charles river

PROTOCOL AMENDMENT No. 6

Testing Facility Study No. Proprietary Info

Sponsor Reference No Proprietary Info

Evaluation of the Interaction Between Proprietary Info Administered Orally and Cocaine Administered Intravenously to Conscious, Radiotelemetry-Instrumented Beagle Dogs

GLP

SPONSOR:
SRI Biosciences
333 Ravenswood Avenue
Menlo Park, CA 94025
United States

TESTING FACILITY:
Charles River Laboratories Ashland, LLC
1407 George Road
Ashland, OH 44805
United States

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SUMMARY OF CHANGES AND JUSTIFICATIONS

Study Protocol effective date: 17 November 2020

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

Item or Section(s)	Justification
Amendment 1	**Effective Date: 04 December 2020**
11.2 Bioanalytical Sample Processing	Storage conditions changed to align with established stability conditions.
Attachment A	Updated bioanalysis sample recipient information
Amendment 2	**Effective Date: 11 February 2021**
2. PROPOSED STUDY SCHEDULE	Updated the initiation of dosing (CV Phase) date to reflect a change in the study schedule.
8.4 Food	Updated timing of food offering based on dose administration time and post dose obsevations.
9. Experimental Design	Updated minimum washout duration
9.1. Administration of Test, Vehicle and Interaction Articles	Added the time following exit of the room to begin dose administration during the CV Phase. Extended duration to allow for doses to be administered at the same time of the day to account for potential dosing delays.
9.2. Jacket and Tether System Procedures	Clarified sham administration articles. Added the time following "sham" oral dose to being administering the "sham" IV dose.
11.1 Bioanalytical Sample Collection	Removed the word approximately from the target volume in the bioanalytical sample collection table.
Amendment 3	**Effective Date: 16 February 2021**
4. Responsible Personnel	Pharmacokinetic phase personnel updated.
6.1 Preparation of formulations	Updated frequency of preparation and storage conditions based on vehicle stability.
8.1 Housing	Deletion of erroneous text. Deleted text represented comments during protocol review. Clarification animals will have continual access to water during periods of fasting.
8.5 Water	Clarification of when water will not be available
9. Experimental Design	Dose levels updated following review of pharmacokinetic data. Clarificatoin of treatment week designation for PK phase and CV phase.
9.1 Administration of Test, Vehicle and Interaction Articles	Dose confirmation added to final report
9.2 Jacket and Tether System Procedures	Clarification of timing for jacket placement. Removal of requirement to place the jacket prior to each day of dosing.
14.2 Statistical Analysis	Phase 1 subphases updated
20. Reporting	Removal of finalization by testing facility if no comments are received by sponsor within 6 months
21.2 Justification of Dose Level Selection	Justification updated based on result of PK phase.

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Item or Section(s)	Justification
Amendment 4	**Effective Date: 02 Mar 2021**
6.1. Preparation of Formulations	Correction of storage conditions in the Preparation Details table for the test article based on the current analytical stability results.
6.3. Sample Collection and Analysis	Addition of footnote a to the Dose Formulation Sample Collection Schedule to indicat that homogeneity analysis will not be conducted on the vehicle treatment.
6.3.1 Analytical Method	Addtion of information regarding storage conditions of the interaction article and reference to the study number under which stability was previously established.
9. Experimental Design	Correction of previous erroneously labeled treatment week for CV 9. Corrected formatting errors from previous Amendment.
Amendment 5	**Effective Date: 09 Mar 2021**
6.3.1 Analytical Method	Correction of the study references for the validated and qualified methods for the test article and interaction article. Addition of wording to differentiate and clarify the two analyses methods.
10.2.2 Video Monitoring	Addition of section to describe the procedures for collection and evaluation of added video monitoring to aid in the evaluation of potential time of occurrence of emesis during the telemetry collection period.
14.2 Statistical Analysis	Corrected the number of subphases and hours for analysis Phase 4.
Amendment 6	**Effective Date: 28 Apr 2021**
4. RESPONSIBLE PERSONNEL	Addition of contact information for the PI performing the pharmacokinetic analysis.
16. REGULATORY COMPLIANCE	Addition of regulatory and agency compliance for the pharmacokinetic analysis portion of the study which will be conducted in Japan.

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1. OBJECTIVE(S)

The objective of this study is to evaluate the potential adverse cardiovascular effects that may result when Proprietary Info (test article) and cocaine (interaction article) are administered together to male Beagle dogs. The study will be conducted in two phases.

In the first phase (pharmacokinetics, PK phase), treatment-naïve Beagle dogs will be exposed to increasing levels of Proprietary Info to determine the pharmacokinetics and its tolerability.

In the second phase (cardiovascular interaction, CV phase), the Beagle dogs will be implanted with telemetry transmitters and subsequently dosed with combinations of orally (gavage) administered Proprietary Info and intravenously administered cocaine to evaluate if Proprietary Info affect the hemodynamic and cardiac effects cocaine. Proprietary Info dose levels in the cardiovascular interaction phase will be informed by the outcome of the pharmacokinetics phase.

2. PROPOSED STUDY SCHEDULE

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

Animal Arrival:	17 Nov 2020
Initiation of Dosing (PK Phase):	24 Nov 2020
Initiation of Dosing (CV Phase):	16 Feb 2021
Completion of In-life:	14 Apr 2021 (Release of animals from study)
Audited Draft Report:	24 Jun 2021
Final Report:	06 Dec 2021 (Expected date of Study Director signature of report)
Final SEND Dataset Package Delivery:	Based on Regulatory Submission

3. SPONSOR

Role	Name	Contact Information
Redacted by agreement		

4. RESPONSIBLE PERSONNEL

Role/Phase	QAU (Quality Assurance Unit)	Name	Contact Information
Redacted by agreement			

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Role/Phase	QAU (Quality Assurance Unit)	Name	Contact Information
Redacted by agreement	Charles River	Redacted by agreement	
	Charles River		
	Charles River		
	Individual Scientist (IS)		
	Charles River	Redacted by agreement	
	Principal Investigator (PI)		
	CMIC, Inc	Redacted by agreement	
	CMIC PharmaScience Co., Ltd.		

[a] Sponsor-designated Test Site

Each IS and PI is required to report any deviations or other circumstances that could affect the quality or integrity of the study to the Study Director in a timely manner for authorization/acknowledgement. Each IS and PI will provide a report addressing their assigned phase of the study, which will be included as an appendix to the Final Report.

The IS Phase Report will include the following:

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

The PI Phase Report will include the following:

- A Statement of Compliance
- A QA Statement (for Sponsor designated PI or for Testing Facility designated PI if audited by a QAU other than that of the Testing Facility)
- The archive site for all records, samples, specimens and reports generated from the phase or segment (alternatively, details regarding the retention of the materials may be provided to the Study Director for inclusion in the Final Report)

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

5. TEST MATERIALS

5.1. Test, Vehicle and Interaction Article Characterization

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

Vehicle and control article components will be characterized according to the product label provided by the manufacturer

The Sponsor has appropriate documentation on file concerning the method of synthesis, fabrication or derivation of the test article, and this information is available to the appropriate regulatory agencies should it be requested.

5.2. Test Article Identification

Test Article Identification

Proprietary Info	
Retest Date:	Concomitant
Physical Description:	To be documented
Purity:	100%
Correction Factor:	-
Storage Conditions:	18°C to 24°C
Provided by:	Sponsor or Sponsor Designee

- = not applicable

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5.3. Interaction Article Identification

Interaction Article Identification

	Interaction Article
Identification:	Cocaine HCl
Alternate Identification:	(-)-Cocaine HCl
Batch/Lot No.:	To be documented
Expiration/Retest Date:	To be documented
Physical Description:	To be documented
Purity:	To be documented
Correction Factor:	-
Storage Conditions:	18°C to 24°C
Provided by:	Sponsor or Sponsor Designee

- = not applicable

5.4. Vehicle Identification

Vehicle Identification (for Test Article Preparations)

	Vehicle Article	Vehicle Component	Vehicle Component
Identification:	0.5% Methylcellulose (400 cps)	Methylcellulose (400 cps)	Deionized (DI) water
Alternate Identification:	-	-	-
Storage Conditions:	Set to maintain a target temperature of 5°C	18°C to 24°C	18°C to 24°C
Provided by:	Testing Facility	Testing Facility	Testing Facility

- = not applicable.

Vehicle Identification (for Interaction Article Preparations)

	Vehicle Article	Vehicle Component	Vehicle Component
Identification:	0.9% sodium chloride for injection, USP	Sodium chloride	Reverse Osmosis (RO) water
Alternate Identification:	-	-	-
Storage Conditions:	18°C to 24°C	18°C to 24°C	18°C to 24°C
Provided by:	Testing Facility	Testing Facility	Testing Facility

- = not applicable.

5.5. Reserve Samples

Reserve samples of the test article will be taken in accordance with Charles River Standard Operating Procedures and stored in the Charles River Archives.

5.6. Test and Interaction Article Inventory and Disposition

Records of the receipt, distribution, storage, and disposition of test materials (including empty containers of Sponsor-provided materials) will be maintained. All unused Sponsor-supplied bulk test materials, with the exception of reserve samples, will be returned to the Sponsor at the address provided in Attachment A.

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5.7. Safety

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

6. DOSE FORMULATION AND ANALYSIS

6.1. Preparation of Formulations

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

Preparation Details

Dose Formulation	Frequency of Preparation	Storage Conditions
Vehicle	At least every 3 weeks	Set to maintain 5°C
Interaction Article	Once, prior to the first CV phase dosing occasion	Set to maintain 18°C to 24°C
Test Article	At least biweekly	Set to maintain 5°C

Frequency of preparation may be adjusted based on stability results. Any residual volumes from each dosing occasion will be discarded unless otherwise requested by the Study Director.

6.2. Preparation Details

Dosing formulations will be prepared at appropriate concentrations to meet dose level requirements. The prepared test article formulations will not be adjusted for purity. The prepared interaction article formulations will not be adjusted for purity. Any procedures not covered by SOPs required for formulation will be approved by the Study Director and included in the study records. Formulation pH will be within SOP range, if applicable.

6.3. Sample Collection and Analysis

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

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Dose Formulation Sample Collection Schedule

Sample Type	Concentrations	Stratum	Sampling From	Number of Samples per Concentration			Sample Volume (mL)	Intervals
				Collected	Analyzed	Backup		
Homogeneity Analyses	All Treatments[a]	Top	Preparation container	4	2	2	1	Each preparation
		Middle		4	2	2	1	
		Bottom		4	2	2	1	
Concentration Analyses	All Treatments	Middle	Preparation container	4	2	2	1	Each preparation

[a] = excluding the vehicle treatment.

Interaction Article Sample Collection Schedule

Sample Type	Concentrations	Stratum	Sampling From	Number of Samples per Concentration			Sample Volume (mL)	Intervals
				Collected	Analyzed	Backup		
Concentration Analyses	All Treatments	Middle	Preparation container	4	2	2	0.5	Each preparation and on each day of dosing[a]

[a] = duplicate 0.5 mL samples to be collected from the residual interaction article dosing container following dosing. One sample will be analyzed and the alternate will be utilized as a backup sample.

Dose analysis results (formulated test article or initial interaction article formulation) will be verified prior to dose administration at each sampling interval if available. If results are deemed unacceptable, the formulations will be prepared again and analyzed.

Interaction samples will be transferred to the analytical chemistry laboratory and stored refrigerated until analyzed. Test article formulation samples (including backups) will be transferred at ambient temperature to the Analytical Chemistry Department at the Testing Facility for same day analysis, where possible or stored for analysis within known formulation stability period.

6.3.1. Analytical Method

Test article formulations have been previously shown to be stable and homogeneous over the range of concentrations used on this study for at least 15 days at room temperature Proprietary Info Proprietary Info Therefore, stability and resuspension homogeneity of test article formulations will not be assessed on this study.

Analyses for the Test Article described below will be performed using a method validated by Charles River Proprietary Info for concentration. Any backup samples kept at Charles River will be discarded following acceptance of the analytical results by the Study Director.

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Interaction article formulations have been previously shown to be stable over the range of concentrations used on this study for at least 106 days at room Proprietary Info Proprietary Info Therefore, stability of the interaction article will not be assessed on this study.

Analyses for the Interaction Article described below will be performed using a method qualified by Charles River Proprietary Info for concentration. Any backup samples kept at Charles River will be discarded following acceptance of the analytical results by the Study Director.

6.3.1.1. Test Article Concentration and Homogeneity Analysis

Sample Allocation:	2 for analysis, 2 for backup
Storage Conditions:	Temperature set to maintain 18-24°C
Acceptance Criteria:	Suspension: For concentration: Mean sample concentration within 100% ± 15% of theoretical concentration. For homogeneity: Relative standard deviation (RSD) of concentrations of ≤ 10% for each group.

6.3.1.2. Interaction Article Concentration Analysis

Sample Allocation:	2 for analysis, 2 for backup
Storage Conditions:	Temperature set to maintain 18-24°C
Acceptance Criteria:	Solution: Mean sample concentration within 100% ± 10% of theoretical concentration.

7. TEST SYSTEM

Species:	Dog
Strain:	Beagle
Condition:	Purpose-bred, naïve
Source:	Specific facility to be documented in study records.
Number and Sex:	7 males
Age at the Initiation of Dosing:	At least 6 months. Animals not utilized on study will be assigned to the Charles River animal colony.

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Weight at the Initiation of Dosing:	At least 5.5 kg

The actual age and weight of the animals at the initiation of dosing will be listed in the Final Report.

7.1. Animal Screening

Method: All animals used on study will have documentation of immunization for parvovirus, distemper, adenovirus type 2, parainfluenza, *Bordetella*, papilloma, and rabies.

Prior to surgery, all animals will have blood samples collected for clinical pathology screening to evaluate health status prior to the surgical procedures. See section 12 for parameters to be evaluated.

7.2. Animal Identification

Method: Tattoo or a subcutaneously implanted electronic identification chip.

7.3. Surgical Preparation of Animals

Method:

Following the PK phase animals will be implanted with radiotelemetry transmitters and vascular access ports (VAPs) to allow for undisturbed IV dosing as described in Charles River SOPs.

Preanesthetics, surgical preparation and implantation details (for the telemetry implant and VAPs), and post-operative care and recovery procedures will be performed as outlined in CRL SOPs Proprietary Info Proprietary Info

The transmitters have a fluid-filled catheter (coated with an antithrombotic film to inhibit thrombus formation) with the tip filled with a patented gel for collection of blood pressure and 2 ECG leads emulating a lead II configuration.

The VAPs will be maintained per Charles River SOPs, and will include weekly assessments of patency until dosing. VAPs will be locked with taurolidine citrate solution (TCS) between patency assessments.

7.4. Jacket Acclimation

Method: Following the PK phase and prior to surgery for the cardiovascular interaction phase, all animals will be acclimated to a tethered infusion system. Animals will initially be conditioned to jackets and collars in a stepwise manner until at least 24 hours of acclimation is achieved. Subsequently, animals will be acclimated to the tether and jackets for a

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period of 4 hours, and for a period of at least 24 hours. Additional sessions may be employed if deemed necessary.

7.5. Environmental Acclimation

Method: Each animal will be inspected by a clinical veterinarian upon receipt. Animals judged to be in good health will be placed immediately in acclimation for at least 6 days. See respective sections for parameters to be evaluated. The animals will have been allowed at least 2 weeks to recover following implantation of the telemetry device before the administration of test and interaction articles for the cardiovascular phase.

7.6. Selection, Assignment, Replacement, and Disposition of Animals

Selection: Near the end of the acclimation period, animals judged to be suitable for testing (based on health as indicated by randomization approval) will be assigned to groups at random based on body weight stratification into a block design using a computer program. A printout containing the animal numbers and individual group assignments will be generated. For the CV phase, animals will be arbitrarily assigned to groups based on health and telemetric assessment.

Replacement: Before the initiation of dosing, any assigned animals considered unsuitable for use in the study will be replaced by alternate animals. After initiation of dosing, study animals may be replaced during the replacement period with alternate animals in the event of accidental injury, non-test article-related health issues, or similar circumstances.

Disposition: This study is non-terminal. Upon completion of the study, the animals will be maintained in the Charles River dog colony for future use or may be euthanized (with intravenous sodium pentobarbital administration and the radiotelemetry devices recovered, as applicable).

8. HUSBANDRY

8.1. Housing

Housing (Dosing Days): Single. Individual housing is necessary during periods of data collection to prevent telemetry signal cross talk and to individually attribute any clinical observations to individual animals to allow for a correlation to the bioanalytical data.

PK Phase: the animals will be separated in the morning prior to dosing, on each day of dosing.

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	Following jacket removal, or the final blood collection timepoint, animals will be returned to social housing.
Housing (Non-Dosing Days):	Group housed (up to 3 animals of the same sex) CV Phase: Animals will be separated in the afternoon on the day prior to dosing at the time of fasting and will remain separated until following jacket removal. Subjects will have continual access to water during periods of fasting. This is to minimize variations in baseline data caused by excitability and stress of animals from separation and placement into telemetry banks.
Caging:	Stainless steel cages with mesh floors.
Cage Identification:	Will indicate animal/tattoo number(s), and sex.

Housing set-up is as specified in the USDA Animal Welfare Act (9 CFR, Parts 1, 2 and 3) and as described in the *Guide for the Care and Use of Laboratory Animals* (National Research Council, 2011). Animals will be separated during designated procedures/activities or will be separated as required for monitoring and/or health purposes, as deemed appropriate by Study Director and/or Clinical Veterinarian.

8.2. Animal Enrichment

Method:	For enrichment, animals will be provided with items such as chew toys, except when interrupted by study procedures/activities. All animals will be given regular opportunity for exercise and socialization and will have enrichment through human interaction during the conduct of procedure acclimation and daily study activities

8.3. Environmental Conditions

The targeted conditions for animal room environment will be as follows:

Temperature:	66°F to 76°F (19°C to 24°C)
Humidity:	30% to 70%
Light Cycle:	12 hours light and 12 hours dark (except during designated procedures)

8.4. Food

Diet:	PMI Nutrition International, LLC Lab Diet Certified Canine Diet 5007
Type:	Kibble (alternate diet may be provided on individual animal basis as warranted as approved by the Study Director).
Frequency:	Approximately 300 g daily.
	Animals will be fasted overnight prior to surgery. The daily ration of food will be offered following recovery from anesthesia. Animals will

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	be fasted overnight before dosing days. On dosing days during the PK phase, the daily ration of food will be provided after the 2 hr plasma collection. On dosing days during the CV phase, food will be returned 4 hr after the cocaine dose (after 4 hr clinical observation post dose). Animals will not be fasted for longer than 24 hours.
Analysis:	Results of analysis for nutritional components and environmental contaminants are provided by the supplier and are on file at the Testing Facility. It is considered that there are no known contaminants in the feed that would interfere with the objectives of the study.

8.5. Water

Type:	Municipal tap water, treated by reverse osmosis and ultraviolet irradiation.
Frequency/Ration:	Freely available to each animal via an automatic watering system (except during body weight measurements, physical examinations, and during surgery).
Analysis:	Periodic analysis of the water is performed, and results of these analyses are on file at the Testing Facility. It is considered that there are no known contaminants in the water that would interfere with the outcome of the study.

8.6. Veterinary Care

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

If deemed necessary, dosing may be suspended for individual animals upon recommendation of the clinical veterinarian in consultation with the study director in order to provide appropriate veterinary care.

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9. EXPERIMENTAL DESIGN

The following table presents the treatment arrangement. Proprietary Info

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Study Design

Treatment No.	Treatment Week	Treatment	Test Article Dose Level (mg/kg)	Test Article Dose Concentration (mg/mL)	Test Article Dose Volume (mL/kg)	Interaction Article Dose Level (mg/kg)[c]	Interaction Article Dose concentration (mg/mL)	Interaction Article Dose Volume (mL/kg)	No. of Males
Pharmacokinetic (PK) Phase[a]									
1	PK 1	Proprietary Info	1	0.1	10	NA	NA	NA	7
2	PK 2		3	0.3	10	NA	NA	NA	7
3	PK 3		10	1	10	NA	NA	NA	7
4	PK 4		30	3	10	NA	NA	NA	7
Cardiovascular Interaction (CV) Phase[b]									
5	CV 1	Vehicle + Saline	0	0	10	0	0	0.25 (Saline)	6
6	CV 2	Vehicle + Cocaine (low)	0	0	10	0.56	2.24	0.25	6
7	CV 3	Vehicle + Cocaine (high)	0	0	10	1.7	6.8	0.25	6
8	CV 4	Proprietary Info (low) + Saline	3	0.3	10	0	0	0.25 (Saline)	6
9	CV 5	Proprietary Info (low) + Cocaine (low)	3	0.3	10	0.56	2.24	0.25	6
10	CV 6	Proprietary Info (low) + Cocaine (high)	3	0.3	10	1.7	6.8	0.25	6
11	CV 7	Proprietary Info (high) + Saline	30	3	10	0	0	0.25 (Saline)	6
12	CV 8	Proprietary Info (high) + Cocaine (low)	30	3	10	0.56	2.24	0.25	6
13	CV 9	Proprietary Info (high) + Cocaine (high)	30	3	10	1.7	6.8	0.25	6

NA = not applicable

[a] The same 7 animals will be used for each treatment in an escalating design with 6 minimum days between doses.

[b] 6 animals will be selected from the animals tested in the PK phase and the same 6 animals will be used for each treatment in ascending treatment number order with 6 minimum days between doses.

[c] The interaction article will be administered at the prescribed dose level at 1 hour (± 5 minutes) following test article dosing via ambulatory intravenous infusion.

[d] Pending outcome of pharmacokinetic phase.

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9.1. Administration of Test, Vehicle and Interaction Articles

PK Phase:

Dose Route:	Oral gavage (test article)
Frequency:	Once daily; single administration for each Treatment
Method:	The dose formulations will be stirred continuously at room temperature during dosing. The doses will be given using a syringe with an attached gavage tube. Each dose will be followed by 15-mL flush using deionized water provided by the formulations department.

CV Phase:

Dose Route:	Oral gavage (test article) followed by intravenous infusion (interaction article)
Frequency:	Once daily; single administration for each Treatment
Method:	Oral route: The vehicle or test article will be stirred continuously at room temperature during dosing. The doses will be given using a syringe with an attached gavage tube. Each dose will be followed by 15-mL flush using deionized water provided by the formulations department. Intravenous route: The interaction article or its vehicle will be administered at 1 hour (± 5 minutes) following the oral dose via intravenous infusion over a 30 second infusion from an infusion pump followed by a 5 mL saline flush administered at the same rate. Doses will be delivered using a calibrated infusion pump with a tethered infusion system. Doses will be administered in absence of technical staff in the dosing room. Doses will be scheduled to initiate at least 30 minutes following exiting of the room. Doses will be delivered via the Cath-in-Cath system to the indwelling catheter appropriately placed. The infusion will be delivered to freely moving animals. Individual doses will be drawn into syringes labeled with the animal number, study number, and date, and documented appropriately. The dosing syringes will be filled with the appropriate dosing volume (plus the additional volume of the dead space in the extension line to the Y connector infusion system) of interaction article required for dosing. Using a second infusion pump for each animal, an additional syringe will be filled with the appropriate volume of saline to flush the extension lines to complete the prescribed dose. Animals will be dosed at approximately the same time (± 1 hour) each dose day. Dose confirmation will be determined by syringe verification and included in the final report.

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9.2. Jacket and Tether System Procedures

Pretreatment Session:

Prior to Dose 1 of the Cardiovascular Interaction Phase, a "sham" dosing procedure imitating the dosing procedure for each treatment session will be performed, including a telemetric recording (cardiovascular, ECG, and body temperature) obtained for at least 4 hours following the "sham" IV infusion (saline). All animals will undergo the pretreatment recording. Vehicle will be used as the oral sham dosing article, and saline will be utilized as the intravenous sham dosing article. Doses will be administered as outlined in section 9.1. These data will be recorded but not reported. The pretreatment session will include a minimum of 90 min recording period prior to the target "sham" oral dose while in telemetry cages, and then continue for at least 4 hr following the "sham" IV infusion dose. The "sham" IV infusion dose will be performed at 1 hr (± 5 minutes) following the "sham" oral dose, as outlined in the CV interaction phase treatment regimen. Hemodynamic data (systolic, diastolic, mean arterial pressure, pulse pressure and heart rate) and ECG intervals will be measured and binned in appropriate intervals as described in Section 14.2.

The ECG tracings will be reviewed for rhythm disturbances (dysrhythmias) for the six animals participating in the study over the duration of recording period. Data from the pretreatment collection will be used to confirm acclimation to testing procedures of the animals placed on study.

During the CV phase, all animals will be placed into jackets prior to dosing. Patency checks will be performed prior to introduction of the jacket system. All animals will be placed on a maintenance infusion of saline (2 mL/hr) in an effort to maintain VAP patency during non-dosing periods. Animals will be maintained in jackets for up to approximately 3 doses. Jackets will be removed for approximately one week before subsequent jacket placement.

10. IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS

General In-life Assessments

Parameter	Population(s)[a]	Frequency (minimum required)	Comments
Mortality	All Animals[a]	At least twice daily[b] (morning and afternoon) beginning upon arrival through termination/release	Animals will be observed within their cage unless necessary for identification or confirmation of possible findings.
Cageside/Postdose Observations[c]	All Main Study Animals	During the PK phase observations will be conducted prior to dosing, and at each PK time point.	Animals will be observed within their cage unless necessary for identification or confirmation of possible findings.

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Parameter	Population(s)[a]	Frequency (minimum required)	Comments
		During the CV phase, observations will be conducted, prior to oral dosing, and at approximately 4 hours postdosing (relative to interaction article administration)	The absence or presence of findings will be recorded for individual animals. Findings noted outside the above-specified observation periods will also be recorded. Only the presence of unscheduled observations will be recorded; the absence of findings will thus not be recorded
Detailed Clinical Observations[c]	All Main Study Animals	Following receipt On the day of randomization On the day prior to each day of dosing (for both the PK and CV Phase) Weekly between the end of the PK phase and beginning of the CV phase	Animals will be removed from the cage. The absence or presence of findings will be recorded for individual animals.
Individual Body Weights	All Main Study Animals	Following receipt On the day of randomization On the day prior to each day of dosing (for both the PK and CV Phase) Weekly between the end of the PK phase and beginning of the CV phase; frequency may increase to every other day if evidence of deterioration is noted (as indicated by clinical condition.)	Body weights of potential replacement animals may also be collected at any of these timepoints. These data will not be statistically analyzed or included in study report.

[a] To include unused replacement animals until released from study.
[b] Except on days of receipt and study termination where frequency will be at least once daily.
[c] For observations that cannot be attributed to an individual animal due to social housing, the observation will be noted to each animal in the socialized group.

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10.1. RADIOTELEMETRY

10.2. Radiotelemetry Data Acquisition and Analysis

10.2.1. Electrocardiography and Hemodynamics

Frequency: Baseline arterial blood pressure (systolic, diastolic, and mean arterial pressure), pulse pressure, heart rate, lead II electrocardiographic (ECG) waveforms (PR, QRS, QT, and QTcV intervals), and body temperature will be collected continuously for at least 90 min prior to administration of vehicle or test article. If a probe failure occurs prior to or during collection of baseline data, the animal will be replaced with a reserve animal for this study, if available, or repeated at a later date.

Following administration of vehicle or test article, the appropriate parameters will be collected continuously for at least 4 hours following intravenous dose of interaction article. Electrocardiography, hemodynamic parameters and body temperature data will be averaged to appropriate time intervals for statistical analysis.

Population(s): All Main Study animals

System: The radiotelemetry system (Data Sciences International, St. Paul, MN) will consist of large animal radiotelemetry transmitters (with capabilities to collect, at minimum, arterial pressure, body temperature, and electrocardiographic waveforms), receivers (RMC-1), and 1 or more data exchange matrices (DEM) that will relay information from the receivers to the computer. An ambient pressure reference monitor (APR-1) will be coupled to the DEM to measure the barometric pressure and provide a digital signal to the DSI PONEMAH system. The DSI PONEMAH system uses the measurements provided by the APR-1 to correct pressure measurements obtained from the implant for changes in barometric pressure.

The hardware connected to the Dataquest™ OpenART™ Acquisition Interface provides direct digital signals to the DSI PONEMAH software. The ECG and arterial waveform and body temperature data will be recorded and analyzed by the DSI PONEMAH data acquisition software, version 5.0 or higher. ECG and arterial pressure waveforms will be sampled at 500 Hz. Temperature data will be sampled at 50 Hz. Data acquired continuously will be logged every 120 seconds. During data processing the logging rate will be changed to 60 seconds. The ECG waveform data will be analyzed by the DSI PONEMAH ECG-PRO Template Analysis software.

Procedure: Blood pressure (systolic, diastolic, and mean), pulse pressure, heart rate, electrocardiographic (ECG) waveforms, and body temperature will be collected continuously.

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Evaluation: Cardiovascular parameters and body temperature data will be averaged to appropriate time intervals for statistical analysis.

Quantitative ECG waveform analysis will be performed using the DSI PONEMAH ECG-PRO Template Analysis software to determine the PR, QRS, RR, and QT intervals. Heart rate-corrected QT (QTc) values will be calculated with the Van de Water correction formula where QTcV = QT - 0.087*(RR-1) (Spence, et al., 1988 and Van de Water, et al., 1989). Additionally, QT will be corrected using an individual correction factor, $QTcH = 10^{\log(QT) - \beta[\log(HR)-\log(HRm)]}$ (Holzgrefe, 2007). The beta value for QTcH will be collected from each animals' vehicle dosing data during the CV phase (slope of QT to RR).

For the purpose of data processing, Noise and Match derived parameters will be collected. These parameters will not be reported or statistically analyzed.

Qualitative assessment of ECG will be performed by trained personnel for disturbances in rhythm and waveform morphology in 1-minute segments for every 30 minutes of data collected following test article or vehicle dosing (e.g., a start event or a dosing event) through 4 hours after the interaction article or its vehicle dose. Abnormal rhythm results will be reported in a table as frequency of events. Qualitative assessment of blood pressure waveforms will not be performed. Abnormal waveforms that are identified by Charles River personnel will be discussed with the Study Director to determine if these and additional waveforms should be presented to a veterinary cardiology specialist for evaluation. In the event that abnormal waveforms are identified and evaluated by a veterinary cardiology specialist, a report with this evaluation will be maintained in the raw data and included in the final report as an appendix.

Within the processing system used to average telemetry data into intervals for statistical analysis and reporting, minimum and maximum limits will be set per the table below. Following review of data, these limits may be changed at the request of the Study Director which will be documented along with reason for change.

Parameter	Waveform Type	Minimum	Maximum
Heart Rate	Blood Pressure	0 beats per minute	No limit
Systolic Blood Pressure	Blood Pressure	0 mmHg	350 mmHg

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Diastolic Blood Pressure	Blood Pressure	0 mmHg	No limit
Mean Arterial Blood Pressure	Blood Pressure	0 mmHg	No limit
Pulse Pressure	Blood Pressure	0 mmHg	150 mmHg
Body Temperature	Temperature	30°C	45°C
PR Interval	ECG	0 msec	10000 msec
QRS Complex	ECG	0 msec	10000 msec
QT Interval	ECG	0 msec	10000 msec
QTc Interval	ECG	0 msec	10000 msec
RR Interval	ECG	0 msec	10000 msec

For parameters indicated as control parameters, if the defined limits are exceeded for a time point then all other parameters at this time point will be omitted from analysis and reporting.

10.2.2. Video Monitoring

Frequency: On each day of telemetry collection, video data synchronized with ECG will be recorded to a secure workstation. Video data will be recorded concurrently during periods of radiotelemetry data collection.

Population(s): All Main Study animals

System: Axis cameras (or equivalent) will be used to collect time matched video data synchronized with the radiotelemetry system.

Procedure: Each camera will be configured to capture the video data for each subject. During data review, video data will be viewed using an appropriate media player.

Evaluation: Video data synchronized with ECG will be used to establish the approximate time of occurrence of retching or emesis, if noted, beginning from the time of test article administration thru the 4-hour period of post-dosing observation after the interaction article dose. This time will be recorded on an appropriate form and will be maintained in the study records. The times

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may be entered into the appropriate LIMS at the discretion of the study director. The video data will be maintained in the study records but will not have any additional evaluations performed.

11. BIOANALYSIS AND PHARMACOKINETIC EVALUATION

11.1. Bioanalytical Sample Collection

Bioanalytical Sample Collection

	Time Postdose on Days 1, 8, 15 and 22							
Treatment No.	**0 hr (predose)**	**0.5 hr**	**1 hr**	**2 hr**	**4 hr**	**8 hr**	**12 hr**	**24 hr**
1	X	X	X	X	X	X	X	X
2	X	X	X	X	X	X	X	X
3	X	X	X	X	X	X	X	X
4	X	X	X	X	X	X	X	X

Method/Comments:	Venipuncture from a jugular vein (saphenous or cephalic vein may be used, if necessary).
Target Volume (mL):	1 mL/time point collected without anesthesia.
Anticoagulant:	Sodium Heparin
Special Requirements:	Keep samples chilled during collection and processing.
Processing:	Plasma

X = sample to be collected; hr = hour

11.2. Bioanalytical Sample Processing

Samples will be mixed gently and centrifuged as soon as practical.

The samples will be centrifuged and the resultant plasma will be separated, transferred to duplicate uniquely labeled polypropylene tubes, and frozen immediately over dry ice until transferred to storage. Samples will be stored in a freezer set to maintain a target of -20°C.

Samples will be shipped by overnight courier to the address provided in Attachment A.

The samples will be shipped in 2 batches (each with 1 set of aliquots). The recipient, Sponsor Representative, and Study Director will be contacted prior to shipment to ensure that the shipment will be handled appropriately upon receipt. Upon receipt at the analytical laboratory, the samples will be stored in a freezer set to maintain a target of -20°C.

11.3. Bioanalytical Sample Analysis

Bioanalytical samples will be analyzed for concentration of Proprietary Info

Proprietary Info

Proprietary Info

Proprietary Info

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Analysis will be performed according to the validated method and SOPs of the performing laboratory. Appropriate computer software will be used for the collection and analysis of data; specific software versions will be noted in the bioanalytical report. Statistical analyses, including regression analysis, and descriptive statistics, including arithmetic means and standard deviations, accuracy and precision will be performed.

11.4. Pharmacokinetic Evaluation

Pharmacokinetic parameters will be estimated using Phoenix pharmacokinetic software. A non-compartmental approach consistent with the oral route of administration will be used for parameter estimation. All parameters will be generated from Proprietary Info individual concentrations in plasma from Days 1, 8, 15, and 22 whenever practical. Parameters will be estimated using sampling times made relative to the start of each dose administration.

Parameters to be Estimated

Parameter	Description of Parameter
t_{max}	The time after dosing at which the maximum concentration was observed.
C_{max}	The maximum observed concentration measured after dosing.
C_{max}/Dose	The C_{max} divided by the dose administered.
AUC_{tlast}	The area under the concentration versus time curve from the start of dose administration to the last observed quantifiable concentration calculated using the linear trapezoidal method.
AUC_{tlast}/Dose	The AUC_{tlast} divided by the dose administered.
t_{last}	The time after dosing at which the last quantifiable concentration was observed

Partial AUCs (between two defined sample times), and corresponding dose-normalized values, may be derived and reported to aid interpretation. Descriptive statistics (e.g., number, arithmetic mean, median, standard deviation, standard error, coefficient of variation) will be reported as deemed appropriate, as well as ratios for appropriate grouping and sorting variables (e.g., AUC) may be generated. Pharmacokinetic tables and graphs will also be generated.

Analysis will be performed according to SOPs of the performing laboratory.

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12. CLINICAL PATHOLOGY

12.1. Sample Collection

Clinical Pathology Sample Collection

Group No(s).	Time Point	Hematology	Clinical Chemistry
All Animals	Prior to PK phase and after surgical implantation	X	X

Fasting:	-	at least 8 hours (no more than 24 hours)
Method/Comments:	Venipuncture from a jugular vein (saphenous or cephalic vein may be used, if necessary)	Venipuncture from a jugular vein (saphenous or cephalic vein may be used, if necessary)
Target Volume (mL)[a]:	1	1.5
Anticoagulant:	K_2EDTA	None
Special Requirements:	-	-
Processing:	None	Serum

X = Sample to be collected; - = Not applicable

[a] = Additional samples may be obtained (e.g., due to clotting of non-serum samples) if permissible sampling frequency and volume are not exceeded.

12.2. Hematology

Hematology Parameters

Red blood cell count	White blood cell count[a]
Hemoglobin concentration	Neutrophil count (absolute)
Hematocrit	Lymphocyte count (absolute)
Mean corpuscular volume	Monocyte count (absolute)
Red blood cell distribution width	Eosinophil count (absolute)
Mean corpuscular hemoglobin concentration	Basophil count (absolute)
Mean corpuscular hemoglobin	Large unstained cells (absolute)
Reticulocyte count (absolute)	Other cells (as appropriate)
Platelet count	Mean platelet volume

[a] If performed manually, results of differential counts will include platelet estimates and RBC morphology (individual tables only).

A blood smear will be prepared from each hematology sample. Blood smears will be labeled,stained, and stored. If additional examination of blood smears is deemed necessary, the smears may be subsequently evaluated and this evaluation will be described in a protocol amendment.

12.3. Clinical Chemistry

Clinical Chemistry Parameters

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Alanine aminotransferase Aspartate aminotransferase Alkaline phosphatase Gamma-glutamyltransferase Creatine kinase Total bilirubin[a] Urea nitrogen Creatinine Calcium Phosphorus	Total protein Albumin Globulin (calculated) Albumin/globulin ratio Glucose Cholesterol Triglycerides Sodium Potassium Chloride Sample quality[b]

[a] When total bilirubin is > 0. 5 mg/dL, direct bilirubin will also be measured and indirect bilirubin will be calculated.

[b] Will include degree of hemolysis, lipemia, and icterus (individual tables only).

13. DISPOSITION OF ANIMALS

This study is non-terminal. Upon completion of the study, the animals will be maintained in the Charles River animal colony for future use or may be euthanized (with intravenous sodium pentobarbital administration and the radiotelemetry probes recovered, as applicable). Animals not used on study will be returned to the Charles River animal colony.

Animals that experience severe or chronic pain or distress that cannot be relieved will be euthanized via intravenous sodium pentobarbital administration. All animals to be euthanized in extremis will have a detailed physical examination and a body weight collected. The animal will then be released for euthanasia and subsequent gross necropsy.

14. STATISTICAL ANALYSIS

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

Each cardiovascular parameter (systolic, diastolic, and mean arterial blood pressure; pulse pressure, heart rate; PR, QRS, QT, and QTc intervals) and body temperature will be analyzed using a SAS® System software. Cardiovascular data and body temperature will be exported to and analyzed in accordance with GLP Regulations. These statistical analyses and tables will be incorporated into the report.

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14.1. Statistical Comparisons

Control Treatment	Comparison (Test Article) Treatments
5	6,7
5	8,11
6	9,12
7	10,13

14.2. Statistical Analysis

The data will be analyzed using the mixed model analysis procedure within the SAS/STAT System (SAS) software. For statistical analysis, telemetry data will be organized into the following phases:

- Baseline: 90-min pre-oral dose baseline
- Phase I: 4 subphases of 15 min each post oral dose phase (prior to interaction article)
- Phase II: 6 subphases of 5 min each for hour 0 through 30 min (post interaction article)
- Phase III: 3 subphases of 10 min each for 30 min through hour 1 (post interaction article)
- Phase IV: 3 subphases of 1 h each for hours 2 through 4 (post interaction article)

The analysis phases and post-dose time intervals will be the same for all study periods. A single value (mean) will be calculated for each period's pre-dose (baseline) and individual post-dose time intervals.

Each cardiovascular parameter and body temperature will be analyzed, separately for each analysis phase, with a repeated measure analysis of covariance (RANCOVA). Fixed actors in the model will include baseline (BASE) as a covariate, treatment group (TRT), time after dose (TIME), and the two way interactions of each of the factors (TRT*TIME, TRT*BASE and BASE*TIME). ANIMAL will be fit as a random effect for autoregressive error structures. The SAS® procedure PROC GLIMMIX will be used for analysis with TIME as the repeated effect and ANIMAL as the subject. The covariance structure across time will be selected by evaluating corrected Akaike's Information Criterion (AICC).

Summary statistics will be reported for each treatment at each time point and across all time points for a given analysis phase. Summary graphs (means with standard error) will be presented for the averaged data for systolic, diastolic, and mean arterial pressure, pulse pressure, heart rate, body temperature and PR, QRS, QT, and QTcV. Individual data will not be presented in the report but will be maintained in the study records. Mean values for each time interval will be presented for individual animals. The statistical analysis summary report will be presented as an appendix in the final report.

Following the initial data review, other data summary intervals and/or segments may be used at the discretion of the Study Director in order to optimize the interpretation of data from this study.

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14.2.1. Descriptive Statistics

Endpoints: Body Temperature

Cardiovascular Endpoints

- Heart Rate
- Systolic, Diastolic, and Mean Arterial Blood Pressures
- Pulse Pressure
- ECG (RR, PR, QRS, QT, and QTc)

Description: The following statistical analyses will be performed for each analysis segment:

The data will be tabulated within each summary time interval and the arithmetic mean (Mean), number of subjects (N), least squares mean (LS Mean), and standard error of the LS Mean (LSM s.e.) will be calculated for each endpoint and treatment.

14.2.2. Repeated Measures Analysis of Covariance

Endpoints: Body Temperature

Cardiovascular Endpoints

- Heart Rate
- Systolic, Diastolic and Mean Arterial Blood Pressures
- Pulse Pressure
- ECG (RR, PR, QRS, QT, and QTc)

15. COMPUTERIZED SYSTEMS

The following computerized systems may be used in the study. The actual computerized systems will be documented in the report.

As Charles River Ashland transitions between various computer systems, the study number may appear as Proprietary Info

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Critical Computerized Systems

Program/System	Description
Advia 120	Hematology
Advia 1800	Serum and Urine Chemistry Analysis
Bio Medic Data Systems (BMDS) Implantable Micro Identification ™ (IMI-500 or IMI-1000)	Animal identification.
Charles River Formulations Dispense System (CR-FDS)	In-house developed system for use in conjunction with Provantis Dispense™ to ensure proper storage and use of formulations.
Dionex Chromeleon® software, Varian MS Workstation® software, Agilent ChemStation® software, or Molecular Devices SpectraMax® software	Used for chromatographic data acquisition and quantitation.
DSI PONEMAH Physiology Platform Model P3 Plus; DSI PONEMAH ECG PRO Template Analysis software; Dataquest™ OpenART™ Acquisition Interface	Computer-based systems (DSI) utilized for the electronic collection and measurement of cardiovascular, and body temperature data.
Deviation Information Library	Deviations
DocuSign©	Collection of Part 11 compliant signature.
Metasys SMP	Controls and monitors animal room environmental conditions.
Microsoft Office 2010 or higher; GraphPad Prism® 2008 or higher	Used in conjunction with the publishing software to generate study reports.
In-house reporting software Nevis 2012 (using SAS)	Reporting of in-life and postmortem data
Provantis®	Test material receipt, accountability, formulation activities, in-life (e.g.,. clinical observations, body weights, food consumption), clinical pathology (clinical chemistry, coagulation, hematology), and/or postmortem (e.g.,. pathology, ovarian contents)
SAS®	Statistical (non-WTDMS™) analyses
Share Document Management System (SDMS)	Reporting
WIL Metasys	In-house developed system used to record and report animal room environmental conditions.
WIL Toxicology Data Management System™ (WTDMS™)	In-house developed system used for collection and reporting of clinical pathology and other data.

Note: Version numbers of WTDMS™ programs used for the study are presented on the report data tables (reporting programs); version numbers and release dates are otherwise maintained in the study records and/or facility records.

Data for parameters not required by protocol, which are automatically generated by analytical devices used will be retained on file but not reported. Statistical analysis results that are generated by the program but are not required by protocol and/or are not scientifically relevant will be retained on file but will not be included in the tabulations.

16. REGULATORY COMPLIANCE

The study will be performed in accordance with the U.S. Department of Health and Human Services, Food and Drug Administration, United States Code of Federal Regulations, Title 21, Part 58: Good Laboratory Practice for Nonclinical Laboratory Studies and as accepted by

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Regulatory Authorities throughout the European Union (OECD Principles of Good Laboratory Practice), Japan (MHLW), and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

Any portion of this study conducted in Japan will be performed in accordance with MHW Ordinance No. 21: Good Laboratory Practice Standards for Non-Clinical Safety Studies on Drugs, 1997 and the Partial Revision (Ordinance No. 114, 2008) and as accepted by Regulatory Authorities throughout the European Union, United States of America (FDA), and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

Exceptions to GLPs include the following study elements:

- Characterization of the test and interaction articles will be/were performed by the Sponsor or Sponsor subcontractor at a laboratory that follows FDA Good Manufacturing Practice (GMP) regulations.
- Characterization of the test and interaction articles will be/were performed by the Sponsor or Sponsor subcontractor according to established SOPs, controls, and approved test methodologies to ensure integrity and validity of the results generated; these analyses will not be/were not conducted in compliance with the GLP or GMP regulations.

17. QUALITY ASSURANCE

Study components performed at sites other than the testing facility will be conducted according to the protocol and that site's applicable SOPs.

Study components performed at sites other than the testing facility will be audited by the QAU of the applicable test site.

17.1. Testing Facility

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

17.2. Test Site(s)/Subcontractor(s)

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

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18. AMENDMENTS AND DEVIATIONS

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

19. RETENTION AND DISPOSITION OF RECORDS, SAMPLES, AND SPECIMENS

All study-specific raw data, electronic data, documentation, protocol, retained samples and specimens, and final reports will be archived by no later than the date of final report issue. All materials generated by Charles River Laboratories from this study will be transferred to a Charles River Laboratories archive. At least 1 year after issue of the Draft Report, the Sponsor will be contacted.

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

Disposition of Residual/Retained Samples

Sample Type	Disposition	Schedule
Dose Formulation Analysis (including backups)	Discard	Following acceptance of the analytical results by the Study Director.

19.1. Study Classification

Study Category:	Safety Pharmacology
Study Type:	Cardiovascular Pharmacology; Pharmacokinetics
Study Design:	Crossover
Primary Treatment CAS Registry Number:	Not Available
Primary Treatment Unique Ingredient ID:	Not Available
Class of Compound:	Not Available

20. REPORTING

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

The Sponsor will receive an electronic version of the Draft and Final Report provided in Adobe Acrobat PDF format (hyperlinked and searchable at final) along with a Microsoft Word version of the text. The PDF document will be created from native electronic files to the extent possible, including text and tables generated by the Testing Facility. Report components not available in

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native electronic files and/or original signature pages will be scanned and converted to PDF image files for incorporation.

A tabulated data summary following the appropriate format as outlined in the ICH Harmonized Tripartite Guideline, *The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Safety – M4S (R2), Nonclinical Overview and Nonclinical Summaries of Module 2, Organisation of Module 4*, will be provided at the same time as the Draft and Final Reports as a separate Microsoft Word document.

Reports should be finalized within 6 months of issue of the audited Draft Report.

20.1. SEND Datasets

SEND datasets will be generated and provided outside the context of the GLP Report. These datasets will not be subject to QA Audit nor will they be used as the basis for the Study Director interpretation of the study results. SEND datasets will be provided for the Report based on regulatory submission date. The Sponsor is expected to provide submission dates.

21. JUSTIFICATIONS AND GUIDELINES

21.1. Justification of Test System and Number of Animals

At this time, studies in laboratory animals provide the best available basis for extrapolation to humans and are required to support regulatory submissions. Acceptable models that do not use live animals currently do not exist.

This species and breed of animal is recognized by regulatory agencies to be appropriate for safety pharmacology studies and it is a widely used breed for which significant historical control data are available.

Only male dogs will be used because no sex differences in exposure are anticipated.

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

21.2. Justification of Route and Dose Levels

Test Article:

PK Phase:

The doses were selected by the NIDA. The oral route of exposure for the test article was selected because this is the intended route of human exposure. The exposure levels of the test article for a substance abuse indication in human subjects is Proprietary Info Proprietary Info Dose levels of test article will be selected to correspond with human plasma levels at intention to treat a 3x multiple of that dose to provide a safety margin in the event of increased exposure in patients attributable to individual differences in metabolism or excess drug taking.

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Withheld pursuant to exemption

Proprietary Info

of the Freedom of Information and Privacy Act

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Interaction Article:

The doses were selected by the NIDA. The intravenous route of exposure for the interaction article was selected because this is a route used by individuals that use cocaine. Proprietary Info

Proprietary Info

21.3. Guidelines for Study

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

- OECD Guideline 417. *Toxicokinetics*.
- ICH Harmonised Tripartite Guideline S3A. *Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies*.
- ICH Harmonised Tripartite Guideline S7A. *Guideline on Safety Pharmacology Studies for Human Pharmaceuticals*.
- ICH Harmonised Tripartite Guideline S7B. *The Non-Clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals*

22. ANIMAL WELFARE

This study will comply with all applicable sections of the Final Rules of the Animal Welfare Act regulations (Code of Federal Regulations, Title 9), the *Public Health Service Policy on Humane Care and Use of Laboratory Animals* from the Office of Laboratory Animal Welfare (Office of Laboratory Animal Welfare, 2015), and the *Guide for the Care and Use of Laboratory Animals* from the National Research Council (2011). The protocol and any amendments or procedures involving the care or use of animals in this study will be reviewed and approved by the Testing Facility Institutional Animal Care and Use Committee before the initiation of such procedures.

If an animal is determined to be in overt pain/distress or appears moribund and is beyond the point where recovery appears reasonable, the animal will be euthanized for humane reasons in accordance with the *American Veterinary Medical Association (AVMA) Guidelines on Euthanasia* and with the procedures outlined in the protocol (American Veterinary Medical Association, 2020).

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

22.1. Institutional Animal Care and Use Committee Approval

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

23. REFERENCES

American Veterinary Medical Association. *AVMA Guidelines on Euthanasia*. January 2020.

Cochran WG, Cox GM. Plans and Tables of Random Permutations. In: Experimental Designs, New York, NY: John Wiley and Sons; 1957;145:577-582.

National Research Council. Guide for the Care and Use of Laboratory Animals, Committee for the Update of the Guide for the Care and Use of Laboratory Animals, Institute for Laboratory Animal Research, Division on Earth and Life Sciences; The National Academies Press: Washington, DC, 2011.

Office of Laboratory Animal Welfare. *Public Health Services Policy on Humane Care and Use of Laboratory Animals*. Bethesda, MD: National Institutes of Health. March 2015.

SAS® Proprietary Software, Version 9.4; SAS Institute, Inc.: Cary, NC, 2002-2014 Spence S, Soper K, Hoe C-M, Coleman J. The heart rate-corrected QT interval of conscious Beagle dogs: a formula based on analysis of covariance. *Toxicol Sci*. 1998;45(2):247-258.

Spence S, Soper K, Hoe C-M, Coleman J. The heart rate-corrected QT interval of conscious Beagle dogs: a formula based on analysis of covariance. *Toxicol Sci*. 1998;45(2):247-258.

Van de Water A, Verheyen J, Xhonneux R, Reneman RS. An improved method to correct the QT interval of the electrocardiogram for changes in heart rate. *J Pharmacol Met*. 1989;22(3):207-217.

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AMENDMENT APPROVAL

Redacted by agreement

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SPONSOR APPROVAL

The signature below indicates that the Sponsor Representative approves the study protocol amendment.

Redacted by agreement

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ATTACHMENT A

Shipment of Samples and Study Records

Matrix[a]	Purpose	Day/ Week/ Aliquot	Proposed Shipment Date	Conditions for Shipment	Recipient/Address
Test Article	Disposition of unused neat test article	-	To be documented	On blue ice packs	Redacted by agreement
Interaction Article	Disposition of unused neat interaction article	-	To be documented	Ambient temperature	
Plasma	Shipment of specimens for Bioanalytical Analysis	-	To be documented	Frozen, on dry ice	

- = not applicable.
[a] Shipments performed via FedEx.

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FINAL PROTOCOL

Testing Facility Study Proprietary Info

Sponsor Reference Proprietary Info

Evaluation of the Interaction Between Proprietary Info Administered Orally and Cocaine Administered Intravenously to Conscious, Radiotelemetry-Instrumented Beagle Dogs

GLP

SPONSOR:
SRI Biosciences
333 Ravenswood Avenue
Menlo Park, CA 94025
United States

TESTING FACILITY:
Charles River Laboratories Ashland, LLC
1407 George Road
Ashland, OH 44805
United States

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TABLE OF CONTENTS

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1. OBJECTIVE(S)

The objective of this study is to evaluate the potential adverse cardiovascular effects that may result when Proprietary Info test article) and cocaine (interaction article) are administered together to male Beagle dogs. Proprietary Info is a proprietary Proprietary Info Proprietary Info Proprietary Info NIDA is considering Proprietary Info as a potential treatment for substance use disorders, including cocaine disorder. The dogs will be implanted with telemetry transmitters and subsequently dosed with combinations of orally (drug in capsule) administered Proprietary Info and intravenously administered cocaine to evaluate if Proprietary Info affects hemodynamic and cardiac effects of cocaine.

2. PROPOSED STUDY SCHEDULE

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

Animal Arrival:	06 May 2021
Initiation of Dosing:	22 Jun 2021
Completion of In-life:	08 September 2021 (Release of animals from study)
Audited Draft Report:	17 November 2021
Final Report:	24 May 2022 (Expected date of Study Director signature of report)
Final SEND Dataset Package Delivery:	Based on Regulatory Submission

3. SPONSOR

Role	Name	Contact Information
Redacted by agreement		

4. RESPONSIBLE PERSONNEL

Role/Phase	QAU (Quality Assurance Unit)	Name	Contact Information
Redacted by agreement			

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Role/Phase	QAU (Quality Assurance Unit)	Name	Contact Information
Redacted by agreement			

Each IS is required to report any deviations or other circumstances that could affect the quality or integrity of the study to the Study Director in a timely manner for authorization/acknowledgement. Each IS will provide a report addressing their assigned phase of the study, which will be included as an appendix to the Final Report.

The IS Phase Report will include the following:

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

5. TEST MATERIALS

5.1. Test, Vehicle and Interaction Article Characterization

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

Vehicle and control article components will be characterized according to the product label provided by the manufacturer.

The Sponsor has appropriate documentation on file concerning the method of synthesis, fabrication or derivation of the test article, and this information is available to the appropriate regulatory agencies should it be requested.

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5.2. Test Article Identification

Test Article Identification

	Test Article
Identification:	Proprietary Info
Proprietary Info	
Retest Date:	Concomitant
Physical Description:	To be documented
Purity:	100%
Correction Factor:	-
Storage Conditions:	18°C to 24°C
Provided by:	Sponsor or Sponsor Designee

- = not applicable

5.3. Interaction Article Identification

Interaction Article Identification

	Interaction Article
Identification:	Cocaine HCl
Alternate Identification:	(-)-Cocaine HCl
Batch/Lot No.:	To be documented
Expiration/Retest Date:	To be documented
Physical Description:	To be documented
Purity:	To be documented
Correction Factor:	-
Storage Conditions:	18°C to 24°C
Provided by:	Sponsor or Sponsor Designee

- = not applicable

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5.4. Vehicle Identification

Vehicle Identification (for Test Article Preparations)

	Vehicle Article
Identification:	Size # 11 gelatin capsules
Alternate Identification:	-
Storage Conditions:	18°C to 24°C
Provided by:	Testing Facility

- = not applicable

Vehicle Identification (for Interaction Article Preparations)

	Vehicle Article
Identification:	0.9% sodium chloride for injection, USP
Alternate Identification:	Saline
Storage Conditions:	18°C to 24°C
Provided by:	Testing Facility

5.5. Reserve Samples

Reserve samples of the test article will be taken in accordance with Charles River Standard Operating Procedures and stored in the Charles River Archives.

5.6. Test and Interaction Article Inventory and Disposition

Records of the receipt, distribution, storage, and disposition of test materials (including empty containers of Sponsor-provided materials) will be maintained. All unused Sponsor-supplied bulk test materials, with the exception of reserve samples, will be returned to the Sponsor at the address provided in Attachment A.

5.7. Safety

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

6. DOSE FORMULATION AND ANALYSIS

6.1. Preparation of Formulations

Capsules will be dispensed on each dosing occasion.

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Preparation Details for Test Article

Dose Formulation	Frequency of Preparation	Storage Conditions
Vehicle[a]	At least weekly	Set to maintain 18°C to 24°C
Test Article	Each day of dosing	Set to maintain 18°C to 24°C

[a] A sufficient number of empty gelatin capsules will be dispensed for oral vehicle administration

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

Preparation Details for Interaction Article

Dose Formulation	Frequency of Preparation	Storage Conditions
Vehicle	At least biweekly	Set to maintain 5°C
Interaction Article	Once, prior to the first interaction dosing occasion	Set to maintain 18°C to 24°C

Frequency of preparation may be adjusted based on stability results. Any residual volumes from each dosing occasion will be discarded unless otherwise requested by the Study Director.

6.2. Preparation Details

Test Article:

The test substance for each animal will be weighed and placed into one or more gelatin capsule(s). Each capsule will be placed in an appropriately labeled and capped containers (study number, animal number, group number, etc.) for dosing. In addition, animals will receive the anticipated number of capsules to be administered to the high dose treatment (calculated based on body weight at the time of the first control dosing session). An adjustment for purity will not be performed. Any procedures not covered by SOPs required for formulation will be approved by the Study Director and included in the study records.

Interaction Article:

Dosing formulations will be prepared at appropriate concentrations to meet dose level requirements. The prepared interaction article formulations will not be adjusted for purity. Any procedures not covered by SOPs required for formulation will be approved by the Study Director and included in the study records. Formulation pH will be within SOP range, if applicable.

6.3. Sample Collection and Analysis

Test Article:

Analysis of the test article formulations will not be conducted for this study as the test article supplied by the Sponsor will be administered neat in capsules, without any further modification. Therefore, stability, homogeneity, and concentration assessment is not necessary.

Interaction Article:

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

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Interaction Article Sample Collection Schedule

Sample Type	Concentrations	Stratum	Sampling From	Number of Samples per Concentration			Sample Volume (mL)	Intervals
				Collected	Analyzed	Backup		
Concentration Analyses	All Treatments	Middle	Preparation container	4	2	2	0.5	Each preparation and on each day of dosing[a]

[a] = duplicate 0.5 mL samples to be collected from the residual interaction article dosing container following dosing. One sample will be analyzed, and the alternate will be utilized as a backup sample.

Interaction article dose analysis results will be verified prior to the first interaction article dose administration. If results are deemed unacceptable, the formulations will be prepared again and analyzed.

Following preparation, and following each dose occasion, interaction article samples will be transferred to the Analytical Chemistry Department and stored refrigerated until analyzed.

6.3.1. Analytical Method

Interaction article formulations have been previously shown to be stable over the range of concentrations used on this study for at least 106 days at room temperature (SRI study No. M225-16 and M449-20). Therefore, stability of the interaction article will not be assessed on this study.

Analyses described below will be performed using a method validated by Charles River Proprietary Info Proprietary Info for concentration. Any backup samples kept at Charles River will be discarded following acceptance of the analytical results by the Study Director.

6.3.1.1. Interaction Article Concentration Analysis

Sample Allocation:	2 for analysis, 2 for backup
Storage Conditions:	Temperature set to maintain 18-24°C
Acceptance Criteria:	Solution: Mean sample concentration within 100% ± 10% of theoretical concentration.

7. TEST SYSTEM

Species: Dog

Strain: Beagle

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Condition:	Purpose-bred, naïve
Source:	Specific facility to be documented in study records.
Number and Sex:	7 males
Age at the Initiation of Dosing:	At least 6 months. Animals not utilized on study will be assigned to the Charles River animal colony.
Weight at the Initiation of Dosing:	At least 5.0 kg

The actual age and weight of the animals at the initiation of dosing will be listed in the Final Report.

7.1. Animal Screening

Method: All animals used on study will have documentation of immunization for parvovirus, distemper, adenovirus type 2, parainfluenza, *Bordetella*, papilloma, and rabies.

Prior to surgery, all animals will have blood samples collected for clinical pathology screening to evaluate health status prior to the surgical procedures. See Section 11 for parameters to be evaluated.

7.2. Animal Identification

Method: Tattoo or a subcutaneously implanted electronic identification chip.

7.3. Surgical Preparation of Animals

Method: Preanesthetics, surgical preparation and implantation details (for the telemetry implant and VAPs), and post-operative care and recovery procedures will be performed as outlined in Proprietary Info Proprietary Info

The transmitters have a fluid-filled catheter (coated with an antithrombotic film to inhibit thrombus formation) with the tip filled with a patented gel for collection of blood pressure and 2 ECG leads emulating a lead II configuration.

The VAPs will be maintained per Charles River SOPs and will include weekly assessments of patency until dosing. VAPs will be locked with taurolidine citrate solution (TCS) between patency assessments.

7.4. Jacket Acclimation

Method: All animals will be acclimated to a tethered infusion system. Animals will initially be conditioned to jackets and collars in a stepwise manner until at least 24 hours of acclimation is achieved. Subsequently, animals

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will be acclimated to the tether and jackets for a period of 4 hours, and for a period of at least 24 hours. Additional sessions may be employed if deemed necessary.

7.5. Environmental Acclimation

Method:	Each animal will be inspected by a clinical veterinarian upon receipt. Animals judged to be in good health will be placed immediately in acclimation for at least 6 days. See respective sections for parameters to be evaluated. The animals will have been allowed at least 2 weeks to recover following implantation of the telemetry device before the administration of vehicle, test article and interaction articles.

7.6. Selection, Assignment, Replacement, and Disposition of Animals

Selection:	Near the end of the acclimation period, animals judged to be suitable for testing (based on health and telemetric assessment as indicated by randomization approval) will be assigned to groups arbitrarily using a computer program. A printout containing the animal numbers and individual group assignments will be generated.
Replacement:	Before the initiation of dosing, any assigned animals considered unsuitable for use in the study will be replaced by alternate animals. After initiation of dosing, study animals may be replaced during the replacement period with alternate animals in the event of accidental injury, non-test article-related health issues, or similar circumstances.
Disposition:	This study is non-terminal. Upon completion of the study, the animals will be maintained in the Charles River dog colony for future use or may be euthanized (with intravenous sodium pentobarbital administration and the radiotelemetry devices recovered, as applicable).

8. HUSBANDRY

8.1. Housing

Housing (Dosing Days):	Single. Individual housing is necessary during periods of data collection to prevent telemetry signal cross talk. Following jacket removal, animals will be returned to social housing.
Housing (Non-Dosing Days):	Group housed (up to 3 animals of the same sex) Animals will be separated in the afternoon on the day prior to dosing at the time of fasting and will remain separated until following jacket removal. This is to minimize variations in baseline data caused by excitability and stress of animals from separation and placement into

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	telemetry banks. Animals will have continual access to water during periods of fasting.
Caging:	Stainless steel cages with mesh floors.
Cage Identification:	Will indicate animal/tattoo number(s), and sex.

Housing set-up is as specified in the USDA Animal Welfare Act (9 CFR, Parts 1, 2 and 3) and as described in the *Guide for the Care and Use of Laboratory Animals* (National Research Council, 2011). Animals will be separated during designated procedures/activities or will be separated as required for monitoring and/or health purposes, as deemed appropriate by Study Director and/or Clinical Veterinarian.

8.2. Animal Enrichment

Method:	For enrichment, animals will be provided with items such as chew toys, except when interrupted by study procedures/activities. All animals will be given regular opportunity for exercise and socialization and will have enrichment through human interaction during the conduct of procedure acclimation and daily study activities

8.3. Environmental Conditions

The targeted conditions for animal room environment will be as follows:

Temperature:	66°F to 76°F (19°C to 24°C)
Humidity:	30% to 70%
Light Cycle:	12 hours light and 12 hours dark (except during designated procedures)

8.4. Food

Diet:	PMI Nutrition International, LLC Lab Diet Certified Canine Diet 5007
Type:	Kibble (alternate diet may be provided on individual animal basis as warranted as approved by the Study Director).
Frequency:	Approximately 300 g daily.
	Animals will be fasted overnight prior to surgery. The daily ration of food will be offered following recovery from anesthesia. Animals will be fasted overnight before dosing days. On dosing days, food will be returned 4 hr after the cocaine dose (after 4 hr clinical observation post dose). Animals will not be fasted for longer than 24 hours. Animals will have continual access to water during periods of fasting.
Analysis:	Results of analysis for nutritional components and environmental contaminants are provided by the supplier and are on file at the Testing

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Facility. It is considered that there are no known contaminants in the feed that would interfere with the objectives of the study.

8.5. Water

Type:	Municipal tap water, treated by reverse osmosis and ultraviolet irradiation.
Frequency/Ration:	Freely available to each animal via an automatic watering system (except during body weight measurements, physical examinations, and during surgery).
Analysis:	Periodic analysis of the water is performed, and results of these analyses are on file at the Testing Facility. It is considered that there are no known contaminants in the water that would interfere with the outcome of the study.

8.6. Veterinary Care

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

If deemed necessary, dosing may be suspended for individual animals upon recommendation of the clinical veterinarian in consultation with the study director in order to provide appropriate veterinary care.

9. EXPERIMENTAL DESIGN

The following table presents the treatment arrangement. Test article and interaction article dose levels were selected based on data provided to NIDA by Proprietary Info (See Section 20.2).

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Study Design

Treatment No.	Treatment	Test Article Proprietary Info Dose Level (mg/kg) [a]	Interaction Article (cocaine) Dose Level (mg/kg)[b]	Interaction Article Dose concentration (mg/mL)	Interaction Article Dose Volume (mL/kg)	No. of Males[c]
1	Vehicle + Saline	0 (empty capsule)	0 (saline)	0	0.25	6
2	Vehicle + Cocaine (low)	0 (empty capsule)	0.56	2.24	0.25	6
3	Vehicle + Cocaine (high)	0 (empty capsule)	1.7	6.8	0.25	6
4	Proprietary Info (low) + Saline	250	0 (saline)	0	0.25	6
5	Proprietary Info low) + Cocaine (low)	250	0.56	2.24	0.25	6
6	Proprietary Info (low) + Cocaine (high)	250	1.7	6.8	0.25	6
7	Proprietary Info high) + Saline	750	0 (saline)	0	0.25	6
8	Proprietary Info (high) + Cocaine (low)	750	0.56	2.24	0.25	6
9	Proprietary Info high) + Cocaine (high)	750	1.7	6.8	0.25	6

NA = not applicable

[a] The test article Proprietary Info will be administered orally as drug in capsule

[b] The interaction article, cocaine, will be administered intravenously at the prescribed dose level at 2 hours (± 5 minutes) following test article dosing via ambulatory infusion

[c] The same 6 animals will be used for each treatment in an escalating design with 6 minimum days between doses.

9.1. Administration of Test, Vehicle and Interaction Articles

Dose Route: Oral capsule (test article) followed by intravenous infusion (interaction article)

Frequency: Once daily; single administration for each Treatment

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Method:

Oral route: The vehicle (empty gelatin capsules) or test article (in gelatin capsules) will be administered orally.

Intravenous route: The interaction article or its vehicle will be administered at 2 hours (± 5 minutes) following the oral dose via intravenous infusion over an approximate 45 second infusion from an infusion pump followed by a 5 mL saline flush administered at the same rate. Doses will be delivered using a calibrated infusion pump with a tethered infusion system. Doses will be administered in absence of technical staff in the dosing room. Doses will be scheduled to initiate (at least 90 minutes) following exiting of the room.

Doses will be delivered via the Cath-in-Cath system to the indwelling catheter appropriately placed. The infusion will be delivered to freely moving animals. Individual doses will be drawn into syringes labeled with the animal number, study number, and date, and documented appropriately. The dosing syringes will be filled with the appropriate dosing volume (plus the additional volume of the dead space in the extension line to the Y connector infusion system) of interaction article required for dosing. Using a second infusion pump for each animal, an additional syringe will be filled with the appropriate volume of saline to flush the extension lines to complete the prescribed dose. Animals will be dosed at approximately the same time (± 1 hour) each dose day. The Sponsor will be notified in a timely manner in the event of any issues surrounding the dose administration (*e.g.*, failed dose, incomplete dose, emesis immediately following dosing, etc.).

9.2. Jacket and Tether System Procedures

Pretreatment Session:

Prior to Dose 1, a "sham" dosing procedure imitating the dosing procedure for each treatment session will be performed, including a telemetric recording (cardiovascular, ECG, and body temperature) obtained for at least 4 hours following the "sham" IV infusion (saline). All animals will undergo the pretreatment recording. An empty capsule will be used as the oral sham dosing article, and saline will be utilized as the intravenous sham dosing article. Doses will be administered as outlined in section 9.1. These data will be recorded but not reported. The pretreatment session will include a minimum of 90 min recording period prior to the target "sham" oral dose while in telemetry cages, and then continue for at least 4 hr following the "sham" IV infusion dose. The "sham" IV infusion dose will be performed at 2 hours (±5 minutes) following the "sham" oral dose, as outlined in the section 9.1. Hemodynamic data (systolic, diastolic, mean arterial pressure, pulse pressure and heart rate) and ECG intervals will be measured and binned in appropriate intervals as described in Section 10.2.

The ECG tracings will be reviewed for rhythm disturbances (dysrhythmias) for the six animals participating in the study over the duration of recording period. Data from the pretreatment

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collection will be used to confirm acclimation to testing procedures of the animals placed on study.

All animals will be placed into jackets prior to dosing. Patency checks will be performed prior to introduction of the jacket system. All animals will be placed on a maintenance infusion of saline (2 mL/hr) in an effort to maintain VAP patency during non-dosing periods. Animals will be maintained in jackets for up to approximately 3 doses. Jackets will be removed for approximately one week before subsequent jacket placement.

10. IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS

General In-life Assessments

Parameter	Population(s)[a]	Frequency (minimum required)	Comments
Mortality	All Animals[a]	At least twice daily[b] (morning and afternoon) beginning upon arrival through termination/release	Animals will be observed within their cage unless necessary for identification or confirmation of possible findings.
Cageside/Postdose Observations[c]	All Main Study Animals	Prior to oral dosing, and at approximately 4 hours postdosing (relative to interaction article administration)	Animals will be observed within their cage unless necessary for identification or confirmation of possible findings. The absence or presence of findings will be recorded for individual animals. Findings noted outside the above-specified observation periods will also be recorded. Only the presence of unscheduled observations will be recorded; the absence of findings will thus not be recorded
Detailed Clinical Observations[c]	All Main Study Animals	Following receipt Weekly during the pretest period On the day of randomization On the day prior to each day of dosing	Animals will be removed from the cage. The absence or presence of findings will be recorded for individual animals.
Individual Body Weights	All Main Study Animals	Following receipt Weekly during the pretest period On the day of randomization	Body weights of potential replacement animals may also be collected at any of these timepoints. These data will not be statistically analyzed or included in study report.

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Parameter	Population(s)[a]	Frequency (minimum required)	Comments
		On the day prior to each day of dosing	

[a] To include unused replacement animals until released from study.
[b] Except on days of receipt and study termination where frequency will be at least once daily.
[c] For observations that cannot be attributed to an individual animal due to social housing, the observation will be noted to each animal in the socialized group.

10.1. RADIOTELEMETRY

10.2. Radiotelemetry Data Acquisition and Analysis

10.2.1. Electrocardiography and Hemodynamics

Frequency: Baseline arterial blood pressure (systolic, diastolic, and mean arterial pressure), pulse pressure, heart rate, lead II electrocardiographic (ECG) waveforms (PR, QRS, QT, QTcV and calculated individual QTc intervals), and body temperature will be collected continuously for at least 90 min prior to administration of the control or test article. If a probe failure occurs prior to or during collection of baseline data, the animal will be replaced with a reserve animal for this study, if available, or repeated at a later date.

Following administration of the control or test article, the appropriate parameters will be collected continuously for at least 4 hours following intravenous dose of interaction article. Electrocardiography, hemodynamic parameters and body temperature data will be averaged to appropriate time intervals for statistical analysis.

Population(s): All Main Study animals

System: The radiotelemetry system (Data Sciences International, St. Paul, MN) will consist of large animal radiotelemetry transmitters (with capabilities to collect, at minimum, arterial pressure, body temperature, and electrocardiographic waveforms), receivers (RMC-1), and 1 or more data exchange matrices (DEM) that will relay information from the receivers to the computer. An ambient pressure reference monitor (APR-1) will be coupled to the DEM to measure the barometric pressure and provide a digital signal to the DSI PONEMAH system. The DSI PONEMAH system uses the measurements provided by the APR-1 to correct pressure measurements obtained from the implant for changes in barometric pressure.

The hardware connected to the Dataquest™ OpenART™ Acquisition Interface provides direct digital signals to the DSI PONEMAH software.

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The ECG and arterial waveform and body temperature data will be recorded and analyzed by the DSI PONEMAH data acquisition software, version 5.0 or higher. ECG and arterial pressure waveforms will be sampled at 500 Hz. Temperature data will be sampled at 50 Hz. Data acquired continuously will be logged every 120 seconds. During data processing the logging rate will be changed to 60 seconds. The ECG waveform data will be analyzed by the DSI PONEMAH ECG-PRO Template Analysis software.

Procedure: Blood pressure (systolic, diastolic, and mean), pulse pressure, heart rate, electrocardiographic (ECG) waveforms, and body temperature will be collected continuously.

Evaluation: Cardiovascular parameters and body temperature data will be averaged to appropriate time intervals for statistical analysis.

Quantitative ECG waveform analysis will be performed using the DSI PONEMAH ECG-PRO Template Analysis software to determine the PR, QRS, RR, and QT intervals. Heart rate-corrected QT (QTc) values will be calculated with the Van de Water correction formula where QTcV = QT - 0.087*(RR-1) (Spence, *et al*., 1988 and Van de Water, *et al*., 1989). Additionally, individual QT rate-corrections (β-values) will be derived from treatment 1 dosing occasion for each animal's dosing session. The heart rate-corrected QT intervals will be calculated using a method based on Spence and modified by Miyazaki & Tagawa and reported (Spence et al, 1998 and Miyazaki and Tagawa, 2002).

For the purpose of data processing, Noise and Match derived parameters will be collected. These parameters will not be reported or statistically analyzed.

Qualitative assessment of ECG will be performed by trained personnel for disturbances in rhythm and waveform morphology in 1-minute segments for every 30 minutes of data collected following test article or control dosing (e.g., a start event or a dosing event) through 4 hours after the interaction article or its vehicle dose. Abnormal rhythm results will be reported in a table as frequency of events. Qualitative assessment of blood pressure waveforms will not be performed. Abnormal waveforms that are identified by Charles River personnel will be discussed with the Study Director to determine if these and additional waveforms should be presented to a veterinary cardiology specialist for evaluation. In the event that abnormal waveforms are identified and evaluated by a veterinary cardiology specialist, a report with this evaluation will be maintained in the raw data and included in the final report as an appendix.

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Within the processing system used to average telemetry data into intervals for statistical analysis and reporting, minimum and maximum limits will be set per the table below. Following review of data, these limits may be changed at the request of the Study Director which will be documented along with reason for change.

Parameter	Waveform Type	Minimum	Maximum
Heart Rate	Blood Pressure	0 beats per minute	No limit
Systolic Blood Pressure	Blood Pressure	0 mmHg	350 mmHg
Diastolic Blood Pressure	Blood Pressure	0 mmHg	No limit
Mean Arterial Blood Pressure	Blood Pressure	0 mmHg	No limit
Pulse Pressure	Blood Pressure	0 mmHg	150 mmHg
Body Temperature	Temperature	30°C	45°C
PR Interval	ECG	0 msec	10000 msec
QRS Complex	ECG	0 msec	10000 msec
QT Interval	ECG	0 msec	10000 msec
QTc Interval	ECG	0 msec	10000 msec
RR Interval	ECG	0 msec	10000 msec

For parameters indicated as control parameters, if the defined limits are exceeded for a time point then all other parameters at this time point will be omitted from analysis and reporting.

10.2.2. Video Monitoring

Frequency: On each day of telemetry collection, video data synchronized with ECG will be recorded to a secure workstation. Video data will be recorded concurrently during periods of radiotelemetry data collection.

Population(s): All Main Study animals

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System: Axis cameras (or equivalent) will be used to collect time matched video data synchronized with the radiotelemetry system.

Procedure: Each camera will be configured to capture the video data for each subject. During data review, video data will be viewed using an appropriate media player.

Evaluation: Video data synchronized with ECG will be used to establish the approximate time of occurrence of retching or emesis, if noted, beginning from the time of test article administration thru the 4-hour period of post-dosing observation after the interaction article dose. This time will be recorded on an appropriate form and will be maintained in the study records. The times may be entered into the appropriate LIMS at the discretion of the study director. The video data will be maintained in the study records but will not have any additional evaluations performed.

11. CLINICAL PATHOLOGY

11.1. Sample Collection

Clinical Pathology Sample Collection

Group No(s).	Time Point	Hematology	Clinical Chemistry
All Animals	Prior to surgical implantation	X	X
Fasting:		-	at least 8 hours (no more than 24 hours)
Method/Comments:		Venipuncture from a jugular vein (saphenous or cephalic vein may be used, if necessary)	Venipuncture from a jugular vein (saphenous or cephalic vein may be used, if necessary)
Target Volume (mL)[a]:		1	1.5
Anticoagulant:		K_2EDTA	None
Special Requirements:		-	-
Processing:		None	Serum

X = Sample to be collected; - = Not applicable

[a] = Additional samples may be obtained (e.g., due to clotting of non-serum samples) if permissible sampling frequency and volume are not exceeded.

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11.2. Hematology

Hematology Parameters

Red blood cell count	White blood cell count[a]
Hemoglobin concentration	Neutrophil count (absolute)
Hematocrit	Lymphocyte count (absolute)
Mean corpuscular volume	Monocyte count (absolute)
Red blood cell distribution width	Eosinophil count (absolute)
Mean corpuscular hemoglobin concentration	Basophil count (absolute)
Mean corpuscular hemoglobin	Large unstained cells (absolute)
Reticulocyte count (absolute)	Other cells (as appropriate)
Platelet count	Mean platelet volume

[a] If performed manually, results of differential counts will include platelet estimates and RBC morphology (individual tables only).

A blood smear will be prepared from each hematology sample. Blood smears will be labeled, stained, and stored. If additional examination of blood smears is deemed necessary, the smears may be subsequently evaluated and this evaluation will be described in a protocol amendment.

11.3. Clinical Chemistry

Clinical Chemistry Parameters

Alanine aminotransferase	Total protein
Aspartate aminotransferase	Albumin
Alkaline phosphatase	Globulin (calculated)
Gamma-glutamyltransferase	Albumin/globulin ratio
Creatine kinase	Glucose
Total bilirubin[a]	Cholesterol
Urea nitrogen	Triglycerides
Creatinine	Sodium
Calcium	Potassium
Phosphorus	Chloride
	Sample quality[b]

[a] When total bilirubin is > 0. 5 mg/dL, direct bilirubin will also be measured and indirect bilirubin will be calculated.

[b] Will include degree of hemolysis, lipemia, and icterus (individual tables only).

12. DISPOSITION OF ANIMALS

This study is non-terminal. Upon completion of the study, the animals will be maintained in the Charles River animal colony for future use or may be euthanized (with intravenous sodium pentobarbital administration and the radiotelemetry probes recovered, as applicable). Animals not used on study will be returned to the Charles River animal colony.

Animals that experience severe or chronic pain or distress that cannot be relieved will be euthanized via intravenous sodium pentobarbital administration. All animals to be euthanized in extremis will have a detailed physical examination and a body weight collected. The animal will then be released for euthanasia and subsequent gross necropsy.

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13. STATISTICAL ANALYSIS

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

Each cardiovascular parameter (systolic, diastolic, and mean arterial blood pressure; pulse pressure, heart rate; PR, QRS, QT, and QTc intervals) and body temperature will be analyzed using a SAS® System software. Cardiovascular data and body temperature will be exported to and analyzed in accordance with GLP Regulations. These statistical analyses and tables will be incorporated into the report.

13.1. Statistical Comparisons

Control Treatment	Comparison (Test Article) Treatments
1	2,3
1	4,7
2	5,8
3	6,9

13.2. Statistical Analysis

The data will be analyzed using the mixed model analysis procedure within the SAS/STAT System (SAS) software. For statistical analysis, telemetry data will be organized into the following phases:

- Baseline: 90-min pre-oral dose baseline
- Phase I: 8 subphases of 15 min each post oral dose phase (prior to interaction article)
- Phase II: 6 subphases of 5 min each for hour 0 through 30 min (post interaction article)
- Phase III: 3 subphases of 10 min each for 30 min through hour 1 (post interaction article)
- Phase IV: 3 subphases of 1 hour each for hours 2 through 4 (post interaction article)

The analysis phases and post-dose time intervals will be the same for all study periods. A single value (mean) will be calculated for each period's pre-dose (baseline) and individual post-dose time intervals.

Each cardiovascular parameter and body temperature will be analyzed, separately for each analysis phase, with a repeated measure analysis of covariance (RANCOVA). Fixed actors in the model will include a covariate (BASE) (90 minute baseline for each dosing occasion), treatment group (TRT), time after dose (TIME), and the two way interactions of each of the factors (TRT*TIME, TRT*BASE and BASE*TIME). ANIMAL will be fit as a random effect for autoregressive error structures. The SAS® procedure PROC GLIMMIX will be used for analysis with TIME as the repeated effect and ANIMAL as the subject. The covariance structure across time will be selected by evaluating corrected Akaike's Information Criterion (AICC).

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Summary statistics will be reported for each treatment at each time point and across all time points for a given analysis phase. Summary graphs (means with standard error) will be presented for the averaged data for systolic, diastolic, and mean arterial pressure, pulse pressure, heart rate, body temperature and PR, QRS, QT, and calculated individual QTc. Individual data will not be presented in the report but will be maintained in the study records. Mean values for each time interval will be presented for individual animals. The statistical analysis summary report will be presented as an appendix in the final report.

Following the initial data review, other data summary intervals and/or segments may be used at the discretion of the Study Director in order to optimize the interpretation of data from this study.

13.2.1. Descriptive Statistics

Endpoints: Body Temperature

Cardiovascular Endpoints

- Heart Rate
- Systolic, Diastolic, and Mean Arterial Blood Pressures
- Pulse Pressure
- ECG (RR, PR, QRS, QT, and QTc)

Description: The following statistical analyses will be performed for each analysis segment:

The data will be tabulated within each summary time interval and the arithmetic mean (Mean), number of subjects (N), least squares mean (LS Mean), and standard error of the LS Mean (LSM s.e.) will be calculated for each endpoint and treatment.

13.2.2. Repeated Measures Analysis of Covariance

Endpoints: Body Temperature

Cardiovascular Endpoints

- Heart Rate
- Systolic, Diastolic and Mean Arterial Blood Pressures
- Pulse Pressure
- ECG (RR, PR, QRS, QT, and QTc)

14. COMPUTERIZED SYSTEMS

The following computerized systems may be used in the study. The actual computerized systems will be documented in the report.

As Charles River Ashland transitions between various computer systems, the study number may appear as Proprietary Info in the data records and report.

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Critical Computerized Systems

Program/System	Description
Advia 120 and/or ADVIA 2120i	Hematology
Advia 1800	Serum and Urine Chemistry Analysis
Bio Medic Data Systems (BMDS) Implantable Micro Identification ™ (IMI-1000)	Animal identification.
Charles River Formulations Dispense System (CR-FDS)	In-house developed system for use in conjunction with Provantis Dispense™ to ensure proper storage and use of formulations.
Dionex Chromeleon® software, Varian MS Workstation® software, Agilent ChemStation® software, or Molecular Devices SpectraMax® software	Used for chromatographic data acquisition and quantitation.
DSI PONEMAH Physiology Platform Model P3 Plus; DSI PONEMAH ECG PRO Template Analysis software; Dataquest™ OpenART™ Acquisition Interface	Computer-based systems (DSI) utilized for the electronic collection and measurement of cardiovascular, and body temperature data.
Deviation Information Library	Deviations
DocuSign©	Collection of Part 11 compliant signature.
Metasys SMP	Controls and monitors animal room environmental conditions.
Microsoft Office 2010 or higher; GraphPad Prism® 2008 or higher	Used in conjunction with the publishing software to generate study reports.
In-house reporting software Nevis 2012 (using SAS)	Reporting of in-life and postmortem data
Provantis®	Test material receipt, accountability, formulation activities, in-life (*e.g.*, clinical observations, body weights, food consumption), clinical pathology (clinical chemistry, coagulation, hematology), and/or postmortem (*e.g.*, pathology)
SAS®	Statistical (non-WTDMS™) analyses
Share Document Management System (SDMS)	Reporting
WIL Metasys	In-house developed system used to record and report animal room environmental conditions.
WIL Toxicology Data Management System™ (WTDMS™)	In-house developed system used for collection and reporting of clinical pathology and other data.

Note: Version numbers of WTDMS™ programs used for the study are presented on the report data tables (reporting programs); version numbers and release dates are otherwise maintained in the study records and/or facility records.

Data for parameters not required by protocol, which are automatically generated by analytical devices used will be retained on file but not reported. Statistical analysis results that are generated by the program but are not required by protocol and/or are not scientifically relevant will be retained on file but will not be included in the tabulations.

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15. REGULATORY COMPLIANCE

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

16. QUALITY ASSURANCE

Study components performed at sites other than the testing facility will be conducted according to the protocol and that site's applicable SOPs.

Study components performed at sites other than the testing facility will be audited by the QAU of the applicable test site.

16.1. Testing Facility

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

16.2. Test Site(s)/Subcontractor(s)

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

17. AMENDMENTS AND DEVIATIONS

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

18. RETENTION AND DISPOSITION OF RECORDS, SAMPLES, AND SPECIMENS

All study-specific raw data, electronic data, documentation, protocol, retained samples and specimens, and final reports will be archived by no later than the date of final report issue. All materials generated by Charles River Laboratories from this study will be transferred to a Charles River Laboratories archive. At least 1 year after issue of the Draft Report, the Sponsor will be contacted.

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

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Disposition of Residual/Retained Samples

Sample Type	Disposition	Schedule
Clinical Pathology	Discard	Prior to issuance of the Final Report.
Dose Formulation Analysis (including backups)	Discard	Following acceptance of the analytical results by the Study Director.

18.1. Study Classification

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

19. REPORTING

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

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

A tabulated data summary following the appropriate format as outlined in the ICH Harmonized Tripartite Guideline, *The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Safety – M4S (R2), Nonclinical Overview and Nonclinical Summaries of Module 2, Organisation of Module 4*, will be provided at the same time as the Draft and Final Reports as a separate Microsoft Word document.

Reports should be finalized within 6 months of issue of the audited Draft Report.

19.1. SEND Datasets

SEND datasets will be generated and provided outside the context of the GLP Report. These datasets will not be subject to QA Audit nor will they be used as the basis for the Study Director interpretation of the study results. SEND datasets will be provided for the Report based on regulatory submission date. The Sponsor is expected to provide submission dates.

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20. JUSTIFICATIONS AND GUIDELINES

20.1. Justification of Test System and Number of Animals

At this time, studies in laboratory animals provide the best available basis for extrapolation to humans and are required to support regulatory submissions. Acceptable models that do not use live animals currently do not exist.

This species and breed of animal is recognized by regulatory agencies to be appropriate for safety pharmacology studies and it is a widely used breed for which significant historical control data are available.

Only male dogs will be used because no sex differences in exposure are anticipated.

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

20.2. Justification of Route and Dose Levels

Test Article:

The dose levels were selected by NIDA. The oral route of exposure was selected because this is the intended route of human exposure.

There are antecedent toxicokinetic data from dogs that received Proprietary Info Proprietary Info Proprietary Info See below.

Proprietary Info

Proprietary Info

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Page 50 of 97 to Page 52 of 97

Withheld pursuant to exemption

Proprietary Info

of the Freedom of Information and Privacy Act

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Proprietary Info

Interaction Article:

The doses were selected by the NIDA. The intravenous route of exposure for the interaction article was selected because this is a route used by individuals that use cocaine. Proprietary Info

Proprietary Info

20.3. Guidelines for Study

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

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

21. ANIMAL WELFARE

This study will comply with all applicable sections of the Final Rules of the Animal Welfare Act regulations (Code of Federal Regulations, Title 9), the *Public Health Service Policy on Humane Care and Use of Laboratory Animals* from the Office of Laboratory Animal Welfare (Office of Laboratory Animal Welfare, 2015), and the *Guide for the Care and Use of Laboratory Animals* from the National Research Council (2011). The protocol and any amendments or procedures involving the care or use of animals in this study will be reviewed and approved by the Testing Facility Institutional Animal Care and Use Committee before the initiation of such procedures.

If an animal is determined to be in overt pain/distress or appears moribund and is beyond the point where recovery appears reasonable, the animal will be euthanized for humane reasons in accordance with the *American Veterinary Medical Association (AVMA) Guidelines on Euthanasia* and with the procedures outlined in the protocol (American Veterinary Medical Association, 2020).

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

21.1. Institutional Animal Care and Use Committee Approval

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

22. REFERENCES

American Veterinary Medical Association. *AVMA Guidelines on Euthanasia*. January 2020.

Cochran WG, Cox GM. Plans and Tables of Random Permutations. In: Experimental Designs, New York, NY: John Wiley and Sons; 1957;145:577-582.

National Research Council. Guide for the Care and Use of Laboratory Animals, Committee for the Update of the Guide for the Care and Use of Laboratory Animals, Institute for Laboratory Animal Research, Division on Earth and Life Sciences; The National Academies Press: Washington, DC, 2011.

Office of Laboratory Animal Welfare. *Public Health Services Policy on Humane Care and Use of Laboratory Animals*. Bethesda, MD: National Institutes of Health. March 2015.

SAS® Proprietary Software, Version 9.4; SAS Institute, Inc.: Cary, NC, 2002-2014 Spence S, Soper K, Hoe C-M, Coleman J. The heart rate-corrected QT interval of conscious Beagle dogs: a formula based on analysis of covariance. *Toxicol Sci*. 1998;45(2):247-258.

Spence S, Soper K, Hoe C-M, Coleman J. The heart rate-corrected QT interval of conscious Beagle dogs: a formula based on analysis of covariance. *Toxicol Sci*. 1998;45(2):247-258.

Van de Water A, Verheyen J, Xhonneux R, Reneman RS. An improved method to correct the QT interval of the electrocardiogram for changes in heart rate. *J Pharmacol Met*. 1989;22(3):207-217.

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TESTING FACILITY APPROVAL

The signature below indicates that Testing Facility Management approves the Study Director identified in this protocol and management's responsibility to the study as defined by the relevant GLP regulations.

DocuSigned by:
Redacted by agreement

The signature below indicates that the Study Director approves the study protocol.

DocuSigned by:
Redacted by agreement

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SPONSOR APPROVAL

Redacted by agreement

-

Proprietary Info

Proprietary Info

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ATTACHMENT A

Shipment of Samples and Study Records

Matrix[a]	Purpose	Day/ Week/ Aliquot	Proposed Shipment Date	Conditions for Shipment	Recipient/Address
Test Article	Disposition of unused neat test article	-	To be documented	On blue ice packs	Redacted by agreement
Interaction Article	Disposition of unused neat interaction article	-	To be documented	Ambient temperature	

- = not applicable.

[a] Shipments performed via FedEx.

Proprietary Info

Proprietary Info

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charles river

FINAL REPORT AMENDMENT NO. 1

Testing Facility Study No Redacted by agreement

Sponsor Reference No. Redacted by

Evaluation of the Interaction Between Proprietary Info Administered Orally and Cocaine Administered Intravenously to Conscious, Radiotelemetry-Instrumented Beagle Dogs

GLP

SPONSOR:
SRI Biosciences
333 Ravenswood Avenue
Menlo Park, CA 94025
United States

TESTING FACILITY:
Charles River Laboratories Ashland, LLC
1407 George Road
Ashland, OH 44805
United States

Final Report Issue Date: 05 November 2021

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Sponsor Reference No. Redacted by agreement

Testing Facility Study No. Redacted by agreement

QUALITY ASSURANCE STATEMENT

Study Number: Redacted by agreement

This Final Report Amendment has been audited by Quality Assurance in accordance with the applicable Good Laboratory Practice regulations. Reports were submitted in accordance with SOPs as follows:

QA INSPECTION DATES

		Dates Findings Submitted to:	
Date(s) of Audit	**Phase(s) Audited**	**Study Director**	**Testing Facility Management**
27-Jan-2022	Final Report Amendment	27-Jan-2022	27-Jan-2022

The Final Report Amendment has been reviewed to assure that it accurately describes the materials and methods, and that the reported results accurately reflect the raw data.

DocuSigned by:
Redacted by agreement
Signing Reason: I approve this document
Signing Time: 10-Feb-2022 | 12:02:08 EST
F87FDA871EC0458A917D8AAE43CFF1A6

Redacted by agreement
Quality Assurance Auditor

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Sponsor Reference No. Redacted by agreement Testing Facility Study No. Redacted by agreement

FINAL REPORT AMENDMENT NO. 1

Section 4.4.3.1. Analytical Method
Final Report Page: 17
Final Report Amendment No. 1 Page: 6

- Original Text: Analyses for the test article described below were performed by a high-performance liquid chromatography (HPLC) method with ultraviolet light absorbance method using a validated analytical procedure Personnel Draft, Proprietary Info).
- Amended Text: Analyses for the test article described below were performed by a high-performance liquid chromatography (HPLC) method with ultraviolet light absorbance method using a validated analytical procedure Personnel **2021**, Proprietary Info).
- Reason for Change: Reference year updated to reflect finalization.

Section 11. References
Final Report Page: 56
Final Report Amendment No. 1 Page: 7

- Original Text: Holzgrefe H, Ferber G, Champeroux P, Gill M, Honda M, Greiter-Wilke A, et al. Preclinical QT safety assessment: Cross-species comparisons and human translation from an industry consortium. Journal of Pharmacological and Toxicological Methods, 2014; 69(1);61-101.

  Personnel Method Validation of a High-Performance Liquid Chromatography Method for the Determination of Test Article Concentration in Dose Formulation (Study No. Proprietary Info Charles River, Ashland, OH, Draft.
- Amended Text: **Holzgrefe HH, Cavero I, Gleason CR, Warner WA, Buchanan LV, Gill MW, et al. Application of a probabilistic method for determination of drug-induced QT prolongation in telemetered cynomolgus monkeys. *J Pharmacol Toxicol Methods.* 2007;55(2):244-254.**

  Personnel Method Validation of a High-Performance Liquid Chromatography Method for the Determination of Test Article Concentration in Dose Formulation (Study No. Proprietary Info Charles River, Ashland, OH, **2021**.
- Reason for Change: Updated to reflect appropriate references.

Appendix 1 Deviations, Amended Protocol, and Protocol
Final Report Pages: 160-199
Final Report Amendment No. 1 Pages: 8-48

- Change: Protocol Amendment No. 7 replaced Protocol Amendment No. 6.
- Reason for Change: Protocol Amendment No 7 was issued following issuance of the Final Report to update reference information.

The changes to this report had no impact on the scientific validity or interpretation of the results of this study.

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Sponsor Reference No. Redacted by agreement Testing Facility Study No. Redacted by agreement

The amendment did not entail generation of new data, revision of calculations or modification of previously submitted data and did not change the conclusion of the study. In addition, the amendment did not result in any changes to the compliance status of the study as discussed on the Compliance Statement in the Final Report. The revisions to the Final Report included in the amendment may have resulted in changes in pagination in the Final Report; any potential changes in pagination are not addressed in this amendment.

The reporting files for this Final Report Amendment are stored on M-Files® and are archived at the Charles River Laboratories facility location in Wilmington, MA. Any non-electronic documentation is stored in the Testing Facility Archives.

The signature below certifies that the amended pages have been reviewed and approved by the Study Director.

DocuSigned by:
Redacted by agreement
Signing Reason: I approve this document
Signing Time: 10-Feb-2022 | 13:39:10 EST
617F5C3E52C34C06ACB0C55EB53BF10C

Redacted by agreement
Study Director

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AMENDED PAGES

Uncovered by a White Coat Waste investigation

4.4.3.1. Analytical Method

Analyses for the test article described below were performed by a high-performance liquid chromatography (HPLC) method with ultraviolet light absorbance method using a validated analytical procedure Personnel 2021, Proprietary Info

Analyses for the interaction article described below were performed by a high-performance liquid chromatography (HPLC) method with ultraviolet light absorbance method using a qualified analytical procedure Personnel 2020, Proprietary Info

Uncovered by a White Coat Waste investigation

11. REFERENCES

Atterson P, Voss K, Kopp G. Occurrence and variance of ECG waveform abnormalities in canines and non-human primates: What is considered normal? Safety Pharmacology Society Meeting Poster, 2009.

Personnel Analytical Qualification and Stability Study of (-)-Cocaine HCl in Aqueous Solution Formulations (Study No. Proprietary Info Charles River, Ashland, OH, 2020.

Holzgrefe HH, Cavero I, Gleason CR, Warner WA, Buchanan LV, Gill MW, et al. Application of a probabilistic method for determination of drug-induced QT prolongation in telemetered cynomolgus monkeys. *J Pharmacol Toxicol Methods*. 2007;55(2):244-254

National Research Council. Guide for the Care and Use of Laboratory Animals, Committee for the Update of the Guide for the Care and Use of Laboratory Animals, Institute for Laboratory Animal Research, Division on Earth and Life Sciences; The National Academies Press: Washington, DC, 2011.

Personnel Method Validation of a High-Performance Liquid Chromatography Method for the Determination of Test Article Concentration in Dose Formulation (Study No. Proprietary Info Charles River, Ashland, OH, 2021.

Richig J, Sleeper M. Electrocardiography of Laboratory Animals. 2nd ed. London, UK: Academic Press Elsevier; 2018.

Spence S, Soper K, Hoe C-M, Coleman J. The heart rate-corrected QT interval of conscious Beagle dogs: a formula based on analysis of covariance. *Toxicol Sci.* 1998;45(2):247-258.

Tilley LP. Essentials of Canine and Feline Electrocardiography: Interpretation and Treatment. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1992.

United States Department of Agriculture. Federal Rules: Animal Welfare; 9 CFR Parts, 1, 2, and 3. Federal Register; 1989;54(168):36112-36163.

Van de Water A, Verheyen J, Xhonneux R, Reneman RS. An improved method to correct the QT interval of the electrocardiogram for changes in heart rate. *J Pharmacol Met.* 1989;22(3):207-217.

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charles river

PROTOCOL AMENDMENT No. 7

Testing Facility Study No. Redacted by

Sponsor Reference No. Redacted by

Evaluation of the Interaction Between Proprietary Info Administered Orally and Cocaine Administered Intravenously to Conscious, Radiotelemetry-Instrumented Beagle Dogs

GLP

SPONSOR:
SRI Biosciences
333 Ravenswood Avenue
Menlo Park, CA 94025
United States

TESTING FACILITY:
Charles River Laboratories Ashland, LLC
1407 George Road
Ashland, OH 44805
United States

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SUMMARY OF CHANGES AND JUSTIFICATIONS

Study Protocol effective date: 17 November 2020

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

Item or Section(s)	Justification
Amendment 1	**Effective Date: 04 December 2020**
11.2 Bioanalytical Sample Processing	Storage conditions changed to align with established stability conditions.
Attachment A	Updated bioanalysis sample recipient information
Amendment 2	**Effective Date: 11 February 2021**
2. PROPOSED STUDY SCHEDULE	Updated the initiation of dosing (CV Phase) date to reflect a change in the study schedule.
8.4 Food	Updated timing of food offering based on dose administration time and post dose obsevations.
9. Experimental Design	Updated minimum washout duration
9.1. Administration of Test, Vehicle and Interaction Articles	Added the time following exit of the room to begin dose administration during the CV Phase. Extended duration to allow for doses to be administered at the same time of the day to account for potential dosing delays.
9.2. Jacket and Tether System Procedures	Clarified sham administration articles. Added the time following "sham" oral dose to being administering the "sham" IV dose.
11.1 Bioanalytical Sample Collection	Removed the word approximately from the target volume in the bioanalytical sample collection table.
Amendment 3	**Effective Date: 16 February 2021**
4. Responsible Personnel	Pharmacokinetic phase personnel updated.
6.1 Preparation of formulations	Updated frequency of preparation and storage conditions based on vehicle stability.
8.1 Housing	Deletion of erroneous text. Deleted text represented comments during protocol review. Clarification animals will have continual access to water during periods of fasting.
8.5 Water	Clarification of when water will not be available
9. Experimental Design	Dose levels updated following review of pharmacokinetic data. Clarificatoin of treatment week designation for PK phase and CV phase.
9.1 Administration of Test, Vehicle and Interaction Articles	Dose confirmation added to final report
9.2 Jacket and Tether System Procedures	Clarification of timing for jacket placement. Removal of requirement to place the jacket prior to each day of dosing.
14.2 Statistical Analysis	Phase 1 subphases updated
20. Reporting	Removal of finalization by testing facility if no comments are received by sponsor within 6 months
21.2 Justification of Dose Level Selection	Justification updated based on result of PK phase.

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Item or Section(s)	Justification
Amendment 4	**Effective Date: 02 Mar 2021**
6.1. Preparation of Formulations	Correction of storage conditions in the Preparation Details table for the test article based on the current analytical stability results.
6.3. Sample Collection and Analysis	Addition of footnote a to the Dose Formulation Sample Collection Schedule to indicat that homogeneity analysis will not be conducted on the vehicle treatment.
6.3.1 Analytical Method	Addtion of information regarding storage conditions of the interaction article and reference to the study number under which stability was previously established.
9. Experimental Design	Correction of previous erroneously labeled treatment week for CV 9. Corrected formatting errors from previous Amendment.
Amendment 5	**Effective Date: 09 Mar 2021**
6.3.1 Analytical Method	Correction of the study references for the validated and qualified methods for the test article and interaction article. Addition of wording to differentiate and clarify the two analyses methods.
10.2.2 Video Monitoring	Addition of section to describe the procedures for collection and evaluation of added video monitoring to aid in the evaluation of potential time of occurrence of emesis during the telemetry collection period.
14.2 Statistical Analysis	Corrected the number of subphases and hours for analysis Phase 4.
Amendment 6	**Effective Date: 28 Apr 2021**
4. RESPONSIBLE PERSONNEL	Addition of contact information for the PI performing the pharmacokinetic analysis.
16. REGULATORY COMPLIANCE	Addition of regulatory and agency compliance for the pharmacokinetic analysis portion of the study which will be conducted in Japan.
Amendment 7	**Effective Date: 26Jan2022**
6.3.1. Analytical Method	Correction of the year of referemce for Charles River Study No. Proprietary Info Personnel
23. REFERENCES	Removal of the Cochran and Cox (1957) reference as it was not relevant to the experimental design; addition of Holzgrefe (2007) reference; addition of Personnel 2020) reference; addition of Personnel (2020) reference.

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TABLE OF CONTENTS

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1. OBJECTIVE(S)

The objective of this study is to evaluate the potential adverse cardiovascular effects that may result when Proprietary Info (test article) and cocaine (interaction article) are administered together to male Beagle dogs. The study will be conducted in two phases.

In the first phase (pharmacokinetics, PK phase), treatment-naïve Beagle dogs will be exposed to increasing levels of Proprietary Info to determine the pharmacokinetics and its tolerability.

In the second phase (cardiovascular interaction, CV phase), the Beagle dogs will be implanted with telemetry transmitters and subsequently dosed with combinations of orally (gavage) administered Proprietary Info and intravenously administered cocaine to evaluate if Proprietary Info affect the hemodynamic and cardiac effects cocaine. Proprietary Info dose levels in the cardiovascular interaction phase will be informed by the outcome of the pharmacokinetics phase.

2. PROPOSED STUDY SCHEDULE

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

Animal Arrival:	17 Nov 2020
Initiation of Dosing (PK Phase):	24 Nov 2020
Initiation of Dosing (CV Phase):	16 Feb 2021
Completion of In-life:	14 Apr 2021 (Release of animals from study)
Audited Draft Report:	24 Jun 2021
Final Report:	06 Dec 2021 (Expected date of Study Director signature of report)
Final SEND Dataset Package Delivery:	Based on Regulatory Submission

3. SPONSOR

Role	Name	Contact Information
Sponsor Representative	Redacted by agreement	Address as cited for Sponsor Tel: Redacted by agreement E-mail: Redacted by agreement

4. RESPONSIBLE PERSONNEL

Role/Phase	QAU (Quality Assurance Unit)	Name	Contact Information
Study Director	Charles River	Redacted by agreement Pharmacology and Discovery Services	Address as cited for Testing Facility Tel: Redacted by agreement E-mail: Redacted by agreement

Uncovered by a White Coat Waste investigation

Role/Phase	QAU (Quality Assurance Unit)	Name	Contact Information
Scientific Coordinator	Charles River	Redacted by agreement Sr. Scientific Coordinator, Pharmacology and Discovery Services	Address as cited for Testing Facility Tel: Redacted by agreement Email: Redacted by agreement
Testing Facility Management	Charles River	Redacted by agreement Executive Director, Global Safety Pharmacology	Address as cited for Testing Facility Tel: Redacted by agreement E-mail: Redacted by agreement
Testing Facility QAU	Charles River	Redacted by agreement	Address as cited for Testing Facility Tel Redacted by agreement E-mail: Redacted by agreement
Individual Scientist (IS)			
Analytical Chemistry	Charles River	Redacted by agreement Senior Scientific Associate, Analytical Chemistry	Address as cited for Testing Facility Tel: Redacted by agreement E-mail: Redacted by agreement
Principal Investigator (PI)			
Bioanalytical Analysis[a]	CMIC, Inc	Redacted by agreement Group Leader, CMIC Inc.	CMIC 2860 Forbs Avenue Hoffman Estates, IL 60192 Tel: Redacted by agreement E-mail: Redacted by agreement Redacted by agreement
Pharmacokinetic Analysis[a]	CMIC PharmaScience Co., Ltd.	Redacted by agreement	CMIC Bioresearch Center, CMIC PharmaScience Co., Ltd 10221 Kobuchisawa-cho, Hokuto-shi, Yamanashi 408-0044, Japan Tel: Redacted by agreement E-mail: Redacted by agreement

[a] Sponsor-designated Test Site

Each IS and PI is required to report any deviations or other circumstances that could affect the quality or integrity of the study to the Study Director in a timely manner for authorization/acknowledgement. Each IS and PI will provide a report addressing their assigned phase of the study, which will be included as an appendix to the Final Report.

The IS Phase Report will include the following:

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

The PI Phase Report will include the following:

- A Statement of Compliance
- A QA Statement (for Sponsor designated PI or for Testing Facility designated PI if audited by a QAU other than that of the Testing Facility)
- The archive site for all records, samples, specimens and reports generated from the phase or segment (alternatively, details regarding the retention of the materials may be provided to the Study Director for inclusion in the Final Report)

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

5. TEST MATERIALS

5.1. Test, Vehicle and Interaction Article Characterization

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

Vehicle and control article components will be characterized according to the product label provided by the manufacturer

The Sponsor has appropriate documentation on file concerning the method of synthesis, fabrication or derivation of the test article, and this information is available to the appropriate regulatory agencies should it be requested.

5.2. Test Article Identification

Test Article Identification

	Test Article
Identification:	Proprietary
Alternate Identification:	-
Batch/Lot No.:	Proprietary Info
Retest Date:	Concomitant
Physical Description:	To be documented
Purity:	100%
Correction Factor:	-
Storage Conditions:	18°C to 24°C
Provided by:	Sponsor or Sponsor Designee

- = not applicable

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5.3. Interaction Article Identification

Interaction Article Identification

	Interaction Article
Identification:	Cocaine HCl
Alternate Identification:	(-)-Cocaine HCl
Batch/Lot No.:	To be documented
Expiration/Retest Date:	To be documented
Physical Description:	To be documented
Purity:	To be documented
Correction Factor:	-
Storage Conditions:	18°C to 24°C
Provided by:	Sponsor or Sponsor Designee

- = not applicable

5.4. Vehicle Identification

Vehicle Identification (for Test Article Preparations)

	Vehicle Article	Vehicle Component	Vehicle Component
Identification:	0.5% Methylcellulose (400 cps)	Methylcellulose (400 cps)	Deionized (DI) water
Alternate Identification:	-	-	-
Storage Conditions:	Set to maintain a target temperature of 5°C	18°C to 24°C	18°C to 24°C
Provided by:	Testing Facility	Testing Facility	Testing Facility

- = not applicable.

Vehicle Identification (for Interaction Article Preparations)

	Vehicle Article	Vehicle Component	Vehicle Component
Identification:	0.9% sodium chloride for injection, USP	Sodium chloride	Reverse Osmosis (RO) water
Alternate Identification:	-	-	-
Storage Conditions:	18°C to 24°C	18°C to 24°C	18°C to 24°C
Provided by:	Testing Facility	Testing Facility	Testing Facility

- = not applicable.

5.5. Reserve Samples

Reserve samples of the test article will be taken in accordance with Charles River Standard Operating Procedures and stored in the Charles River Archives.

5.6. Test and Interaction Article Inventory and Disposition

Records of the receipt, distribution, storage, and disposition of test materials (including empty containers of Sponsor-provided materials) will be maintained. All unused Sponsor-supplied bulk test materials, with the exception of reserve samples, will be returned to the Sponsor at the address provided in Attachment A.

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5.7. Safety

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

6. DOSE FORMULATION AND ANALYSIS

6.1. Preparation of Formulations

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

Preparation Details

Dose Formulation	Frequency of Preparation	Storage Conditions
Vehicle	At least every 3 weeks	Set to maintain 5°C
Interaction Article	Once, prior to the first CV phase dosing occasion	Set to maintain 18°C to 24°C
Test Article	At least biweekly	Set to maintain 5°C

Frequency of preparation may be adjusted based on stability results. Any residual volumes from each dosing occasion will be discarded unless otherwise requested by the Study Director.

6.2. Preparation Details

Dosing formulations will be prepared at appropriate concentrations to meet dose level requirements. The prepared test article formulations will not be adjusted for purity. The prepared interaction article formulations will not be adjusted for purity. Any procedures not covered by SOPs required for formulation will be approved by the Study Director and included in the study records. Formulation pH will be within SOP range, if applicable.

6.3. Sample Collection and Analysis

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

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Dose Formulation Sample Collection Schedule

Sample Type	Concentrations	Stratum	Sampling From	Number of Samples per Concentration			Sample Volume (mL)	Intervals
				Collected	Analyzed	Backup		
Homogeneity Analyses	All Treatments[a]	Top	Preparation container	4	2	2	1	Each preparation
		Middle		4	2	2	1	
		Bottom		4	2	2	1	
Concentration Analyses	All Treatments	Middle	Preparation container	4	2	2	1	Each preparation

[a] = excluding the vehicle treatment.

Interaction Article Sample Collection Schedule

Sample Type	Concentrations	Stratum	Sampling From	Number of Samples per Concentration			Sample Volume (mL)	Intervals
				Collected	Analyzed	Backup		
Concentration Analyses	All Treatments	Middle	Preparation container	4	2	2	0.5	Each preparation and on each day of dosing[a]

[a] = duplicate 0.5 mL samples to be collected from the residual interaction article dosing container following dosing. One sample will be analyzed and the alternate will be utilized as a backup sample.

Dose analysis results (formulated test article or initial interaction article formulation) will be verified prior to dose administration at each sampling interval if available. If results are deemed unacceptable, the formulations will be prepared again and analyzed.

Interaction samples will be transferred to the analytical chemistry laboratory and stored refrigerated until analyzed. Test article formulation samples (including backups) will be transferred at ambient temperature to the Analytical Chemistry Department at the Testing Facility for same day analysis, where possible or stored for analysis within known formulation stability period.

6.3.1. Analytical Method

Test article formulations have been previously shown to be stable and homogeneous over the range of concentrations used on this study for at least 15 days at room temperature (SRI study No. M449-20). Therefore, stability and resuspension homogeneity of test article formulations will not be assessed on this study.

Analyses for the Test Article described below will be performed using a method validated by Charles River (Charles River Study No. Proprietary Info Personnel 2020) for concentration. Any backup samples kept at Charles River will be discarded following acceptance of the analytical results by the Study Director.

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Interaction article formulations have been previously shown to be stable over the range of concentrations used on this study for at least 106 days at room temperature (SRI study No. Proprietary Info [redacted]. Therefore, stability of the interaction article will not be assessed on this study.

Analyses for the Interaction Article described below will be performed using a method qualified by Charles River (Charles River Study No. Proprietary Info [redacted] Personnel [redacted] ~~019~~ **2020**) for concentration. Any backup samples kept at Charles River will be discarded following acceptance of the analytical results by the Study Director.

6.3.1.1. Test Article Concentration and Homogeneity Analysis

Sample Allocation:	2 for analysis, 2 for backup
Storage Conditions:	Temperature set to maintain 18-24°C
Acceptance Criteria:	Suspension: For concentration: Mean sample concentration within 100% ± 15% of theoretical concentration. For homogeneity: Relative standard deviation (RSD) of concentrations of ≤ 10% for each group.

6.3.1.2. Interaction Article Concentration Analysis

Sample Allocation:	2 for analysis, 2 for backup
Storage Conditions:	Temperature set to maintain 18-24°C
Acceptance Criteria:	Solution: Mean sample concentration within 100% ± 10% of theoretical concentration.

7. TEST SYSTEM

Species:	Dog
Strain:	Beagle
Condition:	Purpose-bred, naïve
Source:	Specific facility to be documented in study records.
Number and Sex:	7 males
Age at the Initiation of Dosing:	At least 6 months. Animals not utilized on study will be assigned to the Charles River animal colony.

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Weight at the Initiation of Dosing:	At least 5.5 kg

The actual age and weight of the animals at the initiation of dosing will be listed in the Final Report.

7.1. Animal Screening

Method: All animals used on study will have documentation of immunization for parvovirus, distemper, adenovirus type 2, parainfluenza, *Bordetella*, papilloma, and rabies.

Prior to surgery, all animals will have blood samples collected for clinical pathology screening to evaluate health status prior to the surgical procedures. See section 12 for parameters to be evaluated.

7.2. Animal Identification

Method: Tattoo or a subcutaneously implanted electronic identification chip.

7.3. Surgical Preparation of Animals

Method:

Following the PK phase animals will be implanted with radiotelemetry transmitters and vascular access ports (VAPs) to allow for undisturbed IV dosing as described in Charles River SOPs.

Preanesthetics, surgical preparation and implantation details (for the telemetry implant and VAPs), and post-operative care and recovery procedures will be performed as outlined in CRL SOPs (T10-014, T1-194)

The transmitters have a fluid-filled catheter (coated with an antithrombotic film to inhibit thrombus formation) with the tip filled with a patented gel for collection of blood pressure and 2 ECG leads emulating a lead II configuration.

The VAPs will be maintained per Charles River SOPs, and will include weekly assessments of patency until dosing. VAPs will be locked with taurolidine citrate solution (TCS) between patency assessments.

7.4. Jacket Acclimation

Method: Following the PK phase and prior to surgery for the cardiovascular interaction phase, all animals will be acclimated to a tethered infusion system. Animals will initially be conditioned to jackets and collars in a stepwise manner until at least 24 hours of acclimation is achieved. Subsequently, animals will be acclimated to the tether and jackets for a

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period of 4 hours, and for a period of at least 24 hours. Additional sessions may be employed if deemed necessary.

7.5. Environmental Acclimation

Method: Each animal will be inspected by a clinical veterinarian upon receipt. Animals judged to be in good health will be placed immediately in acclimation for at least 6 days. See respective sections for parameters to be evaluated. The animals will have been allowed at least 2 weeks to recover following implantation of the telemetry device before the administration of test and interaction articles for the cardiovascular phase.

7.6. Selection, Assignment, Replacement, and Disposition of Animals

Selection: Near the end of the acclimation period, animals judged to be suitable for testing (based on health as indicated by randomization approval) will be assigned to groups at random based on body weight stratification into a block design using a computer program. A printout containing the animal numbers and individual group assignments will be generated. For the CV phase, animals will be arbitrarily assigned to groups based on health and telemetric assessment.

Replacement: Before the initiation of dosing, any assigned animals considered unsuitable for use in the study will be replaced by alternate animals. After initiation of dosing, study animals may be replaced during the replacement period with alternate animals in the event of accidental injury, non-test article-related health issues, or similar circumstances.

Disposition: This study is non-terminal. Upon completion of the study, the animals will be maintained in the Charles River dog colony for future use or may be euthanized (with intravenous sodium pentobarbital administration and the radiotelemetry devices recovered, as applicable).

8. HUSBANDRY

8.1. Housing

Housing (Dosing Days): Single. Individual housing is necessary during periods of data collection to prevent telemetry signal cross talk and to individually attribute any clinical observations to individual animals to allow for a correlation to the bioanalytical data.

PK Phase: the animals will be separated in the morning prior to dosing, on each day of dosing.

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	Following jacket removal, or the final blood collection timepoint, animals will be returned to social housing.
Housing (Non-Dosing Days):	Group housed (up to 3 animals of the same sex) CV Phase: Animals will be separated in the afternoon on the day prior to dosing at the time of fasting and will remain separated until following jacket removal. Subjects will have continual access to water during periods of fasting. This is to minimize variations in baseline data caused by excitability and stress of animals from separation and placement into telemetry banks.
Caging:	Stainless steel cages with mesh floors.
Cage Identification:	Will indicate animal/tattoo number(s), and sex.

Housing set-up is as specified in the USDA Animal Welfare Act (9 CFR, Parts 1, 2 and 3) and as described in the *Guide for the Care and Use of Laboratory Animals* (National Research Council, 2011). Animals will be separated during designated procedures/activities or will be separated as required for monitoring and/or health purposes, as deemed appropriate by Study Director and/or Clinical Veterinarian.

8.2. Animal Enrichment

Method:	For enrichment, animals will be provided with items such as chew toys, except when interrupted by study procedures/activities. All animals will be given regular opportunity for exercise and socialization and will have enrichment through human interaction during the conduct of procedure acclimation and daily study activities

8.3. Environmental Conditions

The targeted conditions for animal room environment will be as follows:

Temperature:	66°F to 76°F (19°C to 24°C)
Humidity:	30% to 70%
Light Cycle:	12 hours light and 12 hours dark (except during designated procedures)

8.4. Food

Diet:	PMI Nutrition International, LLC Lab Diet Certified Canine Diet 5007
Type:	Kibble (alternate diet may be provided on individual animal basis as warranted as approved by the Study Director).
Frequency:	Approximately 300 g daily. Animals will be fasted overnight prior to surgery. The daily ration of food will be offered following recovery from anesthesia. Animals will

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be fasted overnight before dosing days. On dosing days during the PK phase, the daily ration of food will be provided after the 2 hr plasma collection. On dosing days during the CV phase, food will be returned 4 hr after the cocaine dose (after 4 hr clinical observation post dose). Animals will not be fasted for longer than 24 hours.

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

8.5. Water

Type: Municipal tap water, treated by reverse osmosis and ultraviolet irradiation.

Frequency/Ration: Freely available to each animal via an automatic watering system (except during body weight measurements, physical examinations, and during surgery).

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

8.6. Veterinary Care

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

If deemed necessary, dosing may be suspended for individual animals upon recommendation of the clinical veterinarian in consultation with the study director in order to provide appropriate veterinary care.

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9. EXPERIMENTAL DESIGN

The following table presents the treatment arrangement. Proprietary Info dose levels in the PK phase were selected based on available data from Proprietary Info Proprietary Info Proprietary Info Proprietary Info Proprietary Info dose levels in the CV phase will be selected based on data from the PK phase. Cocaine dose levels in the CV phase were selected based on data provided by NIDA from Proprietary Info Appendix F, (Proprietary Info Proprietary Info Proprietary Info and Proprietary Info (see Section 21.2).

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Study Design

Treatment No.	Treatment Week	Treatment	Test Article Dose Level (mg/kg)	Test Article Dose Concentration (mg/mL)	Test Article Dose Volume (mL/kg)	Interaction Article Dose Level (mg/kg)[c]	Interaction Article Dose concentration (mg/mL)	Interaction Article Dose Volume (mL/kg)	No. of Males
Pharmacokinetic (PK) Phase[a]									
1	PK 1	Proprietary	1	0.1	10	NA	NA	NA	7
2	PK 2	Proprietary	3	0.3	10	NA	NA	NA	7
3	PK 3	Proprietary	10	1	10	NA	NA	NA	7
4	PK 4	Proprietary	30	3	10	NA	NA	NA	7
Cardiovascular Interaction (CV) Phase[b]									
5	CV 1	Vehicle + Saline	0	0	10	0	0	0.25 (Saline)	6
6	CV 2	Vehicle + Cocaine (low)	0	0	10	0.56	2.24	0.25	6
7	CV 3	Vehicle + Cocaine (high)	0	0	10	1.7	6.8	0.25	6
8	CV 4	Proprietary (low) + Saline	3	0.3	10	0	0	0.25 (Saline)	6
9	CV 5	Proprietary (low) + Cocaine (low)	3	0.3	10	0.56	2.24	0.25	6
10	CV 6	Proprietary (low) + Cocaine (high)	3	0.3	10	1.7	6.8	0.25	6
11	CV 7	Proprietary (high) + Saline	30	3	10	0	0	0.25 (Saline)	6
12	CV 8	Proprietary (high) + Cocaine (low)	30	3	10	0.56	2.24	0.25	6
13	CV 9	Proprietary (high) + Cocaine (high)	30	3	10	1.7	6.8	0.25	6

NA = not applicable

[a] The same 7 animals will be used for each treatment in an escalating design with 6 minimum days between doses.

[b] 6 animals will be selected from the animals tested in the PK phase and the same 6 animals will be used for each treatment in ascending treatment number order with 6 minimum days between doses.

[c] The interaction article will be administered at the prescribed dose level at 1 hour (± 5 minutes) following test article dosing via ambulatory intravenous infusion.

[d] Pending outcome of pharmacokinetic phase.

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9.1. Administration of Test, Vehicle and Interaction Articles

PK Phase:

Dose Route:	Oral gavage (test article)
Frequency:	Once daily; single administration for each Treatment
Method:	The dose formulations will be stirred continuously at room temperature during dosing. The doses will be given using a syringe with an attached gavage tube. Each dose will be followed by 15-mL flush using deionized water provided by the formulations department.

CV Phase:

Dose Route:	Oral gavage (test article) followed by intravenous infusion (interaction article)
Frequency:	Once daily; single administration for each Treatment
Method:	Oral route: The vehicle or test article will be stirred continuously at room temperature during dosing. The doses will be given using a syringe with an attached gavage tube. Each dose will be followed by 15-mL flush using deionized water provided by the formulations department. Intravenous route: The interaction article or its vehicle will be administered at 1 hour (± 5 minutes) following the oral dose via intravenous infusion over a 30 second infusion from an infusion pump followed by a 5 mL saline flush administered at the same rate. Doses will be delivered using a calibrated infusion pump with a tethered infusion system. Doses will be administered in absence of technical staff in the dosing room. Doses will be scheduled to initiate at least 30 minutes following exiting of the room. Doses will be delivered via the Cath-in-Cath system to the indwelling catheter appropriately placed. The infusion will be delivered to freely moving animals. Individual doses will be drawn into syringes labeled with the animal number, study number, and date, and documented appropriately. The dosing syringes will be filled with the appropriate dosing volume (plus the additional volume of the dead space in the extension line to the Y connector infusion system) of interaction article required for dosing. Using a second infusion pump for each animal, an additional syringe will be filled with the appropriate volume of saline to flush the extension lines to complete the prescribed dose. Animals will be dosed at approximately the same time (± 1 hour) each dose day. Dose confirmation will be determined by syringe verification and included in the final report.

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9.2. Jacket and Tether System Procedures

Pretreatment Session:

Prior to Dose 1 of the Cardiovascular Interaction Phase, a "sham" dosing procedure imitating the dosing procedure for each treatment session will be performed, including a telemetric recording (cardiovascular, ECG, and body temperature) obtained for at least 4 hours following the "sham" IV infusion (saline). All animals will undergo the pretreatment recording. Vehicle will be used as the oral sham dosing article, and saline will be utilized as the intravenous sham dosing article. Doses will be administered as outlined in section 9.1. These data will be recorded but not reported. The pretreatment session will include a minimum of 90 min recording period prior to the target "sham" oral dose while in telemetry cages, and then continue for at least 4 hr following the "sham" IV infusion dose. The "sham" IV infusion dose will be performed at 1 hr (± 5 minutes) following the "sham" oral dose, as outlined in the CV interaction phase treatment regimen. Hemodynamic data (systolic, diastolic, mean arterial pressure, pulse pressure and heart rate) and ECG intervals will be measured and binned in appropriate intervals as described in Section 14.2.

The ECG tracings will be reviewed for rhythm disturbances (dysrhythmias) for the six animals participating in the study over the duration of recording period. Data from the pretreatment collection will be used to confirm acclimation to testing procedures of the animals placed on study.

During the CV phase, all animals will be placed into jackets prior to dosing. Patency checks will be performed prior to introduction of the jacket system. All animals will be placed on a maintenance infusion of saline (2 mL/hr) in an effort to maintain VAP patency during non-dosing periods. Animals will be maintained in jackets for up to approximately 3 doses. Jackets will be removed for approximately one week before subsequent jacket placement.

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10. IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS

General In-life Assessments

Parameter	Population(s)[a]	Frequency (minimum required)	Comments
Mortality	All Animals[a]	At least twice daily[b] (morning and afternoon) beginning upon arrival through termination/release	Animals will be observed within their cage unless necessary for identification or confirmation of possible findings.
Cageside/Postdose Observations[c]	All Main Study Animals	During the PK phase observations will be conducted prior to dosing, and at each PK time point. During the CV phase, observations will be conducted, prior to oral dosing, and at approximately 4 hours postdosing (relative to interaction article administration)	Animals will be observed within their cage unless necessary for identification or confirmation of possible findings. The absence or presence of findings will be recorded for individual animals. Findings noted outside the above-specified observation periods will also be recorded. Only the presence of unscheduled observations will be recorded; the absence of findings will thus not be recorded
Detailed Clinical Observations[c]	All Main Study Animals	Following receipt On the day of randomization On the day prior to each day of dosing (for both the PK and CV Phase) Weekly between the end of the PK phase and beginning of the CV phase	Animals will be removed from the cage. The absence or presence of findings will be recorded for individual animals.
Individual Body Weights	All Main Study Animals	Following receipt On the day of randomization On the day prior to each day of dosing (for both the PK and CV Phase) Weekly between the end of the PK phase and beginning of the CV phase; frequency may increase to every other day if evidence of deterioration is noted (as indicated by clinical condition.)	Body weights of potential replacement animals may also be collected at any of these timepoints. These data will not be statistically analyzed or included in study report.

[a] To include unused replacement animals until released from study.
[b] Except on days of receipt and study termination where frequency will be at least once daily.
[c] For observations that cannot be attributed to an individual animal due to social housing, the observation will be noted to each animal in the socialized group.

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10.1. RADIOTELEMETRY

10.2. Radiotelemetry Data Acquisition and Analysis

10.2.1. Electrocardiography and Hemodynamics

Frequency: Baseline arterial blood pressure (systolic, diastolic, and mean arterial pressure), pulse pressure, heart rate, lead II electrocardiographic (ECG) waveforms (PR, QRS, QT, and QTcV intervals), and body temperature will be collected continuously for at least 90 min prior to administration of vehicle or test article. If a probe failure occurs prior to or during collection of baseline data, the animal will be replaced with a reserve animal for this study, if available, or repeated at a later date.

Following administration of vehicle or test article, the appropriate parameters will be collected continuously for at least 4 hours following intravenous dose of interaction article. Electrocardiography, hemodynamic parameters and body temperature data will be averaged to appropriate time intervals for statistical analysis.

Population(s): All Main Study animals

System: The radiotelemetry system (Data Sciences International, St. Paul, MN) will consist of large animal radiotelemetry transmitters (with capabilities to collect, at minimum, arterial pressure, body temperature, and electrocardiographic waveforms), receivers (RMC-1), and 1 or more data exchange matrices (DEM) that will relay information from the receivers to the computer. An ambient pressure reference monitor (APR-1) will be coupled to the DEM to measure the barometric pressure and provide a digital signal to the DSI PONEMAH system. The DSI PONEMAH system uses the measurements provided by the APR-1 to correct pressure measurements obtained from the implant for changes in barometric pressure.

The hardware connected to the Dataquest™ OpenART™ Acquisition Interface provides direct digital signals to the DSI PONEMAH software. The ECG and arterial waveform and body temperature data will be recorded and analyzed by the DSI PONEMAH data acquisition software, version 5.0 or higher. ECG and arterial pressure waveforms will be sampled at 500 Hz. Temperature data will be sampled at 50 Hz. Data acquired continuously will be logged every 120 seconds. During data processing the logging rate will be changed to 60 seconds. The ECG waveform data will be analyzed by the DSI PONEMAH ECG-PRO Template Analysis software.

Procedure: Blood pressure (systolic, diastolic, and mean), pulse pressure, heart rate, electrocardiographic (ECG) waveforms, and body temperature will be collected continuously.

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Evaluation: Cardiovascular parameters and body temperature data will be averaged to appropriate time intervals for statistical analysis.

Quantitative ECG waveform analysis will be performed using the DSI PONEMAH ECG-PRO Template Analysis software to determine the PR, QRS, RR, and QT intervals. Heart rate-corrected QT (QTc) values will be calculated with the Van de Water correction formula where QTcV = QT - 0.087*(RR-1) (Spence, et al., 1988 and Van de Water, et al., 1989). Additionally, QT will be corrected using an individual correction factor, $QTcH = 10^{\log(QT) - \beta[\log(HR)-\log(HRm)]}$ (Holzgrefe, 2007). The beta value for QTcH will be collected from each animals' vehicle dosing data during the CV phase (slope of QT to RR).

For the purpose of data processing, Noise and Match derived parameters will be collected. These parameters will not be reported or statistically analyzed.

Qualitative assessment of ECG will be performed by trained personnel for disturbances in rhythm and waveform morphology in 1-minute segments for every 30 minutes of data collected following test article or vehicle dosing (e.g., a start event or a dosing event) through 4 hours after the interaction article or its vehicle dose. Abnormal rhythm results will be reported in a table as frequency of events. Qualitative assessment of blood pressure waveforms will not be performed. Abnormal waveforms that are identified by Charles River personnel will be discussed with the Study Director to determine if these and additional waveforms should be presented to a veterinary cardiology specialist for evaluation. In the event that abnormal waveforms are identified and evaluated by a veterinary cardiology specialist, a report with this evaluation will be maintained in the raw data and included in the final report as an appendix.

Within the processing system used to average telemetry data into intervals for statistical analysis and reporting, minimum and maximum limits will be set per the table below. Following review of data, these limits may be changed at the request of the Study Director which will be documented along with reason for change.

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Parameter	Waveform Type	Minimum	Maximum
Heart Rate	Blood Pressure	0 beats per minute	No limit
Systolic Blood Pressure	Blood Pressure	0 mmHg	350 mmHg
Diastolic Blood Pressure	Blood Pressure	0 mmHg	No limit
Mean Arterial Blood Pressure	Blood Pressure	0 mmHg	No limit
Pulse Pressure	Blood Pressure	0 mmHg	150 mmHg
Body Temperature	Temperature	30°C	45°C
PR Interval	ECG	0 msec	10000 msec
QRS Complex	ECG	0 msec	10000 msec
QT Interval	ECG	0 msec	10000 msec
QTc Interval	ECG	0 msec	10000 msec
RR Interval	ECG	0 msec	10000 msec

For parameters indicated as control parameters, if the defined limits are exceeded for a time point then all other parameters at this time point will be omitted from analysis and reporting.

10.2.2. Video Monitoring

Frequency: On each day of telemetry collection, video data synchronized with ECG will be recorded to a secure workstation. Video data will be recorded concurrently during periods of radiotelemetry data collection.

Population(s): All Main Study animals

System: Axis cameras (or equivalent) will be used to collect time matched video data synchronized with the radiotelemetry system.

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Procedure: Each camera will be configured to capture the video data for each subject. During data review, video data will be viewed using an appropriate media player.

Evaluation: Video data synchronized with ECG will be used to establish the approximate time of occurrence of retching or emesis, if noted, beginning from the time of test article administration thru the 4-hour period of post-dosing observation after the interaction article dose. This time will be recorded on an appropriate form and will be maintained in the study records. The times may be entered into the appropriate LIMS at the discretion of the study director. The video data will be maintained in the study records but will not have any additional evaluations performed.

11. BIOANALYSIS AND PHARMACOKINETIC EVALUATION

11.1. Bioanalytical Sample Collection

Bioanalytical Sample Collection

	Time Postdose on Days 1, 8, 15 and 22							
Treatment No.	**0 hr (predose)**	**0.5 hr**	**1 hr**	**2 hr**	**4 hr**	**8 hr**	**12 hr**	**24 hr**
1	X	X	X	X	X	X	X	X
2	X	X	X	X	X	X	X	X
3	X	X	X	X	X	X	X	X
4	X	X	X	X	X	X	X	X

Method/Comments:	Venipuncture from a jugular vein (saphenous or cephalic vein may be used, if necessary).
Target Volume (mL):	1 mL/time point collected without anesthesia.
Anticoagulant:	Sodium Heparin
Special Requirements:	Keep samples chilled during collection and processing.
Processing:	Plasma

X = sample to be collected; hr = hour

11.2. Bioanalytical Sample Processing

Samples will be mixed gently and centrifuged as soon as practical.

The samples will be centrifuged and the resultant plasma will be separated, transferred to duplicate uniquely labeled polypropylene tubes, and frozen immediately over dry ice until transferred to storage. Samples will be stored in a freezer set to maintain a target of -20°C.

Samples will be shipped by overnight courier to the address provided in Attachment A.

The samples will be shipped in 2 batches (each with 1 set of aliquots). The recipient, Sponsor Representative, and Study Director will be contacted prior to shipment to ensure that the shipment will be handled appropriately upon receipt. Upon receipt at the analytical laboratory, the samples will be stored in a freezer set to maintain a target of -20°C.

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11.3. Bioanalytical Sample Analysis

Bioanalytical samples will be analyzed for concentration of Proprietary Info Proprietary Info Proprietary Info conducted at CMIC Inc).

Analysis will be performed according to the validated method and SOPs of the performing laboratory. Appropriate computer software will be used for the collection and analysis of data; specific software versions will be noted in the bioanalytical report. Statistical analyses, including regression analysis, and descriptive statistics, including arithmetic means and standard deviations, accuracy and precision will be performed.

11.4. Pharmacokinetic Evaluation

Pharmacokinetic parameters will be estimated using Phoenix pharmacokinetic software. A non-compartmental approach consistent with the oral route of administration will be used for parameter estimation. All parameters will be generated from Proprietary Info individual concentrations in plasma from Days 1, 8, 15, and 22 whenever practical. Parameters will be estimated using sampling times made relative to the start of each dose administration.

Parameters to be Estimated

Parameter	Description of Parameter
t_{max}	The time after dosing at which the maximum concentration was observed.
C_{max}	The maximum observed concentration measured after dosing.
C_{max}/Dose	The C_{max} divided by the dose administered.
AUC_{tlast}	The area under the concentration versus time curve from the start of dose administration to the last observed quantifiable concentration calculated using the linear trapezoidal method.
AUC_{tlast}/Dose	The AUC_{tlast} divided by the dose administered.
t_{last}	The time after dosing at which the last quantifiable concentration was observed

Partial AUCs (between two defined sample times), and corresponding dose-normalized values, may be derived and reported to aid interpretation. Descriptive statistics (e.g., number, arithmetic mean, median, standard deviation, standard error, coefficient of variation) will be reported as deemed appropriate, as well as ratios for appropriate grouping and sorting variables (e.g., AUC) may be generated. Pharmacokinetic tables and graphs will also be generated.

Analysis will be performed according to SOPs of the performing laboratory.

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12. CLINICAL PATHOLOGY

12.1. Sample Collection

Clinical Pathology Sample Collection

Group No(s).	Time Point	Hematology	Clinical Chemistry
All Animals	Prior to PK phase and after surgical implantation	X	X

Fasting:	-	at least 8 hours (no more than 24 hours)
Method/Comments:	Venipuncture from a jugular vein (saphenous or cephalic vein may be used, if necessary)	Venipuncture from a jugular vein (saphenous or cephalic vein may be used, if necessary)
Target Volume (mL)[a]:	1	1.5
Anticoagulant:	K_2EDTA	None
Special Requirements:	-	-
Processing:	None	Serum

X = Sample to be collected; - = Not applicable

[a] = Additional samples may be obtained (e.g., due to clotting of non-serum samples) if permissible sampling frequency and volume are not exceeded.

12.2. Hematology

Hematology Parameters

Red blood cell count	White blood cell count[a]
Hemoglobin concentration	Neutrophil count (absolute)
Hematocrit	Lymphocyte count (absolute)
Mean corpuscular volume	Monocyte count (absolute)
Red blood cell distribution width	Eosinophil count (absolute)
Mean corpuscular hemoglobin concentration	Basophil count (absolute)
Mean corpuscular hemoglobin	Large unstained cells (absolute)
Reticulocyte count (absolute)	Other cells (as appropriate)
Platelet count	Mean platelet volume

[a] If performed manually, results of differential counts will include platelet estimates and RBC morphology (individual tables only).

A blood smear will be prepared from each hematology sample. Blood smears will be labeled,stained, and stored. If additional examination of blood smears is deemed necessary, the smears may be subsequently evaluated and this evaluation will be described in a protocol amendment.

12.3. Clinical Chemistry

Clinical Chemistry Parameters

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Alanine aminotransferase Aspartate aminotransferase Alkaline phosphatase Gamma-glutamyltransferase Creatine kinase Total bilirubin[a] Urea nitrogen Creatinine Calcium Phosphorus	Total protein Albumin Globulin (calculated) Albumin/globulin ratio Glucose Cholesterol Triglycerides Sodium Potassium Chloride Sample quality[b]

[a] When total bilirubin is > 0. 5 mg/dL, direct bilirubin will also be measured and indirect bilirubin will be calculated.

[b] Will include degree of hemolysis, lipemia, and icterus (individual tables only).

13. DISPOSITION OF ANIMALS

This study is non-terminal. Upon completion of the study, the animals will be maintained in the Charles River animal colony for future use or may be euthanized (with intravenous sodium pentobarbital administration and the radiotelemetry probes recovered, as applicable). Animals not used on study will be returned to the Charles River animal colony.

Animals that experience severe or chronic pain or distress that cannot be relieved will be euthanized via intravenous sodium pentobarbital administration. All animals to be euthanized in extremis will have a detailed physical examination and a body weight collected. The animal will then be released for euthanasia and subsequent gross necropsy.

14. STATISTICAL ANALYSIS

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

Each cardiovascular parameter (systolic, diastolic, and mean arterial blood pressure; pulse pressure, heart rate; PR, QRS, QT, and QTc intervals) and body temperature will be analyzed using a SAS® System software. Cardiovascular data and body temperature will be exported to and analyzed in accordance with GLP Regulations. These statistical analyses and tables will be incorporated into the report.

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14.1. Statistical Comparisons

Control Treatment	Comparison (Test Article) Treatments
5	6,7
5	8,11
6	9,12
7	10,13

14.2. Statistical Analysis

The data will be analyzed using the mixed model analysis procedure within the SAS/STAT System (SAS) software. For statistical analysis, telemetry data will be organized into the following phases:

- Baseline: 90-min pre-oral dose baseline
- Phase I: 4 subphases of 15 min each post oral dose phase (prior to interaction article)
- Phase II: 6 subphases of 5 min each for hour 0 through 30 min (post interaction article)
- Phase III: 3 subphases of 10 min each for 30 min through hour 1 (post interaction article)
- Phase IV: 3 subphases of 1 h each for hours 2 through 4 (post interaction article)

The analysis phases and post-dose time intervals will be the same for all study periods. A single value (mean) will be calculated for each period's pre-dose (baseline) and individual post-dose time intervals.

Each cardiovascular parameter and body temperature will be analyzed, separately for each analysis phase, with a repeated measure analysis of covariance (RANCOVA). Fixed actors in the model will include baseline (BASE) as a covariate, treatment group (TRT), time after dose (TIME), and the two way interactions of each of the factors (TRT*TIME, TRT*BASE and BASE*TIME). ANIMAL will be fit as a random effect for autoregressive error structures. The SAS® procedure PROC GLIMMIX will be used for analysis with TIME as the repeated effect and ANIMAL as the subject. The covariance structure across time will be selected by evaluating corrected Akaike's Information Criterion (AICC).

Summary statistics will be reported for each treatment at each time point and across all time points for a given analysis phase. Summary graphs (means with standard error) will be presented for the averaged data for systolic, diastolic, and mean arterial pressure, pulse pressure, heart rate, body temperature and PR, QRS, QT, and QTcV. Individual data will not be presented in the report but will be maintained in the study records. Mean values for each time interval will be presented for individual animals. The statistical analysis summary report will be presented as an appendix in the final report.

Following the initial data review, other data summary intervals and/or segments may be used at the discretion of the Study Director in order to optimize the interpretation of data from this study.

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14.2.1. Descriptive Statistics

Endpoints: Body Temperature

Cardiovascular Endpoints

- Heart Rate
- Systolic, Diastolic, and Mean Arterial Blood Pressures
- Pulse Pressure
- ECG (RR, PR, QRS, QT, and QTc)

Description: The following statistical analyses will be performed for each analysis segment:

The data will be tabulated within each summary time interval and the arithmetic mean (Mean), number of subjects (N), least squares mean (LS Mean), and standard error of the LS Mean (LSM s.e.) will be calculated for each endpoint and treatment.

14.2.2. Repeated Measures Analysis of Covariance

Endpoints: Body Temperature

Cardiovascular Endpoints

- Heart Rate
- Systolic, Diastolic and Mean Arterial Blood Pressures
- Pulse Pressure
- ECG (RR, PR, QRS, QT, and QTc)

15. COMPUTERIZED SYSTEMS

The following computerized systems may be used in the study. The actual computerized systems will be documented in the report.

As Charles River Ashland transitions between various computer systems, the study number may appear as Redacted by agreement Redacted by agreement in the data records and report.

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Critical Computerized Systems

Program/System	Description
Advia 120	Hematology
Advia 1800	Serum and Urine Chemistry Analysis
Bio Medic Data Systems (BMDS) Implantable Micro Identification ™ (IMI-500 or IMI-1000)	Animal identification.
Charles River Formulations Dispense System (CR-FDS)	In-house developed system for use in conjunction with Provantis Dispense™ to ensure proper storage and use of formulations.
Dionex Chromeleon® software, Varian MS Workstation® software, Agilent ChemStation® software, or Molecular Devices SpectraMax® software	Used for chromatographic data acquisition and quantitation.
DSI PONEMAH Physiology Platform Model P3 Plus; DSI PONEMAH ECG PRO Template Analysis software; Dataquest™ OpenART™ Acquisition Interface	Computer-based systems (DSI) utilized for the electronic collection and measurement of cardiovascular, and body temperature data.
Deviation Information Library	Deviations
DocuSign©	Collection of Part 11 compliant signature.
Metasys SMP	Controls and monitors animal room environmental conditions.
Microsoft Office 2010 or higher; GraphPad Prism® 2008 or higher	Used in conjunction with the publishing software to generate study reports.
In-house reporting software Nevis 2012 (using SAS)	Reporting of in-life and postmortem data
Provantis®	Test material receipt, accountability, formulation activities, in-life (e.g.,. clinical observations, body weights, food consumption), clinical pathology (clinical chemistry, coagulation, hematology), and/or postmortem (e.g.,. pathology, ovarian contents)
SAS®	Statistical (non-WTDMS™) analyses
Share Document Management System (SDMS)	Reporting
WIL Metasys	In-house developed system used to record and report animal room environmental conditions.
WIL Toxicology Data Management System™ (WTDMS™)	In-house developed system used for collection and reporting of clinical pathology and other data.

Note: Version numbers of WTDMS™ programs used for the study are presented on the report data tables (reporting programs); version numbers and release dates are otherwise maintained in the study records and/or facility records.

Data for parameters not required by protocol, which are automatically generated by analytical devices used will be retained on file but not reported. Statistical analysis results that are generated by the program but are not required by protocol and/or are not scientifically relevant will be retained on file but will not be included in the tabulations.

16. REGULATORY COMPLIANCE

The study will be performed in accordance with the U.S. Department of Health and Human Services, Food and Drug Administration, United States Code of Federal Regulations, Title 21, Part 58: Good Laboratory Practice for Nonclinical Laboratory Studies and as accepted by

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Regulatory Authorities throughout the European Union (OECD Principles of Good Laboratory Practice), Japan (MHLW), and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

Any portion of this study conducted in Japan will be performed in accordance with MHW Ordinance No. 21: Good Laboratory Practice Standards for Non-Clinical Safety Studies on Drugs, 1997 and the Partial Revision (Ordinance No. 114, 2008) and as accepted by Regulatory Authorities throughout the European Union, United States of America (FDA), and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

Exceptions to GLPs include the following study elements:

- Characterization of the test and interaction articles will be/were performed by the Sponsor or Sponsor subcontractor at a laboratory that follows FDA Good Manufacturing Practice (GMP) regulations.
- Characterization of the test and interaction articles will be/were performed by the Sponsor or Sponsor subcontractor according to established SOPs, controls, and approved test methodologies to ensure integrity and validity of the results generated; these analyses will not be/were not conducted in compliance with the GLP or GMP regulations.

17. QUALITY ASSURANCE

Study components performed at sites other than the testing facility will be conducted according to the protocol and that site's applicable SOPs.

Study components performed at sites other than the testing facility will be audited by the QAU of the applicable test site.

17.1. Testing Facility

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

17.2. Test Site(s)/Subcontractor(s)

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

18. AMENDMENTS AND DEVIATIONS

Changes to the approved protocol shall be made in the form of an amendment, which will be signed and dated by the Study Director. Every reasonable effort will be made to discuss any

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necessary protocol changes in advance with the Sponsor. The Study Director will notify the Sponsor of deviations that may result in a significant impact on the study as soon as possible.

19. RETENTION AND DISPOSITION OF RECORDS, SAMPLES, AND SPECIMENS

All study-specific raw data, electronic data, documentation, protocol, retained samples and specimens, and final reports will be archived by no later than the date of final report issue. All materials generated by Charles River Laboratories from this study will be transferred to a Charles River Laboratories archive. At least 1 year after issue of the Draft Report, the Sponsor will be contacted.

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

Disposition of Residual/Retained Samples

Sample Type	Disposition	Schedule
Dose Formulation Analysis (including backups)	Discard	Following acceptance of the analytical results by the Study Director.

19.1. Study Classification

Study Category:	Safety Pharmacology
Study Type:	Cardiovascular Pharmacology; Pharmacokinetics
Study Design:	Crossover
Primary Treatment CAS Registry Number:	Not Available
Primary Treatment Unique Ingredient ID:	Not Available
Class of Compound:	Not Available

20. REPORTING

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

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

A tabulated data summary following the appropriate format as outlined in the ICH Harmonized Tripartite Guideline, *The Common Technical Document for the Registration of Pharmaceuticals*

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for Human Use: Safety – M4S (R2), Nonclinical Overview and Nonclinical Summaries of Module 2, Organisation of Module 4, will be provided at the same time as the Draft and Final Reports as a separate Microsoft Word document.

Reports should be finalized within 6 months of issue of the audited Draft Report.

20.1. SEND Datasets

SEND datasets will be generated and provided outside the context of the GLP Report. These datasets will not be subject to QA Audit nor will they be used as the basis for the Study Director interpretation of the study results. SEND datasets will be provided for the Report based on regulatory submission date. The Sponsor is expected to provide submission dates.

21. JUSTIFICATIONS AND GUIDELINES

21.1. Justification of Test System and Number of Animals

At this time, studies in laboratory animals provide the best available basis for extrapolation to humans and are required to support regulatory submissions. Acceptable models that do not use live animals currently do not exist.

This species and breed of animal is recognized by regulatory agencies to be appropriate for safety pharmacology studies and it is a widely used breed for which significant historical control data are available.

Only male dogs will be used because no sex differences in exposure are anticipated.

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

21.2. Justification of Route and Dose Levels

Test Article:

PK Phase:

The doses were selected by the NIDA. The oral route of exposure for the test article was selected because this is the intended route of human exposure. The exposure levels of the test article for a substance abuse indication in human subjects is expected to be comparable to Proprietary Info Proprietary Info [redacted] rovide a safety margin in the event of increased exposure in patients attributable to individual differences in metabolism or excess drug taking.

CV Phase:

Oral pharmacokinetics of the test article in dogs were derived from the antecedent pharmacokinetics phase of this study. Emesis was observed in 2/7 dogs dosed with 10 mg/kg and 4/7 dogs dosed with 30 mg/kg, but emesis and exposure were not correlated. Dose levels

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greater than 30 mg/kg caused more severe emesis Proprietary Info The exposure levels of the test article for a substance abuse indication in human subjects is expected to be comparable to Proprietary Info Proprietary Info In view of these data, oral dose levels of test article in the current study will be 3 mg/kg and 30 mg/kg to correspond with human plasma levels at the intention to treat dose and a multiple of that dose to provide a safety margin in the event of increased exposure in patients attributable to individual differences in metabolism or excess drug taking. The interval between Proprietary Info Proprietary Info to reach the desired level. See below.

Plasma Proprietary Info Proprietary Info Time Course in Beagle Dogs after Oral Gavage

Proprietary Info

Proprietary Info

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Dose (mg/kg)	1	3	10	30
Proprietary Info				

Plasma Pharmacokinetic Parameters of Proprietary Info in Humans After Multiple Dosing on Day 14 by Treatment Group Proprietary Info Study Number Proprietary Info)

Dose (n)	AUC_{tau} (h·ng/mL)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	Accumulation (R_{acc} [AUC])
Proprietary Info					

%CV: percent coefficient of variance
NA: not applicable
† n = 9 except for R_{acc} (AUC) where n = 8
n = 9 except for $t_{1/2}$ where n = 8

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Interaction Article:

The doses were selected by the NIDA. The intravenous route of exposure for the interaction article was selected because this is a route used by individuals that use cocaine. Intravenous cocaine doses of 0.56 and 1.7 mg/kg are selected based on the results of previous NIDA studies in the beagle dog (Proprietary Info Appendix F; Proprietary Info ; Proprietary Info Proprietary Info , Proprietary Info). Cocaine at 0.56 mg/kg produces relatively small increases in peak mean arterial blood pressures from baseline. This dose level of cocaine is desirable for drug interaction studies because "ceiling effects" are avoided. Cocaine at 1.7 mg/kg produces more profound increases in peak mean arterial blood pressure. Using a challenge dose of 1.7 mg/kg allows detection of possible adverse test article/cocaine interactions that may only occur at high plasma cocaine plasma. A higher cocaine dose (3.0 mg/kg) produces only slightly greater increases in mean arterial blood pressure and induces central nervous system stimulation and petechial hemorrhages in internal organs.

21.3. Guidelines for Study

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

- OECD Guideline 417. *Toxicokinetics*.
- ICH Harmonised Tripartite Guideline S3A. *Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies*.
- ICH Harmonised Tripartite Guideline S7A. *Guideline on Safety Pharmacology Studies for Human Pharmaceuticals*.
- ICH Harmonised Tripartite Guideline S7B. *The Non-Clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals*

22. ANIMAL WELFARE

This study will comply with all applicable sections of the Final Rules of the Animal Welfare Act regulations (Code of Federal Regulations, Title 9), the *Public Health Service Policy on Humane Care and Use of Laboratory Animals* from the Office of Laboratory Animal Welfare (Office of Laboratory Animal Welfare, 2015), and the *Guide for the Care and Use of Laboratory Animals* from the National Research Council (2011). The protocol and any amendments or procedures involving the care or use of animals in this study will be reviewed and approved by the Testing Facility Institutional Animal Care and Use Committee before the initiation of such procedures.

If an animal is determined to be in overt pain/distress or appears moribund and is beyond the point where recovery appears reasonable, the animal will be euthanized for humane reasons in accordance with the *American Veterinary Medical Association (AVMA) Guidelines on Euthanasia* and with the procedures outlined in the protocol (American Veterinary Medical Association, 2020).

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

22.1. Institutional Animal Care and Use Committee Approval

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

23. REFERENCES

American Veterinary Medical Association. *AVMA Guidelines on Euthanasia*. January 2020.

~~**Cochran WG, Cox GM. Plans and Tables of Random Permutations. In: Experimental Designs, New York, NY: John Wiley and Sons; 1957;145:577-582.**~~

Personnel **Analytical Qualification and Stability Study of (-)-Cocaine HCl in Aqueous Solution Formulations (Charles River Study No.** Proprietary Info **Charles River Laboratories, Ashland, OH, 2020.**

Holzgrefe HH, Cavero I, Gleason CR, Warner WA, Buchanan LV, Gill MW, Burkett DE, Durham SK. Application of a probabilistic method for determination of drug-induced QT prolongation in telemetered cynomolgus monkeys. *J Pharmacol Toxicol Methods*. 2007;55(2):244-254

National Research Council. Guide for the Care and Use of Laboratory Animals, Committee for the Update of the Guide for the Care and Use of Laboratory Animals, Institute for Laboratory Animal Research, Division on Earth and Life Sciences; The National Academies Press: Washington, DC, 2011.

Personnel **N. Method Validation of a High-Performance Liquid Chromatography Method for the Determination of Test Article Concentration in Dose Formulation (Charles River Study No.** Proprietary Info **Charles River Laboratories, Ashland, OH, 2020.**

Office of Laboratory Animal Welfare. *Public Health Services Policy on Humane Care and Use of Laboratory Animals*. Bethesda, MD: National Institutes of Health. March 2015.

SAS® Proprietary Software, Version 9.4; SAS Institute, Inc.: Cary, NC, 2002-2014 Spence S, Soper K, Hoe C-M, Coleman J. The heart rate-corrected QT interval of conscious Beagle dogs: a formula based on analysis of covariance. *Toxicol Sci*. 1998;45(2):247-258.

Spence S, Soper K, Hoe C-M, Coleman J. The heart rate-corrected QT interval of conscious Beagle dogs: a formula based on analysis of covariance. *Toxicol Sci*. 1998;45(2):247-258.

Van de Water A, Verheyen J, Xhonneux R, Reneman RS. An improved method to correct the QT interval of the electrocardiogram for changes in heart rate. *J Pharmacol Met*. 1989;22(3):207-217.

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AMENDMENT APPROVAL

All electronic signatures appear at the end of the document upon finalization.

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SPONSOR APPROVAL

The signature below indicates that the Sponsor Representative approves the study protocol amendment.

Redacted by agreement

Digitally signed by Redacted by agreement
Date: 2022.01.26 14:09:36 -08'00'

Redacted by agreement _____ Date:_____

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ATTACHMENT A

Shipment of Samples and Study Records

Matrix[a]	Purpose	Day/ Week/ Aliquot	Proposed Shipment Date	Conditions for Shipment	Recipient/Address
Test Article	Disposition of unused neat test article	-	To be documented	On blue ice packs	Redacted by agreement SRI Biosciences 333 Ravenswood Avenue Menlo Park, CA 94025 United States Tel: Redacted by agreement E-mail: Redacted by agreement
Interaction Article	Disposition of unused neat interaction article	-	To be documented	Ambient temperature	Redacted by agreement SRI Biosciences 333 Ravenswood Avenue Menlo Park, CA 94025 United States Tel: Redacted by agreement E-mail: Redacted by agreement
Plasma	Shipment of specimens for Bioanalytical Analysis	-	To be documented	Frozen, on dry ice	Redacted by agreement CMIC, Inc. 2860 Forbs Avenue, Hoffman Estates, IL 60192-3702 United States Tel: Redacted by agreement E-mail: Redacted by agreement Redacted by agreement

- = not applicable.
[a] Shipments performed via FedEx.

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Sponsor Reference No. Redacted by agreement

Testing Facility Study No. Redacted by agreement

SIGNATURE(S) FOR DOCUMENT: Redacted by agreement **- Amendment 7**

Study Director Approval: I approve this document.

Name: Redacted by agreement

26-Jan-2022 20:56:52 (UTC+00:00)

Electronically Signed in M-Files

Timestamp

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Final Report • November 10, 2021

EVALUATION OF THE INTERACTION BETWEEN Proprietary Info ADMINISTERED ORALLY AND COCAINE ADMINISTERED INTRAVENOUSLY TO CONSCIOUS, RADIOTELEMETRY-INSTRUMENTED BEAGLE DOGS

Redacted by agreement

SRI International
Biosciences Division
333 Ravenswood Avenue
Menlo Park, CA 94025

Testing Facility
Charles River Laboratories Ashland, LLC
1407 George Road
Ashland, OH 44805
United States

SRI Study Number: Redacted by agreement
CRL's Study Number:
SRI Project Numbers: P25884.200 and 100621.018.TO04.00.0200

Sponsor:
National Institute on Drug Abuse
Division of Pharmacotherapies & Medical Consequences of Drug Abuse
6001 Executive Blvd
Room 4123, MSC 9551
Bethesda, MD
20892

Sponsor's Representative: Redacted by agreement

NIDA Contract and TO Number: HHSN271201800019I, TO#004

Uncovered by a White Coat Waste investigation

Evaluation of the Interaction Between Proprietary Info Administered Orally and Cocaine Administered Intravenously to Conscious, Radiotelemetry-Instrumented Beagle Dogs

SRI Study Redac Redacted by agreement CRL Study Redacted by agreement

APPROVAL SIGNATURES

Written By: Redacted by agreement Digitally signed by Redacted by agreement Date: 2021.11.10 14:34:21 -08'00'

Redacted by agreement

Date

Approved By: Redacted by agreement Digitally signed by Redacted by agreement Date: 2021.11.09 16:06:26 -08'00'

Redacted by agreement

Date

SRI Biosciences

SRI International
Biosciences Division
333 Ravenswood Avenue
Menlo Park, CA 94025

Uncovered by a White Coat Waste investigation

Evaluation of the Interaction Between [redacted] Administered Orally and Cocaine Administered Intravenously to Conscious, Radiotelemetry-Instrumented Beagle Dogs
SRI Study [redacted] CRL Study [redacted]

SUMMARY

The objective of this study was to evaluate the potential adverse cardiovascular effects that may have resulted when [redacted] (test article) and cocaine (interaction article) were administered together to male Beagle dogs. The study was conducted in two phases.

In the first phase (pharmacokinetics, PK phase), treatment-naïve Beagle dogs were exposed to increasing levels of [redacted] to determine the pharmacokinetics and its tolerability.

In the second phase (cardiovascular interaction, CV phase), the Beagle dogs were implanted with telemetry transmitters and subsequently dosed with combinations of orally (gavage) administered [redacted] and intravenously administered cocaine to evaluate if [redacted] affect the hemodynamic and cardiac effects cocaine. [redacted] dose levels in the cardiovascular interaction phase were informed by the outcome of the pharmacokinetics phase.

The study design was as follows:

Text Table 1
Experimental Design

Treatment No.	Treatment	[redacted] (Test Article) Dose Level (mg/kg)	Cocaine (Interaction Article) Dose Level (mg/kg)[a]	No. of Males
PK Phase[b]				
1	[redacted]	1	N/A	7
2	[redacted]	3	N/A	7
3	[redacted]	10	N/A	7
4	[redacted]	30	N/A	7
CV Phase[c]				
5	[redacted] Vehicle + Cocaine Vehicle	0	0	6
6	[redacted] Vehicle + Cocaine (low)	0	0.56	6
7	[redacted] Vehicle + Cocaine (high)	0	1.7	6
8	[redacted] (low) + Cocaine Vehicle	3	0	6
9	[redacted] (low) + Cocaine (low)	3	0.56	6
10	[redacted] (low) + Cocaine (high)	3	1.7	6
11	[redacted] (high) + Cocaine Vehicle	30	0	6
12	[redacted] (high) + Cocaine (low)	30	0.56	6
13	[redacted] (high) + Cocaine (high)	30	1.7	6

N/A = not applicable
[a] The interaction article was administered at the prescribed dose level at 1 hour (± 5 minutes) following test article dosing via ambulatory intravenous infusion.
[b] The same 7 animals were used for each treatment in an ascending design with at least 6 days between doses.
[c] 6 animals were selected from the animals tested in the PK phase and the same 6 animals were used for each treatment in ascending treatment number order with 6 minimum days between doses.

Uncovered by a White Coat Waste investigation

Evaluation of the Interaction Between Proprietary Info Administered Orally and Cocaine Administered Intravenously to Conscious, Radiotelemetry-Instrumented Beagle Dogs
SRI Study Redac Redacted by agreement CRL Study Redacted by agreement

For the PK phase, animals received a single dose of each test article formulation in an ascending dose design via oral gavage. For the CV phase, animals received combinations of Proprietary Info or its vehicle (test article) and cocaine or its vehicle (interaction article). The interval between the test article and interaction article doses was 1 hour (±5 minutes).

During the PK Phase, the following parameters and end points were evaluated: clinical signs and pharmacokinetic parameters.

During the CV Phase, the following parameters and end points were evaluated: clinical signs, heart rate, arterial blood pressure (systolic, diastolic, and mean), pulse pressure, body temperature, and ECG waveforms (from which ECG waveform morphologies and the ECG intervals PR, QRS, QT, and heart rate-corrected QT [QTcH and QTcV] were derived).

During the PK phase, a single oral administration of Proprietary Info at dose levels of 1, 3, 10, and 30 mg/kg to Beagle dogs resulted in clinical observations of salivation and wet fur around the mouth at 3 mg/kg; foamy white vomitus and foamy white material present in the cage pan at 10 mg/kg; and salivation, wet fur around the mouth, foamy white/yellow material present in the cage pan, and partly digested food at 30 mg/kg.

During the CV phase, a single oral administration of Proprietary Info at dose levels of 3 and 30 mg/kg in combination with a single intravenous infusion of cocaine at dose levels of 0.56 and 1.7 mg/kg to Beagle dogs resulted in clinical observations of various material in the cage pan, various vomitus, and salivation in all 30 mg/kg Proprietary Info treatments as well as clinical observations of partly digested food at 30 mg/kg Proprietary Info in combination with 0.56 and 1.7 mg/kg cocaine. In addition, intravenous administration of 0.56 and 1.7 mg/kg (cocaine) interaction article demonstrated expected pharmacodynamic responses (increased systolic, diastolic, mean arterial pressure, and body temperature), thus validating assay sensitivity to detect changes in hemodynamic and electrophysiologic parameters.

Acute oral administration of 3 mg/kg Proprietary Info (in the absence of interaction article) did not result in any biologically relevant changes in cardiovascular, body temperature, or ECG interval durations. Oral administration of 30 mg/kg Proprietary Info resulted in increased heart rate, systolic, diastolic, and mean arterial blood pressure. There were no changes in body temperature, or ECG interval durations following administration of 30 mg/kg Proprietary Info

Oral administration of Proprietary Info at doses of 3 or 30 mg/kg Proprietary Info in combination with intravenous administration of 0.56 or 1.7 mg/kg cocaine (1 hour following oral dosing), exacerbated the interaction article cardiovascular responses in systolic, diastolic, and mean arterial pressure. Administration of the test article (at 3 or 30 mg/kg) in the presence of cocaine interaction article (0.56 or 1.7 mg/kg) did not result in any biologically relevant changes in heart rate, body temperature, or ECG interval duration.

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charles river

FINAL REPORT

Testing Facility Study No. Redacted by agreement

Sponsor Reference No. Redacted by agreement

Evaluation of the Interaction Between Proprietary Info Administered Orally and Cocaine Administered Intravenously to Conscious, Radiotelemetry-Instrumented Beagle Dogs

GLP

SPONSOR:
SRI Biosciences
333 Ravenswood Avenue
Menlo Park, CA 94025
United States

TESTING FACILITY:
Charles River Laboratories Ashland, LLC
1407 George Road
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United States

Uncovered by a White Coat Waste investigation

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QUALITY ASSURANCE STATEMENT

Study Number: Redacted by agreement

This Study has been audited by Quality Assurance in accordance with the applicable Good Laboratory Practice regulations. Reports were submitted in accordance with SOPs as follows:

QA INSPECTION DATES

		Dates Findings Submitted to:	
Date(s) of Audit	**Phase(s) Audited**	**Study Director**	**Testing Facility Management**
01-Dec-2020	Dose Administration	01-Dec-2020	01-Dec-2020
07-May-2021	Data Review - Clinical Pathology	07-May-2021	07-May-2021
07-May-2021	Data Review - Clinical Pathology	07-May-2021	07-May-2021
12-May-2021	Data Review - Sample Management	12-May-2021	12-May-2021
19-May-2021 - 20-May-2021	Data Review - Formulations	24-May-2021	24-May-2021
27-May-2021	Data Review - Cardiology	27-May-2021	27-May-2021
27-May-2021 - 02-Jun-2021	Data Review - Technical Operations	02-Jun-2021	02-Jun-2021
07-Jun-2021 - 08-Jun-2021	Report	08-Jun-2021	08-Jun-2021
08-Jun-2021	Phase Report - Statistics	08-Jun-2021	08-Jun-2021
09-Jun-2021	Data Review - Formulations	09-Jun-2021	09-Jun-2021
09-Jun-2021 - 10-Jun-2021	Data Review - Analytical Chemistry	10-Jun-2021	10-Jun-2021
18-Jun-2021	Phase Report - Analytical Chemistry	18-Jun-2021	18-Jun-2021
02-Nov-2021	Final Report	03-Nov-2021	03-Nov-2021

In addition to the above-mentioned audits, process-based and/or routine facility inspections were also conducted during the course of this study. Inspection findings, if any, specific to this study were reported by Quality Assurance to the Study Director and Testing Facility Management and listed as a Phase Audit on this Quality Assurance Statement.

The Quality Assurance Statements for any work conducted at Test Sites were reviewed and included in the appropriate section of this report, as applicable.

The Final Report has been reviewed to assure that it accurately describes the materials and methods, and that the reported results accurately reflect the raw data.

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QUALITY ASSURANCE STATEMENT - Study Number: Redacted by agreement

QA INSPECTION DATES

Date(s) of Audit	Phase(s) Audited	Dates Findings Submitted to: Study Director	Dates Findings Submitted to: Testing Facility Management

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Redacted by agreement
Signing Reason: I approve this document
Signing Time: 05-Nov-2021 | 15:59:37 EDT
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Quality Assurance Auditor

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COMPLIANCE STATEMENT AND REPORT APPROVAL

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

Any portion of this study conducted in Japan was performed in accordance with MHW Ordinance No. 21: Good Laboratory Practice Standards for Non-Clinical Safety Studies on Drugs, 1997 and the Partial Revision (Ordinance No. 114, 2008) and as accepted by Regulatory Authorities throughout the European Union, United States of America (FDA), and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

SEND data sets were not subject to Quality Assurance Audit nor used as the basis for the Study Director interpretation of the study results.

Exceptions from the above regulations are listed below.

- Characterization of the test and interaction articles was performed by the Sponsor or Sponsor subcontractor at a laboratory that follows FDA Good Manufacturing Practice (GMP) regulations.
- Characterization of the test and interaction articles was performed by the Sponsor or Sponsor subcontractor according to established SOPs, controls, and approved test methodologies to ensure integrity and validity of the results generated; these analyses were not conducted in compliance with the GLP or GMP regulations.

This study was conducted in accordance with the procedures described herein. All deviations authorized/acknowledged by the Study Director are documented in the Study Records. The report represents an accurate and complete record of the results obtained.

There were no deviations from the above regulations that affected the overall integrity of the study or the interpretation of the study results and conclusions.

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Signing Reason: I approve this document
Signing Time: 05-Nov-2021 | 16:33:04 EDT
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1. RESPONSIBLE PERSONNEL

Role/Phase	QAU	Name	Contact Information
Study Director	Charles River	Redacted by agreement	Address as cited for Testing Facility
Scientific Report Review	Charles River		Address as cited for Testing Facility
Testing Facility Management	Charles River		Address as cited for Testing Facility
Testing Facility QAU	Charles River		Address as cited for Testing Facility
		Individual Scientist (IS)	
Analytical Chemistry	Charles River	Redacted by agreement	Address as cited for Testing Facility
		Principal Investigator (PI)	
Bioanalytical Analysis[a]	CMIC, Inc	Redacted by agreement	CMIC 2860 Forbs Avenue Hoffman Estates, IL 60192
Pharmacokinetic Analysis[a]	CMIC PharmaScience Co., Ltd.		CMIC Bioresearch Center, CMIC PharmaScience Co., Ltd 10221 Kobuchisawa-cho, Hokuto-shi, Yamanashi 408-0044, Japan

[a] Sponsor-designated Test Site.

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2. SUMMARY

The objective of this study was to evaluate the potential adverse cardiovascular effects that may have resulted when Proprietary Info (test article) and cocaine (interaction article) were administered together to male Beagle dogs. The study was conducted in two phases.

In the first phase (pharmacokinetics, PK phase), treatment-naïve Beagle dogs were exposed to increasing levels of Proprietary Info to determine the pharmacokinetics and its tolerability.

In the second phase (cardiovascular interaction, CV phase), the Beagle dogs were implanted with telemetry transmitters and subsequently dosed with combinations of orally (gavage) administered Proprietary Info and intravenously administered cocaine to evaluate if Proprietary Info affect the hemodynamic and cardiac effects cocaine. Proprietary Info dose levels in the cardiovascular interaction phase were informed by the outcome of the pharmacokinetics phase.

The study design was as follows:

Text Table 1
Experimental Design

Treatment No.	Treatment	Proprietary (Test Article) Dose Level (mg/kg)	Cocaine (Interaction Article) Dose Level (mg/kg)[a]	No. of Males
PK Phase[b]				
1	Proprietary	1	N/A	7
2	Proprietary	3	N/A	7
3	Proprietary	10	N/A	7
4	Proprietary	30	N/A	7
CV Phase[c]				
5	Proprietary Vehicle + Cocaine Vehicle	0	0	6
6	Proprietary Vehicle + Cocaine (low)	0	0.56	6
7	Proprietary Vehicle + Cocaine (high)	0	1.7	6
8	Proprietary (low) + Cocaine Vehicle	3	0	6
9	Proprietary (low) + Cocaine (low)	3	0.56	6
10	Proprietary (low) + Cocaine (high)	3	1.7	6
11	Proprietary (high) + Cocaine Vehicle	30	0	6
12	Proprietary (high) + Cocaine (low)	30	0.56	6
13	Proprietary (high) + Cocaine (high)	30	1.7	6

N/A = not applicable

[a] The interaction article was administered at the prescribed dose level at 1 hour (± 5 minutes) following test article dosing via ambulatory intravenous infusion.

[b] The same 7 animals were used for each treatment in an ascending design with at least 6 days between doses.

[c] 6 animals were selected from the animals tested in the PK phase and the same 6 animals were used for each treatment in ascending treatment number order with 6 minimum days between doses.

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For the PK phase, animals received a single dose of each test article formulation in an ascending dose design via oral gavage. For the CV phase, animals received combinations of Proprietary Info or its vehicle (test article) and cocaine or its vehicle (interaction article). The interval between the test article and interaction article doses was 1 hour (±5 minutes).

During the PK Phase, the following parameters and end points were evaluated: clinical signs and pharmacokinetic parameters.

During the CV Phase, the following parameters and end points were evaluated: clinical signs, heart rate, arterial blood pressure (systolic, diastolic, and mean), pulse pressure, body temperature, and ECG waveforms (from which ECG waveform morphologies and the ECG intervals PR, QRS, QT, and heart rate-corrected QT [QTcH and QTcV] were derived).

During the PK phase, a single oral administration of Proprietary Info at dose levels of 1, 3, 10, and 30 mg/kg to Beagle dogs resulted in clinical observations of salivation and wet fur around the mouth at 3 mg/kg; foamy white vomitus and foamy white material present in the cage pan at 10 mg/kg; and salivation, wet fur around the mouth, foamy white/yellow material present in the cage pan, and partly digested food at 30 mg/kg.

During the CV phase, a single oral administration of Proprietary Info at dose levels of 3 and 30 mg/kg in combination with a single intravenous infusion of cocaine at dose levels of 0.56 and 1.7 mg/kg to Beagle dogs resulted in clinical observations of various material in the cage pan, various vomitus, and salivation in all 30 mg/kg Proprietary Info treatments as well as clinical observations of partly digested food at 30 mg/kg Proprietary Info in combination with 0.56 and 1.7 mg/kg cocaine. In addition, intravenous administration of 0.56 and 1.7 mg/kg (cocaine) interaction article demonstrated expected pharmacodynamic responses (increased systolic, diastolic, mean arterial pressure, and body temperature), thus validating assay sensitivity to detect changes in hemodynamic and electrophysiologic parameters.

Acute oral administration of 3 mg/kg Proprietary Info (in the absence of interaction article) did not result in any biologically relevant changes in cardiovascular, body temperature, or ECG interval durations. Oral administration of 30 mg/kg Proprietary Info resulted in increased heart rate, systolic, diastolic, and mean arterial blood pressure. There were no changes in body temperature, or ECG interval durations following administration of 30 mg/kg Proprietary Info

Oral administration of Proprietary Info at doses of 3 or 30 mg/kg Proprietary Info in combination with intravenous administration of 0.56 or 1.7 mg/kg cocaine (1 hour following oral dosing), exacerbated the interaction article cardiovascular responses in systolic, diastolic, and mean arterial pressure. Administration of the test article (at 3 or 30 mg/kg) in the presence of cocaine interaction article (0.56 or 1.7 mg/kg) did not result in any biologically relevant changes in heart rate, body temperature, or ECG interval duration.

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3. INTRODUCTION

The objective of this study was to evaluate the potential adverse cardiovascular effects that may have resulted when Proprietary Info (test article) and cocaine (interaction article) were administered together to male Beagle dogs. The study was conducted in two phases.

In the first phase (pharmacokinetics, PK Phase), treatment-naïve Beagle dogs were exposed to increasing levels of Proprietary Info to determine the pharmacokinetics and its tolerability.

In the second phase (cardiovascular interaction, CV Phase), the Beagle dogs were implanted with telemetry transmitters and subsequently dosed with combinations of orally (gavage) administered Proprietary Info and intravenously administered cocaine to evaluate if Proprietary Info affect the hemodynamic and cardiac effects cocaine. Proprietary Info dose levels in the cardiovascular interaction phase were informed by the outcome of the pharmacokinetics phase.

The design of this study is based on OECD Guideline 417 and ICH Harmonised Tripartite Guidelines S7A, S7B, and S3A.

The deviations, last protocol amendment, and protocol are presented in Appendix 1.

Study Initiation Date:	17 Nov 2020
Initiation of Dosing (PK Phase):	24 Nov 2020
Initiation of Dosing (CV Phase):	11 Feb 2021
Completion of In-life:	20 Apr 2021

4. MATERIALS AND METHODS

4.1. Test Materials

4.1.1. Test Article Characterization

The Sponsor provided to the Testing Facility documentation of the identity, strength, purity, composition, and stability for the test article. A Certificate of Analysis was provided to the Testing Facility and is presented in Appendix 2.

Information for vehicle components was limited to that provided by the respective manufacturers.

The Sponsor has appropriate documentation on file concerning the method of synthesis, fabrication or derivation of the test article, and this information is available to the appropriate regulatory agencies should it be requested.

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4.1.2. Test Material Identification

Text Table 2
Test Article Identification

	Test Article
Identification	Proprietary Proprietary Info
Alternate Identification	
Lot No.	
Expiration/Retest Date	Concomitant
Purity	100.3%
Correction Factor	-
Storage Conditions	18°C to 24°C, protected from light
Provided by	Sponsor designee

- = not applicable.

Text Table 3
Interaction Article Identification

	Control Article
Identification	Cocaine HCl
Alternate Identification	(-)-Cocaine HCl
Batch No.	14201-124A
Purity	≥95%
Correction Factor	-
Storage Conditions	18°C to 24°C
Provided by	Sponsor designee

- = not applicable

Text Table 4
Vehicle Identification for Test Article Preparation

	Vehicle	Vehicle Component	Vehicle Component
Identification	0.5% Methylcellulose (400 cPs)	Methylcellulose (400 cPs)	Deionized water
Alternate Identification	-	METHOCEL™ A4C Premium Methylcellulose	DI water
Storage Conditions	Set to maintain a target temperature of 5°C	18°C to 24°C	18°C to 24°C
Provided by	Testing Facility	Testing Facility	Testing Facility

- = not applicable.

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Text Table 5
Vehicle Identification for Interaction Article Preparation

	Vehicle
Identification	0.9% sodium chloride injection, USP
Alternate Identification	Sodium chloride
Storage Conditions	18°C to 24°C
Provided by	Testing Facility

4.2. Reserve Samples

For the test and interaction articles, reserve samples (0.103 and 0.0107 g, respectively) were collected and maintained under the appropriate storage conditions by the Testing Facility.

4.3. Test Article, Interaction Article, and Vehicle Inventory and Disposition

Test materials (e.g., test article, vehicle, interaction article) were received by the Testing Facility for distribution as needed. Records of the receipt, distribution, storage, and disposition of test materials (including empty containers of Sponsor-provided materials) were maintained. All unused bulk test article, with the exception of reserve samples, was returned to the Sponsor.

4.4. Dose Formulation and Analysis

4.4.1. Preparation of Formulations

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

Text Table 6
Preparation Details

Dose Formulation	Frequency of Preparation	Storage Conditions Set to Maintain
Test Article Vehicle	Approximately weekly for each phase	A target temperature of 5°C
Interaction Vehicle	At least every 3 weeks	18°C to 24°C or a target temperature of 5°C
Test Article	At least biweekly	18°C to 24°C, protected from light (PK phase) or a target temperature of 5°C, protected from light (CV phase)
Interaction Article	Once, prior to the first CV phase dosing occasion	18°C to 24°C

Any residual volumes from each dosing occasion were discarded.

4.4.2. Preparation Details

Dosing formulations were prepared at appropriate concentrations to meet dose level requirements.

4.4.3. Sample Collection and Analysis

Dose formulation samples were collected for analysis as indicated in the following table.

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Text Table 7
Dose Formulation Sample Collection Schedule

Sample Type	Concentrations	Stratum	Sampling From	Number of Samples per Concentration			Sample Volume (mL)	Intervals
				Collected	Analyzed	Backup		
Homogeneity Analyses	All Treatments[a]	Top	Preparation container	4	2	2	1	Each preparation
		Middle		4	2	2	1	
		Bottom		4	2	2	1	
Concentration Analyses	All Treatments	Middle	Preparation container	4	2	2	1	Each preparation

[a] = Excluding the vehicle treatments.

Text Table 8
Interaction Article Sample Collection Schedule

Sample Type	Concentrations	Stratum	Sampling From	Number of Samples per Concentration			Sample Volume (mL)	Intervals
				Collected	Analyzed	Backup		
Concentration Analyses	All Treatments	Middle	Preparation container	4	2	2	0.5	Each preparation and on each day of dosing[a]

[a] = Duplicate 0.5 mL samples were collected from the residual interaction article dosing container following dosing. One sample was analyzed, and the alternate was utilized as a backup sample.

Dose analysis results (formulated test article or initial interaction article formulation) were verified prior to dose administration at each sampling interval.

Interaction samples were transferred to the analytical chemistry laboratory and stored refrigerated until analyzed. Test article formulation samples (including backups) were transferred at ambient temperature to the Analytical Chemistry Department at the Testing Facility for same day analysis, where possible or stored for analysis within known formulation stability period.

4.4.3.1. Analytical Method

Analyses for the test article described below were performed by a high-performance liquid chromatography (HPLC) method with ultraviolet light absorbance method using a validated analytical procedure Personnel Draft, Proprietary Info.

Analyses for the interaction article described below were performed by a high-performance liquid chromatography (HPLC) method with ultraviolet light absorbance method using a qualified analytical procedure Personnel 2020, Proprietary Info

4.4.3.2. Concentration and Homogeneity Analysis

4.4.3.2.1. Test Article

Sample Allocation: 2 for analysis, 2 for backup.

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Storage Conditions:	Temperature set to maintain a target of 5°C.
Acceptance Criteria:	For concentration: Mean sample concentration within 100% ± 15% of theoretical concentration. For homogeneity: Relative standard deviation (RSD) of concentrations of ≤ 10% for each group.

4.4.3.2.2. Interaction Article

Sample Allocation:	2 for analysis, 2 for backup.
Storage Conditions:	Temperature set to maintain 18°C to 24°C.
Acceptance Criteria:	For concentration: Mean sample concentration within 100% ± 10% of theoretical concentration.

4.4.3.3. Resuspension Homogeneity and Stability Analysis

Test article formulations have been previously shown to be stable and homogeneous over the range of concentrations used on this study for at least 15 days at room temperature. Therefore, stability and resuspension homogeneity of test article formulations were not assessed on this study.

Interaction article formulations have been previously shown to be stable over the range of concentrations used on this study for at least 106 days at room temperature. Therefore, stability of the interaction article was not assessed on this study.

4.5. Test System

4.5.1. Receipt

On 17 Nov 2020, Beagle dogs were received from Proprietary Info The animals were approximately 6 to 7 months old and weighed between 9 and 11 kg at the initiation of dosing.

Immunizations prior to arrival of the dogs at the Testing Facility included: parvovirus, distemper, adenovirus type 2, parainfluenza, Bordetella, papilloma, and rabies.

4.5.2. Justification for Test System and Number of Animals

At this time, studies in laboratory animals provide the best available basis for extrapolation to humans and are required to support regulatory submissions. Acceptable models that do not use live animals currently do not exist.

This species and breed of animal is recognized by regulatory agencies to be appropriate for safety pharmacology studies and it is a widely used breed for which significant historical control data are available.

Only male dogs were used because no sex differences in exposure were anticipated.

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

4.5.3. Animal Identification

Each animal was identified using a subcutaneously implanted identification chip or a tattoo.

4.5.4. Environmental Acclimation

Each animal was inspected by a clinical veterinarian upon receipt. Animals judged to be in good health were placed in acclimation for at least 6 days. The animals were allowed at least 2 weeks to recover following implantation of the telemetry device before the administration of test and interaction articles for the cardiovascular phase.

4.5.5. Jacket Acclimation

Following the PK phase and prior to surgery for the cardiovascular interaction phase, all animals were acclimated to a tethered infusion system. Animals were initially conditioned to jackets and collars in a stepwise manner until at least 24 hours of acclimation was achieved. Subsequently, animals were acclimated to the tether and jackets for a period of 4 hours, and for a period of at least 24 hours.

4.5.6. Selection, Assignment, and Disposition of Animals

For the PK phase, animals judged to be suitable for testing (based on health as indicated by randomization approval) were assigned to groups based on body weight stratification into a block design using a computer program.

For the CV phase, animals will be arbitrarily assigned to groups based on health and telemetric assessment.

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

4.5.7. Husbandry

4.5.7.1. Housing

Housing (Dosing Days):	Single. Individual housing was necessary during periods of data collection to prevent telemetry signal cross talk and to individually attribute any clinical observations to individual animals to allow for a correlation to the bioanalytical data. PK phase: The animals were separated in the morning prior to dosing, on each day of dosing. Following jacket removal, or the final blood collection timepoint, animals were returned to social housing.
Housing (Nondosing Days):	Group housed (up to 3 animals) CV phase: Animals were separated in the afternoon on the day prior to dosing at the time of fasting and remained separated until following

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jacket removal. Subjects had continual access to water during periods of fasting. Animals were separated in advance of dosing to minimize variations in baseline data caused by excitability and stress of animals from separation and placement into telemetry banks. Animals remained separated until removal of jackets, as socialization was not possible with the tethered infusion system.

Caging: Stainless steel cages with mesh floors.

Cage Identification: Cage card indicating study, animal number(s), and sex.

Housing set-up is as specified in the USDA Animal Welfare Act (9 CFR, Parts 1, 2 and 3) (USDA, 1989) and as described in the Guide for the Care and Use of Laboratory Animals (National Research Council, 2011). Animals were separated during designated procedures/activities or were separated as required for monitoring and/or health purposes, as deemed appropriate by Study Director and/or Clinical Veterinarian.

4.5.7.2. Animal Enrichment

Method: For enrichment, animals were provided with items such as chew toys, except when interrupted by study procedures/activities. All animals were given regular opportunity for exercise and socialization and had enrichment through human interaction during the conduct of procedure acclimation and daily study activities.

4.5.7.3. Environmental Conditions

The targeted conditions for animal room environment was as follows:

Temperature: 66°F to 76°F (19°C to 24°C).

Humidity: 30% to 70%.

Light Cycle: 12 hours light and 12 hours dark (except during designated procedures).

4.5.7.4. Food

Diet: PMI Nutrition International, LLC LabDiet Certified Canine Diet 5007.

Type: Kibble (alternate diet may have been provided on an individual animal basis as warranted and approved by the Study Director).

Frequency: Daily ration of approximately 300 g (for exceptions, see Appendix 1).

Animals were fasted overnight prior to surgery. The daily ration of food was offered following recovery from anesthesia. Animals were fasted overnight before dosing days. On dosing days during the PK phase, the daily ration of food was provided after the 2-hour postdosing plasma collection. On dosing days during the CV phase, food was returned 4 hours after the cocaine dose (after the 4-hour post end of infusion clinical observation). Animals were not fasted for longer than 24 hours (for exceptions, see Appendix 1).

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

4.5.7.5. Water

Type: Municipal tap water, treated by reverse osmosis and ultraviolet irradiation.

Frequency/Ration: Freely available to each animal via an automatic watering system (except during designated procedures). Water bottles were provided, if required.

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

4.5.7.6. Veterinary Care

Veterinary care was available throughout the course of the study, and animals were examined by the veterinary staff as warranted by clinical signs or other changes. All veterinary examinations and recommended therapeutic treatments were documented in the study records and reviewed by the Study Director.

4.6. Surgical Preparation

Following the PK phase, animals were implanted with radiotelemetry transmitters and vascular access ports (VAPs) to allow for undisturbed IV dosing as described in Testing Facility SOPs.

Preanesthetics, surgical preparation and implantation details (for the telemetry implant and VAPs), and post-operative care and recovery procedures were performed as outlined in Testing Facility SOPs.

The transmitters had a fluid-filled catheter (coated with an antithrombotic film to inhibit thrombus formation) with the tip filled with a patented gel for collection of blood pressure and 2 ECG leads emulating a lead II configuration.

The VAPs were maintained per Testing Facility SOPs and included weekly assessments of patency until dosing. VAPs were locked with taurolidine citrate solution (TCS) between patency assessments.

4.7. Experimental Design

The following table presents the treatment arrangement. Proprietary Info Proprietary Info Proprietary Info Proprietary Info Proprietary Info dose levels in the CV phase were selected based on data from the PK phase. Cocaine dose levels in the CV phase were selected based on data provided by National Institute on Drug Abuse (NIDA) from Proprietary Info Appendix F, Proprietary Info Proprietary Info Proprietary Info and Proprietary Info (see section 4.7.3.).

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Text Table 9
Experimental Design

Treatment No.	Treatment Week	Treatment	Proprietary (Test Article) Dose Level (mg/kg)	Proprietary Dose Concentration (mg/mL)	Proprietary or Vehicle Dose Volume (mL/kg)	Cocaine (Interaction Article) Dose Level (mg/kg)[a]	Cocaine Dose Concentration (mg/mL)	Cocaine or Vehicle Dose Volume (mL/kg)	No. of Males
PK Phase[b]									
1	PK 1	Proprietary	1	0.1	10	N/A	N/A	N/A	7
2	PK 2	Proprietary	3	0.3	10	N/A	N/A	N/A	7
3	PK 3	Proprietary	10	1	10	N/A	N/A	N/A	7
4	PK 4	Proprietary	30	3	10	N/A	N/A	N/A	7
CV Phase[c]									
5	CV 1	Proprietary Vehicle + Cocaine Vehicle	0	0	10	0	0	0.25	6
6	CV 2	Proprietary Info Vehicle + Cocaine (low)	0	0	10	0.56	2.24	0.25	6
7	CV 3	Proprietary Info Vehicle + Cocaine (high)	0	0	10	1.7	6.8	0.25	6
8	CV 4	Proprietary Info (low) + Cocaine Vehicle	3	0.3	10	0	0	0.25	6
9	CV 5	Proprietary Info (low) + Cocaine (low)	3	0.3	10	0.56	2.24	0.25	6
10	CV 6	Proprietary (low) + Cocaine (high)	3	0.3	10	1.7	6.8	0.25	6
11	CV 7	Proprietary (high) + Cocaine Vehicle	30	3	10	0	0	0.25	6
12	CV 8	Proprietary (high) + Cocaine (low)	30	3	10	0.56	2.24	0.25	6
13	CV 9	Proprietary (high) + Cocaine (high)	30	3	10	1.7	6.8	0.25	6

N/A = not applicable

[a] The interaction article was administered at the prescribed dose level at 1 hour (± 5 minutes) following test article dosing via ambulatory intravenous infusion.

[b] The same 7 animals were used for each treatment in an ascending design with at least 6 days between doses.

[c] 6 animals were selected from the animals tested in the PK phase and the same 6 animals were used for each treatment in ascending treatment number order with 6 minimum days between doses.

4.7.1. Administration of Test Materials

During the PK phase, each animal received a single dose of each test article formulation in an ascending dose design via oral gavage.

During the CV phase, each animal received a single dose of each test article formulation and vehicle control via oral gavage followed by a single dose of each interaction article formulation and interaction article vehicle via intravenous infusion in an ascending dose design.

The oral doses were given using a syringe with an attached gavage tube. Each oral dose was followed by 15-mL flush using deionized water.

The interaction article or its vehicle were administered at 1 hour (± 5 minutes) following the oral dose via intravenous infusion over a 45-second infusion from an infusion pump followed by a 5 mL saline flush administered at the same rate (see Appendix 1). Doses were delivered using a calibrated infusion pump with a tethered infusion system. Doses were administered in absence of technical staff in the dosing room. Doses were scheduled to initiate at least 30 minutes following exiting of the room.

Intravenous doses were delivered via the Cath-in-Cath system to the appropriately placed indwelling catheter. The infusion was delivered to freely moving animals. Individual doses were drawn into syringes labeled with the animal number, study number, and date, and documented appropriately. The dosing syringes were filled with the appropriate dosing volume of interaction article required for dosing (additional volume of the interaction article was provided to account for the dead space in the extension line to the Y connector infusion system). Using a second infusion pump for each animal, an additional syringe was filled with the appropriate volume of saline to flush the extension lines to complete the prescribed dose. Animals were dosed at approximately the same time (± 1 hour) each dose day. Syringes were visually assessed for residual dosing volume to determine dose confirmation.

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Text Table 10
Dosing Regimen

Treatment No.	Treatment Week	Day	Treatment
PK Phase			
1	PK 1	1	1 mg/kg Proprietary
2	PK 2	8	3 mg/kg Proprietary
3	PK 3	15	10 mg/kg Proprietary
4	PK 4	22	30 mg/kg Proprietary
CV Phase			
5	CV 1	85	Vehicle + Saline
6	CV 2	92	Vehicle + 0.56 mg/kg Cocaine
7	CV 3	99	Vehicle + 1.7 mg/kg Cocaine
8	CV 4	106	3 mg/kg Proprietary + Saline
8	CV 4 re-dose	109[a]	3 mg/kg Proprietary + Saline
9	CV 5	113	3 mg/kg Proprietary Info + 0.56 mg/kg Cocaine
10	CV 6	120	3 mg/kg Proprietary + 1.7 mg/kg Cocaine
11	CV 7	127	30 mg/kg Proprietary + Saline
11	CV 7 re-dose	130[b]	30 mg/kg Proprietary + Saline
12	CV 8	134	30 mg/kg Proprietary + 0.56 mg/kg Cocaine
13	CV 9	141	30 mg/kg Proprietary Info + 1.7 mg/kg Cocaine

[a] = On Day 106 (CV phase Dose 4), observations of slight white material in the cage pan were noted for Male No. 1002 immediately following dosing and Male No. 1005 at 4 hours postdosing. In addition, Male No. 1003 was found with its jacket and tether removed and cath-in-cath tubing chewed through at 4 hours postdosing. Following discussion with the Study Director and Sponsor, CV 4 Treatment No. 8 (3 mg/kg Proprietary + Saline) was re-administered on Day 109 for Male Nos. 1002, 1003, and 1005. This resulted in less than the protocol specified minimum of 6 days between dosing occasions.

[b] = On Day 127 (CV phase Dose 7), Male No. 1005 was noted with an observation of moderate foamy white vomitus immediately following dosing. Following discussion with the Study Director and Sponsor, CV 7 Treatment No. 11 (30 mg/kg Proprietary + Saline) was re-administered on Day 130 for Male No. 1005. This resulted in less than the protocol specified minimum of 6 days between dosing occasions.

4.7.2. Jacket and Tether System Procedures

Prior to Dose 1 of the CV phase, a "sham" dosing procedure imitating the dosing procedure for each treatment session was performed, including a telemetric recording (cardiovascular, ECG, and body temperature) obtained for at least 4 hours following the "sham" IV infusion (saline) (for exceptions, see Appendix 1). All animals underwent the pretreatment recording. Vehicle was used as the oral sham dosing article and saline was utilized as the intravenous sham dosing article. Doses were administered as outlined in section 4.7.1. These data were recorded but not reported. The pretreatment session included a minimum of a 90-minute recording period prior to the target "sham" oral dose while in telemetry cages, and then continue for at least 4 hours following the "sham" IV infusion dose. The "sham" IV infusion dose was performed at 1 hour (± 5 minutes) following the "sham" oral dose, as outlined in the CV phase treatment regimen. Hemodynamic data (systolic, diastolic, mean arterial pressure, pulse pressure and heart rate) and ECG intervals were measured and binned in appropriate intervals as described in section 5.2.

The ECG tracings were reviewed for rhythm disturbances (dysrhythmias) for the six animals participating in the study over the duration of recording period. Data from the pretreatment collection were used to confirm acclimation to testing procedures of the animals placed on study.

During the CV phase, all animals were placed into jackets prior to dosing. Patency checks were performed prior to introduction of the jacket system. All animals were placed on a maintenance infusion of saline (2 mL/hr) in an effort to maintain VAP patency during nondosing periods. Animals were maintained in jackets for up to approximately 3 doses. Jackets were removed for approximately one week before subsequent jacket placement (for exceptions, see Appendix 1).

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4.7.3. Justification of Route and Dose Levels

4.7.3.1. Test Article

For the PK phase, doses were selected based on available data from Proprietary Info Proprietary Info Proprietary Info

For the CV phase, oral pharmacokinetics of the test article in dogs were derived from the antecedent pharmacokinetics phase of this study. Emesis was observed in 2/7 dogs dosed with 10 mg/kg and 4/7 dogs dosed with 30 mg/kg, but emesis and exposure were not correlated. Dose levels greater than 30 mg/kg caused more severe emesis. The exposure levels of the test article for a substance abuse indication in human subjects were expected to be comparable to Proprietary Info Proprietary Info Proprietary Info to reach the desired level. See section 8.3.

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Text Table 11

Proprietary Info

4.7.3.2. Interaction Article:

The intravenous route of exposure for the interaction article was selected because this is a route used by individuals that use cocaine. Intravenous cocaine doses of 0.56 and 1.7 mg/kg were selected based on the results of previous NIDA studies in the Beagle dog. Cocaine at 0.56 mg/kg produces relatively small increases in peak mean arterial blood pressures from baseline. This dose level of cocaine was desirable for drug interaction studies because "ceiling effects" were avoided. Cocaine at 1.7 mg/kg produces more profound increases in peak mean arterial blood pressure. Using a challenge dose of 1.7 mg/kg allowed detection of possible adverse test article/cocaine interactions that may only occur at high plasma cocaine plasma. A higher cocaine dose (3.0 mg/kg) produces only slightly greater increases in mean arterial blood pressure and induces central nervous system stimulation and petechial hemorrhages in internal organs.

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4.8. In-life Procedures, Observations, and Measurements

Text Table 12
General In-Life Assessments

Parameter	Population(s)	Frequency (minimum required)	Comments
Mortality	All animals[a]	At least twice daily[b] (morning and afternoon), beginning upon arrival through release.	Animals were observed within their cage unless necessary for identification or confirmation of possible findings.
Cageside Observations[c]	All PK and CV phase animals	During the PK phase observations were conducted prior to dosing, and at each PK timepoint (for exceptions, see Appendix 1). During the CV phase, observations will be conducted, prior to oral dosing, and at approximately 4 hours postdosing (relative to interaction article administration) (for exceptions, see Appendix 1).	Animals were observed within their cage unless necessary for identification or confirmation of possible findings. The absence or presence of findings was recorded for individual animals. Findings noted outside the above-specified observation periods were also recorded. Only the presence of unscheduled observations was recorded; the absence of findings was thus not recorded.
Detailed Clinical Observations[c]	All animals[a]	On the day prior to each day of dosing (for both the PK and CV Phases). Weekly between the end of the PK phase and beginning of the CV phase	Animals were removed from the cage. The absence or presence of findings was recorded for individual animals.
Individual Body Weights	All animals[a]	On the day prior to each day of dosing (for both the PK and CV Phases). Weekly between the end of the PK phase and beginning of the CV phase.	These data were reported but not statistically analyzed.

[a] Included alternate animals until released from study.
[b] Except on days of receipt and study termination where the frequency was at least once daily.
[c] For observations that could not be attributed to an individual animal due to social housing, the observations were noted for each animal in the socialized group.

4.8.1. Radiotelemetry Evaluations

Frequency: Baseline (for at least 90 minutes prior to administration of vehicle or test article).

Following administration of vehicle or test article, the appropriate parameters were collected continuously for at least 4 hours following the intravenous dose of interaction article.

Population: All CV phase animals

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System: The radiotelemetry system (Data Sciences International, St. Paul, MN) consisted of large animal radiotelemetry transmitters (with capabilities to collect, at minimum, arterial pressure, body temperature, and electrocardiographic waveforms), receivers (RMC-1), and 1 or more data exchange matrices (DEM) that relayed information from the receivers to the computer. An ambient pressure reference monitor (APR-1) was coupled to the DEM to measure the barometric pressure and provide a digital signal to the DSI PONEMAH system. The DSI PONEMAH system used the measurements provided by the APR-1 to correct pressure measurements obtained from the implant for changes in barometric pressure.

The hardware connected to the Dataquest™ OpenART™ Acquisition Interface provided direct digital signals to the DSI PONEMAH software. The ECG and arterial waveform and body temperature data were recorded and analyzed by the DSI PONEMAH data acquisition software. ECG and arterial pressure waveforms were sampled at 500 Hz. Temperature data were sampled at 50 Hz. Data acquired continuously were logged every 120 seconds. During data processing the logging rate was changed to 60 seconds. The ECG waveform data were analyzed by the DSI PONEMAH ECG PRO Template Analysis software.

Procedure: Arterial blood pressure (systolic, diastolic, and mean), pulse pressure, heart rate, electrocardiographic (ECG) waveforms and body temperature, were collected continuously

Evaluation: Cardiovascular parameters and body temperature data were averaged to appropriate time intervals for statistical analysis.

Quantitative ECG waveform analysis were performed using the DSI PONEMAH ECG-PRO Template Analysis software to determine the PR, QRS, RR, and QT intervals. Individual QT rate-corrections (β-values) were derived from the vehicle collection session for each animal. Heart rate-corrected QT (QTc) values were calculated with the Van de Water correction formula where QTcV = QT - 0.087*(RR-1) (Spence et al., 1998 and Van de Water et al., 1989). Additionally, QT was corrected using an individual correction factor, QTcH = 10log(QT) – β[log(HR)-log(HRm)] (Holzgrefe, 2007). The beta value for QTcH was collected from each animals' vehicle dosing data during the CV phase (slope of QT to RR).

For the purpose of data processing, Noise and Match derived parameters were collected. These parameters were not reported or statistically analyzed.

Qualitative assessment of ECG waveforms was performed by trained personnel for disturbances in rhythm and waveform morphology in 1-minute segments for every 30 minutes of data collected following an event assigned to the study (e.g., a start event or a dosing event) through 4 hours after the interaction article or its vehicle dose. Abnormal rhythm

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results were reported in a table as frequency of events. Qualitative assessment of blood pressure waveforms was not performed.

Within the processing system used to average telemetry data into intervals for statistical analysis and reporting, minimum and maximum limits were set according to the table below.

Parameter	Waveform Type	Minimum	Maximum
Heart Rate	Blood Pressure	0 beats per minute	No limit
Systolic Blood Pressure	Blood Pressure	0 mmHg	350 mmHg
Diastolic Blood Pressure	Blood Pressure	0 mmHg	No limit
Mean Arterial Blood Pressure	Blood Pressure	0 mmHg	No limit
Pulse Pressure	Blood Pressure	0 mmHg	150 mmHg
Body Temperature	Temperature	30°C	45°C
PR Interval	ECG	0 msec	10000 msec
QRS Complex	ECG	0 msec	10000 msec
QT Interval	ECG	0 msec	10000 msec
QTc Interval	ECG	0 msec	10000 msec
RR Interval	ECG	0 msec	10000 msec

For parameters indicated as control parameters, if the defined limits were exceeded for a time point then all other parameters at this time point were omitted from analysis and reporting.

4.8.1.1. Video Monitoring

Frequency: On each day of telemetry collection, video data synchronized with ECG were recorded to a secure workstation. Video data were recorded concurrently during periods of radiotelemetry data collection (for exceptions, see Appendix 1).

Population(s): All CV phase animals

System: Axis cameras (or equivalent) were used to collect time matched video data synchronized with the radiotelemetry system.

Procedure: Each camera was configured to capture the video data for each subject. During data review, video data were viewed using an appropriate media player.

Evaluation: Video data synchronized with ECG were used to establish the approximate time of occurrence of retching or emesis, if noted, beginning from the time of test article administration through the 4-hour period of postdosing observation after the interaction article dose. This time was recorded and maintained in the study records. The times were entered into the appropriate LIMS at the discretion of the Study Director. The video data were maintained in the study records but did not have any additional evaluations performed.

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4.9. Laboratory Evaluations

4.9.1. Clinical Pathology

4.9.1.1. Sample Collection

Samples were collected according to Text Table 13.

Text Table 13
Samples for Clinical Pathology Evaluation

Treatment No(s).	Time Point	Hematology	Clinical Chemistry
All animals	Prior to PK phase and after surgical implantation	X	X

Fasting:	-	At least 8 hours (no more than 24 hours)
Method/Comments:	Venipuncture from a jugular vein.	Venipuncture from a jugular vein.
Target Volume (mL):	1	1.5
Anticoagulant:	K_2EDTA	None
Special Requirements:	-	-
Processing:	None	Serum

X = sample to be collected; - = not applicable.

4.9.1.2. Hematology

Blood samples were analyzed for the parameters specified in Text Table 14.

Text Table 14
Hematology Parameters

Red blood cell count	White blood cell count[a]
Hemoglobin concentration	Neutrophil count (absolute)
Hematocrit	Lymphocyte count (absolute)
Mean corpuscular volume	Monocyte count (absolute)
Red blood cell distribution width	Eosinophil count (absolute)
Mean corpuscular hemoglobin concentration	Basophil count (absolute)
Mean corpuscular hemoglobin	Large unstained cells (absolute)
Reticulocyte count (absolute)	Other cells (as appropriate)
Platelet count	Mean platelet volume

[a] If performed manually, results included platelet estimates and RBC morphology on the individual tables.

A blood smear was prepared from each hematology sample. Blood smears were labeled, stained, and stored. Samples were not evaluated.

4.9.1.3. Clinical Chemistry

Blood samples were processed for serum, and the serum was analyzed for the parameters specified in Text Table 15.

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Text Table 15
Clinical Chemistry Parameters

Alanine aminotransferase	Albumin
Aspartate aminotransferase	Globulin (calculated)
Alkaline phosphatase	Albumin/globulin ratio
Gamma-glutamyltransferase	Glucose
Creatine kinase	Cholesterol
Total bilirubin	Triglycerides
Urea nitrogen	Sodium
Creatinine	Potassium
Calcium	Chloride
Phosphorus	Sample quality[a]
Total protein	

[a] Included degree of hemolysis, lipemia, and icterus; presented on individual data tables.

4.9.2. Bioanalysis and Pharmacokinetic Evaluation

4.9.2.1. Bioanalytical Sample Collection

Samples were collected according to Text Table 16.

Text Table 16
Bioanalytical Sample Collection Schedule

Treatment No.	Sample Collection Time Points (Time Postdose) on Days 1, 8, 15, and 22							
	0 hr (predose)	0.5 hr	1 hr	2 hr	4 hr	8 hr	12 hr	24 hr
1	X	X	X	X	X	X	X	X
2	X	X	X	X	X	X	X	X
3	X	X	X	X	X	X	X	X
4	X	X	X	X	X	X	X	X
Method/Comments:	Venipuncture from a jugular or cephalic vein.							
Target Volume (mL):	Approximately 1 mL/time point collected without anesthesia.							
Anticoagulant:	Sodium Heparin							
Special Requirements:	Keep samples chilled during collection and processing.							
Processing:	Plasma							

X = Sample collected; hr = hour.

4.9.2.2. Bioanalytical Sample Processing

Samples were mixed gently and centrifuged as soon as practical. The samples were centrifuged, and the resultant plasma was separated, transferred to duplicate uniquely labelled polypropylene tubes, and frozen immediately over dry ice until transferred to storage. Samples were stored in a freezer set to maintain a target of -20°C. The samples to be analyzed were shipped on dry ice via overnight courier to CMIC, Hoffman Estates, IL.

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4.9.2.3. Bioanalytical Sample Analysis

Bioanalytical samples were analyzed for concentration of Proprietary Info using a validated analytical procedure (Method No. Proprietary Info Details are included in Appendix 6.

4.9.2.4. Pharmacokinetic Evaluation

Pharmacokinetic parameters were estimated using Phoenix pharmacokinetic software. A non-compartmental approach consistent with the oral route of administration was used for parameter estimation. All parameters were generated from Proprietary Info individual concentrations in plasma from Days 1, 8, 15, and 22 whenever practical. Parameters were estimated using sampling times made relative to the start of each dose administration.

Text Table 17
Pharmacokinetic Parameters Estimated

Parameter	Description of Parameter
t_{max}	The time after dosing at which the maximum observed concentration was observed.
C_{max}	The maximum observed concentration measured after dosing.
C_{max}/Dose	The C_{max} divided by the dose administered.
AUC_{tlast}	The area under the concentration versus time curve from the start of dose administration to the last observed quantifiable concentration calculated using the linear trapezoidal method.
AUC_{tlast}/Dose	The AUC_{tlast} divided by the dose administered.
t_{last}	The time after dosing at which the last quantifiable concentration was observed

Partial AUCs (between 2 defined sample times), and corresponding dose-normalized values, may have been derived and reported to aid interpretation. Descriptive statistics (e.g., number, arithmetic mean, median, standard deviation, standard error, coefficient of variation) were reported as deemed appropriate, as well as ratios for appropriate grouping and sorting variables (e.g., AUC) may have been generated. Pharmacokinetic tables and graphs were also generated. Pharmacokinetic evaluation was conducted by CMIC Bioresearch Center, CMIC PharmaScience Co., Ltd, Hokuto-shi, Yamanashi, Japan.

4.10. Terminal Procedures

All animals were transferred to the Charles River animal colony.

4.10.1. Unscheduled Deaths

No animals died during the course of the study.

5. STATISTICAL ANALYSIS

Each cardiovascular parameter (systolic, diastolic, and mean arterial blood pressure; pulse pressure, heart rate; PR, QRS, QT, and QTc intervals) and body temperature was analyzed using a SAS® System software. Cardiovascular and body temperature data were exported to and analyzed in accordance with GLP Regulations. These statistical analyses and tables were incorporated into the report.

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5.1. Statistical Comparisons

Control Treatment	Comparison (Test Article) Treatments
5	6,7
5	8,11
6	9,12
7	10,13

5.2. Statistical Analysis

The data were analyzed using the mixed model analysis procedure within the SAS/STAT System (SAS) software. For statistical analysis, telemetry data were organized into the following phases:

- Baseline: 90-minutes pre-oral dose baseline
- Phase I: 4 subphases of 15 minutes each post oral dose phase (prior to interaction article)
- Phase II: 6 subphases of 5 minutes each for hour 0 through 30 minutes (post interaction article)
- Phase III: 3 subphases of 10 minutes each for 30 minutes through hour 1 (post interaction article)
- Phase IV: 3 subphases of 1 hour each for hours 2 through 4 (post interaction article)

Due to the need to precisely align both the oral and intravenous doses, each analysis (post oral dose and post interaction article) was run independently. Therefore, statistical analysis Phases II, III, and IV were presented as Phases I, II, and III, respectively, within the post interaction article statistical analysis tables.

The analysis phases and postdose time intervals were the same for all study periods. A single value (mean) was calculated for each period's predose (baseline) and individual postdose time intervals.

Each cardiovascular parameter and body temperature were analyzed, separately for each analysis phase, with a repeated measure analysis of covariance (RANCOVA). Fixed factors in the model included baseline (BASE) as a covariate, treatment group (TRT), time after dose (TIME), and the two-way interactions of each of the factors (TRT*TIME, TRT*BASE and BASE*TIME). ANIMAL was fit as a random effect for autoregressive error structures. The SAS® procedure PROC GLIMMIX was used for analysis with TIME as the repeated effect and ANIMAL as the subject. The covariance structure across time as selected by evaluating corrected Akaike's Information Criterion (AICC).

Summary statistics were reported for each treatment at each time point and across all time points for a given analysis phase. Summary graphs (means with standard error) were presented for the averaged data for systolic, diastolic, and mean arterial pressure, pulse pressure, heart rate, body temperature and PR, QRS, QT, QTcH, and QTcV. Individual data were not presented in the report but were maintained in the study records. Mean values for each time interval were presented for individual animals. The statistical analysis summary report was presented as an appendix in the final report.

5.2.1. Descriptive Statistics

Endpoints: Body Temperature

Cardiovascular Endpoints

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- Heart Rate
- Systolic, Diastolic, and Mean Arterial Blood Pressures
- Pulse Pressure
- ECG (RR, PR, QRS, QT, and QTc)

Description: The following statistical analyses were performed for each analysis segment:

The data were tabulated within each summary time interval and the arithmetic mean (Mean), number of subjects (N), least squares mean (LS Mean), and standard error of the LS Mean (LSM s.e.) were calculated for each endpoint and treatment.

5.2.2. Repeated Measures Analysis of Covariance

Endpoints: Body Temperature

Cardiovascular Endpoints

- Heart Rate
- Systolic, Diastolic and Mean Arterial Blood Pressures
- Pulse Pressure
- ECG (RR, PR, QRS, QT, and QTc)

6. COMPUTERIZED SYSTEMS

Critical computerized systems used in the study are listed below or presented in the appropriate phase report. All computerized systems used in the conduct of this study have been validated (with the exception of Microsoft Office and GraphPad Prism® 2008); when a particular system has not satisfied all requirements, appropriate administrative and procedural controls were implemented to assure the quality and integrity of data.

As Charles River Ashland transitions between various computer systems, the study number may appear as Redacted by agreement Redacted by agreement Redacted by agreement or Redacted by agreement in the data records and report.

Text Table 18
Critical Computerized Systems

Program/System	Version No.	Description
ADVIA 120	6.3.2	Hematology
ADVIA 1800	2.03	Clinical Chemistry Analysis
ADVIA 2120i	6.9.0	Hematology.
Cardiopulmonary Automated Reporting System (CARS)	3.1	In-house developed reporting system for cardiopulmonary data.
Deviation Information Library	2.1	Deviations and Notes to File.
DocuSign™	19	Collection of Part 11 compliant signature
DSI PONEMAH Physiology Platform Model P3 Plus; DSI PONEMAH ECG PRO Template Analysis software; Dataquest™ OpenART™ Acquisition Interface	5.2 SP11	Computer-based systems (DSI) utilized for the electronic collection and measurement of cardiovascular, and body temperature data.
EInfoTree	7.6	Excel module for collection of 21 CFR Part 11 compliance requirements, security, audit trail, and electronic signatures.

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Program/System	Version No.	Description
Formulations Dispense System (CR-FDS)	2.06	In-house developed system for use in conjunction with Provantis Dispense™ to ensure proper storage and use of formulations
Metasys SMP	6.0.0.900	Controls and monitors animal room environmental conditions.
M-Files®	21.1	Reporting and collection of 21 CFR Part 11 compliant signature
Microsoft Office 2010 or higher; GraphPad Prism® 2008	N/A	Used in conjunction with the publishing software to generate study reports.
Provantis®	10	Test material receipt, accountability formulation activities, in-life (e.g., clinical observations, body weights, food consumption), clinical pathology (hematology, coagulation, serum/clinical chemistry, and urinalysis), and/or postmortem (e.g., pathology, organ weights).
SAS®	9.4	Statistical analyses
Share Document Management System (SDMS)	1.0	Reporting
WIL Metasys	2.28	In-house developed system used to record and report animal room environmental conditions.
WIL Toxicology Data Management System™ (WTDMS™)	Various	In-house developed system used for collection and reporting of other data.

N/A = not applicable
Note: Version numbers of WTDMS™ programs used for the study are presented in the Study Records (input programs) and Facility Records (release dates).

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

All study-specific raw data, documentation, protocol, and Final Reports from this study were archived at the Testing Facility by no later than the date of Final Report issue unless otherwise specified in the protocol. At least 1 year after issue of the draft report, the Sponsor will be contacted to determine the disposition of materials associated with the study.

Electronic data generated by the Testing Facility were archived as noted above, except that the data collected using Deviation Information Library, DSI PONEMAH software, and Provantis, and reporting files stored on SDMS and M-Files® were archived at the Charles River Laboratories facility location in Wilmington, MA. Electronic data generated using Cardiopulmonary Automated Reporting System and eInfotree were archived at the Charles River facility location in Mattawan.

All raw data, documentation, records, plan (and amendments, if applicable), and the original final report (a copy of the original signed final report will be retained in the archives of the Sponsor) will be retained in the archives of CMIC, Inc. for at least 10 years following the signing of the final report, in accordance with CMIC, Inc. standard operating procedures (SOPs). At least 10 years after signing the final report, the Sponsor will be contacted to determine the final disposition or transfer of the materials. Study samples will be stored at CMIC, Inc. for 6 months. After the 6 months' period, sponsor will be contacted to determine whether to continue storage at CMIC or to destroy the samples or transfer them to another facility. Disposition of residual/retained analytical samples are as described in the table below.

All records, protocol, amendments, reports, analysis data, QC data and other documents generated from Pharmacokinetic Analysis phase were archived at the test site.

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Text Table 19
Disposition of Residual/Retained Samples

Sample Type	Disposition
Dose Formulation Analysis (including backups)	Discarded

8. RESULTS

Proprietary Info

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Withheld pursuant to exemption

Proprietary Info

of the Freedom of Information and Privacy Act

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Redacted by agreement **Contracting Officer's Representative (COR)** **December 22, 2021**
National Institute on Drug Abuse
Division of Therapeutics and Medical Consequences
Redacted by agreement
301 North Stonestreet Ave.
Bethesda, MD 20892

Subject: **SRI International Task Order 01 Letter Report.**
Contract No. HHSN271201800019I
NIDA Reference No. 75N95020F00001, SRI Master Project 100835

Dear Redacted by agreement

This letter report deliverable submission is for NIDA Task Order 04 Interaction Safety Studies in Rats and Dogs. Summaries of the two interaction studies (Redacted by agreement) are listed below.

SRI Study No. Redacted by agreement Evaluation of the Interaction Between Proprietary Info Administered by Oral Gavage and Cocaine Administered Intravenously in Sprague Dawley Rats Effects on Mortality and Convulsions

The objective of this study was to evaluate potential effects on cocaine-induced lethality and convulsions when the test article, Proprietary Info was administered orally prior to intravenous cocaine in male Sprague Dawley rats. This study was conducted in two sessions on consecutive days, with half of the animals in each group being treated on the first day and the remaining untreated rats dosed on the next day at approximately the same time of day. Individual animals were dosed once with either the test article, Proprietary Info (10 or 100 mg/kg) or its vehicle (0.5 w/v% methylcellulose aqueous solution), via oral gavage followed 2 hours later with the interaction article, cocaine (5.6, 10.0 and 17.5 mg/kg) or its vehicle (saline), by intravenous injection via tail vein. Mortality, convulsions and clinical observations were evaluated. All surviving animals were euthanized without necropsy after 4 days.

Proprietary Info

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Proprietary Info

SRI Study No. Redacted by agreement Evaluation of the Interaction Between Proprietary Info Administered Orally and Cocaine Administered Intravenously to Conscious, Radiotelemetry-Instrumented Beagle Dogs

The objective of this study was to evaluate the potential adverse cardiovascular effects that may have resulted when Proprietary Info (test article) and cocaine (interaction article) were administered together to male Beagle dogs. The study was conducted in two phases.

In the first, pharmacokinetics (PK) phase, treatment-naïve Beagle dogs were exposed to increasing levels of Proprietary Info to determine the pharmacokinetics and its tolerability.

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In the second, cardiovascular interaction (CV) phase, the Beagle dogs were implanted with telemetry transmitters and subsequently dosed with combinations of orally (gavage) administered Proprietary Info and intravenously administered cocaine to evaluate if Proprietary Info affected the hemodynamic and cardiac effects of cocaine. Proprietary Info dose levels in the CV phase were informed by the outcome of the PK phase.

For the PK phase, animals received a single dose of Proprietary Info in an ascending dose design at 1, 3, 10, and 30 mg/kg via oral gavage; clinical signs and pharmacokinetic parameters were evaluated. Findings of salivation and wet fur around the mouth were observed at 3 mg/kg; foamy white vomitus and foamy white material present in the cage pan at 10 mg/kg; and salivation, wet fur around the mouth, foamy white/yellow material present in the cage pan, and partly digested food at 30 mg/kg.

For the CV phase, animals received combinations of Proprietary Info or its vehicle (test article) and cocaine or its vehicle (interaction article). The interval between the test and interaction article doses was 1 hour (±5 min). Clinical signs, heart rate, arterial blood pressure (systolic, diastolic, and mean), pulse pressure, body temperature, and ECG waveforms (from which ECG waveform morphologies and the ECG intervals PR, QRS, QT, and heart rate-corrected QT [QTcH and QTcV] were derived) were evaluated.

During the CV phase, a single oral administration of Proprietary Info at 3 and 30 mg/kg in prior to intravenous infusion of cocaine at 0.56 and 1.7 mg/kg resulted in clinical observations of various material in the cage pan, various vomitus, and salivation in all 30 mg/kg Proprietary Info treatments as well as clinical observations of partly digested food at 30 mg/kg Proprietary Info in combination with 0.56 and 1.7 mg/kg cocaine. In addition, 0.56 and 1.7 mg/kg cocaine demonstrated expected pharmacodynamic responses (increased systolic, diastolic, mean arterial pressure, and body temperature), thus validating assay sensitivity to detect changes in hemodynamic and electrophysiologic parameters.

Proprietary Info at 3 mg/kg (in the absence of interaction article) did not result in any biologically relevant changes in cardiovascular, body temperature, or ECG interval durations. Oral Proprietary Info at 30 mg/kg resulted in increased heart rate, systolic, diastolic, and mean arterial blood pressure. There were no changes in body temperature, or ECG interval durations following administration of 30 mg/kg Proprietary Info

Oral Proprietary Info at 3 or 30 mg/kg, in combination with 0.56 or 1.7 mg/kg cocaine, exacerbated the interaction article cardiovascular responses in systolic, diastolic, and mean arterial pressure, but did not result in any biologically relevant changes in heart rate, body temperature, or ECG interval duration.

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Amended Final Report • January 27, 2022

EVALUATION OF THE INTERACTION BETWEEN [Proprietary Info] ADMINISTERED BY ORAL GAVAGE AND COCAINE ADMINISTERED INTRAVENOUSLY IN SPRAGUE DAWLEY RATS: EFFECTS ON MORTALITY AND CONVULSIONS

[Redacted by agreement]

Testing Facility:
SRI International
Biosciences Division
333 Ravenswood Avenue
Menlo Park, CA 94025

SRI Study Number: [Redacted by agreement]
SRI Project Numbers: P25884.100/100621.018.TO04.00.0100

Study Initiation: August 17, 2020

Experimental Work Performed:
Start: August 27, 2020
Finish: October 12, 2020

Study Completion: January 27, 2022

Sponsor:
National Institute on Drug Abuse
Division of Therapeutics and Medical Consequences
[Redacted by agreement]
301 North Stonestreet Ave.
Bethesda, MD 20892
USA

Sponsor's Representative: [Redacted by agreement]

NIDA Contract and TO Number: HHSN271201800019I, TO#004

Uncovered by a White Coat Waste investigation

Evaluation of the Interaction between Proprietary Info **Administered by Oral Gavage and Cocaine Administered Intravenously in Sprague Dawley Rats: Effects on Mortality and Convulsions**
SRI Study No. Redacted by agreement

APPROVAL SIGNATURES

Written By: Redacted by agreement
Redacted by agreement

1/27/2022
Date

Approved By: Redacted by agreement
Redacted by agreement

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SRI Biosciences

SRI International
Biosciences Division
333 Ravenswood Avenue
Menlo Park, CA 94025

Uncovered by a White Coat Waste investigation

Evaluation of the Interaction between Proprietary Info **Administered by Oral Gavage and Cocaine Administered Intravenously in Sprague Dawley Rats: Effects on Mortality and Convulsions**
SRI Study No. Redacted by agreement

SUMMARY OF CHANGES TO THE FINAL REPORT

This amended final report was issued to correct the sequence of report headers within the report body and in the Table of Contents. A citation abbreviation was also added to the table

Proprietary Info

Proprietary Info found on page 12 of this report). This typographical error is also observed in the protocol and study amendment (Appendix G) and has been corrected in the main report.

The study proceeded according to the final protocol amendment and study director direction with no other irregularities noted. All other data results, discussion and overall conclusion of the report remained unchanged.

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APPENDICES

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SUMMARY

The objective of the study was to evaluate potential effects on cocaine-induced lethality and convulsions when test article, Proprietary Info Proprietary Info is administered orally prior to intravenous injection of cocaine, administered as (-)-cocaine HCl, in male Sprague Dawley rats.

This study was conducted in two sessions on consecutive days: Five (5) male rats in each treatment group (60 total) were dosed on the first day (session C). The remaining 60 untreated male rats were dosed on the next day (session D). Dosing on the two treatment days commenced at approximately the same time of day ± 1 hr. Individual animals were dosed once with either the test article, Proprietary Info (10 or 100 mg/kg) or its vehicle (0.5 w/v% methylcellulose aqueous solution), via oral gavage and then, 2 hr later, with the interaction article, cocaine (5.6, 10.0 and 17.5 mg/kg) or its vehicle (saline), by intravenous injection into the tail vein.

Mortality, convulsions and clinical observations were evaluated. All surviving animals were euthanized without necropsy after 4 days. The study results are summarized below.

Proprietary Info

Proprietary Info

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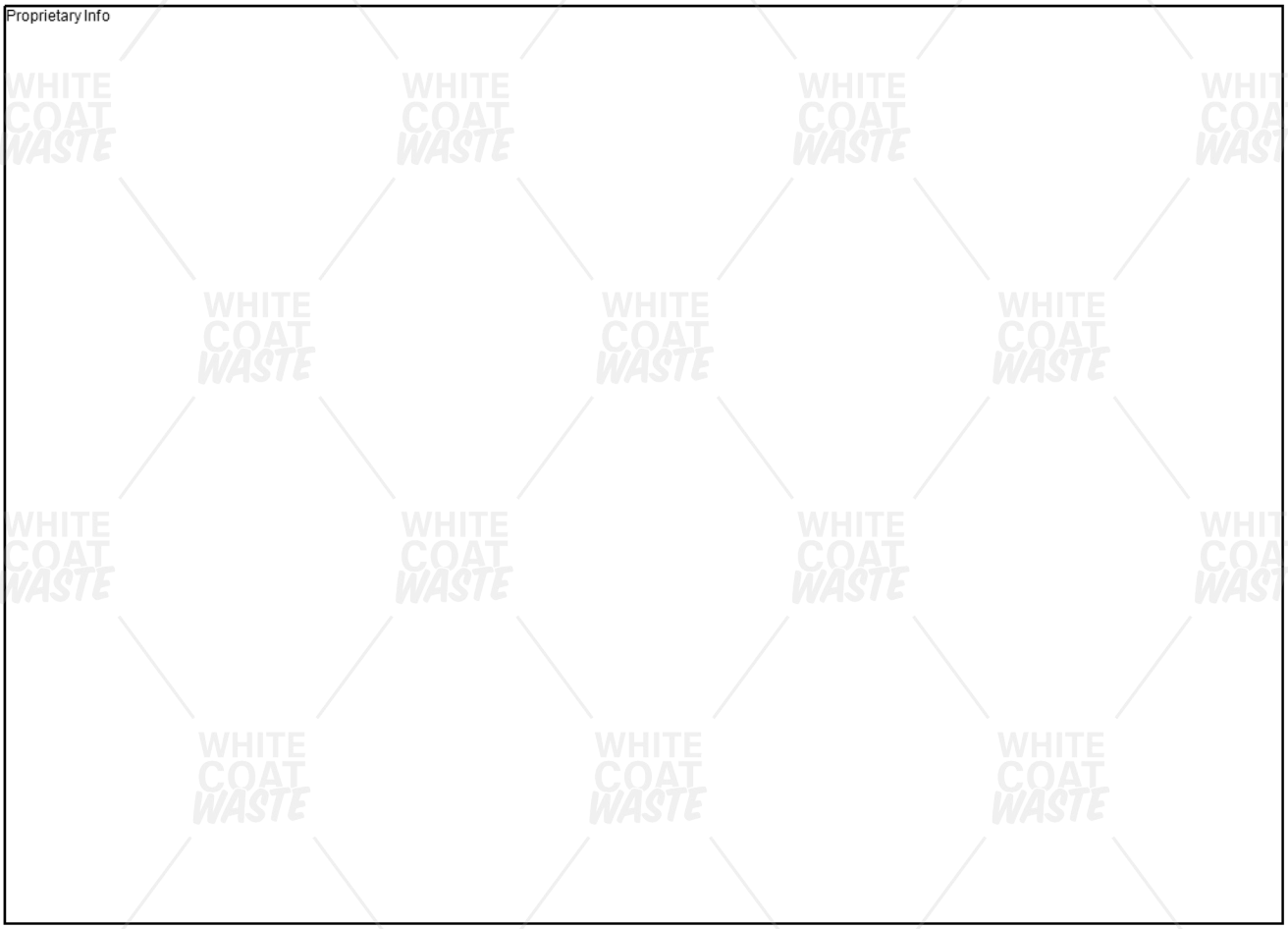

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QUALITY ASSURANCE UNIT

Amended Final Report and Conflict of Interest Statement

SRI's Quality Assurance Unit assures that the study *Evaluation of the Interaction between* Proprietary Info *Administered by Oral Gavage and Cocaine Administered Intravenously in Sprague Dawley Rats: Effects on Mortality and Convulsions*, SRI Study Number Redacted by agreement has been reviewed for adherence to U.S. Food and Drug Administration Good Laboratory Practice Regulations (21 CFR Part 58).

The following inspections were conducted during this study:

Phase Inspected	Date of Inspection	Date Findings Reported to Management/Study Director
Protocol	07-20-20	07-21-20
Protocol Amendment No. 1	08-24-20	08-24-20
Protocol Amendment No. 2	09-15-20	09-15-20
Dose Prep. (Vehicle)	08-20-20	08-20-20
Dose Prep./Analysis (TA)	08-21-20	08-21-20
Dose Prep./Analysis (Cocaine)	08-25-20	08-25-20
Test System, Weights, Dosing, ClinObs	08-27-20	08-27-20
	10-08-20	10-08-20
Raw Data	02-18-21	02-18-21
	03-19-21	03-19-21
Draft Final Report	02-18-21	02-18-21
	03-19-21	03-19-21
	07-07-21	07-08-21
Final Report Verification	07-28-21	07-28-21
Draft Amended Final Report	01-27-22	01-27-22
Amended Final Report Verification	01-27-22	01-27-22

This statement certifies that the personnel listed below participated in the inspections and audit of this study. These personnel have not been involved in the generation or evaluation of the data. Participation by the individuals listed below poses no conflict of interest.

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KEY PERSONNEL

Name	Functional Role
Redacted by agreement	

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Evaluation of the Interaction between Proprietary Info Administered by Oral Gavage and Cocaine Administered Intravenously in Sprague Dawley Rats: Effects on Mortality and Convulsions
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I. PURPOSE OF STUDY

The purpose of this study was to provide data of suitable quality and integrity to support application to the U.S. Food and Drug Administration (FDA) and other regulatory agencies. Therefore, this study was performed in accordance with the U.S. FDA "Good Laboratory Practice for Nonclinical Laboratory Studies" (GLP) as described in 21 CFR Part 58.

II. STUDY OBJECTIVE

The objective of the study was to evaluate potential effects on cocaine-induced lethality and convulsions when the test article, Proprietary Info Proprietary Info Proprietary Info is administered orally prior to intravenous injection of cocaine, administered as (-)-cocaine HCl, to male Sprague Dawley rats.

There were 2 amendments to the Protocol. The original protocol and Amendment #2, which documents all the changes of Amendments #1 and 2, are included in Appendix G.

III. TEST ARTICLE JUSTIFICATION

The test article (TA) in this study, Proprietary Info Proprietary Info Proprietary Info that NIDA is considering as a potential treatment for substance use disorders. Proprietary Info has been tested for safety and tolerability in clinical trials. Single and multiple oral doses of Proprietary Info were well-tolerated. Doses for this study were selected based on previously reported human and rat plasma pharmacokinetic parameters of Proprietary Info as follows:

Proprietary Info

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Plasma Pharmacokinetic Parameters of Proprietary Info Proprietary Info Proprietary Info Proprietary Info

Proprietary Info

%CV: percent coefficient of variance
NA: not applicable
† n = 9 except for R_{acc} (AUC) where n = 8
‡ n = 9 except for $t_{1/2}$ where n = 8

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Exposure Ratios of Proprietary Info Proprietary Info
Proprietary Info

Species/Study Duration (Study Number)	Dose (mg/kg/day)	Sex	C_{max} (ng/mL)		AUC_{24} (ng·h/mL)		Last Dose	
							C_{max}	AUC_{24}
			First Dose	Last Dose	First Dose	Last Dose	Exposure Margin†	
Proprietary Info								

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Proprietary Info Proprietary Info Proprietary Info

Proprietary Info

Proprietary Info

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IV. INTERACTION ARTICLE AND DOSE SELECTION JUSTIFICATION

The interaction article was cocaine. In SRI Study Nos. Proprietary Info intravenous (-)-cocaine HCl doses of 5.6, 10.0, and 17.5 mg/kg caused dose dependent lethality. We employed those cocaine dose levels to facilitate detection of possible potentiating or protective effects of Proprietary Info on cocaine-induced lethality and convulsions.

V. EXPERIMENTAL DESIGN

A. Study Design

There were 12 treatment groups comprised of combinations of Proprietary Info (or its vehicle) and cocaine (or its vehicle). Twenty male rats each were treated with the combinations indicated below. The interval between Proprietary Info (or its vehicle) and cocaine (or its vehicle) was 2 hr (± 10 min).

	Proprietary Info		
Cocaine Vehicle	Group 1 (n = 20♂)	Group 5 (n = 20♂)	Group 9 (n = 20♂)
Cocaine 5.6 mg/kg	Group 2 (n = 20♂)	Group 6 (n = 20♂)	Group 10 (n = 20♂)
Cocaine 10.0 mg/kg	Group 3 (n = 20♂)	Group 7 (n = 20♂)	Group 11 (n = 20♂)
Cocaine 17.5 mg/kg	Group 4 (n = 20♂)	Group 8 (n = 20♂)	Group 12 (n = 20♂)

B. Study Organization

Treatment sessions were staggered due to the large number of animals to be tested. Thus, dosing was conducted initially in two sessions over two consecutive days: Five (5) male rats in each treatment group (60 total) were dosed on the first day (session A). The remaining 60 untreated male rats were dosed on the next day (session B). Dosing on the two treatment days commenced at approximately the same time of day ± 1 hr.

There were significant delays in administration of the interaction article during study session A. As a result, the scientific integrity of the study was compromised because the data from this session could not be compared with that obtained for study session B. Thus, any data obtained during study sessions A and B were excluded from any further analysis and were not included in this report. All data obtained for these two sessions will be maintained with the study records and archived. An additional 120 male rats were added to the study and sessions A and B were repeated as sessions C and D. Animal treatments in sessions C and D followed the same plan as described above for sessions A and B, respectively.

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Evaluation of the Interaction between Proprietary Info Administered by Oral Gavage and Cocaine Administered Intravenously in Sprague Dawley Rats: Effects on Mortality and Convulsions
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Study Session	Treatment Group Number	Test Article (TA)	Proprietary (TA) Dosage (mg/kg)	Proprietary Dose Conc. (mg/ml)	Interaction Article (IA)	Cocaine (IA) Dosage (mg/kg)[a]	Cocaine Dose Conc. (mg/ml)	N
A	1	Vehicle	0	0	Vehicle	0	0.0	5
A	2	Vehicle	0	0	Cocaine	5.6	1.12	5
A	3	Vehicle	0	0	Cocaine	10.0	2.0	5
A	4	Vehicle	0	0	Cocaine	17.5	3.5	5
A	5	Proprietary	10	1	Vehicle	0	0.0	5
A	6	Proprietary	10	1	Cocaine	5.6	1.12	5
A	7	Proprietary	10	1	Cocaine	10.0	2.0	5
A	8	Proprietary	10	1	Cocaine	17.5	3.5	5
A	9	Proprietary	100	10	Vehicle	0	0.0	5
A	10	Proprietary	100	10	Cocaine	5.6	1.12	5
A	11	Proprietary	100	10	Cocaine	10.0	2.0	5
A	12	Proprietary	100	10	Cocaine	17.5	3.5	5
B	12	Proprietary	100	10	Cocaine	17.5	3.5	5
B	11	Proprietary	100	10	Cocaine	10.0	2.0	5
B	10	Proprietary	100	10	Cocaine	5.6	1.12	5
B	9	Proprietary	100	10	Vehicle	0	0.0	5
B	8	Proprietary	10	1	Cocaine	17.5	3.5	5
B	7	Proprietary	10	1	Cocaine	10.0	2.0	5
B	6	Proprietary	10	1	Cocaine	5.6	1.12	5
B	5	Proprietary	10	1	Vehicle	0	0.0	5
B	4	Vehicle	0	0	Cocaine	17.5	3.5	5
B	3	Vehicle	0	0	Cocaine	10.0	2.0	5
B	2	Vehicle	0	0	Cocaine	5.6	1.12	5
B	1	Vehicle	0	0	Vehicle	0	0.0	5
C	1	Vehicle	0	0	Vehicle	0	0.0	5
C	2	Vehicle	0	0	Cocaine	5.6	1.12	5
C	3	Vehicle	0	0	Cocaine	10.0	2.0	5
C	4	Vehicle	0	0	Cocaine	17.5	3.5	5
C	5	Proprietary	10	1	Vehicle	0	0.0	5
C	6	Proprietary	10	1	Cocaine	5.6	1.12	5
C	7	Proprietary	10	1	Cocaine	10.0	2.0	5
C	8	Proprietary	10	1	Cocaine	17.5	3.5	5
C	9	Proprietary	100	10	Vehicle	0	0.0	5
C	10	Proprietary	100	10	Cocaine	5.6	1.12	5
C	11	Proprietary	100	10	Cocaine	10.0	2.0	5
C	12	Proprietary	100	10	Cocaine	17.5	3.5	5
D	12	Proprietary	100	10	Cocaine	17.5	3.5	5
D	11	Proprietary	100	10	Cocaine	10.0	2.0	5
D	10	Proprietary	100	10	Cocaine	5.6	1.12	5
D	9	Proprietary	100	10	Vehicle	0	0.0	5
D	8	Proprietary	10	1	Cocaine	17.5	3.5	5
D	7	Proprietary	10	1	Cocaine	10.0	2.0	5
D	6	Proprietary	10	1	Cocaine	5.6	1.12	5
D	5	Proprietary	10	1	Vehicle	0	0.0	5
D	4	Vehicle	0	0	Cocaine	17.5	3.5	5
D	3	Vehicle	0	0	Cocaine	10.0	2.0	5
D	2	Vehicle	0	0	Cocaine	5.6	1.12	5
D	1	Vehicle	0	0	Vehicle	0	0.0	5
Total 240 Rats								

[a] The interaction article was dosed 2 hr (± 10 min) after the test article dose.

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Species and Strain

Sprague Dawley rat

Route of Administration

Test Article Proprietary Info oral gavage
Interaction Article (Cocaine): intravenous bolus via tail vein delivered over approximately 15 seconds.

Frequency

Test Article: Once
Interaction Article: Once; 2 hr (± 10 min) after the test article or its vehicle

Dosing Volume

Test Article Proprietary Info 10 ml/kg
Interaction Article (Cocaine): 5 ml/kg

Dose volumes were calculated based on the animal's most recent body weight.

Duration of In-Life Phase

Four (4) days for each group

VI. MATERIALS AND METHODS

A. Test and Control Articles

1. Test Article

Proprietary Info Proprietary Info

Supplier

Proprietary Info

Manufacturer

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Lot Number

Proprietary Info

Physical Description

White crystals

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Storage Conditions

Refrigerated, 4.0 to 5.5°C; under desiccation and protected from light as specified by the supplier and agreed to by the NIDA Representative.

The test article storage conditions deviated from the protocol specified conditions of "Room Temperature, 15-30°C" (See Appendix H). However, the storage condition deviation was not expected to have an impact on the study integrity because the test article chromatographic purity indicated that it was stable during the period of use.

Characterization of Test Article

The Sponsor was responsible for characterization and stability of the test article and provided a Certificate of Analysis (CofA) and 36 months stability data to SRI for inclusion in the final report (See Appendix A-1). The raw data generated by the Sponsor in support of this CofA were not verified or maintained by SRI. The test article was used beyond the retest or expiration date, therefore test article chromatographic purity was determined by SRI once on the first dose analysis day, and once after dose preparation was complete to bracket the period of test article use.

2. Interaction Article

(-)-Cocaine HCl

Supplier

Research Triangle Institute (Durham, NC)

Manufacturer

Not provided

Lot Number

14201-101

Physical Description

White solid

Storage Conditions

Room temperature, 20.0 to 25.0°C

Characterization of Interaction Article

The Sponsor was responsible for characterization and stability of the interaction article. A Certificate of Analysis (CofA) was not available, but equivalent (Chemical Data Sheet and NMR Spectrum) documents were provided to SRI for inclusion in the final report (See Appendix A-1). The raw data generated by the Sponsor in support of this CofA's equivalent document, were not verified or maintained by SRI. Because the interaction article was used beyond the retest or expiration date, interaction article chromatographic purity was determined by SRI once before the first dose analysis day,

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and once after dose preparation was complete to ensure the chromatographic purity had not changed during the period of use.

3. Test Article Vehicle

0.5 w/v% Methylcellulose aqueous solution

Vehicle Component #1

Methyl Cellulose, 400 cp

Supplier

Sigma-Aldrich (Saint Louis, MO)

Manufacturer

Sigma-Aldrich (Saint Louis, MO)

Lot Number

SLBP7036V

Physical Description

White to off-white powder

Storage Conditions

Room temperature, 17.0 to 26.5°C

Vehicle Component #2

Sterile Water for Injection

Supplier

Covetrus North America (Visalia, CA)

Manufacturer

Nova-Tech, Inc. (Grand Island, NE)

Lot Number

A2001051

Physical Description

Clear, colorless liquid

Storage Conditions

Room temperature, 19.5 to 26.0°C

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Characterization of Test Article Vehicle

Information on the identity, purity and stability of the article was obtained by recording all of the pertinent information provided on the CofA (See Appendix A-1) .

4. Interaction Article Vehicle

Saline Solution (0.9% Sodium Chloride Injection, USP)

Supplier

Covetrus North America (Visalia, CA)

Manufacturer

Baxter Healthcare Corporation (Deerfield, IL)

Lot Number

Y339957

Physical Description

Clear, colorless liquid

Storage Conditions

Room temperature, 20.0 to 25.0°C

Characterization of Interaction Article Vehicle

Information on the identity, purity and stability of the article was obtained by recording all of the pertinent information provided on the CofA (See Appendix A-1).

5. Preparation of Dose Formulations

Preparation of Proprietary Info (TA) formulation

The Proprietary Info formulation was not corrected for purity because the CofA indicated a purity nearly 100%, and the exact concentration was determined per a qualified reference standard.

To prepare the 0.5% methylcellulose (MC) in sterile water for injection, an appropriate amount of MC was added to ~ 30% volume of preheated (~ 80ºC) sterile water and the mixture was stirred on a magnetic stirrer for 5 to 7 min to thoroughly wet and disperse the solid, then room-temperature sterile water was added to reach the final volume. The solution was stirred for ~ 4 hr then stored at room temperature (20.5 to 24.0ºC) overnight until used for the preparation of dose formulations. The vehicle was observed to be a clear, colorless solution.

Proprietary Info formulations were prepared under yellow light by mixing the appropriate amounts of test article in the vehicle to achieve the target concentrations. The formulations were mixed by sonication for ~ 1 hr and 20 min to 2 hr and 10 min, then formulations were mixed by stir bar on magnetic stirrer for ~ 75 to 90 min. The

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Proprietary Info formulations were homogeneous white suspensions. A stock solution of each concentration was prepared and then aliquoted into amber glass bottles.

Preparation of Cocaine (IA) formulation:

The cocaine formulation was not corrected for salt form and dose levels of cocaine were expressed as the salt.

Cocaine in saline solutions were aseptically prepared under yellow light by combining the appropriate amount of cocaine in saline to achieve target concentrations, then mixing with sterile stir bar on magnetic stirrer for 5 min, and later sonicating for 5 min. The solutions were sterilized by filtration through a Pall Acrodisc® Syringe Filter with 0.2 µm Supor® Membrane (Pall part number 4652), then aliquoted into sterile, amber serum glass bottles. The cocaine solutions in saline were observed to be clear solutions.

Storage of Dose Formulations

Test article dose formulations were stored at room temperature (20.0 - 24.0°C) for up to 8 days until the day of use (based on the dose formulation stability analysis conducted prior to study).

Interaction article and cocaine dose formulations were prepared and stored at room temperature (20.0 - 24.0°C) for up to 8 days until the day of use (based on the dose formulation stability analysis conducted concurrently with the study).

6. Characterization of Dose Formulations

Assays to verify the concentration, homogeneity and stability of the dose formulations were performed by SRI prior to the study (See Attachments A and B). Verification of dose formulation concentration was performed prior to the dose administration and was ±15% of theoretical for the Proprietary Info suspension and ±10% of theoretical for the cocaine solution. The concentration of the formulation did not fall outside the specified range; therefore, the Study Director did not adjust the administration volume. Verification of the dose formulation concentration in the residual interaction article (cocaine) formulations was performed after the dose administration.

7. Test Article Handling

At a minimum, personnel handling the test, interaction and control article formulations wore eye protection, gloves and a protective smock or laboratory coat.

8. Disposition

At the end of the study, any remaining partially used and unused containers of vehicle control, test and interaction articles will be disposed after written concurrence by the NIDA Representative.

Residual dose of the test article Proprietary Info and interaction article (cocaine) formulations were transferred to SRI's Environmental Health & Safety for disposal following the completion of dosing.

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Empty control, test and interaction article containers may be destroyed by SRI on submission of the final report to the NIDA Representative after written concurrence of the NIDA Representative.

See Section VII.B, "Regulatory Compliance", for information about retention of records and study samples.

B. Test System

1. Species

Rat

Strain

Sprague Dawley

Supplier

Proprietary Info

Number of Animals

240 assigned to test.

120 Rats were assigned to sessions A and B but because the scientific integrity of the study was compromised, an additional 120 rats were added to the study and sessions A and B were repeated as sessions C and D.

Sex

Males

Age at First Dose

8-9 weeks

Weight Range at First Dose

292-368 g (See Appendix H)

2. Animal Care

General procedures for animal care and housing were in accordance with the current Association for assessment and Accreditation of Laboratory Animal Care (AAALAC) in recommendations, current requirements stated in the *Guide for the Care and Use of Laboratory Animals* (National Research Council), and current requirements as stated by the U.S. Department of Agriculture through the Animal Welfare Act and Animal Welfare regulations (November 2013).

Quarantine

5 days

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Housing

Single housed

Cages

Microisolator cages with hardwood chip bedding

Bedding

Envigo Teklad Certified Sani-Chips Bedding, #7090C. Bedding was analyzed periodically to ensure that contaminants known to be capable of interfering with the study and are reasonably expected to be present in such bedding are not present at levels that would affect the study. Documentation of bedding analysis is maintained at SRI for reference.

Light Cycle

12 hr light/12 hr dark

Temperature

70-76°F (See Appendix H)

Humidity

48-63%.

Ventilation

At least 10 room volumes per hour, with no recirculation of air

Food

Envigo Teklad Certified Global 18% rodent diet, #2018C, *ad libitum*. Feed was analyzed periodically to ensure that contaminants known to be capable of interfering with the study and are reasonably expected to be present in such feed are not present at levels that would affect the study. Documentation of feed analyses is maintained at SRI for reference. A copy of the lot specific reports provided by the supplier will be maintained in the study records.

Water

Water (purified, reverse osmosis) was provided *ad libitum*. Based on previous reports, no contaminants that could interfere with and affect the results of the study are expected to be present in the water. Copies of annual analysis reports are maintained at SRI for reference.

3. Assignment of Animals to Study Day

3-4 days before initiation of treatment

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Randomization

Animals were randomly assigned to treatment groups via a computerized body weight stratification procedure (Provantis version 10.2.3.1). No animals were excluded based on health, behavior, or inappropriate weight.

Identification

Animals were individually identified by a unique ear punch.

4. Welfare of the Animals

Every effort was made to minimize, if not eliminate, pain and suffering in all animals in this study. Because lethality was an important endpoint to this study, animals were not euthanized in a moribund condition unless in the opinion of the attending veterinarian that the animal was in unacceptable pain, suffering or distress. When considering changes in procedures or removal of animals from study, the Study Director made every effort to protect the scientific validity of the study. Animal enrichment guidelines included placing a nylon bone or other veterinarian approved chew toy for gnawing,

C. Experimental Procedure (In-Life Evaluations)

1. Preparation and Handling of Animals

Animals were transferred from the colony room to the procedure room at least one hour prior to dosing. All rats underwent handling and mock dosing procedures (*i.e.*, being placed into the restraint devices for a brief period of time for iv injection) on 3 occasions in the week prior to the first day of dosing.

2. Dose Administration

Animals were fasted overnight before dose administration. Food was returned ~2 hr after the last animal received its interaction article dose (see Appendix H). The treatment order of dosing on the subsequent day was the opposite of the dosing order on the previous day. Dosing on treatment days commenced at approximately the same time of day ± 1 hr.

Test Article: oral gavage administration 2 hr (± 10 min) prior to interaction article dosing.

Interaction Article: intravenous bolus via tail vein delivered over approximately 15 seconds.

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3. Mortality/Morbidity

Animals were checked at least once daily.

4. Clinical Observations

Observations were limited to those which could be assessed without handling the animals.

Following Test Article: Animals were observed continuously for the first 30 min (± 5 min) following the test article dose and then at 30 min intervals thereafter until the interaction article dose.

Following Interaction Article: Animals were observed continuously for the first 60 min (± 5 min), then once every 30 min for one subsequent hour, then once every 60 min (± 10 min) for two additional hours.

Animals were checked at least once daily on Days 2, 3, and 4. Rats were examined for any altered clinical signs, including stimulation, convulsions, stereotypy, and mortality.

5. Body Weights

Body weights were recorded predose for the purpose of dose calculation and on the 4th respective day after dosing (prior to termination). Body weights were recorded for animals found dead, but these weights were not included in the statistical evaluation (see Appendix H).

D. Necropsy

Interval

On the 4th respective day after dosing (Day 4), all surviving animals were euthanized without necropsy.

Euthanasia

An overdose of sodium pentobarbital was administered via intraperitoneal (ip) injection.

E. Evaluation of Data Parameters

Mean and standard deviation were calculated for body weight data at each evaluation interval. Calculations were performed using Provantis® version 10.2.3.1 and MS Excel 2010. Mortality LD_{50} and convulsion ED_{50} values were calculated in animals treated with cocaine using the MS Excel package.

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Statistical Tests

Body weight data were evaluated by one-way analysis of variance (ANOVA) followed by Dunnett's test (if the ANOVA was significant). All other numeric parameters were evaluated by Student's *t*-test or other appropriate statistical procedures.

Criteria for Null Hypothesis Rejection

$p \leq 0.05$

F. Control of Bias

While evaluating the responses of the animals and conducting the analyses, the technical staff were aware of the treatment history of each animal. Based on the relatively objective endpoints to be examined, bias was not expected to have influenced the results of the study.

VII. REGULATORY COMPLIANCE

A. Good Laboratory Practice Compliance

This study was intended to be submitted to and reviewed by the U.S. FDA or an equivalent regulatory agency, and this study therefore was performed in accordance with the U.S. FDA "Good Laboratory Practice for Nonclinical Laboratory Studies," as described in 21 CFR Part 58, with the following exceptions:

- Receipt and quarantine of animals were performed prior to the approval of the protocol. These activities were conducted according to testing facility SOPs, but because they were conducted before the protocol was signed, they may not be considered by the FDA to have been conducted in compliance with GLP requirements.
- Animal water, bedding, and food analysis were not performed under GLP compliance by the vendors.

B. Retention of Records and Study Samples

The original protocol, amendments, final report, raw data, supporting documents and records specific to this study will be retained and stored by SRI International. All records and materials will be maintained for a period of at least 1 year. At the end of the retention period, the Sponsor will be contacted for instructions regarding disposition of these materials.

VIII. RESULTS

A. Dose Analysis and Stability

Dose Analysis and Stability are presented in Appendices A-2 and A-3.

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Concentration analysis of Proprietary Info showed that the dose concentrations of 1 and 10 mg/ml formulations met the protocol criterion of 100 ± 15 % of the target concentrations. The formulation stability was established prior to study, and the stability results met the acceptance criterion of within 100 ± 10 % of the initial concentration. Homogeneity results of dose formulations (1 and 10 mg/ml) met the protocol requirements of % RSD ≤ 10.0 %. Formulations at a concentration range of 1 - 10 mg/ml (nominal) were stable for at least 15 days at room temperature (21.0 to 25.0°C). Chromatographic purity of the test article was assessed once on the first testing day (07/29/20) and once on the last dose preparation day (09/30/20). Chromatographic purity results met the protocol requirement of within ± 10.0% of the initial purity, indicating that the test article was stable during the study period.

Cocaine

Concentration analysis of the interaction article (cocaine) was tested three times for dose concentration during the study period: 08/25/20 and 10/01/20 for dose verification and the dosing formulation residues on 10/14/20. The dose verification results indicated that the formulations on each dose day had the claimed concentrations (1.12, 2.0 and 3.5 mg/ml). Chromatographic purity of the interaction article was assessed once on the first testing day (8/25/20) and once on the day that the residual formulations were analyzed (10/14/20). Chromatographic purity results met the protocol requirement of within ± 10.0% of the initial purity, indicating that the interaction article was stable during the study period.

B. Mortality/Morbidity and Clinical Observations

Clinical observations before and after cocaine administration are summarized in Table 1A and 1B. Individual clinical observations are presented in Appendix B. Individual mortality and individual time to convulsion or death are presented in Appendices C and D, respectively. Cocaine LD_{50} and cocaine-induced convulsion ED_{50} calculations are presented in Appendix E.

Parameters evaluated during the study included mortality, convulsions and clinical observations. All surviving animals were euthanized without necropsy on Day 4. The mortality and convulsion results are summarized in the table below.

Proprietary Info

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Evaluation of the Interaction between Proprietary Info **Administered by Oral Gavage and Cocaine Administered Intravenously in Sprague Dawley Rats: Effects on Mortality and Convulsions**

SRI Study No. Redacted by agreement

Proprietary Info

Proprietary Info

Uncovered by a White Coat Waste investigation

Evaluation of the Interaction between Proprietary Info **Administered by Oral Gavage and Cocaine Administered Intravenously in Sprague Dawley Rats: Effects on Mortality and Convulsions**

SRI Study No. Redacted by agreement

Proprietary Info

Uncovered by a White Coat Waste investigation

Proprietary Info

C. Body Weights

Body weights are summarized in Table 2. Individual animal body weights are presented in Appendix F.

Treatment with Proprietary Info alone or followed by treatment with cocaine had no effect on body weight.

IX. DISCUSSION AND CONCLUSIONS

Mortality and clinical observations observed in Sprague Dawley rats challenged with intravenous cocaine after Proprietary Info
These data suggest that Proprietary Info Proprietary Info
Proprietary Info

Uncovered by a White Coat Waste investigation

Page 1084 of 1304 to Page 1304 of 1304

Withheld pursuant to exemption

Proprietary Info

of the Freedom of Information and Privacy Act

ORDER FOR SUPPLIES OR SERVICES

PAGE 1 OF PAGES 8

IMPORTANT: Mark all packages and papers with contract and/or order numbers.

1. DATE OF ORDER: 03/25/2020

2. CONTRACT NO. (If any): HHSN271201800019I

3. ORDER NO.: 75N95020F00001

4. REQUISITION/REFERENCE NO.: 5663415

5. ISSUING OFFICE (Address correspondence to):
National Institutes of Health
National Institute on Drug Abuse
Bethesda, MD 20892-7511

6. SHIP TO:

a. NAME OF CONSIGNEE: 6001, NSC, Rockville

b. STREET ADDRESS: Neuroscience Center
6001 Executive Blvd

c. CITY: Rockville

d. STATE: MD

e. ZIP CODE: 20852

7. TO:

a. NAME OF CONTRACTOR: SRI INTERNATIONAL:1110101

b. COMPANY NAME:

c. STREET ADDRESS: 333 RAVENSWOOD AVENUE

d. CITY: MENLO PARK

e. STATE: CA

f. ZIP CODE: 940253493

f. SHIP VIA:

8. TYPE OF ORDER

☐ a. PURCHASE

REFERENCE YOUR: 75N95020F00001 Proposal

Please furnish the following on the terms and conditions specified on both sides of this order and on the attached sheet, if any, including delivery as indicated.

☒ b. DELIVERY

Except for billing instructions on the reverse, this delivery order is subject to instructions contained on this side only of this form and is issued subject to the terms and conditions of the above-numbered contract.

9. ACCOUNTING AND APPROPRIATION DATA: See Schedule

10. REQUISITIONING OFFICE: National Institutes of Health

11. BUSINESS CLASSIFICATION (Check appropriate box(es))

☐ a. SMALL ☒ b. OTHER THAN SMALL ☐ c. DISADVANTAGED ☐ d. WOMEN-OWNED ☐ e. HUBZone

☐ f. SERVICE-DISABLED VETERAN-OWNED ☐ g. WOMEN-OWNED SMALL BUSINESS (WOSB) ELIGIBLE UNDER THE WOSB PROGRAM ☐ h. EDWOSB

12. F.O.B. POINT:

13. PLACE OF

a. INSPECTION: Destination

b. ACCEPTANCE: Destination

14. GOVERNMENT B/L NO.:

15. DELIVER TO F.O.B. POINT ON OR BEFORE (Date): 03/25/2020

16. DISCOUNT TERMS:

17. SCHEDULE (See reverse for Rejections)

ITEM NO. (a)	SUPPLIES OR SERVICES (b)	QUANTITY ORDERED (c)	UNIT (d)	UNIT PRICE (e)	AMOUNT (f)	QUANTITY ACCEPTED (g)
	Purpose: To award Task Order 75N95020F00001 (Interaction Safety Studies in Rats and Dogs) under IDIQ No. HHSN271201800019I for work as described in the attached NIDA Contract Task Order Part I, Section B. Task Description. Continued ...					

SEE BILLING INSTRUCTIONS ON REVERSE

18. SHIPPING POINT:

19. GROSS SHIPPING WEIGHT:

20. INVOICE NO.:

17(h) TOTAL (Cont. pages): $1,113,092.00

21. MAIL INVOICE TO:

a. NAME: Office of Financial Management

b. STREET ADDRESS (or P.O. Box): 2115 E Jefferson St
MSC 8500 Suite 4B 432

c. CITY: Bethesda

d. STATE: MD

e. ZIP CODE: 20892-8500

17(i) GRAND TOTAL: $1,113,092.00

22. UNITED STATES OF AMERICA BY (Signature): Redacted by agreement

AUTHORIZED FOR LOCAL REPRODUCTION
PREVIOUS EDITION NOT USABLE

OPTIONAL FORM 347 (Rev. 2/2012)
Prescribed by GSA/FAR 48 CFR 53.213(f)

Uncovered by a White Coat Waste investigation

IMPORTANT: Mark all packages and papers with contract and/or order numbers.

DATE OF ORDER	CONTRACT NO.	ORDER NO.
03/25/2020	HHSN271201800019I	75N95020F00001

ITEM NO. (a)	SUPPLIES/SERVICES (b)	QUANTITY ORDERED (c)	UNIT (d)	UNIT PRICE (e)	AMOUNT (f)	QUANTITY ACCEPTED (g)
	Task Order Amount: $1,113,092 FY20, Period of Performance: 03/25/2020 to 03/24/2021 Overtime (premium) pay for junior and senior technicians shall not exceed a total of $408.74 under this task order. Admin Office: National Institutes of Health National Institute on Drug Abuse Bethesda, MD 20892-7511 Period of Performance: 03/25/2020 to 03/24/2021					
1	FY20. Task Order No. 75N95020F00001. Period of Performance: March 25, 2020 - March 24, 2021. Delivery To: 4123/JustinDrott Product/Service Code: R499 Product/Service Description: SUPPORT-PROFESSIONAL: OTHER Project Data: 120500.2020.100.HN61 NIDA OD OFC DIR.25103 MGMT&SUPPRT-RESEARCH&DEV.03/02/2020 Accounting Info: 08029320201DAD.2020.01.6100.HN61000000 C.E.00182.406.9999.25103.61000001.9999 .9999.9999 Funded: $1,113,092.00				1,113,092.00	

TOTAL CARRIED FORWARD TO 1ST PAGE (ITEM 17(H)) $1,113,092.00

Uncovered by a White Coat Waste investigation

TASK ORDER (TO)

Contractor: SRI International

T.O. Title: Interaction Safety Studies in Rats and Dogs

Contract No: HHSN271201800019I

T.O. No.: 75N95020F00001
Modification No.: 0

T.O. Originator: NIDA, DTMC, Redacted by agreement

Contracted Task Area(s): 1, 2, 19

T.O. Type: Cost reimbursement (Completion)

PART I. INITIATOR'S REQUEST

A. Period of Performance: 12 Months from Award Date

B. Task Leader Redacted by agreement

C. Activity A

1. Activity Description: Cocaine Interaction Study in Rats (Activity A)

Under Statement of Work (SOW) Task 1, the Contractor shall conduct acute drug interaction studies in rodents. Specific methods to be used in these studies shall be subject to the approval of the Contracting Officer's Representative (COR). Under SOW Task 19, the Contractor shall conduct, as directed by the COR, special in vivo or in vitro toxicology or pharmacokinetic studies, the details of which cannot be specified in advance of the contract award. Examples include modifications of the specified protocols in Tasks 1 to 18, inclusive, to allow for a more specialized evaluation of test articles and development of a protocol with features similar to a clinical situation. The objective of these studies shall be to determine the safety of a test article in combination with cocaine or methamphetamine, an opiate or ethanol. **For purposes of cost estimation only**, assume that a test article to be designated by the COR will be administered by oral gavage and tested in combination with cocaine, the interaction article, administered by intravenous (tail vein) injection, and that the study will be conducted in two sessions. The interval between the test article and cocaine will be 2 hours. Effects on lethality, behavior (to include convulsions) and clinical observations shall be assessed. In this study there would be 12 treatment groups comprised of 10 male rats each. Animals would be observed for treatment effects at intervals for as many as 4 hours on the dosing day and once daily for 3 days thereafter. The animals would be humanely sacrificed approximately 4 days after dosing. All test article and interaction article dosing solutions shall be assayed to verify identity and concentration. NIDA requires a complete report for the study. The study shall be conducted and reported in conformance with Good Laboratory Practice (GLP) guidelines (CFR Title 21 Part 58).

2. Activity A Deliverables:

a. Draft Study Protocol: The Contractor shall provide the NIDA COR with a Draft Study Protocol within 5 business days of the COR's request. The protocol shall comply with GLP guidelines and have a clearly written section that describes appropriate statistical methods for analyzing the experimental data. The protocol shall set forth the experimental and reporting designs in clear detail and be free of ambiguities, typographical errors and contradictions. In-text tables shall be used to supplement explanations provided in the text of the protocol. The draft protocol shall clearly state the anticipated study schedule, including animal arrival, treatment phase, ante-mortem evaluations, disposition of the animals after the study and report preparation. The Contractor shall make NIDA-specified changes to

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Draft Study Protocols and respond within 3 business days of the COR's request. The protocol may be revised multiple times before it is acceptable to the NIDA.

b. Final Study Protocol: The Contractor shall provide the COR with a Final Study Protocol within 2 business days of the COR's authorization to issue the Final Study Protocol.

c. Draft Study Report: The Contractor shall provide the COR with an audited Draft Study Report within 4 weeks after completion of the in-life phase of study. The report shall be free of grammatical and typographical errors, shall be clear, and shall be concise and structured like a manuscript for a reviewed pharmacology or toxicology journal. It shall include a title page, abstract, introduction, methods, results, discussion, summary and bibliography or references. Tables and/or figures shall be included after the bibliography, along with a legend page. As the report may be submitted by NIDA to the FDA, the report shall conform to standards set forth by GLP guidelines. The Contractor shall make NIDA-specified changes to Draft Study Reports within 5 business days of the COR's request. The report may be revised multiple times before it is acceptable to the NIDA.

d. Final Study Report: The Final Study Report shall be issued within 10 business days of the COR's authorization to issue the Final Study Report. It shall conform to GLP Guidelines. The Contractor shall issue one indexed and numerically paginated, continuous from first page to last, bound paper copy of the complete Final Study Report and one each, indexed and numerically paginated, continuous from first page to last, electronic copy of the complete Final Study report as an Adobe PDF file and as a Microsoft Word DOC file. The reports shall include all tables and appendices. The Contractor shall post the electronic versions of the Final Study Report to NIDA's secure server (*e.g.*, Livelink) and, in addition, The Contractor shall post a complete set of all data tables as individual files, to NIDA's secure server. The posted data tables shall be in a format such that the data can be exported or copied (that is, not PDF or an image format) into other computer programs, such as Microsoft Excel and GraphPad Prism, for possible subsequent analysis by NIDA. In addition, the Contractor shall deliver to the NIDA COR the Adobe PDF file, the Microsoft Word DOC file, and the data tables on electronic storage media such as an external hard drive CD, DVD, USB flash drive or SD card, with the Final Study Report.

The Contractor shall ensure that all Study Reports are free from spelling, typographical, or grammatical errors. Study Reports containing such errors shall be deemed unacceptable and returned to the Contractor for correction. A revised report shall be submitted with the date of the revision.

D. Activity B

1. Activity Description: Cardiovascular Safety Interaction Study in Dogs (Activity B)

Under SOW Task 2, the Contractor shall conduct an acute drug interaction study in unrestrained dogs or monkeys. Specific methods to be used in the study shall be subject to the approval of the COR. Under SOW Task 19, the Contractor shall conduct, as directed by the COR, special in vivo or in vitro toxicology or pharmacokinetic studies, the details of which cannot be specified in advance of the contract award. Examples include modifications of the specified protocols in Tasks 1 to 18, inclusive, to allow for a more specialized evaluation of test articles and development of a protocol with features similar to a clinical situation. The objective of this study is to evaluate the cardiovascular safety of a drug (test article) administered via oral gavage and an intravenous drug of abuse (interaction article), for example, cocaine or methamphetamine, in unrestrained freely-moving, telemetered beagle dogs and to collect blood for bioanalysis. **For purposes of cost estimation only**, assume that the study will be conducted in two phases, bioanalytical and interaction, and use 7 dogs (6 on study and 1 spare). For the bioanalytical phase, animals may be treated with up to 4 different dose levels of the test article at one-week intervals. Blood samples will be collected prior to dosing and as many as 8 time points after dosing. The blood samples will be separated by centrifugation and plasma will be collected, divided into 2 aliquots each, and stored frozen for subsequent bioanalysis. The bioanalysis will be will performed by a different laboratory. The NIDA

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COR will provide The Contractor with instructions for sample collection, processing, storage and shipping the aliquots to its designated bioanalytical laboratory. The results of the bioanalysis will be shared with SRI and shall be included in the study report. Telemetry will not be collected in bioanalytical phase. For the interaction phase, each dog will be instrumented with a surgically implanted telemetry unit to monitor and report body temperature, hemodynamic parameters (to include systolic blood pressure, diastolic blood pressure, mean arterial blood pressure and heart rate) and electrocardiograms (to include PR, QRS, RR, QT, QTc, J-Tpeak, and T-peak-Tend intervals) and be implanted with a titanium vascular access port. The general study design of the interaction phase is similar to that in Study Proprietary Info that SRI conducted for NIDA in dogs and monkeys, respectively. In brief, there will be nine treatment sessions. The Contractor will administer combinations of a test article dosed by oral gavage followed by an interaction article dosed by intravenous infusion. The dose levels of the test and the interaction articles, and interval between their doses will be specified by the NIDA COR. The intravenous interaction article and its vehicle will be administered via a surgically implanted vascular access port using a programmable infusion pump carried in a jacket or backpack worn by each animal. Typically, each treatment combination will be separated by at least 5 days. The Contractor shall use infusion pumps that have the capacity to record, store and report the actual time, duration and volume of the interaction article dose. The Contractor shall inspect those data after each treatment session to ensure that animals received the entire dose and include the records in the study report. If there is evidence that an animal did not receive the appropriate dose of interaction article the SRI Study Director shall inform the NIDA COR. The NIDA COR will decide whether the animal that did not receive the appropriate dose will need to be treated again. Telemetry shall be continuously recorded for at least 1.5 h prior to test article administration (to establish the baseline), after the test article is administered (assume 2 hours), and at least 4 hours after the interaction article is administered. Electrocardiograms shall be analyzed by a veterinary cardiologist or a similarly qualified individual. The Contractor shall verify the patency of the vascular access ports and acclimatize the test animals to the jacketing and dosing regimens prior to initiating the treatment sessions.

The order of the study phases may be reversed, or NIDA may decide not to conduct the bioanalysis phase. **For purposes of cost estimation only** assume there will be 6 weeks between the study phases. In view of these considerations The Contractor is asked to provide separate cost estimates for the bioanalytical phase and the interaction phase and for 6 weeks of housing between phases. At the end of the study the animals will be humanely sacrificed, necropsied, and telemetry transmitters recovered for refurbishing and future use. NIDA requires a complete report for the study. The study shall be conducted and reported in conformance with Good Laboratory Practice (GLP) guidelines (CFR Title 21 Part 58).

2. Activity B Deliverables:

a. Draft Study Protocol: The Contractor shall provide the NIDA COR with a Draft Study Protocol within 5 business days of the COR's request. The protocol shall comply with GLP guidelines and have a clearly written section that describes appropriate statistical methods for analyzing the experimental data. The protocol shall set forth the experimental and reporting designs in clear detail and be free of ambiguities, typographical errors and contradictions. In-text tables shall be used to supplement explanations provided in the text of the protocol. The draft protocol shall clearly state the anticipated study schedule, including animal arrival, treatment phase, ante-mortem evaluations, disposition of the animals after the study and report preparation. The Contractor shall make NIDA-specified changes to Draft Study Protocols and respond within 3 business days of the COR's request. The protocol may be revised multiple times before it is acceptable to the NIDA.

b. Final Study Protocol: The Contractor shall provide the COR with a Final Study Protocol within 2 business days of the COR's authorization to issue the Final Study Protocol.

c. Draft Study Report: The Contractor shall provide the COR with an audited Draft Study Report within 12 weeks after completion of the final in-life study. The report shall be free of grammatical and typographical errors, shall be clear, and shall be concise and structured like a manuscript for a

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reviewed pharmacology or toxicology journal. It shall include a title page, abstract, introduction, methods, results, discussion, summary and bibliography or references. Tables and/or figures shall be included after the bibliography, along with a legend page. As the report may be submitted by NIDA to the FDA, the report shall conform to standards set forth by GLP guidelines. The Contractor shall make NIDA-specified changes to Draft Study Reports within 5 business days of the COR's request. The report may be revised multiple times before it is acceptable to the NIDA.

d. Final Study Report: : The Final Study Report shall be issued within 10 business days of the COR's authorization to issue the Final Study Report. It shall conform to GLP Guidelines. The Contractor shall issue one indexed and numerically paginated, continuous from first page to last, bound paper copy of the complete Final Study Report and one each, indexed and numerically paginated, continuous from first page to last, electronic copy of the complete Final Study report as an Adobe PDF file and as a Microsoft Word DOC file. The reports shall include all tables and appendices. The Contractor shall post the electronic versions of the Final Study Report to NIDA's secure server (*e.g.*, Livelink) and, in addition, The Contractor shall post a complete set of all data tables as individual files, to NIDA's secure server. The posted data tables shall be in a format such that the data can be exported or copied (that is, not PDF or an image format) into other computer programs, such as Microsoft Excel and GraphPad Prism, for possible subsequent analysis by NIDA. In addition, the Contractor shall deliver to the NIDA COR the Adobe PDF file, the Microsoft Word DOC file, and the data tables on electronic storage media such as an external hard drive CD, DVD, USB flash drive or SD card, with the Final Study Report.

The Contractor shall ensure that all Study Reports are free from spelling, typographical, or grammatical errors. Study Reports containing such errors shall be deemed unacceptable and returned to the Contractor for correction. A revised report shall be submitted with the date of the revision.

E. Task Order Deliverable: NIDA will not receive value from this Task Order until Final Study Reports of all the prescribed activities have been received so the results therein can be considered holistically. Thus, the contractor shall produce a Comprehensive Final Study Report summarizing the results of the Activities conducted under this Task Order. This report may be issued in the form of a Letter Report to the NIDA COR.

F. Task Order Response Due Date: Sign Part II and email your response to Redacted by agreement at Redacted by agreement by 11/29/2019 (12:00 PM EST).

G. Proposal Instructions: Please complete Part II, "Contractor's Response to TORFP." In addition, SRI will demonstrate its understanding of this task order by describing the work needed to perform it. The Contractor also shall propose and itemize costs for preparation and delivery of all deliverables required under the contract.

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TASK ORDER PROPOSAL RESPONSE

Contractor: SRI International **T.O. Title:** Interaction Safety Studies in Rats and Dogs

Contract No: HHSN271201800019I **T.O Order No:** 75N95020F00001 **Modification No:** 0

T.O. Originator: NIDA, DPMCDA Redacted by agreement

Statement of Work Task Area(s): 1 **Date Prepared:** January 10, 2020

PART II. SRI INTERNATIONAL'S RESPONSE TO TASK ORDER REQUEST FOR PROPOSAL (TORFP)

Under this task order, SRI proposes to perform one interaction safety study in rats and one cardiovascular safety interaction study in dogs in response to the TORFP. The objectives of these studies are to determine the safety of a test article in combination with an abused substance (interaction article). The estimated period of performance is January 15, 2020 through January 14, 2021; however, the actual start date is contingent upon receipt of test articles from the client.

SRI will perform the Activity A, GLP rat interaction study. The Activity B, GLP dog telemetry study, will be outsourced to Charles River Laboratories (CRL) as the hardware and software currently with SRI needs to be updated by the vendors and validated by SRI's QAU before any work can be performed. CRL at Ashland, OH site has the validated equipment and software to perform the NIDA required activities. Due to these reasons and in the interest of cost and time for the NIDA, SRI has decided to outsource this GLP dog telemetry study to the lab that performs this type of study frequently and has previously conducted a NIDA study with similar study design. SRI will serve as the study monitor for the study.

A. Estimated Cost and Effort:

Under this task order SRI proposes an estimated Labor Hours hours of labor and a total cost of Itemized Cost and fee of Itemized Cost for a total cost plus fixed fee of $1,113,092. See Attachment A Estimated Budget for breakdown of each activity cost details. Detailed description of the approach to be used and of the deliverables for Activity A and Activity B:

See Attachment B for a detailed description of approach and deliverables.

APPROVAL TO PROCEED: The Contractor will not exceed the estimated T.O. amount or change the T.O. leader without the prior written approval of the Project Officer and Contracting Officer. The following Accounting and Appropriation Data are applicable to this Task Order.

Uncovered by a White Coat Waste investigation

For the Contractor: Redacted by agreement Date: January 9, 2020

(Signature)

Typed Name: Redacted by agreement

For the Government: _____ Date: _____

Contracting Officer's Representative (COR)

Typed Name: Redacted by agreement Date: _____

Contracting Officer

Uncovered by a White Coat Waste investigation

ORDER FOR SUPPLIES OR SERVICES

PAGE 1 OF PAGES 7

IMPORTANT: Mark all packages and papers with contract and/or order numbers.

1. DATE OF ORDER	09/14/2020
2. CONTRACT NO. *(If any)*	HHSN271201800019I
3. ORDER NO.	75N95020F00002
4. REQUISITION/REFERENCE NO.	5759915

5. ISSUING OFFICE *(Address correspondence to)*
National Institutes of Health
National Institute on Drug Abuse
Bethesda, MD 20892-7511

6. SHIP TO:
a. NAME OF CONSIGNEE
3WFN MSC 6012
b. STREET ADDRESS
3WFN 301 North Stonestreet Ave.6012
c. CITY Bethesda | d. STATE MD | e. ZIP CODE 20892

7. TO:
a. NAME OF CONTRACTOR
SRI INTERNATIONAL:1110101
b. COMPANY NAME
c. STREET ADDRESS
333 RAVENSWOOD AVENUE
d. CITY MENLO PARK | e. STATE CA | f. ZIP CODE 940253493

f. SHIP VIA

8. TYPE OF ORDER
☐ a. PURCHASE
REFERENCE YOUR:
75N95020F00002 Proposal
Please furnish the following on the terms and conditions specified on both sides of this order and on the attached sheet, if any, including delivery as indicated.
☒ b. DELIVERY
Except for billing instructions on the reverse, this delivery order is subject to instructions contained on this side only of this form and is issued subject to the terms and conditions of the above-numbered contract.

9. ACCOUNTING AND APPROPRIATION DATA
See Schedule

10. REQUISITIONING OFFICE
National Institutes of Health

11. BUSINESS CLASSIFICATION *(Check appropriate box(es))*
☐ a. SMALL ☒ b. OTHER THAN SMALL ☐ c. DISADVANTAGED ☐ d. WOMEN-OWNED ☐ e. HUBZone
☐ f. SERVICE-DISABLED VETERAN-OWNED ☐ g. WOMEN-OWNED SMALL BUSINESS (WOSB) ELIGIBLE UNDER THE WOSB PROGRAM ☐ h. EDWOSB

12. F.O.B. POINT

13. PLACE OF		14. GOVERNMENT B/L NO.	15. DELIVER TO F.O.B. POINT ON OR BEFORE *(Date)*	16. DISCOUNT TERMS
a. INSPECTION	b. ACCEPTANCE			
Destination	Destination		07/23/2020	Net 30

17. SCHEDULE ***(See reverse for Rejections)***

ITEM NO. (a)	SUPPLIES OR SERVICES (b)	QUANTITY ORDERED (c)	UNIT (d)	UNIT PRICE (e)	AMOUNT (f)	QUANTITY ACCEPTED (g)
	Purpose: To award Task Order 75N95020F00002 Proprietary Info Proprietary Info under IDIQ No. HHSN271201800019I for work as described in the attached NIDA Contract Task Order Part I, Section B. Task Description. Continued ...					

SEE BILLING INSTRUCTIONS ON REVERSE

18. SHIPPING POINT	19. GROSS SHIPPING WEIGHT	20. INVOICE NO.	17(h) TOTAL *(Cont. pages)*
			$1,256,044.00

21. MAIL INVOICE TO:
a. NAME Office of Financial Management
b. STREET ADDRESS (or P.O. Box) 2115 E Jefferson St MSC 8500 Suite 4B 432
c. CITY Bethesda | d. STATE MD | e. ZIP CODE 20892-8500

17(i) GRAND TOTAL $1,256,044.00

22. UNITED STATES OF AMERICA BY *(Signature)* Redacted by agreement

AUTHORIZED FOR LOCAL REPRODUCTION
PREVIOUS EDITION NOT USABLE

OPTIONAL FORM 347 (Rev. 2/2012)
Prescribed by GSA/FAR 48 CFR 53.213(f)

Uncovered by a White Coat Waste investigation

IMPORTANT: Mark all packages and papers with contract and/or order numbers.

DATE OF ORDER	CONTRACT NO.	ORDER NO.
09/14/2020	HHSN271201800019I	75N95020F00002

ITEM NO. (a)	SUPPLIES/SERVICES (b)	QUANTITY ORDERED (c)	UNIT (d)	UNIT PRICE (e)	AMOUNT (f)	QUANTITY ACCEPTED (g)
	Task Order Amount: $1,256,044 FY20, Period of Performance 09/14/2020 to 09/13/2020 Overtime (premium) pay for junior and senior technicians shall not exceed a total of $441.74 under this task order. Admin Office: National Institutes of Health National Institute on Drug Abuse Bethesda, MD 20892-7511 Period of Performance: 09/14/2020 to 09/13/2021					
1	FY20. Task Order No. 75N95020F00002. Period of Performance: September 14, 2020 to September 13, 2021 Delivery To: 4123/JustinDrott Product/Service Code: R499 Product/Service Description: SUPPORT-PROFESSIONAL: OTHER Project Data: 120500.2020.100.HN61 NIDA OD OFC DIR.25505 RESEARCH AND DEVELOPMENT.07/23/2020 Accounting Info: 08029320201DAD.2020.01.6100.HN61000000 C.E.00182.406.9999.25505.61000001.9999 .9999.9999 Funded: $1,256,044.00				1,256,044.00	

TOTAL CARRIED FORWARD TO 1ST PAGE (ITEM 17(H)) $1,256,044.00

Uncovered by a White Coat Waste investigation

TASK ORDER (TO)

Contractor: SRI International

T.O. Title: Proprietary Info

Contract No: HHSN271201800019I

T.O. No.: 75N95020F00002

T.O. Originator: NIDA, DTMC, Nathan M. Appel, Ph.D.

Contracted Task Area(s): 1, 2, 19

T.O. Type: Cost Reimbursement (Completion)

PART I. INITIATOR'S REQUEST

A. Period of Performance: 12 months from effective date of award.

B. Task Leader: Redacted by agreement

C. Activity A

D. Activity Description: Proprietary Info

Proprietary Info

E. Activity A Deliverables:

a. Draft Study Protocol: The Contractor shall provide the NIDA COR with a Draft Study Protocol within 5 business days of the COR's request. The protocol shall comply with GLP guidelines and have a clearly written section that describes appropriate statistical methods for analyzing the experimental data. The protocol shall set forth the experimental and reporting designs in clear detail and be free of ambiguities, typographical errors and contradictions. In-text tables shall be used to supplement explanations provided in the text of the protocol. The draft protocol shall clearly state the anticipated study schedule, including animal arrival, treatment phase, ante-mortem evaluations, disposition of the animals after the study and report preparation. The Contractor shall make NIDA-specified changes to Draft Study Protocols and respond within 3 business days of the COR's request. The protocol may

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be revised multiple times before it is acceptable to the NIDA.

b. Final Study Protocol: The Contractor shall provide the COR with a Final Study Protocol within 2 business days of the COR's authorization to issue the Final Study Protocol.

c. Draft Study Report: The Contractor shall provide the COR with an audited Draft Study Report within 4 weeks after completion of the in-life phase of study. The report shall be free of grammatical and typographical errors, shall be clear, and shall be concise and structured like a manuscript for a reviewed pharmacology or toxicology journal. It shall include a title page, abstract, introduction, methods, results, discussion, summary and bibliography or references. Tables and/or figures shall be included after the bibliography, along with a legend page. As the report may be submitted by NIDA to the FDA, the report shall conform to standards set forth by GLP guidelines. The Contractor shall make NIDA-specified changes to Draft Study Reports within 5 business days of the COR's request. The report may be revised multiple times before it is acceptable to the NIDA.

d. Final Study Report: The Final Study Report shall be issued within 10 business days of the COR's authorization to issue the Final Study Report. It shall conform to GLP Guidelines. The Contractor shall issue one indexed and numerically paginated, continuous from first page to last, bound paper copy of the complete Final Study Report and one each, indexed and numerically paginated, continuous from first page to last, electronic copy of the complete Final Study report as an Adobe PDF file and as a Microsoft Word DOC file. The reports shall include all tables and appendices. The Contractor shall post the electronic versions of the Final Study Report to NIDA's secure server (*e.g.*, Livelink) and, in addition, The Contractor shall post a complete set of all data tables as individual files, to NIDA's secure server. The posted data tables shall be in a format such that the data can be exported or copied (that is, not PDF or an image format) into other computer programs, such as Microsoft Excel and GraphPad Prism, for possible subsequent analysis by NIDA. In addition, the Contractor shall deliver to the NIDA COR the Adobe PDF file, the Microsoft Word DOC file, and the data tables on electronic storage media such as an external hard drive, USB flash drive, or SD card with the Final Study Report.

The Contractor shall ensure that all Study Reports are free from spelling, typographical, or grammatical errors. Study Reports containing such errors shall be deemed unacceptable and returned to the Contractor for correction. A revised report shall be submitted with the date of the revision.

D. Activity B

1. Activity Description: Proprietary Info

Proprietary Info

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Proprietary Info

2. Activity B Deliverables:

a. Draft Study Protocol: The Contractor shall provide the NIDA COR with a Draft Study Protocol within 5 business days of the COR's request. The protocol shall comply with GLP guidelines and have a clearly written section that describes appropriate statistical methods for analyzing the experimental data. The protocol shall set forth the experimental and reporting designs in clear detail and be free of ambiguities, typographical errors and contradictions. In-text tables and time-course graphs shall be used to supplement explanations provided in the text of the protocol. The draft protocol shall clearly state the anticipated study schedule, including animal arrival, treatment phase, ante-mortem evaluations, disposition of the animals after the study and report preparation. The Contractor shall make NIDA-specified changes to Draft Study Protocols and respond within 3 business days of the COR's request. The protocol may be revised multiple times before it is acceptable to the NIDA.

b. Final Study Protocol: The Contractor shall provide the COR with a Final Study Protocol within 2 business days of the COR's authorization to issue the Final Study Protocol.

c. Draft Study Report: The Contractor shall provide the COR with an audited Draft Study Report within 12 weeks after completion of the final in-life study. The report shall be free of grammatical and typographical errors, shall be clear, and shall be concise and structured like a manuscript for a

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reviewed pharmacology or toxicology journal. It shall include a title page, abstract, introduction, methods, results, discussion, summary and bibliography or references. Tables and/or figures shall be included after the bibliography, along with a legend page. As the report may be submitted by NIDA to the FDA, the report shall conform to standards set forth by GLP guidelines. The Contractor shall make NIDA-specified changes to Draft Study Reports within 5 business days of the COR's request. The report may be revised multiple times before it is acceptable to the NIDA.

d. Final Study Report: : The Final Study Report shall be issued within 10 business days of the COR's authorization to issue the Final Study Report. It shall conform to GLP Guidelines. The Contractor shall issue one indexed and numerically paginated, continuous from first page to last, bound paper copy of the complete Final Study Report and one each, indexed and numerically paginated, continuous from first page to last, electronic copy of the complete Final Study report as an Adobe PDF file and as a Microsoft Word DOC file. The reports shall include all tables and appendices. The Contractor shall post the electronic versions of the Final Study Report to NIDA's secure server (*e.g.*, Livelink) and, in addition, The Contractor shall post a complete set of all data tables as individual files, to NIDA's secure server. The posted data tables shall be in a format such that the data can be exported or copied (that is, not PDF or an image format) into other computer programs, such as Microsoft Excel and GraphPad Prism, for possible subsequent analysis by NIDA. In addition, the Contractor shall deliver to the NIDA COR the Adobe PDF file, the Microsoft Word DOC file, and the data tables on electronic storage media such as an external hard drive, USB flash drive or SD card, with the Final Study Report.

The Contractor shall ensure that all Study Reports are free from spelling, typographical, or grammatical errors. Study Reports containing such errors shall be deemed unacceptable and returned to the Contractor for correction. A revised report shall be submitted with the date of the revision.

E. Task Order Deliverable: NIDA will not receive value from this Task Order until Final Study Reports of all the prescribed activities have been received so the results therein can be considered holistically. Thus, the contractor shall produce a Comprehensive Final Study Report summarizing the results of the Activities conducted under this Task Order. This report may be issued in the form of a Letter Report to the NIDA COR.

F. Task Order Response Due Date: Sign Part II and email your response to Redacted by agreement at Redacted by agreement by 03/20/2020 at 3:00 PM EST.

G. Proposal Instructions: Please complete Part II, "Contractor's Response to TORFP." In addition, The Contractor shall demonstrate its understanding of this task order by describing the work needed to perform it. The Contractor also shall propose and itemize costs for preparation and delivery of all deliverables required under the contract.

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TASK ORDER PROPOSAL RESPONSE

Contractor: SRI International **T.O. Title:** Proprietary Info

Contract No: HHSN271201800019I **T.O Order No:** 75N95020F00002 **Modification No:** 1

T.O. Originator: NIDA, DPMCDA Redacted by agreement

Statement of Work Task Area(s): 1 **Date Prepared:** July 17, 2020

PART II. SRI INTERNATIONAL'S RESPONSE TO TASK ORDER REQUEST FOR PROPOSAL (TORFP)

Proprietary Info

A. Estimated Cost and Effort:

Under this task order SRI proposes an estimated Labor Hours hours of labor and a total cost-plus fixed fee of $1,256,044. See Attachment A Estimated Budget for breakdown of each activity cost details. Detailed description of the approach to be used and of the deliverables for Activity A and Activity B:

See Attachment B for a detailed description of approach and deliverables.

APPROVAL TO PROCEED: The Contractor will not exceed the estimated T.O. amount or change the T.O. leader without the prior written approval of the Project Officer and Contracting Officer. The following Accounting and Appropriation Data are applicable to this Task Order.

For the Contractor: Redacted by agreement Date: July 17, 2020

(Signature)

Typed Name: Redacted by agreement

For the Government: Redacted by agreement

Typed Name:

Contracting Officer

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