4	12.7	3
9/15/2021 10:00	62.0	38.4	62.0	54.1	7.9	13.6	3
9/15/2021 11:00	62.4	38.7	NaN	50.5	11.8	16.7	2
9/15/2021 12:00	56.6	35.6	NaN	46.1	10.5	14.8	2
9/15/2021 13:00	51.9	34.2	NaN	43.0	8.9	12.5	2
9/15/2021 14:00	51.3	34.3	NaN	42.8	8.5	12.0	2
9/15/2021 15:00	55.5	33.8	NaN	44.6	10.9	15.4	2
9/15/2021 16:00	37.9	35.5	NaN	36.7	1.2	1.7	2
9/15/2021 17:00	49.3	35.8	NaN	42.5	6.8	9.6	2
9/15/2021 18:00	41.9	33.3	NaN	37.6	4.3	6.1	2
9/15/2021 19:00	44.3	33.4	NaN	38.9	5.4	7.7	2
9/15/2021 20:00	37.0	NaN	NaN	37.0	0.0	0.0	1
9/15/2021 21:00	35.7	NaN	NaN	35.7	0.0	0.0	1

Table 21: Minute Volume (mL/sec) 2.06 mg/kg 3,4-diaminopyridine Treatment

2.06 mg/kg 3,4-diaminopyridine Treatment							
Minute Volume (mL/sec)							
Date	VL90IA	YR895FD	AL793H	Mean	SE	SD	n
9/10/2021 16:00	3465.3	4084.3	3465.3	3671.6	206.3	357.4	3
9/10/2021 17:00	4081.0	4014.7	4081.0	4058.9	22.1	38.3	3
9/10/2021 18:00	3077.9	3744.8	3077.9	3300.2	222.3	385.0	3
9/10/2021 19:00	1660.5	1441.3	1660.5	1587.4	73.1	126.6	3
9/10/2021 20:00	1734.3	1208.7	1734.3	1559.1	175.2	303.5	3
9/10/2021 21:00	1939.2	1256.9	1939.2	1711.8	227.4	393.9	3
9/10/2021 22:00	2226.1	1302.5	2226.1	1918.2	307.9	533.2	3
9/10/2021 23:00	1883.0	1462.6	1883.0	1742.9	140.1	242.7	3
9/11/2021 0:00	1799.0	1287.1	1799.0	1628.4	170.6	295.5	3
9/11/2021 1:00	1905.7	1290.2	1905.7	1700.5	205.2	355.4	3
9/11/2021 2:00	1812.3	1277.5	1812.3	1634.0	178.3	308.8	3
9/11/2021 3:00	1730.1	1286.7	1730.1	1582.3	147.8	256.0	3
9/11/2021 4:00	1913.8	1177.4	1913.8	1668.3	245.5	425.2	3
9/11/2021 5:00	2043.4	1270.9	2043.4	1785.9	257.5	446.0	3
9/11/2021 6:00	1714.0	1271.6	1714.0	1566.5	147.5	255.4	3
9/11/2021 7:00	2242.7	2340.4	2242.7	2275.3	32.6	56.4	3
9/11/2021 8:00	3119.6	2710.4	3119.6	2983.2	136.4	236.3	3
9/11/2021 9:00	3414.9	2832.5	3414.9	3220.8	194.1	336.2	3
9/11/2021 10:00	3250.0	2773.4	3250.0	3091.1	158.9	275.2	3
9/11/2021 11:00	3904.3	2043.0	3904.3	3283.9	620.4	1074.6	3
9/11/2021 12:00	3364.0	2833.0	3364.0	3187.0	177.0	306.6	3
9/11/2021 13:00	3272.1	2574.1	3272.1	3039.4	232.7	403.0	3
9/11/2021 14:00	3685.7	3093.6	3685.7	3488.3	197.4	341.8	3
9/11/2021 15:00	3315.0	2878.5	3315.0	3169.5	145.5	252.0	3
9/11/2021 16:00	2916.1	2946.6	2916.1	2926.3	10.2	17.6	3
9/11/2021 17:00	4198.1	3944.0	4198.1	4113.4	84.7	146.7	3
9/11/2021 18:00	3397.4	3036.6	3397.4	3277.1	120.3	208.3	3
9/11/2021 19:00	1994.2	1653.3	1994.2	1880.6	113.6	196.8	3
9/11/2021 20:00	2355.5	1464.3	2355.5	2058.4	297.1	514.5	3
9/11/2021 21:00	2180.3	1504.0	2180.3	1954.9	225.4	390.5	3
9/11/2021 22:00	2102.1	1483.7	2102.1	1896.0	206.1	357.0	3

2.06 mg/kg 3,4-diaminopyridine Treatment							
Minute Volume (mL/sec)							
Date	**VL90IA**	**YR895FD**	**AL793H**	**Mean**	**SE**	**SD**	**n**
9/11/2021 23:00	2114.3	1749.6	2114.3	1992.7	121.6	210.6	3
9/12/2021 0:00	2336.7	1465.4	2336.7	2046.3	290.4	503.0	3
9/12/2021 1:00	1928.4	1508.3	1928.4	1788.4	140.0	242.5	3
9/12/2021 2:00	2142.1	1729.9	2142.1	2004.7	137.4	238.0	3
9/12/2021 3:00	2020.6	1405.6	2020.6	1815.6	205.0	355.1	3
9/12/2021 4:00	2101.5	1726.3	2101.5	1976.4	125.1	216.6	3
9/12/2021 5:00	2203.4	1313.0	2203.4	1906.6	296.8	514.1	3
9/12/2021 6:00	2116.3	1286.4	2116.3	1839.7	276.6	479.1	3
9/12/2021 7:00	2489.3	2614.8	2489.3	2531.1	41.8	72.5	3
9/12/2021 8:00	3741.1	3087.0	3741.1	3523.1	218.0	377.6	3
9/12/2021 9:00	3557.9	2298.8	3557.9	3138.2	419.7	726.9	3
9/12/2021 10:00	4039.6	2478.2	4039.6	3519.1	520.5	901.5	3
9/12/2021 11:00	2269.7	2269.6	2269.7	2269.7	0.0	0.1	3
9/12/2021 12:00	2433.4	2383.9	2433.4	2416.9	16.5	28.6	3
9/12/2021 13:00	3160.2	3197.0	3160.2	3172.5	12.3	21.2	3
9/12/2021 14:00	2935.1	3283.1	2935.1	3051.1	116.0	200.9	3
9/12/2021 15:00	4116.3	3053.0	4116.3	3761.9	354.4	613.9	3
9/12/2021 16:00	3555.8	3290.7	3555.8	3467.4	88.4	153.1	3
9/12/2021 17:00	2942.1	3949.3	2942.1	3277.8	335.7	581.5	3
9/12/2021 18:00	2425.5	4113.5	2425.5	2988.2	562.7	974.6	3
9/12/2021 19:00	1721.8	1795.8	1721.8	1746.5	24.7	42.7	3
9/12/2021 20:00	2158.8	1617.2	2158.8	1978.3	180.5	312.7	3
9/12/2021 21:00	1789.0	1305.4	1789.0	1627.8	161.2	279.2	3
9/12/2021 22:00	1814.0	1132.3	1814.0	1586.8	227.2	393.6	3
9/12/2021 23:00	1711.6	1331.0	1711.6	1584.7	126.9	219.7	3
9/13/2021 0:00	2051.6	1251.9	2051.6	1785.0	266.6	461.7	3
9/13/2021 1:00	1531.7	1228.4	1531.7	1430.6	101.1	175.1	3
9/13/2021 2:00	1721.8	1307.1	1721.8	1583.6	138.2	239.4	3
9/13/2021 3:00	1632.9	1110.1	1632.9	1458.6	174.3	301.8	3
9/13/2021 4:00	1641.3	1221.9	1641.3	1501.5	139.8	242.1	3
9/13/2021 5:00	1542.5	1235.5	1542.5	1440.2	102.3	177.2	3
9/13/2021 6:00	1465.9	1396.9	1465.9	1442.9	23.0	39.8	3

2.06 mg/kg 3,4-diaminopyridine Treatment							
Minute Volume (mL/sec)							
Date	**VL90IA**	**YR895FD**	**AL793H**	**Mean**	**SE**	**SD**	**n**
9/13/2021 7:00	1941.0	2097.4	1941.0	1993.1	52.1	90.3	3
9/13/2021 8:00	3174.5	2502.9	3174.5	2950.6	223.9	387.7	3
9/13/2021 9:00	3622.0	2444.6	3622.0	3229.5	392.5	679.8	3
9/13/2021 10:00	3473.1	3064.3	3473.1	3336.8	136.3	236.0	3
9/13/2021 11:00	2760.2	2904.2	2760.2	2808.2	48.0	83.1	3
9/13/2021 12:00	2803.1	2857.8	2803.1	2821.3	18.2	31.6	3
9/13/2021 13:00	2513.9	2552.6	2513.9	2526.8	12.9	22.3	3
9/13/2021 14:00	2811.0	2348.6	2811.0	2656.9	154.1	267.0	3
9/13/2021 15:00	3512.6	2515.8	3512.6	3180.3	332.3	575.5	3
9/13/2021 16:00	3501.3	3339.8	3501.3	3447.5	53.8	93.2	3
9/13/2021 17:00	3314.0	3145.4	3314.0	3257.8	56.2	97.3	3
9/13/2021 18:00	2970.9	3692.6	2970.9	3211.5	240.6	416.7	3
9/13/2021 19:00	1891.2	2040.6	1891.2	1941.0	49.8	86.3	3
9/13/2021 20:00	1951.2	1768.5	1951.2	1890.3	60.9	105.5	3
9/13/2021 21:00	1538.6	1566.0	1538.6	1547.7	9.1	15.8	3
9/13/2021 22:00	1782.9	1352.5	1782.9	1639.4	143.5	248.5	3
9/13/2021 23:00	1670.1	1585.8	1670.1	1642.0	28.1	48.7	3
9/14/2021 0:00	1607.1	1575.2	1607.1	1596.5	10.6	18.4	3
9/14/2021 1:00	1624.2	1319.0	1624.2	1522.5	101.7	176.2	3
9/14/2021 2:00	1592.0	1655.2	1592.0	1613.1	21.1	36.5	3
9/14/2021 3:00	1883.0	1627.4	1883.0	1797.8	85.2	147.6	3
9/14/2021 4:00	1881.0	1835.0	1881.0	1865.7	15.3	26.6	3
9/14/2021 5:00	1548.2	1477.3	1548.2	1524.6	23.6	40.9	3
9/14/2021 6:00	1648.2	1463.0	1648.2	1586.5	61.7	106.9	3
9/14/2021 7:00	2596.9	2504.3	2596.9	2566.0	30.9	53.5	3
9/14/2021 8:00	2928.4	2417.9	2928.4	2758.2	170.2	294.7	3
9/14/2021 9:00	3225.7	2569.9	3225.7	3007.1	218.6	378.6	3
9/14/2021 10:00	3447.3	2582.1	3447.3	3158.9	288.4	499.5	3
9/14/2021 11:00	3043.2	2908.4	3043.2	2998.3	44.9	77.8	3
9/14/2021 12:00	3072.3	2720.1	3072.3	2954.9	117.4	203.3	3
9/14/2021 13:00	3393.3	2613.6	3393.3	3133.4	259.9	450.2	3
9/14/2021 14:00	3178.2	2525.1	3178.2	2960.5	217.7	377.1	3

2.06 mg/kg 3,4-diaminopyridine Treatment							
Minute Volume (mL/sec)							
Date	**VL90IA**	**YR895FD**	**AL793H**	**Mean**	**SE**	**SD**	**n**
9/14/2021 15:00	3221.8	2663.3	3221.8	3035.6	186.2	322.5	3
9/14/2021 16:00	3127.3	3200.8	3127.3	3151.8	24.5	42.4	3
9/14/2021 17:00	3345.8	2944.0	3345.8	3211.9	133.9	232.0	3
9/14/2021 18:00	2300.9	2649.0	2300.9	2416.9	116.0	201.0	3
9/14/2021 19:00	1713.3	1683.1	1713.3	1703.2	10.1	17.4	3
9/14/2021 20:00	2058.9	1922.8	2058.9	2013.5	45.4	78.6	3
9/14/2021 21:00	1729.7	1645.8	1729.7	1701.7	28.0	48.4	3
9/14/2021 22:00	2351.0	2119.8	2351.0	2273.9	77.1	133.5	3
9/14/2021 23:00	2119.2	1644.4	2119.2	1960.9	158.3	274.1	3
9/15/2021 0:00	1845.0	1523.8	1845.0	1737.9	107.1	185.4	3
9/15/2021 1:00	1889.1	1569.3	1889.1	1782.5	106.6	184.6	3
9/15/2021 2:00	1881.5	1696.7	1881.5	1819.9	61.6	106.7	3
9/15/2021 3:00	1998.0	1729.4	1998.0	1908.5	89.5	155.1	3
9/15/2021 4:00	1889.6	1452.2	1889.6	1743.8	145.8	252.5	3
9/15/2021 5:00	1489.2	1582.1	1489.2	1520.2	31.0	53.6	3
9/15/2021 6:00	1758.4	1595.0	1758.4	1703.9	54.5	94.3	3
9/15/2021 7:00	1945.1	1681.2	1945.1	1857.1	88.0	152.4	3
9/15/2021 8:00	1851.3	1606.3	1851.3	1769.6	81.7	141.5	3
9/15/2021 9:00	1598.4	1385.6	1598.4	1527.5	70.9	122.9	3
9/15/2021 10:00	1659.1	1291.4	1659.1	1536.5	122.6	212.3	3
9/15/2021 11:00	1920.3	1327.1	NaN	1623.7	296.6	419.5	2
9/15/2021 12:00	1769.4	1111.1	NaN	1440.3	329.2	465.5	2
9/15/2021 13:00	1606.8	974.5	NaN	1290.7	316.1	447.1	2
9/15/2021 14:00	1507.6	963.0	NaN	1235.3	272.3	385.1	2
9/15/2021 15:00	1865.4	788.7	NaN	1327.1	538.3	761.3	2
9/15/2021 16:00	1107.5	626.0	NaN	866.7	240.8	340.5	2
9/15/2021 17:00	1348.7	1073.5	NaN	1211.1	137.6	194.6	2
9/15/2021 18:00	1051.4	1148.5	NaN	1100.0	48.5	68.7	2
9/15/2021 19:00	1312.0	984.6	NaN	1148.3	163.7	231.5	2
9/15/2021 20:00	1106.4	NaN	NaN	1106.4	0.0	0.0	1
9/15/2021 21:00	800.4	NaN	NaN	800.4	0.0	0.0	1

Table 22: Respiration Rate (bpm) 2.06 mg/kg 3,4-diaminopyridine Treatment

2.06 mg/kg 3,4-diaminopyridine Treatment							
Respiration Rate (bpm)							
Date	VL90IA	YR895FD	AL793H	Mean	SE	SD	n
9/10/2021 16:00	37.2	37.0	37.2	37.1	0.1	0.1	3
9/10/2021 17:00	39.1	37.6	39.1	38.6	0.5	0.9	3
9/10/2021 18:00	35.6	35.8	35.6	35.7	0.1	0.1	3
9/10/2021 19:00	23.9	29.8	23.9	25.8	2.0	3.4	3
9/10/2021 20:00	22.5	26.9	22.5	24.0	1.4	2.5	3
9/10/2021 21:00	22.8	27.1	22.8	24.2	1.4	2.5	3
9/10/2021 22:00	26.8	26.4	26.8	26.7	0.1	0.2	3
9/10/2021 23:00	25.6	25.4	25.6	25.5	0.1	0.1	3
9/11/2021 0:00	25.0	24.4	25.0	24.8	0.2	0.4	3
9/11/2021 1:00	24.5	24.9	24.5	24.7	0.1	0.2	3
9/11/2021 2:00	24.3	24.5	24.3	24.4	0.1	0.1	3
9/11/2021 3:00	24.1	25.2	24.1	24.4	0.4	0.7	3
9/11/2021 4:00	25.7	25.2	25.7	25.6	0.2	0.3	3
9/11/2021 5:00	26.2	24.6	26.2	25.6	0.5	0.9	3
9/11/2021 6:00	25.4	25.4	25.4	25.4	0.0	0.0	3
9/11/2021 7:00	27.4	25.1	27.4	26.6	0.8	1.3	3
9/11/2021 8:00	32.6	27.9	32.6	31.0	1.6	2.7	3
9/11/2021 9:00	33.6	27.2	33.6	31.5	2.2	3.7	3
9/11/2021 10:00	34.8	29.6	34.8	33.0	1.7	3.0	3
9/11/2021 11:00	36.0	30.8	36.0	34.3	1.7	3.0	3
9/11/2021 12:00	33.8	29.2	33.8	32.3	1.6	2.7	3
9/11/2021 13:00	36.1	31.1	36.1	34.4	1.7	2.9	3
9/11/2021 14:00	36.7	31.7	36.7	35.1	1.7	2.9	3
9/11/2021 15:00	33.5	29.0	33.5	32.0	1.5	2.6	3
9/11/2021 16:00	33.9	31.1	33.9	33.0	0.9	1.6	3
9/11/2021 17:00	37.8	31.2	37.8	35.6	2.2	3.8	3
9/11/2021 18:00	36.6	32.5	36.6	35.2	1.4	2.3	3
9/11/2021 19:00	28.4	29.2	28.4	28.6	0.3	0.5	3
9/11/2021 20:00	27.4	28.0	27.4	27.6	0.2	0.3	3
9/11/2021 21:00	25.7	27.9	25.7	26.4	0.7	1.2	3
9/11/2021 22:00	26.0	26.9	26.0	26.3	0.3	0.5	3

2.06 mg/kg 3,4-diaminopyridine Treatment							
Respiration Rate (bpm)							
Date	VL90IA	YR895FD	AL793H	Mean	SE	SD	n
9/11/2021 23:00	27.1	27.9	27.1	27.3	0.3	0.5	3
9/12/2021 0:00	26.9	26.5	26.9	26.8	0.1	0.2	3
9/12/2021 1:00	24.8	25.3	24.8	25.0	0.1	0.3	3
9/12/2021 2:00	31.4	26.9	31.4	29.9	1.5	2.6	3
9/12/2021 3:00	25.3	26.1	25.3	25.6	0.3	0.5	3
9/12/2021 4:00	26.6	27.6	26.6	27.0	0.3	0.5	3
9/12/2021 5:00	28.1	25.2	28.1	27.1	0.9	1.6	3
9/12/2021 6:00	27.6	24.6	27.6	26.6	1.0	1.8	3
9/12/2021 7:00	28.6	26.2	28.6	27.8	0.8	1.4	3
9/12/2021 8:00	34.8	29.2	34.8	32.9	1.9	3.2	3
9/12/2021 9:00	34.5	25.6	34.5	31.5	3.0	5.1	3
9/12/2021 10:00	36.8	28.7	36.8	34.1	2.7	4.7	3
9/12/2021 11:00	29.0	30.2	29.0	29.4	0.4	0.7	3
9/12/2021 12:00	28.4	31.1	28.4	29.3	0.9	1.6	3
9/12/2021 13:00	33.4	33.0	33.4	33.3	0.1	0.2	3
9/12/2021 14:00	34.0	32.0	34.0	33.3	0.6	1.1	3
9/12/2021 15:00	37.6	33.6	37.6	36.2	1.3	2.3	3
9/12/2021 16:00	36.2	33.4	36.2	35.3	0.9	1.6	3
9/12/2021 17:00	33.6	33.5	33.6	33.6	0.0	0.1	3
9/12/2021 18:00	31.0	34.9	31.0	32.3	1.3	2.3	3
9/12/2021 19:00	23.8	35.0	23.8	27.5	3.7	6.5	3
9/12/2021 20:00	25.8	27.3	25.8	26.3	0.5	0.8	3
9/12/2021 21:00	23.7	28.3	23.7	25.2	1.5	2.6	3
9/12/2021 22:00	22.7	25.8	22.7	23.7	1.0	1.8	3
9/12/2021 23:00	25.0	27.8	25.0	25.9	0.9	1.6	3
9/13/2021 0:00	25.2	24.7	25.2	25.0	0.2	0.3	3
9/13/2021 1:00	24.8	25.0	24.8	24.9	0.1	0.1	3
9/13/2021 2:00	25.5	24.6	25.5	25.2	0.3	0.5	3
9/13/2021 3:00	23.6	24.2	23.6	23.8	0.2	0.3	3
9/13/2021 4:00	25.0	24.5	25.0	24.9	0.2	0.3	3
9/13/2021 5:00	24.5	25.6	24.5	24.9	0.4	0.6	3
9/13/2021 6:00	26.2	25.1	26.2	25.8	0.4	0.7	3

2.06 mg/kg 3,4-diaminopyridine Treatment							
Respiration Rate (bpm)							
Date	VL90IA	YR895FD	AL793H	Mean	SE	SD	n
9/13/2021 7:00	25.5	23.9	25.5	25.0	0.5	0.9	3
9/13/2021 8:00	33.7	28.9	33.7	32.1	1.6	2.8	3
9/13/2021 9:00	42.0	29.8	42.0	37.9	4.1	7.0	3
9/13/2021 10:00	37.6	31.4	37.6	35.6	2.1	3.6	3
9/13/2021 11:00	31.1	30.3	31.1	30.8	0.3	0.4	3
9/13/2021 12:00	30.6	28.2	30.6	29.8	0.8	1.4	3
9/13/2021 13:00	29.3	27.2	29.3	28.6	0.7	1.2	3
9/13/2021 14:00	33.7	29.4	33.7	32.3	1.4	2.5	3
9/13/2021 15:00	39.0	31.3	39.0	36.4	2.6	4.4	3
9/13/2021 16:00	37.2	31.6	37.2	35.3	1.8	3.2	3
9/13/2021 17:00	34.7	30.2	34.7	33.2	1.5	2.6	3
9/13/2021 18:00	31.8	31.2	31.8	31.6	0.2	0.3	3
9/13/2021 19:00	26.5	30.6	26.5	27.8	1.4	2.4	3
9/13/2021 20:00	25.3	30.5	25.3	27.0	1.7	3.0	3
9/13/2021 21:00	24.3	29.6	24.3	26.1	1.8	3.1	3
9/13/2021 22:00	25.1	30.6	25.1	27.0	1.8	3.2	3
9/13/2021 23:00	24.4	29.0	24.4	25.9	1.5	2.7	3
9/14/2021 0:00	23.9	29.4	23.9	25.8	1.8	3.2	3
9/14/2021 1:00	24.4	31.4	24.4	26.8	2.3	4.0	3
9/14/2021 2:00	24.2	29.0	24.2	25.8	1.6	2.8	3
9/14/2021 3:00	24.6	28.4	24.6	25.9	1.3	2.2	3
9/14/2021 4:00	25.5	28.6	25.5	26.6	1.0	1.8	3
9/14/2021 5:00	24.7	26.2	24.7	25.2	0.5	0.9	3
9/14/2021 6:00	24.9	27.1	24.9	25.6	0.8	1.3	3
9/14/2021 7:00	29.1	26.5	29.1	28.2	0.9	1.5	3
9/14/2021 8:00	30.2	27.3	30.2	29.2	1.0	1.6	3
9/14/2021 9:00	34.4	28.6	34.4	32.5	1.9	3.3	3
9/14/2021 10:00	32.9	30.6	32.9	32.1	0.8	1.3	3
9/14/2021 11:00	32.6	30.6	32.6	31.9	0.7	1.1	3
9/14/2021 12:00	32.0	31.6	32.0	31.9	0.2	0.3	3
9/14/2021 13:00	34.1	31.6	34.1	33.3	0.8	1.4	3
9/14/2021 14:00	34.6	33.2	34.6	34.1	0.5	0.8	3

2.06 mg/kg 3,4-diaminopyridine Treatment							
Respiration Rate (bpm)							
Date	VL90IA	YR895FD	AL793H	Mean	SE	SD	n
9/14/2021 15:00	34.4	33.6	34.4	34.1	0.2	0.4	3
9/14/2021 16:00	34.2	36.8	34.2	35.1	0.8	1.5	3
9/14/2021 17:00	34.9	33.8	34.9	34.6	0.4	0.7	3
9/14/2021 18:00	31.8	33.3	31.8	32.3	0.5	0.8	3
9/14/2021 19:00	28.7	33.5	28.7	30.3	1.6	2.8	3
9/14/2021 20:00	29.3	32.0	29.3	30.2	0.9	1.5	3
9/14/2021 21:00	28.6	32.3	28.6	29.9	1.2	2.1	3
9/14/2021 22:00	31.7	34.0	31.7	32.5	0.8	1.3	3
9/14/2021 23:00	30.6	34.3	30.6	31.8	1.2	2.2	3
9/15/2021 0:00	28.9	32.7	28.9	30.2	1.3	2.2	3
9/15/2021 1:00	28.2	33.2	28.2	29.9	1.7	2.9	3
9/15/2021 2:00	27.8	32.1	27.8	29.2	1.5	2.5	3
9/15/2021 3:00	28.9	35.8	28.9	31.2	2.3	3.9	3
9/15/2021 4:00	27.1	33.5	27.1	29.3	2.1	3.7	3
9/15/2021 5:00	26.4	34.6	26.4	29.1	2.7	4.7	3
9/15/2021 6:00	26.7	34.2	26.7	29.2	2.5	4.4	3
9/15/2021 7:00	28.0	35.8	28.0	30.6	2.6	4.5	3
9/15/2021 8:00	27.5	34.7	27.5	29.9	2.4	4.2	3
9/15/2021 9:00	25.4	33.9	25.4	28.2	2.8	4.9	3
9/15/2021 10:00	26.8	33.6	26.8	29.0	2.3	4.0	3
9/15/2021 11:00	30.8	34.3	NaN	32.5	1.7	2.5	2
9/15/2021 12:00	31.3	31.2	NaN	31.2	0.0	0.0	2
9/15/2021 13:00	31.0	28.5	NaN	29.7	1.2	1.7	2
9/15/2021 14:00	29.4	28.1	NaN	28.7	0.6	0.9	2
9/15/2021 15:00	33.6	23.4	NaN	28.5	5.1	7.2	2
9/15/2021 16:00	29.2	17.6	NaN	23.4	5.8	8.2	2
9/15/2021 17:00	27.4	30.0	NaN	28.7	1.3	1.9	2
9/15/2021 18:00	25.1	34.5	NaN	29.8	4.7	6.7	2
9/15/2021 19:00	29.6	29.4	NaN	29.5	0.1	0.1	2
9/15/2021 20:00	29.9	NaN	NaN	29.9	0.0	0.0	1
9/15/2021 21:00	22.4	NaN	NaN	22.4	0.0	0.0	1

9.2.3 ECG Parameters – 2.06 mg/kg 3,4-diaminopyridine Treatment

Table 23: Heart Rate (bpm) 2.06 mg/kg 3,4-diaminopyridine Treatment

2.06 mg/kg 3,4-diaminopyridine Treatment							
Heart Rate (bpm)							
Date	VL90IA	YR895FD	AL793H	Mean	SE	SD	n
9/10/2021 16:00	138.2	152.2	148.9	146.4	4.2	7.3	3
9/10/2021 17:00	134.6	142.9	149.0	142.2	4.2	7.2	3
9/10/2021 18:00	119.1	140.6	142.0	133.9	7.4	12.8	3
9/10/2021 19:00	86.1	104.8	120.1	103.6	9.8	17.0	3
9/10/2021 20:00	76.2	94.9	108.1	93.0	9.3	16.0	3
9/10/2021 21:00	81.2	94.0	107.6	94.3	7.6	13.2	3
9/10/2021 22:00	98.1	92.4	112.7	101.1	6.0	10.5	3
9/10/2021 23:00	89.2	89.4	112.8	97.1	7.8	13.6	3
9/11/2021 0:00	87.6	87.6	111.5	95.6	7.9	13.8	3
9/11/2021 1:00	89.5	91.3	105.0	95.2	4.9	8.5	3
9/11/2021 2:00	90.7	90.4	104.3	95.1	4.6	8.0	3
9/11/2021 3:00	91.2	96.4	106.8	98.1	4.6	7.9	3
9/11/2021 4:00	93.1	94.4	103.7	97.1	3.3	5.8	3
9/11/2021 5:00	97.0	96.5	104.0	99.1	2.4	4.2	3
9/11/2021 6:00	87.9	98.1	101.2	95.7	4.0	7.0	3
9/11/2021 7:00	103.3	109.3	116.7	109.8	3.9	6.7	3
9/11/2021 8:00	120.3	121.1	135.3	125.5	4.9	8.4	3
9/11/2021 9:00	122.5	116.8	127.9	122.4	3.2	5.5	3
9/11/2021 10:00	119.3	114.2	128.1	120.5	4.1	7.0	3
9/11/2021 11:00	130.2	97.8	127.5	118.5	10.4	18.0	3
9/11/2021 12:00	128.1	102.8	145.1	125.3	12.3	21.3	3
9/11/2021 13:00	134.7	124.3	143.8	134.2	5.6	9.8	3
9/11/2021 14:00	131.7	121.5	143.6	132.3	6.4	11.1	3
9/11/2021 15:00	120.7	114.0	136.8	123.8	6.8	11.7	3
9/11/2021 16:00	107.1	115.8	121.8	114.9	4.3	7.4	3
9/11/2021 17:00	139.4	137.5	153.6	143.5	5.1	8.8	3
9/11/2021 18:00	131.0	133.5	156.4	140.3	8.1	14.0	3
9/11/2021 19:00	99.5	110.9	137.0	115.8	11.1	19.2	3
9/11/2021 20:00	96.1	113.3	127.1	112.1	9.0	15.5	3
9/11/2021 21:00	96.4	109.0	117.2	107.5	6.1	10.5	3

2.06 mg/kg 3,4-diaminopyridine Treatment							
Heart Rate (bpm)							
Date	VL90IA	YR895FD	AL793H	Mean	SE	SD	n
9/11/2021 22:00	106.1	108.7	110.9	108.6	1.4	2.4	3
9/11/2021 23:00	97.2	106.1	106.4	103.2	3.0	5.3	3
9/12/2021 0:00	97.9	98.9	100.7	99.2	0.8	1.5	3
9/12/2021 1:00	99.5	98.0	104.1	100.5	1.8	3.2	3
9/12/2021 2:00	98.5	102.9	101.1	100.8	1.3	2.2	3
9/12/2021 3:00	90.4	98.0	100.8	96.4	3.1	5.4	3
9/12/2021 4:00	94.8	95.1	102.1	97.3	2.4	4.1	3
9/12/2021 5:00	96.6	91.3	101.6	96.5	2.9	5.1	3
9/12/2021 6:00	97.3	88.4	100.9	95.6	3.7	6.4	3
9/12/2021 7:00	106.1	106.0	127.1	113.1	7.0	12.1	3
9/12/2021 8:00	132.0	123.7	142.5	132.7	5.4	9.4	3
9/12/2021 9:00	128.7	104.2	131.9	121.6	8.7	15.1	3
9/12/2021 10:00	136.7	112.1	141.7	130.2	9.1	15.8	3
9/12/2021 11:00	107.6	99.1	121.9	109.5	6.6	11.5	3
9/12/2021 12:00	107.4	94.7	118.1	106.7	6.8	11.7	3
9/12/2021 13:00	131.8	133.8	148.0	137.8	5.1	8.9	3
9/12/2021 14:00	114.9	125.2	130.2	123.4	4.5	7.8	3
9/12/2021 15:00	131.3	118.8	153.4	134.5	10.1	17.5	3
9/12/2021 16:00	132.9	126.3	152.9	137.3	8.0	13.9	3
9/12/2021 17:00	117.2	129.5	135.2	127.3	5.3	9.2	3
9/12/2021 18:00	100.0	142.9	128.7	123.9	12.6	21.9	3
9/12/2021 19:00	83.8	108.1	107.1	99.7	8.0	13.8	3
9/12/2021 20:00	83.0	95.0	98.5	92.1	4.7	8.1	3
9/12/2021 21:00	78.3	91.5	96.9	88.9	5.5	9.6	3
9/12/2021 22:00	79.1	89.1	103.3	90.5	7.0	12.2	3
9/12/2021 23:00	83.3	90.8	98.4	90.8	4.4	7.6	3
9/13/2021 0:00	86.4	88.8	102.4	92.6	5.0	8.6	3
9/13/2021 1:00	83.6	87.6	95.9	89.0	3.6	6.3	3
9/13/2021 2:00	83.6	87.5	96.7	89.3	3.9	6.7	3
9/13/2021 3:00	84.0	88.0	97.1	89.7	3.9	6.7	3
9/13/2021 4:00	87.5	90.5	94.2	90.7	2.0	3.4	3
9/13/2021 5:00	80.2	89.4	93.2	87.6	3.8	6.6	3

2.06 mg/kg 3,4-diaminopyridine Treatment							
Heart Rate (bpm)							
Date	VL90IA	YR895FD	AL793H	Mean	SE	SD	n
9/13/2021 6:00	83.2	88.3	96.1	89.2	3.7	6.5	3
9/13/2021 7:00	92.8	109.1	114.8	105.6	6.6	11.4	3
9/13/2021 8:00	121.3	121.8	143.5	128.9	7.3	12.7	3
9/13/2021 9:00	185.7	164.9	182.3	177.6	6.4	11.2	3
9/13/2021 10:00	136.4	130.8	142.1	136.5	3.3	5.6	3
9/13/2021 11:00	110.0	122.1	127.0	119.7	5.0	8.7	3
9/13/2021 12:00	112.4	119.0	133.1	121.5	6.1	10.6	3
9/13/2021 13:00	109.7	114.0	137.4	120.4	8.6	14.9	3
9/13/2021 14:00	127.5	121.1	145.9	131.5	7.4	12.9	3
9/13/2021 15:00	132.8	128.4	154.6	138.6	8.1	14.0	3
9/13/2021 16:00	120.1	130.5	144.1	131.6	7.0	12.1	3
9/13/2021 17:00	107.7	116.9	154.3	126.3	14.2	24.7	3
9/13/2021 18:00	100.6	125.3	170.6	132.2	20.5	35.5	3
9/13/2021 19:00	86.1	98.8	131.3	105.4	13.5	23.3	3
9/13/2021 20:00	79.5	96.0	132.8	102.8	15.8	27.3	3
9/13/2021 21:00	76.5	98.9	127.9	101.1	14.9	25.7	3
9/13/2021 22:00	84.0	98.9	126.4	103.1	12.4	21.5	3
9/13/2021 23:00	78.1	101.1	119.4	99.5	12.0	20.7	3
9/14/2021 0:00	77.8	100.7	114.9	97.8	10.8	18.7	3
9/14/2021 1:00	79.4	101.3	107.7	96.1	8.6	14.8	3
9/14/2021 2:00	81.4	98.7	103.5	94.5	6.7	11.6	3
9/14/2021 3:00	80.0	93.9	104.2	92.7	7.0	12.1	3
9/14/2021 4:00	84.7	94.1	103.5	94.1	5.4	9.4	3
9/14/2021 5:00	81.6	94.0	108.1	94.6	7.6	13.2	3
9/14/2021 6:00	83.9	95.9	108.1	95.9	7.0	12.1	3
9/14/2021 7:00	104.1	117.9	133.2	118.4	8.4	14.5	3
9/14/2021 8:00	108.6	124.1	139.2	124.0	8.8	15.3	3
9/14/2021 9:00	123.6	125.8	135.3	128.2	3.6	6.2	3
9/14/2021 10:00	106.5	120.7	134.4	120.6	8.1	14.0	3
9/14/2021 11:00	110.5	122.5	138.6	123.9	8.1	14.1	3
9/14/2021 12:00	103.4	117.5	135.1	118.7	9.2	15.9	3
9/14/2021 13:00	128.4	128.5	149.1	135.3	6.9	11.9	3

2.06 mg/kg 3,4-diaminopyridine Treatment							
Heart Rate (bpm)							
Date	VL90IA	YR895FD	AL793H	Mean	SE	SD	n
9/14/2021 14:00	132.3	128.8	147.7	136.3	5.8	10.0	3
9/14/2021 15:00	119.3	123.7	135.0	126.0	4.7	8.1	3
9/14/2021 16:00	108.0	141.4	151.7	133.7	13.2	22.9	3
9/14/2021 17:00	113.4	128.6	154.6	132.2	12.0	20.8	3
9/14/2021 18:00	95.0	124.2	150.9	123.4	16.1	27.9	3
9/14/2021 19:00	86.8	98.5	123.3	102.9	10.8	18.7	3
9/14/2021 20:00	94.3	103.2	129.1	108.8	10.4	18.1	3
9/14/2021 21:00	90.6	100.6	129.1	106.7	11.5	20.0	3
9/14/2021 22:00	104.8	122.5	130.8	119.4	7.6	13.2	3
9/14/2021 23:00	124.3	127.3	153.9	135.1	9.4	16.3	3
9/15/2021 0:00	103.1	108.6	123.8	111.8	6.2	10.7	3
9/15/2021 1:00	112.3	114.1	136.4	121.0	7.8	13.4	3
9/15/2021 2:00	112.8	114.8	127.4	118.3	4.6	8.0	3
9/15/2021 3:00	133.0	144.7	165.4	147.7	9.5	16.4	3
9/15/2021 4:00	126.5	125.4	141.5	131.1	5.2	9.0	3
9/15/2021 5:00	130.3	133.8	155.0	139.7	7.7	13.3	3
9/15/2021 6:00	149.7	129.4	151.3	143.5	7.1	12.2	3
9/15/2021 7:00	174.5	161.1	190.9	175.5	8.6	14.9	3
9/15/2021 8:00	175.2	166.9	184.2	175.4	5.0	8.7	3
9/15/2021 9:00	181.2	162.5	173.6	172.4	5.4	9.4	3
9/15/2021 10:00	187.5	172.4	176.2	178.7	4.5	7.9	3
9/15/2021 11:00	193.2	190.4	NaN	191.8	1.4	2.0	2
9/15/2021 12:00	178.8	183.6	NaN	181.2	2.4	3.3	2
9/15/2021 13:00	172.5	180.9	NaN	176.7	4.2	5.9	2
9/15/2021 14:00	183.2	186.3	NaN	184.7	1.5	2.1	2
9/15/2021 15:00	208.9	181.3	NaN	195.1	13.8	19.5	2
9/15/2021 16:00	186.8	174.0	NaN	180.4	6.4	9.0	2
9/15/2021 17:00	189.9	165.3	NaN	177.6	12.3	17.4	2
9/15/2021 18:00	185.7	178.0	NaN	181.8	3.8	5.4	2
9/15/2021 19:00	184.0	189.2	NaN	186.6	2.6	3.7	2
9/15/2021 20:00	180.8	NaN	NaN	180.8	0.0	0.0	1
9/15/2021 21:00	175.5	NaN	NaN	175.5	0.0	0.0	1

Table 24: PR Interval (msec) 2.06 mg/kg 3,4-diaminopyridine Treatment

2.06 mg/kg 3,4-diaminopyridine Treatment							
PR Interval (msec)							
Date	VL90IA	YR895FD	AL793H	Mean	SE	SD	n
9/10/2021 16:00	76.0	93.9	70.0	80.0	7.2	12.4	3
9/10/2021 17:00	74.1	92.0	67.3	77.8	7.4	12.8	3
9/10/2021 18:00	75.7	93.7	69.7	79.7	7.2	12.5	3
9/10/2021 19:00	76.9	92.0	72.4	80.4	5.9	10.2	3
9/10/2021 20:00	76.9	92.2	83.6	84.2	4.4	7.7	3
9/10/2021 21:00	77.9	97.4	82.9	86.1	5.8	10.1	3
9/10/2021 22:00	79.3	100.3	77.9	85.8	7.2	12.5	3
9/10/2021 23:00	80.6	99.9	74.9	85.1	7.6	13.1	3
9/11/2021 0:00	78.2	96.5	74.0	82.9	6.9	11.9	3
9/11/2021 1:00	79.4	94.6	73.8	82.6	6.2	10.7	3
9/11/2021 2:00	79.5	96.8	75.6	84.0	6.5	11.3	3
9/11/2021 3:00	77.9	97.4	76.8	84.0	6.7	11.6	3
9/11/2021 4:00	79.1	97.6	76.7	84.5	6.6	11.5	3
9/11/2021 5:00	76.4	97.2	83.5	85.7	6.1	10.6	3
9/11/2021 6:00	76.4	95.6	90.1	87.4	5.7	9.8	3
9/11/2021 7:00	76.9	92.5	83.0	84.1	4.5	7.9	3
9/11/2021 8:00	74.7	95.7	77.3	82.6	6.6	11.5	3
9/11/2021 9:00	75.7	92.8	77.9	82.1	5.4	9.3	3
9/11/2021 10:00	76.2	93.2	75.4	81.6	5.8	10.0	3
9/11/2021 11:00	76.5	94.8	75.5	82.3	6.3	10.8	3
9/11/2021 12:00	75.5	94.8	71.9	80.7	7.1	12.3	3
9/11/2021 13:00	76.2	93.4	72.7	80.8	6.4	11.1	3
9/11/2021 14:00	73.9	92.4	73.6	80.0	6.2	10.7	3
9/11/2021 15:00	76.0	92.4	73.4	80.6	5.9	10.3	3
9/11/2021 16:00	77.3	92.8	80.0	83.4	4.8	8.3	3
9/11/2021 17:00	75.4	92.7	70.7	79.6	6.7	11.6	3
9/11/2021 18:00	74.2	91.4	69.9	78.5	6.6	11.4	3
9/11/2021 19:00	76.9	89.8	71.6	79.4	5.4	9.3	3
9/11/2021 20:00	76.3	91.0	78.2	81.9	4.6	8.0	3
9/11/2021 21:00	77.1	91.1	78.2	82.1	4.5	7.8	3
9/11/2021 22:00	77.2	91.4	81.3	83.3	4.2	7.3	3

2.06 mg/kg 3,4-diaminopyridine Treatment							
PR Interval (msec)							
Date	VL90IA	YR895FD	AL793H	Mean	SE	SD	n
9/11/2021 23:00	77.1	91.4	81.0	83.2	4.2	7.4	3
9/12/2021 0:00	76.8	93.6	81.4	83.9	5.0	8.7	3
9/12/2021 1:00	78.0	95.4	77.7	83.7	5.8	10.1	3
9/12/2021 2:00	77.2	94.5	89.8	87.1	5.2	9.0	3
9/12/2021 3:00	77.0	95.6	87.8	86.8	5.4	9.3	3
9/12/2021 4:00	77.0	96.4	89.1	87.5	5.7	9.8	3
9/12/2021 5:00	77.4	98.5	85.6	87.2	6.2	10.7	3
9/12/2021 6:00	76.9	97.1	89.3	87.8	5.9	10.2	3
9/12/2021 7:00	75.4	97.1	80.4	84.3	6.6	11.4	3
9/12/2021 8:00	73.7	96.8	76.0	82.1	7.3	12.7	3
9/12/2021 9:00	75.9	97.8	77.6	83.7	7.1	12.2	3
9/12/2021 10:00	74.8	97.4	73.1	81.8	7.8	13.6	3
9/12/2021 11:00	77.4	95.8	79.0	84.0	5.9	10.2	3
9/12/2021 12:00	77.2	96.0	81.0	84.7	5.7	10.0	3
9/12/2021 13:00	78.5	94.7	72.2	81.8	6.7	11.6	3
9/12/2021 14:00	78.7	91.0	74.5	81.4	5.0	8.6	3
9/12/2021 15:00	77.3	93.2	69.7	80.1	6.9	12.0	3
9/12/2021 16:00	76.7	91.8	68.3	79.0	6.9	11.9	3
9/12/2021 17:00	79.0	93.2	72.5	81.6	6.1	10.6	3
9/12/2021 18:00	79.5	92.3	77.3	83.0	4.7	8.1	3
9/12/2021 19:00	78.6	94.3	82.5	85.2	4.7	8.2	3
9/12/2021 20:00	78.3	93.4	78.4	83.4	5.0	8.7	3
9/12/2021 21:00	77.7	97.1	86.9	87.2	5.6	9.7	3
9/12/2021 22:00	78.1	99.2	85.2	87.5	6.2	10.7	3
9/12/2021 23:00	76.0	98.7	85.0	86.6	6.6	11.4	3
9/13/2021 0:00	75.5	96.3	85.5	85.8	6.0	10.4	3
9/13/2021 1:00	76.4	96.0	85.0	85.8	5.7	9.8	3
9/13/2021 2:00	75.1	94.8	87.2	85.7	5.8	10.0	3
9/13/2021 3:00	76.5	95.8	88.8	87.1	5.7	9.8	3
9/13/2021 4:00	76.6	94.7	89.6	87.0	5.4	9.3	3
9/13/2021 5:00	77.1	94.9	89.2	87.0	5.3	9.1	3
9/13/2021 6:00	77.0	95.2	86.3	86.2	5.2	9.1	3

2.06 mg/kg 3,4-diaminopyridine Treatment							
PR Interval (msec)							
Date	VL90IA	YR895FD	AL793H	Mean	SE	SD	n
9/13/2021 7:00	77.3	94.4	83.0	84.9	5.0	8.7	3
9/13/2021 8:00	74.7	92.4	75.4	80.8	5.8	10.0	3
9/13/2021 9:00	69.2	89.7	65.9	75.0	7.4	12.9	3
9/13/2021 10:00	73.7	91.1	72.3	79.0	6.1	10.5	3
9/13/2021 11:00	78.0	92.6	75.4	82.0	5.4	9.3	3
9/13/2021 12:00	76.9	94.6	76.6	82.7	5.9	10.3	3
9/13/2021 13:00	76.6	93.5	75.3	81.8	5.9	10.2	3
9/13/2021 14:00	76.8	96.4	74.7	82.6	6.9	11.9	3
9/13/2021 15:00	78.3	95.3	73.1	82.2	6.7	11.6	3
9/13/2021 16:00	78.0	92.8	69.2	80.0	6.9	11.9	3
9/13/2021 17:00	79.3	94.5	69.1	81.0	7.4	12.8	3
9/13/2021 18:00	78.3	95.5	67.5	80.5	8.2	14.1	3
9/13/2021 19:00	78.6	92.7	71.0	80.8	6.4	11.0	3
9/13/2021 20:00	78.8	95.0	70.5	81.4	7.2	12.5	3
9/13/2021 21:00	80.5	95.0	72.4	82.6	6.6	11.4	3
9/13/2021 22:00	79.1	93.9	73.9	82.3	6.0	10.4	3
9/13/2021 23:00	78.6	93.4	78.1	83.4	5.0	8.7	3
9/14/2021 0:00	79.9	92.5	79.0	83.8	4.4	7.6	3
9/14/2021 1:00	80.5	93.1	81.3	84.9	4.1	7.0	3
9/14/2021 2:00	77.8	92.6	82.3	84.2	4.4	7.6	3
9/14/2021 3:00	77.7	93.6	77.4	82.9	5.4	9.3	3
9/14/2021 4:00	76.2	93.5	81.1	83.6	5.1	8.9	3
9/14/2021 5:00	77.8	94.1	80.0	84.0	5.1	8.9	3
9/14/2021 6:00	77.2	94.1	79.5	83.6	5.3	9.1	3
9/14/2021 7:00	77.5	94.4	74.9	82.3	6.1	10.6	3
9/14/2021 8:00	76.5	93.3	75.5	81.8	5.8	10.0	3
9/14/2021 9:00	76.5	93.4	75.4	81.8	5.8	10.1	3
9/14/2021 10:00	77.1	93.9	76.0	82.3	5.8	10.0	3
9/14/2021 11:00	76.9	93.5	74.3	81.6	6.0	10.4	3
9/14/2021 12:00	77.4	93.6	76.8	82.6	5.5	9.6	3
9/14/2021 13:00	74.3	93.4	72.4	80.0	6.7	11.6	3
9/14/2021 14:00	72.7	93.4	71.7	79.3	7.1	12.3	3

2.06 mg/kg 3,4-diaminopyridine Treatment							
PR Interval (msec)							
Date	VL90IA	YR895FD	AL793H	Mean	SE	SD	n
9/14/2021 15:00	76.0	91.6	74.6	80.7	5.4	9.4	3
9/14/2021 16:00	75.4	91.9	71.5	79.6	6.3	10.8	3
9/14/2021 17:00	77.1	92.8	69.9	79.9	6.7	11.7	3
9/14/2021 18:00	77.7	93.8	69.7	80.4	7.1	12.3	3
9/14/2021 19:00	78.8	89.5	76.1	81.5	4.1	7.1	3
9/14/2021 20:00	76.5	91.8	71.5	79.9	6.1	10.6	3
9/14/2021 21:00	76.4	92.3	70.2	79.6	6.6	11.4	3
9/14/2021 22:00	74.0	91.5	67.7	77.7	7.1	12.4	3
9/14/2021 23:00	72.1	88.1	66.7	75.6	6.4	11.1	3
9/15/2021 0:00	74.2	90.3	71.6	78.7	5.8	10.1	3
9/15/2021 1:00	72.5	90.8	68.4	77.3	6.9	11.9	3
9/15/2021 2:00	73.0	89.5	71.1	77.8	5.8	10.1	3
9/15/2021 3:00	70.0	85.0	64.6	73.2	6.1	10.6	3
9/15/2021 4:00	71.4	86.5	66.8	74.9	5.9	10.3	3
9/15/2021 5:00	70.2	87.2	65.7	74.3	6.5	11.3	3
9/15/2021 6:00	69.2	88.1	64.4	73.9	7.2	12.5	3
9/15/2021 7:00	67.0	86.8	62.0	71.9	7.6	13.1	3
9/15/2021 8:00	66.7	85.6	63.1	71.8	7.0	12.1	3
9/15/2021 9:00	67.4	87.1	63.9	72.8	7.2	12.5	3
9/15/2021 10:00	66.1	83.9	66.0	72.0	6.0	10.3	3
9/15/2021 11:00	68.0	81.6	NaN	74.8	6.8	9.6	2
9/15/2021 12:00	68.9	82.5	NaN	75.7	6.8	9.6	2
9/15/2021 13:00	68.8	84.4	NaN	76.6	7.8	11.0	2
9/15/2021 14:00	69.7	83.8	NaN	76.8	7.0	9.9	2
9/15/2021 15:00	66.8	84.6	NaN	75.7	8.9	12.6	2
9/15/2021 16:00	69.3	87.9	NaN	78.6	9.3	13.2	2
9/15/2021 17:00	70.2	89.2	NaN	79.7	9.5	13.4	2
9/15/2021 18:00	71.0	85.8	NaN	78.4	7.4	10.5	2
9/15/2021 19:00	71.0	82.0	NaN	76.5	5.5	7.8	2
9/15/2021 20:00	70.5	NaN	NaN	70.5	0.0	0.0	1
9/15/2021 21:00	68.9	NaN	NaN	68.9	0.0	0.0	1

Table 25: QRS Duration (msec) 2.06 mg/kg 3,4-diaminopyridine Treatment

2.06 mg/kg 3,4-diaminopyridine Treatment							
QRS Duration (msec)							
Date	VL90IA	YR895FD	AL793H	Mean	SE	SD	n
9/10/2021 16:00	35.7	29.4	38.7	34.6	2.8	4.8	3
9/10/2021 17:00	35.3	29.6	38.8	34.6	2.7	4.7	3
9/10/2021 18:00	35.9	29.7	38.9	34.8	2.7	4.7	3
9/10/2021 19:00	35.9	29.0	38.7	34.5	2.9	5.0	3
9/10/2021 20:00	35.3	28.7	38.9	34.3	3.0	5.2	3
9/10/2021 21:00	35.3	31.0	39.9	35.4	2.6	4.5	3
9/10/2021 22:00	37.0	30.4	40.3	35.9	2.9	5.0	3
9/10/2021 23:00	38.1	30.5	44.1	37.6	3.9	6.8	3
9/11/2021 0:00	35.5	30.1	44.1	36.6	4.1	7.1	3
9/11/2021 1:00	35.4	29.5	44.7	36.5	4.4	7.6	3
9/11/2021 2:00	35.6	29.6	44.2	36.5	4.2	7.3	3
9/11/2021 3:00	35.7	30.3	44.3	36.8	4.1	7.1	3
9/11/2021 4:00	34.9	29.8	43.8	36.2	4.1	7.1	3
9/11/2021 5:00	35.3	29.6	40.8	35.2	3.2	5.6	3
9/11/2021 6:00	35.1	29.5	40.9	35.2	3.3	5.7	3
9/11/2021 7:00	35.0	29.5	39.8	34.8	3.0	5.2	3
9/11/2021 8:00	35.7	29.0	39.4	34.7	3.0	5.3	3
9/11/2021 9:00	35.7	29.5	39.1	34.7	2.8	4.9	3
9/11/2021 10:00	35.3	29.6	39.0	34.6	2.7	4.7	3
9/11/2021 11:00	35.4	30.1	38.6	34.7	2.5	4.3	3
9/11/2021 12:00	35.5	30.3	39.2	35.0	2.6	4.5	3
9/11/2021 13:00	35.4	30.0	38.9	34.8	2.6	4.5	3
9/11/2021 14:00	34.9	29.5	38.8	34.4	2.7	4.7	3
9/11/2021 15:00	35.5	29.8	37.0	34.1	2.2	3.8	3
9/11/2021 16:00	35.3	29.8	36.9	34.0	2.1	3.7	3
9/11/2021 17:00	35.3	29.4	36.6	33.8	2.2	3.8	3
9/11/2021 18:00	35.6	30.0	36.7	34.1	2.1	3.6	3
9/11/2021 19:00	35.4	30.6	37.1	34.3	1.9	3.4	3
9/11/2021 20:00	36.5	30.2	36.8	34.5	2.2	3.7	3
9/11/2021 21:00	36.7	30.2	37.0	34.7	2.2	3.8	3
9/11/2021 22:00	36.3	29.3	36.7	34.1	2.4	4.1	3

2.06 mg/kg 3,4-diaminopyridine Treatment							
QRS Duration (msec)							
Date	VL90IA	YR895FD	AL793H	Mean	SE	SD	n
9/11/2021 23:00	35.4	29.7	37.4	34.2	2.3	4.0	3
9/12/2021 0:00	35.7	30.0	37.3	34.3	2.2	3.9	3
9/12/2021 1:00	35.9	29.8	39.5	35.1	2.8	4.9	3
9/12/2021 2:00	36.4	29.7	37.0	34.4	2.3	4.1	3
9/12/2021 3:00	35.6	30.6	36.8	34.3	1.9	3.3	3
9/12/2021 4:00	35.3	29.9	36.8	34.0	2.1	3.6	3
9/12/2021 5:00	35.1	29.7	37.1	34.0	2.2	3.8	3
9/12/2021 6:00	35.0	29.6	36.9	33.8	2.2	3.8	3
9/12/2021 7:00	35.3	29.5	36.8	33.9	2.2	3.9	3
9/12/2021 8:00	35.4	29.6	36.8	33.9	2.2	3.8	3
9/12/2021 9:00	35.6	29.4	36.8	33.9	2.3	4.0	3
9/12/2021 10:00	35.3	30.0	37.0	34.1	2.1	3.6	3
9/12/2021 11:00	34.7	29.7	37.0	33.8	2.2	3.7	3
9/12/2021 12:00	35.1	30.1	36.7	34.0	2.0	3.5	3
9/12/2021 13:00	35.5	29.6	36.8	33.9	2.2	3.8	3
9/12/2021 14:00	35.4	29.6	37.3	34.1	2.3	4.0	3
9/12/2021 15:00	35.5	29.5	36.7	33.9	2.2	3.9	3
9/12/2021 16:00	35.5	29.8	36.7	34.0	2.1	3.7	3
9/12/2021 17:00	35.5	29.5	36.7	33.9	2.2	3.8	3
9/12/2021 18:00	35.6	29.3	36.7	33.9	2.3	4.0	3
9/12/2021 19:00	35.1	29.5	36.6	33.7	2.2	3.8	3
9/12/2021 20:00	34.9	29.9	39.4	34.7	2.7	4.7	3
9/12/2021 21:00	35.0	30.1	36.8	34.0	2.0	3.5	3
9/12/2021 22:00	35.0	30.4	37.2	34.2	2.0	3.4	3
9/12/2021 23:00	35.0	29.9	36.6	33.9	2.0	3.5	3
9/13/2021 0:00	35.2	30.1	36.9	34.1	2.0	3.5	3
9/13/2021 1:00	35.2	29.9	37.8	34.3	2.3	4.0	3
9/13/2021 2:00	35.3	29.6	36.7	33.9	2.2	3.8	3
9/13/2021 3:00	35.2	29.4	36.7	33.8	2.2	3.8	3
9/13/2021 4:00	35.1	29.9	36.9	33.9	2.1	3.6	3
9/13/2021 5:00	35.2	30.0	36.7	34.0	2.0	3.5	3
9/13/2021 6:00	35.2	30.1	36.9	34.0	2.0	3.5	3

2.06 mg/kg 3,4-diaminopyridine Treatment							
QRS Duration (msec)							
Date	VL90IA	YR895FD	AL793H	Mean	SE	SD	n
9/13/2021 7:00	35.3	29.2	36.8	33.8	2.3	4.0	3
9/13/2021 8:00	35.4	29.7	36.4	33.8	2.1	3.6	3
9/13/2021 9:00	35.2	30.1	35.8	33.7	1.8	3.1	3
9/13/2021 10:00	35.7	28.1	37.1	33.7	2.8	4.8	3
9/13/2021 11:00	35.8	29.0	37.1	33.9	2.5	4.4	3
9/13/2021 12:00	36.1	29.1	36.9	34.0	2.5	4.3	3
9/13/2021 13:00	35.5	29.2	36.8	33.8	2.4	4.1	3
9/13/2021 14:00	36.1	29.9	36.9	34.3	2.2	3.8	3
9/13/2021 15:00	35.1	30.8	36.9	34.3	1.8	3.2	3
9/13/2021 16:00	35.1	29.7	37.1	34.0	2.2	3.8	3
9/13/2021 17:00	35.6	29.8	37.0	34.1	2.2	3.8	3
9/13/2021 18:00	35.6	29.7	37.3	34.2	2.3	4.0	3
9/13/2021 19:00	35.4	31.1	40.9	35.8	2.9	4.9	3
9/13/2021 20:00	35.1	31.6	39.1	35.3	2.2	3.8	3
9/13/2021 21:00	34.4	31.6	39.8	35.2	2.4	4.2	3
9/13/2021 22:00	35.1	32.6	38.9	35.5	1.8	3.2	3
9/13/2021 23:00	34.8	31.7	37.9	34.8	1.8	3.1	3
9/14/2021 0:00	34.0	31.5	37.6	34.4	1.8	3.1	3
9/14/2021 1:00	35.5	31.9	37.3	34.9	1.6	2.8	3
9/14/2021 2:00	34.9	30.3	37.7	34.3	2.1	3.7	3
9/14/2021 3:00	35.1	29.5	38.8	34.5	2.7	4.7	3
9/14/2021 4:00	35.2	30.1	38.5	34.6	2.4	4.2	3
9/14/2021 5:00	34.4	29.5	37.8	33.9	2.4	4.2	3
9/14/2021 6:00	34.2	29.8	37.7	33.9	2.3	4.0	3
9/14/2021 7:00	35.1	29.7	36.8	33.9	2.2	3.7	3
9/14/2021 8:00	34.9	29.9	36.8	33.9	2.0	3.5	3
9/14/2021 9:00	35.0	29.1	36.6	33.6	2.3	4.0	3
9/14/2021 10:00	35.2	29.8	36.6	33.9	2.1	3.6	3
9/14/2021 11:00	34.8	29.7	36.8	33.8	2.1	3.7	3
9/14/2021 12:00	35.0	29.8	36.8	33.9	2.1	3.6	3
9/14/2021 13:00	35.0	29.8	36.6	33.8	2.0	3.5	3
9/14/2021 14:00	35.2	30.0	36.7	34.0	2.0	3.5	3

2.06 mg/kg 3,4-diaminopyridine Treatment							
QRS Duration (msec)							
Date	VL90IA	YR895FD	AL793H	Mean	SE	SD	n
9/14/2021 15:00	34.7	28.2	37.5	33.4	2.7	4.8	3
9/14/2021 16:00	35.0	28.3	37.5	33.6	2.7	4.7	3
9/14/2021 17:00	34.8	28.7	37.7	33.7	2.6	4.6	3
9/14/2021 18:00	35.4	29.1	37.8	34.1	2.6	4.5	3
9/14/2021 19:00	36.2	29.6	37.6	34.5	2.5	4.3	3
9/14/2021 20:00	35.7	28.8	38.5	34.3	2.9	5.0	3
9/14/2021 21:00	35.5	29.0	39.1	34.5	2.9	5.1	3
9/14/2021 22:00	34.9	29.3	38.0	34.1	2.6	4.5	3
9/14/2021 23:00	35.5	26.2	37.5	33.1	3.5	6.0	3
9/15/2021 0:00	35.8	26.4	37.1	33.1	3.4	5.9	3
9/15/2021 1:00	35.1	29.1	37.8	34.0	2.6	4.5	3
9/15/2021 2:00	34.7	27.0	37.5	33.1	3.1	5.4	3
9/15/2021 3:00	34.9	27.0	37.2	33.0	3.1	5.3	3
9/15/2021 4:00	35.1	27.2	37.2	33.2	3.1	5.3	3
9/15/2021 5:00	34.7	28.6	37.8	33.7	2.7	4.7	3
9/15/2021 6:00	34.2	29.6	37.7	33.8	2.3	4.1	3
9/15/2021 7:00	34.4	29.7	37.3	33.8	2.2	3.9	3
9/15/2021 8:00	35.0	30.0	37.4	34.1	2.2	3.7	3
9/15/2021 9:00	35.4	27.3	37.3	33.3	3.1	5.3	3
9/15/2021 10:00	36.0	28.5	37.4	34.0	2.8	4.8	3
9/15/2021 11:00	36.1	30.5	NaN	33.3	2.8	4.0	2
9/15/2021 12:00	35.2	28.0	NaN	31.6	3.6	5.1	2
9/15/2021 13:00	35.3	27.8	NaN	31.6	3.7	5.3	2
9/15/2021 14:00	35.4	29.2	NaN	32.3	3.1	4.4	2
9/15/2021 15:00	37.1	28.3	NaN	32.7	4.4	6.2	2
9/15/2021 16:00	35.4	30.2	NaN	32.8	2.6	3.7	2
9/15/2021 17:00	36.1	28.0	NaN	32.1	4.1	5.7	2
9/15/2021 18:00	36.0	27.5	NaN	31.7	4.3	6.1	2
9/15/2021 19:00	37.1	28.2	NaN	32.6	4.4	6.2	2
9/15/2021 20:00	35.1	NaN	NaN	35.1	0.0	0.0	1
9/15/2021 21:00	36.0	NaN	NaN	36.0	0.0	0.0	1

Battelle		Status:	Final
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Table 26: Heart Rate Corrected QT Interval (msec) 2.06 mg/kg 3,4-diaminopyridine Treatment

2.06 mg/kg 3,4-diaminopyridine Treatment							
Heart Rate Corrected QT Interval (msec)							
Date	VL90IA	YR895FD	AL793H	Mean	SE	SD	n
9/10/2021 16:00	343.1	299.9	334.2	325.7	13.2	22.9	3
9/10/2021 17:00	342.3	293.1	336.3	323.9	15.5	26.8	3
9/10/2021 18:00	352.6	293.0	335.7	327.1	17.7	30.7	3
9/10/2021 19:00	373.1	337.1	349.4	353.2	10.6	18.3	3
9/10/2021 20:00	374.6	344.3	360.3	359.7	8.7	15.1	3
9/10/2021 21:00	385.8	348.7	363.7	366.1	10.8	18.7	3
9/10/2021 22:00	395.4	348.1	366.6	370.0	13.8	23.9	3
9/10/2021 23:00	396.3	345.3	366.0	369.2	14.8	25.7	3
9/11/2021 0:00	402.2	344.1	365.8	370.7	17.0	29.4	3
9/11/2021 1:00	401.7	343.1	368.5	371.1	17.0	29.4	3
9/11/2021 2:00	402.2	341.7	368.3	370.7	17.5	30.3	3
9/11/2021 3:00	406.0	342.6	359.7	369.4	18.9	32.8	3
9/11/2021 4:00	397.0	336.5	360.0	364.5	17.6	30.5	3
9/11/2021 5:00	381.8	336.2	358.0	358.7	13.2	22.8	3
9/11/2021 6:00	380.4	332.9	359.5	357.6	13.7	23.8	3
9/11/2021 7:00	376.4	314.3	357.0	349.2	18.4	31.8	3
9/11/2021 8:00	356.8	296.7	350.1	334.6	19.0	32.9	3
9/11/2021 9:00	355.1	299.0	349.0	334.4	17.7	30.7	3
9/11/2021 10:00	346.6	299.4	345.5	330.5	15.5	26.9	3
9/11/2021 11:00	347.1	328.4	344.2	339.9	5.8	10.1	3
9/11/2021 12:00	355.0	323.8	336.2	338.3	9.1	15.7	3
9/11/2021 13:00	344.7	303.9	339.1	329.2	12.8	22.1	3
9/11/2021 14:00	344.9	301.3	345.0	330.4	14.5	25.2	3
9/11/2021 15:00	348.3	302.5	336.5	329.1	13.7	23.8	3
9/11/2021 16:00	356.6	302.9	345.4	335.0	16.4	28.3	3
9/11/2021 17:00	339.9	299.4	334.4	324.6	12.7	22.0	3
9/11/2021 18:00	341.3	308.8	328.2	326.1	9.4	16.3	3
9/11/2021 19:00	366.0	335.7	339.1	346.9	9.6	16.6	3
9/11/2021 20:00	375.1	337.5	344.1	352.2	11.6	20.1	3
9/11/2021 21:00	380.9	335.9	349.4	355.4	13.3	23.1	3

2.06 mg/kg 3,4-diaminopyridine Treatment							
Heart Rate Corrected QT Interval (msec)							
Date	**VL90IA**	**YR895FD**	**AL793H**	**Mean**	**SE**	**SD**	**n**
9/11/2021 22:00	384.4	337.8	354.7	359.0	13.6	23.6	3
9/11/2021 23:00	383.7	333.7	354.9	357.4	14.5	25.1	3
9/12/2021 0:00	386.0	335.6	357.3	359.6	14.6	25.3	3
9/12/2021 1:00	390.2	336.3	350.5	359.0	16.1	27.9	3
9/12/2021 2:00	379.3	330.9	352.7	354.3	14.0	24.2	3
9/12/2021 3:00	379.1	334.9	357.7	357.2	12.7	22.1	3
9/12/2021 4:00	377.7	330.4	357.4	355.2	13.7	23.7	3
9/12/2021 5:00	380.3	332.9	357.0	356.7	13.7	23.7	3
9/12/2021 6:00	375.9	335.3	362.7	358.0	11.9	20.7	3
9/12/2021 7:00	364.1	316.2	346.6	342.3	14.0	24.2	3
9/12/2021 8:00	347.9	303.9	333.9	328.6	13.0	22.4	3
9/12/2021 9:00	350.8	308.6	330.4	329.9	12.2	21.1	3
9/12/2021 10:00	350.8	308.0	339.0	332.6	12.8	22.1	3
9/12/2021 11:00	369.6	315.9	342.8	342.8	15.5	26.8	3
9/12/2021 12:00	368.4	329.5	344.0	347.3	11.4	19.7	3
9/12/2021 13:00	343.2	295.2	338.3	325.6	15.2	26.4	3
9/12/2021 14:00	352.1	295.6	340.5	329.4	17.2	29.8	3
9/12/2021 15:00	340.2	302.3	339.3	327.3	12.5	21.6	3
9/12/2021 16:00	339.4	292.9	335.6	322.6	14.9	25.8	3
9/12/2021 17:00	344.5	295.1	334.6	324.7	15.1	26.1	3
9/12/2021 18:00	352.6	289.2	328.9	323.5	18.5	32.0	3
9/12/2021 19:00	370.7	327.1	345.8	347.9	12.6	21.9	3
9/12/2021 20:00	374.1	328.4	349.8	350.8	13.2	22.8	3
9/12/2021 21:00	378.4	327.7	358.6	354.9	14.8	25.6	3
9/12/2021 22:00	381.9	339.1	356.9	359.3	12.4	21.5	3
9/12/2021 23:00	386.5	343.3	357.1	362.3	12.8	22.1	3
9/13/2021 0:00	386.3	334.8	356.5	359.2	14.9	25.8	3
9/13/2021 1:00	387.6	333.9	353.1	358.2	15.7	27.2	3
9/13/2021 2:00	384.7	332.6	357.9	358.4	15.1	26.1	3
9/13/2021 3:00	377.0	331.7	358.0	355.6	13.1	22.7	3
9/13/2021 4:00	375.6	333.1	358.4	355.7	12.4	21.4	3
9/13/2021 5:00	374.6	332.1	357.2	354.6	12.4	21.4	3

2.06 mg/kg 3,4-diaminopyridine Treatment							
Heart Rate Corrected QT Interval (msec)							
Date	**VL90IA**	**YR895FD**	**AL793H**	**Mean**	**SE**	**SD**	**n**
9/13/2021 6:00	373.0	333.9	353.3	353.4	11.3	19.6	3
9/13/2021 7:00	365.7	310.1	350.0	341.9	16.5	28.6	3
9/13/2021 8:00	356.7	307.9	346.4	337.0	14.9	25.7	3
9/13/2021 9:00	338.7	287.2	324.3	316.7	15.3	26.5	3
9/13/2021 10:00	330.7	289.7	342.3	320.9	16.0	27.7	3
9/13/2021 11:00	338.0	288.4	341.8	322.7	17.2	29.8	3
9/13/2021 12:00	345.1	293.3	341.9	326.8	16.8	29.1	3
9/13/2021 13:00	344.8	292.0	335.6	324.1	16.3	28.2	3
9/13/2021 14:00	340.0	287.4	334.9	320.8	16.7	29.0	3
9/13/2021 15:00	337.5	299.1	360.8	332.5	18.0	31.2	3
9/13/2021 16:00	336.1	294.7	345.4	325.4	15.6	27.0	3
9/13/2021 17:00	340.8	300.4	354.7	332.0	16.3	28.2	3
9/13/2021 18:00	348.1	299.8	369.7	339.2	20.7	35.8	3
9/13/2021 19:00	370.7	330.1	359.1	353.3	12.1	20.9	3
9/13/2021 20:00	373.2	340.5	361.4	358.4	9.5	16.5	3
9/13/2021 21:00	380.1	339.6	362.4	360.7	11.7	20.3	3
9/13/2021 22:00	379.6	339.2	360.3	359.7	11.7	20.2	3
9/13/2021 23:00	382.7	336.3	360.0	359.7	13.4	23.2	3
9/14/2021 0:00	384.6	338.3	362.6	361.8	13.4	23.2	3
9/14/2021 1:00	389.7	336.1	363.5	363.1	15.5	26.8	3
9/14/2021 2:00	383.0	337.5	361.0	360.5	13.1	22.8	3
9/14/2021 3:00	379.6	336.5	358.4	358.1	12.4	21.5	3
9/14/2021 4:00	377.4	336.1	357.7	357.1	11.9	20.7	3
9/14/2021 5:00	377.8	336.3	357.8	357.3	12.0	20.7	3
9/14/2021 6:00	372.1	333.2	356.8	354.0	11.3	19.6	3
9/14/2021 7:00	355.2	314.0	347.7	338.9	12.7	21.9	3
9/14/2021 8:00	347.0	309.2	351.6	335.9	13.4	23.2	3
9/14/2021 9:00	344.3	301.2	350.3	331.9	15.5	26.8	3
9/14/2021 10:00	349.6	303.0	351.2	334.6	15.8	27.4	3
9/14/2021 11:00	339.9	300.4	345.4	328.6	14.2	24.6	3
9/14/2021 12:00	344.0	304.1	345.1	331.1	13.5	23.4	3
9/14/2021 13:00	331.1	296.7	346.8	324.9	14.8	25.6	3

2.06 mg/kg 3,4-diaminopyridine Treatment							
Heart Rate Corrected QT Interval (msec)							
Date	**VL90IA**	**YR895FD**	**AL793H**	**Mean**	**SE**	**SD**	**n**
9/14/2021 14:00	334.2	296.2	348.5	326.3	15.6	27.0	3
9/14/2021 15:00	334.2	294.5	335.9	321.5	13.5	23.4	3
9/14/2021 16:00	338.5	295.9	338.0	324.1	14.1	24.4	3
9/14/2021 17:00	337.0	296.9	338.3	324.1	13.6	23.5	3
9/14/2021 18:00	346.7	302.1	329.7	326.2	13.0	22.5	3
9/14/2021 19:00	369.8	330.3	351.7	350.6	11.4	19.8	3
9/14/2021 20:00	367.8	333.9	353.6	351.8	9.8	17.0	3
9/14/2021 21:00	371.8	325.2	354.0	350.3	13.6	23.5	3
9/14/2021 22:00	369.0	328.9	344.5	347.5	11.7	20.2	3
9/14/2021 23:00	354.5	313.0	342.2	336.6	12.3	21.3	3
9/15/2021 0:00	363.6	331.0	358.6	351.1	10.1	17.5	3
9/15/2021 1:00	358.8	319.9	349.1	342.6	11.7	20.2	3
9/15/2021 2:00	366.4	334.8	354.0	351.7	9.2	15.9	3
9/15/2021 3:00	349.1	309.6	344.0	334.3	12.4	21.5	3
9/15/2021 4:00	354.1	325.0	351.0	343.4	9.2	16.0	3
9/15/2021 5:00	347.4	311.6	346.3	335.1	11.8	20.4	3
9/15/2021 6:00	344.8	321.5	339.4	335.3	7.0	12.2	3
9/15/2021 7:00	338.1	307.2	341.8	329.1	11.0	19.0	3
9/15/2021 8:00	343.4	309.2	346.5	333.0	11.9	20.7	3
9/15/2021 9:00	347.1	311.4	350.3	336.2	12.5	21.6	3
9/15/2021 10:00	352.3	316.7	349.6	339.5	11.4	19.8	3
9/15/2021 11:00	354.7	313.5	NaN	334.1	20.6	29.2	2
9/15/2021 12:00	350.1	320.6	NaN	335.3	14.8	20.9	2
9/15/2021 13:00	351.7	319.5	NaN	335.6	16.1	22.7	2
9/15/2021 14:00	352.3	319.8	NaN	336.0	16.3	23.0	2
9/15/2021 15:00	357.7	322.4	NaN	340.0	17.7	25.0	2
9/15/2021 16:00	362.7	319.4	NaN	341.0	21.7	30.6	2
9/15/2021 17:00	358.3	332.1	NaN	345.2	13.1	18.5	2
9/15/2021 18:00	360.7	338.0	NaN	349.3	11.4	16.1	2
9/15/2021 19:00	370.8	332.5	NaN	351.6	19.1	27.0	2
9/15/2021 20:00	360.6	NaN	NaN	360.6	0.0	0.0	1
9/15/2021 21:00	359.9	NaN	NaN	359.9	0.0	0.0	1

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Table 27: QT Interval (msec) 2.06 mg/kg 3,4-diaminopyridine Treatment

2.06 mg/kg 3,4-diaminopyridine Treatment							
QT Interval (msec)							
Date	VL90IA	YR895FD	AL793H	Mean	SE	SD	n
9/10/2021 16:00	226.1	188.3	212.2	208.8	11.0	19.1	3
9/10/2021 17:00	228.5	189.9	213.4	210.6	11.2	19.5	3
9/10/2021 18:00	250.3	191.4	218.2	220.0	17.0	29.5	3
9/10/2021 19:00	311.5	255.1	247.0	271.2	20.3	35.2	3
9/10/2021 20:00	332.5	273.9	268.5	291.6	20.5	35.5	3
9/10/2021 21:00	331.7	278.6	271.6	294.0	19.0	32.9	3
9/10/2021 22:00	309.2	280.5	267.5	285.7	12.3	21.3	3
9/10/2021 23:00	325.1	282.9	267.0	291.6	17.3	30.0	3
9/11/2021 0:00	332.8	284.7	268.4	295.3	19.3	33.5	3
9/11/2021 1:00	328.9	278.1	278.6	295.2	16.9	29.2	3
9/11/2021 2:00	327.2	278.4	279.3	295.0	16.1	27.9	3
9/11/2021 3:00	329.2	270.3	269.6	289.7	19.8	34.2	3
9/11/2021 4:00	318.7	268.2	273.8	286.9	16.0	27.7	3
9/11/2021 5:00	300.4	265.1	272.0	279.1	10.8	18.7	3
9/11/2021 6:00	314.4	260.4	276.9	283.9	16.0	27.7	3
9/11/2021 7:00	286.8	232.8	256.0	258.6	15.6	27.1	3
9/11/2021 8:00	252.0	208.9	233.2	231.4	12.5	21.6	3
9/11/2021 9:00	248.5	214.3	239.0	233.9	10.2	17.7	3
9/11/2021 10:00	245.8	217.0	236.5	233.1	8.5	14.7	3
9/11/2021 11:00	235.7	257.3	236.1	243.0	7.1	12.4	3
9/11/2021 12:00	243.0	247.4	216.2	235.5	9.7	16.9	3
9/11/2021 13:00	230.1	211.2	219.1	220.1	5.5	9.5	3
9/11/2021 14:00	232.8	211.7	223.0	222.5	6.1	10.5	3
9/11/2021 15:00	245.6	219.5	222.8	229.3	8.2	14.2	3
9/11/2021 16:00	267.0	218.1	242.4	242.5	14.1	24.4	3
9/11/2021 17:00	223.0	197.8	209.0	210.0	7.3	12.6	3
9/11/2021 18:00	231.0	207.0	203.3	213.8	8.7	15.0	3
9/11/2021 19:00	284.2	246.9	224.4	251.9	17.4	30.2	3
9/11/2021 20:00	296.4	245.6	236.5	259.5	18.6	32.3	3
9/11/2021 21:00	300.6	249.2	250.0	266.6	17.0	29.4	3
9/11/2021 22:00	289.1	251.0	260.9	267.0	11.4	19.8	3

2.06 mg/kg 3,4-diaminopyridine Treatment							
QT Interval (msec)							
Date	**VL90IA**	**YR895FD**	**AL793H**	**Mean**	**SE**	**SD**	**n**
9/11/2021 23:00	301.5	250.9	266.5	273.0	14.9	25.9	3
9/12/2021 0:00	302.3	261.4	275.7	279.8	12.0	20.8	3
9/12/2021 1:00	303.1	263.1	266.1	277.4	12.9	22.3	3
9/12/2021 2:00	295.9	252.8	271.7	273.5	12.5	21.6	3
9/12/2021 3:00	308.9	262.0	276.0	282.3	13.9	24.0	3
9/12/2021 4:00	300.6	262.4	273.9	279.0	11.3	19.6	3
9/12/2021 5:00	299.7	269.8	274.4	281.3	9.3	16.1	3
9/12/2021 6:00	295.1	276.2	279.7	283.7	5.8	10.0	3
9/12/2021 7:00	273.8	237.9	238.2	249.9	11.9	20.6	3
9/12/2021 8:00	234.6	211.7	216.7	221.0	6.9	12.0	3
9/12/2021 9:00	239.5	234.1	222.9	232.2	4.9	8.5	3
9/12/2021 10:00	232.4	225.3	220.6	226.1	3.4	5.9	3
9/12/2021 11:00	276.0	245.8	240.5	254.1	11.1	19.2	3
9/12/2021 12:00	275.4	262.3	245.2	261.0	8.8	15.2	3
9/12/2021 13:00	231.6	197.7	215.4	214.9	9.8	16.9	3
9/12/2021 14:00	254.4	204.6	231.1	230.1	14.4	24.9	3
9/12/2021 15:00	229.9	214.9	212.2	219.0	5.5	9.6	3
9/12/2021 16:00	228.1	201.9	210.2	213.4	7.7	13.4	3
9/12/2021 17:00	246.5	200.9	222.9	223.4	13.2	22.8	3
9/12/2021 18:00	273.2	187.4	224.5	228.4	24.8	43.0	3
9/12/2021 19:00	313.8	243.7	258.8	272.1	21.3	36.9	3
9/12/2021 20:00	318.2	261.1	273.0	284.1	17.4	30.1	3
9/12/2021 21:00	331.2	265.4	282.1	292.9	19.8	34.2	3
9/12/2021 22:00	332.6	278.3	272.0	294.3	19.2	33.3	3
9/12/2021 23:00	328.0	279.1	278.8	295.3	16.4	28.3	3
9/13/2021 0:00	321.9	275.2	272.8	290.0	16.0	27.7	3
9/13/2021 1:00	328.3	276.4	279.3	294.6	16.8	29.2	3
9/13/2021 2:00	325.9	275.4	281.9	294.4	15.9	27.5	3
9/13/2021 3:00	318.7	274.0	281.4	291.4	13.8	24.0	3
9/13/2021 4:00	311.1	271.3	286.0	289.4	11.6	20.1	3
9/13/2021 5:00	323.9	272.0	286.6	294.2	15.5	26.8	3
9/13/2021 6:00	316.7	275.2	279.2	290.3	13.2	22.9	3

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2.06 mg/kg 3,4-diaminopyridine Treatment							
QT Interval (msec)							
Date	**VL90IA**	**YR895FD**	**AL793H**	**Mean**	**SE**	**SD**	**n**
9/13/2021 7:00	294.0	230.0	253.1	259.0	18.7	32.4	3
9/13/2021 8:00	250.9	216.1	223.9	230.3	10.5	18.3	3
9/13/2021 9:00	192.5	173.3	186.1	184.0	5.7	9.8	3
9/13/2021 10:00	219.3	196.2	222.4	212.6	8.3	14.4	3
9/13/2021 11:00	249.6	202.2	234.9	228.9	14.0	24.3	3
9/13/2021 12:00	252.2	208.3	229.6	230.0	12.7	22.0	3
9/13/2021 13:00	255.0	211.8	221.8	229.5	13.0	22.6	3
9/13/2021 14:00	233.2	202.3	214.8	216.8	9.0	15.6	3
9/13/2021 15:00	226.9	204.5	224.8	218.7	7.1	12.4	3
9/13/2021 16:00	237.6	199.8	222.8	220.1	11.0	19.0	3
9/13/2021 17:00	254.4	215.2	221.2	230.2	12.2	21.1	3
9/13/2021 18:00	268.9	207.5	219.2	231.8	18.8	32.6	3
9/13/2021 19:00	309.5	257.3	242.7	269.8	20.3	35.1	3
9/13/2021 20:00	324.2	269.1	242.9	278.8	24.0	41.5	3
9/13/2021 21:00	336.5	264.5	248.3	283.1	27.1	47.0	3
9/13/2021 22:00	320.8	264.2	248.3	277.7	22.0	38.1	3
9/13/2021 23:00	335.5	259.1	255.2	283.3	26.1	45.3	3
9/14/2021 0:00	337.8	261.1	262.0	287.0	25.4	44.0	3
9/14/2021 1:00	338.8	258.7	271.3	289.6	24.8	43.0	3
9/14/2021 2:00	328.8	263.1	274.8	288.9	20.2	35.0	3
9/14/2021 3:00	328.6	268.9	272.0	289.8	19.4	33.6	3
9/14/2021 4:00	317.7	268.3	272.3	286.1	15.8	27.4	3
9/14/2021 5:00	323.9	268.6	266.6	286.4	18.8	32.5	3
9/14/2021 6:00	314.8	263.5	265.8	281.4	16.7	29.0	3
9/14/2021 7:00	269.6	224.0	233.3	242.3	13.9	24.1	3
9/14/2021 8:00	257.9	215.0	230.8	234.6	12.5	21.7	3
9/14/2021 9:00	239.9	208.1	233.3	227.1	9.7	16.8	3
9/14/2021 10:00	262.4	213.6	234.6	236.9	14.1	24.5	3
9/14/2021 11:00	250.4	210.2	227.3	229.3	11.7	20.2	3
9/14/2021 12:00	262.1	217.3	230.0	236.5	13.3	23.1	3
9/14/2021 13:00	226.4	202.7	220.0	216.4	7.1	12.2	3
9/14/2021 14:00	225.1	202.1	222.1	216.4	7.2	12.5	3

2.06 mg/kg 3,4-diaminopyridine Treatment							
QT Interval (msec)							
Date	**VL90IA**	**YR895FD**	**AL793H**	**Mean**	**SE**	**SD**	**n**
9/14/2021 15:00	237.0	205.1	224.0	222.0	9.2	16.0	3
9/14/2021 16:00	252.3	192.7	212.5	219.2	17.5	30.3	3
9/14/2021 17:00	245.2	202.8	210.7	219.6	13.0	22.5	3
9/14/2021 18:00	275.5	210.0	207.9	231.1	22.2	38.5	3
9/14/2021 19:00	307.4	257.8	245.3	270.2	19.0	32.9	3
9/14/2021 20:00	293.4	254.7	241.1	263.1	15.7	27.1	3
9/14/2021 21:00	302.6	251.2	241.4	265.0	19.0	32.9	3
9/14/2021 22:00	279.2	230.2	233.4	247.6	15.8	27.4	3
9/14/2021 23:00	246.4	214.9	213.7	225.0	10.7	18.5	3
9/15/2021 0:00	277.4	246.1	249.6	257.7	9.9	17.1	3
9/15/2021 1:00	262.2	232.0	231.5	241.9	10.2	17.6	3
9/15/2021 2:00	267.3	242.1	242.9	250.8	8.3	14.3	3
9/15/2021 3:00	234.5	199.4	207.2	213.7	10.6	18.4	3
9/15/2021 4:00	243.9	224.9	228.6	232.4	5.8	10.1	3
9/15/2021 5:00	235.7	208.7	215.5	220.0	8.1	14.1	3
9/15/2021 6:00	218.3	219.0	213.7	217.0	1.7	2.9	3
9/15/2021 7:00	198.3	187.5	191.6	192.5	3.2	5.5	3
9/15/2021 8:00	201.0	185.4	197.8	194.7	4.7	8.2	3
9/15/2021 9:00	199.7	189.2	205.9	198.3	4.9	8.4	3
9/15/2021 10:00	199.3	186.8	204.0	196.7	5.1	8.9	3
9/15/2021 11:00	197.7	176.0	NaN	186.8	10.9	15.4	2
9/15/2021 12:00	202.8	183.3	NaN	193.0	9.8	13.8	2
9/15/2021 13:00	207.4	184.0	NaN	195.7	11.7	16.5	2
9/15/2021 14:00	201.6	181.5	NaN	191.6	10.1	14.2	2
9/15/2021 15:00	191.7	185.4	NaN	188.6	3.1	4.4	2
9/15/2021 16:00	205.6	187.6	NaN	196.6	9.0	12.7	2
9/15/2021 17:00	201.4	200.1	NaN	200.7	0.7	0.9	2
9/15/2021 18:00	205.0	196.2	NaN	200.6	4.4	6.2	2
9/15/2021 19:00	211.7	187.2	NaN	199.5	12.3	17.3	2
9/15/2021 20:00	207.7	NaN	NaN	207.7	0.0	0.0	1
9/15/2021 21:00	210.4	NaN	NaN	210.4	0.0	0.0	1

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Table 28: RR Interval (msec) 2.06 mg/kg 3,4-diaminopyridine Treatment

2.06 mg/kg 3,4-diaminopyridine Treatment							
RR Interval (msec)							
Date	VL90IA	YR895FD	AL793H	Mean	SE	SD	n
9/10/2021 16:00	434.2	394.3	402.9	410.4	12.1	21.0	3
9/10/2021 17:00	445.7	419.8	402.8	422.7	12.5	21.6	3
9/10/2021 18:00	504.0	426.9	422.6	451.2	26.4	45.8	3
9/10/2021 19:00	697.1	572.7	499.6	589.8	57.7	99.9	3
9/10/2021 20:00	787.7	632.6	555.2	658.5	68.4	118.4	3
9/10/2021 21:00	739.3	638.3	557.5	645.0	52.6	91.1	3
9/10/2021 22:00	611.4	649.4	532.3	597.7	34.5	59.7	3
9/10/2021 23:00	672.7	671.2	532.1	625.4	46.6	80.8	3
9/11/2021 0:00	684.8	684.6	538.3	635.9	48.8	84.5	3
9/11/2021 1:00	670.6	657.3	571.7	633.2	31.0	53.7	3
9/11/2021 2:00	661.7	663.9	575.2	633.6	29.2	50.6	3
9/11/2021 3:00	657.6	622.3	561.9	614.0	27.9	48.4	3
9/11/2021 4:00	644.3	635.5	578.4	619.4	20.6	35.7	3
9/11/2021 5:00	618.8	621.7	577.1	605.9	14.4	25.0	3
9/11/2021 6:00	683.0	611.5	593.2	629.2	27.4	47.4	3
9/11/2021 7:00	580.7	548.8	514.2	547.9	19.2	33.3	3
9/11/2021 8:00	498.9	495.4	443.6	479.3	17.9	31.0	3
9/11/2021 9:00	489.7	513.5	469.2	490.8	12.8	22.2	3
9/11/2021 10:00	503.1	525.4	468.4	499.0	16.6	28.7	3
9/11/2021 11:00	461.0	613.8	470.5	515.1	49.4	85.6	3
9/11/2021 12:00	468.5	583.9	413.6	488.7	50.2	86.9	3
9/11/2021 13:00	445.6	482.8	417.2	448.5	19.0	32.9	3
9/11/2021 14:00	455.5	493.8	417.8	455.7	22.0	38.0	3
9/11/2021 15:00	497.0	526.2	438.6	487.3	25.8	44.6	3
9/11/2021 16:00	560.3	518.3	492.5	523.7	19.8	34.2	3
9/11/2021 17:00	430.6	436.4	390.7	419.2	14.4	24.9	3
9/11/2021 18:00	458.2	449.4	383.8	430.5	23.5	40.7	3
9/11/2021 19:00	602.9	541.1	438.1	527.4	48.1	83.3	3
9/11/2021 20:00	624.7	529.7	472.2	542.2	44.4	77.0	3
9/11/2021 21:00	622.7	550.3	512.0	561.6	32.5	56.2	3
9/11/2021 22:00	565.5	552.1	540.8	552.8	7.1	12.3	3

2.06 mg/kg 3,4-diaminopyridine Treatment							
RR Interval (msec)							
Date	VL90IA	YR895FD	AL793H	Mean	SE	SD	n
9/11/2021 23:00	617.5	565.3	563.9	582.3	17.6	30.5	3
9/12/2021 0:00	613.2	606.6	595.6	605.1	5.1	8.9	3
9/12/2021 1:00	603.3	611.9	576.2	597.1	10.8	18.7	3
9/12/2021 2:00	608.9	583.3	593.5	595.3	7.4	12.9	3
9/12/2021 3:00	663.9	612.1	595.3	623.8	20.6	35.8	3
9/12/2021 4:00	633.2	630.6	587.5	617.1	14.8	25.7	3
9/12/2021 5:00	620.8	656.9	590.8	622.9	19.1	33.1	3
9/12/2021 6:00	616.4	678.5	594.7	629.9	25.1	43.5	3
9/12/2021 7:00	565.3	565.9	472.1	534.4	31.2	54.0	3
9/12/2021 8:00	454.7	485.2	421.2	453.7	18.5	32.0	3
9/12/2021 9:00	466.2	575.7	455.0	499.0	38.5	66.7	3
9/12/2021 10:00	439.0	535.2	423.5	465.9	34.9	60.5	3
9/12/2021 11:00	557.8	605.2	492.3	551.8	32.7	56.7	3
9/12/2021 12:00	558.9	633.8	508.0	566.9	36.6	63.3	3
9/12/2021 13:00	455.4	448.6	405.3	436.4	15.7	27.2	3
9/12/2021 14:00	522.2	479.3	460.8	487.4	18.2	31.5	3
9/12/2021 15:00	456.9	505.1	391.1	451.0	33.0	57.2	3
9/12/2021 16:00	451.6	475.2	392.4	439.7	24.6	42.7	3
9/12/2021 17:00	511.9	463.2	443.8	473.0	20.2	35.1	3
9/12/2021 18:00	600.3	420.0	466.1	495.5	54.1	93.7	3
9/12/2021 19:00	716.2	554.8	560.1	610.4	53.0	91.7	3
9/12/2021 20:00	723.3	631.9	609.2	654.8	34.9	60.4	3
9/12/2021 21:00	766.1	655.7	619.0	680.3	44.2	76.5	3
9/12/2021 22:00	758.5	673.6	580.9	671.0	51.3	88.8	3
9/12/2021 23:00	720.3	660.9	609.6	663.6	32.0	55.4	3
9/13/2021 0:00	694.3	675.5	585.7	651.8	33.5	58.0	3
9/13/2021 1:00	717.5	685.3	625.5	676.1	27.0	46.7	3
9/13/2021 2:00	717.6	685.7	620.4	674.6	28.6	49.5	3
9/13/2021 3:00	714.7	682.1	617.8	671.5	28.5	49.3	3
9/13/2021 4:00	685.8	663.2	636.7	661.9	14.2	24.6	3
9/13/2021 5:00	747.7	671.0	644.0	687.6	31.1	53.8	3
9/13/2021 6:00	721.0	679.3	624.3	674.8	28.0	48.5	3

2.06 mg/kg 3,4-diaminopyridine Treatment							
RR Interval (msec)							
Date	VL90IA	YR895FD	AL793H	Mean	SE	SD	n
9/13/2021 7:00	646.4	550.0	522.9	573.1	37.5	64.9	3
9/13/2021 8:00	494.7	492.5	418.0	468.4	25.2	43.6	3
9/13/2021 9:00	323.1	363.9	329.2	338.7	12.7	22.0	3
9/13/2021 10:00	439.8	458.6	422.2	440.2	10.5	18.2	3
9/13/2021 11:00	545.3	491.6	472.4	503.1	21.8	37.8	3
9/13/2021 12:00	534.0	504.4	450.7	496.4	24.4	42.2	3
9/13/2021 13:00	546.8	526.4	436.7	503.3	33.8	58.5	3
9/13/2021 14:00	470.6	495.5	411.3	459.1	25.0	43.3	3
9/13/2021 15:00	451.8	467.4	388.1	435.8	24.2	42.0	3
9/13/2021 16:00	499.8	459.8	416.4	458.6	24.1	41.7	3
9/13/2021 17:00	557.2	513.1	388.9	486.4	50.4	87.3	3
9/13/2021 18:00	596.5	478.9	351.6	475.7	70.7	122.5	3
9/13/2021 19:00	696.9	607.4	456.9	587.1	70.0	121.3	3
9/13/2021 20:00	754.9	624.8	451.7	610.4	87.8	152.1	3
9/13/2021 21:00	784.0	606.7	469.2	620.0	91.1	157.8	3
9/13/2021 22:00	713.9	606.6	474.9	598.5	69.1	119.7	3
9/13/2021 23:00	768.6	593.6	502.6	621.6	78.1	135.2	3
9/14/2021 0:00	771.5	596.0	522.1	629.8	74.0	128.1	3
9/14/2021 1:00	755.7	592.5	556.9	635.0	61.2	106.0	3
9/14/2021 2:00	737.1	608.0	579.6	641.6	48.5	84.0	3
9/14/2021 3:00	749.7	638.8	575.8	654.8	50.8	88.0	3
9/14/2021 4:00	708.7	637.6	579.6	641.9	37.3	64.6	3
9/14/2021 5:00	735.0	638.1	555.1	642.7	52.0	90.0	3
9/14/2021 6:00	715.5	625.8	555.1	632.1	46.4	80.4	3
9/14/2021 7:00	576.2	509.1	450.5	511.9	36.3	62.9	3
9/14/2021 8:00	552.5	483.6	431.0	489.0	35.2	61.0	3
9/14/2021 9:00	485.5	477.1	443.5	468.7	12.8	22.3	3
9/14/2021 10:00	563.3	497.1	446.3	502.2	33.9	58.6	3
9/14/2021 11:00	542.8	489.8	433.1	488.6	31.7	54.9	3
9/14/2021 12:00	580.4	510.6	444.2	511.7	39.3	68.1	3
9/14/2021 13:00	467.4	466.8	402.3	445.5	21.6	37.4	3
9/14/2021 14:00	453.6	465.7	406.3	441.9	18.1	31.4	3

2.06 mg/kg 3,4-diaminopyridine Treatment							
RR Interval (msec)							
Date	VL90IA	YR895FD	AL793H	Mean	SE	SD	n
9/14/2021 15:00	502.8	485.0	444.5	477.5	17.2	29.9	3
9/14/2021 16:00	555.5	424.2	395.4	458.4	49.3	85.3	3
9/14/2021 17:00	529.3	466.5	388.2	461.3	40.8	70.7	3
9/14/2021 18:00	631.7	483.0	397.7	504.1	68.4	118.4	3
9/14/2021 19:00	691.2	609.4	486.5	595.7	59.5	103.0	3
9/14/2021 20:00	636.5	581.7	464.9	561.0	50.6	87.6	3
9/14/2021 21:00	662.5	596.5	464.9	574.6	58.1	100.6	3
9/14/2021 22:00	572.3	489.8	458.9	507.0	33.8	58.6	3
9/14/2021 23:00	482.9	471.5	390.0	448.1	29.3	50.7	3
9/15/2021 0:00	581.9	552.5	484.7	539.7	28.8	49.9	3
9/15/2021 1:00	534.2	525.9	439.8	500.0	30.2	52.3	3
9/15/2021 2:00	532.1	522.8	470.8	508.6	19.1	33.0	3
9/15/2021 3:00	451.0	414.6	362.7	409.4	25.6	44.4	3
9/15/2021 4:00	474.3	478.7	424.1	459.0	17.5	30.3	3
9/15/2021 5:00	460.4	448.6	387.2	432.0	22.7	39.3	3
9/15/2021 6:00	400.8	463.8	396.5	420.4	21.8	37.7	3
9/15/2021 7:00	343.9	372.4	314.3	343.5	16.8	29.0	3
9/15/2021 8:00	342.6	359.5	325.7	342.6	9.8	16.9	3
9/15/2021 9:00	331.1	369.3	345.7	348.7	11.1	19.3	3
9/15/2021 10:00	320.0	348.1	340.4	336.2	8.4	14.5	3
9/15/2021 11:00	310.6	315.2	NaN	312.9	2.3	3.3	2
9/15/2021 12:00	335.5	326.8	NaN	331.2	4.3	6.1	2
9/15/2021 13:00	347.8	331.8	NaN	339.8	8.0	11.4	2
9/15/2021 14:00	327.5	322.2	NaN	324.8	2.7	3.8	2
9/15/2021 15:00	287.2	331.0	NaN	309.1	21.9	31.0	2
9/15/2021 16:00	321.3	344.9	NaN	333.1	11.8	16.7	2
9/15/2021 17:00	316.0	363.0	NaN	339.5	23.5	33.2	2
9/15/2021 18:00	323.2	337.1	NaN	330.1	7.0	9.9	2
9/15/2021 19:00	326.2	317.1	NaN	321.6	4.6	6.4	2
9/15/2021 20:00	331.8	NaN	NaN	331.8	0.0	0.0	1
9/15/2021 21:00	342.0	NaN	NaN	342.0	0.0	0.0	1

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Table 29: Temperature (°C) 4.12 mg/kg 3,4-diaminopyridine Treatment

4.12 mg/kg 3,4-diaminopyridine Treatment							
Temperature (°C)							
Date	SA180D	BF873I	AP55D	Mean	SE	SD	n
9/10/2021 16:00	37.2	37.6	37.7	37.5	0.2	0.3	3
9/10/2021 17:00	37.0	37.4	37.3	37.2	0.1	0.2	3
9/10/2021 18:00	36.9	37.5	37.3	37.2	0.2	0.3	3
9/10/2021 19:00	36.8	37.2	37.4	37.1	0.2	0.3	3
9/10/2021 20:00	36.0	36.5	37.0	36.5	0.3	0.5	3
9/10/2021 21:00	35.7	36.4	36.5	36.2	0.2	0.4	3
9/10/2021 22:00	35.4	36.2	36.0	35.9	0.3	0.5	3
9/10/2021 23:00	35.5	35.8	35.7	35.6	0.1	0.2	3
9/11/2021 0:00	35.8	36.3	35.7	35.9	0.2	0.3	3
9/11/2021 1:00	35.8	36.2	35.6	35.8	0.2	0.3	3
9/11/2021 2:00	35.8	36.2	35.5	35.8	0.2	0.3	3
9/11/2021 3:00	35.9	36.2	35.3	35.8	0.3	0.5	3
9/11/2021 4:00	35.9	36.1	35.3	35.7	0.2	0.4	3
9/11/2021 5:00	35.9	36.2	35.7	35.9	0.2	0.3	3
9/11/2021 6:00	36.4	36.3	35.7	36.1	0.2	0.4	3
9/11/2021 7:00	36.7	36.7	36.7	36.7	0.0	0.0	3
9/11/2021 8:00	36.8	37.2	37.2	37.1	0.1	0.2	3
9/11/2021 9:00	36.8	37.1	37.2	37.0	0.1	0.2	3
9/11/2021 10:00	36.8	37.1	36.9	36.9	0.1	0.1	3
9/11/2021 11:00	36.6	37.0	36.8	36.8	0.1	0.2	3
9/11/2021 12:00	36.9	37.3	36.6	36.9	0.2	0.3	3
9/11/2021 13:00	36.8	37.4	37.1	37.1	0.2	0.3	3
9/11/2021 14:00	37.0	37.5	37.1	37.2	0.2	0.3	3
9/11/2021 15:00	36.9	37.1	37.0	37.0	0.1	0.1	3
9/11/2021 16:00	36.9	37.2	36.8	37.0	0.1	0.2	3
9/11/2021 17:00	36.9	37.5	37.2	37.2	0.2	0.3	3
9/11/2021 18:00	36.9	37.6	37.4	37.3	0.2	0.4	3
9/11/2021 19:00	36.4	37.1	37.1	36.8	0.2	0.4	3
9/11/2021 20:00	36.3	36.2	36.6	36.4	0.1	0.2	3
9/11/2021 21:00	36.0	36.3	36.1	36.1	0.1	0.1	3
9/11/2021 22:00	35.9	36.2	35.9	36.0	0.1	0.2	3

4.12 mg/kg 3,4-diaminopyridine Treatment							
Temperature (°C)							
Date	SA180D	BF873I	AP55D	Mean	SE	SD	n
9/11/2021 23:00	35.7	36.1	35.5	35.8	0.2	0.3	3
9/12/2021 0:00	36.0	36.1	35.3	35.8	0.3	0.4	3
9/12/2021 1:00	36.0	36.1	35.1	35.7	0.3	0.5	3
9/12/2021 2:00	35.7	36.2	35.5	35.8	0.2	0.4	3
9/12/2021 3:00	35.7	36.0	35.1	35.6	0.3	0.5	3
9/12/2021 4:00	35.8	35.8	35.4	35.7	0.1	0.2	3
9/12/2021 5:00	35.9	36.0	35.3	35.7	0.2	0.4	3
9/12/2021 6:00	36.3	36.2	35.8	36.1	0.2	0.3	3
9/12/2021 7:00	36.4	36.8	36.6	36.6	0.1	0.2	3
9/12/2021 8:00	36.6	37.3	37.3	37.1	0.2	0.4	3
9/12/2021 9:00	36.4	37.1	37.0	36.8	0.2	0.4	3
9/12/2021 10:00	36.7	37.2	36.9	36.9	0.2	0.3	3
9/12/2021 11:00	36.7	37.1	36.9	36.9	0.1	0.2	3
9/12/2021 12:00	36.9	37.0	36.8	36.9	0.1	0.1	3
9/12/2021 13:00	37.0	37.3	36.9	37.1	0.1	0.2	3
9/12/2021 14:00	37.0	37.3	37.3	37.2	0.1	0.2	3
9/12/2021 15:00	37.0	37.5	37.4	37.3	0.2	0.3	3
9/12/2021 16:00	37.2	37.7	37.6	37.5	0.1	0.2	3
9/12/2021 17:00	37.0	37.5	37.3	37.3	0.1	0.2	3
9/12/2021 18:00	37.0	37.6	37.5	37.4	0.2	0.3	3
9/12/2021 19:00	36.3	37.0	37.0	36.8	0.2	0.4	3
9/12/2021 20:00	35.8	36.4	36.0	36.1	0.2	0.3	3
9/12/2021 21:00	35.5	36.2	36.3	36.0	0.3	0.5	3
9/12/2021 22:00	35.9	36.5	36.2	36.2	0.2	0.3	3
9/12/2021 23:00	36.0	36.3	36.3	36.2	0.1	0.2	3
9/13/2021 0:00	35.5	36.0	35.6	35.7	0.1	0.3	3
9/13/2021 1:00	35.3	35.9	35.3	35.5	0.2	0.3	3
9/13/2021 2:00	35.4	36.1	35.9	35.8	0.2	0.4	3
9/13/2021 3:00	35.4	36.2	35.7	35.8	0.2	0.4	3
9/13/2021 4:00	35.7	36.0	35.7	35.8	0.1	0.2	3
9/13/2021 5:00	35.7	36.1	35.8	35.8	0.1	0.2	3
9/13/2021 6:00	36.1	36.2	36.1	36.1	0.1	0.1	3

4.12 mg/kg 3,4-diaminopyridine Treatment							
Temperature (°C)							
Date	SA180D	BF873I	AP55D	Mean	SE	SD	n
9/13/2021 7:00	36.4	36.6	36.7	36.6	0.1	0.1	3
9/13/2021 8:00	37.0	37.5	37.4	37.3	0.2	0.3	3
9/13/2021 9:00	37.4	38.3	38.8	38.2	0.4	0.7	3
9/13/2021 10:00	37.4	37.8	37.9	37.7	0.1	0.2	3
9/13/2021 11:00	37.2	37.3	37.2	37.2	0.0	0.0	3
9/13/2021 12:00	37.1	37.3	37.1	37.2	0.0	0.1	3
9/13/2021 13:00	37.1	37.4	37.2	37.2	0.1	0.2	3
9/13/2021 14:00	37.5	37.8	37.8	37.7	0.1	0.2	3
9/13/2021 15:00	37.3	37.8	37.7	37.6	0.1	0.2	3
9/13/2021 16:00	37.3	37.4	37.4	37.4	0.1	0.1	3
9/13/2021 17:00	37.2	37.4	37.3	37.3	0.1	0.1	3
9/13/2021 18:00	37.3	37.5	37.2	37.3	0.1	0.2	3
9/13/2021 19:00	36.7	37.1	37.0	37.0	0.1	0.2	3
9/13/2021 20:00	35.9	36.1	35.9	36.0	0.1	0.1	3
9/13/2021 21:00	35.6	35.7	35.2	35.5	0.1	0.2	3
9/13/2021 22:00	35.6	35.6	35.5	35.6	0.0	0.1	3
9/13/2021 23:00	35.4	35.6	35.3	35.4	0.1	0.1	3
9/14/2021 0:00	35.4	35.7	35.4	35.5	0.1	0.2	3
9/14/2021 1:00	35.2	35.9	35.9	35.7	0.2	0.4	3
9/14/2021 2:00	35.4	35.9	35.1	35.5	0.2	0.4	3
9/14/2021 3:00	35.6	35.7	35.3	35.6	0.1	0.2	3
9/14/2021 4:00	35.6	36.2	35.7	35.9	0.2	0.3	3
9/14/2021 5:00	35.8	36.1	35.6	35.8	0.2	0.3	3
9/14/2021 6:00	35.9	36.3	36.6	36.3	0.2	0.3	3
9/14/2021 7:00	36.7	36.7	36.8	36.7	0.0	0.1	3
9/14/2021 8:00	36.9	37.1	37.3	37.1	0.1	0.2	3
9/14/2021 9:00	37.3	37.5	37.7	37.5	0.1	0.2	3
9/14/2021 10:00	37.0	37.2	37.2	37.1	0.1	0.1	3
9/14/2021 11:00	37.2	37.4	37.5	37.4	0.1	0.2	3
9/14/2021 12:00	37.1	37.2	37.1	37.1	0.0	0.1	3
9/14/2021 13:00	37.4	37.5	37.5	37.5	0.0	0.0	3
9/14/2021 14:00	37.2	37.6	37.7	37.5	0.1	0.2	3

4.12 mg/kg 3,4-diaminopyridine Treatment							
Temperature (°C)							
Date	SA180D	BF873I	AP55D	Mean	SE	SD	n
9/14/2021 15:00	37.3	37.5	37.6	37.5	0.1	0.2	3
9/14/2021 16:00	37.0	37.2	37.5	37.2	0.1	0.2	3
9/14/2021 17:00	37.1	37.4	37.7	37.4	0.2	0.3	3
9/14/2021 18:00	36.9	37.4	37.5	37.3	0.2	0.3	3
9/14/2021 19:00	36.4	37.1	37.0	36.9	0.2	0.4	3
9/14/2021 20:00	35.6	36.1	36.7	36.1	0.3	0.5	3
9/14/2021 21:00	35.8	36.5	36.9	36.4	0.3	0.5	3
9/14/2021 22:00	35.8	35.9	36.9	36.2	0.4	0.6	3
9/14/2021 23:00	36.4	36.8	37.1	36.8	0.2	0.4	3
9/15/2021 0:00	35.7	36.0	36.7	36.1	0.3	0.5	3
9/15/2021 1:00	35.9	36.5	36.7	36.4	0.2	0.4	3
9/15/2021 2:00	35.7	36.2	36.6	36.2	0.3	0.4	3
9/15/2021 3:00	36.5	36.7	36.9	36.7	0.1	0.2	3
9/15/2021 4:00	36.0	36.3	36.9	36.4	0.3	0.4	3
9/15/2021 5:00	36.5	36.6	36.9	36.7	0.1	0.2	3
9/15/2021 6:00	36.4	36.5	36.7	36.5	0.1	0.1	3
9/15/2021 7:00	37.0	36.7	36.5	36.7	0.1	0.2	3
9/15/2021 8:00	37.0	36.7	36.8	36.8	0.1	0.2	3
9/15/2021 9:00	37.0	36.5	36.6	36.7	0.2	0.3	3
9/15/2021 10:00	36.5	36.5	36.1	36.3	0.1	0.2	3
9/15/2021 11:00	36.4	36.9	35.3	36.2	0.5	0.8	3
9/15/2021 12:00	36.6	36.7	35.4	36.2	0.4	0.7	3
9/15/2021 13:00	36.6	36.7	35.4	36.2	0.4	0.7	3
9/15/2021 14:00	36.6	36.5	35.0	36.1	0.5	0.9	3
9/15/2021 15:00	36.6	36.6	NaN	36.6	0.0	0.1	2
9/15/2021 16:00	36.9	36.2	NaN	36.6	0.4	0.5	2
9/15/2021 17:00	37.1	35.7	NaN	36.4	0.7	1.0	2
9/15/2021 18:00	37.3	36.3	NaN	36.8	0.5	0.7	2
9/15/2021 19:00	36.8	36.7	NaN	36.7	0.1	0.1	2
9/15/2021 20:00	37.6	36.6	NaN	37.1	0.5	0.7	2
9/15/2021 21:00	37.3	36.5	NaN	36.9	0.4	0.6	2
9/15/2021 22:00	37.0	36.7	NaN	36.9	0.2	0.2	2

4.12 mg/kg 3,4-diaminopyridine Treatment							
Temperature (°C)							
Date	**SA180D**	**BF873I**	**AP55D**	**Mean**	**SE**	**SD**	**n**
9/15/2021 23:00	37.0	36.7	NaN	36.8	0.1	0.2	2
9/16/2021 0:00	37.2	36.4	NaN	36.8	0.4	0.6	2
9/16/2021 1:00	37.3	36.4	NaN	36.8	0.4	0.6	2
9/16/2021 2:00	36.8	36.5	NaN	36.6	0.1	0.2	2
9/16/2021 3:00	36.4	36.5	NaN	36.4	0.0	0.1	2
9/16/2021 4:00	36.5	36.2	NaN	36.3	0.2	0.2	2
9/16/2021 5:00	36.5	35.9	NaN	36.2	0.3	0.4	2
9/16/2021 6:00	35.8	36.0	NaN	35.9	0.1	0.1	2
9/16/2021 7:00	35.0	35.9	NaN	35.4	0.4	0.6	2
9/16/2021 8:00	35.5	35.6	NaN	35.5	0.0	0.0	2
9/16/2021 9:00	35.6	35.2	NaN	35.4	0.2	0.2	2
9/16/2021 10:00	NaN	35.5	NaN	35.5	0.0	0.0	1
9/16/2021 11:00	NaN	35.4	NaN	35.4	0.0	0.0	1

9.3 4.12 mg/kg 3,4-diaminopyridine Treatment

9.3.1 Temperature and Activity – 4.12 mg/kg 3,4-diaminopyridine Treatment

Table 30: Activity 4.12 mg/kg 3,4-diaminopyridine Treatment

4.12 mg/kg 3,4-diaminopyridine Treatment							
Activity							
Date	SA180D	BF873I	AP55D	Mean	SE	SD	n
9/10/2021 16:00	711.8	817.5	808.1	779.2	33.8	58.5	3
9/10/2021 17:00	612.8	616.0	1042.2	757.0	142.6	247.0	3
9/10/2021 18:00	436.8	756.1	760.8	651.2	107.2	185.7	3
9/10/2021 19:00	127.2	250.4	197.4	191.7	35.7	61.8	3
9/10/2021 20:00	162.9	209.2	146.3	172.8	18.8	32.6	3
9/10/2021 21:00	113.4	175.1	164.5	151.0	19.0	33.0	3
9/10/2021 22:00	108.5	222.2	177.3	169.3	33.1	57.2	3
9/10/2021 23:00	137.6	200.1	153.0	163.5	18.8	32.6	3
9/11/2021 0:00	117.8	197.4	183.8	166.3	24.6	42.5	3
9/11/2021 1:00	165.1	231.7	170.6	189.1	21.4	37.0	3
9/11/2021 2:00	130.8	238.8	155.1	174.9	32.7	56.6	3
9/11/2021 3:00	129.1	226.4	184.2	179.9	28.2	48.8	3
9/11/2021 4:00	160.7	228.0	160.1	182.9	22.6	39.1	3
9/11/2021 5:00	129.0	207.1	162.9	166.3	22.6	39.2	3
9/11/2021 6:00	134.9	185.4	177.5	165.9	15.7	27.2	3
9/11/2021 7:00	422.7	646.3	793.3	620.8	107.7	186.6	3
9/11/2021 8:00	804.2	727.6	1170.5	900.8	136.7	236.7	3
9/11/2021 9:00	710.8	619.3	860.0	730.0	70.2	121.5	3
9/11/2021 10:00	425.9	523.8	755.3	568.3	97.7	169.2	3
9/11/2021 11:00	713.0	929.1	214.1	618.7	211.7	366.7	3
9/11/2021 12:00	442.4	810.6	639.2	630.7	106.4	184.2	3
9/11/2021 13:00	525.8	744.8	573.1	614.6	66.5	115.2	3
9/11/2021 14:00	295.1	677.5	810.7	594.4	154.5	267.7	3
9/11/2021 15:00	397.1	339.0	745.3	493.8	126.9	219.7	3
9/11/2021 16:00	450.3	551.8	570.1	524.1	37.3	64.6	3
9/11/2021 17:00	634.9	696.0	1134.8	821.9	157.4	272.7	3
9/11/2021 18:00	440.9	685.5	782.8	636.4	101.7	176.2	3
9/11/2021 19:00	194.0	306.3	255.4	251.9	32.5	56.2	3

4.12 mg/kg 3,4-diaminopyridine Treatment							
Activity							
Date	SA180D	BF873I	AP55D	Mean	SE	SD	n
9/11/2021 20:00	135.7	216.9	167.9	173.5	23.6	40.9	3
9/11/2021 21:00	208.8	234.9	170.1	204.6	18.8	32.6	3
9/11/2021 22:00	117.4	173.4	150.5	147.1	16.2	28.1	3
9/11/2021 23:00	170.1	224.1	218.6	204.2	17.2	29.7	3
9/12/2021 0:00	171.2	236.3	144.0	183.8	27.4	47.4	3
9/12/2021 1:00	129.2	201.1	145.0	158.5	21.8	37.8	3
9/12/2021 2:00	152.6	177.0	202.9	177.5	14.5	25.2	3
9/12/2021 3:00	141.8	245.3	141.2	176.1	34.6	59.9	3
9/12/2021 4:00	152.7	194.1	179.4	175.4	12.1	21.0	3
9/12/2021 5:00	114.0	210.0	173.7	165.9	28.0	48.4	3
9/12/2021 6:00	147.3	184.9	168.7	166.9	10.9	18.8	3
9/12/2021 7:00	405.6	889.1	901.6	732.1	163.3	282.8	3
9/12/2021 8:00	741.1	931.8	1143.0	938.6	116.1	201.1	3
9/12/2021 9:00	766.9	463.8	791.1	673.9	105.3	182.4	3
9/12/2021 10:00	643.5	743.2	1087.4	824.7	134.5	232.9	3
9/12/2021 11:00	508.0	533.4	600.3	547.2	27.5	47.7	3
9/12/2021 12:00	304.8	329.9	408.9	347.9	31.4	54.3	3
9/12/2021 13:00	555.1	731.0	811.5	699.2	75.7	131.1	3
9/12/2021 14:00	337.2	406.3	1147.9	630.5	259.5	449.4	3
9/12/2021 15:00	625.0	1403.3	1047.0	1025.1	224.9	389.6	3
9/12/2021 16:00	605.6	1032.5	1177.7	938.6	171.7	297.4	3
9/12/2021 17:00	427.2	669.7	858.2	651.7	124.7	216.0	3
9/12/2021 18:00	319.3	660.6	1348.7	776.2	302.7	524.4	3
9/12/2021 19:00	136.2	273.6	240.4	216.7	41.4	71.7	3
9/12/2021 20:00	129.2	274.4	284.4	229.3	50.1	86.9	3
9/12/2021 21:00	113.2	169.3	239.2	173.9	36.4	63.1	3
9/12/2021 22:00	160.0	210.5	150.5	173.6	18.6	32.3	3
9/12/2021 23:00	156.9	317.4	167.6	214.0	51.8	89.8	3
9/13/2021 0:00	160.0	265.0	182.5	202.5	31.9	55.2	3
9/13/2021 1:00	131.3	166.6	149.5	149.1	10.2	17.6	3
9/13/2021 2:00	125.2	187.1	196.8	169.7	22.4	38.8	3
9/13/2021 3:00	155.8	177.9	150.5	161.4	8.4	14.5	3

4.12 mg/kg 3,4-diaminopyridine Treatment							
Activity							
Date	SA180D	BF873I	AP55D	Mean	SE	SD	n
9/13/2021 4:00	153.8	240.6	172.6	189.0	26.4	45.7	3
9/13/2021 5:00	137.5	193.9	164.7	165.4	16.3	28.2	3
9/13/2021 6:00	155.6	225.6	184.9	188.7	20.3	35.2	3
9/13/2021 7:00	357.2	464.8	577.9	466.6	63.7	110.4	3
9/13/2021 8:00	744.1	666.4	906.4	772.3	70.7	122.4	3
9/13/2021 9:00	906.0	841.9	1020.7	922.9	52.3	90.6	3
9/13/2021 10:00	1034.8	1320.9	1473.2	1276.3	128.5	222.6	3
9/13/2021 11:00	824.5	1050.3	972.5	949.1	66.2	114.7	3
9/13/2021 12:00	653.2	962.9	776.4	797.5	90.0	155.9	3
9/13/2021 13:00	435.8	876.4	724.1	678.8	129.2	223.7	3
9/13/2021 14:00	535.7	720.4	728.8	661.6	63.0	109.1	3
9/13/2021 15:00	548.2	1014.1	754.1	772.1	134.8	233.5	3
9/13/2021 16:00	702.7	1081.9	865.7	883.4	109.8	190.2	3
9/13/2021 17:00	734.4	801.0	623.7	719.7	51.7	89.5	3
9/13/2021 18:00	772.5	937.6	779.3	829.8	53.9	93.4	3
9/13/2021 19:00	198.4	594.8	521.6	438.3	121.8	210.9	3
9/13/2021 20:00	110.1	185.2	139.8	145.0	21.8	37.8	3
9/13/2021 21:00	164.6	207.4	144.8	172.3	18.5	32.0	3
9/13/2021 22:00	109.8	187.0	141.3	146.0	22.4	38.8	3
9/13/2021 23:00	120.6	164.0	146.0	143.5	12.6	21.8	3
9/14/2021 0:00	176.9	225.8	136.4	179.7	25.8	44.8	3
9/14/2021 1:00	127.7	208.6	155.8	164.0	23.7	41.1	3
9/14/2021 2:00	175.6	185.2	150.1	170.3	10.5	18.2	3
9/14/2021 3:00	115.8	261.9	170.4	182.7	42.6	73.8	3
9/14/2021 4:00	132.6	229.5	182.3	181.4	28.0	48.5	3
9/14/2021 5:00	117.3	188.3	180.4	162.0	22.5	38.9	3
9/14/2021 6:00	160.0	230.1	197.6	195.9	20.3	35.1	3
9/14/2021 7:00	503.6	560.2	821.8	628.5	98.0	169.8	3
9/14/2021 8:00	473.9	645.9	753.2	624.3	81.3	140.9	3
9/14/2021 9:00	682.9	826.5	999.5	836.3	91.5	158.5	3
9/14/2021 10:00	677.9	882.5	826.1	795.5	61.0	105.7	3
9/14/2021 11:00	546.6	919.9	849.4	772.0	114.5	198.3	3

4.12 mg/kg 3,4-diaminopyridine Treatment							
Activity							
Date	SA180D	BF873I	AP55D	Mean	SE	SD	n
9/14/2021 12:00	602.0	703.7	602.6	636.1	33.8	58.5	3
9/14/2021 13:00	426.6	621.4	885.0	644.3	132.8	230.1	3
9/14/2021 14:00	401.7	682.4	670.6	584.9	91.7	158.8	3
9/14/2021 15:00	475.3	785.7	674.2	645.1	90.8	157.2	3
9/14/2021 16:00	432.1	731.5	764.3	642.7	105.7	183.0	3
9/14/2021 17:00	337.8	751.9	630.4	573.4	122.9	212.9	3
9/14/2021 18:00	369.9	698.3	555.8	541.3	95.1	164.6	3
9/14/2021 19:00	174.5	316.3	306.8	265.9	45.8	79.3	3
9/14/2021 20:00	205.1	381.4	425.4	337.3	67.3	116.6	3
9/14/2021 21:00	121.6	215.9	274.2	203.9	44.4	77.0	3
9/14/2021 22:00	384.7	382.5	510.4	425.9	42.3	73.2	3
9/14/2021 23:00	284.7	373.2	585.0	414.3	89.1	154.3	3
9/15/2021 0:00	164.5	273.0	456.1	297.8	85.1	147.4	3
9/15/2021 1:00	232.6	208.8	507.9	316.4	96.0	166.2	3
9/15/2021 2:00	278.0	321.7	371.3	323.7	27.0	46.7	3
9/15/2021 3:00	325.4	330.0	596.7	417.3	89.7	155.3	3
9/15/2021 4:00	263.2	288.7	380.5	310.8	35.6	61.7	3
9/15/2021 5:00	234.5	320.3	355.2	303.4	35.9	62.1	3
9/15/2021 6:00	243.0	258.4	409.4	303.6	53.1	91.9	3
9/15/2021 7:00	445.0	407.6	461.5	438.0	16.0	27.6	3
9/15/2021 8:00	366.5	425.6	421.2	404.4	19.0	32.9	3
9/15/2021 9:00	341.2	324.9	414.3	360.1	27.5	47.6	3
9/15/2021 10:00	384.2	428.9	355.3	389.5	21.4	37.1	3
9/15/2021 11:00	433.0	410.9	326.6	390.1	32.4	56.1	3
9/15/2021 12:00	342.0	431.8	320.5	364.8	34.1	59.1	3
9/15/2021 13:00	251.7	465.4	352.2	356.4	61.7	106.9	3
9/15/2021 14:00	360.2	290.5	367.5	339.4	24.5	42.5	3
9/15/2021 15:00	502.0	416.6	NaN	459.3	42.7	60.4	2
9/15/2021 16:00	353.1	629.0	NaN	491.0	137.9	195.0	2
9/15/2021 17:00	272.2	332.9	NaN	302.5	30.4	43.0	2
9/15/2021 18:00	421.4	318.2	NaN	369.8	51.6	73.0	2
9/15/2021 19:00	516.3	421.6	NaN	468.9	47.4	67.0	2

4.12 mg/kg 3,4-diaminopyridine Treatment							
Activity							
Date	**SA180D**	**BF873I**	**AP55D**	**Mean**	**SE**	**SD**	**n**
9/15/2021 20:00	297.6	574.0	NaN	435.8	138.2	195.4	2
9/15/2021 21:00	228.6	273.4	NaN	251.0	22.4	31.7	2
9/15/2021 22:00	375.7	297.3	NaN	336.5	39.2	55.5	2
9/15/2021 23:00	354.1	403.2	NaN	378.6	24.5	34.7	2
9/16/2021 0:00	200.8	417.6	NaN	309.2	108.4	153.3	2
9/16/2021 1:00	300.7	411.9	NaN	356.3	55.6	78.6	2
9/16/2021 2:00	378.4	334.6	NaN	356.5	21.9	31.0	2
9/16/2021 3:00	217.8	330.5	NaN	274.2	56.4	79.7	2
9/16/2021 4:00	227.3	461.5	NaN	344.4	117.1	165.6	2
9/16/2021 5:00	357.1	306.4	NaN	331.7	25.4	35.9	2
9/16/2021 6:00	264.3	247.0	NaN	255.6	8.7	12.3	2
9/16/2021 7:00	336.7	522.5	NaN	429.6	92.9	131.4	2
9/16/2021 8:00	354.4	599.2	NaN	476.8	122.4	173.1	2
9/16/2021 9:00	282.9	480.9	NaN	381.9	99.0	140.0	2
9/16/2021 10:00	NaN	487.3	NaN	487.3	0.0	0.0	1
9/16/2021 11:00	NaN	599.3	NaN	599.3	0.0	0.0	1

9.3.2 Respiratory Parameters – 4.12 mg/kg 3,4-diaminopyridine Treatment

Table 31: Tidal Volume (mL) 4.12 mg/kg 3,4-diaminopyridine Treatment

4.12 mg/kg 3,4-diaminopyridine Treatment							
Tidal Volume (mL)							
Date	SA180D	BF873I	AP55D	Mean	SE	SD	n
9/10/2021 16:00	139.9	108.5	99.4	115.9	12.3	21.2	3
9/10/2021 17:00	131.5	99.4	119.6	116.8	9.4	16.3	3
9/10/2021 18:00	102.9	118.9	114.2	112.0	4.7	8.2	3
9/10/2021 19:00	56.0	83.6	65.7	68.4	8.1	14.0	3
9/10/2021 20:00	62.5	78.1	65.5	68.7	4.8	8.3	3
9/10/2021 21:00	42.3	75.6	61.0	59.6	9.7	16.7	3
9/10/2021 22:00	64.8	79.0	63.5	69.1	5.0	8.6	3
9/10/2021 23:00	72.5	73.3	52.4	66.1	6.9	11.9	3
9/11/2021 0:00	38.7	70.8	53.9	54.5	9.3	16.0	3
9/11/2021 1:00	74.8	57.7	62.4	65.0	5.1	8.8	3
9/11/2021 2:00	59.0	49.2	58.5	55.6	3.2	5.5	3
9/11/2021 3:00	66.6	72.1	58.2	65.6	4.0	7.0	3
9/11/2021 4:00	85.9	79.2	68.3	77.8	5.1	8.9	3
9/11/2021 5:00	73.0	82.5	72.1	75.9	3.3	5.8	3
9/11/2021 6:00	95.8	75.8	77.7	83.1	6.4	11.0	3
9/11/2021 7:00	142.6	111.8	116.8	123.7	9.5	16.5	3
9/11/2021 8:00	185.4	112.3	132.7	143.5	21.8	37.7	3
9/11/2021 9:00	159.3	106.5	112.0	125.9	16.8	29.1	3
9/11/2021 10:00	101.9	103.4	110.2	105.1	2.6	4.4	3
9/11/2021 11:00	155.6	125.0	83.9	121.5	20.8	36.0	3
9/11/2021 12:00	126.8	124.5	118.1	123.1	2.6	4.5	3
9/11/2021 13:00	124.6	115.3	105.8	115.2	5.4	9.4	3
9/11/2021 14:00	89.9	119.0	123.7	110.9	10.6	18.3	3
9/11/2021 15:00	113.5	106.1	124.2	114.6	5.3	9.1	3
9/11/2021 16:00	109.4	110.4	119.8	113.2	3.3	5.7	3
9/11/2021 17:00	136.3	115.0	146.4	132.6	9.3	16.0	3
9/11/2021 18:00	108.5	110.7	118.3	112.5	3.0	5.2	3
9/11/2021 19:00	66.3	77.2	90.4	77.9	7.0	12.1	3
9/11/2021 20:00	54.6	65.6	83.6	67.9	8.4	14.6	3
9/11/2021 21:00	60.8	66.2	85.3	70.8	7.4	12.8	3

4.12 mg/kg 3,4-diaminopyridine Treatment							
Tidal Volume (mL)							
Date	SA180D	BF873I	AP55D	Mean	SE	SD	n
9/11/2021 22:00	67.2	61.7	85.5	71.4	7.2	12.5	3
9/11/2021 23:00	71.2	74.1	97.5	80.9	8.3	14.4	3
9/12/2021 0:00	56.0	68.5	76.4	66.9	5.9	10.3	3
9/12/2021 1:00	51.6	73.0	81.1	68.5	8.8	15.2	3
9/12/2021 2:00	59.9	80.9	88.0	76.3	8.4	14.6	3
9/12/2021 3:00	65.5	71.5	75.0	70.7	2.8	4.8	3
9/12/2021 4:00	70.6	75.3	83.0	76.3	3.6	6.3	3
9/12/2021 5:00	83.0	80.3	78.2	80.5	1.4	2.4	3
9/12/2021 6:00	82.7	89.7	77.0	83.2	3.7	6.3	3
9/12/2021 7:00	129.0	125.9	127.3	127.4	0.9	1.5	3
9/12/2021 8:00	176.2	122.5	122.6	140.5	17.9	31.0	3
9/12/2021 9:00	186.1	95.7	114.3	132.0	27.6	47.7	3
9/12/2021 10:00	163.6	107.6	121.9	131.0	16.8	29.1	3
9/12/2021 11:00	149.2	102.3	100.0	117.1	16.0	27.8	3
9/12/2021 12:00	104.1	106.5	96.6	102.4	3.0	5.2	3
9/12/2021 13:00	133.8	127.0	123.0	128.0	3.2	5.5	3
9/12/2021 14:00	108.5	104.6	136.1	116.4	9.9	17.2	3
9/12/2021 15:00	136.5	139.1	122.9	132.9	5.0	8.7	3
9/12/2021 16:00	129.4	125.9	115.2	123.5	4.3	7.4	3
9/12/2021 17:00	100.5	115.1	121.7	112.4	6.3	10.9	3
9/12/2021 18:00	90.8	112.6	128.8	110.7	11.0	19.1	3
9/12/2021 19:00	71.4	56.9	77.5	68.6	6.1	10.6	3
9/12/2021 20:00	81.8	74.6	80.2	78.9	2.2	3.8	3
9/12/2021 21:00	89.5	63.9	70.4	74.6	7.7	13.3	3
9/12/2021 22:00	59.5	77.4	58.8	65.2	6.1	10.5	3
9/12/2021 23:00	61.1	80.9	57.5	66.5	7.3	12.6	3
9/13/2021 0:00	80.4	63.7	64.0	69.4	5.5	9.5	3
9/13/2021 1:00	61.3	62.0	60.3	61.2	0.5	0.9	3
9/13/2021 2:00	83.1	84.3	55.2	74.2	9.5	16.5	3
9/13/2021 3:00	83.0	78.4	53.7	71.7	9.1	15.8	3
9/13/2021 4:00	67.1	69.0	55.6	63.9	4.2	7.3	3
9/13/2021 5:00	93.9	63.0	59.7	72.2	10.9	18.9	3

4.12 mg/kg 3,4-diaminopyridine Treatment							
Tidal Volume (mL)							
Date	SA180D	BF873I	AP55D	Mean	SE	SD	n
9/13/2021 6:00	94.7	68.4	74.1	79.1	8.0	13.9	3
9/13/2021 7:00	129.4	107.0	109.2	115.2	7.1	12.4	3
9/13/2021 8:00	178.1	105.7	112.0	131.9	23.2	40.1	3
9/13/2021 9:00	158.9	100.2	104.5	121.2	18.9	32.7	3
9/13/2021 10:00	184.0	108.0	118.3	136.8	23.8	41.2	3
9/13/2021 11:00	160.7	110.1	123.8	131.5	15.1	26.2	3
9/13/2021 12:00	164.8	118.9	119.3	134.3	15.2	26.4	3
9/13/2021 13:00	141.0	124.2	109.1	124.7	9.2	16.0	3
9/13/2021 14:00	145.4	114.9	106.2	122.2	11.9	20.6	3
9/13/2021 15:00	129.3	120.2	109.8	119.8	5.6	9.8	3
9/13/2021 16:00	155.2	136.2	121.2	137.5	9.8	17.0	3
9/13/2021 17:00	161.3	130.2	110.6	134.0	14.8	25.6	3
9/13/2021 18:00	151.2	130.5	125.7	135.8	7.8	13.5	3
9/13/2021 19:00	86.3	92.1	107.0	95.1	6.2	10.7	3
9/13/2021 20:00	63.3	64.3	74.3	67.3	3.5	6.1	3
9/13/2021 21:00	77.4	64.4	73.2	71.7	3.8	6.6	3
9/13/2021 22:00	53.1	63.0	62.8	59.6	3.3	5.7	3
9/13/2021 23:00	58.8	67.4	67.0	64.4	2.8	4.8	3
9/14/2021 0:00	66.5	93.2	49.1	69.6	12.8	22.2	3
9/14/2021 1:00	59.8	80.0	50.5	63.4	8.7	15.1	3
9/14/2021 2:00	71.5	70.1	49.1	63.6	7.2	12.6	3
9/14/2021 3:00	57.5	78.9	55.8	64.1	7.4	12.9	3
9/14/2021 4:00	64.3	92.6	63.8	73.5	9.5	16.5	3
9/14/2021 5:00	69.9	77.4	63.8	70.3	3.9	6.8	3
9/14/2021 6:00	83.9	85.4	74.1	81.1	3.6	6.2	3
9/14/2021 7:00	146.4	113.7	126.8	128.9	9.5	16.5	3
9/14/2021 8:00	140.7	114.8	111.0	122.2	9.3	16.2	3
9/14/2021 9:00	159.4	115.9	115.0	130.1	14.6	25.3	3
9/14/2021 10:00	158.9	116.6	120.7	132.1	13.5	23.3	3
9/14/2021 11:00	119.1	117.2	108.8	115.0	3.2	5.5	3
9/14/2021 12:00	142.8	109.8	104.1	118.9	12.0	20.9	3
9/14/2021 13:00	114.7	104.0	106.7	108.5	3.2	5.6	3

4.12 mg/kg 3,4-diaminopyridine Treatment							
Tidal Volume (mL)							
Date	SA180D	BF873I	AP55D	Mean	SE	SD	n
9/14/2021 14:00	108.5	108.8	100.7	106.0	2.7	4.6	3
9/14/2021 15:00	96.8	108.3	97.9	101.0	3.7	6.4	3
9/14/2021 16:00	100.4	119.9	104.9	108.4	5.9	10.2	3
9/14/2021 17:00	72.5	113.6	91.3	92.5	11.9	20.6	3
9/14/2021 18:00	77.0	118.5	91.7	95.7	12.2	21.1	3
9/14/2021 19:00	40.6	85.5	73.6	66.6	13.4	23.3	3
9/14/2021 20:00	54.1	97.0	78.5	76.6	12.4	21.6	3
9/14/2021 21:00	31.4	78.9	78.0	62.7	15.7	27.2	3
9/14/2021 22:00	81.7	102.7	72.7	85.7	8.9	15.4	3
9/14/2021 23:00	56.1	80.1	86.0	74.1	9.1	15.8	3
9/15/2021 0:00	43.5	75.0	72.1	63.5	10.1	17.4	3
9/15/2021 1:00	42.0	64.8	78.7	61.8	10.7	18.5	3
9/15/2021 2:00	54.5	93.6	65.3	71.1	11.7	20.2	3
9/15/2021 3:00	59.0	87.3	79.2	75.2	8.4	14.6	3
9/15/2021 4:00	51.2	84.3	61.2	65.6	9.8	17.0	3
9/15/2021 5:00	52.4	80.9	52.4	61.9	9.5	16.5	3
9/15/2021 6:00	56.9	79.8	64.5	67.1	6.7	11.6	3
9/15/2021 7:00	88.9	83.6	68.3	80.3	6.2	10.7	3
9/15/2021 8:00	85.8	79.9	61.0	75.6	7.5	12.9	3
9/15/2021 9:00	70.6	64.9	65.6	67.0	1.8	3.1	3
9/15/2021 10:00	68.0	77.2	62.7	69.3	4.3	7.4	3
9/15/2021 11:00	92.1	73.0	53.6	72.9	11.1	19.3	3
9/15/2021 12:00	82.3	74.3	52.1	69.6	9.0	15.6	3
9/15/2021 13:00	67.0	72.0	44.5	61.2	8.5	14.7	3
9/15/2021 14:00	68.8	64.9	41.2	58.3	8.6	14.9	3
9/15/2021 15:00	81.1	64.0	NaN	72.6	8.5	12.1	2
9/15/2021 16:00	66.4	79.3	NaN	72.8	6.4	9.1	2
9/15/2021 17:00	50.7	64.5	NaN	57.6	6.9	9.7	2
9/15/2021 18:00	61.2	64.8	NaN	63.0	1.8	2.6	2
9/15/2021 19:00	78.3	63.7	NaN	71.0	7.3	10.4	2
9/15/2021 20:00	50.4	65.1	NaN	57.7	7.4	10.4	2
9/15/2021 21:00	43.3	51.7	NaN	47.5	4.2	5.9	2

4.12 mg/kg 3,4-diaminopyridine Treatment							
Tidal Volume (mL)							
Date	**SA180D**	**BF873I**	**AP55D**	**Mean**	**SE**	**SD**	**n**
9/15/2021 22:00	55.9	54.9	NaN	55.4	0.5	0.8	2
9/15/2021 23:00	58.5	58.1	NaN	58.3	0.2	0.2	2
9/16/2021 0:00	48.8	56.7	NaN	52.8	4.0	5.6	2
9/16/2021 1:00	56.3	59.6	NaN	57.9	1.6	2.3	2
9/16/2021 2:00	56.8	54.4	NaN	55.6	1.2	1.7	2
9/16/2021 3:00	39.7	50.2	NaN	45.0	5.2	7.4	2
9/16/2021 4:00	59.8	59.9	NaN	59.9	0.0	0.0	2
9/16/2021 5:00	66.9	55.7	NaN	61.3	5.6	8.0	2
9/16/2021 6:00	53.7	51.4	NaN	52.5	1.1	1.6	2
9/16/2021 7:00	58.8	59.3	NaN	59.0	0.2	0.3	2
9/16/2021 8:00	63.5	61.1	NaN	62.3	1.2	1.7	2
9/16/2021 9:00	60.5	63.9	NaN	62.2	1.7	2.5	2
9/16/2021 10:00	NaN	58.0	NaN	58.0	0.0	0.0	1
9/16/2021 11:00	NaN	56.7	NaN	56.7	0.0	0.0	1

Table 32: Minute Volume (mL/sec) 4.12 mg/kg 3,4-diaminopyridine Treatment

4.12 mg/kg 3,4-diaminopyridine Treatment							
Minute Volume (mL/sec)							
Date	SA180D	BF873I	AP55D	Mean	SE	SD	n
9/10/2021 16:00	4066.9	3467.2	3380.2	3638.1	215.9	373.9	3
9/10/2021 17:00	3537.0	3031.0	3881.2	3483.1	246.9	427.7	3
9/10/2021 18:00	2457.1	3672.4	3581.5	3237.0	390.8	676.9	3
9/10/2021 19:00	1317.7	1945.3	1857.9	1707.0	196.3	339.9	3
9/10/2021 20:00	1428.5	1741.5	1921.4	1697.1	144.0	249.4	3
9/10/2021 21:00	1023.9	1654.2	1651.2	1443.1	209.6	363.0	3
9/10/2021 22:00	1541.0	1957.9	1824.4	1774.4	122.9	212.9	3
9/10/2021 23:00	1741.2	1837.8	1718.2	1765.7	36.6	63.5	3
9/11/2021 0:00	959.4	1680.5	1812.2	1484.0	265.1	459.1	3
9/11/2021 1:00	1777.5	1559.1	1875.6	1737.4	93.5	162.0	3
9/11/2021 2:00	1455.3	1692.1	1790.7	1646.0	99.5	172.4	3
9/11/2021 3:00	1635.9	1987.7	1670.4	1764.7	112.0	193.9	3
9/11/2021 4:00	2001.5	2153.4	1876.0	2010.3	80.2	138.9	3
9/11/2021 5:00	1799.0	2279.4	1899.2	1992.5	146.3	253.4	3
9/11/2021 6:00	2343.2	2055.9	2088.0	2162.4	90.9	157.4	3
9/11/2021 7:00	3087.1	3064.6	3289.8	3147.2	71.6	124.0	3
9/11/2021 8:00	4860.0	3247.2	4206.1	4104.4	468.3	811.2	3
9/11/2021 9:00	3920.6	2907.6	3500.4	3442.9	293.8	508.9	3
9/11/2021 10:00	2356.4	2747.0	3435.2	2846.2	315.3	546.2	3
9/11/2021 11:00	4031.8	3816.0	2213.6	3353.8	573.5	993.3	3
9/11/2021 12:00	3148.1	3780.6	3286.5	3405.1	192.0	332.5	3
9/11/2021 13:00	3490.1	3851.5	3586.9	3642.8	108.0	187.1	3
9/11/2021 14:00	2329.4	3750.5	4106.1	3395.3	542.8	940.1	3
9/11/2021 15:00	3038.3	2736.1	3887.8	3220.7	344.8	597.1	3
9/11/2021 16:00	2828.5	3558.0	3663.3	3349.9	262.5	454.6	3
9/11/2021 17:00	3698.2	3594.5	4770.9	4021.2	376.0	651.3	3
9/11/2021 18:00	2929.7	3562.0	3837.3	3443.0	268.7	465.4	3
9/11/2021 19:00	1824.2	2266.3	2420.9	2170.5	178.8	309.7	3
9/11/2021 20:00	1465.4	1731.1	2229.6	1808.7	224.0	388.0	3
9/11/2021 21:00	1674.6	1884.6	2357.0	1972.1	201.8	349.5	3
9/11/2021 22:00	1708.1	1649.7	2445.0	1934.3	255.9	443.3	3

4.12 mg/kg 3,4-diaminopyridine Treatment							
Minute Volume (mL/sec)							
Date	**SA180D**	**BF873I**	**AP55D**	**Mean**	**SE**	**SD**	**n**
9/11/2021 23:00	1854.6	1886.7	2898.4	2213.2	342.7	593.6	3
9/12/2021 0:00	1360.5	1793.2	2180.2	1778.0	236.7	410.1	3
9/12/2021 1:00	1222.5	1880.6	2250.6	1784.6	300.6	520.7	3
9/12/2021 2:00	1482.5	1758.3	2356.6	1865.8	258.0	446.9	3
9/12/2021 3:00	1577.5	1930.9	2013.9	1840.8	133.8	231.7	3
9/12/2021 4:00	1822.0	1876.9	2154.9	1951.3	103.0	178.5	3
9/12/2021 5:00	1993.2	2198.5	2099.1	2096.9	59.3	102.7	3
9/12/2021 6:00	2004.5	2137.7	2133.0	2091.7	43.6	75.6	3
9/12/2021 7:00	2770.1	3527.6	3524.7	3274.1	252.0	436.5	3
9/12/2021 8:00	4571.9	3658.8	4001.9	4077.5	266.3	461.2	3
9/12/2021 9:00	4356.8	2415.2	3418.6	3396.9	560.6	971.0	3
9/12/2021 10:00	3878.1	2823.0	3914.3	3538.5	357.9	619.9	3
9/12/2021 11:00	3637.0	2665.8	2911.4	3071.4	291.6	505.0	3
9/12/2021 12:00	2587.1	2648.2	2544.1	2593.1	30.2	52.3	3
9/12/2021 13:00	3839.7	3900.0	4187.2	3975.6	107.2	185.7	3
9/12/2021 14:00	2848.8	2975.2	4462.0	3428.7	518.0	897.1	3
9/12/2021 15:00	3541.2	4685.3	3949.6	4058.7	334.7	579.8	3
9/12/2021 16:00	3498.6	4059.4	3913.2	3823.7	168.0	290.9	3
9/12/2021 17:00	2666.1	3551.7	4049.8	3422.5	404.6	700.8	3
9/12/2021 18:00	2239.4	3505.9	4601.4	3448.9	682.4	1182.0	3
9/12/2021 19:00	1937.2	1974.7	2001.7	1971.2	18.7	32.4	3
9/12/2021 20:00	2238.6	1920.8	2145.5	2101.6	94.3	163.4	3
9/12/2021 21:00	2459.6	1806.9	1740.6	2002.4	229.4	397.4	3
9/12/2021 22:00	1456.9	1927.4	1449.6	1611.3	158.1	273.8	3
9/12/2021 23:00	1431.8	2264.2	1362.4	1686.1	289.7	501.8	3
9/13/2021 0:00	2027.6	1972.6	1619.9	1873.4	127.7	221.2	3
9/13/2021 1:00	1397.5	1708.7	1506.7	1537.6	91.2	157.9	3
9/13/2021 2:00	1695.7	1828.8	1364.4	1629.6	138.1	239.1	3
9/13/2021 3:00	1907.4	1697.0	1343.7	1649.4	164.5	284.9	3
9/13/2021 4:00	1547.0	1719.5	1431.3	1565.9	83.7	145.0	3
9/13/2021 5:00	2163.0	1632.3	1533.9	1776.4	195.4	338.4	3
9/13/2021 6:00	2261.0	1791.7	1883.5	1978.7	143.6	248.7	3

4.12 mg/kg 3,4-diaminopyridine Treatment							
Minute Volume (mL/sec)							
Date	**SA180D**	**BF873I**	**AP55D**	**Mean**	**SE**	**SD**	**n**
9/13/2021 7:00	2724.1	2596.8	2857.1	2726.0	75.1	130.2	3
9/13/2021 8:00	5333.1	3205.4	3870.3	4136.3	628.4	1088.5	3
9/13/2021 9:00	5452.9	3264.2	3780.0	4165.7	660.6	1144.2	3
9/13/2021 10:00	5188.9	3469.3	4150.6	4269.6	500.0	866.0	3
9/13/2021 11:00	4263.5	3420.8	3937.6	3874.0	245.3	424.9	3
9/13/2021 12:00	4080.0	3726.6	3599.3	3802.0	143.8	249.1	3
9/13/2021 13:00	3608.4	3860.6	3184.3	3551.1	197.3	341.8	3
9/13/2021 14:00	4103.4	3401.0	3709.4	3737.9	203.3	352.1	3
9/13/2021 15:00	4163.1	4118.0	4085.9	4122.3	22.4	38.8	3
9/13/2021 16:00	4696.2	4535.7	4317.9	4516.6	109.6	189.9	3
9/13/2021 17:00	4473.4	3942.4	3417.5	3944.4	304.8	528.0	3
9/13/2021 18:00	4130.6	4087.5	3705.4	3974.5	135.1	234.0	3
9/13/2021 19:00	2195.9	2763.3	3133.7	2697.6	272.7	472.3	3
9/13/2021 20:00	1605.4	1837.0	2179.2	1873.9	166.7	288.7	3
9/13/2021 21:00	1893.5	1798.1	2214.4	1968.7	125.9	218.1	3
9/13/2021 22:00	1300.3	1633.0	1824.1	1585.8	153.0	265.1	3
9/13/2021 23:00	1354.2	1746.0	1919.4	1673.2	167.2	289.5	3
9/14/2021 0:00	1452.3	2402.3	1296.2	1716.9	345.6	598.7	3
9/14/2021 1:00	1284.6	2016.4	1341.4	1547.5	235.0	407.1	3
9/14/2021 2:00	1559.6	1664.7	1337.7	1520.7	96.4	166.9	3
9/14/2021 3:00	1243.6	1917.6	1550.1	1570.4	194.8	337.5	3
9/14/2021 4:00	1437.7	2099.9	1720.0	1752.5	191.9	332.3	3
9/14/2021 5:00	1585.1	1804.5	1756.5	1715.4	66.6	115.3	3
9/14/2021 6:00	1900.0	1928.3	1973.7	1934.0	21.5	37.2	3
9/14/2021 7:00	3224.6	2761.2	3722.6	3236.1	277.6	480.8	3
9/14/2021 8:00	3517.3	2896.7	3720.2	3378.1	247.7	429.0	3
9/14/2021 9:00	4196.0	3200.7	3915.5	3770.7	296.3	513.2	3
9/14/2021 10:00	4218.0	3280.6	3984.4	3827.7	281.7	488.0	3
9/14/2021 11:00	3129.9	3316.3	3608.4	3351.5	139.2	241.2	3
9/14/2021 12:00	3750.2	2979.5	3324.6	3351.4	222.9	386.1	3
9/14/2021 13:00	3190.6	2800.5	3513.2	3168.1	206.0	356.9	3
9/14/2021 14:00	2868.5	3040.7	3377.5	3095.6	149.5	258.9	3

4.12 mg/kg 3,4-diaminopyridine Treatment							
Minute Volume (mL/sec)							
Date	SA180D	BF873I	AP55D	Mean	SE	SD	n
9/14/2021 15:00	2698.6	3280.0	3408.9	3129.2	218.5	378.4	3
9/14/2021 16:00	2768.1	3675.9	3747.9	3397.3	315.3	546.1	3
9/14/2021 17:00	2043.2	3322.9	3076.5	2814.2	392.0	679.0	3
9/14/2021 18:00	2085.7	3482.2	3214.5	2927.5	427.9	741.2	3
9/14/2021 19:00	1071.8	2422.0	2276.8	1923.5	427.9	741.2	3
9/14/2021 20:00	1584.7	2655.9	2405.2	2215.3	323.5	560.3	3
9/14/2021 21:00	863.1	2176.3	2367.6	1802.3	472.9	819.0	3
9/14/2021 22:00	2321.8	2935.2	2467.6	2574.9	185.0	320.5	3
9/14/2021 23:00	1674.4	2344.0	2979.4	2332.6	376.8	652.6	3
9/15/2021 0:00	1304.6	2142.2	2439.8	1962.2	339.8	588.6	3
9/15/2021 1:00	1282.7	1898.9	2520.1	1900.6	357.2	618.7	3
9/15/2021 2:00	1660.5	2501.7	2191.4	2117.9	245.6	425.4	3
9/15/2021 3:00	1845.0	2456.4	2704.2	2335.2	255.3	442.2	3
9/15/2021 4:00	1634.1	2197.3	2009.3	1946.9	165.5	286.7	3
9/15/2021 5:00	1566.2	2235.5	1677.3	1826.3	207.1	358.7	3
9/15/2021 6:00	1794.1	2166.1	2067.6	2009.3	111.3	192.7	3
9/15/2021 7:00	2710.5	2493.3	2364.4	2522.7	101.0	174.9	3
9/15/2021 8:00	2642.8	2455.8	2111.0	2403.2	155.8	269.8	3
9/15/2021 9:00	1997.4	1828.7	2273.9	2033.3	129.8	224.8	3
9/15/2021 10:00	1941.0	2289.5	1917.4	2049.3	120.3	208.4	3
9/15/2021 11:00	3459.1	2242.1	1751.2	2484.1	507.7	879.3	3
9/15/2021 12:00	2762.5	2231.4	1735.7	2243.2	296.5	513.5	3
9/15/2021 13:00	2192.0	2130.7	1531.1	1951.3	210.8	365.2	3
9/15/2021 14:00	2298.4	1896.5	1412.9	1869.3	256.0	443.4	3
9/15/2021 15:00	2952.0	1831.9	NaN	2392.0	560.1	792.0	2
9/15/2021 16:00	2181.1	1778.1	NaN	1979.6	201.5	285.0	2
9/15/2021 17:00	1820.6	1793.0	NaN	1806.8	13.8	19.5	2
9/15/2021 18:00	2172.9	1992.7	NaN	2082.8	90.1	127.4	2
9/15/2021 19:00	2797.1	2027.4	NaN	2412.3	384.9	544.3	2
9/15/2021 20:00	1504.1	1955.5	NaN	1729.8	225.7	319.2	2
9/15/2021 21:00	1134.8	1573.7	NaN	1354.3	219.5	310.3	2
9/15/2021 22:00	1430.4	1717.8	NaN	1574.1	143.7	203.2	2

4.12 mg/kg 3,4-diaminopyridine Treatment							
Minute Volume (mL/sec)							
Date	**SA180D**	**BF873I**	**AP55D**	**Mean**	**SE**	**SD**	**n**
9/15/2021 23:00	1924.6	1853.6	NaN	1889.1	35.5	50.2	2
9/16/2021 0:00	1045.8	1647.5	NaN	1346.7	300.9	425.5	2
9/16/2021 1:00	1349.8	1915.6	NaN	1632.7	282.9	400.1	2
9/16/2021 2:00	1298.9	1727.2	NaN	1513.1	214.2	302.9	2
9/16/2021 3:00	1304.6	1513.0	NaN	1408.8	104.2	147.4	2
9/16/2021 4:00	858.6	1723.5	NaN	1291.0	432.5	611.6	2
9/16/2021 5:00	1117.1	1662.7	NaN	1389.9	272.8	385.8	2
9/16/2021 6:00	878.2	1481.5	NaN	1179.9	301.6	426.6	2
9/16/2021 7:00	1758.5	1761.5	NaN	1760.0	1.5	2.1	2
9/16/2021 8:00	1787.2	1681.9	NaN	1734.6	52.7	74.5	2
9/16/2021 9:00	1120.4	1913.1	NaN	1516.8	396.4	560.5	2
9/16/2021 10:00	NaN	1717.5	NaN	1717.5	0.0	0.0	1
9/16/2021 11:00	NaN	1504.9	NaN	1504.9	0.0	0.0	1

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Table 33: Respiration Rate (bpm) 4.12 mg/kg 3,4-diaminopyridine Treatment

4.12 mg/kg 3,4-diaminopyridine Treatment							
Respiration Rate (bpm)							
Date	SA180D	BF873I	AP55D	Mean	SE	SD	n
9/10/2021 16:00	29.1	32.0	34.0	31.7	1.4	2.5	3
9/10/2021 17:00	26.9	30.5	32.4	29.9	1.6	2.8	3
9/10/2021 18:00	23.9	30.9	31.4	28.7	2.4	4.2	3
9/10/2021 19:00	23.5	23.3	28.3	25.0	1.6	2.8	3
9/10/2021 20:00	22.9	22.3	29.3	24.8	2.3	3.9	3
9/10/2021 21:00	24.2	21.9	27.1	24.4	1.5	2.6	3
9/10/2021 22:00	23.8	24.8	28.7	25.8	1.5	2.6	3
9/10/2021 23:00	24.0	25.1	32.8	27.3	2.8	4.8	3
9/11/2021 0:00	24.8	23.8	33.6	27.4	3.1	5.4	3
9/11/2021 1:00	23.8	27.0	30.0	26.9	1.8	3.1	3
9/11/2021 2:00	24.7	34.4	30.6	29.9	2.8	4.9	3
9/11/2021 3:00	24.6	27.6	28.7	26.9	1.2	2.1	3
9/11/2021 4:00	23.3	27.2	27.5	26.0	1.3	2.3	3
9/11/2021 5:00	24.7	27.6	26.3	26.2	0.9	1.5	3
9/11/2021 6:00	24.5	27.1	26.9	26.2	0.8	1.5	3
9/11/2021 7:00	21.6	27.4	28.2	25.7	2.1	3.6	3
9/11/2021 8:00	26.2	28.9	31.7	28.9	1.6	2.7	3
9/11/2021 9:00	24.6	27.3	31.3	27.7	1.9	3.3	3
9/11/2021 10:00	23.1	26.6	31.2	27.0	2.3	4.0	3
9/11/2021 11:00	25.9	30.5	26.4	27.6	1.5	2.5	3
9/11/2021 12:00	24.8	30.4	27.8	27.7	1.6	2.8	3
9/11/2021 13:00	28.0	33.4	33.9	31.8	1.9	3.3	3
9/11/2021 14:00	25.9	31.5	33.2	30.2	2.2	3.8	3
9/11/2021 15:00	26.8	25.8	31.3	28.0	1.7	2.9	3
9/11/2021 16:00	25.8	32.2	30.6	29.6	1.9	3.3	3
9/11/2021 17:00	27.1	31.3	32.6	30.3	1.6	2.8	3
9/11/2021 18:00	27.0	32.2	32.4	30.5	1.8	3.1	3
9/11/2021 19:00	27.5	29.4	26.8	27.9	0.8	1.3	3
9/11/2021 20:00	26.8	26.4	26.7	26.6	0.1	0.2	3
9/11/2021 21:00	27.5	28.5	27.6	27.9	0.3	0.5	3
9/11/2021 22:00	25.4	26.8	28.6	26.9	0.9	1.6	3

4.12 mg/kg 3,4-diaminopyridine Treatment							
Respiration Rate (bpm)							
Date	SA180D	BF873I	AP55D	Mean	SE	SD	n
9/11/2021 23:00	26.0	25.5	29.7	27.1	1.3	2.3	3
9/12/2021 0:00	24.3	26.2	28.6	26.4	1.2	2.1	3
9/12/2021 1:00	23.7	25.8	27.8	25.7	1.2	2.0	3
9/12/2021 2:00	24.7	21.7	26.8	24.4	1.5	2.5	3
9/12/2021 3:00	24.1	27.0	26.8	26.0	0.9	1.6	3
9/12/2021 4:00	25.8	24.9	26.0	25.6	0.3	0.5	3
9/12/2021 5:00	24.0	27.4	26.9	26.1	1.0	1.8	3
9/12/2021 6:00	24.2	23.8	27.7	25.3	1.2	2.1	3
9/12/2021 7:00	21.5	28.0	27.7	25.7	2.1	3.7	3
9/12/2021 8:00	25.9	29.9	32.6	29.5	1.9	3.4	3
9/12/2021 9:00	23.4	25.2	29.9	26.2	1.9	3.3	3
9/12/2021 10:00	23.7	26.2	32.1	27.4	2.5	4.3	3
9/12/2021 11:00	24.4	26.1	29.1	26.5	1.4	2.4	3
9/12/2021 12:00	24.9	24.9	26.3	25.4	0.5	0.9	3
9/12/2021 13:00	28.7	30.7	34.0	31.1	1.6	2.7	3
9/12/2021 14:00	26.3	28.4	32.8	29.2	1.9	3.3	3
9/12/2021 15:00	25.9	33.7	32.1	30.6	2.4	4.1	3
9/12/2021 16:00	27.0	32.3	34.0	31.1	2.1	3.6	3
9/12/2021 17:00	26.5	30.9	33.3	30.2	2.0	3.4	3
9/12/2021 18:00	24.7	31.1	35.7	30.5	3.2	5.6	3
9/12/2021 19:00	27.1	34.7	25.8	29.2	2.8	4.8	3
9/12/2021 20:00	27.4	25.7	26.8	26.6	0.5	0.8	3
9/12/2021 21:00	27.5	28.3	24.7	26.8	1.1	1.9	3
9/12/2021 22:00	24.5	24.9	24.7	24.7	0.1	0.2	3
9/12/2021 23:00	23.4	28.0	23.7	25.0	1.5	2.6	3
9/13/2021 0:00	25.2	31.0	25.3	27.2	1.9	3.3	3
9/13/2021 1:00	22.8	27.6	25.0	25.1	1.4	2.4	3
9/13/2021 2:00	20.4	21.7	24.7	22.3	1.3	2.2	3
9/13/2021 3:00	23.0	21.6	25.0	23.2	1.0	1.7	3
9/13/2021 4:00	23.0	24.9	25.8	24.6	0.8	1.4	3
9/13/2021 5:00	23.0	25.9	25.7	24.9	0.9	1.6	3
9/13/2021 6:00	23.9	26.2	25.4	25.2	0.7	1.2	3

4.12 mg/kg 3,4-diaminopyridine Treatment							
Respiration Rate (bpm)							
Date	SA180D	BF873I	AP55D	Mean	SE	SD	n
9/13/2021 7:00	21.0	24.3	26.2	23.8	1.5	2.6	3
9/13/2021 8:00	29.9	30.3	34.6	31.6	1.5	2.6	3
9/13/2021 9:00	34.3	32.6	36.2	34.4	1.0	1.8	3
9/13/2021 10:00	28.2	32.1	35.1	31.8	2.0	3.5	3
9/13/2021 11:00	26.5	31.1	31.8	29.8	1.7	2.9	3
9/13/2021 12:00	24.8	31.4	30.2	28.8	2.0	3.5	3
9/13/2021 13:00	25.6	31.1	29.2	28.6	1.6	2.8	3
9/13/2021 14:00	28.2	29.6	34.9	30.9	2.1	3.6	3
9/13/2021 15:00	32.2	34.3	37.2	34.6	1.5	2.5	3
9/13/2021 16:00	30.3	33.3	35.6	33.1	1.6	2.7	3
9/13/2021 17:00	27.7	30.3	30.9	29.6	1.0	1.7	3
9/13/2021 18:00	27.3	31.3	29.5	29.4	1.2	2.0	3
9/13/2021 19:00	25.5	30.0	29.3	28.3	1.4	2.5	3
9/13/2021 20:00	25.4	28.6	29.3	27.8	1.2	2.1	3
9/13/2021 21:00	24.5	27.9	30.2	27.5	1.7	2.9	3
9/13/2021 22:00	24.5	25.9	29.0	26.5	1.3	2.3	3
9/13/2021 23:00	23.0	25.9	28.7	25.9	1.6	2.8	3
9/14/2021 0:00	21.8	25.8	26.4	24.7	1.4	2.5	3
9/14/2021 1:00	21.5	25.2	26.6	24.4	1.5	2.6	3
9/14/2021 2:00	21.8	23.7	27.3	24.3	1.6	2.8	3
9/14/2021 3:00	21.6	24.3	27.8	24.6	1.8	3.1	3
9/14/2021 4:00	22.4	22.7	27.0	24.0	1.5	2.6	3
9/14/2021 5:00	22.7	23.3	27.5	24.5	1.5	2.6	3
9/14/2021 6:00	22.6	22.6	26.7	24.0	1.3	2.3	3
9/14/2021 7:00	22.0	24.3	29.4	25.2	2.2	3.8	3
9/14/2021 8:00	25.0	25.2	33.5	27.9	2.8	4.9	3
9/14/2021 9:00	26.3	27.6	34.0	29.3	2.4	4.1	3
9/14/2021 10:00	26.5	28.1	33.0	29.2	1.9	3.4	3
9/14/2021 11:00	26.3	28.3	33.2	29.2	2.0	3.5	3
9/14/2021 12:00	26.3	27.1	31.9	28.4	1.8	3.0	3
9/14/2021 13:00	27.8	26.9	32.9	29.2	1.9	3.2	3
9/14/2021 14:00	26.4	28.0	33.5	29.3	2.2	3.7	3

4.12 mg/kg 3,4-diaminopyridine Treatment							
Respiration Rate (bpm)							
Date	SA180D	BF873I	AP55D	Mean	SE	SD	n
9/14/2021 15:00	27.9	30.3	34.8	31.0	2.0	3.5	3
9/14/2021 16:00	27.6	30.7	35.7	31.3	2.4	4.1	3
9/14/2021 17:00	28.2	29.2	33.7	30.4	1.7	2.9	3
9/14/2021 18:00	27.1	29.4	35.0	30.5	2.4	4.1	3
9/14/2021 19:00	26.4	28.3	30.9	28.6	1.3	2.3	3
9/14/2021 20:00	29.3	27.4	30.6	29.1	0.9	1.6	3
9/14/2021 21:00	27.5	27.6	30.4	28.5	0.9	1.6	3
9/14/2021 22:00	28.4	28.6	33.9	30.3	1.8	3.1	3
9/14/2021 23:00	29.8	29.2	34.6	31.2	1.7	3.0	3
9/15/2021 0:00	30.0	28.6	33.8	30.8	1.6	2.7	3
9/15/2021 1:00	30.6	29.3	32.0	30.6	0.8	1.4	3
9/15/2021 2:00	30.5	26.7	33.6	30.3	2.0	3.4	3
9/15/2021 3:00	31.3	28.1	34.1	31.2	1.7	3.0	3
9/15/2021 4:00	31.9	26.1	32.8	30.3	2.1	3.7	3
9/15/2021 5:00	29.9	27.6	32.0	29.9	1.3	2.2	3
9/15/2021 6:00	31.5	27.2	32.1	30.2	1.6	2.7	3
9/15/2021 7:00	30.5	29.8	34.6	31.6	1.5	2.6	3
9/15/2021 8:00	30.8	30.7	34.6	32.0	1.3	2.2	3
9/15/2021 9:00	28.3	28.2	34.7	30.4	2.1	3.7	3
9/15/2021 10:00	28.6	29.6	30.6	29.6	0.6	1.0	3
9/15/2021 11:00	37.5	30.7	32.7	33.7	2.0	3.5	3
9/15/2021 12:00	33.6	30.0	33.3	32.3	1.1	2.0	3
9/15/2021 13:00	32.7	29.6	34.4	32.2	1.4	2.5	3
9/15/2021 14:00	33.4	29.2	34.3	32.3	1.6	2.7	3
9/15/2021 15:00	36.4	28.6	NaN	32.5	3.9	5.5	2
9/15/2021 16:00	32.9	22.4	NaN	27.6	5.2	7.4	2
9/15/2021 17:00	35.9	27.8	NaN	31.8	4.0	5.7	2
9/15/2021 18:00	35.5	30.7	NaN	33.1	2.4	3.4	2
9/15/2021 19:00	35.7	31.8	NaN	33.8	1.9	2.7	2
9/15/2021 20:00	29.9	30.0	NaN	30.0	0.1	0.1	2
9/15/2021 21:00	26.2	30.5	NaN	28.3	2.1	3.0	2
9/15/2021 22:00	25.6	31.3	NaN	28.4	2.9	4.1	2

4.12 mg/kg 3,4-diaminopyridine Treatment							
Respiration Rate (bpm)							
Date	**SA180D**	**BF873I**	**AP55D**	**Mean**	**SE**	**SD**	**n**
9/15/2021 23:00	32.9	31.9	NaN	32.4	0.5	0.7	2
9/16/2021 0:00	21.4	29.0	NaN	25.2	3.8	5.4	2
9/16/2021 1:00	24.0	32.1	NaN	28.1	4.1	5.8	2
9/16/2021 2:00	22.9	31.8	NaN	27.3	4.5	6.3	2
9/16/2021 3:00	32.9	30.1	NaN	31.5	1.4	1.9	2
9/16/2021 4:00	14.4	28.8	NaN	21.6	7.2	10.2	2
9/16/2021 5:00	16.7	29.9	NaN	23.3	6.6	9.3	2
9/16/2021 6:00	16.4	28.8	NaN	22.6	6.2	8.8	2
9/16/2021 7:00	29.9	29.7	NaN	29.8	0.1	0.1	2
9/16/2021 8:00	28.2	27.5	NaN	27.8	0.3	0.5	2
9/16/2021 9:00	18.5	29.9	NaN	24.2	5.7	8.1	2
9/16/2021 10:00	NaN	29.6	NaN	29.6	0.0	0.0	1
9/16/2021 11:00	NaN	26.6	NaN	26.6	0.0	0.0	1

9.3.3 ECG Parameters – 4.12 mg/kg 3,4-diaminopyridine Treatment

Table 34: Heart Rate (bpm) 4.12 mg/kg 3,4-diaminopyridine Treatment

4.12 mg/kg 3,4-diaminopyridine Treatment							
Heart Rate (bpm)							
Date	SA180D	BF873I	AP55D	Mean	SE	SD	n
9/10/2021 16:00	119.5	166.4	156.4	147.4	14.3	24.7	3
9/10/2021 17:00	108.5	143.5	147.4	133.1	12.4	21.4	3
9/10/2021 18:00	97.1	148.9	140.9	129.0	16.1	27.9	3
9/10/2021 19:00	102.1	126.1	119.7	116.0	7.2	12.4	3
9/10/2021 20:00	92.8	117.7	114.7	108.4	7.8	13.6	3
9/10/2021 21:00	95.4	113.3	124.2	111.0	8.4	14.6	3
9/10/2021 22:00	94.0	125.2	125.4	114.9	10.4	18.1	3
9/10/2021 23:00	97.0	123.9	128.7	116.5	9.9	17.1	3
9/11/2021 0:00	93.5	126.0	133.7	117.8	12.3	21.3	3
9/11/2021 1:00	100.1	133.0	131.5	121.5	10.7	18.6	3
9/11/2021 2:00	97.0	145.4	128.8	123.7	14.2	24.6	3
9/11/2021 3:00	100.9	139.5	129.0	123.1	11.5	20.0	3
9/11/2021 4:00	100.7	143.3	125.3	123.1	12.4	21.4	3
9/11/2021 5:00	100.1	145.9	124.4	123.4	13.2	22.9	3
9/11/2021 6:00	109.9	145.7	128.0	127.9	10.3	17.9	3
9/11/2021 7:00	115.8	154.6	152.7	141.0	12.6	21.8	3
9/11/2021 8:00	123.7	150.7	161.7	145.4	11.3	19.5	3
9/11/2021 9:00	113.4	146.7	153.1	137.7	12.3	21.3	3
9/11/2021 10:00	97.6	141.4	143.8	127.6	15.0	26.0	3
9/11/2021 11:00	112.0	161.8	115.5	129.8	16.1	27.8	3
9/11/2021 12:00	104.4	151.7	136.9	131.0	14.0	24.2	3
9/11/2021 13:00	116.1	164.2	146.2	142.2	14.0	24.3	3
9/11/2021 14:00	104.7	157.6	142.9	135.1	15.8	27.3	3
9/11/2021 15:00	110.9	144.0	136.4	130.5	10.0	17.3	3
9/11/2021 16:00	106.5	161.0	135.2	134.2	15.7	27.2	3
9/11/2021 17:00	112.6	155.5	156.5	141.5	14.5	25.0	3
9/11/2021 18:00	110.5	159.7	144.4	138.2	14.5	25.2	3
9/11/2021 19:00	112.8	150.6	125.7	129.7	11.1	19.2	3
9/11/2021 20:00	102.8	149.6	115.5	122.7	14.0	24.2	3
9/11/2021 21:00	108.9	154.1	118.3	127.1	13.8	23.9	3

4.12 mg/kg 3,4-diaminopyridine Treatment							
Heart Rate (bpm)							
Date	SA180D	BF873I	AP55D	Mean	SE	SD	n
9/11/2021 22:00	104.2	149.0	115.5	122.9	13.4	23.3	3
9/11/2021 23:00	107.1	145.6	121.8	124.8	11.2	19.4	3
9/12/2021 0:00	96.5	144.6	113.1	118.1	14.1	24.4	3
9/12/2021 1:00	94.6	138.1	112.2	115.0	12.6	21.9	3
9/12/2021 2:00	97.9	138.9	113.3	116.7	11.9	20.7	3
9/12/2021 3:00	93.4	142.5	116.2	117.3	14.2	24.6	3
9/12/2021 4:00	98.3	140.6	121.3	120.1	12.2	21.2	3
9/12/2021 5:00	98.6	145.0	125.0	122.9	13.4	23.2	3
9/12/2021 6:00	103.9	147.2	128.6	126.6	12.5	21.7	3
9/12/2021 7:00	108.3	166.9	150.3	141.8	17.4	30.2	3
9/12/2021 8:00	113.8	163.2	159.5	145.5	15.9	27.5	3
9/12/2021 9:00	109.5	149.3	139.2	132.7	11.9	20.7	3
9/12/2021 10:00	104.5	143.9	148.1	132.2	13.9	24.1	3
9/12/2021 11:00	107.3	146.2	130.5	128.0	11.3	19.6	3
9/12/2021 12:00	100.6	149.6	116.7	122.3	14.4	25.0	3
9/12/2021 13:00	124.2	169.1	149.1	147.4	13.0	22.5	3
9/12/2021 14:00	105.8	147.7	148.1	133.9	14.1	24.3	3
9/12/2021 15:00	111.8	163.3	142.4	139.2	14.9	25.9	3
9/12/2021 16:00	114.0	161.3	146.1	140.5	13.9	24.2	3
9/12/2021 17:00	103.1	148.7	146.2	132.7	14.8	25.6	3
9/12/2021 18:00	97.6	149.2	158.9	135.3	19.0	32.9	3
9/12/2021 19:00	103.0	136.5	117.8	119.1	9.7	16.8	3
9/12/2021 20:00	98.7	138.8	112.9	116.8	11.7	20.3	3
9/12/2021 21:00	101.1	129.6	112.7	114.4	8.3	14.3	3
9/12/2021 22:00	100.3	134.1	110.7	115.0	10.0	17.3	3
9/12/2021 23:00	96.1	139.0	111.0	115.4	12.6	21.8	3
9/13/2021 0:00	96.2	136.4	111.0	114.5	11.7	20.4	3
9/13/2021 1:00	88.1	126.9	105.3	106.8	11.2	19.4	3
9/13/2021 2:00	86.5	123.6	114.7	108.3	11.2	19.3	3
9/13/2021 3:00	92.5	124.7	114.7	110.6	9.5	16.5	3
9/13/2021 4:00	91.9	127.1	114.0	111.0	10.3	17.8	3
9/13/2021 5:00	95.2	130.0	114.9	113.4	10.1	17.4	3

4.12 mg/kg 3,4-diaminopyridine Treatment							
Heart Rate (bpm)							
Date	SA180D	BF873I	AP55D	Mean	SE	SD	n
9/13/2021 6:00	107.0	137.8	117.4	120.7	9.0	15.6	3
9/13/2021 7:00	106.9	152.7	141.0	133.5	13.7	23.8	3
9/13/2021 8:00	152.7	176.2	170.1	166.3	7.0	12.2	3
9/13/2021 9:00	187.9	204.3	196.9	196.4	4.7	8.2	3
9/13/2021 10:00	144.9	168.0	163.5	158.8	7.1	12.2	3
9/13/2021 11:00	121.8	156.6	143.9	140.7	10.2	17.6	3
9/13/2021 12:00	113.3	157.6	139.1	136.6	12.8	22.3	3
9/13/2021 13:00	111.3	157.9	133.3	134.2	13.5	23.3	3
9/13/2021 14:00	124.7	169.9	164.7	153.1	14.3	24.8	3
9/13/2021 15:00	130.8	171.0	157.2	153.0	11.8	20.4	3
9/13/2021 16:00	131.0	158.7	146.8	145.5	8.0	13.9	3
9/13/2021 17:00	118.6	153.7	135.3	135.8	10.1	17.5	3
9/13/2021 18:00	121.2	148.8	143.4	137.8	8.5	14.7	3
9/13/2021 19:00	108.1	141.2	128.7	126.0	9.7	16.7	3
9/13/2021 20:00	95.5	127.0	106.3	109.6	9.2	16.0	3
9/13/2021 21:00	101.3	129.4	109.6	113.4	8.3	14.5	3
9/13/2021 22:00	95.7	130.3	113.2	113.1	10.0	17.3	3
9/13/2021 23:00	93.3	128.2	108.5	110.0	10.1	17.5	3
9/14/2021 0:00	97.3	137.4	109.2	114.6	11.9	20.6	3
9/14/2021 1:00	93.9	138.2	118.6	116.9	12.8	22.2	3
9/14/2021 2:00	100.5	132.5	116.0	116.3	9.2	16.0	3
9/14/2021 3:00	93.9	134.2	122.3	116.8	12.0	20.7	3
9/14/2021 4:00	95.5	130.4	120.1	115.3	10.3	17.9	3
9/14/2021 5:00	103.4	127.6	122.5	117.9	7.4	12.7	3
9/14/2021 6:00	109.1	138.0	132.5	126.5	8.8	15.3	3
9/14/2021 7:00	117.2	150.9	152.5	140.2	11.5	19.9	3
9/14/2021 8:00	127.4	160.0	155.0	147.5	10.1	17.6	3
9/14/2021 9:00	125.8	160.7	160.4	148.9	11.6	20.1	3
9/14/2021 10:00	115.8	154.8	142.0	137.6	11.5	19.9	3
9/14/2021 11:00	117.9	154.9	146.2	139.7	11.2	19.3	3
9/14/2021 12:00	114.1	152.2	123.6	130.0	11.5	19.8	3
9/14/2021 13:00	126.6	162.6	156.1	148.4	11.1	19.2	3

4.12 mg/kg 3,4-diaminopyridine Treatment							
Heart Rate (bpm)							
Date	SA180D	BF873I	AP55D	Mean	SE	SD	n
9/14/2021 14:00	112.9	161.2	146.9	140.3	14.3	24.8	3
9/14/2021 15:00	119.5	157.3	148.4	141.7	11.4	19.8	3
9/14/2021 16:00	114.1	153.7	150.8	139.5	12.8	22.1	3
9/14/2021 17:00	108.3	149.9	143.1	133.8	12.9	22.3	3
9/14/2021 18:00	105.6	145.8	144.1	131.9	13.1	22.8	3
9/14/2021 19:00	98.6	132.5	136.5	122.6	12.0	20.8	3
9/14/2021 20:00	96.9	131.6	161.1	129.8	18.5	32.1	3
9/14/2021 21:00	93.4	127.4	154.3	125.0	17.6	30.5	3
9/14/2021 22:00	110.8	151.2	187.0	149.7	22.0	38.2	3
9/14/2021 23:00	132.0	150.4	168.1	150.2	10.4	18.1	3
9/15/2021 0:00	102.9	132.3	150.3	128.5	13.8	23.9	3
9/15/2021 1:00	110.4	134.1	158.4	134.3	13.8	24.0	3
9/15/2021 2:00	109.8	135.6	173.0	139.5	18.3	31.7	3
9/15/2021 3:00	142.4	153.4	176.5	157.4	10.0	17.4	3
9/15/2021 4:00	116.0	138.0	169.7	141.3	15.6	27.0	3
9/15/2021 5:00	134.5	150.7	169.6	151.6	10.2	17.6	3
9/15/2021 6:00	131.9	146.8	175.8	151.5	12.9	22.3	3
9/15/2021 7:00	164.2	175.1	178.4	172.6	4.3	7.5	3
9/15/2021 8:00	154.5	176.8	178.3	169.9	7.7	13.3	3
9/15/2021 9:00	146.6	161.5	172.1	160.1	7.4	12.8	3
9/15/2021 10:00	148.1	183.6	179.1	170.3	11.2	19.4	3
9/15/2021 11:00	185.1	190.7	188.6	188.2	1.7	2.9	3
9/15/2021 12:00	141.8	186.0	184.9	170.9	14.6	25.2	3
9/15/2021 13:00	142.1	186.5	192.4	173.7	15.9	27.5	3
9/15/2021 14:00	152.6	182.9	200.3	178.6	13.9	24.1	3
9/15/2021 15:00	176.4	190.5	NaN	183.5	7.0	9.9	2
9/15/2021 16:00	147.8	195.7	NaN	171.7	24.0	33.9	2
9/15/2021 17:00	149.9	188.9	NaN	169.4	19.5	27.5	2
9/15/2021 18:00	167.8	179.6	NaN	173.7	5.9	8.4	2
9/15/2021 19:00	186.4	174.9	NaN	180.7	5.8	8.1	2
9/15/2021 20:00	154.7	189.1	NaN	171.9	17.2	24.3	2
9/15/2021 21:00	148.5	167.0	NaN	157.8	9.2	13.1	2

4.12 mg/kg 3,4-diaminopyridine Treatment							
Heart Rate (bpm)							
Date	**SA180D**	**BF873I**	**AP55D**	**Mean**	**SE**	**SD**	**n**
9/15/2021 22:00	170.1	165.1	NaN	167.6	2.5	3.5	2
9/15/2021 23:00	155.5	175.3	NaN	165.4	9.9	14.0	2
9/16/2021 0:00	143.2	178.5	NaN	160.9	17.7	25.0	2
9/16/2021 1:00	158.1	174.9	NaN	166.5	8.4	11.8	2
9/16/2021 2:00	165.3	163.2	NaN	164.3	1.0	1.5	2
9/16/2021 3:00	136.1	153.9	NaN	145.0	8.9	12.6	2
9/16/2021 4:00	140.7	156.4	NaN	148.6	7.9	11.1	2
9/16/2021 5:00	157.1	160.0	NaN	158.5	1.5	2.1	2
9/16/2021 6:00	157.3	141.0	NaN	149.1	8.2	11.6	2
9/16/2021 7:00	136.6	171.7	NaN	154.2	17.6	24.9	2
9/16/2021 8:00	148.1	172.7	NaN	160.4	12.3	17.4	2
9/16/2021 9:00	156.2	171.1	NaN	163.7	7.5	10.6	2
9/16/2021 10:00	NaN	165.8	NaN	165.8	0.0	0.0	1
9/16/2021 11:00	NaN	165.3	NaN	165.3	0.0	0.0	1

Table 35: PR Interval (msec) 4.12 mg/kg 3,4-diaminopyridine Treatment

4.12 mg/kg 3,4-diaminopyridine Treatment							
PR Interval (msec)							
Date	SA180D	BF873I	AP55D	Mean	SE	SD	n
9/10/2021 16:00	82.2	80.8	82.9	82.0	0.6	1.1	3
9/10/2021 17:00	82.4	84.7	83.2	83.4	0.7	1.2	3
9/10/2021 18:00	83.5	84.3	85.5	84.5	0.6	1.0	3
9/10/2021 19:00	85.7	89.3	90.7	88.6	1.5	2.6	3
9/10/2021 20:00	88.3	90.4	91.6	90.1	1.0	1.7	3
9/10/2021 21:00	86.9	91.5	87.4	88.6	1.5	2.5	3
9/10/2021 22:00	85.2	91.1	87.1	87.8	1.7	3.0	3
9/10/2021 23:00	85.2	92.4	86.0	87.9	2.3	4.0	3
9/11/2021 0:00	90.2	91.9	82.1	88.0	3.0	5.2	3
9/11/2021 1:00	86.7	89.5	82.9	86.4	1.9	3.3	3
9/11/2021 2:00	87.1	86.1	82.4	85.2	1.4	2.5	3
9/11/2021 3:00	88.1	86.3	82.8	85.7	1.5	2.7	3
9/11/2021 4:00	87.5	87.7	84.6	86.6	1.0	1.8	3
9/11/2021 5:00	87.0	88.9	87.7	87.9	0.5	0.9	3
9/11/2021 6:00	83.5	86.3	84.4	84.7	0.8	1.4	3
9/11/2021 7:00	83.8	78.9	82.9	81.9	1.5	2.6	3
9/11/2021 8:00	84.3	80.3	81.5	82.1	1.2	2.1	3
9/11/2021 9:00	85.8	84.3	82.7	84.2	0.9	1.5	3
9/11/2021 10:00	87.4	85.8	86.3	86.5	0.5	0.8	3
9/11/2021 11:00	86.2	83.3	90.0	86.5	2.0	3.4	3
9/11/2021 12:00	86.0	81.2	87.7	85.0	1.9	3.4	3
9/11/2021 13:00	85.7	82.5	86.5	84.9	1.2	2.1	3
9/11/2021 14:00	86.2	80.9	85.2	84.1	1.6	2.8	3
9/11/2021 15:00	85.3	84.0	87.0	85.4	0.9	1.5	3
9/11/2021 16:00	85.5	82.1	88.3	85.3	1.8	3.1	3
9/11/2021 17:00	84.3	81.1	84.5	83.3	1.1	1.9	3
9/11/2021 18:00	83.8	79.9	85.3	83.0	1.6	2.8	3
9/11/2021 19:00	83.5	83.1	91.0	85.9	2.6	4.4	3
9/11/2021 20:00	86.8	81.5	92.4	86.9	3.1	5.4	3
9/11/2021 21:00	84.9	80.4	93.3	86.2	3.8	6.6	3
9/11/2021 22:00	86.0	79.9	94.2	86.7	4.2	7.2	3

4.12 mg/kg 3,4-diaminopyridine Treatment							
PR Interval (msec)							
Date	**SA180D**	**BF873I**	**AP55D**	**Mean**	**SE**	**SD**	**n**
9/11/2021 23:00	84.3	80.2	88.1	84.2	2.3	3.9	3
9/12/2021 0:00	87.9	79.5	84.7	84.0	2.5	4.3	3
9/12/2021 1:00	88.0	82.2	84.3	84.8	1.7	3.0	3
9/12/2021 2:00	85.3	83.3	86.3	85.0	0.9	1.5	3
9/12/2021 3:00	86.6	82.3	87.2	85.4	1.5	2.7	3
9/12/2021 4:00	86.1	83.0	84.8	84.6	0.9	1.5	3
9/12/2021 5:00	86.2	82.5	86.1	84.9	1.2	2.1	3
9/12/2021 6:00	85.5	82.7	85.7	84.6	1.0	1.7	3
9/12/2021 7:00	86.0	76.5	84.6	82.4	3.0	5.2	3
9/12/2021 8:00	85.0	77.5	82.1	81.5	2.2	3.8	3
9/12/2021 9:00	86.6	81.4	86.8	84.9	1.8	3.1	3
9/12/2021 10:00	86.7	81.7	84.8	84.4	1.5	2.5	3
9/12/2021 11:00	86.6	84.7	87.3	86.2	0.8	1.3	3
9/12/2021 12:00	86.7	85.1	89.2	87.0	1.2	2.1	3
9/12/2021 13:00	83.7	79.6	86.4	83.2	2.0	3.4	3
9/12/2021 14:00	85.8	83.1	85.9	85.0	0.9	1.6	3
9/12/2021 15:00	84.2	80.8	86.5	83.8	1.7	2.9	3
9/12/2021 16:00	84.7	80.1	85.5	83.4	1.7	2.9	3
9/12/2021 17:00	85.4	82.3	87.1	84.9	1.4	2.4	3
9/12/2021 18:00	86.0	81.6	81.6	83.1	1.5	2.5	3
9/12/2021 19:00	84.5	86.7	87.8	86.3	1.0	1.7	3
9/12/2021 20:00	83.0	83.8	89.1	85.3	1.9	3.3	3
9/12/2021 21:00	83.3	88.4	88.5	86.7	1.7	3.0	3
9/12/2021 22:00	86.0	88.2	88.0	87.4	0.7	1.2	3
9/12/2021 23:00	87.2	85.3	87.9	86.8	0.8	1.4	3
9/13/2021 0:00	85.4	83.3	86.8	85.2	1.0	1.7	3
9/13/2021 1:00	87.9	87.3	87.6	87.6	0.2	0.3	3
9/13/2021 2:00	89.3	88.6	85.4	87.8	1.2	2.1	3
9/13/2021 3:00	86.4	88.7	85.4	86.8	1.0	1.7	3
9/13/2021 4:00	87.8	87.8	85.3	87.0	0.8	1.4	3
9/13/2021 5:00	85.6	87.5	85.2	86.1	0.7	1.2	3
9/13/2021 6:00	84.1	85.6	84.6	84.8	0.5	0.8	3

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4.12 mg/kg 3,4-diaminopyridine Treatment							
PR Interval (msec)							
Date	**SA180D**	**BF873I**	**AP55D**	**Mean**	**SE**	**SD**	**n**
9/13/2021 7:00	84.9	81.9	85.2	84.0	1.1	1.8	3
9/13/2021 8:00	76.8	79.9	79.2	78.6	0.9	1.6	3
9/13/2021 9:00	69.1	70.8	76.0	72.0	2.1	3.6	3
9/13/2021 10:00	75.6	76.3	78.6	76.8	0.9	1.6	3
9/13/2021 11:00	82.2	80.1	84.2	82.2	1.2	2.0	3
9/13/2021 12:00	84.7	80.5	86.2	83.8	1.7	3.0	3
9/13/2021 13:00	85.2	81.3	87.0	84.5	1.7	2.9	3
9/13/2021 14:00	82.4	82.7	79.8	81.7	0.9	1.6	3
9/13/2021 15:00	82.7	80.8	83.7	82.4	0.8	1.5	3
9/13/2021 16:00	79.6	81.2	84.2	81.7	1.3	2.3	3
9/13/2021 17:00	81.5	82.8	86.9	83.7	1.6	2.8	3
9/13/2021 18:00	80.5	81.7	84.5	82.2	1.2	2.0	3
9/13/2021 19:00	82.8	86.9	84.5	84.7	1.2	2.0	3
9/13/2021 20:00	85.5	91.1	89.6	88.7	1.7	2.9	3
9/13/2021 21:00	84.6	87.3	90.3	87.4	1.6	2.8	3
9/13/2021 22:00	86.6	84.3	88.8	86.6	1.3	2.2	3
9/13/2021 23:00	86.7	83.2	85.8	85.2	1.0	1.8	3
9/14/2021 0:00	85.8	81.4	88.8	85.3	2.2	3.7	3
9/14/2021 1:00	86.6	81.4	89.5	85.9	2.4	4.1	3
9/14/2021 2:00	85.1	83.9	86.0	85.0	0.6	1.0	3
9/14/2021 3:00	86.5	83.0	86.5	85.3	1.2	2.0	3
9/14/2021 4:00	86.4	84.7	85.7	85.6	0.5	0.9	3
9/14/2021 5:00	85.2	86.3	84.4	85.3	0.5	0.9	3
9/14/2021 6:00	83.4	84.5	87.1	85.0	1.1	1.9	3
9/14/2021 7:00	84.8	80.5	82.6	82.6	1.2	2.1	3
9/14/2021 8:00	82.2	78.7	83.0	81.3	1.3	2.3	3
9/14/2021 9:00	82.0	79.8	80.4	80.8	0.6	1.1	3
9/14/2021 10:00	84.4	81.8	83.2	83.1	0.8	1.3	3
9/14/2021 11:00	84.3	82.2	83.1	83.2	0.6	1.0	3
9/14/2021 12:00	85.4	84.1	88.8	86.1	1.4	2.4	3
9/14/2021 13:00	80.8	79.5	79.5	80.0	0.4	0.8	3
9/14/2021 14:00	82.1	79.4	80.8	80.8	0.8	1.3	3

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4.12 mg/kg 3,4-diaminopyridine Treatment							
PR Interval (msec)							
Date	**SA180D**	**BF873I**	**AP55D**	**Mean**	**SE**	**SD**	**n**
9/14/2021 15:00	83.6	81.5	81.4	82.2	0.7	1.2	3
9/14/2021 16:00	82.8	83.1	78.9	81.6	1.4	2.3	3
9/14/2021 17:00	82.4	82.7	80.3	81.8	0.8	1.3	3
9/14/2021 18:00	81.8	82.2	80.4	81.4	0.6	1.0	3
9/14/2021 19:00	83.2	83.1	80.4	82.2	0.9	1.6	3
9/14/2021 20:00	83.1	85.9	74.1	81.0	3.5	6.1	3
9/14/2021 21:00	84.2	87.1	76.6	82.6	3.1	5.4	3
9/14/2021 22:00	80.3	80.0	68.4	76.3	3.9	6.8	3
9/14/2021 23:00	75.8	79.2	72.5	75.8	1.9	3.3	3
9/15/2021 0:00	81.4	83.8	78.6	81.3	1.5	2.6	3
9/15/2021 1:00	80.0	82.3	76.8	79.7	1.6	2.8	3
9/15/2021 2:00	80.8	82.6	72.8	78.7	3.0	5.2	3
9/15/2021 3:00	75.2	77.7	73.4	75.4	1.2	2.1	3
9/15/2021 4:00	79.1	83.1	74.3	78.8	2.5	4.4	3
9/15/2021 5:00	77.8	80.4	74.3	77.5	1.8	3.1	3
9/15/2021 6:00	75.8	81.5	71.8	76.4	2.8	4.9	3
9/15/2021 7:00	73.0	76.3	72.5	73.9	1.2	2.1	3
9/15/2021 8:00	74.4	76.1	71.6	74.0	1.3	2.3	3
9/15/2021 9:00	76.1	80.7	72.5	76.5	2.4	4.1	3
9/15/2021 10:00	75.4	74.8	71.1	73.7	1.3	2.3	3
9/15/2021 11:00	68.6	73.6	76.8	73.0	2.4	4.2	3
9/15/2021 12:00	76.3	74.5	74.8	75.2	0.5	0.9	3
9/15/2021 13:00	77.4	74.7	74.1	75.4	1.0	1.7	3
9/15/2021 14:00	76.8	76.7	74.7	76.1	0.7	1.2	3
9/15/2021 15:00	73.1	73.6	NaN	73.4	0.3	0.4	2
9/15/2021 16:00	78.4	71.3	NaN	74.9	3.6	5.0	2
9/15/2021 17:00	77.6	77.2	NaN	77.4	0.2	0.3	2
9/15/2021 18:00	76.0	78.5	NaN	77.3	1.2	1.8	2
9/15/2021 19:00	69.9	79.9	NaN	74.9	5.0	7.1	2
9/15/2021 20:00	75.2	76.0	NaN	75.6	0.4	0.6	2
9/15/2021 21:00	76.0	83.4	NaN	79.7	3.7	5.2	2
9/15/2021 22:00	74.9	80.1	NaN	77.5	2.6	3.7	2

4.12 mg/kg 3,4-diaminopyridine Treatment							
PR Interval (msec)							
Date	**SA180D**	**BF873I**	**AP55D**	**Mean**	**SE**	**SD**	**n**
9/15/2021 23:00	75.8	78.7	NaN	77.3	1.4	2.0	2
9/16/2021 0:00	79.5	77.6	NaN	78.6	1.0	1.3	2
9/16/2021 1:00	75.3	78.9	NaN	77.1	1.8	2.5	2
9/16/2021 2:00	74.2	79.1	NaN	76.7	2.5	3.5	2
9/16/2021 3:00	79.1	81.6	NaN	80.3	1.3	1.8	2
9/16/2021 4:00	77.6	79.4	NaN	78.5	0.9	1.3	2
9/16/2021 5:00	74.0	79.8	NaN	76.9	2.9	4.1	2
9/16/2021 6:00	72.9	79.7	NaN	76.3	3.4	4.8	2
9/16/2021 7:00	80.3	75.6	NaN	78.0	2.3	3.3	2
9/16/2021 8:00	75.9	76.0	NaN	76.0	0.0	0.1	2
9/16/2021 9:00	72.3	75.9	NaN	74.1	1.8	2.5	2
9/16/2021 10:00	NaN	75.6	NaN	75.6	0.0	0.0	1
9/16/2021 11:00	NaN	75.1	NaN	75.1	0.0	0.0	1

Table 36: QRS Duration (msec) 4.12 mg/kg 3,4-diaminopyridine Treatment

4.12 mg/kg 3,4-diaminopyridine Treatment							
QRS Duration (msec)							
Date	SA180D	BF873I	AP55D	Mean	SE	SD	n
9/10/2021 16:00	38.3	39.0	39.4	38.9	0.3	0.5	3
9/10/2021 17:00	38.3	39.0	38.9	38.7	0.2	0.4	3
9/10/2021 18:00	38.9	39.2	38.1	38.7	0.3	0.6	3
9/10/2021 19:00	38.2	40.2	34.0	37.5	1.8	3.2	3
9/10/2021 20:00	38.5	38.4	34.1	37.0	1.5	2.5	3
9/10/2021 21:00	42.5	40.9	35.1	39.5	2.3	3.9	3
9/10/2021 22:00	43.8	38.2	35.7	39.2	2.4	4.1	3
9/10/2021 23:00	42.2	36.2	34.6	37.6	2.3	4.0	3
9/11/2021 0:00	38.9	38.1	37.5	38.1	0.4	0.7	3
9/11/2021 1:00	40.2	37.9	33.4	37.2	2.0	3.5	3
9/11/2021 2:00	41.8	37.5	35.0	38.1	2.0	3.5	3
9/11/2021 3:00	41.6	37.4	33.9	37.6	2.2	3.9	3
9/11/2021 4:00	40.6	38.0	34.0	37.6	1.9	3.3	3
9/11/2021 5:00	39.4	38.6	34.2	37.4	1.6	2.8	3
9/11/2021 6:00	41.8	39.3	34.0	38.3	2.3	4.0	3
9/11/2021 7:00	38.6	38.6	39.5	38.9	0.3	0.5	3
9/11/2021 8:00	38.1	38.7	38.6	38.5	0.2	0.3	3
9/11/2021 9:00	38.1	39.0	38.6	38.6	0.3	0.5	3
9/11/2021 10:00	38.1	38.7	37.9	38.2	0.2	0.4	3
9/11/2021 11:00	38.3	38.7	35.8	37.6	0.9	1.6	3
9/11/2021 12:00	39.1	38.5	38.1	38.6	0.3	0.5	3
9/11/2021 13:00	38.7	38.1	39.4	38.7	0.4	0.6	3
9/11/2021 14:00	38.5	38.2	39.3	38.7	0.3	0.6	3
9/11/2021 15:00	39.3	36.1	38.9	38.1	1.0	1.8	3
9/11/2021 16:00	38.7	38.3	38.7	38.6	0.1	0.2	3
9/11/2021 17:00	38.7	38.4	39.9	39.0	0.5	0.8	3
9/11/2021 18:00	38.5	38.3	38.2	38.3	0.1	0.1	3
9/11/2021 19:00	39.3	36.0	35.7	37.0	1.1	2.0	3
9/11/2021 20:00	38.4	35.4	36.6	36.8	0.8	1.5	3
9/11/2021 21:00	39.8	36.4	34.3	36.8	1.6	2.7	3
9/11/2021 22:00	39.8	35.3	33.9	36.3	1.8	3.1	3

4.12 mg/kg 3,4-diaminopyridine Treatment							
QRS Duration (msec)							
Date	SA180D	BF873I	AP55D	Mean	SE	SD	n
9/11/2021 23:00	39.3	36.0	34.2	36.5	1.5	2.6	3
9/12/2021 0:00	38.3	35.8	35.9	36.7	0.8	1.4	3
9/12/2021 1:00	38.6	39.4	34.5	37.5	1.5	2.6	3
9/12/2021 2:00	41.3	40.9	35.5	39.2	1.9	3.2	3
9/12/2021 3:00	41.0	39.6	35.9	38.8	1.5	2.6	3
9/12/2021 4:00	41.6	39.1	34.5	38.4	2.1	3.6	3
9/12/2021 5:00	43.3	37.9	34.2	38.5	2.6	4.6	3
9/12/2021 6:00	42.4	40.6	34.4	39.1	2.4	4.2	3
9/12/2021 7:00	38.2	37.6	39.4	38.4	0.5	0.9	3
9/12/2021 8:00	38.4	37.6	39.2	38.4	0.4	0.8	3
9/12/2021 9:00	38.1	38.7	38.4	38.4	0.2	0.3	3
9/12/2021 10:00	38.0	38.0	39.4	38.5	0.5	0.8	3
9/12/2021 11:00	37.9	39.8	39.9	39.2	0.6	1.1	3
9/12/2021 12:00	40.7	39.2	39.2	39.7	0.5	0.9	3
9/12/2021 13:00	38.8	38.2	39.9	39.0	0.5	0.9	3
9/12/2021 14:00	38.7	37.9	40.1	38.9	0.6	1.1	3
9/12/2021 15:00	38.4	37.9	39.5	38.6	0.5	0.8	3
9/12/2021 16:00	38.3	38.5	39.5	38.8	0.4	0.6	3
9/12/2021 17:00	38.6	37.5	39.1	38.4	0.5	0.8	3
9/12/2021 18:00	38.6	38.3	39.6	38.8	0.4	0.7	3
9/12/2021 19:00	43.3	36.3	36.2	38.6	2.3	4.0	3
9/12/2021 20:00	43.4	37.9	35.6	38.9	2.3	4.0	3
9/12/2021 21:00	43.5	35.1	35.5	38.0	2.7	4.7	3
9/12/2021 22:00	38.9	37.3	34.5	36.9	1.3	2.2	3
9/12/2021 23:00	37.8	37.9	34.6	36.8	1.1	1.9	3
9/13/2021 0:00	41.4	38.5	34.2	38.0	2.1	3.6	3
9/13/2021 1:00	39.5	38.3	33.9	37.2	1.7	3.0	3
9/13/2021 2:00	37.2	39.8	34.9	37.3	1.4	2.5	3
9/13/2021 3:00	42.9	40.1	34.7	39.2	2.4	4.2	3
9/13/2021 4:00	40.0	39.5	34.3	37.9	1.8	3.1	3
9/13/2021 5:00	43.2	38.9	34.9	39.0	2.4	4.2	3
9/13/2021 6:00	43.1	38.1	34.9	38.7	2.4	4.1	3

4.12 mg/kg 3,4-diaminopyridine Treatment							
QRS Duration (msec)							
Date	SA180D	BF873I	AP55D	Mean	SE	SD	n
9/13/2021 7:00	38.1	38.1	38.3	38.2	0.1	0.1	3
9/13/2021 8:00	37.0	36.7	35.9	36.5	0.3	0.6	3
9/13/2021 9:00	36.1	35.7	34.6	35.5	0.5	0.8	3
9/13/2021 10:00	36.4	38.0	38.8	37.7	0.7	1.2	3
9/13/2021 11:00	37.3	37.9	39.1	38.1	0.5	0.9	3
9/13/2021 12:00	37.1	37.6	38.6	37.8	0.4	0.7	3
9/13/2021 13:00	37.1	37.3	37.0	37.1	0.1	0.2	3
9/13/2021 14:00	36.9	37.0	38.6	37.5	0.6	1.0	3
9/13/2021 15:00	38.2	37.2	39.5	38.3	0.7	1.2	3
9/13/2021 16:00	38.0	37.7	40.3	38.7	0.8	1.4	3
9/13/2021 17:00	37.9	38.2	38.3	38.1	0.1	0.2	3
9/13/2021 18:00	38.2	38.1	39.4	38.6	0.4	0.7	3
9/13/2021 19:00	39.9	35.8	38.0	37.9	1.2	2.1	3
9/13/2021 20:00	40.3	35.5	35.3	37.0	1.7	2.9	3
9/13/2021 21:00	40.6	35.6	33.8	36.7	2.0	3.5	3
9/13/2021 22:00	42.5	35.7	34.5	37.6	2.5	4.3	3
9/13/2021 23:00	42.5	35.7	35.8	38.0	2.2	3.9	3
9/14/2021 0:00	42.0	36.7	33.5	37.4	2.5	4.3	3
9/14/2021 1:00	42.0	36.2	35.0	37.7	2.2	3.8	3
9/14/2021 2:00	39.6	36.2	34.4	36.7	1.5	2.6	3
9/14/2021 3:00	39.7	36.4	34.1	36.7	1.6	2.8	3
9/14/2021 4:00	40.2	37.3	34.2	37.2	1.7	3.0	3
9/14/2021 5:00	40.0	36.4	34.3	36.9	1.7	2.9	3
9/14/2021 6:00	40.7	37.7	36.2	38.2	1.3	2.3	3
9/14/2021 7:00	37.6	37.4	40.1	38.4	0.9	1.5	3
9/14/2021 8:00	37.4	37.0	37.7	37.3	0.2	0.4	3
9/14/2021 9:00	37.1	37.5	39.5	38.0	0.7	1.3	3
9/14/2021 10:00	37.5	37.4	38.7	37.9	0.4	0.7	3
9/14/2021 11:00	37.6	37.4	39.2	38.1	0.6	1.0	3
9/14/2021 12:00	37.7	37.2	36.7	37.2	0.3	0.5	3
9/14/2021 13:00	37.4	36.7	38.7	37.6	0.6	1.0	3
9/14/2021 14:00	37.1	36.9	37.8	37.3	0.3	0.5	3

4.12 mg/kg 3,4-diaminopyridine Treatment							
QRS Duration (msec)							
Date	SA180D	BF873I	AP55D	Mean	SE	SD	n
9/14/2021 15:00	38.7	37.6	38.8	38.4	0.4	0.6	3
9/14/2021 16:00	38.4	36.9	38.0	37.8	0.4	0.8	3
9/14/2021 17:00	41.5	37.0	38.2	38.9	1.3	2.3	3
9/14/2021 18:00	40.8	37.1	37.4	38.4	1.2	2.0	3
9/14/2021 19:00	42.2	36.4	36.3	38.3	2.0	3.4	3
9/14/2021 20:00	42.2	35.9	36.7	38.3	2.0	3.4	3
9/14/2021 21:00	42.6	36.5	37.0	38.7	2.0	3.4	3
9/14/2021 22:00	40.4	35.8	36.8	37.7	1.4	2.5	3
9/14/2021 23:00	40.1	35.5	38.6	38.1	1.3	2.3	3
9/15/2021 0:00	42.4	35.8	38.8	39.0	1.9	3.3	3
9/15/2021 1:00	41.1	36.3	38.8	38.7	1.4	2.4	3
9/15/2021 2:00	42.0	38.0	35.9	38.6	1.8	3.1	3
9/15/2021 3:00	38.4	37.2	37.4	37.7	0.4	0.6	3
9/15/2021 4:00	39.8	37.7	36.3	37.9	1.0	1.8	3
9/15/2021 5:00	37.8	38.4	36.3	37.5	0.6	1.1	3
9/15/2021 6:00	38.3	37.9	38.5	38.2	0.2	0.3	3
9/15/2021 7:00	37.0	35.6	36.7	36.4	0.4	0.7	3
9/15/2021 8:00	37.2	36.8	36.0	36.7	0.3	0.6	3
9/15/2021 9:00	38.3	37.0	37.7	37.7	0.4	0.6	3
9/15/2021 10:00	38.8	36.5	38.4	37.9	0.7	1.2	3
9/15/2021 11:00	36.9	36.4	33.2	35.5	1.2	2.0	3
9/15/2021 12:00	37.8	36.0	36.0	36.6	0.6	1.1	3
9/15/2021 13:00	38.6	36.4	34.4	36.5	1.2	2.1	3
9/15/2021 14:00	38.8	36.3	33.9	36.3	1.4	2.5	3
9/15/2021 15:00	38.4	36.8	NaN	37.6	0.8	1.1	2
9/15/2021 16:00	39.3	37.3	NaN	38.3	1.0	1.4	2
9/15/2021 17:00	38.6	35.6	NaN	37.1	1.5	2.1	2
9/15/2021 18:00	39.0	35.2	NaN	37.1	1.9	2.7	2
9/15/2021 19:00	38.5	35.3	NaN	36.9	1.6	2.3	2
9/15/2021 20:00	39.1	35.9	NaN	37.5	1.6	2.3	2
9/15/2021 21:00	39.5	35.4	NaN	37.5	2.0	2.9	2
9/15/2021 22:00	39.2	35.5	NaN	37.4	1.9	2.6	2

4.12 mg/kg 3,4-diaminopyridine Treatment							
QRS Duration (msec)							
Date	**SA180D**	**BF873I**	**AP55D**	**Mean**	**SE**	**SD**	**n**
9/15/2021 23:00	38.6	35.5	NaN	37.1	1.6	2.2	2
9/16/2021 0:00	38.8	35.3	NaN	37.1	1.8	2.5	2
9/16/2021 1:00	39.2	35.6	NaN	37.4	1.8	2.6	2
9/16/2021 2:00	39.3	35.7	NaN	37.5	1.8	2.6	2
9/16/2021 3:00	39.2	35.8	NaN	37.5	1.7	2.4	2
9/16/2021 4:00	39.6	36.3	NaN	37.9	1.7	2.3	2
9/16/2021 5:00	39.3	35.5	NaN	37.4	1.9	2.7	2
9/16/2021 6:00	39.4	36.0	NaN	37.7	1.7	2.4	2
9/16/2021 7:00	39.1	35.7	NaN	37.4	1.7	2.5	2
9/16/2021 8:00	39.6	36.0	NaN	37.8	1.8	2.5	2
9/16/2021 9:00	39.5	35.6	NaN	37.6	1.9	2.7	2
9/16/2021 10:00	NaN	35.6	NaN	35.6	0.0	0.0	1
9/16/2021 11:00	NaN	35.4	NaN	35.4	0.0	0.0	1

Table 37: Heart Rate Corrected QT Interval (msec) 4.12 mg/kg 3,4-diaminopyridine Treatment

4.12 mg/kg 3,4-diaminopyridine Treatment							
Heart Rate Corrected QT Interval (msec)							
Date	SA180D	BF873I	AP55D	Mean	SE	SD	n
9/10/2021 16:00	306.6	351.4	360.8	339.6	16.7	29.0	3
9/10/2021 17:00	311.4	351.5	360.0	341.0	15.0	26.0	3
9/10/2021 18:00	321.2	351.5	361.3	344.7	12.1	20.9	3
9/10/2021 19:00	349.6	374.9	384.8	369.8	10.5	18.2	3
9/10/2021 20:00	340.4	379.3	392.2	370.6	15.6	27.0	3
9/10/2021 21:00	346.2	379.7	390.4	372.1	13.3	23.1	3
9/10/2021 22:00	348.5	379.0	389.4	372.3	12.3	21.2	3
9/10/2021 23:00	347.9	380.9	388.0	372.2	12.4	21.4	3
9/11/2021 0:00	349.0	386.0	379.2	371.4	11.4	19.7	3
9/11/2021 1:00	352.1	382.6	383.1	372.6	10.2	17.7	3
9/11/2021 2:00	347.4	377.9	382.2	369.2	10.9	18.9	3
9/11/2021 3:00	348.4	375.0	388.5	370.6	11.8	20.4	3
9/11/2021 4:00	345.0	371.3	381.5	365.9	10.9	18.9	3
9/11/2021 5:00	340.7	365.8	386.6	364.4	13.3	23.0	3
9/11/2021 6:00	336.8	361.8	383.2	360.6	13.4	23.2	3
9/11/2021 7:00	332.9	352.9	365.8	350.5	9.6	16.6	3
9/11/2021 8:00	324.9	353.7	357.8	345.5	10.4	17.9	3
9/11/2021 9:00	324.0	352.0	365.2	347.0	12.2	21.0	3
9/11/2021 10:00	331.9	350.9	366.0	349.6	9.9	17.1	3
9/11/2021 11:00	320.7	347.5	387.2	351.8	19.3	33.5	3
9/11/2021 12:00	320.8	346.4	379.8	349.0	17.1	29.6	3
9/11/2021 13:00	310.1	345.6	364.4	340.1	15.9	27.6	3
9/11/2021 14:00	317.8	348.4	368.2	344.8	14.6	25.4	3
9/11/2021 15:00	314.9	352.2	375.9	347.7	17.8	30.8	3
9/11/2021 16:00	315.9	347.8	377.0	346.9	17.6	30.5	3
9/11/2021 17:00	313.2	351.4	368.5	344.4	16.3	28.3	3
9/11/2021 18:00	317.5	350.8	371.6	346.7	15.8	27.3	3
9/11/2021 19:00	340.0	364.9	394.2	366.4	15.7	27.2	3
9/11/2021 20:00	341.5	365.1	404.3	370.3	18.3	31.7	3
9/11/2021 21:00	341.8	363.3	397.5	367.5	16.2	28.1	3

4.12 mg/kg 3,4-diaminopyridine Treatment							
Heart Rate Corrected QT Interval (msec)							
Date	**SA180D**	**BF873I**	**AP55D**	**Mean**	**SE**	**SD**	**n**
9/11/2021 22:00	346.6	360.7	394.4	367.2	14.2	24.6	3
9/11/2021 23:00	344.6	360.1	384.4	363.0	11.6	20.1	3
9/12/2021 0:00	346.1	361.4	388.1	365.2	12.3	21.3	3
9/12/2021 1:00	346.9	365.4	396.3	369.6	14.4	24.9	3
9/12/2021 2:00	347.3	369.0	396.2	370.8	14.1	24.5	3
9/12/2021 3:00	349.4	364.1	397.4	370.3	14.2	24.6	3
9/12/2021 4:00	346.1	366.4	394.5	369.0	14.0	24.3	3
9/12/2021 5:00	345.3	359.2	392.8	365.8	14.1	24.4	3
9/12/2021 6:00	347.6	358.5	388.9	365.0	12.4	21.4	3
9/12/2021 7:00	340.2	352.5	370.5	354.4	8.8	15.2	3
9/12/2021 8:00	326.9	350.9	358.1	345.3	9.4	16.3	3
9/12/2021 9:00	325.9	360.5	372.3	352.9	13.9	24.1	3
9/12/2021 10:00	326.2	360.9	364.5	350.5	12.2	21.2	3
9/12/2021 11:00	323.9	361.1	368.6	351.2	13.8	24.0	3
9/12/2021 12:00	329.3	358.7	381.6	356.5	15.2	26.3	3
9/12/2021 13:00	320.0	352.7	362.2	345.0	12.8	22.1	3
9/12/2021 14:00	322.3	351.5	371.7	348.5	14.3	24.8	3
9/12/2021 15:00	319.0	350.6	370.3	346.6	14.9	25.9	3
9/12/2021 16:00	319.3	350.3	367.2	345.6	14.0	24.3	3
9/12/2021 17:00	320.6	353.5	365.4	346.5	13.4	23.2	3
9/12/2021 18:00	329.0	353.9	359.2	347.4	9.3	16.1	3
9/12/2021 19:00	352.2	370.2	380.7	367.7	8.3	14.4	3
9/12/2021 20:00	352.4	371.0	392.0	371.8	11.4	19.8	3
9/12/2021 21:00	356.3	364.0	384.5	368.3	8.4	14.6	3
9/12/2021 22:00	347.6	374.5	395.5	372.5	13.9	24.0	3
9/12/2021 23:00	354.6	371.9	396.9	374.5	12.3	21.3	3
9/13/2021 0:00	352.9	367.6	392.8	371.1	11.7	20.2	3
9/13/2021 1:00	357.2	375.7	399.1	377.4	12.1	21.0	3
9/13/2021 2:00	358.1	373.4	397.6	376.4	11.5	19.9	3
9/13/2021 3:00	354.7	372.3	397.7	374.9	12.5	21.6	3
9/13/2021 4:00	358.1	371.5	393.8	374.5	10.4	18.1	3
9/13/2021 5:00	354.0	369.9	392.1	372.0	11.0	19.1	3

4.12 mg/kg 3,4-diaminopyridine Treatment							
Heart Rate Corrected QT Interval (msec)							
Date	**SA180D**	**BF873I**	**AP55D**	**Mean**	**SE**	**SD**	**n**
9/13/2021 6:00	353.7	364.7	393.3	370.6	11.8	20.4	3
9/13/2021 7:00	344.0	359.7	376.9	360.2	9.5	16.4	3
9/13/2021 8:00	334.2	373.0	368.0	358.4	12.2	21.1	3
9/13/2021 9:00	316.0	348.3	340.5	334.9	9.7	16.9	3
9/13/2021 10:00	316.2	350.0	354.4	340.2	12.1	20.9	3
9/13/2021 11:00	322.4	350.9	366.6	346.7	12.9	22.4	3
9/13/2021 12:00	325.6	348.9	366.2	346.9	11.8	20.4	3
9/13/2021 13:00	323.7	349.6	361.3	344.9	11.1	19.2	3
9/13/2021 14:00	315.5	350.5	349.4	338.4	11.5	19.9	3
9/13/2021 15:00	313.7	353.8	359.3	342.3	14.3	24.8	3
9/13/2021 16:00	316.2	352.0	366.3	344.8	14.9	25.8	3
9/13/2021 17:00	317.9	353.0	361.1	344.0	13.3	23.0	3
9/13/2021 18:00	319.5	349.0	361.9	343.5	12.5	21.7	3
9/13/2021 19:00	344.4	367.7	373.5	361.9	8.9	15.4	3
9/13/2021 20:00	356.4	367.6	399.8	374.6	13.0	22.5	3
9/13/2021 21:00	353.1	366.0	398.4	372.5	13.5	23.3	3
9/13/2021 22:00	352.2	365.2	389.8	369.1	11.0	19.1	3
9/13/2021 23:00	359.4	367.6	398.7	375.2	12.0	20.7	3
9/14/2021 0:00	359.0	365.1	400.5	374.9	12.9	22.4	3
9/14/2021 1:00	356.8	364.3	399.4	373.5	13.1	22.8	3
9/14/2021 2:00	355.0	366.5	398.8	373.4	13.1	22.7	3
9/14/2021 3:00	352.0	365.4	391.1	369.5	11.5	19.9	3
9/14/2021 4:00	347.3	365.0	393.3	368.5	13.4	23.2	3
9/14/2021 5:00	339.9	364.6	389.6	364.7	14.3	24.8	3
9/14/2021 6:00	343.6	362.6	389.6	365.3	13.3	23.1	3
9/14/2021 7:00	337.9	355.9	371.4	355.1	9.7	16.7	3
9/14/2021 8:00	334.6	360.0	363.9	352.8	9.2	15.9	3
9/14/2021 9:00	326.1	353.1	361.0	346.7	10.6	18.3	3
9/14/2021 10:00	327.5	354.9	367.3	349.9	11.7	20.3	3
9/14/2021 11:00	326.6	356.4	361.3	348.1	10.9	18.8	3
9/14/2021 12:00	324.1	357.4	371.7	351.1	14.1	24.4	3
9/14/2021 13:00	320.1	359.8	362.0	347.3	13.6	23.6	3

4.12 mg/kg 3,4-diaminopyridine Treatment							
Heart Rate Corrected QT Interval (msec)							
Date	SA180D	BF873I	AP55D	Mean	SE	SD	n
9/14/2021 14:00	317.2	358.8	360.1	345.4	14.1	24.4	3
9/14/2021 15:00	315.1	342.4	359.4	338.9	12.9	22.4	3
9/14/2021 16:00	318.6	341.4	354.6	338.2	10.5	18.3	3
9/14/2021 17:00	320.3	347.3	358.0	341.8	11.2	19.4	3
9/14/2021 18:00	322.2	349.0	363.4	344.9	12.1	20.9	3
9/14/2021 19:00	345.0	363.9	373.2	360.7	8.3	14.4	3
9/14/2021 20:00	336.2	362.4	358.9	352.5	8.2	14.2	3
9/14/2021 21:00	344.9	368.1	362.6	358.5	7.0	12.1	3
9/14/2021 22:00	347.7	357.0	349.9	351.5	2.8	4.8	3
9/14/2021 23:00	328.8	353.9	353.3	345.3	8.3	14.3	3
9/15/2021 0:00	340.8	365.9	382.2	363.0	12.1	20.9	3
9/15/2021 1:00	333.6	365.1	378.9	359.2	13.4	23.2	3
9/15/2021 2:00	347.8	364.5	370.9	361.1	6.9	11.9	3
9/15/2021 3:00	335.3	356.3	363.0	351.5	8.4	14.5	3
9/15/2021 4:00	337.5	363.9	376.4	359.3	11.5	19.8	3
9/15/2021 5:00	324.8	359.1	373.1	352.3	14.3	24.8	3
9/15/2021 6:00	332.6	361.5	368.7	354.3	11.0	19.1	3
9/15/2021 7:00	326.5	353.3	363.2	347.6	11.0	19.0	3
9/15/2021 8:00	326.4	356.5	370.9	351.3	13.1	22.7	3
9/15/2021 9:00	323.7	364.8	374.2	354.2	15.5	26.9	3
9/15/2021 10:00	328.7	360.2	365.4	351.5	11.5	19.8	3
9/15/2021 11:00	318.7	354.8	381.4	351.7	18.2	31.5	3
9/15/2021 12:00	338.0	358.2	383.6	359.9	13.2	22.8	3
9/15/2021 13:00	344.3	358.2	405.0	369.2	18.4	31.8	3
9/15/2021 14:00	335.6	364.6	396.7	365.6	17.6	30.5	3
9/15/2021 15:00	333.3	355.2	NaN	344.2	11.0	15.5	2
9/15/2021 16:00	341.6	344.1	NaN	342.8	1.3	1.8	2
9/15/2021 17:00	336.4	362.5	NaN	349.5	13.1	18.5	2
9/15/2021 18:00	340.6	374.5	NaN	357.5	17.0	24.0	2
9/15/2021 19:00	331.8	376.4	NaN	354.1	22.3	31.6	2
9/15/2021 20:00	335.3	367.1	NaN	351.2	15.9	22.5	2
9/15/2021 21:00	337.1	375.4	NaN	356.2	19.2	27.1	2

4.12 mg/kg 3,4-diaminopyridine Treatment							
Heart Rate Corrected QT Interval (msec)							
Date	**SA180D**	**BF873I**	**AP55D**	**Mean**	**SE**	**SD**	**n**
9/15/2021 22:00	333.9	382.8	NaN	358.3	24.5	34.6	2
9/15/2021 23:00	333.1	379.6	NaN	356.3	23.3	32.9	2
9/16/2021 0:00	337.2	375.4	NaN	356.3	19.1	27.1	2
9/16/2021 1:00	331.5	377.8	NaN	354.7	23.1	32.7	2
9/16/2021 2:00	338.0	382.2	NaN	360.1	22.1	31.3	2
9/16/2021 3:00	338.0	383.2	NaN	360.6	22.6	31.9	2
9/16/2021 4:00	336.0	381.0	NaN	358.5	22.5	31.8	2
9/16/2021 5:00	336.8	383.3	NaN	360.0	23.2	32.9	2
9/16/2021 6:00	340.0	385.5	NaN	362.7	22.8	32.2	2
9/16/2021 7:00	353.5	380.6	NaN	367.0	13.6	19.2	2
9/16/2021 8:00	345.6	376.9	NaN	361.3	15.6	22.1	2
9/16/2021 9:00	345.2	380.9	NaN	363.0	17.9	25.3	2
9/16/2021 10:00	NaN	382.8	NaN	382.8	0.0	0.0	1
9/16/2021 11:00	NaN	379.7	NaN	379.7	0.0	0.0	1

Table 38: QT Interval (msec) 4.12 mg/kg 3,4-diaminopyridine Treatment

4.12 mg/kg 3,4-diaminopyridine Treatment							
QT Interval (msec)							
Date	SA180D	BF873I	AP55D	Mean	SE	SD	n
9/10/2021 16:00	217.3	211.1	223.5	217.3	3.6	6.2	3
9/10/2021 17:00	231.6	227.4	229.7	229.6	1.2	2.1	3
9/10/2021 18:00	252.4	223.1	235.8	237.1	8.5	14.7	3
9/10/2021 19:00	268.0	258.7	272.4	266.3	4.1	7.0	3
9/10/2021 20:00	273.6	270.8	283.7	276.0	3.9	6.8	3
9/10/2021 21:00	274.5	276.3	271.3	274.0	1.5	2.5	3
9/10/2021 22:00	278.5	262.4	269.4	270.1	4.7	8.1	3
9/10/2021 23:00	273.6	265.1	264.9	267.9	2.9	5.0	3
9/11/2021 0:00	279.5	266.3	254.0	266.6	7.4	12.8	3
9/11/2021 1:00	272.5	257.0	258.8	262.7	4.9	8.5	3
9/11/2021 2:00	273.3	242.8	260.9	259.0	8.9	15.3	3
9/11/2021 3:00	268.7	245.9	265.0	259.8	7.0	12.2	3
9/11/2021 4:00	266.3	240.2	264.0	256.9	8.4	14.5	3
9/11/2021 5:00	263.9	234.6	268.5	255.7	10.6	18.4	3
9/11/2021 6:00	248.9	232.2	262.4	247.8	8.7	15.1	3
9/11/2021 7:00	239.6	219.9	229.3	229.6	5.7	9.8	3
9/11/2021 8:00	226.2	223.2	218.0	222.5	2.4	4.2	3
9/11/2021 9:00	235.7	225.1	228.6	229.8	3.1	5.4	3
9/11/2021 10:00	260.2	228.6	236.4	241.7	9.5	16.5	3
9/11/2021 11:00	234.7	211.6	279.1	241.8	19.8	34.3	3
9/11/2021 12:00	243.2	217.8	251.4	237.5	10.1	17.5	3
9/11/2021 13:00	222.9	208.9	233.4	221.8	7.1	12.3	3
9/11/2021 14:00	240.7	215.0	238.6	231.4	8.2	14.3	3
9/11/2021 15:00	231.6	227.4	249.3	236.1	6.7	11.6	3
9/11/2021 16:00	237.1	212.3	251.1	233.5	11.3	19.6	3
9/11/2021 17:00	228.7	218.3	228.2	225.0	3.4	5.8	3
9/11/2021 18:00	234.0	215.1	239.5	229.5	7.4	12.8	3
9/11/2021 19:00	248.0	230.4	272.3	250.2	12.2	21.1	3
9/11/2021 20:00	260.9	231.3	291.4	261.2	17.3	30.1	3
9/11/2021 21:00	253.7	226.7	283.1	254.5	16.3	28.2	3
9/11/2021 22:00	263.0	228.9	284.3	258.7	16.1	27.9	3

4.12 mg/kg 3,4-diaminopyridine Treatment							
QT Interval (msec)							
Date	**SA180D**	**BF873I**	**AP55D**	**Mean**	**SE**	**SD**	**n**
9/11/2021 23:00	258.0	231.2	269.8	253.0	11.4	19.8	3
9/12/2021 0:00	272.9	232.8	282.7	262.8	15.3	26.5	3
9/12/2021 1:00	276.4	240.9	289.8	269.0	14.6	25.3	3
9/12/2021 2:00	271.8	242.6	288.3	267.6	13.4	23.1	3
9/12/2021 3:00	280.1	236.3	285.6	267.3	15.6	27.0	3
9/12/2021 4:00	270.4	239.4	277.4	262.4	11.7	20.3	3
9/12/2021 5:00	269.4	231.1	272.1	257.5	13.3	23.0	3
9/12/2021 6:00	264.1	228.9	265.7	252.9	12.0	20.8	3
9/12/2021 7:00	253.3	211.4	234.0	232.9	12.1	21.0	3
9/12/2021 8:00	237.4	212.8	219.6	223.2	7.3	12.7	3
9/12/2021 9:00	241.2	228.6	244.4	238.1	4.8	8.4	3
9/12/2021 10:00	247.2	233.0	232.0	237.4	4.9	8.5	3
9/12/2021 11:00	242.1	231.3	249.9	241.1	5.4	9.4	3
9/12/2021 12:00	254.3	227.2	273.6	251.7	13.5	23.3	3
9/12/2021 13:00	222.5	210.1	229.8	220.8	5.7	9.9	3
9/12/2021 14:00	242.8	224.0	236.5	234.4	5.5	9.5	3
9/12/2021 15:00	233.7	212.5	240.4	228.9	8.4	14.5	3
9/12/2021 16:00	231.7	213.7	235.3	226.9	6.7	11.6	3
9/12/2021 17:00	244.6	224.5	234.0	234.4	5.8	10.0	3
9/12/2021 18:00	257.9	224.4	220.7	234.4	11.8	20.5	3
9/12/2021 19:00	268.9	245.4	271.8	262.0	8.3	14.4	3
9/12/2021 20:00	274.7	243.9	285.7	268.1	12.5	21.7	3
9/12/2021 21:00	274.5	247.7	280.6	267.6	10.1	17.5	3
9/12/2021 22:00	268.8	250.5	291.2	270.2	11.8	20.4	3
9/12/2021 23:00	280.1	244.3	291.9	272.1	14.3	24.8	3
9/13/2021 0:00	278.8	243.8	288.9	270.5	13.7	23.7	3
9/13/2021 1:00	294.7	258.4	301.3	284.8	13.4	23.1	3
9/13/2021 2:00	298.2	260.2	287.5	282.0	11.3	19.6	3
9/13/2021 3:00	285.6	258.2	287.6	277.2	9.5	16.4	3
9/13/2021 4:00	289.4	255.2	285.7	276.8	10.8	18.8	3
9/13/2021 5:00	281.0	251.3	283.4	271.9	10.3	17.9	3
9/13/2021 6:00	264.9	240.7	281.1	262.2	11.8	20.4	3

4.12 mg/kg 3,4-diaminopyridine Treatment							
QT Interval (msec)							
Date	**SA180D**	**BF873I**	**AP55D**	**Mean**	**SE**	**SD**	**n**
9/13/2021 7:00	257.7	225.5	245.8	243.0	9.4	16.3	3
9/13/2021 8:00	209.5	217.7	218.6	215.2	2.9	5.0	3
9/13/2021 9:00	178.5	188.8	188.0	185.1	3.3	5.7	3
9/13/2021 10:00	203.5	209.2	214.7	209.1	3.2	5.6	3
9/13/2021 11:00	226.3	217.3	236.7	226.8	5.6	9.7	3
9/13/2021 12:00	237.0	215.3	240.5	231.0	7.9	13.7	3
9/13/2021 13:00	237.7	215.5	242.3	231.8	8.3	14.3	3
9/13/2021 14:00	218.9	208.3	210.9	212.7	3.2	5.5	3
9/13/2021 15:00	212.5	209.6	221.9	214.7	3.7	6.5	3
9/13/2021 16:00	214.0	216.4	234.2	221.5	6.3	11.0	3
9/13/2021 17:00	226.1	220.6	240.5	229.1	5.9	10.3	3
9/13/2021 18:00	224.8	221.6	234.0	226.8	3.7	6.5	3
9/13/2021 19:00	256.6	239.7	255.0	250.4	5.4	9.3	3
9/13/2021 20:00	282.5	252.7	300.4	278.5	13.9	24.1	3
9/13/2021 21:00	271.8	249.2	294.9	272.0	13.2	22.8	3
9/13/2021 22:00	278.8	247.8	283.7	270.1	11.2	19.5	3
9/13/2021 23:00	288.3	251.5	296.5	278.8	13.8	24.0	3
9/14/2021 0:00	281.9	241.2	296.9	273.3	16.6	28.8	3
9/14/2021 1:00	285.2	240.1	284.1	269.8	14.9	25.7	3
9/14/2021 2:00	274.2	246.7	286.7	269.2	11.8	20.5	3
9/14/2021 3:00	281.4	244.3	274.0	266.6	11.3	19.6	3
9/14/2021 4:00	275.3	247.6	278.0	267.0	9.7	16.8	3
9/14/2021 5:00	258.9	250.0	272.7	260.5	6.6	11.4	3
9/14/2021 6:00	254.8	239.1	262.2	252.0	6.8	11.8	3
9/14/2021 7:00	241.8	224.4	232.9	233.0	5.0	8.7	3
9/14/2021 8:00	229.6	220.4	226.4	225.5	2.7	4.6	3
9/14/2021 9:00	225.3	215.8	220.8	220.6	2.7	4.7	3
9/14/2021 10:00	235.7	221.0	238.7	231.8	5.5	9.5	3
9/14/2021 11:00	233.0	221.9	231.4	228.8	3.5	6.0	3
9/14/2021 12:00	235.1	224.4	258.9	239.5	10.2	17.7	3
9/14/2021 13:00	220.4	218.6	224.4	221.1	1.7	3.0	3
9/14/2021 14:00	231.2	218.9	230.2	226.8	3.9	6.8	3

4.12 mg/kg 3,4-diaminopyridine Treatment							
QT Interval (msec)							
Date	**SA180D**	**BF873I**	**AP55D**	**Mean**	**SE**	**SD**	**n**
9/14/2021 15:00	223.2	211.4	228.5	221.1	5.1	8.8	3
9/14/2021 16:00	231.1	213.3	223.7	222.7	5.2	8.9	3
9/14/2021 17:00	238.4	219.7	231.8	229.9	5.5	9.5	3
9/14/2021 18:00	242.9	223.9	234.4	233.7	5.5	9.5	3
9/14/2021 19:00	269.1	244.9	247.4	253.8	7.7	13.3	3
9/14/2021 20:00	264.6	244.8	219.1	242.8	13.2	22.8	3
9/14/2021 21:00	276.4	252.6	226.1	251.7	14.5	25.1	3
9/14/2021 22:00	255.9	224.9	198.2	226.3	16.7	28.9	3
9/14/2021 23:00	221.7	223.6	211.1	218.8	3.9	6.7	3
9/15/2021 0:00	260.2	246.4	241.5	249.4	5.6	9.7	3
9/15/2021 1:00	245.9	244.2	233.2	241.1	4.0	6.9	3
9/15/2021 2:00	257.1	242.5	218.4	239.3	11.3	19.5	3
9/15/2021 3:00	217.7	222.8	211.7	217.4	3.2	5.6	3
9/15/2021 4:00	242.7	239.9	223.8	235.5	5.9	10.2	3
9/15/2021 5:00	217.0	226.6	221.9	221.8	2.8	4.8	3
9/15/2021 6:00	224.3	231.1	215.4	223.6	4.5	7.9	3
9/15/2021 7:00	197.3	206.8	210.6	204.9	3.9	6.8	3
9/15/2021 8:00	203.4	207.7	215.2	208.8	3.4	5.9	3
9/15/2021 9:00	207.1	222.4	221.0	216.8	4.9	8.5	3
9/15/2021 10:00	209.3	205.9	211.5	208.9	1.6	2.8	3
9/15/2021 11:00	181.5	199.0	215.1	198.5	9.7	16.8	3
9/15/2021 12:00	219.9	203.5	218.5	213.9	5.3	9.1	3
9/15/2021 13:00	223.8	203.1	226.2	217.7	7.3	12.7	3
9/15/2021 14:00	210.4	208.8	217.1	212.1	2.5	4.4	3
9/15/2021 15:00	194.4	199.4	NaN	196.9	2.5	3.5	2
9/15/2021 16:00	217.7	190.5	NaN	204.1	13.6	19.2	2
9/15/2021 17:00	212.8	204.3	NaN	208.6	4.2	6.0	2
9/15/2021 18:00	203.7	216.5	NaN	210.1	6.4	9.1	2
9/15/2021 19:00	188.2	220.4	NaN	204.3	16.1	22.8	2
9/15/2021 20:00	208.8	206.8	NaN	207.8	1.0	1.4	2
9/15/2021 21:00	214.2	225.0	NaN	219.6	5.4	7.6	2
9/15/2021 22:00	198.3	230.8	NaN	214.5	16.2	22.9	2

4.12 mg/kg 3,4-diaminopyridine Treatment							
QT Interval (msec)							
Date	**SA180D**	**BF873I**	**AP55D**	**Mean**	**SE**	**SD**	**n**
9/15/2021 23:00	206.9	222.1	NaN	214.5	7.6	10.8	2
9/16/2021 0:00	218.3	217.7	NaN	218.0	0.3	0.4	2
9/16/2021 1:00	204.2	221.3	NaN	212.8	8.5	12.1	2
9/16/2021 2:00	203.6	231.7	NaN	217.7	14.1	19.9	2
9/16/2021 3:00	224.4	239.3	NaN	231.9	7.4	10.5	2
9/16/2021 4:00	219.4	235.9	NaN	227.7	8.3	11.7	2
9/16/2021 5:00	208.2	234.7	NaN	221.4	13.3	18.8	2
9/16/2021 6:00	210.0	251.5	NaN	230.8	20.8	29.4	2
9/16/2021 7:00	234.3	225.0	NaN	229.6	4.6	6.6	2
9/16/2021 8:00	220.0	222.2	NaN	221.1	1.1	1.5	2
9/16/2021 9:00	213.9	225.5	NaN	219.7	5.8	8.2	2
9/16/2021 10:00	NaN	230.3	NaN	230.3	0.0	0.0	1
9/16/2021 11:00	NaN	228.8	NaN	228.8	0.0	0.0	1

Table 39: RR Interval (msec) 4.12 mg/kg 3,4-diaminopyridine Treatment

4.12 mg/kg 3,4-diaminopyridine Treatment							
RR Interval (msec)							
Date	SA180D	BF873I	AP55D	Mean	SE	SD	n
9/10/2021 16:00	502.2	360.7	383.6	415.5	43.8	75.9	3
9/10/2021 17:00	553.2	418.3	407.1	459.5	47.0	81.3	3
9/10/2021 18:00	617.7	402.9	425.8	482.1	68.1	118.0	3
9/10/2021 19:00	587.8	476.0	501.1	521.6	33.9	58.7	3
9/10/2021 20:00	646.4	509.7	523.3	559.8	43.5	75.3	3
9/10/2021 21:00	628.9	529.5	483.0	547.1	43.1	74.6	3
9/10/2021 22:00	638.4	479.1	478.7	532.1	53.2	92.1	3
9/10/2021 23:00	618.7	484.4	466.1	523.1	48.1	83.3	3
9/11/2021 0:00	641.7	476.1	448.7	522.2	60.3	104.4	3
9/11/2021 1:00	599.2	451.2	456.2	502.2	48.5	84.0	3
9/11/2021 2:00	618.7	412.8	466.0	499.1	61.7	106.9	3
9/11/2021 3:00	594.6	430.0	465.1	496.6	50.0	86.7	3
9/11/2021 4:00	596.1	418.6	479.0	497.9	52.1	90.2	3
9/11/2021 5:00	599.7	411.2	482.5	497.8	54.9	95.2	3
9/11/2021 6:00	546.0	411.9	468.7	475.5	38.8	67.3	3
9/11/2021 7:00	518.1	388.2	392.9	433.1	42.5	73.6	3
9/11/2021 8:00	484.9	398.3	371.1	418.1	34.3	59.4	3
9/11/2021 9:00	529.3	409.0	392.0	443.4	43.2	74.9	3
9/11/2021 10:00	614.7	424.3	417.2	485.4	64.7	112.0	3
9/11/2021 11:00	535.5	370.7	519.4	475.2	52.4	90.8	3
9/11/2021 12:00	575.0	395.5	438.2	469.6	54.1	93.8	3
9/11/2021 13:00	516.7	365.4	410.4	430.8	44.8	77.7	3
9/11/2021 14:00	573.4	380.6	419.9	458.0	58.8	101.9	3
9/11/2021 15:00	540.9	416.7	439.8	465.8	38.1	66.1	3
9/11/2021 16:00	563.3	372.7	443.8	459.9	55.6	96.3	3
9/11/2021 17:00	532.9	385.9	383.5	434.1	49.4	85.6	3
9/11/2021 18:00	543.2	375.8	415.4	444.8	50.5	87.5	3
9/11/2021 19:00	532.1	398.5	477.2	469.3	38.8	67.1	3
9/11/2021 20:00	583.4	401.1	519.3	501.3	53.4	92.5	3
9/11/2021 21:00	551.0	389.3	507.2	482.5	48.3	83.6	3
9/11/2021 22:00	575.7	402.8	519.5	499.3	50.9	88.2	3

4.12 mg/kg 3,4-diaminopyridine Treatment							
RR Interval (msec)							
Date	SA180D	BF873I	AP55D	Mean	SE	SD	n
9/11/2021 23:00	560.5	412.1	492.8	488.5	42.9	74.3	3
9/12/2021 0:00	621.5	414.9	530.7	522.3	59.8	103.6	3
9/12/2021 1:00	634.6	434.5	534.6	534.5	57.8	100.0	3
9/12/2021 2:00	612.6	432.1	529.6	524.8	52.1	90.3	3
9/12/2021 3:00	642.7	421.2	516.6	526.8	64.1	111.1	3
9/12/2021 4:00	610.6	426.7	494.6	510.6	53.7	93.0	3
9/12/2021 5:00	608.5	414.0	480.0	500.8	57.1	98.9	3
9/12/2021 6:00	577.6	407.6	466.6	483.9	49.8	86.3	3
9/12/2021 7:00	554.2	359.6	399.1	437.6	59.4	102.9	3
9/12/2021 8:00	527.2	367.6	376.2	423.7	51.8	89.8	3
9/12/2021 9:00	547.8	402.0	431.0	460.3	44.6	77.2	3
9/12/2021 10:00	574.3	417.0	405.2	465.5	54.5	94.4	3
9/12/2021 11:00	559.0	410.3	459.6	476.3	43.7	75.7	3
9/12/2021 12:00	596.3	401.1	514.0	503.8	56.6	98.0	3
9/12/2021 13:00	483.2	354.9	402.4	413.5	37.5	64.9	3
9/12/2021 14:00	567.3	406.3	405.0	459.5	53.9	93.4	3
9/12/2021 15:00	536.6	367.5	421.5	441.8	49.9	86.4	3
9/12/2021 16:00	526.4	372.0	410.6	436.3	46.4	80.3	3
9/12/2021 17:00	581.8	403.5	410.3	465.2	58.3	101.1	3
9/12/2021 18:00	614.5	402.2	377.5	464.7	75.2	130.3	3
9/12/2021 19:00	582.8	439.5	509.6	510.6	41.4	71.6	3
9/12/2021 20:00	607.6	432.2	531.3	523.7	50.8	88.0	3
9/12/2021 21:00	593.7	463.2	532.4	529.8	37.7	65.3	3
9/12/2021 22:00	598.1	447.5	542.0	529.2	44.0	76.1	3
9/12/2021 23:00	624.1	431.6	540.7	532.1	55.7	96.6	3
9/13/2021 0:00	624.0	439.9	540.8	534.9	53.2	92.2	3
9/13/2021 1:00	680.8	472.8	569.7	574.4	60.1	104.1	3
9/13/2021 2:00	693.4	485.6	523.1	567.4	64.0	110.8	3
9/13/2021 3:00	648.4	481.2	523.1	550.9	50.3	87.0	3
9/13/2021 4:00	653.0	471.9	526.3	550.4	53.7	92.9	3
9/13/2021 5:00	630.1	461.6	522.2	538.0	49.3	85.4	3
9/13/2021 6:00	560.8	435.5	510.9	502.4	36.4	63.1	3

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4.12 mg/kg 3,4-diaminopyridine Treatment							
RR Interval (msec)							
Date	**SA180D**	**BF873I**	**AP55D**	**Mean**	**SE**	**SD**	**n**
9/13/2021 7:00	561.1	393.0	425.5	459.9	51.5	89.1	3
9/13/2021 8:00	392.9	340.5	352.8	362.1	15.8	27.4	3
9/13/2021 9:00	319.3	293.7	304.7	305.9	7.4	12.8	3
9/13/2021 10:00	414.0	357.2	367.0	379.4	17.5	30.4	3
9/13/2021 11:00	492.8	383.2	416.9	431.0	32.4	56.1	3
9/13/2021 12:00	529.8	380.8	431.4	447.3	43.7	75.7	3
9/13/2021 13:00	539.1	380.0	450.0	456.3	46.0	79.7	3
9/13/2021 14:00	481.2	353.2	364.2	399.5	41.0	71.0	3
9/13/2021 15:00	458.6	350.9	381.6	397.0	32.0	55.5	3
9/13/2021 16:00	458.2	378.1	408.7	415.0	23.3	40.4	3
9/13/2021 17:00	506.0	390.5	443.6	446.7	33.4	57.8	3
9/13/2021 18:00	495.2	403.1	418.3	438.9	28.5	49.4	3
9/13/2021 19:00	555.2	425.0	466.1	482.1	38.4	66.5	3
9/13/2021 20:00	628.2	472.6	564.6	555.1	45.1	78.2	3
9/13/2021 21:00	592.4	463.6	547.7	534.6	37.8	65.4	3
9/13/2021 22:00	626.7	460.4	529.8	539.0	48.2	83.5	3
9/13/2021 23:00	643.3	468.0	553.0	554.8	50.6	87.6	3
9/14/2021 0:00	616.3	436.7	549.5	534.2	52.4	90.8	3
9/14/2021 1:00	639.2	434.1	505.7	526.3	60.1	104.1	3
9/14/2021 2:00	596.8	453.0	517.1	522.3	41.6	72.1	3
9/14/2021 3:00	639.2	447.1	490.6	525.6	58.2	100.7	3
9/14/2021 4:00	628.3	460.3	499.7	529.4	50.7	87.9	3
9/14/2021 5:00	580.1	470.1	489.9	513.4	33.8	58.6	3
9/14/2021 6:00	549.8	434.8	452.9	479.2	35.7	61.8	3
9/14/2021 7:00	511.9	397.7	393.4	434.3	38.8	67.2	3
9/14/2021 8:00	470.9	374.9	387.2	411.0	30.2	52.3	3
9/14/2021 9:00	477.1	373.4	374.1	408.2	34.4	59.6	3
9/14/2021 10:00	518.0	387.6	422.5	442.7	39.0	67.5	3
9/14/2021 11:00	508.9	387.4	410.4	435.6	37.3	64.6	3
9/14/2021 12:00	525.9	394.1	485.3	468.5	39.0	67.5	3
9/14/2021 13:00	474.0	369.1	384.5	409.2	32.7	56.7	3
9/14/2021 14:00	531.3	372.2	408.6	437.4	48.2	83.4	3

4.12 mg/kg 3,4-diaminopyridine Treatment							
RR Interval (msec)							
Date	SA180D	BF873I	AP55D	Mean	SE	SD	n
9/14/2021 15:00	502.1	381.3	404.3	429.3	37.0	64.1	3
9/14/2021 16:00	526.1	390.3	397.8	438.1	44.1	76.3	3
9/14/2021 17:00	553.8	400.2	419.3	457.7	48.3	83.7	3
9/14/2021 18:00	568.2	411.4	416.3	465.3	51.5	89.2	3
9/14/2021 19:00	608.3	452.7	439.4	500.1	54.2	93.9	3
9/14/2021 20:00	619.2	456.1	372.5	482.6	72.4	125.5	3
9/14/2021 21:00	642.3	470.9	388.8	500.7	74.7	129.3	3
9/14/2021 22:00	541.6	396.8	320.8	419.7	64.8	112.2	3
9/14/2021 23:00	454.6	399.0	357.0	403.5	28.3	49.0	3
9/15/2021 0:00	582.9	453.5	399.2	478.5	54.5	94.4	3
9/15/2021 1:00	543.3	447.3	378.8	456.5	47.7	82.6	3
9/15/2021 2:00	546.3	442.5	346.9	445.2	57.6	99.7	3
9/15/2021 3:00	421.5	391.1	340.0	384.2	23.8	41.2	3
9/15/2021 4:00	517.1	434.7	353.6	435.1	47.2	81.8	3
9/15/2021 5:00	446.2	398.2	353.7	399.4	26.7	46.3	3
9/15/2021 6:00	454.9	408.8	341.3	401.7	33.0	57.1	3
9/15/2021 7:00	365.4	342.6	336.3	348.1	8.9	15.3	3
9/15/2021 8:00	388.4	339.4	336.6	354.8	16.8	29.1	3
9/15/2021 9:00	409.3	371.6	348.7	376.5	17.7	30.6	3
9/15/2021 10:00	405.2	326.8	334.9	355.6	24.9	43.1	3
9/15/2021 11:00	324.2	314.6	318.1	318.9	2.8	4.9	3
9/15/2021 12:00	423.3	322.7	324.5	356.8	33.2	57.6	3
9/15/2021 13:00	422.3	321.7	311.9	351.9	35.3	61.1	3
9/15/2021 14:00	393.1	328.0	299.6	340.3	27.7	48.0	3
9/15/2021 15:00	340.1	315.0	NaN	327.6	12.5	17.7	2
9/15/2021 16:00	406.1	306.7	NaN	356.4	49.7	70.3	2
9/15/2021 17:00	400.2	317.7	NaN	358.9	41.2	58.3	2
9/15/2021 18:00	357.7	334.2	NaN	345.9	11.8	16.6	2
9/15/2021 19:00	321.8	343.0	NaN	332.4	10.6	15.0	2
9/15/2021 20:00	387.9	317.4	NaN	352.6	35.2	49.8	2
9/15/2021 21:00	403.9	359.3	NaN	381.6	22.3	31.6	2
9/15/2021 22:00	352.8	363.3	NaN	358.1	5.2	7.4	2

4.12 mg/kg 3,4-diaminopyridine Treatment							
RR Interval (msec)							
Date	**SA180D**	**BF873I**	**AP55D**	**Mean**	**SE**	**SD**	**n**
9/15/2021 23:00	385.9	342.4	NaN	364.1	21.8	30.8	2
9/16/2021 0:00	419.0	336.1	NaN	377.6	41.5	58.6	2
9/16/2021 1:00	379.4	343.1	NaN	361.3	18.2	25.7	2
9/16/2021 2:00	363.0	367.6	NaN	365.3	2.3	3.3	2
9/16/2021 3:00	440.9	389.9	NaN	415.4	25.5	36.1	2
9/16/2021 4:00	426.4	383.6	NaN	405.0	21.4	30.3	2
9/16/2021 5:00	382.0	375.1	NaN	378.6	3.5	4.9	2
9/16/2021 6:00	381.5	425.7	NaN	403.6	22.1	31.3	2
9/16/2021 7:00	439.3	349.4	NaN	394.3	45.0	63.6	2
9/16/2021 8:00	405.1	347.4	NaN	376.3	28.8	40.8	2
9/16/2021 9:00	384.1	350.6	NaN	367.4	16.8	23.7	2
9/16/2021 10:00	NaN	361.9	NaN	361.9	0.0	0.0	1
9/16/2021 11:00	NaN	362.9	NaN	362.9	0.0	0.0	1

31.1 Arrhythmia Summary

Table 40: Incidences of Arrhythmia

Treatment	Subject ID	File[1] (period)	PAC	VPC	Junctional Escape Beat	2nd Deg AV Block	Intermittent Supraventricular Tachycardia	Ventricular Tachycardia	Other	Terminal ECG Pattern
1	G180JD	1 (BL)				x				n/a
		2 (BL)			x	x				n/a
		3 (BL & C)			x	x				n/a
		4 (PC)			x	x				n/a
		6 (PC)	Many	Many						Sino-atrial arrest/junctional escape complexes/bundle branch block
	N378ALE	1 (BL)				x				n/a
		2 (BL)				x				n/a
		3 (BL & C)			x	x				n/a
		4 (PC)			x	x				n/a
		6 (PC)	x							n/a
		7 (PC)		Many					Multiple VPCs	VPCs/second degree AV block
2	AL793H	1 (BL)	x	x						n/a
		2 (BL)		x						n/a
		3 (BL & C)		x	x	x				n/a
		5 (PC)		x						n/a
		6 (PC)		Many					VPC triplet, Multiple VPCs	Second degree AV block/bundle branch block/ VPCs
	VL90IA	1 (BL)	x							n/a
		2 (BL)	x	x	x					n/a

Treatment	Subject ID	File[1] (period)	PAC	VPC	Junctional Escape Beat	2nd Deg AV Block	Intermittent Supraventricular Tachycardia	Ventricular Tachycardia	Other	Terminal ECG Pattern
		3 (BL & C)	x	x						n/a
		4 (PC)	x	x	x					n/a
		5 (PC)		x	x					n/a
		6 (PC)	x	x	x					ST segment depression/ bundle branch block with intermittent ventricular rhythm
	YR895FD	1 (BL)			x					n/a
		3 (BL & C)			x					n/a
		4 (PC)			x					n/a
		5 (PC)		Many	x				Multiple VPCs	n/a
		6 (PC)	Many	Many				Many		VPCs and a bundle branch block pattern
3	AP55D	1 (BL)	Many			x				n/a
		2 (BL)	Many				x			n/a
		3 (BL & C)	x	x						n/a
		4 (PC)	Many		x	x	Many			n/a
		5 (PC)		Many	x	x		x	Multiple VPCs, VPC couplet	n/a
		6 (PC)		Many	Many	Many			Multiple VPCs	Sino atrial arrest-junctional escape complexes/ST segment elevation and depression
	BF873I	1 (BL)			x	x				n/a
		2 (BL)			x	x				n/a
		3 (BL & C)		x						n/a
		4 (PC)			x	x				n/a

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Treatment	Subject ID	File[1] (period)	PAC	VPC	Junctional Escape Beat	2nd Deg AV Block	Intermittent Supraventricular Tachycardia	Ventricular Tachycardia	Other	Terminal ECG Pattern
		5 (PC)		Many					Multiple VPCs	n/a
		6 (PC)		Many	x	x				n/a
		7 (PC)		Many					Multiple VPCs	Junctional and ventricular escape complexes
	SA180D	2 (BL)		x					VPC Triplet	n/a
		6 (PC)	x	Many					VPC couplet, Multiple VPCs	n/a
		7 (PC)		x						VPCs/ventricular escape complexes

Multiple VPCs= couplets, triplets, bigeminy, etc., ventricular tachycardia occurring in 10-5 mins

Many= Many occurrences of arrhythmia throughout dataset

[1]File 1 started on 9/10/2021 at 14:14 hrs for 24 hours, and each subsequent File started at 14:00 hrs and each calendar data such that file 3 started on 9/12/2021 and so far.
BL=Baseline, C=Challenge, PC=Post Challenge