Pharmacokinetic Analysis of 3,4-Diaminopyridine in the Cynomolgus Monkey

Final Report

On

March 30, 2022

For

Study Number B05928

To

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

by

STUDY DIRECTOR/PRINCIPAL INVESTIGATOR:
Phillip H. Beske, PhD, DABT

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TESTING FACILITY:
AmplifyBio
1425 State Route 142 (Plain City-Georgesville Road)
West Jefferson, OH 43162

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Distribution approved for public release; distribution is unlimited

BATTELLE

SIGNATURES

Phillip H. Beske, PhD, DABT
Study Director

30 March 2022
Date

for Kemla Siddoway, BS
Manager, High Hazard Containment–Chemistry

30 MAR 2022
Date

GLP COMPLIANCE STATEMENT

This study was conducted at AmplifyBio (formerly Battelle – West Jefferson) and 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 pharmacokinetics of 3,4-diaminopyridine free base (3,4-DAP) in the cynomolgus monkey following single or repeat administration of 3,4-diaminopyridine phosphate (3,4-DAPP) via intravenous (IV), subcutaneous (SC), and oral (PO) routes. To accomplish this, male cynomolgus monkeys (of Mauritius origin) were surgically implanted with vascular access ports (VAPs) for ease of repeated blood collection. Animals were then dosed at the 1.03, 2.06, and 4.12 mg/kg of 3,4-diaminopyridine phosphate (amifampridine phosphate drug substance; 3,4-DAPP) for each dose route investigated. Dosing was performed as either a single administration or a repeat administration with a second dose administered approximately 4 hours after the first dose. Baseline blood samples were collected prior to animals receiving their first or second dose (as applicable). Post-administration blood samples collected from animals at 5, 15, 30, and 60 minutes and 2, 4, and 6 hours after receiving their first or second dose (as applicable). Animals were allowed a washout period of at least 3 days between escalating to the next dose levels for a given route, with an additional washout period of at least 2 weeks before proceeding to the next dosing route. Collected blood samples were processed to plasma and submitted for analysis of 3,4-diaminopyridine (free base, aka 3,4-DAP) concentrations, as the phosphate salt form of the test article is known to rapidly dissociate when formulated in solution. Samples were analyzed using developed methods for high performance liquid chromatography tandem mass spectrometry (LC-MS/MS). The concentrations of 3,4-DAP in collected samples were then submitted for pharmacokinetic evaluation. Endpoints used to evaluate potential toxicity were survival and clinical observations.

Dosing of cynomolgus monkeys with 3,4-DAPP was found to be generally well-tolerated, with the exception of abnormal emetic observations in some, but not all, animals dosed IV and SC at the highest 3,4-DAPP dose level tested (4.12 mg/kg). The abnormal emetic observations were transient and were found to resolve shortly after occurrence. Transient emesis was considered to be test article-related as manifestation was found to occur in timeframes shortly after dose administration.

Other abnormal observations occurring on study were considered related to VAP surgery, VAP erosion and surgical repair, VAP infection and/or subsequent antibiotic treatments. These observations included discolored skin, limb weakness, skin abrasions, low food consumption, diarrhea, and soft feces. These observations were not attributed to test article administration as they did not directly manifest in response to dosing activities.

When comparing the three routes of test article administration investigated in this study (IV, SC, and PO), animals dosed through the IV and SC route had similar pharmacokinetic parameters for 3,4-DAP. Accumulation between repeat dosing was not observed as C_{max} values following the first and second dosing were generally similar. Similar systemic exposure parameters between IV and SC groups suggest approximately 100% bioavailability following SC administration. However, there was a marked difference following PO administration where all systemic exposure parameters were less than 10% that of the IV groups, thereby showing poor bioavailability following PO administration.

Collectively, given the well-characterized pharmacokinetic profiles achieved following 3,4-DAPP administration, the study objective was considered to be successfully met.

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1 INTRODUCTION

The purpose of this study was to evaluate the pharmacokinetics of 3,4-diaminopyridine (free base form abbreviated as 3,4-DAP) in the plasma of cynomolgus monkey following intravenous, subcutaneous, and oral routes of administration with 3,4-diaminopyridine phosphate (phosphate form abbreviated as 3,4-DAPP).

This study was conducted at Battelle – West Jefferson (currently AmplifyBio) under the direction of Phillip H. Beske, PhD, DABT. The study was initiated on December 9, 2020, with the signing of the protocol. The in-life portion of the study began on March 1, 2021, with initiation of dose administration. The last day of dose administration was April 19, 2021.

Does administration for 3,4-DAPP was performed across a total of nine (9) independent dosing days, with dosing performed at the 1.03, 2.06, and 4.12 mg/kg dose level for each dose route investigated (intravenous, subcutaneous, and oral). Dosing was performed as either a single administration or a repeat administration with a second dose administered approximately 4 hours later. Blood was collected for the analysis of 3,4-DAP concentration in plasma using developed methods for high performance liquid chromatography tandem mass spectrometry (LC-MS/MS). The Battelle Biomedical Research Center (BBRC) was designated as the test site for analysis of collected plasma samples. The concentrations of 3,4-DAP in collected samples was submitted for pharmacokinetic evaluation. Endpoints used to evaluate potential toxicity were survival and clinical observations.

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

The study protocol, protocol amendments, and a summary of deviations from the protocol are presented in Appendix A.

2 MATERIALS AND METHODS

2.1 TEST ARTICLE AND VEHICLE

2.1.1 Test Article

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

Product Name:	Amifampridine Phosphate Drug Substance (synonym 3,4-DAPP)
Batch/Lot Number:	P528FPM-19-002
Purity:	99.2%
Storage Conditions:	Powder stored at controlled room temperature until 2 mg/mL formulation in saline (for IV and SC dosing) or water (for PO dosing), then 2 to 8°C for up to 6 hours before administration
Retest Date:	Dec 2022

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

2.1.2 Vehicle

The vehicle for intravenous and subcutaneous dosing solutions was identified as follows:

Name:	0.9% Sodium Chloride for Injection
Batch/Lot Number:	22-507-FW
Expiry Date:	October 10, 2022
Storage Conditions:	Controlled room temperature
Supplier:	ICU Medical

The vehicle for oral dosing solutions was identified as follows:

Name:	Sterile Water for Injection, USP
Batch/Lot Number:	91-264-DK
Expiry Date:	July 1, 2021
Storage Conditions:	Controlled room temperature
Supplier:	Hospira

Certificates of Analysis and stability/expiration information for the vehicles are included in Appendix B.

2.2 Test Article Preparation

Dose formulations were prepared fresh on each day of use, maintained at 2 to 8°C when not in use, and visually inspected prior to administration. For intravenous and subcutaneous dosing, 3,4-DAPP was prepared at a concentration of 2 mg/mL in 0.9% sodium chloride. For oral dosing, 3,4-DAPP was prepared in sterile water at a concentration of 2 mg/mL.

Details of formulation preparation are included in Appendix B.

2.3 Formulation Analysis

Pre-test formulation analysis of the dosing solution preparation consisted of a visual inspection and pH measurement. 3,4-DAPP at a concentration of 2 mg/mL dissolved almost immediately in sodium chloride, produced a clear colorless liquid, and had a measured pH of 4.66. 3,4-DAPP at a concentration of 2 mg/mL similarly dissolved almost immediately in deionized water, produced a clear colorless liquid, and had a measured pH of 5.00. Pre-test analysis was performed once prior to dosing activities but was not performed each day on the dosing solutions that were used on study.

2.4 Reserve Samples

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

2.5 DISPOSITION OF TEST ARTICLE

Unused bulk test article was transferred to the Battelle Biomedical Research Center (BBRC) for use on future studies.

2.6 EXPERIMENTAL ANIMALS

A total of nine male cynomolgus monkeys were received on December 10, 2020, from PreLabs (Lehigh Acres, FL). Animals were quarantined for 37 days and acclimated to the laboratory environment prior to initiation of dosing. Fecal exams, tuberculous testing, physical exams, and clinical pathology health screens (hematology and serum chemistry only) were performed in order to ensure only healthy NHPs were dosed. One animal (AR7K) succumbed following VAP surgery prior to placement on in-life study. Animal AR7K was not replaced, and eight total animals were ultimately used on study.

The animals were conditioned to a restraint chair prior to the start of dosing. The animals were progressively acclimated for 3 events to accept up to 30 consecutive minutes of chair restraint.

Male animals were approximately 2 to 3 years of age at group assignment with body weights ranging from 3.5 to 4.2 kg. At the conclusion of in-life dosing activities, animals were held for observations, room care, and veterinary care (as needed) before transfer to Battelle Study B05929 on June 24, 2021.

2.6.1 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 quarantine and prior to VAP surgery. Following VAP surgery, animals were single housed for approximately 3 to 5 days for recovery. During periods of dosing activities for each administration route, animals were single housed. 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. Room temperature and relative humidity controls were set to maintain ranges of 64 to 84°F and 30 to 70%, respectively. Actual room temperature and relative humidity ranges during the study were 72 to 75°F and 22 to 72%, respectively. A total of three excursions outside of the specified target humidity range occurred on 2 days, which were promptly corrected.

2.6.2 Feed and Water

Animals were offered certified feed (LabDiet 5048) twice daily, except when removed from the home cage or during periods of scheduled fasting. 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.

2.6.3 Environmental Enrichment

Animals were provided fresh fruits or fresh vegetables and/or other enrichment items to promote and enhance psychological well-being.

2.6.4 Animal Identification and Group Assignment

During the quarantine/acclimation period, animals were identified by the supplier's tattoo designation. Animals were assigned to dose groups using a stratified randomization program (Provantis) designed to maintain similar group mean body weights. After assignment to groups, each animal was identified by cage card that included species/strain, tattoo number, study number, and gender. Additional identification was performed after randomization through assignment of the unique cage identification numbers.

Table 1. Animal Identification and Group Assignment

Group 1		Group 2	
Animal ID	**Cage ID**	**Animal ID**	**Cage ID**
VL90IA	101	BF8731	201
YR895FD	102	G180JD	202
AL793H	103	N378ALE	203
AL110O	104	AP55D	204

2.6.5 Animal Surgery

Animals were implanted with two vascular access ports (VAPs), with one catheter implanted in femoral vein and one catheter implanted in the femoral artery (see DR-B05928-WJ-0004). Surgeries were performed on beginning on January 13, 2021 and were completed on February 16, 2021. Briefly, an incision was made over the target vessels. The vessels were dissected, punctured, and an indwelling catheter was inserted into the lumen of each vessel. The catheters were then sutured in place. An incision was made on the posterior surface of the animal. A trocar was passed from the incision site overlying the vessels to the incision site on the dorsal surface. The free ends of the catheters were fed to the incision on the animal's posterior surface. The free ends were connected to ports which were sutured to the muscle on the animal's posterior surface. Both incision sites were then sutured closed.

Anesthetics, analgesics, and antibiotics used pre-operatively, operatively, and post-operatively are listed below. All dosage and treatment regimens were performed according to veterinarian discretion and are detailed in the study file on treatment sheets and/or equipment lists.

Pre-operative: ketamine, isoflurane, buprenorphine, lidocaine, enrofloxacin, carprofen

Operative: isoflurane

Post-operative: buprenorphine (2 days), carprofen (4 days), enrofloxacin (2 days) then a switch to oral antibiotics for 4 days (Clavamox)

Following surgery, VAPs were maintained as directed by the study veterinarian.

2.6.6 Post-Surgical Animal Health

Following VAP surgery, some animals displayed varying health concerns requiring veterinary-guided treatment regimens to restore animal health. A summary of post-surgical health concerns and treatments for each animal is provided below. Complete records of veterinary care are maintained in the study file. All animals used for each dosing day were deemed to be fit for use on study by a veterinarian.

Table 2. Summary of Animal Health Complications

Animal ID	VAP Surgical Date	Health Concern	Date Identified	Treatment Strategy
AL110O	1/13/2021	Limb weakness and decreased use in catheterized leg	1/19/2021	Physical therapy
		Thermal burns (inner bicep)	1/19/2021	Collasate dressing and lidocaine ointment
		Animal removed and severed placed catheter-in-catheter lines	3/3/21	Surgical repair
		VAP erosion	3/21/2021	Surgical relocation, Betadine flush, carprofen, enrofloxacin, buprenorphine, Clavamox
		VAP erosion	4/8/2021	Carprofen, Clavamox, buprenorphine, withheld from dosing activities on 4/12/2021 and 4/15/2021 for additional recovery
		Lethargic, decreased appetite, elevated body temperature	4/16/2021	Bloodwork analysis, carprofen, intravenous fluids, food enrichment, antibiotic cessation. VAP removal after study completion.
N378ALE	1/14/2021	Arterial VAP placement (catheter not able to be fully inserted into artery)	1/14/2021	Arterial VAP not placed
		Thermal burns (inner bicep)	1/19/2021	Collasate dressing and lidocaine ointment
		Migration of venous port (inability to place catheter-in-catheter line)	2/8/2021	Incision and port repositioning with antibiotics and pain medication
		VAP erosion	3/29/2021	Surgical relocation, enrofloxacin, buprenorphine, carprofen, Clavamox
		VAP erosion	4/19/2021*	Surgical removal of VAP

Animal ID	VAP Surgical Date	Health Concern	Date Identified	Treatment Strategy
AR7K	2/9/2021	Blood and swelling at incision site.	2/9/2021	Sedation and examination.
		Respiratory collapse following intubation tube blockage during anesthetized surgical exploration.	2/9/2021	Ventilatory support and epinephrine. Animal succumbed.
BF873I	2/8/2021	Limb weakness and decreased use in catheterized leg	2/15/2021	Physical therapy
		Port infection	3/3/2021	Oral antibiotics
		Port infection	4/19/2021*	Oral antibiotics; Surgical removal of VAPs
VL90IA	2/15/2021	Lethargy, decreased appetite, slight anemia	2/16/2021	Intravenous fluids with dextrose, bloodwork analysis, iron-dense food enrichment
YR895FD	2/16/2021	Limb weakness and decreased use in catheterized leg	2/19/2021	Physical therapy
		Abraded skin at right hip	2/28/2021	Collasate dressing
		Infection/swelling at abraded skin site.	3/21/2021	Enrofloxacin, Clavamox
		Open wound at abrasion site on hip.	4/13/2021	Suture, glue, carprofen, Clavamox
		Port erosion and infection	4/19/2021*	Surgical removal of VAPs
AL793H	2/12/2021	Port erosion	4/19/2021*	Surgical removal of VAPs

* denotes date after the completion of in-life dosing activities

3 EXPERIMENTAL DESIGN

Eight male cynomolgus monkeys were assigned to dose groups as presented in the table below.

Table 3. Experimental Design

Dose Day*	Group	Route	3,4-DAPP Dose (mg/kg)	Dose Frequency	Blood Collection Time (minutes)	No. of Animals Dosed
IV^1	1	IV	1.03	Single	**Single**: Baseline, 5 (±30 sec), 15 (±1 min), 30 (±1 min), 60 (±2 min), 120 (±5 min), 240 (±5 min), 360 (±5 min)	4
	2			Repeat		4
IV^2	2		2.06	Single		4
	1			Repeat		4
IV^3	1		4.12	Single		4
	2			Repeat		4
SC^1	2	SC	1.03	Single		4
	1			Repeat		4
SC^2	1		2.06	Single	**Repeat (time after 2nd treatment)**: Baseline, 5 (±30 sec), 15 (±1 min), 30 (±1 min), 60 (±2 min), 120 (±5 min), 240 (±5 min), 360 (±5 min)	4
	2			Repeat		4
SC^3	2		4.12	Single		4
	1			Repeat		4
PO^1	1	PO	1.03	Single		4
	2			Repeat		4
PO^2	2		2.06	Single		4
	1			Repeat		4
PO^3	1		4.12	Single		4
	2			Repeat		4

* IV^1 denotes "intravenous dose day #1"; IV^2 denotes "intravenous dose day #2"; etc.

3.1 DOSE ADMINISTRATION

The study was conducted over a total of 9 dose days, 3 days for each route (IV, SC, and PO). The first day of dosing was defined as Study Day 1. The 3,4-DAPP doses tested for each dose route were 1.03 mg/kg (low), 2.06 mg/kg (mid), and 4.12 mg/kg (high).

Animals were chair restrained for all dosing procedures. 3,4-DAPP was administered as a single or repeat bolus treatment. The time between bolus treatments for animals receiving repeat administrations was approximately 4 hours. Intravenous dosing of 3,4-DAPP was performed into the saphenous vein (contralateral from the catheterized limb used for blood sampling). Subcutaneous dosing of 3,4-DAPP was performed at the hip (contralateral from the catheterized limb used for blood sampling). PO dosing of 3,4-DAPP was performed through oral gavage. All dosing was performed using a 2 mg/mL 3,4-DAPP dosing solution. The range of 3,4-DAPP dosing volumes employed for each dosing day are presented below Table 4.

Table 4. Dosing Volumes

Dose Route	Study Day	Date	3,4-DAPP Dose (mg/kg)	Dose Volume Range (mL)
IV	1	March 1, 2021	1.03	1.80 – 2.16
	4	March 4, 2021	2.06	3.61 – 4.33
	8	March 8, 2021	4.12	7.21 – 8.65
SC	22	March 22, 2021	1.03	1.79 – 2.16
	25	March 25, 2021	2.06	3.58 – 4.33
	29	March 29, 2021	4.12	7.17 – 8.65
PO	43	April 12, 2021	1.03	1.74 – 2.22
	46	April 15, 2021	2.06	3.48 – 4.45
	50	April 19, 2021	4.12	6.96 – 8.90

At each dosing day, all animals deemed fit for study by a veterinarian were dosed. For each dose day, eight total animals were dosed (4 single and 4 repeat), except on the first and second PO dose day (April 12, 2021 and April 15, 2021, respectively) where a single animal was excluded from dosing activities as that animal was not deemed fit for study at that time (Animal AL110O). Doses progressed from low to mid to high for a given route. Following completion of a dose day, an approximate 3-day washout period was performed before proceeding to the next dose day. Animals that received a single treatment on the first dose day received a repeat treatment the following dose day (and vice versa). Rotation of animals receiving single or repeat treatments of 3,4-DAPP was alternated throughout. Following the completion of the third dose day for a given route, animals were allowed to washout for approximately 2 weeks before proceeding to the first dosing day for the next dose route.

3.2 CLINICAL OBSERVATIONS

Observations for moribundity and mortality were performed a minimum of twice daily during the quarantine and study periods.

On days of 3,4-DAPP dosing, clinical observations were recorded approximate to each blood collection timepoint (pre-dose and 5, 15, 30, and 60 minutes and 2, 4, and 6 hours). Additional observations outside of defined collection times were collected as needed. During non-dosing days, twice daily AM/PM observations were performed until the subsequent dose day (see DR-B05928-WJ-0001 and DR-B05928-WJ-0003).

3.3 BODY WEIGHTS

Animals were weighed three times during quarantine and were weighed again prior to the first dosing day (Day -3) for randomization to groups by body weight. Day -3 body weights were also used for dose calculations for intravenous administration. Animals were re-weighed again for the purposes of updating dose calculations 3 days before proceeding to dosing activities in the next dosing route (Day 19 for subcutaneous dosing calculations, Day 40 for oral dosing calculations).

3.4 BIOANALYTICAL ANALYSIS AND TOXICOKINETIC EVALUATION

3.4.1 Blood Specimen Collection

Whole blood samples (target volume 0.5 mL) were collected from unanesthetized animals using the venous VAP, arterial VAP, or accessible vessel. Blood was collected into sodium heparin tubes, processed to plasma, and stored at -85 to -60°C. Whole blood samples were collected at baseline (pre-dose) and at the following times following the single or repeat dose: 5 (±30 sec), 15 (±1 min), 30 (±1 min), 60 (±2 min), 120 (±5 min), 240 (±5 min), 360 (±5 min) (see DR-B05928-WJ-0001 and DR-B05928-WJ-0003). The baseline sample collected from animals assigned to repeat dosing was performed just prior to administration of the repeat dose (at approximately 4 hours after receiving the first dose).

3.4.2 Bioanalysis

Plasma collected from study animals was transferred to the BBRC test site and analyzed in accordance with developed methods under NA-5927 and in accordance with Battelle SOP BBRC.III-133 using high performance liquid chromatography tandem mass spectrometry (LC-MS/MS). The 3,4-DAPP reference standard (amifampridine phosphate) was obtained from Catalyst Pharmaceuticals and was manufactured by Patheon (Lot No. P507S5-14-001 (Micron Lot# 154023), July 31, 2021 expiration, purity of 99.8%). The 2,4-diaminopyridine (free base) internal reference standard was obtained from Sigma-Aldrich (Lot No. STBG7483, October 5, 2025 expiration, purity of 99.9%).

3.4.3 Pharmacokinetic Evaluation

3,4-DAPP quickly separates into 3,4-DAP (free base) and phosphate salt ions once in aqueous solution. As dosing solutions of 3,4-DAPP were prepared in saline (for IV and SC dosing) or water (for PO dosing) prior to animal dosing, pharmacokinetic evaluation was performed on 3,4-DAP free base plasma concentrations. The noncompartmental analysis (NCA) module in the Phoenix WinNonlin software package was used to for pharmacokinetic evaluation.

The PK parameters evaluated for 3,4-DAP were:

- C_{max} (the maximum observed plasma concentration)
- T_{max} (the time to reach the maximum observed plasma concentration)
- elimination half-life which is associated with the terminal elimination phase
- clearance (an estimate of the volume of plasma cleared of the analyte over time)
- volume of distribution (an estimate of the apparent volume in which the analyte is distributed)
- AUC_{last}, and AUC_{∞} (area under the curve from time zero to the last observed time point or extrapolated to infinity, which provide an evaluation of systemic exposure).

The following acceptance criteria established by the pharmacokineticist were used to evaluate the concentration-time profiles:

(i) Coefficient of determination (r^2) for the terminal linear phase was greater than or equal to 0.85
(ii) Time of the last observed concentration was greater than three times the half-life
(iii) $AUC\infty$ had less than 20% of the area extrapolated.

3.5 STUDY TERMINATION

Following completion of dosing and sample collection, animals were held for observations, room care, and veterinary care (as needed) before transfer to Battelle Study B05929 on June 24, 2021.

4 COMPUTER SYSTEMS FOR DATA MANAGEMENT

The following computer systems were used for toxicology data management:

Table 5. 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
Sample Tracking System	4.1.1.1	Battelle	Barcoded sample tracking for sample disposition and location
WinNonlin	8.3	Pharsight Corp	PK Analysis
Analyst	1.7.1	AB Sciex	Bioanalytical (3,4-DAP levels in plasma)

5 STATISTICAL ANALYSIS

Descriptive statistics of PK parameters were performed (mean and standard error) for each dose route and dose level. Estimation of the terminal elimination constant was accomplished in Phoenix WinNonlin by performing a regression of the natural logarithm of the concentration values in the range of the sampling times with the best fit. Statistical outlier tests on concentration data was not performed and all data were included in PK analysis and reported.

6 STORAGE OF STUDY MATERIALS AND RECORDS RETENTION

All records generated at the testing facility required to reconstruct the study and the final report are archived at the testing facility.

Any specimens, raw data, or documentation generated from analyses performed by a designated test site are archived at the Battelle archives. Residual plasma samples from bioanalytical analysis are retained at the BBRC for potential disposal or shipment to a Sponsor-designated facility.

7 RESULTS

7.1 MORTALITY

No mortality was observed in animals used for dosing activities. All 8 animals placed on study and dosed with 3,4-DAPP survived until scheduled removal from the study.

7.2 CLINICAL OBSERVATIONS

Dosing Day Data: Table C-1 through Table C-3
Complete Study Data: Table C-4

A complete listing of abnormal clinical observations after placement on study is provided in the referenced Appendices. Abnormal observations considered related to VAP implantation and/or secondary animal health issues and treatments included: discolored skin (ventral body, right hind limb), limb weakness (hind right limb), skin abrasions (ventral body, face, right and left forelimb, right hind limb), low food consumption, diarrhea, and soft feces. The observations discussed below are thus restricted in context to days of 3,4-DAPP administration.

7.2.1 Intravenous Dosing

Abnormal signs were not observed in response to 3,4-DAPP dosing at 1.03 and 2.06 mg/kg as all animals were observed in a normal status following intravenous administration. At the 4.12 mg/kg dose level of 3,4-DAPP, emesis (white, foamy) was observed shortly after intravenous administration (5 or 15 minutes) in some animals. One (1) incidence of emesis was observed approximately 3 minutes after the first dosing, and 3 incidences were observed within 15 minutes in animals receiving the second repeat dosing. Emesis was considered to be test article related as this observation was present in multiple animals at similar time-points after 3,4-DAPP administration.

7.2.2 Subcutaneous Dosing

Abnormal signs were not observed at a 3,4-DAPP dose level of 1.03 and 2.06 mg/kg as all animals were observed in a normal status following subcutaneous dosing. At the 4.12 mg/kg subcutaneous dose level of 3,4-DAPP, emesis (white, foamy, or food) was observed after dose administration in 3 of 8 animals. Two (2) incidences occurred at approximately 1 hour after the first delivered dose, and 1 incidence occurred approximately 1.5 hours after the second delivered dose. Emesis was considered to be test article related as the incidence was present in multiple animals at similar time-points after 3,4-DAPP administration.

7.2.3 Oral Dosing

Abnormal signs were not observed in response to 3,4-DAPP oral dosing at 1.03, 2.06, and 4.12 mg/kg as all animals were found to be in normal status at all observation time-points conducted following oral administration (see DR-B05928-WJ-0003).

7.3 BODY WEIGHTS

Individual Data: Table C-5

Animal weights collected prior to intravenous dosing ranged from 3.5 to 4.2 kg. Animal weights collected prior to subcutaneous dosing ranged from 3.48 to 4.20 kg. Animal weights collected prior to intravenous dosing ranged from 3.38 to 4.32 kg.

7.4 BIOANALYTICAL AND PHARMACOKINETIC EVALUATION

Bioanalytical Data: Table D-1
Pharmacokinetic Data: Table D-2

The dose of 3,4-DAPP administered to animals represents the phosphate form of the test article (1.03, 2.06, and 4.12 mg/kg). The bioanalytical measurements reported in plasma from samples collected after dosing represent the concentration of free base form of 3,4-DAP.

7.4.1 Intravenous Dosing

Following IV administration, the shape of the 3,4-DAP plasma concentration-time curves showed an apparent biphasic decline after both a single and repeat administrations of 3,4-DAPP. Except for one animal on the 1.03 mg/kg dose day, all animals passed the acceptance criteria for evaluation of the concentration-time profiles for all IV dose days. Intravenous T_{max} occurred at the first target sample collection time of 5 minutes for all animals, as would be expected for IV administration. Group mean elimination half-life values were consistent across the three dose groups after both single and repeat administration, ranging from 65.1 to 83.6 minutes. In addition, clearance and volume of distribution showed no apparent dose or repeat administration effects. When comparing single and repeat administration for a given dose, both C_{max} and AUC values were within 2-fold of each other and were considered similar. Over the 1.03 to 4.12 mg/kg dose range AUC increased in a near dose proportional manner while C_{max} increased in a slightly greater than dose proportional manner.

Concentration-time plots for each intravenous dose group are illustrated in Figure 1. A summary of PK parameters is provided in Table 6.

7.4.2 Subcutaneous Dosing

Following SC administration, the shape of the 3,4-DAP plasma concentration-time curves showed an apparent biphasic decline after both a single administration of 3,4-DAPP and repeat administrations of 3,4-DAPP, similar to following IV administration. All animals passed the acceptance criteria for evaluation of the concentration-time profiles on all dose days. Absorption following SC dosing was rapid, as all but one animal had a T_{max} at the first target sample collection time of 5 minutes. Group mean elimination half-life values were consistent across the three dose groups after both single and repeat administration. These group mean values ranged from 60.9 to 80.1 minutes; values which were similar to the IV group means. Clearance and volume of distribution showed no apparent dose or repeat administration effects. When comparing single and repeat administration for a given dose, both C_{max} and AUC values were within 2-fold of each other and were considered similar. Over the 1.03 to 4.12 mg/kg dose range both C_{max} and AUC increased in a near dose proportional manner.

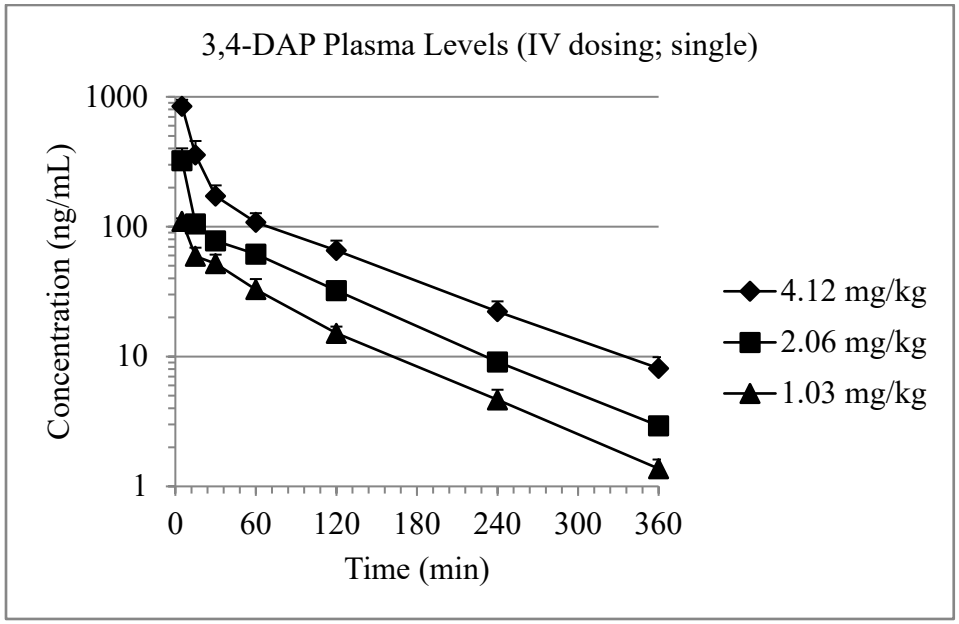
Concentration-time plots for each subcutaneous dose group are illustrated in Figure 2. A summary of PK parameters is provided in Table 6.

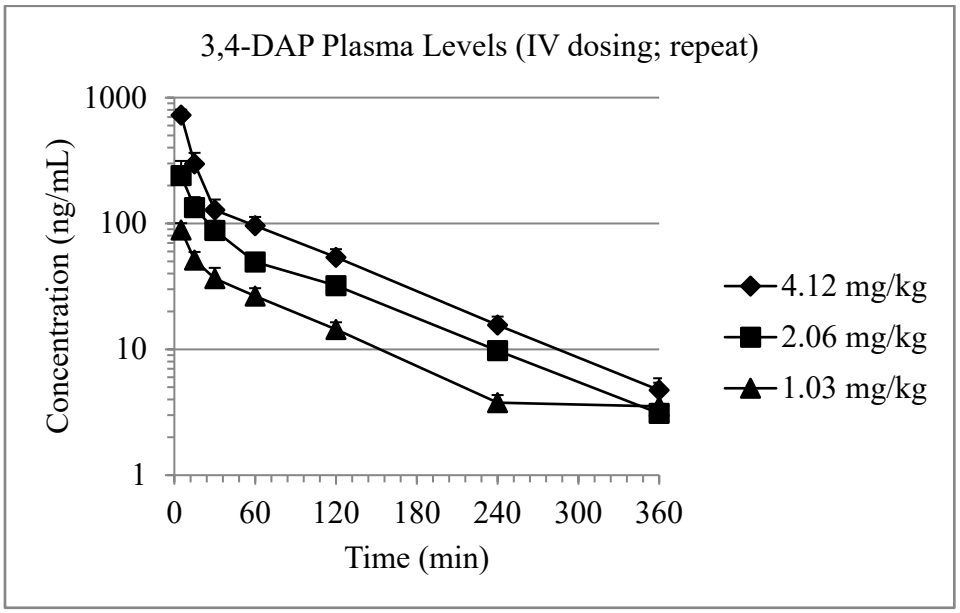
7.4.3 Oral Dosing

Following PO administration, the typical shape of the 3,4-DAP plasma concentration-time curves showed an absorption phase followed by an apparent monophasic decline after both a single administration and repeat administrations of 3,4-DAPP. Many of the animals from the 1.03 and 2.06 mg/kg groups did not have sufficient measurable concentrations to fully characterize the concentration-time profile (LLOQ < 0.5 ng/mL). Except for one animal, all animals orally dosed with 4.12 mg/kg 3,4-DAP passed all of the acceptance criteria for a well characterized concentration-time profile. Absorption was fast, but not as fast as the SC route. Most animals had a T_{max} at the 15- or 30-minute target sample collection time. Group mean elimination half-life values were similar for the single and repeat administration 4.12 mg/kg groups: 92.3 and 78.5 min, respectively. These values were similar to the IV and SC groups. The only animal from the 1.03 and 2.06 mg/kg groups which passed all three acceptance criteria had an elimination half-life of 78.0 minutes, similar to the other dosing routes (IV and SC). In addition, clearance and volume of distribution following 4.12 mg/kg administration showed no apparent repeat administration effects. When comparing single and repeat administration at 4.12 mg/kg 3,4-DAP, both C_{max} and AUC values were within 2-fold of each other and were considered similar. While AUC∞ comparisons could not be made due to the lack of AUC∞ estimates for many 1.03 and 2.06 mg/kg animals, C_{max} values were found to increase in a slightly greater than dose proportional manner.

Concentration-time plots for each oral dose group are illustrated in Figure 3. A summary of PK parameters is provided in Table 6.

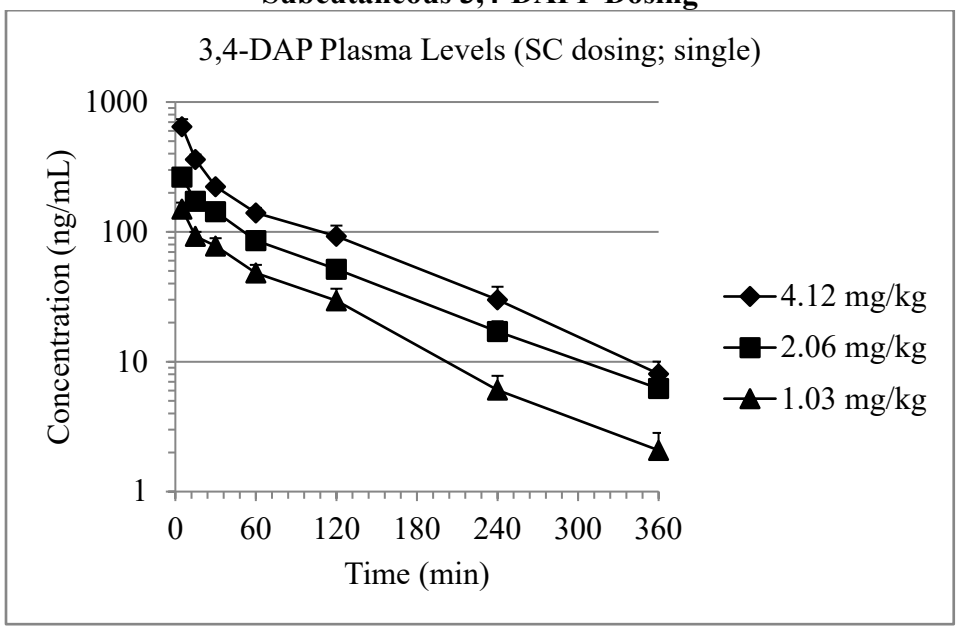
Figure 1. Plasma Levels of 3,4-DAP following a Single (top) or Repeat (bottom) Intravenous 3,4-DAPP Dosing

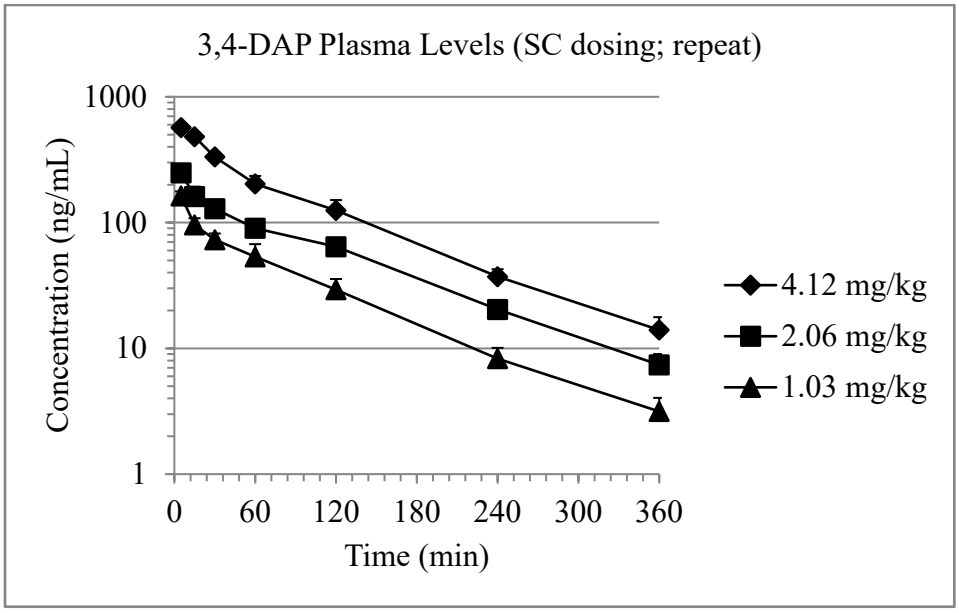




NOTE: Time values for the repeat dosing represent the time relative to animals receiving their second dose (approximately 4 hours after the first dosing).

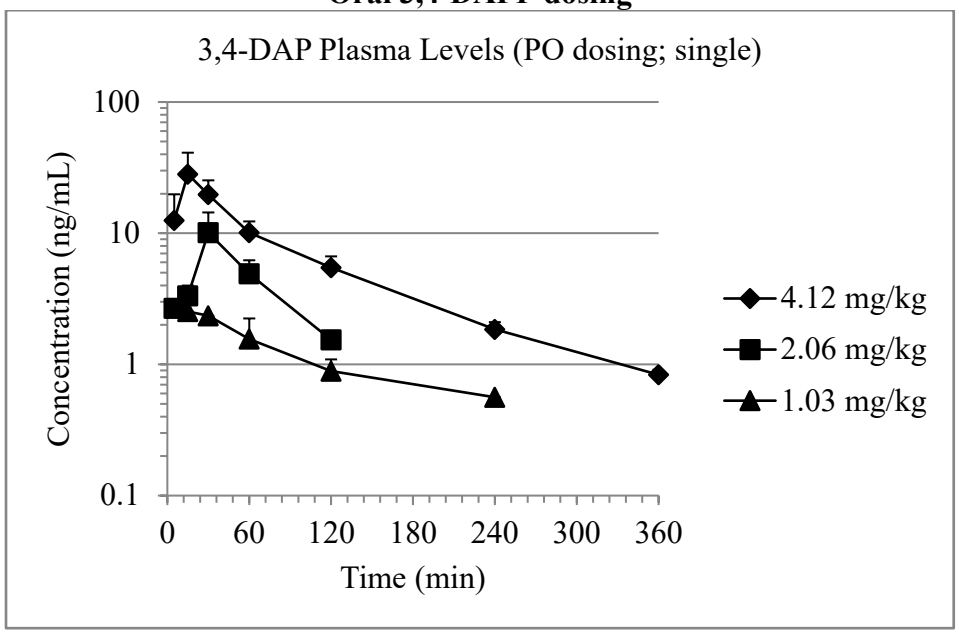
Figure 2. Plasma Levels of 3,4-DAP following a Single (top) or Repeat (bottom) Subcutaneous 3,4-DAPP Dosing

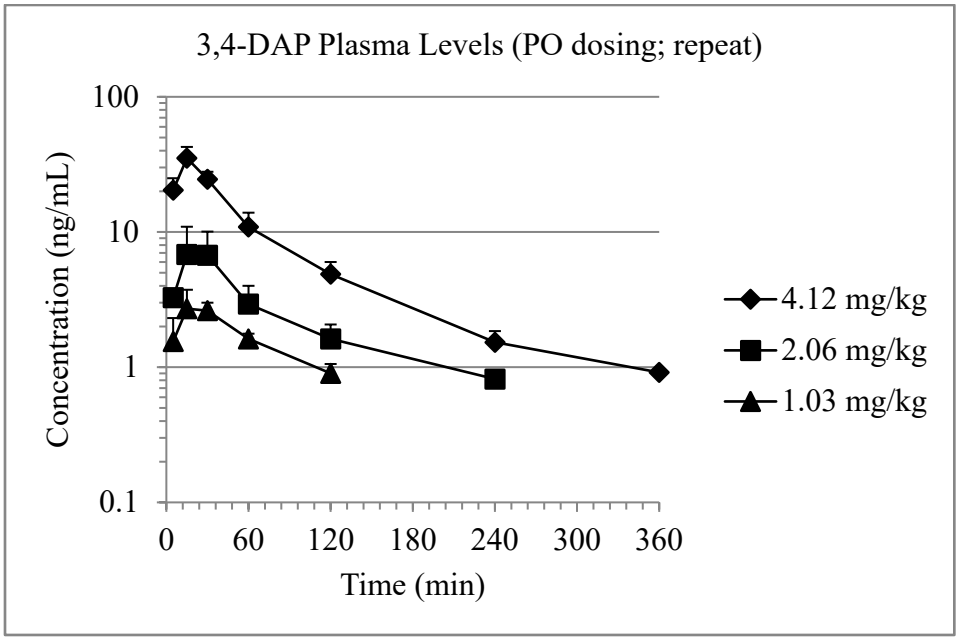




NOTE: Time values for the repeat dosing represent the time relative to animals receiving their second dose (approximately 4 hours after the first dosing).

Figure 3. Plasma Levels of 3,4-DAP following a Single (top) or Repeat (bottom) Oral 3,4-DAPP dosing





NOTE: Time values for the repeat dosing represent the time relative to animals receiving their second dose (approximately 4 hours after the first dosing).

Table 6. Group PK Parameter Summary

Route	3,4-DAPP Dose (mg/kg)	Dosing Interval	C_{max} (ng/mL)	T_{max} (min)	Elimination Half-Life (min)	Apparent Clearance (mL/min/kg)	Apparent Volume of Distribution (mL/kg)	AUC_{last} (min*ng/mL)	AUC_{∞} (min*ng/mL)
IV	1.03	Single	110 (6)	5.50 (0.50)	65.1 (1.2)	161 (22)	15,300 (2,300)	6,630 (920)	6,760 (940)
		Repeat	88.7 (11.8)	5.46 (0.61)	77.6 (13.2)	184 (22)	20,300 (3,400)	5,610 (790)	5,880 (800)
	2.06	Single	322 (79)	5.00 (0.00)	69.9 (3.2)	150 (15)	15,200 (1700)	13,900 (1,400)	14,100 (1,400)
		Repeat	240 (74)	5.15 (0.15)	72.2 (5.8)	165 (19)	17,500 (3,200)	12,700 (1,800)	13,100 (1,800)
	4.12	Single	846 (103)	5.28 (0.16)	83.6 (8.3)	134 (26)	16,800 (4,600)	32,500 (4,900)	33,400 (5,000)
		Repeat	726 (77)	5.37 (0.21)	71.3 (6.3)	155 (15)	16,200 (2,700)	26,900 (3,000)	27,400 (3,000)
SC	1.03	Single	150 (18)	5.00 (0.00)	60.9 (4.1)	110 (14)	9,390 (700)	9,750 (1,340)	9,930 (1,420)
		Repeat	163 (14)	5.24 (0.24)	67.0 (5.0)	107 (15)	10,100 (1,200)	10,200 (1,900)	10,500 (2,000)
	2.06	Single	265 (31)	7.83 (2.41)	78.1 (5.5)	118 (21)	13,300 (2,700)	18,200 (2.600)	18,900 (2,700)
		Repeat	249 (43)	5.76 (0.76)	80.1 (9.8)	103 (7)	12,000 (2,100)	19,500 (1,600)	20,400 (1,400)
	4.12	Single	646 (93)	5.00 (0.00)	68.8 (2.6)	123 (10)	12,100 (600)	33,300 (2,400)	34,100 (2,600)
		Repeat	569 (28)	5.48 (0.29)	74.4 (5.9)	94.1 (8.1)	10,100 (1,200)	43,400 (4,000)	44,900 (4,300)
PO	1.03	Single	2.08 (1.19)	45.0 (15.0)	ND (ND)	ND (ND)	ND (ND)	223 (110)	ND (ND)
		Repeat	3.16 (0.89)	26.3 (3.8)	83.5 (ND)	2,830 (ND)	312,000 (ND)	215 (50)	374 (ND)
	2.06	Single	10.3 (4.2)	45.00 (8.70)	ND (ND)	ND (ND)	ND (ND)	609 (92)	ND (ND)
		Repeat	7.44 (3.74)	20.00 (5.00)	145 (ND)	3,120 (ND)	696,000 (ND)	565 (278)	839 (ND)
	4.12	Single	33.8 (11.2)	22.50 (4.30	92.3 (9.5)	2,140 (540)	299,900 (99,000)	2,070 (410)	2,200 (380)
		Repeat	36.8 (5.9)	18.80 (3.80)	78.5 (7.7)	1,920 (300)	215,000 (36,000)	2,250 (470)	2,360 (470)

Values presented = mean (standard error); ND = not determined

8 DISCUSSION

Dosing of male cynomolgus monkeys with 3,4-DAPP at the dose levels (1.03, 2.06, and 4.12 mg/kg) and dose routes (IV, SC, and PO) tested in this study was found to be generally well-tolerated. At the low- and mid-dose levels of 3,4-DAPP, abnormal observations in response to dosing were not present following IV and SC administration. Transient emesis was observed in some, but not all, after receiving 4.12 mg/kg of 3,4-DAPP through the IV and SC route. In animals displaying emesis, the observation was transient and was resolved shortly after onset. In contrast to IV and SC dosing, similar emetic observations were not observed following PO administration at the highest dose level tested (4.12 mg/kg). The lack of this observation in response to PO dosing is consistent with the lower systemic levels achieved relative to IV and SC dosing. The abnormal observations of emesis in response to IV and SC 3,4-DAPP dosing were considered to be related to test article administration. Given the mechanism of action of 3,4-DAP, the pharmacologic basis for the emetic observations is hypothesized be the result of increased neurotransmission. It remains unclear if similar observations will manifest at comparable 3,4-DAPP dose levels in test subjects with underlying neurotransmission deficits (e.g. botulism).

When comparing the three routes of 3,4-DAPP administration investigated on this study (IV, SC, and PO), animals dosed through the IV and SC route had similar pharmacokinetic parameters. Elimination half-life values were similar across all three dose levels for both the IV and SC routes of administration. In addition, apparent clearance and apparent volume of distribution following SC dosing were similar to values following IV administration. Given the assumption that IV administration gives 100% bioavailability, and given the similarity in PK profiles between the IV and SC dose routes, these data suggest that the fraction of dose absorbed following SC administration was near 100%. Similar systemic exposure parameters between IV and SC groups further suggest approximately 100% bioavailability following SC administration. Following PO administration, elimination half-life values for well-characterized concentration-time profiles were similar to the IV and SC groups. However, there was a marked difference following PO administration, where all systemic exposure parameters were less than 10% that of the IV groups showing poor bioavailability following PO administration.

Collectively, due to the poor bioavailability of 3,4-DAP following oral dosing (< 10%) at the dose range tested (1.03 to 4.12 mg/kg), it is not currently recommended to utilize PO dosing for any follow-on botulinum neurotoxin (BoNT) efficacy studies in the cynomolgus monkey test system as these levels are hypothesized to be unlikely to elicit a positive pharmacologic effect. Further characterization would be required to identify oral dosing strategies that result in greater plasma concentration levels of 3,4-DAP. It is recommended that 3,4-DAPP dosing be employed through the IV or SC route for planned follow-on efficacy testing efforts.

As PK parameters of SC dosing were similar to those following IV dosing, the IV and SC dose routes can be considered near equivalent. Some advantage for efficacy testing of 3,4-DAPP as a candidate BoNT countermeasure is conferred to the SC route based on ease of dosing and the potential for field use in an autoinjector format. The IV dose route may be more practical for a higher level of care in a hospital setting.

For 3,4-DAPP dose selection consideration in planned follow-on efficacy studies, it remains unknown what minimum plasma concentration levels of 3,4-DAP are required to elicit any pharmacologic effects in cynomolgus monkeys intoxicated by BoNTs. As such, all projections of appropriate dosing strategies are strictly hypothetical and should be interpreted with caution. Assuming a plasma concentration of > 50 ng/mL of 3,4-DAP is requisite in cynomolgus monkeys for a positive neuromuscular effect in BoNT-intoxicated synapses, it can be supposed that 3,4-DAPP dosing performed at a dose level of 2.06 mg/kg may elicit a sustained therapeutic benefit approximating 2 hours post-dosing. Using the same assumptions, at dose levels of ≥ 4.12 mg/kg, a pharmacologic effect is likely to persist longer and may extend to 3 hours post-dosing. The duration of potential therapeutic benefit following 3,4-DAPP dosing is predicted to be largely dependent on the minimum 3,4-DAP plasma levels required for positive pharmacologic modulation in BoNT-intoxicated cynomolgus monkeys. If this threshold is lower than anticipated (i.e. 25 ng/mL), therapeutic benefit may extend for out to 4 hours post-dosing at dose levels of ≥4.12 mg/kg. If this threshold is higher than anticipated (i.e. 100 ng/mL), therapeutic benefit may be restricted to within 90 minutes after administration. The duration of therapeutic benefit will also likely be dependent on the neuromuscular residency of 3,4-DAP and receptor binding kinetics. Resolution of these factors was outside of the scope of this current work and cannot be determined through the pharmacokinetics of 3,4-DAP in plasma alone. However, once the pharmacology is better understood in BoNT-intoxicated cynomolgus monkeys, along with the well-characterized pharmacokinetics produced in this study, appropriate 3,4-DAPP dose levels and dosing intervals can be more accurately selected for studies utilizing survival as a primary endpoint of efficacy.

Collectively, given the well-characterized 3,4-DAP pharmacokinetic profiles achieved in this study using 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 7. Principal Contributors

Role	Name
Study Director	Phillip H. Beske, PhD, DABT
Study Coordinator	Megan Bell, MS
Director of Veterinary Sciences, Nonclinical Toxicology, and Safety Pharmacology	Roy E. Barnewall, DVM, PhD
Attending Veterinarian	Tracy A. Peace, DVM, MS, DACLAM
Study Surgeon/Veterinarian	Carolyn Fetzek, DVM
Director of Pathology	Sabrina N. McGraw, DVM, MS, PhD, DACVP
Director of Study Oversight	Dean J. Kobs, MS
Testing Facility Manager	Harry Ledebur, Jr., PhD
Principal Investigator, Bioanalysis	Brent McCracken, BA
Principal Investigator, Pharmacokinetics	Seth T. Gibbs, PhD

10 REFERENCES

Battelle Transfer Report NA-5927. 2020. Analysis of 3,4-Diaminopyridine in Cynomolgus Monkey Plasma Using High Performance Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS).

National Research Council (NRC). 2011. *Guide for the Care and Use of Laboratory Animals*. 8th Ed. National Academies Press, Washington D.C.

U.S. Food and Drug Administration. 1987. Guidance for Industry. 21 CFR Part 58 Good Laboratory Practice Regulations, Final Rule.

Appendix A Protocol, Amendments, and Summary of Deviations

(Amended 5/21[3])

Pharmacokinetic Analysis of 3,4-Diaminopyridine in the Cynomolgus Monkey

Amended Protocol 3 Date: May 1, 2021
Original Protocol Date: December 9, 2020

Study Number B05928

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

GLP Compliance Status: non-GLP

Battelle Memorial Institute
505 King Ave
Columbus, OH 43201

Testing Facility
[~~Battelle – West Jefferson (JM10)~~ ***AmplifyBio***][3]
1425 State Route 142 (Plain City-Georgesville Road)
West Jefferson, OH 43162

SIGNATURES

APPROVED, TESTING FACILITY:

Phillip H. Beske

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

09-December-2020
Date

Dean J. Kobs, M.S.
Manager, Safety Assessment

9-DECEMBER-2020
Date

APPROVED, SPONSOR:

See Attachment
for Signature

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

Date

SIGNATURES

APPROVED, TESTING FACILITY:

See Attachment for Signature

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

Date

See Attachment for Signature

Dean J. Kobs, M.S.
Manager, Safety Assessment

Date

APPROVED, SPONSOR:

ODELL.LINDSAY.THOMAS.1242936830

Digitally signed by ODELL.LINDSAY.THOMAS.1242936830
Date: 2020.12.09 11:02:17 -05'00'

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

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 abstract 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 (i.e. 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 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, establishing relevant dosing levels of 3,4-DAP in NHPs is an important step prior to efficacy evaluation.

2.0 PURPOSE

Following a single or repeat administration of 3,4-DAP by three different dose routes: intravenous (IV), subcutaneous (SC), and oral (PO), the objective of this study is to evaluate the pharmacokinetics of 3,4-DAP 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 – West Jefferson~~ ***AmplifyBio***][3]
1425 State Route 142 (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 BATTELLE BIOMEDICAL RESEARCH CENTER

Test Site for:	Bioanalytical analysis
Address:	Battelle Biomedical Research Center 1425 State Route 142 (Plain-City Georgesville Road) West Jefferson, OH 43162
Principal Investigator:	Brent McCracken, B.A. Email: [~~mccraken@battelle.org~~ ***mccrackenb@battelle.org***][2]

[~~**5.2 BATTELLE – WEST JEFFERSON**~~

~~Test Site for: Pharmacokinetic analysis~~

~~Address: Battelle~~
~~505 King Avenue~~
~~Columbus, OH 43201~~

~~Principal Investigator: Seth Gibbs, Ph.D.~~
~~Email: gibbs@battelle.org~~][3]

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 Ste 6201, Fort Belvoir, VA 22060

6.2 SPONSOR'S REPRESENTATIVE

Lindsay Odell, Ph.D.
Team Lead, Therapeutics
Telephone: (571) 616-6202
Email: lindsay.t.odell.civ@mail.mil

7.0 PROPOSED STUDY SCHEDULE

Proposed dates for selected study events are listed below.

Animal Receipt:	December 2020
Animal Surgery:	January 2021
In-Life:	February 2021 – March 2021
Sample Analysis and Reporting:	January 2021 – May 2021

8.0 TEST ARTICLE AND VEHICLE CONTROL MATERIAL

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

8.1 TEST ARTICLE

Name:	3,4-diaminopyridine phosphate (3,4-DAP)
Description:	Active Pharmaceutical Ingredient (API) powder of Firdapse®; provided by Catalyst Pharmaceuticals. Final IV and SC dosing solutions in saline will be prepared by [~~Battelle~~ ***AmplifyBio***][3]. Final PO dosing solution in water will be prepared by [~~Battelle~~ ***AmplifyBio***][3]. 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~~ ***AmplifyBio***][3] 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 to remain within 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.

8.2 VEHICLE

Name:	IV and SQ: Saline; 0.9% sodium chloride for injection.

	PO: distilled deionized (DDI) water or water for injection.
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. 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)
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:	Two vascular access ports (1 venous and 1 arterial). Surgical procedures for implantation of vascular access ports will be performed at [~~Battelle~~ ***AmplifyBio***][3] (described below in Section 9.3). Venous access ports will be used for blood draws (if patent). Arterial access ports will not be used unless the venous access port is not patent.

9.1 ANIMALS

Animal care and medical records provided from PreLabs will be included in the study file. Tattoos with animal identification numbers will be placed prior to arrival at [~~Battelle~~ ***AmplifyBio***][3]. All animals will be research naïve and will not have been utilized as part of the test system on any previous research.

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 and cage cards will be used to identify each animal. The cage card will state, at a minimum, the species/strain, tattoo number, study number, and gender. [***If present, identification chips may be used to aid in animal identification.***][2]

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 two vascular access ports (VAPs), with one catheter implanted in either the jugular or femoral vein and one catheter implanted in either the femoral or carotid artery. An incision will be made over the target vessels. The vessels will be dissected, punctured, and an indwelling catheter will be inserted into the lumen of each vessel. The catheters will then be sutured in place. An incision will be made on the posterior surface of the animal. A trocar will be passed from the incision site overlying the vessels to the incision site on the dorsal surface. The free ends of the catheters will be fed to the incision on the animal's posterior surface. The free ends will be connected to ports which will be sutured to the muscle on the animal's posterior surface. Both incision site will then be sutured or stapled closed.

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 approved facility regimens or at veterinarian discretion:

> *Pre-operative:* ketamine, isoflurane, buprenorphine, lidocaine (or bupivacaine), enrofloxacin, carprofen
>
> *Operative:* isoflurane
>
> *Post-operative:* buprenorphine (2 days), carprofen (4 days), enrofloxacin (2 days) then a switch to oral antibiotics for 4 days (cephalexin or Clavamox)

Following surgery, VAPs will be maintained according to SOP Number ARF.II-050. A blood sample (target volume of 2 mL) may be collected during the first week following surgery for determination of bacteremia. Samples may be transported to the BBRC for analysis. For any collected samples, blood culture will be performed according to SOP BBRC.X-096 with enrichment in broth media prior to plating for identification of gram-positive and gram-negative bacteria growth.

10.0 EXPERIMENTAL DESIGN

This study will be conducted in accordance with the protocol, protocol amendments, and applicable [~~Battelle~~ ***AmplifyBio***][3] SOPs. An abbreviated list of procedures used in this study can be found in Section 17.0. This study will evaluate the pharmacokinetic parameters of 3,4-DAP in cynomolgus monkeys when administered as a single or repeat treatment by three (3) different dose routes: oral, subcutaneous, intravenous.

Doses to be tested will be maintained the same for each dose route and will be anchored by an initial estimation of a human equivalent dose (HED) based on nonbinding body surface area conversion guidance provided by the FDA [6]. The following assumptions are made to estimate an initial HED of 1.03 mg/kg of 3,4-DAP in cynomolgus monkeys:

1) Assumes the currently approved oral dose of 3,4-DAP in humans is 20 mg
2) Assumes a 60 kg human
3) Assumes a 3.1x correction factor for body surface conversion to monkeys

The study will be conducted over a total of nine (9) dose days, three (3) for each route (IV, SC, and PO). Animals will be restrained chair restrained for all dosing procedures. Doses to be tested for each dose route will be 1x, 2x, and 4x the estimated HED, corresponding to 1.03 mg/kg (low), 2.06 mg/kg (mid), and 4.12 mg/kg (high). Doses to be tested may be changed in consultation with the Sponsor. Selected doses between dose days may be lowered with Sponsor concurrence pending documented observations of adverse events at a given dose level for a given dose route. Administered dose volumes will not exceed IACUC recommended limits for bolus administration: IV (5 mL/kg); SC (5 mL/kg); and PO (5 mL/kg).

3,4-DAP will either be administered as a single or repeat bolus treatment. The time between bolus treatments for animals receiving repeat administrations will be determined in consultation with the Sponsor (2, 4, or 6 hours). IV dosing of 3,4-DAP will be performed into the saphenous vein or other suitable vessel. SQ dosing of 3,4-DAP will be performed between the scapulae. The specific intra-scapular location will rotate as needed between injections to avoid overlapping injections to the same site. PO dosing of 3,4-DAP will be performed through oral gavage. In all cases, low-dose ketamine (4-6 mg/kg; IM) may be used to sedate the animal and facilitate the dosing and subsequent sample collection procedures (if required).

All animals will be dosed in a single dose day. Doses will progress from low to mid to high for a given route. Following completion of a dose day, an approximate 3-day washout period will be performed before proceeding to the next dose day. Animals that receive a single treatment on the first dose day will receive a repeat treatment the following dose day (and vice versa). Rotation of animals receiving single or repeat treatments of 3,4-DAP will be alternated

throughout. Following the completion of Dose Day 3 for a given route, animals will be allowed

to washout for a ~2 weeks before proceeding to Dose Day 1 for the next dose route. A summary of the Study Design is presented below in Table 1.

Table 1. Study Design

Dose Day	Group	Route	3,4-DAP Dose*	Dose Frequency	Blood Collection Time (minutes)	# of Animals Dosed[^][2]
IV[1]	1	IV	1.03 mg/kg	single	**Single:** Baseline, 5 (±30 sec), 15 (±1 min), 30 (±1 min), 60 (±2 min), 120 (±5 min), 240 (±5 min), 360 (±5 min)	4
	2			repeat		4
IV[2]	2		2.06 mg/kg	single		4
	1			repeat	**Repeat (time after 2nd treatment):** Baseline, 5 (±30 sec), 15 (±1 min), 30 (±1 min), 60 (±2 min), 120 (±5 min), 240 (±5 min), 360 (±5 min)	4
IV[3]	1		4.12 mg/kg	single		4
	2			repeat		4
SC[1]	2	SC	1.03 mg/kg	single	**Single:** Baseline, 5 (±30 sec), 15 (±1 min), 30 (±1 min), 60 (±2 min), 120 (±5 min), 240 (±5 min), 360 (±5 min)	4
	1			repeat		4
SC[2]	1		2.06 mg/kg	single		4
	2			repeat	**Repeat (time after 2nd treatment):** Baseline, 5 (±30 sec), 15 (±1 min), 30 (±1 min), 60 (±2 min), 120 (±5 min), 240 (±5 min), 360 (±5 min)	4
SC[3]	2		4.12 mg/kg	single		4
	1			repeat		4
PO[1]	1	PO	1.03 mg/kg	single	**Single:** Baseline, 5 (±30 sec), 15 (±1 min), 30 (±1 min), 60 (±2 min), 120 (±5 min), 240 (±5 min), 360 (±5 min)	4
	2			repeat		4
PO[2]	2		2.06 mg/kg	single		4
	1			repeat	**Repeat (time after 2nd treatment):** Baseline, 5 (±30 sec), 15 (±1 min), 30 (±1 min), 60 (±2 min), 120 (±5 min), 240 (±5 min), 360 (±5 min)	4
PO[3]	1		4.12 mg/kg	single		4
	2			repeat		4
TOTAL = 8 NHPs on study (1 extra)						

* Doses administered may be changed in consultation with the Sponsor.
[^ *The number of animals dosed on each day represents the maximum number of animals. If experimental or animal health issues prevent the availability of eight animals fit for study on a given dose day, dosing will be performed in all available animals.*][2]

10.1 ANIMAL RANDOMIZATION

Animals will be randomized to groups during quarantine by weight. Randomization will be performed using the Provantis computer system in accordance with **[~~Battelle~~ *AmplifyBio*][3]** SOP Number COR.IV-006 to ensure similar group mean weights. Randomization will be performed based on body weights collected prior to the first dose day (Day -3, Day -2, or Day -1). 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.

[***In the event that eight animals are not available or fit for study on a given dose day, animal re-assignment may be performed by the Study Director and a reason for the re-assignment will be documented in the study file.***][2]

10.2 BODY WEIGHTS

Animals will be weighed during quarantine and may be re-weighed as necessary for medical monitoring purposes. Animals will be weighed prior to the first dose day for randomization to groups by body weight (Day -3, Day -2, or Day -1) and for dose calculations. Animals will be re-weighed again between dose routes (Day -3, Day -2, or Day -1) for the purposes of updating dose calculations before proceeding to the next dose route. Additional weights may be taken at any time for medical monitoring purposes for any health or veterinarian related issues or if an animal appears to be losing weight over the course of the study. Body weights will be collected in accordance with [~~Battelle~~ ***AmplifyBio***][3] SOP COR.V-012 and will be recorded in Provantis in accordance with SOP COR.IV-008.

10.3 ANIMAL OBSERVATIONS

10.3.1 Prior to Dosing

Cage-side AM/PM clinical observations will be performed twice daily in accordance with [~~Battelle~~ ***AmplifyBio***][3] SOP COR.V-005, except on the day of receipt where only a single observation may be performed. Clinical observations will be recorded in Provantis in accordance with [~~Battelle~~ ***AmplifyBio***][3] SOP COR.IV-009.

10.3.2 Post-Dosing

After 3,4-DAP dosing, clinical observations will be recorded at each blood collection time-point. Clinical signs as described in [~~Battelle~~ ***AmplifyBio***][3] SOP COR.V-005 will be documented. Clinical observations will be recorded in Provantis according to [~~Battelle~~ ***AmplifyBio***][3] SOP Number COR.IV-009. Paper documentation of observations may be performed if required. During washout between dose days and/or dose routes, twice daily AM/PM observations will be performed until the subsequent dose day.

10.4 BLOOD COLLECTION

Animals will be chair restrained for all collections. To reduce handling, animals may remain in chair restraint for baseline blood collection (pre-dose), subsequent dosing, and the first two scheduled blood collection time-points (5- and 15-minutes post-dosing). Animals may be transported back to home caging between blood collections thereafter.

Whole blood samples will be collected from unanesthetized animals using the venous VAP[***; animals may be sedated with low-dose ketamine (4-6 mg/kg; IM) as needed to facilitate blood collection)***][2]. If the venous VAP is not patent, a sample may be alternatively collected from the arterial VAP [***(if present)***][2]. If both VAPs are not patent [***(or an arterial VAP is not present)***][2], a suitable vessel may be used to collect the blood sample. The location of blood collection (venous VAP, arterial VAP, or suitable vessel) will be documented for each blood draw. Whole blood samples will be collected at baseline (pre-dose) and at the following times following the single or repeat dose: 5 (±30 sec), 15 (±1 min), 30 (±1 min),

60 (±2 min), 120 (±5 min), 240 (±5 min), 360 (±5 min). [***The baseline sample collected from animals assigned to repeat dosing will be performed as soon as immediately practical prior to administration of the repeat dose.***][2] Collected sample volumes will be approximately 0.5 mL of whole blood. Samples will be collected into [~~K_3EDTA blood~~ ***sodium heparin***][2] tubes, processed to plasma, and stored at -85 to -60°C according to facility SOPs. All blood will be collected IAW [~~Battelle~~ ***AmplifyBio***][3] SOP Number ARF.II-050 and [~~Battelle~~ ***AmplifyBio***][3] SOP Number COR.V-018 as applicable.

10.5 ANALYSIS OF 3,4-DAP LEVELS IN PLASMA

Plasma collected from animals on study will be analyzed in accordance with developed methods under NA-5927 and IAW Battelle SOP BBRC.III-133 using High Performance Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS). Data values will be reported in ng/mL (or other appropriate value such as molarity) for further PK analysis.

10.6 PHARMACOKINETIC ANALYSIS

PK analysis of the 3,4-DAP plasma concentrations determined by [~~Battelle~~ ***AmplifyBio***][3] will be performed using the noncompartmental analysis (NCA) module in the Phoenix WinNonlin software package. PK parameters to be evaluated will include, but may not be limited to, observed C_{max}, observed T_{max}, elimination half-life, and AUC (to C_{last} and infinity) and Volume of Distribution. The results of the PK evaluation will be provided to the Study Director for inclusion in the final study report. Additional modeling to estimate the 3,4-DAP dose level for each dose route to achieve reported therapeutic human plasma concentrations may also be performed.

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 AND QUARANTINE

Receipt and quarantine of animals will be performed in accordance with [~~Battelle~~ ***AmplifyBio***][3] SOPs. Animals will be visually examined by a [~~Battelle~~ ***AmplifyBio***][3] veterinarian prior to quarantine release. NHPs will be tested and verified negative for tuberculosis and will be prescreened within 45 days prior to receipt at [~~Battelle~~ ***AmplifyBio***][3] 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). RMs will be quarantined at [~~Battelle~~ ***AmplifyBio***][3] for a minimum of 5 weeks per [~~Battelle~~ ***AmplifyBio***][3] SOPs ARF.II-013 and ARF.II-019. Pole/collar and other training may be initiated during quarantine and continue into the pre-dosing period as necessary. Prior to dosing, all animals will be acclimated to chair restraint IAW [~~Battelle~~ ***AmplifyBio***][3] policies. Only NHPs that are determined to be healthy and released from quarantine by a [~~Battelle~~ ***AmplifyBio***][3] clinical veterinarian will be transferred to this study protocol. Documentation of the release from quarantine and 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~~ ***AmplifyBio***][3] veterinarian for determination of treatment or disposition. In such cases, and if in the opinion of a [~~Battelle~~ ***AmplifyBio***][3] veterinarian, an animal who is in a moribund state prior to challenge will be euthanized in accordance with [~~Battelle~~ ***AmplifyBio***][3] SOPs.

11.3 PAIN AND DISTRESS

Discomfort and distress will be limited to that which is unavoidable in the conduct of scientifically valuable research. Administration of 3,4-DAP at the proposed dose levels is not anticipated to result in significant pain and distress. 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~~ ***AmplifyBio***][3] veterinarian for determination of treatment or disposition. In such cases, if in the opinion of the Study Director and a [~~Battelle~~ ***AmplifyBio***][3] 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

While not expected, should euthanasia be required, a trained life sciences technician, [~~Battelle~~ ***AmplifyBio***][3] veterinarian, or Study Director may determine if an NHP is in a moribund state. 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.

If an animal is euthanized in moribund state or succumbs to dosing activities, a full gross necropsy with all gross lesions observed and recorded will be performed IAW [~~Battelle~~ ***AmplifyBio***][3] SOP

PATH.I-001. If the animal is not necropsied immediately after death, it will be maintained in a refrigerator (not freezer) until the necropsy is performed.

11.5 ANIMAL HOUSING AND ENVIRONMENTAL CONDITIONS

11.5.1 Housing

[~~Animals will be single housed due to the presence of surgically implanted VAPs.~~ ***Animals may be socially housed (to the extent possible) during quarantine and prior to VAP surgery. Following VAP surgery, animals will be single housed for approximately 3-5 days for recovery or at veterinary discretion. Thereafter, animals may be single or socially housed at veterinary discretion. On dosing days, animals may be single housed for study activities. During periods of single housing, socialization]***[1] ~~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~~ ***AmplifyBio***][3] SOP ARF.III-010, 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~~ ***AmplifyBio***][3] SOP ARF.III-010. 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~~ ***AmplifyBio***][3] SOP ARF.III-010. 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~~ ***AmplifyBio***][3] SOP COR.V-015.

11.5.6 Diet

NHPs will be fed Purina Certified Monkey Chow IAW [~~Battelle~~ ***AmplifyBio***][3] SOP ARF.II-004. 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~~ ***AmplifyBio***][3] SOP ARF.II-014 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~~ ***AmplifyBio***][3] SOP ARF.II-025. 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~~ ***AmplifyBio***][3] SOP COR.V-008. Documentation of the supplementation will be maintained in the study files.

12.0 COMPUTER SYSTEMS FOR DATA MANAGEMENT

The following computer systems are used for data management:

Table 2. 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, gross pathology
Sample Tracking System#	Battelle	Barcoded sample tracking for sample disposition and location
WinNonlin	Pharsight Corp	PK Analysis
[***Analyst***	***AB Sciex***	***Bioanalytical (3,4-DAP levels in plasma)***][2]

* Actual 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

Descriptive statistics of PK parameters will be performed (mean, standard deviation, etc). Additional analysis may be performed with Study Director and Sponsor concurrence.

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 3. Storage of Study Materials

Study Material	Location or Disposition
Raw data from [~~Battelle~~ ***AmplifyBio***][3]	Raw data will be archived at Battelle [***Archive***][3]
Residual test article	Retention samples will not be archived. Residual test article will be retained for use on a future study.
Animals	NHPs will remain at [~~Battelle~~ ***AmplifyBio***][3] for transfer to a future study.
Remaining plasma samples	Disposition details will be included in the study records and described in the final report.
Final Report	Report will be archived at Battelle [***Archive***][3]

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. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). *Guidance for Industry: Estimating*

the Maxium Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. July 2005.

Standard Operating Procedures

Handling of Nonhuman Primates.....ARF.II-004

Receipt of Animals other than Rats and Mice ARF.II-013

Feed Source, Storage, and Handling.....ARF.II-014

Test System Quarantine and Preventative Medicine Program for Species other than Rats and Mice.....ARF.II-019

Supplying Water to Animals.....ARF.II-025

Euthanasia of Species other than Rats and Mice ARF.II-037

Preparation to Perform Surgery on Animal Models ARF.II-038

Care of Anesthetized Animals ARF.II-039

Surgical Procedures ARF.II-047

Maintenance, Blood Collection and IV Infusion using Vascular Access Ports (VAPs) in Laboratory Animals.....ARF.II-050

Lighting Conditions of Animal Rooms..... ARF.III-010

Equipment Cleaning and Sanitization..... ARF.III-011

Extraction of 3,4-diaminopyridine in Cynomolgus Monkey Plasma and Quantitation Using High Performance Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS). BBRC.III-133

Qualitative Analysis of Bacteria in Blood and Tissue.....BBRC.X-096

Operation of Archives.....COR.I-002

Randomization and Animal Management in the Provantis Computer System.....COR.IV-006

Defining In-Life Data Entry Sessions in the Provantis Computer System.....COR.IV-007

Entering Body Weights, Recording Generalized Results, and Marking Animals Dead in the Provantis Computer System COR.IV-008

Entering Clinical Observations in the Provantis Computer System COR.IV-009

Conducting Clinical Observations COR.V-005

Oral Dosing of Animals COR.V-007

Environmental Enrichment of Nonhuman Primates COR.V-008

Injections.....COR.V-009

Measuring Body Weight, Food Consumption, and Water Consumption COR.V-012
HVAC Systems in Animal Resources COR.V-015
Blood Collection COR.V-018
Necropsy PATH.I-001

Attachment 1. Protocol Amendments

List of Changes in Amended Protocol 1:

1. a. Page 15, Section **11.5.1 Housing**. The first sentence in this section has been changed from:

   "Animals will be single housed due to the presence of surgically implanted VAPs."

   to:

   "Animals may be socially housed (to the extent possible) during quarantine and prior to VAP surgery. Following VAP surgery, animals will be single housed for approximately 3-5 days for recovery or at veterinary discretion. Thereafter, animals may be single or socially housed at veterinary discretion. On dosing days, animals may be single housed for study activities. During periods of single housing, socialization will be achieved will be achieved by housing animals in the same room with visual and auditory contact."

   b. The reason for this change was to allow for animals to be socially housed at veterinary discretion as appropriate throughout the study.

In addition to the changes listed above, (referenced throughout the protocol by "Amended"), the Title Page has been updated to reflect this amendment.

AMENDED PROTOCOL 1 SIGNATURES

APPROVED, TESTING FACILITY:

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

17 December 2020
Date

Dean J. Kobs, M.S.
Manager, Safety Assessment

17-DEC-2020
Date

APPROVED, SPONSOR:

ODELL.LINDSAY.THOMAS.1242936830

Digitally signed by ODELL.LINDSAY.THOMAS.1242936830
Date: 2020.12.16 08:14:25 -05'00'

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

Date

List of Changes in Amended Protocol 2:

1. a. Page 5, Section **5.1 BATTELLE BIOMEDICAL RESEARCH CENTER**. The Principal Investigator email address has been changed from:

   "mccraken@battelle.org"

   to:

   "mccrackenb@battelle.org"

   b. The reason for this change was to correct a typographical error.

2. a. Page 9, Section **9.2 ANIMAL IDENTIFICATION**. The following was added to the end of this section:

   "If present, identification chips may be used to aid in animal identification."

   b. The reason for this change was to include the optional use of identification chips. The femoral incision site for VAP placement was near the site of animal tattoos making the tattoo difficult to read.

3. a. Page 11, Section **10.0 EXPERIMENTAL DESIGN**. The following footnote was added to Table 1 in this section:

   "^ The number of animals dosed on each day represents the maximum number of animals. If experimental or animal health issues prevent the availability of eight animals fit for study on a given dose day, dosing will be performed in all available animals."

   b. Additionally, footnote indicator "^" was added to the header row of Table 1.

   c. The reason for this change was to clarify that study activities will proceed with a reduced number of animals in the event fewer than eight animals are available for study.

4. a. Page 11, Section **10.1 ANIMAL RANDOMIZATION**. The following was added to the end of this section:

   "In the event that eight animals are not available or fit for study on a given dose day, animal re-assignment may be performed by the Study Director and a reason for the re-assignment will be documented in the study file."

   b. The reason for this change was to include the optional reassignment of animals following randomization. Given potential reduction in the number of animals fit for study on any given dosing day, the Study Director may manually assign animals to ensure appropriate group numbers to accomplish the study objectives.

5. a. Page 12, Section **10.4 BLOOD COLLECTION**. In the second paragraph in this section, the following was changed from:

   "Whole blood samples will be collected from unanesthetized animals using the venous VAP. If the venous VAP is not patent, a sample may be alternatively collected from the arterial VAP. If both VAPs are not patent, a suitable vessel may be used to collect the blood sample."

   to:

   "Whole blood samples will be collected from unanesthetized animals using the venous VAP; animals may be sedated with low-dose ketamine (4-6 mg/kg; IM) as needed to facilitate blood collection). If the venous VAP is not patent, a sample may be alternatively collected from the arterial VAP (if present). If both VAPs are not patent (or an arterial VAP is not present), a suitable vessel may be used to collect the blood sample."

   b. The following was added to this section:

   "The baseline sample collected from animals assigned to repeat dosing will be performed as soon as immediately practical prior to administration of the repeat dose."

   c. The reference to "K_3EDTA blood" collection tubes was changed to "sodium heparin" tubes.

   d. The reasons for these changes were a) to clarify blood collection procedures, b) clarify the timing of collection of baseline samples for repeat-dose animals, and c) to update the anticoagulant to be used for blood collection to align with the developed method for analysis of 3,4-DAP in heparinized nonhuman primate plasma.

6. a. Page 16, Section **12.0 COMPUTER SYSTEMS FOR DATA MANAGEMENT**. The following was added to Table 2 in this section:

   "

Analyst	AB Sciex	Bioanalytical (3,4-DAP levels in plasma)

   "

   b. The reason for this change was to include the computer system to be used for analysis of 3,4-DAP levels in plasma.

In addition to the changes listed above, (referenced throughout the protocol by "Amended"), the Title Page has been updated to reflect this amendment.

AMENDED PROTOCOL 2 SIGNATURES

APPROVED, TESTING FACILITY:

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

01 March 2021
Date

Dean J. Kobs, M.S.
Manager, Safety Assessment

04 MARCH 2021
Date

APPROVED, SPONSOR:

See Attachment
for Signature

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

Date

AMENDED PROTOCOL 2 SIGNATURES

APPROVED, TESTING FACILITY:

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

Date

Dean J. Kobs, M.S.
Manager, Safety Assessment

Date

APPROVED, SPONSOR:

ODELL.LINDSAY.THOMAS.1242936830

Digitally signed by ODELL.LINDSAY.THOMAS.1242936830
Date: 2021.03.01 16:11:49 -05'00'

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

Date

List of Changes in Amended Protocol 3

The following items have been changed/revied from Amended Protocol 2 signed on March 1, 2021:

1. a. Title Page. The name of the testing facility has been changed from "Battelle – West Jefferson (JM10) to "AmplifyBio".
   b. The reason for this change is to reflect the name change of the testing facility.
2. a. Page 5, Section **4.1 TESTING FACILITY**. The testing facility name has been changed from "Battelle – West Jefferson" to "AmplifyBio".
3. a. Page 6, Section 5.2 **BATTELLE – WEST JEFFERSON**. The principal investigator for Pharmacokinetic Analysis has been removed.
   b. The reason for this change was to reflect the change in the Principal Investigator to a Contributing Scientist within the testing facility.
4. a. Page 7, Section **8.1 TEST ARTICLE**. In the second and third sentences of the test article description, "Battelle" has been changed to AmplifyBio".
   b. In the paragraph immiedately following Expiration Date, "Battelle" has been changed to "AmplifyBio".
   c. The reason for this change is to reflect the name change of the testing facility.
5. a. Page 8, Section **9.0 TEST SYSTEM**. In the second sentence of Special Consideration, "Battelle" has been changed to "AmplifyBio".
   b. The reason for this change is to reflect the name change of the testing facility.
6. a. Page 8, Section **9.1 ANIMALS**. In the second sentence of this section, "Battelle" has been changed to "AmplifyBio".
   b. The reason for this change is to reflect the name change of the testing facility.
7. a. Page 13, Section **10.6 PHARMACOKINETIC ANALYSIS**. In the first sentence of this section, "Battelle" has been changed to "AmplifyBio".
   b. The reason for this change is to reflect the name change of the testing facility.
8. a. Pages 13 and 14, Section **11.1 RECEIPT AND QUARANTINE**. Throughout this section, "Battelle" has been changed to "AmplifyBio".
   b. The reason for this change is to reflect the name change of the testing facility.
9. a. Page 14, Section **11.2 VETERINARY CARE**. In the second and third sentences of this section, "Battelle" has been changed to "AmplifyBio".
   b. The reason for this change is to reflect the name change of the testing facility.

10. a. Page 14, Section **11.3 PAIN AND DISTRESS**. In the first and second sentences of the second paragraph of this section, "Battelle" has been changed to "AmplifyBio".

    b. The reason for this change is to reflect the name change of the testing facility.

11. a. Page 14, Section **11.4 CRITERIA FOR EUTHANASIA**. In the first sentence of the first paragraph in this section, "Battelle" has been changed to "AmplifyBio".

    b. In the first sentence of the second paragraph in this section, "Battelle" has been changed to "AmplifyBio".

    c. The reason for this change is to reflect the name change of the testing facility.

12. a. Page 17, Section **15.0 STORAGE OF STUDY MATERIALS AND RECORDS RETENTION**. Table 3 Storage of Study Materials has been updat4ed.

    b. The reason for this change was to reflect the name change of the testing facility, and to clarify the storage location of study materials.

13. a. Page 17, Section 16.0 Biosafety Considerations. In the first sentence of this section, "Battelle" has been changed to "AmplifyBio".

    b. The reason for these changes is to reflect the name change of the testing facility.

14. a. Throughout. References to "Battelle SOPs" or specific "Battelle" SOP numbers have been updated to "AmplifyBio SOPs" or specific "AmplifyBio SOP" numbers.

    b. The reason for these changes is to reflect the name change of the testing facility.

In addition to the changes listed above (referenced throughout the protocol by "Amended"), the Title Page has been updated to reflect this amendment and the updated testing facility logo, and the header of all pages has been updated to reflect the correct study number.

AMENDED PROTOCOL 3 SIGNATURES

APPROVED, TESTING FACILITY:

Phillip H. Beske — 01 May 2021

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

Date

See Attachment for Signature

Dean J. Kobs, M.S.
Director of Study Oversight

Date

APPROVED, SPONSOR:

See Attachment for Signature

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

Date

AMENDED PROTOCOL 3 SIGNATURES

APPROVED, TESTING FACILITY:

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

Date

Dean J. Kobs, M.S.
Director of Study Oversight

June 3, 2021
Date

APPROVED, SPONSOR:

ODELL.LINDSAY.THOMAS.1242936830

Digitally signed by ODELL.LINDSAY.THOMAS.1242936830
Date: 2021.04.29 12:36:13 -04'00'

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

Date

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-B05928-WJ-0001	3/1/2021-3/8/2021	Protocol section 10.4 (Blood Collection) states, "Whole blood samples will be collected at baseline (pre-dose) and at the following times following the single or repeat dose: 5 (±30 sec), 15 (±1 min), 30 (±1 min), 60 (±2 min), 120 (±5 min), 240 (±5 min), 360 (±5 min). On IV Dose Day 1, 4 animals (6 timepoints) had blood collected outside of the protocol-specified time range by 1 to 5 minutes. On IV Dose Day 2, 2 animals (2 timepoints) had blood collected outside of the protocol-specified time range by <1 to 3 minutes. On IV Dose Day 3, 5 animals (6 timepoints) had blood collected outside of the protocol-specified time range by <1 to 2 minutes.	The out-of-specification blood collection times are minimally outside of a relatively narrow protocol-specified time window relative to dosing. These out-of-specification collections are not anticipated to adversely impact interpretation of study results. Data will be reviewed by a trained pharmacokineticist and excluded from analysis as warranted.
		Protocol section 10.3.2 (Post-Dosing) states, "…clinical observations will be recorded at each blood collection timepoint." On IV Dose Day 1, the clinical observation (at the time of blood collection) was recorded for 2 animals at 1 to 5 minutes outside the scheduled timepoint.	The intent of the protocol was to collect clinical observations at or approximate to each blood collection time-point. Observations shortly before or after blood collection (actual range of 1-5 minutes) meets the intent of the protocol and does not adversely interpretation of study results. Clinically normal status was maintained throughout IV dosing, with few exceptions on Dose Day 3 (4.12 mg/kg 3,4-DAP).

Deviation Number	Date Occurred	Description	Impact
DR-B05928-WJ-0003	4/12/2021-4/19/2021	Protocol section 10.4 (Blood Collection) states, "Whole blood samples will be collected at baseline (pre-dose) and at the following times following the single or repeat dose: 5 (±30 sec), 15 (±1 min), 30 (±1 min), 60 (±2 min), 120 (±5 min), 240 (±5 min), 360 (±5 min). On PO Dose Day 1, 4 animals (6 timepoints) had blood collected outside of the protocol-specified time range by <1 to 6 minutes. On PO Dose Day 2, 4 animals (4 timepoints) had blood collected outside of the protocol-specified time range by <1 to 9 minutes. On PO Dose Day 3, 2 animals (2 timepoints) had blood collected outside of the protocol-specified time range by <1 to 2 minutes.	The out-of-specification blood collection times are minimally outside of a relatively narrow protocol-specified time window relative to dosing. These out of specification collections are not anticipated to adversely impact interpretation of study results. Data will be reviewed by a trained pharmacokineticist and excluded from analysis as warranted.
		Protocol Section 10.3.1 (Prior to Dosing) states "Cage-side AM/PM clinical observations will be performed twice daily in accordance with AmplifyBio SOP COR.V-005, except on the day of receipt where only a single observation may be performed." The AM observation for Animal AL110O was not performed on PO Dose Day 1.	The missing AM observation does not adversely impact the study as Animal AL110O was not dosed on 12Apr2021. A PM observation was performed and the NHP was observed as clinically normal except for discolored skin.
		Protocol Section 10.3.2 (Post-Dosing) states "…clinical observations will be recorded at each blood collection timepoint." On PO Dose Day 1, an observation was not recorded for Animal ID BF873I at the 60-minute time point.	The missing clinical observation at the 60-minute time point does not adversely impact the study as the animal was observed as clinically normal in the following 3 time points.
DR-B05928-WJ-0004		Section 9.3 of the Study Protocol states: "Animals will be implanted with two vascular access ports (VAPs), with one cathether implanted in either the jugular or femoral vein and one catheters implanted in either the femoral or carotid artery." For surgeries performed on January 14, 2021, Animal N378ALE only had a femoral vein VAP implanted. An arterial catheter was not able to be placed due to size constraints.	The implantation of only a venous catheter did not adversely impact the study objective. Animal N378ALE was successfully dosed throughout the study and blood samples were successfully collected to determine 3,4-DAP levels in collected samples.

Appendix B Test and Control Article Information

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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309 Delaware Street
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

Version # 5.0

Hospira Inc, a Pfizer Company
DOC # WGFCFMQAIN

REVW:	03/17/2020	**EFFC:**	08/25/2020	**SUBTYPE:**	9	**AREA:**	Q
DESC:	Manufacturing Quality Index Sheet						
Written By/Date:	H. Bodas 3-17-20			**FE:**	None	**UNIT:**	FCF/Rocky Mount
Approved By/Date:	BRQ R. Slade	7-31-20					

Specification and SOP No.:	QCP.05.001, BFCF_MQA_WOAUD00.EWI

Technical Notes:	None

Lab Data Checklist:

Biological (BQ)	Yes	N/A
Chemistry (CQ)	Yes	N/A

I verified that the above packages are present in the batch record.

25NOV2020
Batch Release Specialist/Designee

7983-04-64 22-507-FW EXP. DATE 1OCT2022
0.9% SODIUM CHLORIDE INJ., USP

Comments: PERRYHM 10/06/20

Technical Notes:

The Batch Record Specialist/Designee must complete the checklist below to ensure that all packages within each batch record are inclusive/present and have been audited prior to final release. N/A indicates that the package is not required.

Batch Record Package Checklist:

Solution	Yes	N/A
Equipment	Yes	N/A
Commodity	Yes	N/A
Filling	Yes	N/A
R2 Labeling	Yes	N/A
Label Room	Yes	N/A
Finishing	Yes	N/A
Overwrap	Yes	N/A
Fabrication	Yes	N/A
Sterilizer	Yes	N/A

I have verified that the above packages have been audited and are present in the batch record.

25 NOV 2020

Batch Release Specialist/Designee

Version # 5.0

Hospira Inc, a Pfizer Company
DOC # WGFCFMQAIN

Overall Page: 1258 of 1259
Page 3 of 4

STEP/PROCEDURE	REF. DOC.	EXCEPTION DOCUMENTS	ENTERED BY DATE
1. If batch record requires exception documents, then exception document numbers are:	S6100_0070 S6100_0203		(✓) N/A
2. Is this package a Master/Reference batch record? YES (NO) (circle one) If yes then all Master/Reference requirements must be met.	S6116_0357		
3. I certify that the following batch record has met all specifications relevant to the production, control, and release of this lot.			25NOV2020 FINAL BATCH RECORD REVIEW

Final Approval Release Information

Matitm/List (1) Batch Record Acc. No. (1)

Manufacturing Department: (1) ( ) FCF-0580 ( ) DCIC-0504

Entry Code: (1) ( ) 307 ( ) 309-DCIC

Load	Quantity	Load	Quantity	Load	Quantity
N/A (1)	9178 N/A (1)	N/A (1)		N/A (1)	

Check Appropriate Box: (✓) Final Release ( ) Partial Release
( ) Lot Rejection

Material Status Change By: _____ Date: 25NOV2020

END OF DOCUMENT

Expiration date 10012022 verified to be correct for lot 22-507-FW 25NOV2020 Verified by N.S. 11.25.2020

(1) N/A's information not needed 25NOV2020

7983-04-64 22-507-FW EXP. DATE 1OCT2022
0.9% SODIUM CHLORIDE INJ., USP

Comments: PERRYHM 10/06/20

Version # 7.0

Hospira Inc, a Pfizer Company
DOC # W7983CQA

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Page 1 of 7

REVW:	05/05/2020	EFFC:	06/15/2020	SUBTYPE:	7	AREA:	T
DESC:	Certificate of Analysis Hospira, Inc. (Rocky Mount N.C.) CQ						
Written By/Date:	D. Hedrick 5-5-20			FE:	None	UNIT:	FCF/PF/Rocky Mount
Approved By/Date:	CQ T. Hardison	6-8-20		BRQ M. Thorne			6-8-20

Specification No.:	60.07983ALLCODE

Technical Note:

1. This product has been manufactured and tested in current good manufacturing practices (CGMP) facilities in accordance with appropriate regulations. This product meets applicable specifications, applicable regulatory submissions or marketing authorizations and, where appropriate, compendial requirements. The undersigned certifies this to be a true representation of the results.
2. Pfizer list 079830424 corresponds to ICU List 079830416
3. Pfizer list 079830464 corresponds to ICU List 079830466
4. Pfizer list 079830473 corresponds to ICU List 079830456
5. Pfizer list 079830489 corresponds to ICU List 079830450

Product Manufacturing Information

Date of Manufacture: 26 Oct 2020 Batch Size 1290000L NDC No.: 0990798303

Final Released Accountability: 220272 Units 9178 Cases

STEP/PROCEDURE	DOC. REF.	SIGNATURE/DATE
Manufacturing Formula	92.D-7983 Current Date: 01-30-14	
Commodity and Process Summary	35.079830464 Current Date: 06-13-19	
Printed Material Summary	40.0798304AC Current Date: 05-26-20	
Sampling and Testing Requirements	60.07983ALLCODE Current Date: 08-20-19	

Dates Manufactured From 26 Oct 2020 To 28 Oct 2020

Enter By/Date 25 NOV 2020

Water For Injection, USP - Pass ✓ Fail ____

Signature/Date 25 NOV 2020

7983-04-64 22-507-FW EXP. DATE 1OCT2022
0.9% SODIUM CHLORIDE INJ., USP

Comments: PERRYHM 10/06/20

Version # 7.0

Hospira Inc, a Pfizer Company
DOC # W7983CQA

Overall Page: 1244 of 1259
Page 2 of 7

PRODUCT TEST RESULTS

STEP/PROCEDURE	DOC. REF.	RESULTS	SIGNATURE/DATE
Batch Release Systems I. Physical Requirements: A. Clarity. 1. Solution must be clear. 2. Solution must not contain one or more particles which are visible upon attentive examination.	90.P-0416	Pass ✓ Fail___	
B. Volume (250 mL) 250 to 300 mL (500 mL) 500 to 560 mL (1000 mL) 1000 to 1055 mL	90.P-0759	539 mL Average	
C. Sterility Must meet Requirements of Parametric release.	90.M-0476 (04-44,04-49) 90.M-0477 (All other codes)	Pass ✓ Fail___	
D. QAR Yes ( ) No (✓) Check Applicable Box QAR Number___ QAR Number___ QAR Number N/A QAR Number___			

25/10/2020
BRQ REVIEW

7983-04-64 22-507-FW EXP. DATE 1OCT2022
0.9% SODIUM CHLORIDE INJ., USP

Comments: PERRYHM 10/06/20

Version # 7.0

Hospira Inc, a Pfizer Company
DOC # W7983CQA

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STEP/PROCEDURE	DOC. REF.	RESULTS	SIGNATURE/DATE
II. Chemical Requirements:			
A. Sodium Chloride Final product limits 95.0% to 105.0%	90.C-0042 (1)	97.5 %	
B. Elemental Impurities	90.C-2377 (1)	Pass Pass ✓ Fail ___	
Hg NMT 0.75 ng/mL		LT 0.38 ng/mL	
Cd NMT 1.0 ng/mL		LT 0.50 ng/mL	
Pb NMT 2.5 ng/mL		None Detected ng/mL	
Co NMT 2.5 ng/mL		None Detected ng/mL	
Tl NMT 4 ng/mL		LT 2.00 ng/mL	
Ir NMT 5 ng/mL		None Detected ng/mL	
Os NMT 5 ng/mL		LT 2.50 ng/mL	
Pt NMT 5 ng/mL		None Detected ng/mL	
Pd NMT 5 ng/mL		LT 2.50 ng/mL	

(1) Results transcribed from g-lims. [illegible] 11/25/20

7983-04-64 22-507-FW EXP. DATE 1OCT2022
0.9% SODIUM CHLORIDE INJ., USP

Comments:

PERRYHM 10/06/20

Version # 7.0

Hospira Inc, a Pfizer Company
DOC # W7983CQA

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STEP/PROCEDURE	DOC. REF.	RESULTS	SIGNATURE/DATE
Rh NMT 5 ng/mL	(1)	LT 2.50 ng/mL	
Ru NMT 5 ng/mL	(1)	LT 2.50 ng/mL	
V NMT 5 ng/mL	(1)	LT 2.50 ng/mL	
As NMT 7.5 ng/mL	(1)	LT 3.75 ng/mL	
Ag NMT 5 ng/mL	(1)	None Detected ng/mL	
Ni NMT 10 ng/mL	(1)	None Detected ng/mL	
Mo NMT 45 ng/mL	(1)	LT 20.0 ng/mL	
Se NMT 40 ng/mL	(1)	None Detected ng/mL	
Au NMT 50 ng/mL	(1)	LT 25.0 ng/mL	
Cu NMT 65 ng/mL	(1)	LT 25.0 ng/mL	
Li NMT 125 ng/mL	(1)	LT 25.0 ng/mL	
Sb NMT 45 ng/mL	(1)	None Detected ng/mL	
Sn NMT 300 ng/mL	(1)	LT 25.0 ng/mL	
Cr NMT 550 ng/mL	(1)	None Detected ng/mL	

(1) Refer to Sample manager COA. [illegible] 11/25/20

7983-04-64 22-507-FW EXP. DATE 1OCT2022
0.9% SODIUM CHLORIDE INJ., USP

Comments:

PERRYHM 10/06/20

Version # 7.0

Hospira Inc, a Pfizer Company
DOC # W7983CQA

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Page 5 of 7

STEP/PROCEDURE	DOC. REF.	RESULTS	SIGNATURE/DATE
Ba NMT 350 ng/mL	①	None. Detected ng/mL	
Zn NMT 650 ng/mL	①	LT 1.63 ng/mL	
Mn NMT 125 ng/mL	①	None Detected ng/mL	
Fe NMT 650 ng/mL	①	LT 1.63 ng/mL	

① Results transcribed from g-lims. [illegible] 11/25/20

7983-04-64 22-507-FW EXP. DATE 1OCT2022
0.9% SODIUM CHLORIDE INJ., USP

Comments: PERRYHM 10/06/20

Version # 7.0

Hospira Inc, a Pfizer Company
DOC # W7983CQA

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STEP/PROCEDURE	DOC. REF.	RESULTS	SIGNATURE/DATE
C. Iron Final product limits: Not more than 0.0002% (2 ppm)	90.C-0869 (1)	NMT 0.0002 %	
D. Identification Responds to test for: Sodium Chloride	 90.C-1648 (1) 90.C-0003 (1)	 Pass ✓ Fail ___ Pass ✓ Fail ___	
E. pH Final product limits: 4.5 and 7.0	90.C-0021 (1)	6.2	
F. Residual Solvents Meets USP <467>	N/A	No Class 1, Class 2, Class 3 or other solvents used. Drug product testing is not required.	
		(2) N/A CQ REVIEW	

(1) Results transcribed from g-lims. [illegible] 11/25/20
(2) Electronic Signature. [illegible] 11/25/20

60.Document Exceptions:
Please list all exceptions to the 60.document, related tests, the date these tests were initiated, and the test results.

Document #	Related Test	Date Test Initialized	Test Results
	N	[illegible] 25 NOV 2020	
	A		

STEP/PROCEDURE	SIGNATURE/DATE
The undersigned certifies that the information contained herein is accurate and complete, and the release for distribution was approved.	[illegible] 25 NOV 2020 QUALITY HOSPIRA, INC. ROCKY MOUNT, NC

7983-04-64 22-507-FW EXP. DATE 1OCT2022
0.9% SODIUM CHLORIDE INJ., USP

Comments: PERRYHM 10/06/20

Note: Once product is released, email a copy of the completed Certificate of Analysis to:

DL-Distribution-Quality@icumed.com

A H Randolph
Sent By

25Nov2020
Date

END OF DOCUMENT

Version # 5.0

Hospira Inc, a Pfizer Company
DOC # W7983BQAC

Overall Page: 1252 of 1259
Page 1 of 1

REVW:	04/05/2013	EFFC:	08/26/2013	SUBTYPE:	8	AREA:	B
DESC:	Certificate of Analysis Hospira, Inc. (Rocky Mount N.C.) BQ						
Written By/Date:	L. Debusk 4-11-13			FE:	None	UNIT:	FCF/PF/Rocky Mount
Approved By/Date:	BQ J. Miles	8-19-13					

Specification No.:	60.07983ALLCODE, QPO.18.004

Technical Note:

1. This product has been manufactured and tested in current good manufacturing practices (CGMP) facilities in accordance with appropriate regulations. This product meets applicable specifications, applicable regulatory submissions or marketing authorizations and, where appropriate, compendial requirements. The undersigned certifies this to be a true representation of the results.

Product Test Results

STEP/PROCEDURE	DOC. REF.	RESULTS	SIGNATURE/DATE
I. Physical Requirements A. Particulate Matter 1. Must meet test requirements.	90.P-0452 (1) LIMS Generated	Pass ✓ Fail___	
2. Report the numerical results found.		≥ 10UM ≥ 25UM 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0	(2) N/A TRANSCRIBED BY
II. Biological Requirements A. Bacterial Endotoxin Not more than 0.50 EU/ML	90.B-0813 (1) LIMS Generated	<0.25 EU/ML	
B. Solution Bioburden Must meet requirements	QPO.29.001 WGENVIRO	Pass ✓ Fail___	AWLO 11-6-20 (3) N/A BQ REVIEW

END OF DOCUMENT

(1) Results transcribed from g-lims. [illegible] 11/25/20
(2) lines not needed. [illegible] 11/25/20
(3) Electronic Signature. [illegible] 11/25/20

7983-04-64 22-507-FW EXP. DATE 1OCT2022
0.9% SODIUM CHLORIDE INJ., USP

Comments: PERRYHM 10/06/20

HOSPIRA, INC. - ROCKY MOUNT, NC

DATED: 10-05-17 W4887CQA PAGE 1

REVW *10-04-09* EFFC *10-05-17* SUBTYPE-7 AREA-T
Desc: Certificate of Analysis Hospira, Inc. (Rocky Mount N.C.) CQ
Written By/Date: B. Catlett 4-20-10 Unit: SVP/Rocky Mount
Approved By/Date: CQ D. Short 4-23-10 BRQ M. Thorne 5-13-10
O2O J. Brown 4-23-10

Specification No.: QPO.18.004

Technical Note:

1. This product has been manufactured and tested in current good manufacturing practices (CGMP) facilities in accordance with appropriate regulations. This product meets applicable specifications, applicable regulatory submissions or marketing authorizations and, where appropriate, compendial requirements. The undersigned certifies this to be a true representation of the results.

Product Manufacturing Information

Date of Manufacture: 16 Jul 2018 Batch Size 6000 L NDC/DIN No.: 0409488799

STEP/PROCEDURE	DOC. REF.	SIGNATURE/DATE
Manufacturing Formula	92.D-4887 Current Date: 01/25/17	
Commodity and Process Summary	35. 048870485 Current Date: 02/22/17	
Printed Material Summary	40. 048870 2AC Current Date: 02/23/16	
Sampling and Testing Requirements	60.04887ALLCODE Current Date: 04/12/17	B. White 09 Aug 2018

****

Date Manufactured 16 Jul 2018

Water For Injection, USP - Pass ✓ Fail

Signature/Date B. White 09 Aug 2018

4887-04-85 100ML 2 91-264-DK EXP. DATE 1JUL2021 JD21182
STERILE WATER FOR INJ.,USP

COMMENTS:

ISSUER: JEFFRCL 07/13/18

HOSPIRA, INC. - ROCKY MOUNT, NC
DATED: 10-05-17 W4887CQA PAGE 2

PRODUCT TEST RESULTS

STEP/PROCEDURE	DOC. REF.	RESULTS	SIGNATURE/DATE
I. Batch Release Systems			
A. Clarity	90.P-0146	Pass ✓ Fail___	
1. Solution must be clear			
2. Solution must not contain one or more particles which are visible			
B. Volume	90.P-0129	105.0 mL	
1.1 to 1.3 ml		Average	
10.3 to 11.3 ml			
20.5 to 22.5 ml			
25.5 to 27.5 ml			
51.0 to 55.0 ml			
102.0 to 108.0 ml			
C. Sterility Must meet requirements of parametric release	90.M-0477	Pass ✓ Fail___	B. White 09Aug 2018 BRQ REVIEW

4887-04-85 100ML 2 91-264-DK EXP. DATE 1JUL2021 JD21182
STERILE WATER FOR INJ.,USP

COMMENTS:

ISSUER: JEFFRCL 07/13/18

HOSPIRA, INC. - ROCKY MOUNT, NC
DATED: 10-05-17 W4887CQA PAGE 3

STEP/PROCEDURE	DOC. REF.	RESULTS	SIGNATURE/DATE
II. Chemical Requirements			
A. Color Solution must be colorless.	90.P-0613		
B. Oxidizable Substance Passes USP test	90.C-0062		
C. Conductivity NMT 25 US/CM (Fill volumes of 10ml or less) NMT 5 US/CM (Fill volumes of greater than 10ml)	90.C-1330	① N/A	
D. Residual Solvents Meets USP <467>	N/A	No Class 1, Class 2, Class 3 or other solvents are used in the manufacturing of this product. Drug product testing is not required.	① N/A CQ REVIEW

ER-High Yes ( ) No (✓) Check applicable box ER No. NA Bulk Date 09/19/2018

****

END OF DOCUMENT

① Refer to sample manager (QA). 08/01/18

4887-04-85 100ML 2 91-264-DK EXP. DATE 1JUL2021 JD21182
STERILE WATER FOR INJ.,USP

COMMENTS:

ISSUER: JEFFRCL 07/13/18

HOSPIRA, INC. - ROCKY MOUNT, NC

DATED: 13-08-26 W4887BQAC PAGE 1

REVW *13-04-05* EFFC *13-08-26* SUBTYPE-8 AREA-B
Desc: Certificate of Analysis Hospira, Inc. (Rocky Mount N.C.) BQ
Written By/Date: L. Debusk 4-11-13 Unit: SVP/Rocky Mount
Approved By/Date: BQ J. Miles 8-19-13

Specification No.: 60.04887ALLCODE, QPO.18.004

Technical Note:
1. This product has been manufactured and tested in current good manufacturing practices (CGMP) facilities in accordance with appropriate regulations. This product meets applicable specifications, applicable regulatory submissions or marketing authorizations and, where appropriate, compendial requirements. The undersigned certifies this to be a true representation of the results.

Product Test Results

STEP/PROCEDURE	DOC. REF.	TARGET	RESULTS	
I. Physical Requirements	90.P-1078	Must meet	Pass___	Fail___
A. Particulate Matter	LIMS Generated	USP test requirement		① N/A
		Report numerical results found	≥ 10UM	≥ 25UM
II. Biological Requirements				
A. Bacterial Endotoxin Test	90.B-0610 LIMS Generated	Less than 0.25 EU/ML		EU/ML
B. Solution Bioburden Must meet requirements	QPO.29.001 WGENVIRO	Pass ✓ Fail___		

Entered By/Date: Nutt 7-23-18

Transcription verified by/Date: Cjenl Cabett ② ~~23 JUL~~ 23 JUL 2018

② ~~Dater~~

****

END OF DOCUMENT

② entry error Cjenl Cabett 23 JUL 2018

4887-04-85 100ML 2 91-264-DK EXP. DATE 1JUL2021 JD21182
STERILE WATER FOR INJ.,USP

COMMENTS: ① Reference LIMS COA. Nutt 7-23-18

ISSUER: JEFFRCL 07/13/18

Hospira

Highway 301 North
Rocky Mount, North Carolina 27801

Certificate of Analysis for BQ and CQ
Product Lot

List Number:
4887 0485

Product Name:
STERILE WATER FOR INJECTION, USP

Lot Number:
91-264-DK

Expiration Date:
July 01, 2021

Test	Specification	Results
Bacterial Endotoxin / B0610	<0.25 EU/ml	Less Than 0.06 EU/ml
Oxidizable Substance / C0062	PASSES USP TEST	PASSES USP TEST
Conductivity Reported > 10 mL / C1330	<=5 uS/cm	2 uS/cm
Color / P0613	SOLUTION MUST BE COLORLESS	SOLUTION IS COLORLESS
Average of Beg 1(10 microns) / P1078	<6000	520
Average of Beg 1(25 microns) / P1078	<600	0
Average of Beg 2(10 microns) / P1078	<6000	280
Average of Beg 2(25 microns) / P1078	<600	0
Average of Beg 3(10 microns) / P1078	<6000	460
Average of Beg 3(25 microns) / P1078	<600	0
Particulate Matter / P1078	MEETS TEST REQUIREMENTS	MEETS TEST REQUIREMENTS
Average of Middle 1(10 microns) / P1078	<6000	233
Average of Middle 1(25 microns) / P1078	<600	0
Average of Middle 2(10 microns) / P1078	<6000	133
Average of Middle 2(25 microns) / P1078	<600	0
Average of Middle 3(10 microns) / P1078	<6000	533
Average of Middle 3(25 microns) / P1078	<600	0
Average of Middle 4(10 microns) / P1078	<6000	680
Average of Middle 4(25 microns) / P1078	<600	0
Particulate Matter / P1078	MEETS TEST REQUIREMENTS	MEETS TEST REQUIREMENTS
Average of End 1(10 microns) / P1078	<6000	507

List Number:

4887 0485

Product Name:

STERILE WATER FOR INJECTION, USP

Lot Number:

91-264-DK

Expiration Date:

July 01, 2021

Test	Specification	Results
Average of End 1(25 microns) / P1078	<600	0
Average of End 2(10 microns) / P1078	<6000	780
Average of End 2(25 microns) / P1078	<600	0
Average of End 3(10 microns) / P1078	<6000	460
Average of End 3(25 microns) / P1078	<600	0
Particulate Matter / P1078	MEETS TEST REQUIREMENTS	MEETS TEST REQUIREMENTS

This is to Certify that Quality Assurance of the above mentioned production lot including testing, investigation, quality control and general standards of workmanship has been audited by the Quality Assurance Auditor(s) and have found that STERILE WATER FOR INJECTION, USP to be in COMPLIANCE with the requirements per procedures and/or recognized standards.

Authorized By: Geneva Fuller

Authorized Date: August 01, 2018

Printed By: GFuller

Print Date: 08/01/18

Confidential

Appendix C In-Life Animal Data

Table C-1. Intravenous Dose Day Observations

Study B05928
Dose Day Observations

ID	Dose Day	Group	Route	3,4-DAPP Dose	Dose Frequency	Clinical Observations Relative To First Dosing (single) or Second Dosing (repeat)							
						5 min Post	15 min Post	30 min Post	60 min Post	120 min Post	240 min Post	360 min Post	Additional Comments
VL90IA	IV[1]	1	IV	1.03 mg/kg	single	N	N	N	N	N	N	N	
YR895FD						N	N	N	N	N	N	N	LW
AL793H						N	N	N	N	N	N	N	
AL110O						N	N	N	N	N	N	N	
BF8731		2			repeat	N	N	N	N	N	N	N	LW
G180JD						N	N	N	N	N	N	N	
N378ALE						N	N	N	N	N	N	N	
AP55D						N	N	N	N	N	N	N	
BF8731	IV[2]	2		2.06 mg/kg	single	N	N	N	N	N	N	N	LW
G180JD						N	N	N	N	N	N	N	
N378ALE						N	N	N	N	N	N	N	
AP55D						N	N	N	N	N	N	N	
VL90IA		1			repeat	N	N	N	N	N	N	N	
YR895FD						N	N	N	N	N	N	N	LW
AL793H						N	N	N	N	N	N	N	
AL110O						N	N	N	N	N	N	N	
VL90IA	IV[3]	1		4.12 mg/kg	single	N	N	N	N	N	N	N	
YR895FD						N	N	N	N	N	N	N	LW, RF
AL793H						N	N	N	N	N	N	N	
AL110O						N	N	N	N	N	N	N	
BF8731		2			repeat	N	EM (F, W)	N	N	N	N	N	LW
G180JD						EM (F,W)	N	N	N	N	N	N	C1
N378ALE						N	N	N	N	N	N	N	
AP55D						EM (F, W)	N	N	N	N	N	N	

IV = intravenous
N = Normal
LW = limb weakness, hind limb, right

RF = low food consumption (half or less of total food)
EM = emesis (F = foamy, W = white)

C1 = emesis at 3 min after first dosing

Table C-2. Subcutaneous Dose Day Observations

Study B05928
Dose Day Observations

ID	Dose Day	Group	Route	3,4-DAPP Dose	Dose Frequency	Clinical Observations Relative To First Dosing (single) or Second Dosing (repeat)							
						5 min Post	15 min Post	30 min Post	60 min Post	120 min Post	240 min Post	360 min Post	Additional Comments
BF8731	SC[1]	2	SC	1.03 mg/kg	single	N	N	N	N	N	N	N	
G180JD						N	N	N	N	N	N	N	
N378ALE						N	N	N	N	N	N	N	
AP55D						N	N	N	N	N	N	N	
VL90IA		1			repeat	N	N	N	N	N	N	N	
YR895FD						N	N	N	N	N	N	N	
AL793H						N	N	N	N	N	N	N	
AL110O						N	N	N	N	N	N	N	
VL90IA	SC[2]	1		2.06 mg/kg	single	N	N	N	N	N	N	N	
YR895FD						N	N	N	N	N	N	N	
AL793H						N	N	N	N	N	N	N	
AL110O						N	N	N	N	N	N	N	
BF8731		2			repeat	N	N	N	N	N	N	N	
G180JD						N	N	N	N	N	N	N	
N378ALE						N	N	N	N	N	N	N	
AP55D						N	N	N	N	N	N	N	
BF8731	SC[3]	2		4.12 mg/kg	single	N	N	N	N	N	N	N	
G180JD						N	N	N	N	N	N	N	
N378ALE						N	N	N	N	N	N	N	
AP55D						N	N	N	N	N	N	N	
VL90IA		1			repeat	N	N	N	N	N	N	N	
YR895FD						N	N	N	N	N	N	N	C2
AL793H						N	N	N	N	N	N	N	C3
AL110O						N	N	N	N	N	N	N	C4

SC = subcutaneous
N = Normal
LW = limb weakness, hind limb, right

EM = emesis (F = foamy, W = white)
C2 = E (F,W) at 1 hr 29 min after repeat dose
C3 = E (food) at 1 hr 11 min after first dosing

C4 = E (F) at 1 hr 6 min after first dosing

Table C-3. Oral Dose Day Observations

Study B05928
Dose Day Observations

ID	Dose Day	Group	Route	3,4-DAPP Dose	Dose Frequency	Clinical Observations Relative To First Dosing (single) or Second Dosing (repeat)							
						5 min Post	15 min Post	30 min Post	60 min Post	120 min Post	240 min Post	360 min Post	Additional Comments
VL90IA	PO[1]	1	PO	1.03 mg/kg	single	N	N	N	N	N	N	N	
YR895FD						N	N	N	N	N	N	N	
AL793H						N	N	N	N	N	N	N	
AL110O						Animal Not Dosed							
BF8731		2			repeat	N	N	N		N	N	N	
G180JD						N	N	N	N	N	N	N	
N378ALE						N	N	N	N	N	N	N	
AP55D						N	N	N	N	N	N	N	
BF8731	PO[2]	2		2.06 mg/kg	single	N	N	N	N	N	N	N	
G180JD						N	N	N	N	N	N	N	
N378ALE						N	N	N	N	N	N	N	
AP55D						N	N	N	N	N	N	N	
VL90IA		1			repeat	N	N	N	N	N	N	N	
YR895FD						N	N	N	N	N	N	N	LW
AL793H						N	N	N	N	N	N	N	
AL110O						Animal Not Dosed							
VL90IA	PO[3]	1		4.12 mg/kg	single	N	N	N	N	N	N	N	
YR895FD						N	N	N	N	N	N	N	
AL793H						N	N	N	N	N	N	N	
AL110O						N	N	N	N	N	N	N	
BF8731		2			repeat	N		N	N	N	N	N	
G180JD						N		N	N	N	N	N	
N378ALE						N		N	N	N	N	N	
AP55D						N		N	N	N	N	N	

PO = oral
N = Normal
LW = limb weakness, hind limb, right

Table C-4. Individual Animal Clinical Signs

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Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		-3	-2	-1	1	2	3	4
VL90IA !	Normal	X	X	.	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Skin Abrasion, Forelimb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	X	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
YR895FD !	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Limb Weakness, Hind Limb	RT	RT	RT	RT	RT	RT	RT
	Skin Abrasion, Body Dorsal	RT	.	.	.	.	.	.
	Skin Abrasion, Body Ventral	BT	.	.	.	.	.	.
	Skin Abrasion, Forelimb	.	.	.	.	.	.	.
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	X	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
AL793H !	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Food	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
AL110O !	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.

!=Result comment recorded against 1 or more clinical observations. X=Present; RT=Right; BT=Both

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Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		-3	-2	-1	1	2	3	4
AL110O !	Emesis, Foamy	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.

!=Result comment recorded against 1 or more clinical observations.

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		5	6	7	8	9	10	11
VL90IA !	Normal	.	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Skin Abrasion, Forelimb	.	.	.	.	.	.	.
	Low Food Consumption	RFC	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
YR895FD !	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Limb Weakness, Hind Limb	RT	RT	RT	RT	RT	RT	RT
	Skin Abrasion, Body Dorsal	.	.	.	.	.	.	.
	Skin Abrasion, Body Ventral	.	.	.	.	.	.	.
	Skin Abrasion, Forelimb	.	.	.	.	.	.	.
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	RFC	.	.	RFC	.	.	.
	Diarrhea	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
AL793H !	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Food	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
AL110O !	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.

!=Result comment recorded against 1 or more clinical observations. X=Present; RFC=1/2 or Less of Total Food; RT=Right

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		5	6	7	8	9	10	11
AL110O !	Emesis, Foamy	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.

!=Result comment recorded against 1 or more clinical observations.

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Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		12	13	14	15	16	17	18
VL90IA	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Skin Abrasion, Forelimb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
YR895FD	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Limb Weakness, Hind Limb	RT	RT	RT	RT	RT	RT	RT
	Skin Abrasion, Body Dorsal	.	.	.	.	.	.	.
	Skin Abrasion, Body Ventral	.	.	.	.	.	.	.
	Skin Abrasion, Forelimb	.	.	.	.	.	.	.
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
AL793H	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Food	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
AL110O	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.

X=Present; RT=Right

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		12	13	14	15	16	17	18
AL110O	Emesis, Foamy	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		19	20	21	22	23	24	25
VL90IA !	Normal	X	X	X	X	.	.	.
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Skin Abrasion, Forelimb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	RFC	.	.
	Diarrhea	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	X	.
YR895FD !	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Limb Weakness, Hind Limb	RT	RT	RT	.	RT	RT	.
	Skin Abrasion, Body Dorsal	.	.	.	.	.	.	.
	Skin Abrasion, Body Ventral	.	.	.	.	.	.	.
	Skin Abrasion, Forelimb	.	.	.	.	.	.	.
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	RFC	RFC	.
	Diarrhea	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
AL793H !	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Food	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
AL110O !	Normal	X	X	X	X	.	.	.
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.

!=Result comment recorded against 1 or more clinical observations. X=Present; RFC=1/2 or Less of Total Food; RT=Right

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		19	20	21	22	23	24	25
AL110O !	Emesis, Foamy	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	RFC	RFC	.
	Diarrhea	.	.	.	.	.	.	.

!=Result comment recorded against 1 or more clinical observations. RFC=1/2 or Less of Total Food

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		26	27	28	29	30	31	32
VL90IA !	Normal	X	X	X	X	.	.	X
	Discolored Skin, Body Ventral	.	.	.	.	Red	Red	.
	Skin Abrasion, Forelimb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	RFC	.	.
	Diarrhea	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
YR895FD !	Discolored Skin, Body Ventral	.	.	.	.	Red	Red	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	WH	.	.	.
	Limb Weakness, Hind Limb	RT	RT	RT	RT	RT	RT	RT
	Skin Abrasion, Body Dorsal	.	.	.	.	.	.	.
	Skin Abrasion, Body Ventral	.	.	.	.	.	.	.
	Skin Abrasion, Forelimb	.	.	.	.	.	.	.
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	RFC	.	.	.	RFC	.	.
	Diarrhea	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
AL793H !	Normal	X	X	X	.	.	X	X
	Discolored Skin, Body Ventral	.	.	.	.	Red	.	.
	Emesis, Food	.	.	.	X	.	.	.
	Low Food Consumption	.	.	.	.	RFC	.	.
	Soft Feces	.	.	.	.	.	.	.
AL110O !	Normal	.	X	X	.	.	.	.
	Discolored Skin, Body Ventral	.	.	.	.	Red	Red	Red
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.

!=Result comment recorded against 1 or more clinical observations. X=Present; Red=Red; RFC=1/2 or Less of Total Food; WH=White; RT=Right

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		26	27	28	29	30	31	32
AL110O !	Emesis, Foamy	.	.	.	X	.	.	.
	Low Food Consumption	RFC	.	.	.	RFC	.	.
	Diarrhea	.	.	.	.	.	.	X

!=Result comment recorded against 1 or more clinical observations. X=Present; RFC=1/2 or Less of Total Food

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		33	34	35	36	37	38	39
VL90IA	Normal	.	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Skin Abrasion, Forelimb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
	Soft Feces	X	.	.	.	.	.	.
YR895FD	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Limb Weakness, Hind Limb	RT	RT	RT	RT	RT	RT	RT
	Skin Abrasion, Body Dorsal	.	.	.	.	.	.	.
	Skin Abrasion, Body Ventral	.	.	.	.	.	.	.
	Skin Abrasion, Forelimb	.	.	.	.	.	.	.
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
	Soft Feces	X	.	.	.	.	.	.
AL793H	Normal	.	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Food	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Soft Feces	X	.	.	.	.	.	.
AL110O	Normal	.	.	.	.	.	.	.
	Discolored Skin, Body Ventral	Red	Red	Red	Red	Red	Red	Red
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.

X=Present; RT=Right; Red=Red

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		33	34	35	36	37	38	39
AL110O	Emesis, Foamy	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		40	41	42	43	44	45	46
VL90IA !	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Skin Abrasion, Forelimb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
YR895FD !	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Limb Weakness, Hind Limb	RT	RT	RT	.	RT	RT	RT
	Skin Abrasion, Body Dorsal	.	.	.	.	.	.	.
	Skin Abrasion, Body Ventral	.	.	.	.	.	.	.
	Skin Abrasion, Forelimb	.	.	.	.	.	.	.
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	RFC	RFC	.	RFC	.	.
	Diarrhea	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
AL793H !	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Food	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
AL110O	Normal	.	.	.	.	.	X	X
	Discolored Skin, Body Ventral	Red	Red	Red	Red	Red	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.

!=Result comment recorded against 1 or more clinical observations. X=Present; RT=Right; RFC=1/2 or Less of Total Food; Red=Red

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		40	41	42	43	44	45	46
AL110O	Emesis, Foamy	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		47	48	49	50	51	52	53
VL90IA !	Normal	X	X	X	X	X	X	.
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Skin Abrasion, Forelimb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	X
YR895FD !	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	Red	Red	Red	.	Red	Red	Red
	Emesis, Foamy	.	.	.	.	.	.	.
	Limb Weakness, Hind Limb	RT	RT	RT	.	RT	RT	RT
	Skin Abrasion, Body Dorsal	.	.	.	.	.	.	.
	Skin Abrasion, Body Ventral	.	.	.	.	.	.	.
	Skin Abrasion, Forelimb	.	.	.	.	.	.	.
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	RFC	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	X
AL793H !	Normal	X	X	X	X	X	X	.
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Food	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	X
AL110O !	Normal	X	.	.	.	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.

!=Result comment recorded against 1 or more clinical observations. X=Present; Red=Red; RT=Right; RFC=1/2 or Less of Total Food

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		47	48	49	50	51	52	53
AL110O !	Emesis, Foamy	.	.	.	.	.	.	.
	Low Food Consumption	.	RFC	RFC	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.

!=Result comment recorded against 1 or more clinical observations. RFC=1/2 or Less of Total Food

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		54	55	56	57	58	59	60
VL90IA	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Skin Abrasion, Forelimb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
YR895FD !	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	Red	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Limb Weakness, Hind Limb	RT	RT	RT	RT	RT	RT	RT
	Skin Abrasion, Body Dorsal	.	.	.	.	.	.	.
	Skin Abrasion, Body Ventral	.	.	.	.	.	.	.
	Skin Abrasion, Forelimb	.	.	.	.	.	.	.
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
AL793H	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Food	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
AL110O !	Normal	X	X	X	X	.	.	.
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	Red	Red

!=Result comment recorded against 1 or more clinical observations. X=Present; Red=Red; RT=Right

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		54	55	56	57	58	59	60
AL110O !	Emesis, Foamy	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	RFC	.	.
	Diarrhea	.	.	.	.	.	.	.

!=Result comment recorded against 1 or more clinical observations. RFC=1/2 or Less of Total Food

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		61	62	63	64	65	66	67
VL90IA	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Skin Abrasion, Forelimb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
YR895FD	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Limb Weakness, Hind Limb	RT	RT	RT	RT	RT	RT	RT
	Skin Abrasion, Body Dorsal	.	.	.	.	.	.	.
	Skin Abrasion, Body Ventral	.	.	.	.	.	.	.
	Skin Abrasion, Forelimb	.	.	.	.	.	.	.
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
AL793H	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Food	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
AL110O !	Normal	.	.	.	.	.	.	.
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	Red	Red	Red	Red	Red	Red	Red

!=Result comment recorded against 1 or more clinical observations. X=Present; RT=Right; Red=Red

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		61	62	63	64	65	66	67
AL110O !	Emesis, Foamy	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.

!=Result comment recorded against 1 or more clinical observations.

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		68	69	70	71	72	73	74
VL90IA	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Skin Abrasion, Forelimb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
YR895FD	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Limb Weakness, Hind Limb	RT	RT	RT	RT	RT	RT	RT
	Skin Abrasion, Body Dorsal	.	.	.	.	.	.	.
	Skin Abrasion, Body Ventral	.	.	.	.	.	.	.
	Skin Abrasion, Forelimb	.	.	.	.	.	.	.
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
AL793H	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Food	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
AL110O	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.

X=Present; RT=Right

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		68	69	70	71	72	73	74
AL110O	Emesis, Foamy	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		75	76	77	78	79	80	81
VL90IA	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Skin Abrasion, Forelimb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
YR895FD	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Limb Weakness, Hind Limb	RT	RT	RT	RT	RT	RT	RT
	Skin Abrasion, Body Dorsal	.	.	.	.	.	.	.
	Skin Abrasion, Body Ventral	.	.	.	.	.	.	.
	Skin Abrasion, Forelimb	.	.	.	.	.	.	.
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
AL793H	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Food	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
AL110O	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.

X=Present; RT=Right

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		75	76	77	78	79	80	81
AL110O	Emesis, Foamy	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		82	83	84	85	86	87	88
VL90IA	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Skin Abrasion, Forelimb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
YR895FD	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Limb Weakness, Hind Limb	RT	RT	RT	RT	RT	RT	RT
	Skin Abrasion, Body Dorsal	.	.	.	.	.	.	.
	Skin Abrasion, Body Ventral	.	.	.	.	.	.	.
	Skin Abrasion, Forelimb	.	.	.	.	.	.	.
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
AL793H	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Food	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
AL110O	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.

X=Present; RT=Right

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		82	83	84	85	86	87	88
AL110O	Emesis, Foamy	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		89	90	91	92	93	94	95
VL90IA	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Skin Abrasion, Forelimb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
YR895FD	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Limb Weakness, Hind Limb	RT	RT	RT	RT	RT	RT	RT
	Skin Abrasion, Body Dorsal	.	.	.	.	.	.	.
	Skin Abrasion, Body Ventral	.	.	.	.	.	.	.
	Skin Abrasion, Forelimb	.	.	.	.	.	.	.
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
AL793H	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Food	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
AL110O	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.

X=Present; RT=Right

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		89	90	91	92	93	94	95
AL110O	Emesis, Foamy	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		96	97	98	99	100	101	102
VL90IA	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Skin Abrasion, Forelimb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
YR895FD	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Limb Weakness, Hind Limb	RT	RT	RT	RT	RT	RT	RT
	Skin Abrasion, Body Dorsal	.	.	.	.	.	.	.
	Skin Abrasion, Body Ventral	.	.	.	.	.	.	.
	Skin Abrasion, Forelimb	.	.	.	.	.	.	.
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
AL793H	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Food	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
AL110O	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.

X=Present; RT=Right

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		96	97	98	99	100	101	102
AL110O	Emesis, Foamy	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		103	104	105	106	107	108	109
VL90IA	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Skin Abrasion, Forelimb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
YR895FD	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Limb Weakness, Hind Limb	RT	RT	RT	RT	RT	RT	RT
	Skin Abrasion, Body Dorsal	.	.	.	.	.	.	.
	Skin Abrasion, Body Ventral	.	.	.	.	.	.	.
	Skin Abrasion, Forelimb	.	.	.	RT	RT	RT	.
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
AL793H	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Food	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
AL110O	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.

X=Present; RT=Right

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		103	104	105	106	107	108	109
AL110O	Emesis, Foamy	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		110	111	112	113	114	115	116
VL90IA	Normal	X	X	X	.	.	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Skin Abrasion, Forelimb	.	.	.	LT	LT	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
YR895FD	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Limb Weakness, Hind Limb	RT	RT	RT	RT	RT	RT	RT
	Skin Abrasion, Body Dorsal	.	.	.	.	.	.	.
	Skin Abrasion, Body Ventral	.	.	.	.	.	.	.
	Skin Abrasion, Forelimb	.	.	.	.	.	.	.
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	RT
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
AL793H	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Food	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.
AL110O	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.

X=Present; LT=Left; RT=Right

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		110	111	112	113	114	115	116
AL110O	Emesis, Foamy	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		117						
VL90IA	Normal	X						
	Discolored Skin, Body Ventral	.						
	Skin Abrasion, Forelimb	.						
	Low Food Consumption	.						
	Diarrhea	.						
	Soft Feces	.						
YR895FD	Discolored Skin, Body Ventral	.						
	Discolored Skin, Hind Limb, Right	.						
	Emesis, Foamy	.						
	Limb Weakness, Hind Limb	.						
	Skin Abrasion, Body Dorsal	.						
	Skin Abrasion, Body Ventral	.						
	Skin Abrasion, Forelimb	.						
	Skin Abrasion, Hind Limb	RT						
	Low Food Consumption	.						
	Diarrhea	.						
	Soft Feces	.						
AL793H	Normal	X						
	Discolored Skin, Body Ventral	.						
	Emesis, Food	.						
	Low Food Consumption	.						
	Soft Feces	.						
AL110O	Normal	X						
	Discolored Skin, Body Ventral	.						
	Discolored Skin, Hind Limb, Right	.						

X=Present; RT=Right

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		117						
AL110O	Emesis, Foamy	.						
	Low Food Consumption	.						
	Diarrhea	.						

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 2 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		-3	-2	-1	1	2	3	4
BF873I !	Normal	.	.	.	.	.	.	.
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Limb Weakness, Hind Limb	RT	RT	RT	RT	RT	RT	RT
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
G180JD !	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
N378ALE !	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
AP55D !	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.
	Emesis	.	.	.	.	.	.	.
	Skin Abrasion, Face	.	.	.	.	.	.	.
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.

!=Result comment recorded against 1 or more clinical observations. RT=Right; X=Present

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 2 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		5	6	7	8	9	10	11
BF873I !	Normal	.	.	.	.	.	.	.
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	X	.	.	.
	Limb Weakness, Hind Limb	RT	RT	RT	RT	RT	RT	RT
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
G180JD !	Normal	X	X	X	.	.	.	.
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	WH	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
N378ALE !	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
AP55D !	Normal	X	X	X	.	.	.	.
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.
	Emesis	.	.	.	WH	.	.	.
	Skin Abrasion, Face	.	.	.	.	.	.	.
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.

!=Result comment recorded against 1 or more clinical observations. X=Present; RT=Right; WH=White

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 2 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		12	13	14	15	16	17	18
BF873I	Normal	.	.	.	.	.	.	.
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Limb Weakness, Hind Limb	RT	RT	RT	RT	RT	RT	RT
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
G180JD	Normal	.	.	.	.	.	.	.
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
N378ALE	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
AP55D	Normal	.	.	.	.	.	.	.
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.
	Emesis	.	.	.	.	.	.	.
	Skin Abrasion, Face	.	.	.	.	.	.	.
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.

RT=Right; X=Present

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 2 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		19	20	21	22	23	24	25
BF873I !	Normal	.	.	.	.	.	.	.
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Limb Weakness, Hind Limb	RT	RT	RT	.	RT	RT	.
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
G180JD !	Normal	.	.	.	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
N378ALE !	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
AP55D !	Normal	.	.	.	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.
	Emesis	.	.	.	.	.	.	.
	Skin Abrasion, Face	.	.	.	.	.	.	.
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.

!=Result comment recorded against 1 or more clinical observations. RT=Right; X=Present

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 2 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		26	27	28	29	30	31	32
BF873I !	Normal	.	.	.	.	.	.	.
	Discolored Skin, Body Ventral	.	.	.	.	Red	Red	Red
	Emesis, Foamy	.	.	.	.	.	.	.
	Limb Weakness, Hind Limb	RT	RT	RT	.	RT	RT	RT
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	RFC	.	RFC	.	.
	Diarrhea	.	.	.	.	.	.	X
G180JD !	Normal	X	X	X	X	.	X	.
	Discolored Skin, Body Ventral	.	.	.	.	Red	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	RFC	.	.
	Diarrhea	.	.	.	.	.	.	X
N378ALE !	Normal	X	.	X	X	.	X	.
	Discolored Skin, Body Ventral	.	.	.	.	Red	.	.
	Low Food Consumption	.	RFC	.	.	RFC	.	.
	Diarrhea	.	.	.	.	.	.	X
AP55D !	Normal	X	X	X	X	.	X	X
	Discolored Skin, Body Ventral	.	.	.	.	Red	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.
	Emesis	.	.	.	.	.	.	.
	Skin Abrasion, Face	.	.	.	.	.	.	.
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	RFC	.	.
	Soft Feces	.	.	.	.	.	.	.

!=Result comment recorded against 1 or more clinical observations. Red=Red; RT=Right; RFC=1/2 or Less of Total Food; X=Present

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 2 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		33	34	35	36	37	38	39
BF873I	Normal	.	.	.	.	.	.	.
	Discolored Skin, Body Ventral	Red	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Limb Weakness, Hind Limb	RT	RT	RT	RT	RT	RT	RT
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
G180JD	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
N378ALE	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
AP55D	Normal	.	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.
	Emesis	.	.	.	.	.	.	.
	Skin Abrasion, Face	.	.	.	.	.	.	.
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Soft Feces	X	.	.	.	.	.	.

Red=Red; RT=Right; X=Present

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 2 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		40	41	42	43	44	45	46
BF873I !	Normal	.	.	.	.	.	.	.
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Limb Weakness, Hind Limb	RT	RT	RT	.	RT	RT	.
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	RFC	RFC	.	RFC	.	.
	Diarrhea	.	.	.	.	.	.	.
G180JD !	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
N378ALE !	Normal	X	X	X	X	.	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	RFC	.	.
	Diarrhea	.	.	.	.	.	.	.
AP55D !	Normal	X	X	X	X	.	.	.
	Discolored Skin, Body Ventral	.	.	.	.	Red	Red	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.
	Emesis	.	.	.	.	.	.	.
	Skin Abrasion, Face	.	.	.	.	.	.	.
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.

!=Result comment recorded against 1 or more clinical observations. RT=Right; RFC=1/2 or Less of Total Food; X=Present; Red=Red

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 2 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		47	48	49	50	51	52	53
BF873I !	Normal	.	.	.	.	.	.	.
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Limb Weakness, Hind Limb	RT	RT	RT	.	RT	RT	RT
	Skin Abrasion, Hind Limb	.	.	.	.	RT	RT	RT
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
G180JD !	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
N378ALE !	Normal	X	.	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Low Food Consumption	.	RFC	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
AP55D !	Normal	.	X	X	X	X	X	.
	Discolored Skin, Body Ventral	Red	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.
	Emesis	.	.	.	.	.	.	.
	Skin Abrasion, Face	.	.	.	.	.	.	.
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	X

!=Result comment recorded against 1 or more clinical observations. RT=Right; X=Present; RFC=1/2 or Less of Total Food; Red=Red

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 2 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		54	55	56	57	58	59	60
BF873I	Normal	.	.	.	.	.	.	.
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Limb Weakness, Hind Limb	RT	RT	RT	RT	RT	RT	RT
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
G180JD	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
N378ALE	Normal	X	X	X	X	.	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	RFC	.	.
	Diarrhea	.	.	.	.	.	.	.
AP55D	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.
	Emesis	.	.	.	.	.	.	.
	Skin Abrasion, Face	.	.	.	.	.	.	.
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.

RT=Right; X=Present; RFC=1/2 or Less of Total Food

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 2 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		61	62	63	64	65	66	67
BF873I	Normal	.	.	.	.	.	.	.
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Limb Weakness, Hind Limb	RT	RT	RT	RT	RT	RT	RT
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
G180JD	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
N378ALE	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
AP55D !	Normal	X	X	X	.	.	.	.
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	X	X	Red	Red
	Emesis	.	.	.	.	.	.	.
	Skin Abrasion, Face	.	.	.	.	.	.	.
	Skin Abrasion, Hind Limb	.	.	.	.	RT	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.

!=Result comment recorded against 1 or more clinical observations. RT=Right; X=Present; Red=Red

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 2 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		68	69	70	71	72	73	74
BF873I	Normal	.	.	.	.	.	.	.
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Limb Weakness, Hind Limb	RT	RT	RT	RT	RT	RT	RT
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
G180JD	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
N378ALE	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
AP55D	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.
	Emesis	.	.	.	.	.	.	.
	Skin Abrasion, Face	.	.	.	.	.	.	.
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.

RT=Right; X=Present

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 2 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		75	76	77	78	79	80	81
BF873I	Normal	.	.	X	.	.	.	.
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Limb Weakness, Hind Limb	RT	RT	.	RT	RT	RT	RT
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
G180JD	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
N378ALE	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
AP55D !	Normal	X	X	X	X	X	.	.
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.
	Emesis	.	.	.	.	.	.	.
	Skin Abrasion, Face	.	.	.	.	.	BT	BT
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.

!=Result comment recorded against 1 or more clinical observations. X=Present; RT=Right; BT=Both

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 2 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		82	83	84	85	86	87	88
BF873I	Normal	.	.	.	.	.	.	.
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Limb Weakness, Hind Limb	RT	RT	RT	RT	RT	RT	RT
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
G180JD	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
N378ALE	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
AP55D !	Normal	.	.	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.
	Emesis	.	.	.	.	.	.	.
	Skin Abrasion, Face	BT	BT	.	.	.	.	.
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.

!=Result comment recorded against 1 or more clinical observations. RT=Right; X=Present; BT=Both

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 2 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		89	90	91	92	93	94	95
BF873I	Normal	.	.	.	.	.	.	.
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Limb Weakness, Hind Limb	RT	RT	RT	RT	RT	RT	RT
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
G180JD	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
N378ALE	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
AP55D	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.
	Emesis	.	.	.	.	.	.	.
	Skin Abrasion, Face	.	.	.	.	.	.	.
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.

RT=Right; X=Present

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 2 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		96	97	98	99	100	101	102
BF873I	Normal	.	.	.	.	.	.	.
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Limb Weakness, Hind Limb	RT	RT	RT	RT	RT	RT	RT
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
G180JD	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
N378ALE	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
AP55D	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.
	Emesis	.	.	.	.	.	.	.
	Skin Abrasion, Face	.	.	.	.	.	.	.
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.

RT=Right; X=Present

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 2 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		103	104	105	106	107	108	109
BF873I	Normal	.	.	.	.	.	.	.
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Limb Weakness, Hind Limb	RT	RT	RT	RT	RT	RT	RT
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
G180JD	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
N378ALE	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
AP55D	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.
	Emesis	.	.	.	.	.	.	.
	Skin Abrasion, Face	.	.	.	.	.	.	.
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.

RT=Right; X=Present

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 2 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		110	111	112	113	114	115	116
BF873I	Normal	.	.	.	.	.	.	.
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Limb Weakness, Hind Limb	RT	RT	RT	RT	RT	RT	RT
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
G180JD	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Emesis, Foamy	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
N378ALE	Normal	X	X	X	X	X	X	X
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Low Food Consumption	.	.	.	.	.	.	.
	Diarrhea	.	.	.	.	.	.	.
AP55D	Normal	X	X	X	X	X	X	.
	Discolored Skin, Body Ventral	.	.	.	.	.	.	.
	Discolored Skin, Hind Limb, Right	.	.	.	.	.	.	.
	Emesis	.	.	.	.	.	.	.
	Skin Abrasion, Face	.	.	.	.	.	.	.
	Skin Abrasion, Hind Limb	.	.	.	.	.	.	RT
	Low Food Consumption	.	.	.	.	.	.	.
	Soft Feces	.	.	.	.	.	.	.

RT=Right; X=Present

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Group 2 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		117						
BF873I	Normal	.						
	Discolored Skin, Body Ventral	.						
	Emesis, Foamy	.						
	Limb Weakness, Hind Limb	RT						
	Skin Abrasion, Hind Limb	.						
	Low Food Consumption	.						
	Diarrhea	.						
G180JD	Normal	X						
	Discolored Skin, Body Ventral	.						
	Emesis, Foamy	.						
	Low Food Consumption	.						
	Diarrhea	.						
N378ALE	Normal	X						
	Discolored Skin, Body Ventral	.						
	Low Food Consumption	.						
	Diarrhea	.						
AP55D	Normal	.						
	Discolored Skin, Body Ventral	.						
	Discolored Skin, Hind Limb, Right	.						
	Emesis	.						
	Skin Abrasion, Face	.						
	Skin Abrasion, Hind Limb	RT						
	Low Food Consumption	.						
	Soft Feces	.						

RT=Right; X=Present

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Comment Information

Group	Sex	Animal	Day	Observation Type	Comment
Group 1	Male	VL90IA	1	All Types	Time is 0856h
Group 1	Male	VL90IA	1	All Types	Time is 0906h
Group 1	Male	VL90IA	1	All Types	Time is 0921h
Group 1	Male	VL90IA	1	All Types	Time is 0952h
Group 1	Male	VL90IA	1	All Types	Time is 1051h
Group 1	Male	VL90IA	1	All Types	Time is 1251h
Group 1	Male	VL90IA	1	All Types	Time is 1451h
Group 1	Male	VL90IA	4	All Types	Time is 1152h
Group 1	Male	VL90IA	4	All Types	Time is 1208h
Group 1	Male	VL90IA	4	All Types	Time is 1218h
Group 1	Male	VL90IA	4	All Types	Time is 1233h
Group 1	Male	VL90IA	4	All Types	Time is 1302h
Group 1	Male	VL90IA	4	All Types	Time is 1403h
Group 1	Male	VL90IA	4	All Types	Time is 1607h
Group 1	Male	VL90IA	4	All Types	Time is 1805h
Group 1	Male	VL90IA	8	All Types	Time is 0906h
Group 1	Male	VL90IA	8	All Types	Time is 0922h
Group 1	Male	VL90IA	8	All Types	Time is 0951h
Group 1	Male	VL90IA	8	All Types	Time is 1047h
Group 1	Male	VL90IA	8	All Types	Time is 1251h
Group 1	Male	VL90IA	8	All Types	Time is 1450h
Group 1	Male	VL90IA	8	All Types	Time is 0856h
Group 1	Male	VL90IA	22	All Types	Time is 1419h
Group 1	Male	VL90IA	22	All Types	Time is 1622h

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Comment Information (Continued)

Group	Sex	Animal	Day	Observation Type	Comment
Group 1	Male	VL90IA	22	All Types	Time is 1823h
Group 1	Male	VL90IA	22	All Types	Time is 1207h
Group 1	Male	VL90IA	22	All Types	Time is 1226h
Group 1	Male	VL90IA	22	All Types	Time is 1236h
Group 1	Male	VL90IA	22	All Types	Time is 1251h
Group 1	Male	VL90IA	22	All Types	Time is 1321h
Group 1	Male	VL90IA	25	All Types	Time is 0820h
Group 1	Male	VL90IA	25	All Types	Time is 0831h
Group 1	Male	VL90IA	25	All Types	Time is 0841h
Group 1	Male	VL90IA	25	All Types	Time is 0856h
Group 1	Male	VL90IA	25	All Types	Time is 1025h
Group 1	Male	VL90IA	25	All Types	Time is 1226h
Group 1	Male	VL90IA	25	All Types	Time is 1427h
Group 1	Male	VL90IA	25	All Types	Time is 0927h
Group 1	Male	VL90IA	29	All Types	Time is 1151h
Group 1	Male	VL90IA	29	All Types	Time is 1206h
Group 1	Male	VL90IA	29	All Types	Time is 1216h
Group 1	Male	VL90IA	29	All Types	Time is 1300h
Group 1	Male	VL90IA	29	All Types	Time is 1231h
Group 1	Male	VL90IA	29	All Types	Time is 1400h
Group 1	Male	VL90IA	29	All Types	Time is 1605h
Group 1	Male	VL90IA	29	All Types	Time is 1759h
Group 1	Male	VL90IA	43	All Types	Time is 0824h
Group 1	Male	VL90IA	43	All Types	Time is 0843h

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Comment Information (Continued)

Group	Sex	Animal	Day	Observation Type	Comment
Group 1	Male	VL90IA	43	All Types	Time is 0853h
Group 1	Male	VL90IA	43	All Types	Time is 0908h
Group 1	Male	VL90IA	43	All Types	Time is 0938h
Group 1	Male	VL90IA	43	All Types	Time is 1037h
Group 1	Male	VL90IA	43	All Types	Time is 1236h
Group 1	Male	VL90IA	43	All Types	Time is 1437h
Group 1	Male	VL90IA	46	All Types	Time is 1209h
Group 1	Male	VL90IA	46	All Types	Time is 1220h
Group 1	Male	VL90IA	46	All Types	Time is 1230h
Group 1	Male	VL90IA	46	All Types	Time is 1245h
Group 1	Male	VL90IA	46	All Types	Time is 1315h
Group 1	Male	VL90IA	46	All Types	Time is 1416h
Group 1	Male	VL90IA	46	All Types	Time is 1616h
Group 1	Male	VL90IA	46	All Types	Time is 1814h
Group 1	Male	VL90IA	50	All Types	Time is 0816h
Group 1	Male	VL90IA	50	All Types	Time is 0851h
Group 1	Male	VL90IA	50	All Types	Time is 0902h
Group 1	Male	VL90IA	50	All Types	Time is 0916h
Group 1	Male	VL90IA	50	All Types	Time is 0946h
Group 1	Male	VL90IA	50	All Types	Time is 1047h
Group 1	Male	VL90IA	50	All Types	Time is 1244h
Group 1	Male	VL90IA	50	All Types	Time is 1442h
Group 1	Male	YR895FD	47	All Types	Red discoloration near tattoo
Group 1	Male	YR895FD	47	All Types	Red discoloration near tattoo

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Comment Information (Continued)

Group	Sex	Animal	Day	Observation Type	Comment
Group 1	Male	YR895FD	48	All Types	Red discoloration near tattoo
Group 1	Male	YR895FD	48	All Types	Red discoloration near tattoo
Group 1	Male	YR895FD	49	All Types	Red discoloration near tattoo
Group 1	Male	YR895FD	49	All Types	Red discoloration near tattoo
Group 1	Male	YR895FD	51	All Types	Red discoloration near tattoo
Group 1	Male	YR895FD	51	All Types	Red discoloration near tattoo
Group 1	Male	YR895FD	52	All Types	Red discoloration near tattoo
Group 1	Male	YR895FD	52	All Types	Red discoloration near tattoo
Group 1	Male	YR895FD	53	All Types	Red discoloration near tattoo
Group 1	Male	YR895FD	53	All Types	Red discoloration near tattoo
Group 1	Male	YR895FD	54	All Types	Red discoloration near tattoo
Group 1	Male	YR895FD	1	All Types	Time is 0912h
Group 1	Male	YR895FD	1	All Types	Time is 0923h
Group 1	Male	YR895FD	1	All Types	Time is 0937h
Group 1	Male	YR895FD	1	All Types	Time is 1007h
Group 1	Male	YR895FD	1	All Types	Time is 1107h
Group 1	Male	YR895FD	1	All Types	Time is 1308h
Group 1	Male	YR895FD	1	All Types	Time is 1507h
Group 1	Male	YR895FD	4	All Types	Time is 1157h
Group 1	Male	YR895FD	4	All Types	Time is 1218h
Group 1	Male	YR895FD	4	All Types	Time is 1228h
Group 1	Male	YR895FD	4	All Types	Time is 1243h
Group 1	Male	YR895FD	4	All Types	Time is 1312h
Group 1	Male	YR895FD	4	All Types	Time is 1410h

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Comment Information (Continued)

Group	Sex	Animal	Day	Observation Type	Comment
Group 1	Male	YR895FD	4	All Types	Time is 1615h
Group 1	Male	YR895FD	4	All Types	Time is 1812h
Group 1	Male	YR895FD	8	All Types	Time is 0917h
Group 1	Male	YR895FD	8	All Types	Time is 0932h
Group 1	Male	YR895FD	8	All Types	Time is 1002h
Group 1	Male	YR895FD	8	All Types	Time is 1058h
Group 1	Male	YR895FD	8	All Types	Time is 1300h
Group 1	Male	YR895FD	8	All Types	Time is 1500h
Group 1	Male	YR895FD	8	All Types	Time is 0907h
Group 1	Male	YR895FD	22	All Types	Time is 1425h
Group 1	Male	YR895FD	22	All Types	Time is 1626h
Group 1	Male	YR895FD	22	All Types	Time is 1827h
Group 1	Male	YR895FD	22	All Types	Time is 1211h
Group 1	Male	YR895FD	22	All Types	Time is 1230h
Group 1	Male	YR895FD	22	All Types	Time is 1242h
Group 1	Male	YR895FD	22	All Types	Time is 1255h
Group 1	Male	YR895FD	22	All Types	Time is 1326h
Group 1	Male	YR895FD	25	All Types	Time is 0826h
Group 1	Male	YR895FD	25	All Types	Time is 0835h
Group 1	Male	YR895FD	25	All Types	Time is 0853h
Group 1	Male	YR895FD	25	All Types	Time is 0900h
Group 1	Male	YR895FD	25	All Types	Time is 1030h
Group 1	Male	YR895FD	25	All Types	Time is 1233h
Group 1	Male	YR895FD	25	All Types	Time is 1432h

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Comment Information (Continued)

Group	Sex	Animal	Day	Observation Type	Comment
Group 1	Male	YR895FD	25	All Types	Time is 0930h
Group 1	Male	YR895FD	29	All Types	Time is 1151h
Group 1	Male	YR895FD	29	All Types	Time is 1210h
Group 1	Male	YR895FD	29	All Types	Time is 1221h
Group 1	Male	YR895FD	29	All Types	Time is 1305h
Group 1	Male	YR895FD	29	All Types	Time is 1235h
Group 1	Male	YR895FD	29	All Types	Time is 1404h
Group 1	Male	YR895FD	29	All Types	Time is 1610h
Group 1	Male	YR895FD	29	All Types	Time is 1802h
Group 1	Male	YR895FD	43	All Types	Time is 0830h
Group 1	Male	YR895FD	43	All Types	Time is 0847h
Group 1	Male	YR895FD	43	All Types	Time is 0857h
Group 1	Male	YR895FD	43	All Types	Time is 0912h
Group 1	Male	YR895FD	43	All Types	Time is 0942h
Group 1	Male	YR895FD	43	All Types	Time is 1041h
Group 1	Male	YR895FD	43	All Types	Time is 1241h
Group 1	Male	YR895FD	43	All Types	Time is 1442h
Group 1	Male	YR895FD	46	All Types	Time is 1208h
Group 1	Male	YR895FD	46	All Types	Time is 1224h
Group 1	Male	YR895FD	46	All Types	Time is 1234h
Group 1	Male	YR895FD	46	All Types	Time is 1248h
Group 1	Male	YR895FD	46	All Types	Time is 1320h
Group 1	Male	YR895FD	46	All Types	Time is 1420h
Group 1	Male	YR895FD	46	All Types	Time is 1623h

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Comment Information (Continued)

Group	Sex	Animal	Day	Observation Type	Comment
Group 1	Male	YR895FD	46	All Types	Time is 1819h
Group 1	Male	YR895FD	50	All Types	Time is 0824h
Group 1	Male	YR895FD	50	All Types	Time is 0857h
Group 1	Male	YR895FD	50	All Types	Time is 0905h
Group 1	Male	YR895FD	50	All Types	Time is 0920h
Group 1	Male	YR895FD	50	All Types	Time is 0950h
Group 1	Male	YR895FD	50	All Types	Time is 1050h
Group 1	Male	YR895FD	50	All Types	Time is 1249h
Group 1	Male	YR895FD	50	All Types	Time is 1449h
Group 1	Male	AL793H	1	All Types	Time is 0924h
Group 1	Male	AL793H	1	All Types	Time is 0934h
Group 1	Male	AL793H	1	All Types	Time is 0949h
Group 1	Male	AL793H	1	All Types	Time is 1019h
Group 1	Male	AL793H	1	All Types	Time is 1122h
Group 1	Male	AL793H	1	All Types	Time is 1319h
Group 1	Male	AL793H	1	All Types	Time is 1519h
Group 1	Male	AL793H	4	All Types	Time is 1203h
Group 1	Male	AL793H	4	All Types	Time is 1230h
Group 1	Male	AL793H	4	All Types	Time is 1239h
Group 1	Male	AL793H	4	All Types	Time is 1255h
Group 1	Male	AL793H	4	All Types	Time is 1324h
Group 1	Male	AL793H	4	All Types	Time is 1424h
Group 1	Male	AL793H	4	All Types	Time is 1626h
Group 1	Male	AL793H	4	All Types	Time is 1823h

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Comment Information (Continued)

Group	Sex	Animal	Day	Observation Type	Comment
Group 1	Male	AL793H	8	All Types	Time is 0929h
Group 1	Male	AL793H	8	All Types	Time is 0945h
Group 1	Male	AL793H	8	All Types	Time is 1013h
Group 1	Male	AL793H	8	All Types	Time is 1111h
Group 1	Male	AL793H	8	All Types	Time is 1316h
Group 1	Male	AL793H	8	All Types	Time is 1510h
Group 1	Male	AL793H	8	All Types	Time is 0920h
Group 1	Male	AL793H	22	All Types	Time is 1431h
Group 1	Male	AL793H	22	All Types	Time is 1630h
Group 1	Male	AL793H	22	All Types	Time is 1831h
Group 1	Male	AL793H	22	All Types	Time is 1212h
Group 1	Male	AL793H	22	All Types	Time is 1234h
Group 1	Male	AL793H	22	All Types	Time is 1244h
Group 1	Male	AL793H	22	All Types	Time is 1258h
Group 1	Male	AL793H	22	All Types	Time is 1331h
Group 1	Male	AL793H	25	All Types	Time is 0835h
Group 1	Male	AL793H	25	All Types	Time is 0844h
Group 1	Male	AL793H	25	All Types	Time is 0853h
Group 1	Male	AL793H	25	All Types	Time is 0908h
Group 1	Male	AL793H	25	All Types	Time is 1036h
Group 1	Male	AL793H	25	All Types	Time is 1239h
Group 1	Male	AL793H	25	All Types	Time is 1440h
Group 1	Male	AL793H	25	All Types	Time is 0939h
Group 1	Male	AL793H	29	All Types	Time is 1157h

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Individual Animal Clinical Signs

Comment Information (Continued)

Group	Sex	Animal	Day	Observation Type	Comment
Group 1	Male	AL793H	29	All Types	Time is 1215h
Group 1	Male	AL793H	29	All Types	Time is 1224h
Group 1	Male	AL793H	29	All Types	Time is 1310h
Group 1	Male	AL793H	29	All Types	Time is 1240h
Group 1	Male	AL793H	29	All Types	Time is 1408h
Group 1	Male	AL793H	29	All Types	Time is 1613h
Group 1	Male	AL793H	29	All Types	Time is 1806h
Group 1	Male	AL793H	43	All Types	Time is 0835h
Group 1	Male	AL793H	43	All Types	Time is 0851h
Group 1	Male	AL793H	43	All Types	Time is 0901h
Group 1	Male	AL793H	43	All Types	Time is 0916h
Group 1	Male	AL793H	43	All Types	Time is 0947h
Group 1	Male	AL793H	43	All Types	Time is 1044h
Group 1	Male	AL793H	43	All Types	Time is 1248h
Group 1	Male	AL793H	43	All Types	Time is 1448h
Group 1	Male	AL793H	46	All Types	Time is 1211h
Group 1	Male	AL793H	46	All Types	Time is 1228h
Group 1	Male	AL793H	46	All Types	Time is 1237h
Group 1	Male	AL793H	46	All Types	Time is 1252h
Group 1	Male	AL793H	46	All Types	Time is 1325h
Group 1	Male	AL793H	46	All Types	Time is 1424h
Group 1	Male	AL793H	46	All Types	Time is 1632h
Group 1	Male	AL793H	46	All Types	Time is 1824h
Group 1	Male	AL793H	50	All Types	Time is 0830h

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Comment Information (Continued)

Group	Sex	Animal	Day	Observation Type	Comment
Group 1	Male	AL793H	50	All Types	Time is 0859h
Group 1	Male	AL793H	50	All Types	Time is 0909h
Group 1	Male	AL793H	50	All Types	Time is 0924h
Group 1	Male	AL793H	50	All Types	Time is 0955h
Group 1	Male	AL793H	50	All Types	Time is 1056h
Group 1	Male	AL793H	50	All Types	Time is 1256h
Group 1	Male	AL793H	50	All Types	Time is 1454h
Group 1	Male	AL110O	59	All Types	around femoral incision area
Group 1	Male	AL110O	60	All Types	around femoral incision area
Group 1	Male	AL110O	60	All Types	around femoral incision area
Group 1	Male	AL110O	61	All Types	around femoral incision area
Group 1	Male	AL110O	61	All Types	around femoral incision area
Group 1	Male	AL110O	62	All Types	around femoral incision area
Group 1	Male	AL110O	62	All Types	around femoral incision area
Group 1	Male	AL110O	63	All Types	around femoral incision area
Group 1	Male	AL110O	63	All Types	around femoral incision area
Group 1	Male	AL110O	64	All Types	around femoral incision area
Group 1	Male	AL110O	64	All Types	around femoral incision area
Group 1	Male	AL110O	65	All Types	around femoral incision area
Group 1	Male	AL110O	65	All Types	around femoral incision area
Group 1	Male	AL110O	66	All Types	around femoral incision area
Group 1	Male	AL110O	66	All Types	around femoral incision area
Group 1	Male	AL110O	67	All Types	around femoral incision area
Group 1	Male	AL110O	67	All Types	around femoral incision area

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Individual Animal Clinical Signs

Comment Information (Continued)

Group	Sex	Animal	Day	Observation Type	Comment
Group 1	Male	AL110O	1	All Types	Time is 0947h
Group 1	Male	AL110O	1	All Types	Time is 0955h
Group 1	Male	AL110O	1	All Types	Time is 1010h
Group 1	Male	AL110O	1	All Types	Time is 1043h
Group 1	Male	AL110O	1	All Types	Time is 1137h
Group 1	Male	AL110O	1	All Types	Time is 1340h
Group 1	Male	AL110O	1	All Types	Time is 1542h
Group 1	Male	AL110O	4	All Types	Time is 1221h
Group 1	Male	AL110O	4	All Types	Time is 1242h
Group 1	Male	AL110O	4	All Types	Time is 1252h
Group 1	Male	AL110O	4	All Types	Time is 1307h
Group 1	Male	AL110O	4	All Types	Time is 1335h
Group 1	Male	AL110O	4	All Types	Time is 1436h
Group 1	Male	AL110O	4	All Types	Time is 1637h
Group 1	Male	AL110O	4	All Types	Time is 1834h
Group 1	Male	AL110O	8	All Types	Time is 0950h
Group 1	Male	AL110O	8	All Types	Time is 1007h
Group 1	Male	AL110O	8	All Types	Time is 1037h
Group 1	Male	AL110O	8	All Types	Time is 1134h
Group 1	Male	AL110O	8	All Types	Time is 1334h
Group 1	Male	AL110O	8	All Types	Time is 1531h
Group 1	Male	AL110O	8	All Types	Time is 0940h
Group 1	Male	AL110O	22	All Types	Time is 1438h
Group 1	Male	AL110O	22	All Types	Time is 1635h

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Individual Animal Clinical Signs

Comment Information (Continued)

Group	Sex	Animal	Day	Observation Type	Comment
Group 1	Male	AL110O	22	All Types	Time is 1834h
Group 1	Male	AL110O	22	All Types	Time is 1216h
Group 1	Male	AL110O	22	All Types	Time is 1239h
Group 1	Male	AL110O	22	All Types	Time is 1248h
Group 1	Male	AL110O	22	All Types	Time is 1303h
Group 1	Male	AL110O	22	All Types	Time is 1335h
Group 1	Male	AL110O	25	All Types	Time is 0841h
Group 1	Male	AL110O	25	All Types	Time is 0854h
Group 1	Male	AL110O	25	All Types	Time is 0904h
Group 1	Male	AL110O	25	All Types	Time is 0920h
Group 1	Male	AL110O	25	All Types	Time is 1045h
Group 1	Male	AL110O	25	All Types	Time is 1246h
Group 1	Male	AL110O	25	All Types	Time is 1447h
Group 1	Male	AL110O	25	All Types	Time is 0948h
Group 1	Male	AL110O	29	All Types	Time is 1157h
Group 1	Male	AL110O	29	All Types	Time is 1218h
Group 1	Male	AL110O	29	All Types	Time is 1228h
Group 1	Male	AL110O	29	All Types	Time is 1313h
Group 1	Male	AL110O	29	All Types	Time is 1243h
Group 1	Male	AL110O	29	All Types	Time is 1412h
Group 1	Male	AL110O	29	All Types	Time is 1613h
Group 1	Male	AL110O	29	All Types	Time is 1811h
Group 1	Male	AL110O	50	All Types	Time is 0841h
Group 1	Male	AL110O	50	All Types	Time is 0915h

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Individual Animal Clinical Signs

Comment Information (Continued)

Group	Sex	Animal	Day	Observation Type	Comment
Group 1	Male	AL110O	50	All Types	Time is 0925h
Group 1	Male	AL110O	50	All Types	Time is 0940h
Group 1	Male	AL110O	50	All Types	Time is 1009h
Group 1	Male	AL110O	50	All Types	Time is 1105h
Group 1	Male	AL110O	50	All Types	Time is 1309h
Group 1	Male	AL110O	50	All Types	Time is 1505h
Group 2	Male	BF873I	51	All Types	Abrasion near femoral inscision site
Group 2	Male	BF873I	51	All Types	Abrasion near femoral inscision site
Group 2	Male	BF873I	52	All Types	Abrasion near femoral inscision site
Group 2	Male	BF873I	52	All Types	Abrasion near femoral inscision site
Group 2	Male	BF873I	53	All Types	Abrasion near femoral inscision site
Group 2	Male	BF873I	53	All Types	Abrasion near femoral inscision site
Group 2	Male	BF873I	1	All Types	Time is 1232h
Group 2	Male	BF873I	1	All Types	Time is 1205h
Group 2	Male	BF873I	1	All Types	Time is 1242h
Group 2	Male	BF873I	1	All Types	Time is 1257h
Group 2	Male	BF873I	1	All Types	Time is 1327h
Group 2	Male	BF873I	1	All Types	Time is 1427h
Group 2	Male	BF873I	1	All Types	Time is 1628h
Group 2	Male	BF873I	1	All Types	Time is 1827h
Group 2	Male	BF873I	4	All Types	Time is 0856h
Group 2	Male	BF873I	4	All Types	Time is 0907h
Group 2	Male	BF873I	4	All Types	Time is 0924h
Group 2	Male	BF873I	4	All Types	Time is 0952h

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Individual Animal Clinical Signs

Comment Information (Continued)

Group	Sex	Animal	Day	Observation Type	Comment
Group 2	Male	BF873I	4	All Types	Time is 1055h
Group 2	Male	BF873I	4	All Types	Time is 1249h
Group 2	Male	BF873I	4	All Types	Time is 1448h
Group 2	Male	BF873I	8	All Types	Time is 1210h
Group 2	Male	BF873I	8	All Types	Time is 1220h; emesis was white, foamy.
Group 2	Male	BF873I	8	All Types	Time is 1235h.
Group 2	Male	BF873I	8	All Types	Time is 1309h.
Group 2	Male	BF873I	8	All Types	Time is 1404h.
Group 2	Male	BF873I	8	All Types	Time is 1607h.
Group 2	Male	BF873I	8	All Types	Time is 1806h.
Group 2	Male	BF873I	22	All Types	Time is 0843h.
Group 2	Male	BF873I	22	All Types	Time is 0853h.
Group 2	Male	BF873I	22	All Types	Time is 0910h.
Group 2	Male	BF873I	22	All Types	Time is 0940h.
Group 2	Male	BF873I	22	All Types	Time is 1037h.
Group 2	Male	BF873I	22	All Types	Time is 1238h.
Group 2	Male	BF873I	22	All Types	Time is 1442h.
Group 2	Male	BF873I	22	All Types	Time is 0834h.
Group 2	Male	BF873I	25	All Types	Time is 1149h.
Group 2	Male	BF873I	25	All Types	Time is 1207h.
Group 2	Male	BF873I	25	All Types	Time is 1233h.
Group 2	Male	BF873I	25	All Types	Time is 1217h.
Group 2	Male	BF873I	25	All Types	Time is 1301h.
Group 2	Male	BF873I	25	All Types	Time is 1404h.

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Individual Animal Clinical Signs

Comment Information (Continued)

Group	Sex	Animal	Day	Observation Type	Comment
Group 2	Male	BF873I	25	All Types	Time is 1602h.
Group 2	Male	BF873I	25	All Types	Time is 1802h.
Group 2	Male	BF873I	29	All Types	Time is 0829h.
Group 2	Male	BF873I	29	All Types	Time is 0843h.
Group 2	Male	BF873I	29	All Types	Time is 0853h.
Group 2	Male	BF873I	29	All Types	Time is 0908h.
Group 2	Male	BF873I	29	All Types	Time is 0937h.
Group 2	Male	BF873I	29	All Types	Time is 1039h.
Group 2	Male	BF873I	29	All Types	Time is 1235h.
Group 2	Male	BF873I	29	All Types	Time is 1442h.
Group 2	Male	BF873I	43	All Types	Time is 1201h.
Group 2	Male	BF873I	43	All Types	Time is 1214h.
Group 2	Male	BF873I	43	All Types	Time is 1225h.
Group 2	Male	BF873I	43	All Types	Time is 1240h.
Group 2	Male	BF873I	43	All Types	Time is 1412h.
Group 2	Male	BF873I	43	All Types	Time is 1611h.
Group 2	Male	BF873I	43	All Types	Time is 1804h.
Group 2	Male	BF873I	46	All Types	Time is 0825h.
Group 2	Male	BF873I	46	All Types	Time is 0845h.
Group 2	Male	BF873I	46	All Types	Time is 0855h.
Group 2	Male	BF873I	46	All Types	Time is 0910h.
Group 2	Male	BF873I	46	All Types	Time is 0939h.
Group 2	Male	BF873I	46	All Types	Time is 1040h.
Group 2	Male	BF873I	46	All Types	Time is 1240h.

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Individual Animal Clinical Signs

Comment Information (Continued)

Group	Sex	Animal	Day	Observation Type	Comment
Group 2	Male	BF873I	46	All Types	Time is 1435h.
Group 2	Male	BF873I	50	All Types	Time is 1204h.
Group 2	Male	BF873I	50	All Types	Time is 1221h.
Group 2	Male	BF873I	50	All Types	Time is 1231h.
Group 2	Male	BF873I	50	All Types	Time is 1246h.
Group 2	Male	BF873I	50	All Types	Time is 1315h.
Group 2	Male	BF873I	50	All Types	Time is 1415h.
Group 2	Male	BF873I	50	All Types	Time is 1612h.
Group 2	Male	BF873I	50	All Types	Time is 1812h.
Group 2	Male	G180JD	8	All Types	emesis following dosing
Group 2	Male	G180JD	1	All Types	Time is 1237h
Group 2	Male	G180JD	1	All Types	Time is 1215h
Group 2	Male	G180JD	1	All Types	Time is 1247h
Group 2	Male	G180JD	1	All Types	Time is 1302h
Group 2	Male	G180JD	1	All Types	Time is 1332h
Group 2	Male	G180JD	1	All Types	Time is 1432h
Group 2	Male	G180JD	1	All Types	Time is 1632h
Group 2	Male	G180JD	1	All Types	Time is 1832h
Group 2	Male	G180JD	4	All Types	Time is 0907h
Group 2	Male	G180JD	4	All Types	Time is 0918h
Group 2	Male	G180JD	4	All Types	Time is 0933h
Group 2	Male	G180JD	4	All Types	Time is 1003h
Group 2	Male	G180JD	4	All Types	Time is 1101h
Group 2	Male	G180JD	4	All Types	Time is 1301h

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Individual Animal Clinical Signs

Comment Information (Continued)

Group	Sex	Animal	Day	Observation Type	Comment
Group 2	Male	G180JD	4	All Types	Time is 1503h
Group 2	Male	G180JD	8	All Types	Time is 1221h; Emesis was white and foamy.
Group 2	Male	G180JD	8	All Types	Time is 1231h.
Group 2	Male	G180JD	8	All Types	Time is 1247h.
Group 2	Male	G180JD	8	All Types	Time is 1314h.
Group 2	Male	G180JD	8	All Types	Time is 1417h.
Group 2	Male	G180JD	8	All Types	Time is 1616h.
Group 2	Male	G180JD	8	All Types	Time is 1816h.
Group 2	Male	G180JD	22	All Types	Time is 0848h.
Group 2	Male	G180JD	22	All Types	Time is 0859h.
Group 2	Male	G180JD	22	All Types	Time is 0915h.
Group 2	Male	G180JD	22	All Types	Time is 0946h.
Group 2	Male	G180JD	22	All Types	Time is 1044h.
Group 2	Male	G180JD	22	All Types	Time is 1246h.
Group 2	Male	G180JD	22	All Types	Time is 1446h.
Group 2	Male	G180JD	22	All Types	Time is 0838h.
Group 2	Male	G180JD	25	All Types	Time is 1156h.
Group 2	Male	G180JD	25	All Types	Time is 1211h.
Group 2	Male	G180JD	25	All Types	Time is 1237h.
Group 2	Male	G180JD	25	All Types	Time is 1221h.
Group 2	Male	G180JD	25	All Types	Time is 1307h.
Group 2	Male	G180JD	25	All Types	Time is 1407h.
Group 2	Male	G180JD	25	All Types	Time is 1606h.
Group 2	Male	G180JD	25	All Types	Time is 1806h.

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Individual Animal Clinical Signs

Comment Information (Continued)

Group	Sex	Animal	Day	Observation Type	Comment
Group 2	Male	G180JD	29	All Types	Time is 0830h.
Group 2	Male	G180JD	29	All Types	Time is 0847h.
Group 2	Male	G180JD	29	All Types	Time is 0857h.
Group 2	Male	G180JD	29	All Types	Time is 0913h.
Group 2	Male	G180JD	29	All Types	Time is 0943h.
Group 2	Male	G180JD	29	All Types	Time is 1045h.
Group 2	Male	G180JD	29	All Types	Time is 1240h.
Group 2	Male	G180JD	29	All Types	Time is 1445h.
Group 2	Male	G180JD	43	All Types	Time is 1204h.
Group 2	Male	G180JD	43	All Types	Time is 1218h.
Group 2	Male	G180JD	43	All Types	Time is 1228h.
Group 2	Male	G180JD	43	All Types	Time is 1243h.
Group 2	Male	G180JD	43	All Types	Time is 1314h.
Group 2	Male	G180JD	43	All Types	Time is 1419h.
Group 2	Male	G180JD	43	All Types	Time is 1615h.
Group 2	Male	G180JD	43	All Types	Time is 1809h.
Group 2	Male	G180JD	46	All Types	Time is 0832h.
Group 2	Male	G180JD	46	All Types	Time is 0849h.
Group 2	Male	G180JD	46	All Types	Time is 0901h.
Group 2	Male	G180JD	46	All Types	Time is 0913h.
Group 2	Male	G180JD	46	All Types	Time is 0944h.
Group 2	Male	G180JD	46	All Types	Time is 1043h.
Group 2	Male	G180JD	46	All Types	Time is 1240h.
Group 2	Male	G180JD	46	All Types	Time is 1441h.

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Individual Animal Clinical Signs

Comment Information (Continued)

Group	Sex	Animal	Day	Observation Type	Comment
Group 2	Male	G180JD	50	All Types	Time is 1210h.
Group 2	Male	G180JD	50	All Types	Time is 1225h.
Group 2	Male	G180JD	50	All Types	Time is 1236h.
Group 2	Male	G180JD	50	All Types	Time is 1249h.
Group 2	Male	G180JD	50	All Types	Time is 1320h.
Group 2	Male	G180JD	50	All Types	Time is 1419h.
Group 2	Male	G180JD	50	All Types	Time is 1617h.
Group 2	Male	G180JD	50	All Types	Time is 1817h.
Group 2	Male	N378ALE	1	All Types	Time is 1249h
Group 2	Male	N378ALE	1	All Types	Time is 1240h
Group 2	Male	N378ALE	1	All Types	Time is 1258h
Group 2	Male	N378ALE	1	All Types	Time is 1314h
Group 2	Male	N378ALE	1	All Types	Time is 1344h
Group 2	Male	N378ALE	1	All Types	Time is 1443h
Group 2	Male	N378ALE	1	All Types	Time is 1643h
Group 2	Male	N378ALE	1	All Types	Time is 1843h
Group 2	Male	N378ALE	4	All Types	Time is 0918h
Group 2	Male	N378ALE	4	All Types	Time is 0928h
Group 2	Male	N378ALE	4	All Types	Time is 0943h
Group 2	Male	N378ALE	4	All Types	Time is 1013h
Group 2	Male	N378ALE	4	All Types	Time is 1112h
Group 2	Male	N378ALE	4	All Types	Time is 1311h
Group 2	Male	N378ALE	4	All Types	Time is 1513h
Group 2	Male	N378ALE	8	All Types	Time is 1232h

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Individual Animal Clinical Signs

Comment Information (Continued)

Group	Sex	Animal	Day	Observation Type	Comment
Group 2	Male	N378ALE	8	All Types	Time is 1242h
Group 2	Male	N378ALE	8	All Types	Time is 1257h
Group 2	Male	N378ALE	8	All Types	Time is 1328h
Group 2	Male	N378ALE	8	All Types	Time is 1423h
Group 2	Male	N378ALE	8	All Types	Time is 1625h
Group 2	Male	N378ALE	8	All Types	Time is 1827h
Group 2	Male	N378ALE	22	All Types	Time is 0858h
Group 2	Male	N378ALE	22	All Types	Time is 0908h
Group 2	Male	N378ALE	22	All Types	Time is 0923h
Group 2	Male	N378ALE	22	All Types	Time is 0951h
Group 2	Male	N378ALE	22	All Types	Time is 1051h
Group 2	Male	N378ALE	22	All Types	Time is 1253h
Group 2	Male	N378ALE	22	All Types	Time is 1453h
Group 2	Male	N378ALE	22	All Types	Time is 0847h
Group 2	Male	N378ALE	25	All Types	Time is 1159h
Group 2	Male	N378ALE	25	All Types	Time is 1215h
Group 2	Male	N378ALE	25	All Types	Time is 1240h
Group 2	Male	N378ALE	25	All Types	Time is 1225h
Group 2	Male	N378ALE	25	All Types	Time is 1312h
Group 2	Male	N378ALE	25	All Types	Time is 1412h
Group 2	Male	N378ALE	25	All Types	Time is 1611h
Group 2	Male	N378ALE	25	All Types	Time is 1811h
Group 2	Male	N378ALE	29	All Types	Time is 0835h
Group 2	Male	N378ALE	29	All Types	Time is 0851h

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Individual Animal Clinical Signs

Comment Information (Continued)

Group	Sex	Animal	Day	Observation Type	Comment
Group 2	Male	N378ALE	29	All Types	Time is 0903h
Group 2	Male	N378ALE	29	All Types	Time is 0916h
Group 2	Male	N378ALE	29	All Types	Time is 0947h
Group 2	Male	N378ALE	29	All Types	Time is 1049h
Group 2	Male	N378ALE	29	All Types	Time is 1247h
Group 2	Male	N378ALE	29	All Types	Time is 1448h.
Group 2	Male	N378ALE	43	All Types	Time is 1206h.
Group 2	Male	N378ALE	43	All Types	Time is 1222h.
Group 2	Male	N378ALE	43	All Types	Time is 1231h.
Group 2	Male	N378ALE	43	All Types	Time is 1248h.
Group 2	Male	N378ALE	43	All Types	Time is 1318h.
Group 2	Male	N378ALE	43	All Types	Time is 1422h.
Group 2	Male	N378ALE	43	All Types	Time is 1620h.
Group 2	Male	N378ALE	43	All Types	Time is 1812h.
Group 2	Male	N378ALE	46	All Types	Time is 0836h.
Group 2	Male	N378ALE	46	All Types	Time is 0853h.
Group 2	Male	N378ALE	46	All Types	Time is 0903h.
Group 2	Male	N378ALE	46	All Types	Time is 0917h.
Group 2	Male	N378ALE	46	All Types	Time is 0950h.
Group 2	Male	N378ALE	46	All Types	Time is 1049h.
Group 2	Male	N378ALE	46	All Types	Time is 1248h.
Group 2	Male	N378ALE	46	All Types	Time is 1446h.
Group 2	Male	N378ALE	50	All Types	Time is 1209h.
Group 2	Male	N378ALE	50	All Types	Time is 1229h.

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Individual Animal Clinical Signs

Comment Information (Continued)

Group	Sex	Animal	Day	Observation Type	Comment
Group 2	Male	N378ALE	50	All Types	Time is 1239h.
Group 2	Male	N378ALE	50	All Types	Time is 1254h.
Group 2	Male	N378ALE	50	All Types	Time is 1324h.
Group 2	Male	N378ALE	50	All Types	Time is 1423h.
Group 2	Male	N378ALE	50	All Types	Time is 1621h.
Group 2	Male	N378ALE	50	All Types	Time is 1825h.
Group 2	Male	AP55D	64	All Types	around femoral incision area
Group 2	Male	AP55D	64	All Types	around femoral incision area
Group 2	Male	AP55D	65	All Types	around femoral incision area
Group 2	Male	AP55D	66	All Types	Below femoral incision
Group 2	Male	AP55D	66	All Types	Below femoral incision
Group 2	Male	AP55D	67	All Types	Below femoral incision
Group 2	Male	AP55D	67	All Types	Below femoral incision
Group 2	Male	AP55D	80	All Types	abrasion on nose
Group 2	Male	AP55D	80	All Types	abrasion on nose
Group 2	Male	AP55D	81	All Types	abrasion on nose
Group 2	Male	AP55D	81	All Types	abrasion on nose
Group 2	Male	AP55D	82	All Types	abrasion on nose
Group 2	Male	AP55D	82	All Types	abrasion on nose
Group 2	Male	AP55D	83	All Types	abrasion on nose
Group 2	Male	AP55D	83	All Types	abrasion on nose
Group 2	Male	AP55D	1	All Types	Time is 1309h
Group 2	Male	AP55D	1	All Types	Time is 1255h
Group 2	Male	AP55D	1	All Types	Time is 1319h

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Comment Information (Continued)

Group	Sex	Animal	Day	Observation Type	Comment
Group 2	Male	AP55D	1	All Types	Time is 1333h
Group 2	Male	AP55D	1	All Types	Time is 1404h
Group 2	Male	AP55D	1	All Types	Time is 1503h
Group 2	Male	AP55D	1	All Types	Time is 1703h
Group 2	Male	AP55D	1	All Types	Time is 1902h
Group 2	Male	AP55D	4	All Types	Time is 0927h
Group 2	Male	AP55D	4	All Types	Time is 0937h
Group 2	Male	AP55D	4	All Types	Time is 0952h
Group 2	Male	AP55D	4	All Types	Time is 1022h
Group 2	Male	AP55D	4	All Types	Time is 1123h
Group 2	Male	AP55D	4	All Types	Time is 1321h
Group 2	Male	AP55D	4	All Types	Time is 1522h
Group 2	Male	AP55D	8	All Types	Time is 1243h; Emesis is white and foamy.
Group 2	Male	AP55D	8	All Types	Time is 1253h.
Group 2	Male	AP55D	8	All Types	Time is 1308h.
Group 2	Male	AP55D	8	All Types	Time is 1338h.
Group 2	Male	AP55D	8	All Types	Time is 1439h.
Group 2	Male	AP55D	8	All Types	Time is 1638h.
Group 2	Male	AP55D	8	All Types	Time is 1839h.
Group 2	Male	AP55D	22	All Types	Time is 0907h.
Group 2	Male	AP55D	22	All Types	Time is 0917h.
Group 2	Male	AP55D	22	All Types	Time is 0937h.
Group 2	Male	AP55D	22	All Types	Time is 1001h.
Group 2	Male	AP55D	22	All Types	Time is 1059h.

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Comment Information (Continued)

Group	Sex	Animal	Day	Observation Type	Comment
Group 2	Male	AP55D	22	All Types	Time is 1303h.
Group 2	Male	AP55D	22	All Types	Time is 1502h.
Group 2	Male	AP55D	22	All Types	Time is 0856h.
Group 2	Male	AP55D	25	All Types	Time is 1205h.
Group 2	Male	AP55D	25	All Types	Time is 1222h.
Group 2	Male	AP55D	25	All Types	Time is 1245h.
Group 2	Male	AP55D	25	All Types	Time is 1234h.
Group 2	Male	AP55D	25	All Types	Time is 1316h.
Group 2	Male	AP55D	25	All Types	Time is 1414h.
Group 2	Male	AP55D	25	All Types	Time is 1616h.
Group 2	Male	AP55D	25	All Types	Time is 1816h.
Group 2	Male	AP55D	29	All Types	Time is 0839h.
Group 2	Male	AP55D	29	All Types	Time is 0855h.
Group 2	Male	AP55D	29	All Types	Time is 0905h.
Group 2	Male	AP55D	29	All Types	Time is 0921h.
Group 2	Male	AP55D	29	All Types	Time is 0953h.
Group 2	Male	AP55D	29	All Types	Time is 1053h.
Group 2	Male	AP55D	29	All Types	Time is 1252h.
Group 2	Male	AP55D	29	All Types	Time is 1452h.
Group 2	Male	AP55D	43	All Types	Time is 1209h.
Group 2	Male	AP55D	43	All Types	Time is 1227h.
Group 2	Male	AP55D	43	All Types	Time is 1235h.
Group 2	Male	AP55D	43	All Types	Time is 1251h.
Group 2	Male	AP55D	43	All Types	Time is 1322h.

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Comment Information (Continued)

Group	Sex	Animal	Day	Observation Type	Comment
Group 2	Male	AP55D	43	All Types	Time is 1425h.
Group 2	Male	AP55D	43	All Types	Time is 1624h.
Group 2	Male	AP55D	43	All Types	Time is 1817h.
Group 2	Male	AP55D	46	All Types	Time is 0838h.
Group 2	Male	AP55D	46	All Types	Time is 0858h.
Group 2	Male	AP55D	46	All Types	Time is 0906h.
Group 2	Male	AP55D	46	All Types	Time is 0921h.
Group 2	Male	AP55D	46	All Types	Time is 0953h.
Group 2	Male	AP55D	46	All Types	Time is 1053h.
Group 2	Male	AP55D	46	All Types	Time is 1253h.
Group 2	Male	AP55D	46	All Types	Time is 1450h.
Group 2	Male	AP55D	50	All Types	Time is 1216h.
Group 2	Male	AP55D	50	All Types	Time is 1233h.
Group 2	Male	AP55D	50	All Types	Time is 1243h.
Group 2	Male	AP55D	50	All Types	Time is 1258h.
Group 2	Male	AP55D	50	All Types	Time is 1327h.
Group 2	Male	AP55D	50	All Types	Time is 1428h.
Group 2	Male	AP55D	50	All Types	Time is 1625h.
Group 2	Male	AP55D	50	All Types	Time is 1832h.

Amplify-Bio Study Number B05928

Individual Animal Clinical Signs

Key Page

Group Information

Short Name	Long Name	Type	Report Headings
1	Group 1	Control	Group 1
2	Group 2	Dose	Group 2

Table C-5. Individual Animal Body Weight and Weight Gain

Amplify-Bio Study Number B05928

Individual Animal Body Weight & Weight Gain

Sex: Male Body Weight (kg)

Group 1	Day(s) Relative to Start Date		
	-3	19	40
VL90IA	4.0	4.12	4.14
YR895FD	3.6	3.59	3.38
AL793H	4.1	4.18	4.27
AL110O	3.7	3.55	3.60

Amplify-Bio Study Number B05928

Individual Animal Body Weight & Weight Gain

Sex: Male Body Weight (kg)

Group 2	Day(s) Relative to Start Date		
	-3	19	40
BF873I	3.5	3.48	3.76
G180JD	3.7	3.75	3.78
N378ALE	3.7	3.77	3.70
AP55D	4.2	4.20	4.32

Amplify-Bio Study Number B05928

Individual Animal Body Weight & Weight Gain

Sex: Male Mean Weight (kg) Gain (kg/Day)

Group 1	Day(s) Relative to Start Date	
	-3 → 19	19 → 40
VL90IA	0.01	0.00
YR895FD	0.00	-0.01
AL793H	0.00	0.00
AL110O	-0.01	0.00

Amplify-Bio Study Number B05928

Individual Animal Body Weight & Weight Gain

Sex: Male Mean Weight (kg) Gain (kg/Day)

Group 2	Day(s) Relative to Start Date	
	-3 → 19	19 → 40
BF873I	0.00	0.01
G180JD	0.00	0.00
N378ALE	0.00	0.00
AP55D	0.00	0.01

Amplify-Bio Study Number B05928

Individual Animal Body Weight & Weight Gain

Key Page

Measurement Descriptions

Headings Used	Description
Body Weight	Body Weight
Mean Weight (kg) Gain	Mean Weight (kg) Gain

Group Information

Short Name	Long Name	Type	Report Headings 1-4
1	Group 1	Control	Group 1
2	Group 2	Dose	Group 2

Appendix D Bioanalytical Analysis and Pharmacokinetic Evaluation

B05928
3,4-Diaminopyridine Study Sample Summary

Animal ID	Cage	Dose Day	Group	Route	3,4-DAPP Dose	Dose Frequency	Determined Concentrations (ng/mL)							
							Pre-Dose	5 min Post	15 min Post	30 min Post	60 min Post	120 min Post	240 min Post	360 min Post
VL90IA	101	IV[1]	1	IV	1.03 mg/kg	single	ND	123	40.2	42.1	25.9	13.7	3.82	1.15
YR895FD	102						ND	107	64.4	52.1	36.3	18.2	4.44	1.46
AL793H	103						ND	94.6	48.0	36.9	19.0	10.4	3.07	0.867
AL110O	104						3.40	116	84.1	76.9	49.8	18.1	7.22	2.00
BF8731	201		2			repeat	3.39	75.2	49.4	28.8	25.1	10.7	2.75	0.883
G180JD	202						4.18	90.7	36.5	29.0	18.4	13.9	3.78	0.860
N378ALE	203						1.87	67.9	44.9	27.9	24.6	13.0	3.21	10.6
AP55D	204						3.90	121	74.3	60.3	37.9	20.1	5.32	1.73
BF8731	201	IV[2]	2		2.06 mg/kg	single	ND	183	77.7	71.0	82.9	30.3	9.97	3.19
G180JD	202						ND	188	97.4	74.1	40.4	33.6	7.53	2.65
N378ALE	203						ND	442	108	69.3	52.7	30.6	10.1	3.43
AP55D	204						ND	475	137	96.3	70.1	34.3	8.74	2.43
VL90IA	101		1			repeat	13.6	128	80.7	62.6	38.8	26.4	10.9	4.04
YR895FD	102						14.1	190	113	76.3	54.3	32.9	9.83	2.87
AL793H	103						15.2	182	131	75.3	46.1	35.2	8.72	2.37
AL110O	104						13.5	458	213	138	58.4	34.0	9.64	3.11
VL90IA	101	IV[3]	1		4.12 mg/kg	single	ND	837	206	127	108	80.8	24.9	13.0
YR895FD	102						ND	595	183	96.4	54.6	28.4	11.4	5.27
AL793H	103						ND	1100	605	249	138	74.0	32.2	8.42
AL110O	104						ND	851	434	216	131	79.3	20.2	5.78
BF8731	201		2			repeat	11.7	748	157	98.2	114	36.4	8.34	2.80
G180JD	202						36.8	624	320	76.2	55.4	43.0	20.0	5.29
N378ALE	203						26.0	595	246	142	83.7	63.1	15.7	4.85
AP55D	204						20.0	935	468	197	131	73.1	18.3	6.03

B05928
3,4-Diaminopyridine Study Sample Summary

Animal ID	Cage	Dose Day	Group	Route	3,4-DAPP Dose	Dose Frequency	Determined Concentrations (ng/mL)							
							Pre-Dose	5 min Post	15 min Post	30 min Post	60 min Post	120 min Post	240 min Post	360 min Post
BF8731	201	SC[1]	2	SC	1.03 mg/kg	single	ND	177	99.6	57.4	32.6	16.2	2.69	0.898
G180JD	202						ND	135	82.6	109	43.1	21.0	4.11	1.32
N378ALE	203						ND	107	77.6	64.3	49.4	33.0	6.78	1.85
AP55D	204						ND	180	110	81.0	68.0	47.8	10.6	4.24
VL90IA	101		1			repeat	8.63	201	128	99.3	94.9	48.2	13.7	5.75
YR895FD	102						7.22	150	72.8	61.8	39.1	22.7	6.21	1.74
AL793H	103						6.27	163	102	65.2	35.8	23.4	6.49	2.28
AL110O	104						5.73	138	80.6	66.0	44.1	22.7	6.72	2.84
VL90IA	101	SC[2]	1		2.06 mg/kg	single	ND	200	203	195	109	68.8	25.3	11.2
YR895FD	102						ND	297	160	146	104	60.0	19.0	5.91
AL793H	103						ND	224	142	92.3	42.3	27.7	9.26	3.65
AL110O	104						ND	334	181	139	87.9	49.9	14.9	4.10
BF8731	201		2			repeat	15.1	343	190	138	92.9	39.1	11.6	3.90
G180JD	202						11.6	183	129	139	44.9	53.5	22.6	11.7
N378ALE	203						18.9	301	235	157	106	78.7	17.7	6.46
AP55D	204						19.7	168	89.4	80.8	117	85.9	29.5	7.48
BF8731	201	SC[3]	2		4.12 mg/kg	single	ND	747	408	235	123	53.5	13.2	3.92
G180JD	202						ND	503	265	210	140	133	44.8	11.5
N378ALE	203						ND	856	368	202	121	66.8	20.1	5.57
AP55D	204						ND	479	402	246	176	117	41.8	11.3
VL90IA	101		1			repeat	64.7	496	468	322	261	203	52.7	24.0
YR895FD	102						54.3	608	512	334	187	101	31.8	11.6
AL793H	103						39.5	553	418	312	118	101	36.0	13.7
AL110O	104						40.0	619	531	364	245	96.4	28.1	6.51

B05928
3,4-Diaminopyridine Study Sample Summary

Animal ID	Cage	Dose Day	Group	Route	3,4-DAPP Dose	Dose Frequency	Determined Concentrations (ng/mL)							
							Pre-Dose	5 min Post	15 min Post	30 min Post	60 min Post	120 min Post	240 min Post	360 min Post
VL90IA	101	PO[1]	1	PO	1.03 mg/kg	single	ND	0.965	4.44	3.86	2.88	1.27	0.602	BLQ
YR895FD	102						ND	ND	BLQ	BLQ	0.637	0.578	BLQ	BLQ
AL793H	103						ND	BLQ	0.628	0.845	1.15	0.820	0.522	BLQ
AL110O	104						NS	NS	NS	NS	NS	NS	NS	NS
BF8731	201		2			repeat	BLQ	BLQ	2.28	2.87	1.52	0.769	BLQ	BLQ
G180JD	202						BLQ	3.06	5.75	3.59	1.70	0.724	BLQ	BLQ
N378ALE	203						BLQ	0.691	1.42	1.97	1.27	BLQ	BLQ	ND
AP55D	204						0.698	0.899	1.39	2.05	1.97	1.21	0.714	ND
BF8731	201	PO[2]	2		2.06 mg/kg	single	ND	4.81	5.07	8.34	8.64	1.58	BLQ	BLQ
G180JD	202						ND	BLQ	3.07	5.08	3.06	1.45	BLQ	BLQ
N378ALE	203						ND	0.544	3.29	22.6	3.07	0.911	BLQ	BLQ
AP55D	204						ND	BLQ	1.87	4.25	4.85	2.20	1.96	BLQ
VL90IA	101		1			repeat	1.05	4.45	14.9	13.4	4.95	2.37	1.04	0.627
YR895FD	102						BLQ	BLQ	1.43	3.29	2.51	1.66	BLQ	BLQ
AL793H	103						0.584	2.08	4.12	3.52	1.32	0.828	0.595	BLQ
AL110O	104						NS	NS	NS	NS	NS	NS	NS	NS
VL90IA	101	PO[3]	1		4.12 mg/kg	single	ND	12.7	33.0	27.1	12.5	6.82	2.55	0.988
YR895FD	102						ND	3.18	6.49	7.96	4.64	3.25	1.48	BLQ
AL793H	103						ND	33.0	62.8	12.5	8.57	3.68	1.50	0.770
AL110O	104						ND	1.25	10.5	31.4	14.5	8.14	1.85	0.743
BF8731	201		2			repeat	0.798	22.7	44.4	20.4	9.43	3.72	1.09	BLQ
G180JD	202						1.13	7.42	15.2	21.9	7.06	4.04	1.31	BLQ
N378ALE	203						0.929	21.8	33.0	21.5	7.35	3.52	1.22	0.590
AP55D	204						2.24	29.5	48.0	34.4	19.9	8.22	2.49	1.24

IV = intravenous
SC = subcutaneous
PO = oral
ND = peak not detected
NS = no sample
BLQ = Below Limit of Quantitation (0.500 ng/mL)

Study B05928
Phamacokinetic Summary

Route	3,4-DAPP Dose (mg/kg)	Dosing Interval	Animal ID	C_{max} (ng/mL)	T_{max} (min)	Elimination Half-Life (min)	Clearance (mL/min/kg)	Volume of Distribution (mL/kg)	AUC_{last} (min*ng/mL)	AUC_{∞} (min*ng/mL)
IV	1.03	single	AL110O	116	7.00	63.6	112	10300	9000	9180
			AL793H	94.6	5.00	67.4	216	21000	4680	4770
			VL90IA	123	5.00	66.6	173	16700	5840	5940
			YR895FD	107	5.00	62.7	144	13000	7020	7140
			Mean	**110**	**5.50**	**65.1**	**161**	**15300**	**6630**	**6760**
			SE	**6**	**0.50**	**1.2**	**22**	**2300**	**920**	**940**
IV	1.03	repeat	AP55D	121	6.10	66.9	127	12300	7920	8080
			BF8731	75.2	4.00	66.7	225	21600	4500	4590
			G180JD	90.7	5.00	59.8	214	18500	4730	4810
			N378ALE	67.9	6.75	117	170	28700	5280	6050
			Mean	**88.7**	**5.46**	**77.6**	**184**	**20300**	**5610**	**5880**
			SE	**11.8**	**0.61**	**13.2**	**22**	**3400**	**790**	**800**
IV	2.06	single	AP55D	475	5.00	61.8	119	10600	17100	17300
			BF8731	183	5.00	73.9	161	17100	12500	12800
			G180JD	188	5.00	67.9	186	18200	10900	11100
			N378ALE	442	5.00	76.0	134	14700	15000	15400
			Mean	**322**	**5.00**	**69.9**	**150**	**15200**	**13900**	**14100**
			SE	**79**	**0.00**	**3.2**	**15**	**1700**	**1400**	**1400**
IV	2.06	repeat	AL110O	458	5.00	70.2	113	11400	17900	18200
			AL793H	182	5.58	61.7	173	15400	11700	11900
			VL90IA	128	5.00	88.6	206	26400	9450	9980
			YR895FD	190	5.00	68.2	169	16600	11900	12200
			Mean	**240**	**5.15**	**72.2**	**165**	**17500**	**12700**	**13100**
			SE	**74**	**0.15**	**5.8**	**19**	**3200**	**1800**	**1800**
IV	4.12	single	AL110O	851	5.00	63.5	114	10400	35800	36300
			AL793H	1100	5.00	76.6	95.0	10500	42400	43400
			VL90IA	837	5.53	95.6	119	16500	32800	34500
			YR895FD	595	5.58	98.8	210	29900	18900	19600
			Mean	**846**	**5.28**	**83.6**	**134**	**16800**	**32500**	**33400**
			SE	**103**	**0.16**	**8.3**	**26**	**4600**	**4900**	**5000**
IV	4.12	repeat	AP55D	935	5.00	65.5	114	10800	35600	36200
			BF8731	748	5.78	64.9	162	15200	25200	25400
			G180JD	624	5.00	90.1	183	23800	21700	22500
			N378ALE	595	5.70	64.8	161	15000	25200	25600
			Mean	**726**	**5.37**	**71.3**	**155**	**16200**	**26900**	**27400**
			SE	**77**	**0.21**	**6.3**	**15**	**2700**	**3000**	**3000**

Study B05928
Phamacokinetic Summary

Route	3,4-DAPP Dose (mg/kg)	Dosing Interval	Animal ID	C_{max} (ng/mL)	T_{max} (min)	Elimination Half-Life (min)	Apparent Clearance (mL/min/kg)	Apparent Volume of Distribution (mL/kg)	AUC_{last} (min*ng/mL)	AUC_{∞} (min*ng/mL)
SC	1.03	single	AP55D	180	5.00	72.7	73.8	7740	13500	14000
			BF8731	177	5.00	54.4	141	11100	7230	7290
			G180JD	135	5.00	58.7	114	9690	8900	9000
			N378ALE	107	5.00	57.7	109	9050	9340	9480
			Mean	**150**	**5.00**	**60.9**	**110**	**9390**	**9750**	**9930**
			SE	**18**	**0.00**	**4.1**	**14**	**700**	**1340**	**1420**
SC	1.03	repeat	AL110O	138	5.97	53.8	125	9680	7930	8270
			AL793H	163	5.00	73.7	117	12400	8600	8830
			VL90IA	201	5.00	75.6	62.4	6800	15900	16500
			YR895FD	150	5.00	64.8	124	11600	8170	8330
			Mean	**163**	**5.24**	**67.0**	**107**	**10100**	**10200**	**10500**
			SE	**14**	**0.24**	**5.0**	**15**	**1200**	**1900**	**2000**
SC	2.06	single	AL110O	334	5.00	66.6	110	10500	18400	18800
			AL793H	224	6.32	83.5	178	21400	11200	11600
			VL90IA	203	15.0	90.5	83.8	10900	23200	24600
			YR895FD	297	5.00	71.8	98.8	10200	20200	20800
			Mean	**265**	**7.83**	**78.1**	**118**	**13300**	**18200**	**18900**
			SE	**31**	**2.41**	**5.5**	**21**	**2700**	**2600**	**2700**
SC	2.06	repeat	AP55D	168	8.03	68.2	94.4	9280	21000	21800
			BF8731	343	5.00	72.2	116	12100	17400	17800
			G180JD	183	5.00	109	114	17900	16400	18100
			N378ALE	301	5.00	70.8	86.8	8870	23100	23700
			Mean	**249**	**5.76**	**80.1**	**103**	**12000**	**19500**	**20400**
			SE	**43**	**0.76**	**9.8**	**7**	**2100**	**1600**	**1400**
SC	4.12	single	AP55D	479	5.00	76.0	104	11400	38300	39700
			BF8731	747	5.00	63.7	145	13300	28200	28500
			G180JD	503	5.00	68.0	110	10800	36100	37300
			N378ALE	856	5.00	67.6	133	13000	30400	31000
			Mean	**646**	**5.00**	**68.8**	**123**	**12100**	**33300**	**34100**
			SE	**93**	**0.00**	**2.6**	**10**	**600**	**2400**	**2600**
SC	4.12	repeat	AL110O	619	5.78	57.6	95.2	7920	42700	43300
			AL793H	553	6.13	83.3	110	13300	35700	37300
			VL90IA	496	5.00	82.1	72.0	8520	54600	57300
			YR895FD	608	5.00	74.8	98.8	10700	40500	41700
			Mean	**569**	**5.48**	**74.4**	**94.1**	**10100**	**43400**	**44900**
			SE	**28**	**0.29**	**5.9**	**8.1**	**1200**	**4000**	**4300**

Study B05928
Phamacokinetic Summary

Route	3,4-DAPP Dose (mg/kg)	Dosing Interval	Animal ID	C_{max} (ng/mL)	T_{max} (min)	Elimination Half-Life (min)	Apparent Clearance (mL/min/kg)	Apparent Volume of Distribution (mL/kg)	AUC_{last} (min*ng/mL)	AUC_{∞} (min*ng/mL)
PO	1.03	single	AL110O							
			AL793H	1.15	60.0				185	
			VL90IA	4.44	15.0	78.0	2100	236000	430	492
			YR895FD	0.637	60.0				55.6	
			Mean	**2.08**	**45.0**	**NA**	**NA**	**NA**	**223**	**NA**
			SE	**1.19**	**15.0**	**NA**	**NA**	**NA**	**110**	**NA**
PO	1.03	repeat	AP55D	2.05	30.0	127	2360	432000	310	436
			BF8731	2.87	30.0				190	
			G180JD	5.75	15.0	40.1	3300	191000	272	312
			N378ALE	1.97	30.0				86.3	
			Mean	**3.16**	**26.3**	**83.5**	**2830**	**312000**	**215**	**374**
			SE	**0.89**	**3.8**	**NA**	**NA**	**NA**	**50**	**NA**
PO	2.06	single	AP55D	4.85	60.0				658	
			BF8731	8.64	60.0				723	
			G180JD	5.08	30.0				336	
			N378ALE	22.6	30.0				718	
			Mean	**10.3**	**45.0**				**609**	
			SE	**4.2**	**8.7**				**92**	
PO	2.06	repeat	AL110O							
			AL793H	4.12	15.0	166	4560	1090000	316	452
			VL90IA	14.9	15.0	125	1680	303000	1120	1230
			YR895FD	3.29	30.0				258	
			Mean	**7.44**	**20.0**	**145**	**3120**	**696000**	**565**	**839**
			SE	**3.74**	**5.0**	**NA**	**NA**	**NA**	**278**	**NA**
PO	4.12	single	AL110O	31.4	30.0	68.2	1610	158000	2500	2560
			AL793H	62.8	15.0	106	1740	267000	2260	2370
			VL90IA	33.0	15.0	86.1	1480	184000	2660	2780
			YR895FD	7.96	30.0	109	3740	587000	867	1100
			Mean	**33.8**	**22.5**	**92.3**	**2140**	**299000**	**2070**	**2200**
			SE	**11.2**	**4.3**	**9.5**	**540**	**99000**	**410**	**380**
PO	4.12	repeat	AP55D	48.0	15.0	88.0	1100	139000	3600	3750
			BF8731	44.4	15.0	59.1	1960	167000	2010	2100
			G180JD	21.9	30.0	74.0	2510	269000	1500	1640
			N378ALE	33.0	15.0	93.1	2110	283000	1880	1950
			Mean	**36.8**	**18.8**	**78.5**	**1920**	**215000**	**2250**	**2360**
			SE	**5.9**	**3.8**	**7.65**	**300**	**36000**	**470**	**470**