CONFIDENTIAL

FINAL REPORT

A Maximum Tolerated Dose Study of SOPH-110S Administered to Rats via Intravenous Bolus Injection

Attentive Science Study No.

1124-8751

Sponsor:

Sophrosyne Pharmaceuticals Limited
540 W Madison St, Suite 2500
Chicago, IL 60661, USA

Test Facility:

Attentive Science
17745 Metcalf Avenue
Building #4
Stilwell, KS 66085, USA

REPORT APPROVAL

Tabitha Frye

Tabitha Frye
Study Director
Attentive Science

21MAR25
Date

The study described in this report was peer reviewed and approved by the undersigned:

Phil Atterson, MS
Test Facility Management
Attentive Science

20 Mar 2025
Date

COMPLIANCE STATEMENT

This study was conducted according to the principles of Good Laboratory Practice (GLP), but was not audited for compliance and is therefore considered non-GLP. The procedures described in the protocol were performed in accordance with the respective Test Facility and/or Test Site Standard Operating Procedures (SOPs).

Tabitha Frye
Study Director
Attentive Science

26 MAR 25
Date

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1 SUMMARY

The objective of this study were to evaluate the tolerability of SOPH-110S when administered once by intravenous bolus to rats.

The following table presents the study group arrangement:

Group	Treatment	Dose Level (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	Number of Animals	
					Males	Females
1	SOPH-110S	30	6	5	3	3
2	SOPH-110S	100	25	4	3	3
3	SOPH-110S	140	35	4	3	3
4	SOPH-110S	200	50	4	1	1

A single dose of SOPH-110S was administered to all groups in an escalating dose design at dose levels of 30, 100, 140 and 200 mg/kg.

The following parameters were evaluated: mortality, clinical observations, body weights, food consumption and macroscopic observations.

Administration of SOPH-110S at a dose of 200 mg/kg resulted in mortality in a single male. There were no mortalities at doses of 30, 100, or 140 mg/kg. At doses > 30 mg/kg, SOPH-110S-related clinical observations included hypoactivity, salivation, squinting, and increased respirations. There were no test article-related effects on body weight, food consumption or macroscopic observations. Based on these findings, the maximum tolerated dose (MTD) was considered to be 140 mg/kg in both males and females.

2 RESPONSIBLE PERSONNEL

2.1 Sponsor Personnel

Study Monitor	Andrew Fowlie, PhD Independent Consultant Stonehaven Nonclinical Consulting LLC 3 Bridlepath Road West Simsbury, CT 06092 Phone: (978) 560-9885 E-mail: afowlie@stonehavennonclinical.com

2.2 Test Facility Personnel

Study Director	Tabitha Frye Research Scientist I Phone: (913) 308-0700 ext 5010 E-mail: tabitha@attentivescience.com
Test Facility Management	Phil Atterson, MS Chief Operating Officer Phone: (913) 308-0700 ext 5021 E-mail: phil@attentivescience.com

3 OBJECTIVE

The objective of this study were to evaluate the tolerability of SOPH-110S when administered once by i.v. bolus to rats.

4 STUDY SCHEDULE

Study Initiation Date:	29 OCT 2024
Experimental Starting Date (Animal Transfer):	30 OCT 2024
Dose Initiation:	Group 1: 30 OCT 2024 Group 2: 01 NOV 2024 Group 3: 05 NOV 2024 Group 4: 07 NOV 2024
Euthanasia:	Group 1: 01 NOV 2024 Group 2: 04 NOV 2024 Group 3: 07 NOV 2024 Group 4: 11 NOV 2024
Experimental Completion Date:	11 NOV 2024

5 EXPERIMENTAL DESIGN

Group	Treatment	Dose Level (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	Number of Animals	
					Males	Females
1	SOPH-110S	30	6	5	3	3
2	SOPH-110S	100	25	4	3	3
3	SOPH-110S	140	35	4	3	3
4	SOPH-110S	200	50	4	1	1

5.1 Justification of Dose, Route, Species and Animal Number

The design of this study was based on the study objective(s). The Sponsor affirms this study did not unnecessarily duplicate previous experiments.

The route of administration was intravenous (bolus) to maximize the systemic exposure of the test article.

In a previous study, a single intravenous (bolus) was tolerated at 10 mg/kg. Therefore, the first dose was set at 30 mg/kg. Dose selection for Groups 2, 3, and 4 were based on the outcome of the previous dose(s).

A May 2023 literature search of the Pub Med and Google Scholar for alternatives to animal testing was completed. No acceptable *in vitro* or non-animal alternatives for providing essential information to extrapolate the effects of test articles from animal to human were identified. Relevant keywords were used in the search. The literature search is on file at the Test Facility.

As a result, studies in laboratory animals provide the best available basis for extrapolation to humans and are required to support regulatory submissions.[1][2] The rat was chosen as the animal model for this study as it is an accepted rodent species for preclinical toxicity testing by regulatory agencies for which historical control data are available.

This study was designed such that it did not require an unnecessary number of animals to accomplish its objectives. Males and females were chosen to determine if there were sex-related differences in exposure and/or general toxicity. The total number of animals used in this study is considered to be the minimum required to properly characterize the effects of the test article and is generally accepted as the standard for the assessment of toxicology.

6 TEST ARTICLE AND VEHICLE INFORMATION

6.1 Test Article

Identification	SOPH-110S
Batch/Lot Number	L-23-0011-S-8015
Purity or Correction Factor	No correction factor was used for preparation of the test article formulations.
Expiration/ Retest Date	31 MAR 2025
Physical Description	White Solid
Storage Conditions	Stored at -15 to -30 ºC, inert atmosphere (N_2), in well-sealed amber glass vial with desiccant
Sample Retention	No retention samples were collected as part of this non-GLP study.
Disposition	Any remaining test article was maintained for a subsequent study.

6.2 Vehicle

Identification	Phosphate Buffered Saline, pH 6.0 ± 0.1
Component Batch/Lot Number	Phosephate Bufferd Saline Supplier: Fisher Lot Number: BP2438/241827 Expiration Date: Jul 2027
Component Storage Conditions	Stored at 15–25 °C

6.3 Safety Precautions

A Safety Data Sheet (SDS) was provided by the Sponsor. Routine safety precautions were followed. Appropriate safety equipment was worn by individuals working with neat test article or formulations.

7 TEST SYSTEM

Species	Rat
Strain/Breed	Sprague Dawley
Source	Charles River
Number of Animals	Assigned to Study: 10/sex Transferred from Colony: 14/sex After the end of the replacement period, animals not utilized on study were assigned to the Attentive Science stock colony.
Approximate Age and Weight	Age at Receipt: 10–11 weeks Weight on Dosing: 462.7–385.9g (males) or 300.8–264.8g (females) Females were nulliparous and nonpregnant.

7.1 Animal Receipt, Randomization, and Acclimation

Each animal was inspected by qualified personnel upon receipt. Animals judged to be in good health were placed immediately in acclimation in accordance with Attentive Science SOP.

Animals judged to be in good health were randomized into cages upon arrival. Animals were placed into appropriate cages in a stepwise fashion (first animal was placed in the first Group 1 cage, second animal was placed in the first Group 2 cage, etc.). Cages were arbitrarily assigned group designations prior to dosing.

7.2 Animal Identification

Each animal was identified using a subcutaneously-implanted electronic chip or other alternate unique identifier.

7.3 Animal Housing and Environmental Conditions

All animals were group housed by sex and dose group in solid bottom cages with appropriate bedding material.

Items were provided for environmental enrichment and/or to aid in maintaining the animals' oral health, beginning during the acclimation/pre-treatment period and continuing throughout the course of the study.

Animal rooms were monitored for appropriate temperature, relative humidity, light cycle and air changes for the test system in use, as per Attentive Science SOPs.

The animal room and equipment were cleaned at regular intervals throughout the study, as per facility SOPs. Equipment and bedding changes were recorded in the facility records. Contaminant-free contact bedding was used and the results of an example lot are on file at Attentive Science.

7.4 Diet and Drinking Water

Tap water from the municipal water department was available *ad libitum*. Water supplying the laboratory was analyzed for contaminants by the municipal water department and an independent laboratory.

A certified laboratory diet (PMI Nutrition International, LLC Certified Rodent LabDiet® 5002) was offered *ad libitum* during the study. Each lot utilized was identified and recorded. Each lot of diet was analyzed for contaminants by the manufacturer.

No contaminants were present in the water or certified diet at concentrations that would interfere with the purpose or conduct of the study. The results of the water and certified diet analyses are maintained in the facility records.

7.5 Animal Welfare

In conjunction with the 3Rs of animal research, procedures involving the care and use of animals in this study were reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) prior to conduct. This study complied with all applicable sections of the Final Rules of the Animal Welfare Act regulations (9 CFR).

Attentive is fully accredited by AAALAC International and is registered with the United States Department of Agriculture (USDA).

All procedures involving animals were conducted humanely and performed by or under the direction of trained or experienced personnel. The study was not initiated until the protocol was reviewed and approved by the IACUC of Attentive. The Veterinarian was consulted in the overall study design for this study type. This study did not unnecessarily duplicate previous studies.

8 DOSE FORMULATION AND ANALYSIS

8.1 Preparation of Dosing Formulations

Formulation	Frequency of Preparation	Storage Conditions	Disposition
Vehicle	As needed	Stored at 15-25 °C	Discarded after completion
Test Article	On the day of dosing	Stored at 2–8 °C, when not in use	Discarded after completion

Dosing formulations were prepared under asceptic conditions and/or were sterile filtered prior to use.

9 IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS

9.1 Administration of Dose Formulations

Frequency and Duration	Once
Method of Administration	Intravenous Injection: Each dose was administered via bolus injection to the tail vein
Adjustment of Dose Volume	Individual doses were calculated based upon the most recent individual body weights.
Comments	The first day of dosing was designated as Day 1.

9.2 Animal Observations

9.2.1 Mortality Checks

Starting on Day 1, all animals were observed for mortality/moribundity at least twice daily with the exception of day of termination and non-dosing days that fall on weekends and holidays. When mortality checks were performed twice daily, there was a minimum of 4 hours between checks; once in the morning (am) and once in the afternoon (pm).

9.2.2 Clinical Observations

At minimum, all study animals were observed as follows:

- 0.5–1 hours post dosing
- At least once daily on non-dosing days
- Unscheduled observations, if noted

The absence or presence of findings was recorded for individual animals. The presence of findings noted outside the above-specified observation periods (unscheduled observations) was also recorded.

9.3 Individual Body Weights

At minimum, all main study had body weights recorded as follows:

- Study Day 1 (prior to dosing)
- Daily until day of euthanasia (inclusive)

9.4 Food Consumption

At minimum, food was weighed and recorded for all study animals as follows:

- Daily, beginning on Day 1

Food consumption data was collected per cage for cohoused animals. For reporting purposes, cohoused food consumption data was divided by the number of animals per cage and reported as individual animal data.

10 TERMINAL PROCEDURES

10.1 Animals Euthanized in Extremis

Moribund animals were euthanized and necropsied as soon as possible. Animals found dead were necropsied as soon as possible to reduce possible tissue loss due to autolysis.

Animals euthanized *in extremis* were euthanized by CO_2 inhalation followed by exsanguination. If possible, final collections as outlined in the table below were attempted based on the clinical condition of the animal.

	Unscheduled Animal Euthanasia	Animals Found Dead
Detailed Observations	X	-
Body Weights	X	-
Macroscopic Examination	X	X

X = Activity carried out; - = Not applicable

[a] Animals received an abbreviated necropsy in an attempt to determine the cause of death.

10.2 Scheduled Euthanasia

Study Animals	All surviving study animals were euthanized according to Attentive SOPs, a gross necropsy was performed, and then discarded without tissue collection.
Method of Euthanasia	Animals euthanized at terminal necropsy were euthanized by CO_2 inhalation followed by exsanguination.

10.2.1 Macroscopic Examination

A complete necropsy was conducted at each scheduled necropsy and included examination of the external surface, all orifices and the cranial, thoracic, abdominal and pelvic cavities, including viscera.

11 STATISTICAL METHODS

Statistical analyses were not performed due to the absence of a concurrent control group. However, means and standard deviations were calculated, as appropriate.

12 DATA CAPTURE

In-life Data Collection:	Provantis (version 10.5.3 and 11.0.1 or higher)
Room Environment:	HOBO monitoring system
Cold Storage Locations:	InTemp monitoring system

13 WORK PRODUCT

Sponsor has title to all documentation records, raw data, slides, specimens, or other work product generated during the performance of the study.

All work product including: raw paper data, pertinent electronic storage media and specimens, will be retained at no charge in the Attentive Science archives for a period of 12 months following issuance of the final report. Thereafter, Attentive Science may extend the archiving period or ship work product to an archive facility at the request of the Sponsor.

Any work product shipped by Attentive Science to another location were appropriately packaged and addressed as defined by Attentive Science SOPs and delivered to a common carrier for shipment. Attentive Science is not responsible for shipment following delivery to the common carrier.

14 SEND DATA SET

Unless otherwise specified, SEND-compliant data must be provided for inclusion within the SEND data set package from each Principal Investigator.

A submission-ready SEND data set will be prepared from the unaudited data set and provided to the Sponsor following report finalization. The SEND data set is not audited.

15 RESULTS

15.1 Mortality

(Individual Data: Table 1)

There was single test article-related death. Animal 4003 (male; 200 mg/kg) male was found dead on Day 5 following dose administration.

All other animals survived to their scheduled necropsy.

15.2 Clinical Observations

(Summary Data: Table 2; Individual Data: Table 6)

There were test article-related clinical observations noted.

Test article-related observations seen in >30 mg/kg males and/or females included hypoacitivty, salivation, squinting, and increased respiration.

Other observations noted included barbering (foot), hair thinning (foot), hypersensitive, staining (eyes, nose/snout, back) and discoloration (ears) but were not considered test article-related as they were transient and/or were isolated to single instances.

15.3 Body weights

(Summary Data: Table 3; Individual Data: Table 7)

There were no SOPH-110S-related effects on body weights during the duration of this study.

15.4 Food Consumption

(Summary Data: Table 4; Individual Data: Table 8)

There were no test article-related effects on food consumption during the duration of this study.

15.5 Terminal Procedures

15.5.1 Macroscopic Examination

(Summary: Table 5; Individual: Table 9)

Macroscopic observations noted in a single 100 mg/kg female included dark discorloration in the ovaries and enlarged pituitary glands. Additionally, enlarged kidneys were also noted in a single 200 mg/kg male. These were not considered test article-related due to a single occurrence.

All other animals presented no visible lesions.

16 CONCLUSION

Administration of SOPH-110S at a dose of 200 mg/kg resulted in mortality in a single male. There were no mortalities at doses of 30, 100, or 140 mg/kg. At doses > 30 mg/kg, SOPH-110S-related clinical observations included hypoactivity, salivation, squinting, and increased respirations. There were no test article-related effects on body weight, food consumption or macroscopic observations. Based on these findings, the maximum tolerated dose (MTD) was considered to be 140 mg/kg in both males and females.

17 REFERENCES

1. Guidance for Industry. Safety Testing of Drug Metabolites. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, *Pharmacology and Toxicology*. March 2020.

2. Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals M3(R2). *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline,* January 2010.

3. *Guide for the Care and Use of Laboratory Animals*; National Research Council, National Academies Press: Washington, DC, 2011.

18 ABBREVIATIONS

Note: General abbreviations that may have been used throughout the report and associated tables include, but are not limited to, the following:

bpm	Beats per minute
BID	Twice daily dosing
Conc.	Concentration
CRO	Contract Research Organization
e.g.	For example
FDA	Food and Drug Administration
g or G	Grams or gravitational acceleration
GLP	Good Laboratory Practice
h	Hour
ID	Identification
i.e.	that is
kg	Kilogram
M	Male
mg	Milligram
mL	Milliliter
Min	Minute
ms	Milliseconds
MTD	Maximum tolerated dose
No. or #	Number
%	Percent
SD	Standard deviation
SDS	Safety Data Sheet
SOP	Standard Operating Procedure
USA	United States of America

19 DEVIATIONS

There were occasional procedural deviations that were minor and did not impact the integrity or outcome of the study. Such instances of protocol deviations were documented and acknowledged by the Study Director within the study records. All protocol deviations are summarized below. Other minor procedural (SOP) deviations were similarly documented and acknowledged by the Study Director within the study records but are not reported unless otherwise deemed necessary by the Study Director.

<table>
<tr><th>DEVIATION</th><th>PROTOCOL SECTION</th></tr>
<tr><td>Clinical observations were completed outside of the protocol-specified window.
<table>
<tr><th>Date</th><th>Group</th><th>Animal</th><th>Time Point (HH:MM)</th><th>Clinical Observation Times</th></tr>
<tr><td>01Nov24</td><td>2</td><td>2103</td><td>0:30–1:00</td><td>29 minutes (1 minute early)</td></tr>
</table></td><td>8.2.2</td></tr>
</table>

20 TABLES

Table 1: Individual Mortality Data

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Individual Mortality

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Group	Dose Level	Sex	Animal	Cage	Removal Day	Removal Week	Removal Date	Removal Time	Time Slot	Removal Symptom	Pathology Reason
Gr 1	30 mg/kg SOPH-110S	Male	1001	1001	3	1	11/01/24	13:53	.	.	Term
			1002	1001	3	1	11/01/24	14:34	.	.	Term
			1003	1003	3	1	11/01/24	14:50	.	.	Term
Gr 1	30 mg/kg SOPH-110S	Female	1101	1101	3	1	11/01/24	15:28	.	.	Term
			1102	1101	3	1	11/01/24	15:28	.	.	Term
			1103	1103	3	1	11/01/24	15:52	.	.	Term
Gr 2	100 mg/kg SOPH-110S	Male	2001	2001	4	1	11/04/24	11:34	.	.	Term
			2002	2001	4	1	11/04/24	11:40	.	.	Term
			2003	2003	4	1	11/04/24	11:18	.	.	Term
Gr 2	100 mg/kg SOPH-110S	Female	2101	2101	4	1	11/04/24	12:13	.	.	Term
			2102	2101	4	1	11/04/24	12:11	.	.	Term
			2103	2103	4	1	11/04/24	10:55	.	.	Term
Gr 3	140 mg/kg SOPH-110S	Male	3001	3001	3	1	11/07/24	14:42	.	.	Term
			3002	3001	3	1	11/07/24	14:39	.	.	Term
			3003	3003	3	1	11/07/24	14:46	.	.	Term
Gr 3	140 mg/kg SOPH-110S	Female	3101	3101	3	1	11/07/24	14:49	.	.	Term
			3102	3101	3	1	11/07/24	14:49	.	.	Term
			3103	3103	3	1	11/07/24	14:46	.	.	Term
Gr 4	200 mg/kg SOPH-110S	Male	4003	4003	5	1	11/11/24	10:46	.	.	FD
Gr 4	200 mg/kg SOPH-110S	Female	4103	4103	5	1	11/11/24	9:50	.	.	Term

Individual Mortality

1124-8751 - A Maximum Tolerated Dose Study of SOPH-11OS in Rats

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Pathology Removal Reasons

Abbreviation	Description
Term	Killed Terminal
FD	Found Dead

Table 2: Summary Clinical Observations

Intergroup Comparison of Clinical Observations Across Time

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Sex: Male	Observation Type: Routine	Day(s) Relative to Start Date						
		1	2	3	4	5		
Group 1	Normal	3	3	3	.	.		
Group 2	Normal	2	3	2	2	.		
	Activity, Moderate, Hypoactive	1	.	.	.	.		
	Activity, Slight, Hypoactive	3	.	.	.	.		
	Barbering, Foot, Front Both, Slight	.	.	.	1	.		
	Hair Thinning, Foot, Front Left, Slight	.	.	1	.	.		
	Salivation, Moderate	1	.	.	.	.		
	Salivation, Slight	1	.	.	.	.		
	Squinting, Eyes, Both, Slight	1	.	.	.	.		
	Staining, Eyes, Both, Slight	1	.	.	.	.		
	Staining, Nose/Snout, Slight	1	.	.	.	.		
Group 3	Normal	.	3	3	.	.		
	Activity, Slight, Hypoactive	3	.	.	.	.		
	Activity, Slight, Lethargic	1	.	.	.	.		
	Hypersensitive, Slight	1	.	.	.	.		
	Respiration, Increased	2	.	.	.	.		
	Respiration, Increased, Labored	3	.	.	.	.		
	Salivation, Slight	2	.	.	.	.		
	Squinting, Eyes, Both, Minimal	2	.	.	.	.		
	Squinting, Eyes, Both, Moderate	1	.	.	.	.		
	Squinting, Eyes, Both, Slight	2	.	.	.	.		
	Staining, Nose/Snout, Slight	2	.	.	.	.		
	Staining, Nose/Snout, Slight, Red	1	.	.	.	.		
Group 4	Normal	.	1	1	1	1		
	Activity, Slight, Hypoactive	2	.	.	.	.		

Values = Specific Number of Animals Affected

Intergroup Comparison of Clinical Observations Across Time

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Sex: Female	Observation Type: Routine	Day(s) Relative to Start Date						
		1	2	3	4	5		
Group 1	Normal	3	3	3	.	.		
Group 2	Normal	3	3	1	.	.		
	Activity, Slight, Hypoactive	2	.	.	.	.		
	Activity, Slight	1	.	.	.	.		
	Barbering, Foot, Front Both, Slight	.	.	1	1	.		
	Hair Thinning, Back, Slight	.	.	1	1	.		
	Salivation, Slight	3	.	.	.	.		
	Squinting, Eyes, Both, Slight	3	.	.	.	.		
	Staining, Back, Slight	.	.	.	1	.		
	Staining, Nose/Snout, Slight, Clear	1	.	.	.	.		
Group 3	Normal	2	2	2	.	.		
	Activity, Slight, Hypoactive	3	.	.	.	.		
	Activity, Slight, Lethargic	1	.	.	.	.		
	Discoloration, Ears Both, Slight, Red	1	.	.	.	.		
	Respiration, Decreased, Labored	2	.	.	.	.		
	Respiration, Increased	2	.	.	.	.		
	Respiration, Increased, Labored	3	.	.	.	.		
	Salivation, Slight	1	.	.	.	.		
	Squinting, Eyes, Both, Moderate	1	.	.	.	.		
	Squinting, Eyes, Both, Slight	2	.	.	.	.		
	Squinting, Eyes, Both, Slight, Hypoactive	1	.	.	.	.		
	Staining, Back, Slight	.	1	1	.	.		
	Staining, Nose/Snout, Slight	1	.	.	.	.		
	Staining, Nose/Snout, Slight, Red	1	.	.	.	.		
Group 4	Normal	.	1	1	1	.		
	Activity, Slight, Hypoactive	1	.	.	.	.		
	Staining, Back, Minimal	.	.	.	.	1		

Values = Specific Number of Animals Affected

Intergroup Comparison of Clinical Observations Across Time

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Sex: Female	Observation Type: Routine	Day(s) Relative to Start Date						
		1	2	3	4	5		
Group 4	Staining, Eyes, Both, Slight	1	.	.	.	.		

Values = Specific Number of Animals Affected

Intergroup Comparison of Clinical Observations Across Time

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Sex: Male	Observation Type: Unscheduled Observation	Day(s) Relative to Start Date
		1
Group 4	Activity, Slight, Hypoactive	1
	Reluctant to Move, Moderate	1
	Salivation, Slight	1
	Squinting, Eyes, Both, Slight	1
	Staining, Nose/Snout, Slight	1

Values = Specific Number of Animals Affected

Intergroup Comparison of Clinical Observations Across Time

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Sex: Female	Observation Type: Unscheduled Observation	Day(s) Relative to Start Date
		1
Group 4	Activity, Slight, Lethargic	1
	Reluctant to Move, Moderate	1
	Salivation, Slight	1
	Squinting, Eyes, Both, Slight	1
	Staining, Nose/Snout, Slight	1

Values = Specific Number of Animals Affected

Intergroup Comparison of Clinical Observations Across Time

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Key Page

Group Information

Short Name	Long Name	Type	Report Headings	
Gr 1	Group 1	Control	30 mg/kg	SOPH-110S
Gr 2	Group 2	Dose	100 mg/kg	SOPH-110S
Gr 3	Group 3	Dose	140 mg/kg	SOPH-110S
Gr 4	Group 4	Dose	200 mg/kg	SOPH-110S

Table 3: Summary Body Weight Data

Summary Body Weight Data

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Day(s) Relative to Start Date

Sex: Male		Body Weight (Grams) [a]	Body Weight (Grams) [a]	Body Weight (Grams) [a]	Body Weight (Grams) [I]	Body Weight (Grams) [I]
		1	2	3	4	5
30 mg/kg SOPH-110S	Mean	414.0	405.9	409.9	-	-
	SD	32.2	32.2	33.0	-	-
	N	3	3	3	-	-
100 mg/kg SOPH-110S	Mean	427.8	427.3	432.4	431.7 n	-
	SD	25.8	19.9	27.7	27.3	-
	N	3	3	3	3	-
140 mg/kg SOPH-110S	Mean	409.3	402.5	399.1	-	-
	SD	15.5	15.7	18.5	-	-
	N	3	3	3	-	-
200 mg/kg SOPH-110S	Mean	462.7 n	450.7 n	431.2 n	422.9 n	400.9 n
	SD	-	-	-	-	-
	N	1	1	1	1	1
Spare	Mean	402.5 n	409.6 n	408.7 n	-	-
	SD	15.1	11.7	6.2	-	-
	N	2	2	2	-	-

[a] - Anova & Dunnett: n - Inappropriate for statistics
[I] - n - Inappropriate for statistics

Summary Body Weight Data

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Day(s) Relative to Start Date

Sex: Female		Body Weight (Grams) [a]	Body Weight (Grams) [a]	Body Weight (Grams) [a]	Body Weight (Grams) [I]	Body Weight (Grams) [I]
		1	2	3	4	5
30 mg/kg SOPH-110S	Mean	282.9	274.4	277.8	-	-
	SD	10.0	16.1	14.3	-	-
	N	3	3	3	-	-
100 mg/kg SOPH-110S	Mean	291.2	286.6	286.3	279.5 n	-
	SD	16.1	16.3	26.3	11.2	-
	N	3	3	3	3	-
140 mg/kg SOPH-110S	Mean	286.8	285.2	281.6	-	-
	SD	19.2	19.6	17.4	-	-
	N	3	3	3	-	-
200 mg/kg SOPH-110S	Mean	285.4 n	272.8 n	268.2 n	271.9 n	271.7 n
	SD	-	-	-	-	-
	N	1	1	1	1	1
Spare	Mean	288.6 n	284.5 n	270.8 n	-	-
	SD	6.2	4.0	7.4	-	-
	N	2	2	2	-	-

[a] - Anova & Dunnett: n - Inappropriate for statistics
[I] - n - Inappropriate for statistics

Summary Body Weight Data

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Comments and Markers

Page	Measurement	Group	Sex	Day	Marker	Comment
1	Body Weight	Gr 2	Male	4	n	n - Inappropriate for statistics
1	Body Weight	Gr 4	Male	1	n	Anova & Dunnett: n - Inappropriate for statistics
1	Body Weight	Gr 4	Male	2	n	Anova & Dunnett: n - Inappropriate for statistics
1	Body Weight	Gr 4	Male	3	n	Anova & Dunnett: n - Inappropriate for statistics
1	Body Weight	Gr 4	Male	4	n	n - Inappropriate for statistics
1	Body Weight	Gr 4	Male	5	n	n - Inappropriate for statistics
1	Body Weight	SPR	Male	1	n	Anova & Dunnett: n - Inappropriate for statistics
1	Body Weight	SPR	Male	2	n	Anova & Dunnett: n - Inappropriate for statistics
1	Body Weight	SPR	Male	3	n	Anova & Dunnett: n - Inappropriate for statistics
2	Body Weight	Gr 2	Female	4	n	n - Inappropriate for statistics
2	Body Weight	Gr 4	Female	1	n	Anova & Dunnett: n - Inappropriate for statistics
2	Body Weight	Gr 4	Female	2	n	Anova & Dunnett: n - Inappropriate for statistics
2	Body Weight	Gr 4	Female	3	n	Anova & Dunnett: n - Inappropriate for statistics
2	Body Weight	Gr 4	Female	4	n	n - Inappropriate for statistics
2	Body Weight	Gr 4	Female	5	n	n - Inappropriate for statistics
2	Body Weight	SPR	Female	1	n	Anova & Dunnett: n - Inappropriate for statistics
2	Body Weight	SPR	Female	2	n	Anova & Dunnett: n - Inappropriate for statistics
2	Body Weight	SPR	Female	3	n	Anova & Dunnett: n - Inappropriate for statistics

Summary Body Weight Data

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Key Page

Measurement Descriptions

Headings Used	Description
Body Weight	Body Weight

Unit Descriptions

Headings Used	Description
Grams	g

Measurement/Statistics

Measurement	Descriptive	Comparative	Arithmetic /Adjusted	Transformation
Body Weight	Mean Standard Deviation Count	Anova & Dunnett's Test 2 Sided	Arithmetic	Identity (No Transformation)

Group Information

Short Name	Long Name	Type	Report Headings 1-4	
Gr 1	Group 1	Control	30 mg/kg	SOPH-110S
Gr 2	Group 2	Dose	100 mg/kg	SOPH-110S
Gr 3	Group 3	Dose	140 mg/kg	SOPH-110S
Gr 4	Group 4	Dose	200 mg/kg	SOPH-110S
SPR	Spare	Dose	Spare	

Pairwise Comparisons

Group	Vs	Group

Summary Body Weight Data

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Key Page

Pairwise Comparisons (Continued)

Group	Vs	Group
Gr 1		Gr 2
Gr 1		Gr 3
Gr 1		Gr 4
Gr 1		SPR

Statistical Test Descriptions

Headings Used	Description
a	Anova & Dunnett's Test

Table 4: Summary Food Consumption Data

Summary of Food Consumption Data

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Daily Food Cons Per Animal (g)

Sex: Male		Day(s) Relative to Animal Start Date			
		1 → 2	2 → 3	3 → 4	4 → 5
30 mg/kg SOPH-110S	Mean	19 n	28 n	-	-
	SD	0	1	-	-
	N	2	2	-	-
100 mg/kg SOPH-110S	Mean	17 n	20 n	26 n	-
	SD	4	2	2	-
	N	2	2	2	-
140 mg/kg SOPH-110S	Mean	18 n	18 n	-	-
	SD	1	3	-	-
	N	2	2	-	-
200 mg/kg SOPH-110S	Mean	6 n	14 n	19 n	8 n
	SD	-	-	-	-
	N	1	1	1	1
Spare	Mean	26 n	30 n	-	-
	SD	-	-	-	-
	N	1	1	-	-

n - Inappropriate for statistics

Summary of Food Consumption Data

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Daily Food Cons Per Animal (g)

Sex: Female		Day(s) Relative to Animal Start Date			
		1 → 2	2 → 3	3 → 4	4 → 5
30 mg/kg SOPH-110S	Mean	12 n	21 n	-	-
	SD	3	4	-	-
	N	2	2	-	-
100 mg/kg SOPH-110S	Mean	10 n	14 n	14 n	-
	SD	1	1	3	-
	N	2	2	2	-
140 mg/kg SOPH-110S	Mean	11 n	22 n	-	-
	SD	2	15	-	-
	N	2	2	-	-
200 mg/kg SOPH-110S	Mean	7 n	10 n	15 n	19 n
	SD	-	-	-	-
	N	1	1	1	1
Spare	Mean	17 n	13 n	-	-
	SD	-	-	-	-
	N	1	1	-	-

n - Inappropriate for statistics

Summary of Food Consumption Data

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Comments and Markers

Page	Measurement	Group	Sex	Day	Marker	Comment
1	Daily Food Cons Per Animal	Gr 1	Male	1 - 2	n	n - Inappropriate for statistics
1	Daily Food Cons Per Animal	Gr 1	Male	2 - 3	n	n - Inappropriate for statistics
1	Daily Food Cons Per Animal	Gr 2	Male	1 - 2	n	n - Inappropriate for statistics
1	Daily Food Cons Per Animal	Gr 2	Male	2 - 3	n	n - Inappropriate for statistics
1	Daily Food Cons Per Animal	Gr 2	Male	3 - 4	n	n - Inappropriate for statistics
1	Daily Food Cons Per Animal	Gr 3	Male	1 - 2	n	n - Inappropriate for statistics
1	Daily Food Cons Per Animal	Gr 3	Male	2 - 3	n	n - Inappropriate for statistics
1	Daily Food Cons Per Animal	Gr 4	Male	1 - 2	n	n - Inappropriate for statistics
1	Daily Food Cons Per Animal	Gr 4	Male	2 - 3	n	n - Inappropriate for statistics
1	Daily Food Cons Per Animal	Gr 4	Male	3 - 4	n	n - Inappropriate for statistics
1	Daily Food Cons Per Animal	Gr 4	Male	4 - 5	n	n - Inappropriate for statistics
1	Daily Food Cons Per Animal	SPR	Male	1 - 2	n	n - Inappropriate for statistics
1	Daily Food Cons Per Animal	SPR	Male	2 - 3	n	n - Inappropriate for statistics
2	Daily Food Cons Per Animal	Gr 1	Female	1 - 2	n	n - Inappropriate for statistics
2	Daily Food Cons Per Animal	Gr 1	Female	2 - 3	n	n - Inappropriate for statistics
2	Daily Food Cons Per Animal	Gr 2	Female	1 - 2	n	n - Inappropriate for statistics
2	Daily Food Cons Per Animal	Gr 2	Female	2 - 3	n	n - Inappropriate for statistics
2	Daily Food Cons Per Animal	Gr 2	Female	3 - 4	n	n - Inappropriate for statistics
2	Daily Food Cons Per Animal	Gr 3	Female	1 - 2	n	n - Inappropriate for statistics
2	Daily Food Cons Per Animal	Gr 3	Female	2 - 3	n	n - Inappropriate for statistics
2	Daily Food Cons Per Animal	Gr 4	Female	1 - 2	n	n - Inappropriate for statistics
2	Daily Food Cons Per Animal	Gr 4	Female	2 - 3	n	n - Inappropriate for statistics
2	Daily Food Cons Per Animal	Gr 4	Female	3 - 4	n	n - Inappropriate for statistics
2	Daily Food Cons Per Animal	Gr 4	Female	4 - 5	n	n - Inappropriate for statistics
2	Daily Food Cons Per Animal	SPR	Female	1 - 2	n	n - Inappropriate for statistics
2	Daily Food Cons Per Animal	SPR	Female	2 - 3	n	n - Inappropriate for statistics

Summary of Food Consumption Data

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Key Page

Measurement Descriptions

Headings Used	Description
Daily Food Cons Per Animal	Mean Daily Food Cons. Per Animal

Measurement/Statistics

Measurement	Descriptive	Comparative	Arithmetic /Adjusted	Transformation
Daily Food Cons Per Animal	Mean Standard Deviation Count	Anova & Dunnett's Test 2 Sided	Arithmetic	Identity (No Transformation)

Group Information

Short Name	Long Name	Type	Report Headings 1-4	
Gr 1	Group 1	Control	30 mg/kg	SOPH-110S
Gr 2	Group 2	Dose	100 mg/kg	SOPH-110S
Gr 3	Group 3	Dose	140 mg/kg	SOPH-110S
Gr 4	Group 4	Dose	200 mg/kg	SOPH-110S
SPR	Spare	Dose	Spare	

Pairwise Comparisons

Group	Vs	Group
Gr 1		Gr 2
Gr 1		Gr 3
Gr 1		Gr 4
Gr 1		SPR

Table 5: Summary Macroscopic Observations

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Intergroup Comparison of Macroscopic Observations

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Removal Reason: Killed Terminal	MALES				FEMALES			
	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S
Number of Animals on Study :	3	3	3	0	3	3	3	1
Number of Animals Completed:	(3)	(3)	(1)	(0)	(3)	(2)	(0)	(0)
ADMINISTRATION SITE;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
ADRENAL GLANDS;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
ANIMAL IDENTIFICATION;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
APPENDIX;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
AORTA;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
ARTERY, LARGE;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
ARTERY, SMALL;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
BIOANALYSIS; FECES;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
BIOANALYSIS; LIVER;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
BONE MARROW, FEMUR;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)

Intergroup Comparison of Macroscopic Observations

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Removal Reason: Killed Terminal	MALES				FEMALES			
	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S
Number of Animals on Study :	3	3	3	0	3	3	3	1
Number of Animals Completed:	(3)	(3)	(1)	(0)	(3)	(2)	(0)	(0)
BONE MARROW, FEMUR; (continued)								
No Visible Lesions	3	3	3	0	3	3	3	1
BONE MARROW, STERNUM;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
BONE, MARROW SMEAR (RIB);								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
BONE, FEMUR;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
BONE, STERNUM;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
BONE, TIBIOFIBULAR/PATELLOFEMORAL JOINT;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
BRAIN;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
BRAIN, CEREBELLUM;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
BRAIN, CEREBRUM;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
BRAIN, MEDULLA OBLONGATA;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1

Intergroup Comparison of Macroscopic Observations

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Removal Reason: Killed Terminal	MALES				FEMALES			
	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S
Number of Animals on Study :	3	3	3	0	3	3	3	1
Number of Animals Completed:	(3)	(3)	(1)	(0)	(3)	(2)	(0)	(0)
BRAIN, MENINGES;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
CERVIX;								
Submitted	(-)	(-)	(-)	(-)	(3)	(3)	(0)	(1)
No Visible Lesions	-	-	-	-	3	3	3	1
CHEST CAVITY;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
CSF SAMPLE;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
COLON, SPIRAL;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
COLON, TRANSVERSE;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(1)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
COLON, DECENDING;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
EPIDIDYMIDES;								
Submitted	(3)	(3)	(1)	(0)	(-)	(-)	(-)	(-)
No Visible Lesions	3	3	3	0	-	-	-	-
ESOPHAGUS;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
EYES;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)

Intergroup Comparison of Macroscopic Observations

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Removal Reason: Killed Terminal	MALES				FEMALES			
	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S
Number of Animals on Study :	3	3	3	0	3	3	3	1
Number of Animals Completed:	(3)	(3)	(1)	(0)	(3)	(2)	(0)	(0)
EYES; (continued)								
No Visible Lesions	3	3	3	0	3	3	3	1
EYES WITH OPTIC NERVES;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
EYE W/OPTIC NERVE (WT);								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
FECES SAMPLE;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(1)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
GASTROINTESTINAL TRACT;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
GALLBLADDER;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
GROSS LESIONS;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
HARDERIAN GLANDS;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
HEART;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(1)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
INJECTION SITE;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1

Intergroup Comparison of Macroscopic Observations

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Removal Reason: Killed Terminal	MALES				FEMALES			
	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S
Number of Animals on Study :	3	3	3	0	3	3	3	1
Number of Animals Completed:	(3)	(3)	(1)	(0)	(3)	(2)	(0)	(0)
INTESTINE, CECUM;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
INTESTINE, COLON;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
INTESTINE, DUODENUM;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(1)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
INTESTINE, ILEUM WITH PEYERS PATCH;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
INTESTINE, ILEUM;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
INTESTINE, JEJUNUM;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
INTESTINE, RECTUM;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
KIDNEYS;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
LACRIMAL GLANDS;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
LARYNX;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)

Intergroup Comparison of Macroscopic Observations

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Removal Reason: Killed Terminal	MALES				FEMALES			
	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S
Number of Animals on Study :	3	3	3	0	3	3	3	1
Number of Animals Completed:	(3)	(3)	(1)	(0)	(3)	(2)	(0)	(0)
LARYNX; (continued)								
No Visible Lesions	3	3	3	0	3	3	3	1
LIVER;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(1)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
LIVER (WEIGHED WITH DRAINED GALLBLADDER);								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
LUNGS;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
LUNGS WITH BRONCHI;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
LYMPH NODE, AXILLARY;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
LYMPH NODE, BRONCHIAL;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
LYMPH NODE, CERVICAL;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
LYMPH NODE, INGUINAL;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
LYMPH NODE, MANDIBULAR;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1

Intergroup Comparison of Macroscopic Observations

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Removal Reason: Killed Terminal	MALES				FEMALES			
	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S
Number of Animals on Study :	3	3	3	0	3	3	3	1
Number of Animals Completed:	(3)	(3)	(1)	(0)	(3)	(2)	(0)	(0)
LYMPH NODE, MANDIBULAR (WT);								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
LYMPH NODE, MEDIASTINAL;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
LYMPH NODE, MESENTERIC;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
LYMPH NODE, SUBMAXILLARY;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
MAMMARY GLANDS;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
MESENTERY;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
MUSCLE FROM INJECTION SITE;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
NASOLACRIMAL DUCT;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
NERVE, OPTIC;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
NERVE, PERIPHERAL;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)

Intergroup Comparison of Macroscopic Observations

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Removal Reason: Killed Terminal	MALES				FEMALES			
	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S
Number of Animals on Study :	3	3	3	0	3	3	3	1
Number of Animals Completed:	(3)	(3)	(1)	(0)	(3)	(2)	(0)	(0)
NERVE, PERIPHERAL; (continued)								
No Visible Lesions	3	3	3	0	3	3	3	1
NERVE, SCIATIC;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
NERVE, SURAL;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(1)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
NERVE, TIBIAL;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
OVARIES;								
Submitted	(-)	(-)	(-)	(-)	(3)	(3)	(0)	(1)
No Visible Lesions	-	-	-	-	3	2	3	1
Discoloration; Dark; Symmetric	(-)	(-)	(-)	(-)	(0)	(1)	(0)	(0)
Mild	-	-	-	-	0	1	0	0
OVARY WITH OVIDUCT;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
OVIDUCTS;								
Submitted	(-)	(-)	(-)	(-)	(3)	(3)	(0)	(1)
No Visible Lesions	-	-	-	-	3	3	3	1
PANCREAS;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
PARATHYROID GLANDS;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1

Intergroup Comparison of Macroscopic Observations

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Removal Reason: Killed Terminal	MALES				FEMALES			
	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S
Number of Animals on Study :	3	3	3	0	3	3	3	1
Number of Animals Completed:	(3)	(3)	(1)	(0)	(3)	(2)	(0)	(0)
PHARYNX;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
PITUITARY GLAND;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	2	3	1
Enlarged	0	0	0	0	0	1	0	0
PEYERS PATCH;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
PROSTATE GLAND;								
Submitted	(3)	(3)	(1)	(0)	(-)	(-)	(-)	(-)
No Visible Lesions	3	3	3	0	-	-	-	-
SALIVA;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
SALIVARY GLAND, MANDIBULAR;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
SALIVARY GLAND, MANDIBULAR (WT);								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
SEMINAL VESICLES;								
Submitted	(3)	(3)	(1)	(0)	(-)	(-)	(-)	(-)
No Visible Lesions	3	3	3	0	-	-	-	-
SEMINAL VESICLES WITH COAGULATING GLANDS;								
Submitted	(3)	(3)	(1)	(0)	(-)	(-)	(-)	(-)
No Visible Lesions	3	3	3	0	-	-	-	-

Intergroup Comparison of Macroscopic Observations

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Removal Reason: Killed Terminal	MALES				FEMALES			
	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S
Number of Animals on Study :	3	3	3	0	3	3	3	1
Number of Animals Completed:	(3)	(3)	(1)	(0)	(3)	(2)	(0)	(0)
SKELETAL MUSCLE (WT);								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
SKELETAL MUSCLE, BICEP FEMORIS;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
SKELETAL MUSCLE, GASTROCNEMIUS;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
SKELETAL MUSCLE, QUADRICEPS FEMORIS;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
SKIN/SUBCUTIS;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
SKIN/SUBCUTIS (WT);								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
SKULL;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
SPINAL COLUMN, CERVICAL;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
SPINAL COLUMN, THORACIC;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
SPINAL COLUMN, LUMBAR;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)

Intergroup Comparison of Macroscopic Observations

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Removal Reason: Killed Terminal	MALES				FEMALES			
	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S
Number of Animals on Study :	3	3	3	0	3	3	3	1
Number of Animals Completed:	(3)	(3)	(1)	(0)	(3)	(2)	(0)	(0)
SPINAL COLUMN, LUMBAR; (continued)								
No Visible Lesions	3	3	3	0	3	3	3	1
SPINAL CORD;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
SPINAL CORD, CERVICAL;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
SPINAL CORD, LUMBAR;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
SPINAL CORD, THORACIC;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
SPLEEN;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
STOMACH;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
TESTES;								
Submitted	(3)	(3)	(1)	(0)	(-)	(-)	(-)	(-)
No Visible Lesions	3	3	3	0	-	-	-	-
THYMUS;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
THYMUS (WITH PARATHYROID);								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1

Intergroup Comparison of Macroscopic Observations

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Removal Reason: Killed Terminal	MALES				FEMALES			
	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S
Number of Animals on Study :	3	3	3	0	3	3	3	1
Number of Animals Completed:	(3)	(3)	(1)	(0)	(3)	(2)	(0)	(0)
THYROID GLANDS;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
THYROID WITH PARATHYROID;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
TONGUE;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
TRACHEA;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
UNTREATED SKIN;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
URETERS;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
URETHRA;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
URINE SAMPLE;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
URINARY BLADDER;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
UTERUS;								
Submitted	(-)	(-)	(-)	(-)	(3)	(3)	(0)	(1)

Intergroup Comparison of Macroscopic Observations

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Removal Reason: Killed Terminal	MALES				FEMALES			
	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S
Number of Animals on Study :	3	3	3	0	3	3	3	1
Number of Animals Completed:	(3)	(3)	(1)	(0)	(3)	(2)	(0)	(0)
UTERUS; (continued)								
No Visible Lesions	-	-	-	-	3	3	3	1
UTERUS/CERVIX;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
UTERUS (WEIGHED WITH CERVIX);								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1
VAGINA;								
Submitted	(-)	(-)	(-)	(-)	(3)	(3)	(1)	(1)
No Visible Lesions	-	-	-	-	3	3	3	1
WHOLE BLOOD;								
Submitted	(3)	(3)	(1)	(0)	(3)	(3)	(0)	(1)
No Visible Lesions	3	3	3	0	3	3	3	1

Intergroup Comparison of Macroscopic Observations

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Removal Reason: Found Dead	MALES				FEMALES			
	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S
Number of Animals on Study :	0	0	0	1	0	0	0	0
Number of Animals Completed:	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
ADMINISTRATION SITE;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
ADRENAL GLANDS;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
ANIMAL IDENTIFICATION;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
APPENDIX;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
AORTA;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
ARTERY, LARGE;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
ARTERY, SMALL;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
BIOANALYSIS; FECES;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
BIOANALYSIS; LIVER;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
BONE MARROW, FEMUR;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)

Intergroup Comparison of Macroscopic Observations

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Removal Reason: Found Dead	MALES				FEMALES			
	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S
Number of Animals on Study :	0	0	0	1	0	0	0	0
Number of Animals Completed:	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
BONE MARROW, FEMUR; (continued)								
No Visible Lesions	0	0	0	1	0	0	0	0
BONE MARROW, STERNUM;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
BONE, MARROW SMEAR (RIB);								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
BONE, FEMUR;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
BONE, STERNUM;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
BONE, TIBIOFIBULAR/PATELLOFEMORAL JOINT;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
BRAIN;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
BRAIN, CEREBELLUM;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
BRAIN, CEREBRUM;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
BRAIN, MEDULLA OBLONGATA;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0

Intergroup Comparison of Macroscopic Observations

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Removal Reason: Found Dead	MALES				FEMALES			
	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S
Number of Animals on Study :	0	0	0	1	0	0	0	0
Number of Animals Completed:	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
BRAIN, MENINGES;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
CHEST CAVITY;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
CSF SAMPLE;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
COLON, SPIRAL;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
COLON, TRANSVERSE;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
COLON, DECENDING;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
EPIDIDYMIDES;								
Submitted	(0)	(0)	(0)	(1)	(-)	(-)	(-)	(-)
No Visible Lesions	0	0	0	1	-	-	-	-
ESOPHAGUS;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
EYES;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
EYES WITH OPTIC NERVES;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)

Intergroup Comparison of Macroscopic Observations

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Removal Reason: Found Dead	MALES				FEMALES			
	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S
Number of Animals on Study :	0	0	0	1	0	0	0	0
Number of Animals Completed:	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
EYES WITH OPTIC NERVES; (continued)								
No Visible Lesions	0	0	0	1	0	0	0	0
EYE W/OPTIC NERVE (WT);								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
FECES SAMPLE;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
GASTROINTESTINAL TRACT;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
GALLBLADDER;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
GROSS LESIONS;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
HARDERIAN GLANDS;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
HEART;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
INJECTION SITE;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
INTESTINE, CECUM;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0

Intergroup Comparison of Macroscopic Observations

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Removal Reason: Found Dead	MALES				FEMALES			
	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S
Number of Animals on Study :	0	0	0	1	0	0	0	0
Number of Animals Completed:	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
INTESTINE, COLON;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
INTESTINE, DUODENUM;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
INTESTINE, ILEUM WITH PEYERS PATCH;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
INTESTINE, ILEUM;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
INTESTINE, JEJUNUM;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
INTESTINE, RECTUM;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
KIDNEYS;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	0	0	0	0	0
Enlarged; Multiple	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
Minimal	0	0	0	1	0	0	0	0
LACRIMAL GLANDS;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
LARYNX;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0

Intergroup Comparison of Macroscopic Observations

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Removal Reason: Found Dead	MALES				FEMALES			
	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S
Number of Animals on Study :	0	0	0	1	0	0	0	0
Number of Animals Completed:	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
LIVER;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
LIVER (WEIGHED WITH DRAINED GALLBLADDER);								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
LUNGS;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
LUNGS WITH BRONCHI;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
LYMPH NODE, AXILLARY;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
LYMPH NODE, BRONCHIAL;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
LYMPH NODE, CERVICAL;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
LYMPH NODE, INGUINAL;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
LYMPH NODE, MANDIBULAR;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
LYMPH NODE, MANDIBULAR (WT);								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)

Intergroup Comparison of Macroscopic Observations

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Removal Reason: Found Dead	MALES				FEMALES			
	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S
Number of Animals on Study :	0	0	0	1	0	0	0	0
Number of Animals Completed:	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
LYMPH NODE, MANDIBULAR (WT); (continued)								
No Visible Lesions	0	0	0	1	0	0	0	0
LYMPH NODE, MEDIASTINAL;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
LYMPH NODE, MESENTERIC;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
LYMPH NODE, SUBMAXILLARY;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
MAMMARY GLANDS;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
MESENTERY;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
MUSCLE FROM INJECTION SITE;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
NASOLACRIMAL DUCT;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
NERVE, OPTIC;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
NERVE, PERIPHERAL;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0

Intergroup Comparison of Macroscopic Observations

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Removal Reason: Found Dead	MALES				FEMALES			
	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S
Number of Animals on Study :	0	0	0	1	0	0	0	0
Number of Animals Completed:	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
NERVE, SCIATIC;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
NERVE, SURAL;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
NERVE, TIBIAL;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
OVARY WITH OVIDUCT;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
PANCREAS;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
PARATHYROID GLANDS;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
PHARYNX;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
PITUITARY GLAND;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
PEYERS PATCH;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
PROSTATE GLAND;								
Submitted	(0)	(0)	(0)	(1)	(-)	(-)	(-)	(-)

Intergroup Comparison of Macroscopic Observations

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Removal Reason: Found Dead	MALES				FEMALES			
	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S
Number of Animals on Study :	0	0	0	1	0	0	0	0
Number of Animals Completed:	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
PROSTATE GLAND; (continued)								
No Visible Lesions	0	0	0	1	-	-	-	-
SALIVA;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
SALIVARY GLAND, MANDIBULAR;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
SALIVARY GLAND, MANDIBULAR (WT);								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
SEMINAL VESICLES;								
Submitted	(0)	(0)	(0)	(1)	(-)	(-)	(-)	(-)
No Visible Lesions	0	0	0	1	-	-	-	-
SEMINAL VESICLES WITH COAGULATING GLANDS;								
Submitted	(0)	(0)	(0)	(1)	(-)	(-)	(-)	(-)
No Visible Lesions	0	0	0	1	-	-	-	-
SKELETAL MUSCLE (WT);								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
SKELETAL MUSCLE, BICEP FEMORIS;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
SKELETAL MUSCLE, GASTROCNEMIUS;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
SKELETAL MUSCLE, QUADRICEPS FEMORIS;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0

Intergroup Comparison of Macroscopic Observations

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Removal Reason: Found Dead	MALES				FEMALES			
	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S
Number of Animals on Study :	0	0	0	1	0	0	0	0
Number of Animals Completed:	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
SKIN/SUBCUTIS;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
SKIN/SUBCUTIS (WT);								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
SKULL;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
SPINAL COLUMN, CERVICAL;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
SPINAL COLUMN, THORACIC;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
SPINAL COLUMN, LUMBAR;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
SPINAL CORD;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
SPINAL CORD, CERVICAL;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
SPINAL CORD, LUMBAR;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
SPINAL CORD, THORACIC;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)

Intergroup Comparison of Macroscopic Observations

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Removal Reason: Found Dead	MALES				FEMALES			
	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S
Number of Animals on Study :	0	0	0	1	0	0	0	0
Number of Animals Completed:	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
SPINAL CORD, THORACIC; (continued)								
No Visible Lesions	0	0	0	1	0	0	0	0
SPLEEN;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
STOMACH;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
TESTES;								
Submitted	(0)	(0)	(0)	(1)	(-)	(-)	(-)	(-)
No Visible Lesions	0	0	0	1	-	-	-	-
THYMUS;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
THYMUS (WITH PARATHYROID);								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
THYROID GLANDS;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
THYROID WITH PARATHYROID;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
TONGUE;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
TRACHEA;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0

Intergroup Comparison of Macroscopic Observations

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Removal Reason: Found Dead	MALES				FEMALES			
	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S	30 mg/kg SOPH-110S	100 mg/kg SOPH-110S	140 mg/kg SOPH-110S	200 mg/kg SOPH-110S
Number of Animals on Study :	0	0	0	1	0	0	0	0
Number of Animals Completed:	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
UNTREATED SKIN;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
URETERS;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
URETHRA;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
URINE SAMPLE;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
URINARY BLADDER;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
UTERUS/CERVIX;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
UTERUS (WEIGHED WITH CERVIX);								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0
WHOLE BLOOD;								
Submitted	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
No Visible Lesions	0	0	0	1	0	0	0	0

Table 6: Individual Clinical Observations

Clinical Observations - Animals by Time

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

30 mg/kg SOPH-110S Sex: Male	Observation Type: Routine	Day(s) Relative to Start Date						
		1 30 m	1 Unsc	2 am	3 am	4 am	5 am	
1001	Normal	X	.	X	X	.	.	
1002	Normal	X	.	X	X	.	.	
1003	Normal	X	.	X	X	.	.	

X=Present

Clinical Observations - Animals by Time

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

100 mg/kg SOPH-110S Sex: Male	Observation Type: Routine	Day(s) Relative to Start Date						
		1 30 m	1 Unsc	2 am	3 am	4 am	5 am	
2001 !	Normal	X	.	X	X	X	.	
	Activity, Slight	.	Hypo	.	.	.	.	
	Salivation	.	Slig	.	.	.	.	
2002 !	Normal	X	.	X	.	.	.	
	Activity, Slight	.	Hypo	.	.	.	.	
	Barbering, Foot, Front Both	.	.	.	.	Slig	.	
	Hair Thinning, Foot, Front Left	.	.	.	Slig	.	.	
	Salivation	.	Mode	.	.	.	.	
2003 !	Normal	.	.	X	X	X	.	
	Activity, Moderate	.	Hypo	.	.	.	.	
	Activity, Slight	Hypo	.	.	.	.	.	
	Squinting, Eyes, Both, Slight	X	X	.	.	.	.	
	Staining, Eyes, Both, Slight	X	.	.	.	.	.	
	Staining, Nose/Snout, Slight	X	.	.	.	.	.	

!=Result comment recorded against 1 or more clinical observations. X=Present; Hypo=Hypoactive; Slig=Slight; Mode=Moderate

Clinical Observations - Animals by Time

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

140 mg/kg SOPH-110S Sex: Male	Observation Type: Routine	Day(s) Relative to Start Date						
		1 30 m	1 Unsc	2 am	3 am	4 am	5 am	
3001 !	Normal	.	.	X	X	.	.	
	Activity, Slight	Hypo	.	.	.	.	.	
	Respiration, Increased	.	Labo	.	.	.	.	
	Squinting, Eyes, Both, Minimal	X	.	.	.	.	.	
	Squinting, Eyes, Both, Moderate	.	X	.	.	.	.	
	Squinting, Eyes, Both, Slight	.	X	.	.	.	.	
	Staining, Nose/Snout, Slight	X	.	.	.	.	.	
3002 !	Normal	.	.	X	X	.	.	
	Activity, Slight	Hypo	Leth	.	.	.	.	
	Respiration, Increased	.	Labo	.	.	.	.	
	Salivation	.	Slig	.	.	.	.	
3003 !	Normal	.	.	X	X	.	.	
	Activity, Slight	.	Hypo	.	.	.	.	
	Hypersensitive	Slig	.	.	.	.	.	
	Respiration, Increased	.	Labo	.	.	.	.	
	Salivation	.	Slig	.	.	.	.	
	Squinting, Eyes, Both, Minimal	X	.	.	.	.	.	
	Squinting, Eyes, Both, Slight	.	X	.	.	.	.	
	Staining, Nose/Snout, Slight	X	.	.	.	.	.	
	Staining, Nose/Snout, Slight, Red	.	X	.	.	.	.	

!=Result comment recorded against 1 or more clinical observations. X=Present; Hypo=Hypoactive; Labo=Labored; Leth=Lethargic; Slig=Slight

Clinical Observations - Animals by Time

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

200 mg/kg SOPH-110S Sex: Male	Observation Type: Routine	Day(s) Relative to Start Date						
		1 30 m	1 Unsc	2 am	3 am	4 am	5 am	
4001	Activity, Slight	Hypo	.	.	.	.	.	
4003 !	Normal	.	.	X	X	X	X	
	Activity, Slight	Hypo	.	.	.	.	.	

!=Result comment recorded against 1 or more clinical observations. Hypo=Hypoactive; X=Present

Clinical Observations - Animals by Time

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

30 mg/kg SOPH-110S Sex: Female	Observation Type: Routine	Day(s) Relative to Start Date						
		1 30 m	1 Unsc	2 am	3 am	4 am	5 am	
1101	Normal	X	.	X	X	.	.	
1102	Normal	X	.	X	X	.	.	
1103	Normal	X	.	X	X	.	.	

X=Present

Clinical Observations - Animals by Time

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

100 mg/kg SOPH-110S Sex: Female	Observation Type: Routine	Day(s) Relative to Start Date						
		1 30 m	1 Unsc	2 am	3 am	4 am	5 am	
2101 !	Normal	X	.	X	.	.	.	
	Activity, Slight	.	X	.	.	.	.	
	Barbering, Foot, Front Both	.	.	.	Slig	Slig	.	
	Salivation	.	Slig	.	.	.	.	
	Squinting, Eyes, Both, Slight	.	X	.	.	.	.	
2102	Normal	X	.	X	.	.	.	
	Activity, Slight	.	Hypo	.	.	.	.	
	Hair Thinning, Back	.	.	.	Slig	Slig	.	
	Salivation	.	Slig	.	.	.	.	
	Squinting, Eyes, Both, Slight	.	X	.	.	.	.	
	Staining, Nose/Snout, Slight	.	Clea	.	.	.	.	
2103 !	Normal	X	.	X	X	.	.	
	Activity, Slight	.	Hypo	.	.	.	.	
	Salivation	.	Slig	.	.	.	.	
	Squinting, Eyes, Both, Slight	.	X	.	.	.	.	
	Staining, Back, Slight	.	.	.	.	X	.	

!=Result comment recorded against 1 or more clinical observations. X=Present; Slig=Slight; Hypo=Hypoactive; Clea=Clear

Clinical Observations - Animals by Time

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

140 mg/kg SOPH-110S Sex: Female	Observation Type: Routine	Day(s) Relative to Start Date						
		1 30 m	1 Unsc	2 am	3 am	4 am	5 am	
3101 !	Normal	.	.	X	X	.	.	
	Activity, Slight	Hypo	Hypo	.	.	.	.	
	Discoloration, Ears Both, Slight	Red	.	.	.	.	.	
	Respiration, Decreased	Labo	.	.	.	.	.	
	Respiration, Increased	.	Labo	.	.	.	.	
	Squinting, Eyes, Both, Slight	.	X	.	.	.	.	
	Staining, Nose/Snout, Slight	X	.	.	.	.	.	
	Staining, Nose/Snout, Slight, Red	.	X	.	.	.	.	
3102	Normal	X	.	X	X	.	.	
	Activity, Slight	.	Leth	.	.	.	.	
	Respiration, Decreased	.	Labo	.	.	.	.	
	Respiration, Increased	.	Labo	.	.	.	.	
	Squinting, Eyes, Both, Slight	.	Hypo	.	.	.	.	
3103 !	Normal	X	.	.	.	.	.	
	Activity, Slight	.	Hypo	.	.	.	.	
	Respiration, Increased	.	Labo	.	.	.	.	
	Salivation	.	Slig	.	.	.	.	
	Squinting, Eyes, Both, Moderate	.	X	.	.	.	.	
	Squinting, Eyes, Both, Slight	.	X	.	.	.	.	
	Staining, Back, Slight	.	.	X	X	.	.	

!=Result comment recorded against 1 or more clinical observations. X=Present; Hypo=Hypoactive; Red=Red; Labo=Labored; Leth=Lethargic; Slig=Slight

Clinical Observations - Animals by Time

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

200 mg/kg SOPH-110S Sex: Female	Observation Type: Routine	Day(s) Relative to Start Date						
		1 30 m	1 Unsc	2 am	3 am	4 am	5 am	
4103	Normal	.	.	X	X	X	.	
	Activity, Slight	Hypo	.	.	.	.	.	
	Staining, Back, Minimal	.	.	.	.	.	X	
	Staining, Eyes, Both, Slight	X	.	.	.	.	.	

X=Present; Hypo=Hypoactive

Clinical Observations - Animals by Time

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

200 mg/kg SOPH-110S Sex: Male	Observation Type: Unscheduled Observation	Day(s) Relative to Start Date						
		1 am						
4003 !	Activity, Slight	Hypo						
	Reluctant to Move	Mode						
	Salivation	Slig						
	Squinting, Eyes, Both, Slight	X						
	Staining, Nose/Snout, Slight	X						

!=Result comment recorded against 1 or more clinical observations. Hypo=Hypoactive; Mode=Moderate; Slig=Slight; X=Present

Clinical Observations - Animals by Time

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

200 mg/kg SOPH-110S Sex: Female	Observation Type: Unscheduled Observation	Day(s) Relative to Start Date						
		1 am						
4103 !	Activity, Slight	Leth						
	Reluctant to Move	Mode						
	Salivation	Slig						
	Squinting, Eyes, Both, Slight	X						
	Staining, Nose/Snout, Slight	X						

!=Result comment recorded against 1 or more clinical observations. Leth=Lethargic; Mode=Moderate; Slig=Slight; X=Present

Clinical Observations - Animals by Time

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Comment Information

Group	Sex	Animal	Day	Observation Type	Comment
Group 2	Male	2001	1 (Unsc)	Routine	Observations began immediately following dose administration.
Group 2	Male	2002	1 (Unsc)	Routine	Observations began immediately following dose administration.
Group 2	Male	2003	1 (Unsc)	Routine	Observations began immediately following dose administration.
Group 3	Male	3001	1 (Unsc)	Routine	Slight mal-odor
Group 3	Male	3002	1 (Unsc)	Routine	Extreme mal-odor
Group 3	Male	3003	1 (Unsc)	Routine	Extreme mal-odor
Group 3	Male	3003	1 (Unsc)	Routine	Extreme mal-odor
Group 4	Male	4003	5 (am)	Routine	found dead at mortality check
Group 2	Female	2101	1 (Unsc)	Routine	Observations began immediately following dose administration.
Group 2	Female	2103	1 (Unsc)	Routine	Observations began immediately following dose administration.
Group 3	Female	3101	1 (Unsc)	Routine	Extreme mal-odor
Group 3	Female	3101	1 (30 m)	Routine	Ears appear vascular.
Group 3	Female	3103	1 (Unsc)	Routine	Extreme mal-odor
Group 4	Male	4003	1 (am)	Unscheduled Observation	Foul odor upon completion of dose administration. Clenching of front toes. Tucking front limbs under body
Group 4	Female	4103	1 (am)	Unscheduled Observation	Foul odor upon completion of dose administration

Clinical Observations - Animals by Time

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Key Page

Group Information

Short Name	Long Name	Type	Report Headings	
Gr 1	Group 1	Control	30 mg/kg	SOPH-110S
Gr 2	Group 2	Dose	100 mg/kg	SOPH-110S
Gr 3	Group 3	Dose	140 mg/kg	SOPH-110S
Gr 4	Group 4	Dose	200 mg/kg	SOPH-110S

Timeslot Definition

Abbreviation	Description
am	a.m.
30 m	30 min Post Dose
Unsc	Unscheduled

Table 7: Individual Body Weight Data

Individual Animal Body Weight Data

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Sex: Male Day(s) Relative to Start Date

30 mg/kg SOPH-110S	Body Weight (Grams)	Body Weight (Grams)	Body Weight (Grams)
	1	2	3
1001	449.1	440.6	446.7
1002	385.9	376.9	382.9
1003	407.0	400.1	400.1
Mean	414.0	405.9	409.9
SD	32.2	32.2	33.0
N	3	3	3

Individual Animal Body Weight Data

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Sex: Male Day(s) Relative to Start Date

100 mg/kg SOPH-110S	Body Weight (Grams)	Body Weight (Grams)	Body Weight (Grams)	Body Weight (Grams)
	1	2	3	4
2001	455.7	450.1	462.5	461.3
2002	423.1	418.5	426.6	426.2
2003	404.7	413.3	408.0	407.5
Mean	427.8	427.3	432.4	431.7
SD	25.8	19.9	27.7	27.3
N	3	3	3	3

Individual Animal Body Weight Data

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Sex: Male Day(s) Relative to Start Date

140 mg/kg SOPH-110S	Body Weight (Grams)	Body Weight (Grams)	Body Weight (Grams)
	1	2	3
3001	400.4	393.7	394.2
3002	427.2	420.6	419.5
3003	400.3	393.1	383.5
Mean	409.3	402.5	399.1
SD	15.5	15.7	18.5
N	3	3	3

Individual Animal Body Weight Data

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Sex: Male Day(s) Relative to Start Date

200 mg/kg SOPH-110S	Body Weight (Grams)	Body Weight (Grams)	Body Weight (Grams)	Body Weight (Grams)	Body Weight (Grams)
	1	2	3	4	5
4003	462.7	450.7	431.2	422.9	400.9
Mean	462.7	450.7	431.2	422.9	400.9
SD	-	-	-	-	-
N	1	1	1	1	1

Individual Animal Body Weight Data

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Sex: Male Day(s) Relative to Start Date

Spare	Body Weight (Grams)	Body Weight (Grams)	Body Weight (Grams)
	1	2	3
SM1	413.1	417.9	413.0
SM2	391.8	401.3	404.3
Mean	402.5	409.6	408.7
SD	15.1	11.7	6.2
N	2	2	2

Individual Animal Body Weight Data

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Sex: Female Day(s) Relative to Start Date

30 mg/kg SOPH-110S	Body Weight (Grams)	Body Weight (Grams)	Body Weight (Grams)
	1	2	3
1101	272.2	257.6	264.1
1102	292.0	289.8	292.7
1103	284.5 [a]	275.7	276.7
Mean	282.9	274.4	277.8
SD	10.0	16.1	14.3
N	3	3	3

[a] [RC:correct weight is 284.5g]

Individual Animal Body Weight Data

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Sex: Female Day(s) Relative to Start Date

100 mg/kg SOPH-110S	Body Weight (Grams)	Body Weight (Grams)	Body Weight (Grams)	Body Weight (Grams)
	1	2	3	4
2101	300.3	298.2	301.5	279.9
2102	300.8	293.5	301.5	290.5
2103	272.6	268.0	256.0	268.1
Mean	291.2	286.6	286.3	279.5
SD	16.1	16.3	26.3	11.2
N	3	3	3	3

Individual Animal Body Weight Data

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Sex: Female Day(s) Relative to Start Date

140 mg/kg SOPH-110S	Body Weight (Grams)	Body Weight (Grams)	Body Weight (Grams)
	1	2	3
3101	264.8	262.7	262.2
3102	300.3	298.4	295.8
3103	295.2	294.4	286.9
Mean	286.8	285.2	281.6
SD	19.2	19.6	17.4
N	3	3	3

Individual Animal Body Weight Data

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Sex: Female Day(s) Relative to Start Date

200 mg/kg SOPH-110S	Body Weight (Grams)	Body Weight (Grams)	Body Weight (Grams)	Body Weight (Grams)	Body Weight (Grams)
	1	2	3	4	5
4103	285.4	272.8	268.2	271.9	271.7
Mean	285.4	272.8	268.2	271.9	271.7
SD	-	-	-	-	-
N	1	1	1	1	1

Individual Animal Body Weight Data

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Sex: Female Day(s) Relative to Start Date

Spare	Body Weight (Grams)	Body Weight (Grams)	Body Weight (Grams)
	1	2	3
SF1	284.2	281.6	265.5
SF2	293.0	287.3	276.0
Mean	288.6	284.5	270.8
SD	6.2	4.0	7.4
N	2	2	2

Individual Animal Body Weight Data

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Comments and Markers

Page	Day	Group	Sex	Subject	Measurement	Type	Marker
6	1	Gr 1	Female	1103	Body Weight	Result	

Comment: correct weight is 284.5g

Individual Animal Body Weight Data

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Key Page

Measurement Descriptions

Headings Used	Description
Body Weight	Body Weight

Unit Descriptions

Headings Used	Description
Grams	g

Measurement/Statistics

Measurement	Descriptive
Body Weight	Mean
	Standard Deviation
	Count

Group Information

Short Name	Long Name	Type	Report Headings 1-4	
Gr 1	Group 1	Control	30 mg/kg	SOPH-110S
Gr 2	Group 2	Dose	100 mg/kg	SOPH-110S
Gr 3	Group 3	Dose	140 mg/kg	SOPH-110S
Gr 4	Group 4	Dose	200 mg/kg	SOPH-110S
SPR	Spare	Dose	Spare	

Individual Animal Body Weight Data

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Key Page

Comment Abbreviations

RC = Result Comment

Table 8: Individual Food Consumption Data

Individual Food Consumption Data

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Sex: Male Daily Food Cons Per Animal (g)

30 mg/kg SOPH-110S	No. in Cage	Day(s) Relative to Animal Start Date	
		1 → 2	2 → 3
1001	2	19.0	28.9
1003	1	18.8	27.5
	Mean	19	28
	SD	0	1
	N	2	2

Individual Food Consumption Data

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Sex: Male Daily Food Cons Per Animal (g)

100 mg/kg SOPH-110S	No. in Cage	Day(s) Relative to Animal Start Date		
		1 → 2	2 → 3	3 → 4
2001	2	20.2	21.8	24.5
2003	1	13.9	18.7	27.2
	Mean	17	20	26
	SD	4	2	2
	N	2	2	2

Individual Food Consumption Data

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Sex: Male Daily Food Cons Per Animal (g)

140 mg/kg SOPH-110S	No. in Cage	Day(s) Relative to Animal Start Date	
		1 → 2	2 → 3
3001	2	17.1	19.9
3003	1	18.6	16.3
	Mean	18	18
	SD	1	3
	N	2	2

Individual Food Consumption Data

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Sex: Male Daily Food Cons Per Animal (g)

200 mg/kg SOPH-110S	No. in Cage	Day(s) Relative to Animal Start Date			
		1 → 2	2 → 3	3 → 4	4 → 5
4003	1	6.1	13.7	18.7	7.8
	Mean	6	14	19	8
	SD	-	-	-	-
	N	1	1	1	1

Individual Food Consumption Data

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Sex: Male Daily Food Cons Per Animal (g)

Spare	No. in Cage	Day(s) Relative to Animal Start Date	
		1 → 2	2 → 3
1	2	26.4	29.7
	Mean	26	30
	SD	-	-
	N	1	1

Individual Food Consumption Data

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Sex: Female Daily Food Cons Per Animal (g)

30 mg/kg SOPH-110S	No. in Cage	Day(s) Relative to Animal Start Date	
		1 → 2	2 → 3
1101	2	10.6	18.4
1103	1	14.2	23.3
	Mean	12	21
	SD	3	4
	N	2	2

Individual Food Consumption Data

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Sex: Female Daily Food Cons Per Animal (g)

100 mg/kg SOPH-110S	No. in Cage	Day(s) Relative to Animal Start Date		
		1 → 2	2 → 3	3 → 4
2101	2	10.5	14.7	11.9
2103	1	9.0	13.0	16.6
	Mean	10	14	14
	SD	1	1	3
	N	2	2	2

Individual Food Consumption Data

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Sex: Female Daily Food Cons Per Animal (g)

140 mg/kg SOPH-110S	No. in Cage	Day(s) Relative to Animal Start Date	
		1 → 2	2 → 3
3101	2	9.8	32.2
3103	1	12.7	11.2
	Mean	11	22
	SD	2	15
	N	2	2

Individual Food Consumption Data

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Sex: Female Daily Food Cons Per Animal (g)

200 mg/kg SOPH-110S	No. in Cage	Day(s) Relative to Animal Start Date			
		1 → 2	2 → 3	3 → 4	4 → 5
4103	1	7.1	9.5	15.1	18.9
	Mean	7	10	15	19
	SD	-	-	-	-
	N	1	1	1	1

Individual Food Consumption Data

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Sex: Female Daily Food Cons Per Animal (g)

Spare	No. in Cage	Day(s) Relative to Animal Start Date	
		1 → 2	2 → 3
3	2	16.9	13.0
	Mean	17	13
	SD	-	-
	N	1	1

Individual Food Consumption Data

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Key Page

Cage Contents

Cage Number	Animal Numbers	Cage Number	Animal Numbers
1	SM1, SM2	3	SF1, SF2
1,001	1001, 1002	1,003	1003
1,101	1101, 1102	1,103	1103
2,001	2001, 2002	2,003	2003
2,101	2101, 2102	2,103	2103
3,001	3001, 3002	3,003	3003
3,101	3101, 3102	3,103	3103
4,003	4003	4,103	4103

Measurement Descriptions

Headings Used	Description
Daily Food Cons Per Animal	Mean Daily Food Cons. Per Animal

Measurement/Statistics

Measurement	Descriptive
Daily Food Cons Per Animal	Mean
	Standard Deviation
	Count

Individual Food Consumption Data

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Key Page

Group Information

Short Name	Long Name	Type	Report Headings 1-4	
Gr 1	Group 1	Control	30 mg/kg	SOPH-110S
Gr 2	Group 2	Dose	100 mg/kg	SOPH-110S
Gr 3	Group 3	Dose	140 mg/kg	SOPH-110S
Gr 4	Group 4	Dose	200 mg/kg	SOPH-110S
SPR	Spare	Dose	Spare	

Table 9: Individual Macroscopic Observations

Individual Macroscopic Observations

1124-8751 - A Maximum Tolerated Dose Study of SOPH-11OS in Rats

Group: 1 Dose: 30 mg/kg SOPH-1 Sex: Male

Animal Ref.	Mode Of Death	Death Day	(Week)	Observation(s)
1001	Killed Terminal	3	(1)	No Visible Lesions
1002	Killed Terminal	3	(1)	No Visible Lesions
1003	Killed Terminal	3	(1)	No Visible Lesions

Individual Macroscopic Observations

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Group: 1 Dose: 30 mg/kg SOPH-1 Sex: Female

Animal Ref.	Mode Of Death	Death Day	(Week)	Observation(s)
1101	Killed Terminal	3	(1)	No Visible Lesions
1102	Killed Terminal	3	(1)	No Visible Lesions
1103	Killed Terminal	3	(1)	No Visible Lesions

Individual Macroscopic Observations

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Group: 2 Dose: 100 mg/kg SOPH- Sex: Male

Animal Ref.	Mode Of Death	Death Day	(Week)	Observation(s)
2001	Killed Terminal	4	(1)	No Visible Lesions
2002	Killed Terminal	4	(1)	No Visible Lesions
2003	Killed Terminal	4	(1)	No Visible Lesions

Individual Macroscopic Observations

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Group: 2 Dose: 100 mg/kg SOPH- Sex: Female

Animal Ref.	Mode Of Death	Death Day	(Week)	Observation(s)
2101	Killed Terminal	4	(1)	OVARIES; Discoloration; Dark; Symmetric; Mild (TGL) PITUITARY GLAND; Enlarged (TGL) Any remaining protocol required tissues, which have been examined, have no visible lesions
2102	Killed Terminal	4	(1)	No Visible Lesions
2103	Killed Terminal	4	(1)	No Visible Lesions

Individual Macroscopic Observations

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Group: 3 Dose: 140 mg/kg SOPH- Sex: Male

Animal Ref.	Mode Of Death	Death Day	(Week)	Observation(s)
3001	Killed Terminal	3	(1)	No Visible Lesions
3002	Killed Terminal	3	(1)	No Visible Lesions
3003	Killed Terminal	3	(1)	No Visible Lesions

Individual Macroscopic Observations

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Group: 3 Dose: 140 mg/kg SOPH- Sex: Female

Animal Ref.	Mode Of Death	Death Day	(Week)	Observation(s)
3101	Killed Terminal	3	(1)	No Visible Lesions
3102	Killed Terminal	3	(1)	No Visible Lesions
3103	Killed Terminal	3	(1)	No Visible Lesions

Individual Macroscopic Observations

1124-8751 - A Maximum Tolerated Dose Study of SOPH-11OS in Rats

Group: 4 Dose: 200 mg/kg SOPH- Sex: Male

Animal Ref.	Mode Of Death	Death Day	(Week)	Observation(s)
4003	Found Dead	5	(1)	KIDNEYS; Enlarged; Multiple; Minimal (TGL) Any remaining protocol required tissues, which have been examined, have no visible lesions

Individual Macroscopic Observations

1124-8751 - A Maximum Tolerated Dose Study of SOPH-110S in Rats

Group: 4 Dose: 200 mg/kg SOPH- Sex: Female

Animal Ref.	Mode Of Death	Death Day	(Week)	Observation(s)
4103	Killed Terminal	5	(1)	No Visible Lesions

APPENDIX A

Final Protocol and Amendments

FINAL PROTOCOL

A Maximum Tolerated Dose Study of SOPH-110S Administered to Rats via Intravenous Bolus Injection

Attentive Science Study No.

1124-8751

Sponsor:

Sophrosyne Pharmaceuticals Limited
540 W Madison St, Suite 2500
Chicago, IL 60661, USA

Test Facility:

Attentive Science
17745 Metcalf Avenue
Building #4
Stilwell, KS 66085, USA

PROTOCOL APPROVAL

The protocol was approved by the Sponsor by e-mail on the date designated below. The correspondence giving approval will be archived, as appropriate with other Sponsor communications.

28 Oct 2024
Date

Attentive Science, LLC

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

James Randazzo, PhD, DABT
Study Director

29 Oct 2024
Date

The signature below indicates that Test Facility Management approves the Study Director identified in this protocol and acknowledges the study.

Test Facility Management

29 Oct 2024
Date

REGULATORY COMPLIANCE

This study will be conducted according to the principles of Good Laboratory Practice (GLP), but will not be audited for compliance and is therefore considered non-GLP. The procedures described in this protocol will be performed in accordance with the respective Test Facility and/or Test Site Standard Operating Procedures (SOPs).

TABLE OF CONTENTS

1 RESPONSIBLE PERSONNEL

1.1 Sponsor Personnel

Study Monitor	Andrew Fowlie, PhD Independent Consultant Stonehaven Nonclinical Consulting LLC 3 Bridlepath Road West Simsbury, CT 06092 Phone: (978) 560-9885 E-mail: afowlie@stonehavennonclinical.com

1.2 Test Facility Personnel

Study Director	James Randazzo, PhD, DABT Director of Toxicology Phone: (913) 308-0700 ext 5023 E-mail: james@attentivescience.com
Test Facility Management	Phil Atterson, MS Chief Operating Officer Phone: (913) 308-0700 ext 5021 E-mail: phil@attentivescience.com

2 OBJECTIVE

The objective of this study are to evaluate the tolerability of SOPH-110S when administered once by i.v. bolus to rats.

3 PROPOSED STUDY SCHEDULE

Experimental Starting Date (Animal Transfer):	30 OCT 2024
Dose Initiation:	Group 1: 30 OCT 2024 Group 2: 01 NOV 2024 Group 3: 05 NOV 2024 Group 4: 07 NOV 2024
Euthanasia:	Group 1: 01 NOV 2024 Group 2: 04 NOV 2024 Group 3: 07 NOV 2024 Group 4: 11 NOV 2024
Experimental Completion Date:	11 NOV 2024
Draft Report:	06 DEC 2024

4 EXPERIMENTAL DESIGN

Group	Treatment	Dose Level (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	Number of Animals	
					Males	Females
1	SOPH-110S	30	6	5	3	3
2	SOPH-110S	TBD	TBD	5	3	3
3	SOPH-110S	TBD	TBD	5	3	3
4	SOPH-110S	TBD	TBD	5	3	3

4.1 Justification of Dose, Route, Species and Animal Number

The design of this study was based on the study objective(s). The Sponsor affirms this study does not unnecessarily duplicate previous experiments.

The route of administration will be intravenous (bolus) to maximize the systemic exposure of the test article.

In a previous study, a single intravenous (bolus) was tolerated at 10 mg/kg. Therefore, the first dose was set at 30 mg/kg. Dose selection for Groups 2, 3, and 4 will be based on the outcome of the previous dose(s).

A May 2023 literature search of the Pub Med and Google Scholar for alternatives to animal testing was completed. No acceptable *in vitro* or non-animal alternatives for providing essential information to extrapolate the effects of test articles from animal to human were identified. Relevant keywords were used in the search. The literature search is on file at the Test Facility.

As a result, studies in laboratory animals provide the best available basis for extrapolation to humans and are required to support regulatory submissions.[1][2] The rat was chosen as the

animal model for this study as it is an accepted rodent species for preclinical toxicity testing by regulatory agencies for which historical control data are available.

This study has been designed such that it does not require an unnecessary number of animals to accomplish its objectives. Males and females were chosen to determine if there are sex-related differences in exposure and/or general toxicity. The total number of animals to be used in this study is considered to be the minimum required to properly characterize the effects of the test article and is generally accepted as the standard for the assessment of toxicology.

5 TEST ARTICLE AND VEHICLE INFORMATION

5.1 Test Article

Identification	SOPH-110S
Batch/Lot Number	L-23-0011-S-8015
Purity or Correction Factor	No correction factor will be used for preparation of the test article formulations.
Expiration/ Retest Date	To be documented by the Test Facility
Physical Description	To be documented by the Test Facility
Storage Conditions	Store at -15 to -30 ºC, inert atmosphere (N_2), in well-sealed amber glass vial with desiccant
Sample Retention	No retention samples will be collected as part of this non-GLP study.
Disposition	Any remaining test article will be maintained for a subsequent study.

5.2 Vehicle

Identification	Phosphate Buffered Saline, pH 6.0 ± 0.1
Component Batch/Lot Number	To be documented by the Test Facility
Component Storage Conditions	Store at 15–25 °C

5.3 Safety Precautions

A Safety Data Sheet (SDS), or equivalent, 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 safety equipment will be worn by individuals working with neat test article or formulations.

6 TEST SYSTEM

Species	Rat
Strain/Breed	Sprague Dawley
Source	Charles River
Number of Animals	Assigned to Study: 12/sex Transferred from Colony: 14/sex After the end of the replacement period, animals not utilized on study will be assigned to the Attentive Science stock colony or euthanized per SOP and discarded.
Approximate Age and Weight	Age at Receipt: 7–8 weeks Weight on Dosing: At least 240 g (males) or 200 g (females) The actual age and weight of the animals at the initiation of dosing will be listed in the final report. Females will be nulliparous and nonpregnant.

6.1 Animal Receipt, Randomization, and Acclimation

Each animal was inspected by qualified personnel upon receipt. Animals judged to be in good health were placed immediately in acclimation in accordance with Attentive Science SOP.

Animals judged to be in good health were randomized into cages upon arrival. Animals were placed into appropriate cages in a stepwise fashion (first animal will be placed in the first Group 1 cage, second animal will be placed in the first Group 2 cage, etc.). Cages will be arbitrarily assigned group designations prior to dosing.

Following randomization, it may be necessary to replace individual animal(s) either prior to or shortly after initiation of dosing up to Study Day 1. Replacement animals will be selected from the remaining unassigned animals and assigned arbitrarily. The reason(s) for replacement will be appropriately documented in the study records.

6.2 Animal Identification

Each animal will be identified using a subcutaneously-implanted electronic chip or other alternate unique identifier.

6.3 Animal Housing and Environmental Conditions

All animals will be group housed by sex and dose group in solid bottom cages with appropriate bedding material. Animals may be housed individually, if necessary, for study related events, observation attribution, cage mate death and/or behavioral issues.

Items will be provided for environmental enrichment and/or to aid in maintaining the animals' oral health, beginning during the acclimation/pre-treatment period and continuing throughout the course of the study.

Animal rooms will be monitored for appropriate temperature, relative humidity, light cycle and air changes for the test system in use, as per Attentive Science SOPs.

The animal room and equipment will be cleaned at regular intervals throughout the study, as per facility SOPs. Equipment and bedding changes will be recorded in the facility records. Contaminant-free contact bedding will be used and the results of an example lot are on file at Attentive Science.

6.4 Diet and Drinking Water

Tap water from the municipal water department will be available *ad libitum*. Water supplying the laboratory will be analyzed for contaminants by the municipal water department and an independent laboratory.

A certified laboratory diet (PMI Nutrition International, LLC Certified Rodent LabDiet® 5002) will be offered *ad libitum* during the study. Each lot utilized will be identified and recorded. Each lot of diet has been analyzed for contaminants by the manufacturer. Supplements may be provided on individual animal basis as warranted and directed by the Veterinarian in consultation with the Study Director.

No contaminants are expected to be present in the water or certified diet at concentrations that would interfere with the purpose or conduct of the study. The results of the water and certified diet analyses will be maintained in the facility records.

6.5 Animal Welfare

This study will comply with all applicable sections of the Final Rules of the Animal Welfare Act regulations (9 CFR) and all applicable AAALAC International standards.[3] The Sponsor should make particular note of the following:

Whenever possible, procedures used in this study have been designed to avoid or minimize discomfort, distress or pain to animals. It is expected that animals on this study will experience up to a pain category D, as defined by Attentive Science IACUC (alleviated momentary pain or distress). Exact categorization for each animal will be noted in the study and/or facility records, as appropriate. All methods are described in this study protocol and/or are in written laboratory SOPs or Attentive Science IACUC Pain and Distress Guidance document.

In the event that animals show signs of illness or distress, initial recommendations about treatment of the animal(s) and/or alteration of study procedures (including dosing holidays) will be communicated by the veterinary staff to the Study Director. Any condition that may require or warrants medical intervention will be treated at the discretion of the veterinary staff, after consultation with the Study Director and Sponsor, if possible. If the condition of the animal(s) is such that emergency measures must be taken to alleviate suffering, the Study Director and/or Veterinarian has authority to act immediately. The Sponsor will be fully informed of any such events.

7 DOSE FORMULATION AND ANALYSIS

7.1 Preparation of Dosing Formulations

Formulation	Frequency of Preparation	Storage Conditions	Disposition
Vehicle	As needed	Store at 15-25 °C	Discard after completion
Test Article	On the day of dosing	Store at 2–8 °C, when not in use	Discard after completion

Dosing formulations will either be prepared under asceptic conditions and/or will be sterile filtered prior to use.

8 IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS

8.1 Administration of Dose Formulations

Frequency and Duration	Once
Method of Administration	Intravenous Injection: Each dose will be administered via bolus injection to the tail vein
Adjustment of Dose Volume	Individual doses will be calculated based upon the most recent individual body weights.
Comments	The first day of dosing will be designated as Day 1.

8.2 Animal Observations

8.2.1 Mortality Checks

Starting on Day 1, all animals will be observed for mortality/moribundity at least twice daily with the exception of day of termination and non-dosing days that fall on weekends and holidays. When mortality checks are performed twice daily, there should be a minimum of 4 hours between checks; once in the morning (am) and once in the afternoon (pm).

8.2.2 Clinical Observations

At minimum, all study animals will be observed as follows:

- 0.5–1 hours post dosing
- At least once daily on non-dosing days
- Unscheduled observations, if noted

The absence or presence of findings will be recorded for individual animals. The presence of findings noted outside the above-specified observation periods (unscheduled observations) will also be recorded.

8.3 Individual Body Weights

At minimum, all main study will have body weights recorded as follows:

- Study Day 1 (prior to dosing)
- Daily until day of euthanasia (inclusive)

To include spare animals until transferred to colony or disposed.

8.4 Food Consumption

At minimum, food will be weighed and recorded for all study animals as follows:

- Daily, beginning on Day 1

To include spare animals until transferred to colony or disposed.

Food consumption data will be collected per cage for cohoused animals. For reporting purposes, cohoused food consumption data will be divided by the number of animals per cage and reported as individual animal data.

9 TERMINAL PROCEDURES

9.1 Animals to be Euthanized in Extremis

Moribund animals will be euthanized and necropsied as soon as possible. Animals found dead will be necropsied as soon as possible to reduce possible tissue loss due to autolysis.

Animals to be euthanized *in extremis* will be euthanized by CO_2 inhalation followed by exsanguination. If possible, final collections as outlined in the table below will be attempted based on the clinical condition of the animal.

	Unscheduled Animal Euthanasia	Animals Found Dead
Detailed Observations	X	-
Body Weights	X	-
Macroscopic Examination	X	X

X = Activity to be carried out; - = Not applicable

[a] Animals will receive an abbreviated necropsy in an attempt to determine the cause of death.

9.2 Scheduled Euthanasia

Study Animals	All surviving study animals will be euthanized according to Attentive SOPs, a gross necropsy will be performed, and then will be discarded without tissue collection.
Method of Euthanasia	Animals to be euthanized at terminal necropsy will be euthanized by CO_2 inhalation followed by exsanguination.

9.2.1 Macroscopic Examination

A complete necropsy will be conducted at each scheduled necropsy and will include examination of the external surface, all orifices and the cranial, thoracic, abdominal and pelvic cavities, including viscera.

9.2.2 Organ Weights

Not applicable.

9.2.3 Tissue Collection and Preservation

Not applicable.

10 PROTOCOL MODIFICATION

Modification of the protocol may be required during the course of this investigation. However, no changes will be made in the study design without the verbal or written permission of the Sponsor. If changes to the protocol are needed, appropriate documentation in the form of protocol amendment(s) will be made. If changes are required for scientific or humane reasons, and the Sponsor cannot be contacted, the Study Director will implement the changes and inform the Sponsor at the earliest opportunity. The amendment(s) will include the section of the protocol to be amended, the reason(s) for the change(s), and at least the signature of the Study Director and the date of signing.

11 STATISTICAL METHODS

Statistical analyses will not be performed due to the absence of a concurrent control group. However, means and standard deviations will be calculated, as appropriate.

12 DATA CAPTURE

The data capture systems (along with version numbers, if applicable) will be included in the study records.

13 WORK PRODUCT

Sponsor will have title to all documentation records, raw data, slides, specimens, or other work product generated during the performance of the study.

All work product including: raw paper data, pertinent electronic storage media and specimens, will be retained at no charge in the Attentive Science archives for a period of 12 months following issuance of the final report. Thereafter, Attentive Science may extend the archiving period or ship work product to an archive facility at the request of the Sponsor.

Any work product, to be shipped by Attentive Science to another location will be appropriately packaged and addressed as defined by Attentive Science SOPs and delivered to a common carrier for shipment. Attentive Science will not be responsible for shipment following delivery to the common carrier.

14 REPORTING

14.1 Main Report

The abbreviated report will contain a summary, test article information, methods and procedures, appropriate individual animal and summary data tables, a copy of the protocol and amendment(s), and an interpretation and discussion of the study results.

Attentive Science will submit an electronic copy (PDF with an MS Word copy of the report text for editing and comments) of the draft report in a timely manner upon completion of data collection prior to issuance of the final report. If the Sponsor's comments and/or authorization to finalize the report have not been received at Attentive Science within 6 months following submission of the draft report, Attentive Science may elect to finalize the report following appropriate written notification to the Sponsor. An electronic copy (bookmarked and hyperlinked PDF) of the final report will be provided.

15 SEND DATA SET

Unless otherwise specified, SEND-compliant data must be provided for inclusion within the SEND data set package from each Principal Investigator.

A submission-ready SEND data set will be prepared from the unaudited data set and provided to the Sponsor following report finalization. The SEND data set is not audited.

16 REFERENCES

1. Guidance for Industry. Safety Testing of Drug Metabolites. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, *Pharmacology and Toxicology*. March 2020.

2. Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals M3(R2). *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline,* January 2010.

3. *Guide for the Care and Use of Laboratory Animals*; National Research Council, National Academies Press: Washington, DC, 2011.

PROTOCOL AMENDMENT 4

A Maximum Tolerated Dose Study of SOPH-110S Administered to Rats via Intravenous Bolus Injection

Attentive Science Study No.

1124-8751

Sponsor:

Sophrosyne Pharmaceuticals Limited
540 W Madison St, Suite 2500
Chicago, IL 60661, USA

Test Facility:

Attentive Science
17745 Metcalf Avenue
Building #4
Stilwell, KS 66085, USA

PROTOCOL CHANGES

All additions to the protocol will be in bold and all removals from the protocol will be lined through. The table below provides section and reason for change.

PROTOCOL AMENDMENT 4	
Section 1.2: Test Facility Personnel	**Page: 6**
Reason for Change: Reassignment of Study Director.	

PROTOCOL AMENDMENT 3 Effective Date: November 06, 2024
Section 4: Experimental Design
Reason for Change: Information for Group 4 added/updated following review of observations from Groups 1, 2, and 3.
Section 6: Test System
Reason for Change: Reduced number of animals in Group 4 from N=3/sex to N=1/sex, section updated accordingly.

PROTOCOL AMENDMENT 2 Effective Date: November 04, 2024
Section 4: Experimental Design
Reason for Change: Information for Group 3 added/updated following review of observations from Groups 1 and 2.

PROTOCOL AMENDMENT 1 Effective Date: October 31, 2024
Section 4: Experimental Design
Reason for Change: Information for Group 2 added/updated following review of observations from Group 1.

PROTOCOL AMENDMENT APPROVAL

The protocol amendment was approved by the Sponsor by e-mail on the date designated below. The correspondence giving approval will be archived, as appropriate with other Sponsor communications.

13Dec24
Date

Attentive Science, LLC

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

Tabitha Frye
Tabitha Frye
Study Director

12Dec24
Date

The signature below indicates that Test Facility Management approves the Study Director identified in this protocol amendment and acknowledges the study.

Test Facility Management

13 Dec 2024
Date

REGULATORY COMPLIANCE

This study will be conducted according to the principles of Good Laboratory Practice (GLP), but will not be audited for compliance and is therefore considered non-GLP. The procedures described in this protocol will be performed in accordance with the respective Test Facility and/or Test Site Standard Operating Procedures (SOPs).

TABLE OF CONTENTS

1 RESPONSIBLE PERSONNEL

1.1 Sponsor Personnel

Study Monitor	Andrew Fowlie, PhD Independent Consultant Stonehaven Nonclinical Consulting LLC 3 Bridlepath Road West Simsbury, CT 06092 Phone: (978) 560-9885 E-mail: afowlie@stonehavennonclinical.com

1.2 Test Facility Personnel

Study Director	~~James Randazzo, PhD, DABT~~ ~~Director of Toxicology~~ ~~Phone: (913) 308-0700 ext 5023~~ ~~E-mail: james@attentivescience.com~~ **Tabitha Frye** **Research Scientist I** **Phone: (913) 308-0700 ext 5010** **E-mail: tabitha@attentivescience.com**
Test Facility Management	Phil Atterson, MS Chief Operating Officer Phone: (913) 308-0700 ext 5021 E-mail: phil@attentivescience.com

2 OBJECTIVE

The objective of this study are to evaluate the tolerability of SOPH-110S when administered once by i.v. bolus to rats.

3 PROPOSED STUDY SCHEDULE

Experimental Starting Date (Animal Transfer):	30 OCT 2024
Dose Initiation:	Group 1: 30 OCT 2024 Group 2: 01 NOV 2024 Group 3: 05 NOV 2024 Group 4: 07 NOV 2024
Euthanasia:	Group 1: 01 NOV 2024 Group 2: 04 NOV 2024 Group 3: 07 NOV 2024 Group 4: 11 NOV 2024
Experimental Completion Date:	11 NOV 2024
Draft Report:	06 DEC 2024

4 EXPERIMENTAL DESIGN

Group	Treatment	Dose Level (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	Number of Animals	
					Males	Females
1	SOPH-110S	30	6	5	3	3
2	SOPH-110S	100	25	4	3	3
3	SOPH-110S	140	35	4	3	3
4	SOPH-110S	200	50	4	1	1

4.1 Justification of Dose, Route, Species and Animal Number

The design of this study was based on the study objective(s). The Sponsor affirms this study does not unnecessarily duplicate previous experiments.

The route of administration will be intravenous (bolus) to maximize the systemic exposure of the test article.

In a previous study, a single intravenous (bolus) was tolerated at 10 mg/kg. Therefore, the first dose was set at 30 mg/kg. Dose selection for Groups 2, 3, and 4 will be based on the outcome of the previous dose(s).

A May 2023 literature search of the Pub Med and Google Scholar for alternatives to animal testing was completed. No acceptable *in vitro* or non-animal alternatives for providing essential information to extrapolate the effects of test articles from animal to human were identified. Relevant keywords were used in the search. The literature search is on file at the Test Facility.

As a result, studies in laboratory animals provide the best available basis for extrapolation to humans and are required to support regulatory submissions.[1][2] The rat was chosen as the

animal model for this study as it is an accepted rodent species for preclinical toxicity testing by regulatory agencies for which historical control data are available.

This study has been designed such that it does not require an unnecessary number of animals to accomplish its objectives. Males and females were chosen to determine if there are sex-related differences in exposure and/or general toxicity. The total number of animals to be used in this study is considered to be the minimum required to properly characterize the effects of the test article and is generally accepted as the standard for the assessment of toxicology.

5 TEST ARTICLE AND VEHICLE INFORMATION

5.1 Test Article

Identification	SOPH-110S
Batch/Lot Number	L-23-0011-S-8015
Purity or Correction Factor	No correction factor will be used for preparation of the test article formulations.
Expiration/ Retest Date	To be documented by the Test Facility
Physical Description	To be documented by the Test Facility
Storage Conditions	Store at -15 to -30 ºC, inert atmosphere (N_2), in well-sealed amber glass vial with desiccant
Sample Retention	No retention samples will be collected as part of this non-GLP study.
Disposition	Any remaining test article will be maintained for a subsequent study.

5.2 Vehicle

Identification	Phosphate Buffered Saline, pH 6.0 ± 0.1
Component Batch/Lot Number	To be documented by the Test Facility
Component Storage Conditions	Store at 15–25 °C

5.3 Safety Precautions

A Safety Data Sheet (SDS), or equivalent, 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 safety equipment will be worn by individuals working with neat test article or formulations.

6 TEST SYSTEM

Species	Rat
Strain/Breed	Sprague Dawley
Source	Charles River
Number of Animals	Assigned to Study: 10/sex Transferred from Colony: 14/sex After the end of the replacement period, animals not utilized on study will be assigned to the Attentive Science stock colony or euthanized per SOP and discarded.
Approximate Age and Weight	Age at Receipt: 7–8 weeks Weight on Dosing: At least 240 g (males) or 200 g (females) The actual age and weight of the animals at the initiation of dosing will be listed in the final report. Females will be nulliparous and nonpregnant.

6.1 Animal Receipt, Randomization, and Acclimation

Each animal was inspected by qualified personnel upon receipt. Animals judged to be in good health were placed immediately in acclimation in accordance with Attentive Science SOP.

Animals judged to be in good health were randomized into cages upon arrival. Animals were placed into appropriate cages in a stepwise fashion (first animal will be placed in the first Group 1 cage, second animal will be placed in the first Group 2 cage, etc.). Cages will be arbitrarily assigned group designations prior to dosing.

Following randomization, it may be necessary to replace individual animal(s) either prior to or shortly after initiation of dosing up to Study Day 1. Replacement animals will be selected from the remaining unassigned animals and assigned arbitrarily. The reason(s) for replacement will be appropriately documented in the study records.

6.2 Animal Identification

Each animal will be identified using a subcutaneously-implanted electronic chip or other alternate unique identifier.

6.3 Animal Housing and Environmental Conditions

All animals will be group housed by sex and dose group in solid bottom cages with appropriate bedding material. Animals may be housed individually, if necessary, for study related events, observation attribution, cage mate death and/or behavioral issues.

Items will be provided for environmental enrichment and/or to aid in maintaining the animals' oral health, beginning during the acclimation/pre-treatment period and continuing throughout the course of the study.

Animal rooms will be monitored for appropriate temperature, relative humidity, light cycle and air changes for the test system in use, as per Attentive Science SOPs.

The animal room and equipment will be cleaned at regular intervals throughout the study, as per facility SOPs. Equipment and bedding changes will be recorded in the facility records. Contaminant-free contact bedding will be used and the results of an example lot are on file at Attentive Science.

6.4 Diet and Drinking Water

Tap water from the municipal water department will be available *ad libitum*. Water supplying the laboratory will be analyzed for contaminants by the municipal water department and an independent laboratory.

A certified laboratory diet (PMI Nutrition International, LLC Certified Rodent LabDiet® 5002) will be offered *ad libitum* during the study. Each lot utilized will be identified and recorded. Each lot of diet has been analyzed for contaminants by the manufacturer. Supplements may be provided on individual animal basis as warranted and directed by the Veterinarian in consultation with the Study Director.

No contaminants are expected to be present in the water or certified diet at concentrations that would interfere with the purpose or conduct of the study. The results of the water and certified diet analyses will be maintained in the facility records.

6.5 Animal Welfare

This study will comply with all applicable sections of the Final Rules of the Animal Welfare Act regulations (9 CFR) and all applicable AAALAC International standards.[3] The Sponsor should make particular note of the following:

Whenever possible, procedures used in this study have been designed to avoid or minimize discomfort, distress or pain to animals. It is expected that animals on this study will experience up to a pain category D, as defined by Attentive Science IACUC (alleviated momentary pain or distress). Exact categorization for each animal will be noted in the study and/or facility records, as appropriate. All methods are described in this study protocol and/or are in written laboratory SOPs or Attentive Science IACUC Pain and Distress Guidance document.

In the event that animals show signs of illness or distress, initial recommendations about treatment of the animal(s) and/or alteration of study procedures (including dosing holidays) will be communicated by the veterinary staff to the Study Director. Any condition that may require or warrants medical intervention will be treated at the discretion of the veterinary staff, after consultation with the Study Director and Sponsor, if possible. If the condition of the animal(s) is such that emergency measures must be taken to alleviate suffering, the Study Director and/or Veterinarian has authority to act immediately. The Sponsor will be fully informed of any such events.

7 DOSE FORMULATION AND ANALYSIS

7.1 Preparation of Dosing Formulations

Formulation	Frequency of Preparation	Storage Conditions	Disposition
Vehicle	As needed	Store at 15-25 °C	Discard after completion
Test Article	On the day of dosing	Store at 2–8 °C, when not in use	Discard after completion

Dosing formulations will either be prepared under asceptic conditions and/or will be sterile filtered prior to use.

8 IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS

8.1 Administration of Dose Formulations

Frequency and Duration	Once
Method of Administration	Intravenous Injection: Each dose will be administered via bolus injection to the tail vein
Adjustment of Dose Volume	Individual doses will be calculated based upon the most recent individual body weights.
Comments	The first day of dosing will be designated as Day 1.

8.2 Animal Observations

8.2.1 Mortality Checks

Starting on Day 1, all animals will be observed for mortality/moribundity at least twice daily with the exception of day of termination and non-dosing days that fall on weekends and holidays. When mortality checks are performed twice daily, there should be a minimum of 4 hours between checks; once in the morning (am) and once in the afternoon (pm).

8.2.2 Clinical Observations

At minimum, all study animals will be observed as follows:

- 0.5–1 hours post dosing
- At least once daily on non-dosing days
- Unscheduled observations, if noted

The absence or presence of findings will be recorded for individual animals. The presence of findings noted outside the above-specified observation periods (unscheduled observations) will also be recorded.

8.3 Individual Body Weights

At minimum, all main study will have body weights recorded as follows:

- Study Day 1 (prior to dosing)
- Daily until day of euthanasia (inclusive)

To include spare animals until transferred to colony or disposed.

8.4 Food Consumption

At minimum, food will be weighed and recorded for all study animals as follows:

- Daily, beginning on Day 1

To include spare animals until transferred to colony or disposed.

Food consumption data will be collected per cage for cohoused animals. For reporting purposes, cohoused food consumption data will be divided by the number of animals per cage and reported as individual animal data.

9 TERMINAL PROCEDURES

9.1 Animals to be Euthanized in Extremis

Moribund animals will be euthanized and necropsied as soon as possible. Animals found dead will be necropsied as soon as possible to reduce possible tissue loss due to autolysis.

Animals to be euthanized *in extremis* will be euthanized by CO_2 inhalation followed by exsanguination. If possible, final collections as outlined in the table below will be attempted based on the clinical condition of the animal.

	Unscheduled Animal Euthanasia	Animals Found Dead
Detailed Observations	X	-
Body Weights	X	-
Macroscopic Examination	X	X

X = Activity to be carried out; - = Not applicable

[a] Animals will receive an abbreviated necropsy in an attempt to determine the cause of death.

9.2 Scheduled Euthanasia

Study Animals	All surviving study animals will be euthanized according to Attentive SOPs, a gross necropsy will be performed, and then will be discarded without tissue collection.
Method of Euthanasia	Animals to be euthanized at terminal necropsy will be euthanized by CO_2 inhalation followed by exsanguination.

9.2.1 Macroscopic Examination

A complete necropsy will be conducted at each scheduled necropsy and will include examination of the external surface, all orifices and the cranial, thoracic, abdominal and pelvic cavities, including viscera.

9.2.2 Organ Weights

Not applicable.

9.2.3 Tissue Collection and Preservation

Not applicable.

10 PROTOCOL MODIFICATION

Modification of the protocol may be required during the course of this investigation. However, no changes will be made in the study design without the verbal or written permission of the Sponsor. If changes to the protocol are needed, appropriate documentation in the form of protocol amendment(s) will be made. If changes are required for scientific or humane reasons, and the Sponsor cannot be contacted, the Study Director will implement the changes and inform the Sponsor at the earliest opportunity. The amendment(s) will include the section of the protocol to be amended, the reason(s) for the change(s), and at least the signature of the Study Director and the date of signing.

11 STATISTICAL METHODS

Statistical analyses will not be performed due to the absence of a concurrent control group. However, means and standard deviations will be calculated, as appropriate.

12 DATA CAPTURE

The data capture systems (along with version numbers, if applicable) will be included in the study records.

13 WORK PRODUCT

Sponsor will have title to all documentation records, raw data, slides, specimens, or other work product generated during the performance of the study.

All work product including: raw paper data, pertinent electronic storage media and specimens, will be retained at no charge in the Attentive Science archives for a period of 12 months following issuance of the final report. Thereafter, Attentive Science may extend the archiving period or ship work product to an archive facility at the request of the Sponsor.

Any work product, to be shipped by Attentive Science to another location will be appropriately packaged and addressed as defined by Attentive Science SOPs and delivered to a common carrier for shipment. Attentive Science will not be responsible for shipment following delivery to the common carrier.

14 REPORTING

14.1 Main Report

The abbreviated report will contain a summary, test article information, methods and procedures, appropriate individual animal and summary data tables, a copy of the protocol and amendment(s), and an interpretation and discussion of the study results.

Attentive Science will submit an electronic copy (PDF with an MS Word copy of the report text for editing and comments) of the draft report in a timely manner upon completion of data collection prior to issuance of the final report. If the Sponsor's comments and/or authorization to finalize the report have not been received at Attentive Science within 6 months following submission of the draft report, Attentive Science may elect to finalize the report following appropriate written notification to the Sponsor. An electronic copy (bookmarked and hyperlinked PDF) of the final report will be provided.

15 SEND DATA SET

Unless otherwise specified, SEND-compliant data must be provided for inclusion within the SEND data set package from each Principal Investigator.

A submission-ready SEND data set will be prepared from the unaudited data set and provided to the Sponsor following report finalization. The SEND data set is not audited.

16 REFERENCES

1. Guidance for Industry. Safety Testing of Drug Metabolites. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, *Pharmacology and Toxicology*. March 2020.

2. Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals M3(R2). *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline,* January 2010.

3. *Guide for the Care and Use of Laboratory Animals*; National Research Council, National Academies Press: Washington, DC, 2011.